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Ischemic Stroke Therapeutics

A Comprehensive Guide

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Foreword

Fifteen years into the new millennium comes a truly contemporary and dynamic compendium for a new generation of physicians and care providers. Drs. Ovbiagele and Turan, and their contributors, bring forward a new book for a new era of stroke care. In a field once characterized by nihilism, minimalist therapy and long discussions over the dose of aspirin, these authors capture the emerging enthusiasm for stroke therapeutics at the inflection point in its evolution where the care spectrum is expanding to encompass the prehospital space and extending well beyond the acute hospitalization into rehabilitation and recovery. Much has changed, not just the therapeutics we have to offer, but the ways and means of delivering that care within "*stroke systems of care*" and using remote evaluation and treatment with telemedicine. There is a great deal to learn from this book as the field of stroke care matures and expands into new areas such as aggressive endovascular therapy and brain stimulation to enhance recovery. The editors and contributors have accomplished an important task and the reader will be rewarded for engaging *Ischemic Stroke Therapeutics: A comprehensive Guide*.

Charleston, SC, USA — Robert J. Adams, M.S., M.D.

Preface

Stroke exacts a huge toll throughout the world by way of its dreaded complications, death, disability, and dementia. Fortunately, the historic nihilism in stroke care has been replaced with a sense of optimism, due to a better understanding of its various underlying mechanisms, robust evidence to either support or discredit several interventions, and a measureable decline in the incidence of stroke over the last decade in many developed nations. Ischemic stroke, the more preponderant of the two main stroke types, has especially benefitted from major therapeutic strides forward in its acute management and secondary prevention. Just as thrilling is the prospect of future data from ongoing and planned clinical trials, testing a variety of treatments and strategies, aimed at improving stroke outcomes.

Ischemic Stroke Therapeutics is a timely and consolidated resource for clinicians, which captures state-of-the-art strategies and the accelerated pace of discovery that is revolutionizing what we know about ischemic stroke and its treatment. Therapeutics for acute management, secondary prevention, recovery/rehabilitation, asymptomatic cerebral ischemia, and implementation of stroke systems of care are all discussed in this comprehensive yet practical treatise. Leading academicians with extensive clinical practice experience from all over the world present the scientific evidence behind prevailing therapeutic strategies for managing ischemic cerebrovascular disease.

Each section follows a similar format. An introductory general concepts subsection written by a senior academician provides an overview of the key issues pertinent to that area of stroke management and is followed by chapters covering important individual topics in that section that review currently available therapies in that area, describe unresolved major issues, and present promising future areas of therapeutic focus under investigation.

Medicine is best taught case by case, so where applicable, chapters include a concise case vignette (emphasizing a key take-home point), followed by discussions of the relevant evidence-based treatments including results of clinical trials, meta-analyses of existing trial or cohort data, and "real-world" studies (hospital and community registries), along with user-friendly statistical concepts such as number needed to treat (NNT) and number needed to harm (NNH). Noteworthy differential effects of treatments in special populations (e.g., women, very elderly, race-ethnic minorities) and data on cost implications (where available) are also detailed. Where evidence is sparse or lacking, expert contributors acknowledge this and present their own management recommendations. Finally, select interventions in research development with a strong potential for transforming future care of the ischemic stroke patient are mentioned. Updated reference lists at the end of each chapter serve to direct readers to specific articles for more in-depth reading on a subject.

Ischemic Stroke Therapeutics will be of value to Primary Care Physicians, Geriatricians, Emergency Care Physicians, Hospitalists, General Neurologists, Neuro-Hospitalists, Vascular-Neurologists-in-training, and Vascular Neurology Board Re-certification Candidates, because

it provides a comprehensive review of the most up-to-date evidence-based therapy for everyday management of ischemic stroke patients and a peek at promising future therapeutic strategies by world-renowned experts.

We are greatly indebted to our contributors, families, and especially our patients from whom we have been privileged to learn so much.

Charleston, SC, USA

Bruce Ovbiagele
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General Concepts: Management of Acute Ischemic Stroke

1

Harold P. Adams, Jr.

Introduction

In this introductory chapter, I review the current status of emergency management of ischemic stroke and outline some goals for the future.

Ischemic stroke is a leading cause of death and disability in the world. Because of the nature of the disease, which leads to a broad spectrum of motor, sensory, and cognitive impairments, stroke is a leading cause of human suffering. It adversely affects the patient, his/her family, and society as a whole. Ischemic stroke is expensive in terms of health-care costs, but it also has a major financial impact on society because of its effects on productivity. With the aging of the population in many countries, including the USA, and with improved survival among patients with severe heart disease, the medical community should anticipate that ischemic stroke will grow as a public health problem.

Management of patients with ischemic cerebrovascular disease is multifaceted and the priorities change during the course of an individual patient's illness (Table 1.1). Patients with acute ischemic stroke are seriously ill and need complex multidimensional treatment that includes early administration of interventions to limit the brain injury, general life support measures, and therapies aimed at preventing or controlling acute neurological and medical complications. Initial management usually occurs in an emergency department setting. Subsequently, patients usually are hospitalized for continued treatment of the stroke, prevention and treatment of both medical and neurological complications, evaluation for the presumed cause of stroke, initiation of therapies to prevent recurrent events, and the commencement of rehabilitation.

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Historical Perspective on Acute Stroke Care

During the last 40 years, management of patients with ischemic stroke has advanced (Table 1.2). Basic science research provides information about the causes of stroke and the vascular/cellular consequences from an arterial occlusion. We have learned that the course of acute brain ischemia evolves over a few hours and that dysfunctional brain tissue can be saved. Early treatment is crucial—time is brain. This knowledge serves as the foundation for therapies that treat stroke. The diagnosis of ischemic stroke and its underlying causes has been greatly expedited with advances in technology; in particular brain, vascular, and cardiac imaging. The introduction of computed tomography (CT) in the 1970s, which facilitated the differentiation of hemorrhagic or ischemic stroke and which was much more accurate than clinicians, was the first step in the revolution of acute stroke care. Magnetic resonance imaging followed. The development of promising pharmacological agents and new strategies to treat acute ischemic stroke were rapid during the last two decades of the twentieth century. Some interventions were aimed at limiting the neurological consequences (neuroprotective therapy) of the acute ischemic process while others focused on the restoration or improvement of the circulation. Subsequently, clinical research in treatment of acute ischemic stroke used an integrated series of projects to test for safety, to screen for potential efficacy, and to develop criteria for patient selection. The preliminary steps provided the bases for testing efficacy within larger Phase III clinical trials. Some trials demonstrated the non-utility of time-honored interventions such as emergency anticoagulation and, to date, the trials of neuroprotective agents are negative. Still, the results of large Phase III trials are used by regulatory bodies to approve new therapies for stroke. The first governmental approval for any treatment of acute ischemic stroke, intravenous thrombolysis, was by the US Food and Drug Administration (FDA) in 1996. The authors of evidence-based treatment guidelines also use the results of clinical trials as the basis of recommendations for patient care [1].

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Table 1.1 Components of management patients with ischemic cerebrovascular disease

Prevention
Acute management
General emergency management
Treatment of the acute ischemic stroke itself
Intravenous thrombolysis
Endovascular interventions
Prevention or treatment of acute complications
Subsequent stroke management
Prevention or treatment of subacute or chronic complications
Treatment of serious comorbid diseases
Evaluation for the cause of stroke
Rehabilitation and recovery
Prevention of recurrent stroke

Table 1.2 Advances in the management of patients with ischemic cerebrovascular disease

Prevention
Public health life style changes including smoking cessation
Statins and new antihypertensive agents
Antiplatelet agents for patients with arterial causes of stroke
Vitamin K antagonist anticoagulants for patients with atrial fibrillation
New oral anticoagulants for patients with atrial fibrillation
Carotid endarterectomy
Angioplasty and stenting
General management of acute stroke
Multidisciplinary treatment in a stroke unit
Anticoagulants for prevention of deep vein thrombosis
Rehabilitation
Medications to foster recovery after stroke
Emergency treatment of acute ischemic stroke
Brain, vascular, and cardiac imaging
General emergency treatment
Intravenous thrombolysis
Endovascular interventions

The guidelines in stroke, which first appeared in the USA, are replicated around the world and these statements are revised and updated with advances in knowledge of management of acute ischemic stroke.

As a result of these advances, the treatment of patients with ischemic stroke is vastly different than it was just 20 years ago.

The Revolution in Emergency Stroke Care: Intravenous Thrombolysis

In the 1960s, physicians tested the utility of thrombolytic therapy in patients with stroke with disappointing results. The studies, which were performed prior to the advent of CT, probably enrolled some patients with intracranial hemorrhages and the interval from onset of stroke until treatment (approximately 24 h) was exceedingly long [2]. Despite these negative studies, research continued. Experimental studies showed that rapid restoration of blood flow could limit the neurological consequences of a thromboembolic occlusion. The success of reperfusion therapy in improving outcomes among patients with acute coronary artery occlusions also provided an impetus for new research on intravenous thrombolysis for stroke. A number of agents were tested. In 1995, the investigators of the National Institute of Neurological Disorders and Stroke (NINDS) trial of intravenous administration of recombinant tissue plasminogen activator (rtPA) reported that early administration of the agent (<3 h of onset of stroke) was associated with an increased likelihood of a favorable outcome at 3 months [3]. For the first time, an intervention of proven utility was available to treat acute ischemic stroke.

While there is considerable enthusiasm about the success of intravenous thrombolysis, skeptics question the utility of treatment [4, 5]. These criticisms led to an independent review of the data; the result was the conclusion that intravenous thrombolysis was effective [6]. Additional trials were performed including one that showed efficacy of treatment up to 4.5 h after onset of stroke, and another which confirmed the efficacy of treatment in both younger and older patients [7, 8]. Although the FDA has not approved the use of rtPA in the 3–4.5 h time period, it is approved in Europe and American guidelines recommend its use [1, 9]. While some resistance to the use of intravenous thrombolysis in treatment of acute ischemic stroke persists, a meta-analysis of the clinical trials confirms the utility of intravenous thrombolysis [10]. Frankly, the debate about the utility of intravenous thrombolysis in the mainstream scientific medical community is over. Intravenous thrombolysis is efficacious; it should be administered to those patients who are eligible for treatment.

The results of the trials also provide additional safety and efficacy data that affects management decisions; for example, the sooner the patient is treated, the better are the chances for a good outcome [11]. The agent must be treated with respect; it is a potent thrombolytic agent that may be complicated by serious bleeding. Despite an increased risk of hemorrhagic complications and increased likelihood of death within the first days after stroke, long-term stroke mortality is not increased [10]. The patients at highest risk for bleeding complications with thrombolysis, including hemorrhagic transformation of the ischemic lesion, also have severe strokes that if left untreated have the highest risk for malignant cerebral infarction with herniation and death.

Intravenous thrombolysis has several advantages. It is relatively patient-, doctor- and health-care system friendly. The indications and contraindications for treatment are clearly described in the Guidelines for the Emergency Management of Acute Ischemic Stroke [1]. While not all patients recover following treatment with intravenous rtPA, many patients do have clinical improvement. The screening tests before treatment are limited and they can be performed rapidly. The latest

version of the Guidelines for the Emergency Management of Acute Ischemic Stroke states that only the results of the blood glucose value and the brain imaging study are required to be known prior to treatment [1]. The medication may be ordered by any physician; it does not require special expertise. Instructions for the dosage and methods for administration are available and potential pitfalls for nursing and pharmacy personnel are known. While the cost of rtPA is considerable, it is much less expensive than long-term care or prolonged rehabilitation. Overall, it is a cost-effective therapy.

Unfortunately, some patients do not improve despite treatment. The likelihood of reestablishing perfusion is limited, particularly when a thrombosis is extensive and occludes a large-caliber artery. Thus, there is considerable room for improvement.

Endovascular Interventions

Endovascular treatment, an alternative reperfusion strategy, is a rapidly evolving field that involves intra-arterial administration of medications including rtPA or the use of mechanical interventions to remove or break up an arterial thrombosis. Endovascular therapy has many advantages. It administers the intervention at the site of the arterial occlusion. Recanalization, particularly with the newer clot extraction devices, can be achieved in a high percentage of patients [12]. Restoring adequate blood flow is associated with improved neurological outcomes. Treatment may be given to some patients who are not eligible for intravenous therapy, such as those with coagulation abnormalities. An endovascular intervention may complement intravenous treatment and it could be delivered as a rescue therapy to those patients who do not improve following thrombolysis. Conversely, endovascular therapy has limitations. It requires considerable physician expertise and expensive technology, which is not widely available; as a result, most patients with stroke likely cannot be treated. The costs of endovascular interventions, not including transport to a center where this service available, are considerably higher than those that accompany intravenous treatment. The current limitations imply that the overall impact of endovascular treatment on the public's health may be small.

Evidence for success of endovascular treatment is currently lacking. Recent clinical trials were unable to demonstrate the superiority of: (1) endovascular administration of rtPA, (2) an advantage of combined intravenous and endovascular treatment, or (3) success of endovascular treatment selected on the basis of baseline brain imaging findings [13–15], as further described in Chap. 4. Given that the trials are negative, third-party payers may be reluctant to reimburse hospitals and physicians for these expensive procedures. This would be regrettable because many physicians involved in the care of patients with acute ischemic stroke believe that these interventions may be very helpful in treating carefully selected patients. In addition, the recent trials have limitations; in particular, the more advanced devices, which are associated with the greatest chances of reperfusion, were not employed. In effect, the recent trials may have been premature. Still, one conclusion that can be drawn from this research is that intravenous treatment should not be withheld from an eligible patient in order for the patient to receive an endovascular intervention.

Brain Attack

While reperfusion therapy is effective, its utility is limited in that far too few patients are being treated [16, 17] (Fig. 1.1). Although approximately 20 years have passed since the FDA approved the use of rtPA, only approximately 5 % of American patients with acute ischemic stroke are receiving thrombolytic therapy. In addition, the impact of endovascular treatment is very small. These numbers are dismal.

In response to the low rates, the Brain Attack program was initiated to increase awareness of the public and health-care providers about the utility of emergency stroke care [18]. A basic message is to treat stroke in the same way as acute myocardial ischemia is treated (Table 1.3). In fact, there are many similarities in both acute stroke and cardiac care and the acute stroke care projects can be built on those used for acute cardiac care. Both require an integrated program adapted to local needs to address all hurdles to emergency evaluation and treatment. Among the most important recommendations is the development of a code stroke system that fosters the treatment of patients within 60 min of the patient's arrival in the emergency department [19–21].

Several reasons for the non-utilization of reperfusion therapy exist. Physicians, particularly those in primary care and emergency medicine, often are uncomfortable in treating patients with acute brain disease and they desire help from colleagues with neurological expertise. The physicians (and in some cases physician extenders) who are in emergency departments are apprehensive about treating patients with serious acute brain diseases including the potential for a secondary intracerebral hemorrhage. These issues are reflected by data that show that the utilization of thrombolytic therapy is very low (<2 % of potentially eligible patients treated) in hospitals that do not have neurology departments (surrogate measure—presence of neurology residents) [17].

The rates of administration of rtPA are especially low in smaller community hospitals, often located in rural parts of the USA [16]. Because of issues related to geography, distance and the relatively short time window for safe and effective administration of rtPA, patients cannot be transported to a larger stroke center in time for treatment. Thus, methods to extend stroke care to these smaller centers have been developed. A hub-and-spoke system permits a central comprehensive stroke center that interacts with smaller hospitals

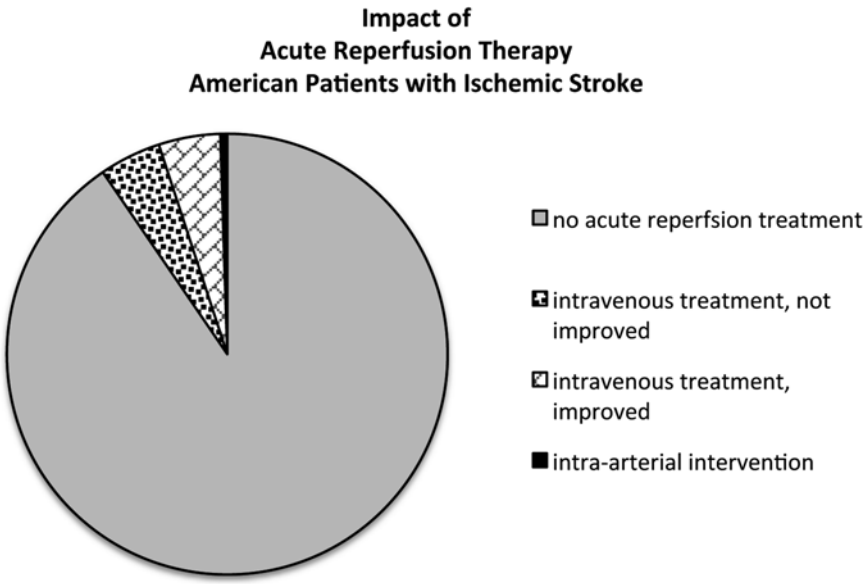

Fig. 1.1 Approximate percentages of patients with acute ischemic stroke that are receiving reperfusion therapy in the USA

Table 1.3 Brain attack and heart attack similarities of acute cerebral ischemia and acute myocardial ischemia

Both are due to an acute thromboembolic occlusion to a major organ
Both are a potentially life-threatening disease
Both are accompanied by acute and severe complications
Both are treated with early reperfusion therapy
Thrombolytic agents
Endovascular interventions
In both, early reperfusion is associated with improved outcomes
"Time is heart", "time is brain"

to provide coordinated acute stroke care [22, 23]. Physicians at the hub hospital assist their colleagues located at the smaller institution via telephone consultation or telemedicine. The success of telemedicine in providing emergency medical assessment and treatment by skilled physicians, in which outcomes are similar to those achieved among patients treated at the larger hospital serves as an impetus to expand the use of this technology [22, 24]. In addition, the paradigm of "drip-and-ship," which is built on the hub-and-spoke program, has been successfully implemented in which the patient is treated locally with rtPA and then transferred to a larger hospital for subsequent care [25].

Another major issue is the lag between the onset of stroke and the time the patient arrives in an emergency department. Delay in their arrival is the primary reason patients with stroke are not treated. Several groups including the American Heart Association/American Stroke Association (AHA/ASA,) the National Stroke Association (NSA) and NINDS sponsor public education programs to teach persons about the symptoms of stroke and the importance of seeking medical attention immediately. The Centers for Disease Control (CDC) through its Coverdell Program is assessing health-care system-related issues that may hamper emergency stroke care [26]. A particular emphasis has been on addressing possible gaps in the emergency medical services (EMS) systems. Recently, programs that involve emergency evaluation, including CT, and treatment in the ambulance have been developed [27]. These advancements are described further in Chap. 2.

Several steps have been employed to improve the quality of stroke care. The Joint Commission, in collaboration with the AHA/ASA, has developed a certification program that designates those hospitals that can provide excellent emergency stroke care (primary stroke centers) and those institutions that have a wide range of services for treatment of those patients with complex stroke problems (comprehensive stroke centers) [28, 29]. These activities are complemented by the AHA/ASA Get With The Guidelines (GWTG), which provides services for collection of data and quality improvement [30]. Already, reports from this group show increases in the numbers of patients with ischemic stroke that a being treated with intravenous thrombolysis [21, 31].

Future Emergency Management

As described previously, a number of tactics are being employed to increase the number of patients with acute ischemic stroke that may be successfully treated with reperfusion therapy. These collaborative efforts, which involve governmental groups, insurance companies, emergency medicine services, hospitals, physicians, other health-care providers, and the public, must be augmented. This is the best approach for increasing the use of the currently available therapies.

In addition, research is needed. Expansion of the time period from stroke onset to effective treatment would be

welcomed. Thrombolytic agents that may be superior to rtPA should be tested. Refinement of processes, possibly using imaging or other markers, may improve the selection of patients who should be treated; hopefully, the resultant changes will result in an increased number of patients who can be successfully treated. The role of mechanical devices or intra-arterial pharmacological interventions ought to be clarified; these interventions are likely to be useful in some patients, but further evidence is still needed. Interventions that bolster the effects of reperfusion therapy, such as neuroprotective agents that limit the cellular consequences and antithrombotic agents that forestall reocclusion, should be evaluated. Other components of emergency care, which can affect responses to reperfusion therapy, including the optimal management of hypertension and hyperglycemia, also must be tested.

Conclusion

This is an exciting time for physicians and patients. Now acute ischemic stroke can be treated as the life-threatening and life-changing disease it is. While the progress has been great, there are opportunities for further improvement in stroke care. The successes should serve as the springboard for future advances.

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Prehospital Stroke Treatment (EMS Stabilization Protocols)

2

Edward C. Jauch, David M. French, and Todd McGeorge

Abbreviations

ABC	Airway breathing, circulation
AIS	Acute ischemic stroke
BP	Blood pressure
CPSS	Cincinnati Prehospital Stroke Scale
CT	Computed tomography
ED	Emergency department
EMS	Emergency medical services
IA	Intra-arterial
IVDA	Intravenous drug abuse
LAMS	Los Angeles Motor Score
MCA	Middle cerebral artery
NIHSS	National Institutes of Health Stroke Scale
NPO	Nothing by mouth
rtPA	Recombinant tissue plasminogen activator

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Though improved prevention and early treatment of stroke have markedly reduced the morbidity and mortality of cerebrovascular disease, it remains a significant health and social burden. Within the past decade, stroke dropped from the third to the fourth leading cause of death in the USA and in 2012 alone the mortality rate for stroke dropped by 2.6 % and yet it remains a leading cause of adult disability. Economically, the cost of stroke is crippling, both in direct costs and lost opportunity. The global circumstances of stroke are even direr—in many countries it is the second leading cause of death, and the incidence of stroke is projected to double by 2030. To make an impact on this growing societal epidemic, the health-care community must continue to improve our prevention and overall management of stroke.

Fortunately, health-care professionals involved in stroke care can learn from other clinical situations and the successful development of systems of care. For medical conditions where timely identification, transport, and intervention may mean the difference between life or death, integrated systems of care, including prehospital care coordinated with regional hospital services, save lives [1]. Outcome data clearly show the benefits of such systems of care for trauma and ST-segment elevation myocardial infarction (STEMI). More recently, data from similar systems of care for stroke suggest improved outcomes and less morbidity.

Case Presentation: A 911 Call for Ill Person at Wal-Mart

Details of the case: The regional 911-communication center receives a call regarding an ill person at Wal-Mart. The security person tells the dispatcher that an employee was found on the ground between aisles where she was stocking shelves. Currently the employee is unable to speak and is looking to her left. After asking the baseline questions the dispatcher recognizes that this could be a potential stroke and turns to the Emergency Medical Dispatch guide for possible stroke and asks several key questions.

"*Is the patient alert*?"

She is awake but not talking or moving her right side

"*Can the patient answer your questions*?"

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No she just looks to the left and does not follow my commands

"*Does the patient have any medical problems*?"

I don't know her but her coworkers say she has diabetes and high blood pressure

"*When was the patient last seen normal*?"

A fellow employee had seen her 15 min earlier and noticed no issues.

Based on these responses the 911 dispatcher assigns a high priority ALS response.

Prehospital Stroke Management

Ideally, prehospital management begins when patients or bystanders recognize stroke signs and symptoms and call 911, but rapid assessment and transport are of little utility if the patients do not arrive at the appropriate hospital within treatment windows. With that in mind, the American Stroke Association (AHA) has developed the stroke chain of survival (Detection, Dispatch, Delivery, Door, Data, Decision, Drug), where the initial links focus on stroke recognition and EMS engagement. Community education on stroke symptoms and early EMS access are critical components of any regional stroke system. Most recently the message of think "FAST" is being used to educate the public on stroke. The presence of Facial droop, Arm weakness, or difficulty with Speech could represent ongoing stroke, and thus should prompt people to act FAST and call 911 for the sake of Time. While some educational programs have successfully increased awareness of stroke symptoms, the majority of patients still miss the treatment window [2]. Clearly, continued public education is key.

911 Activation

Once 911 is activated, stroke recognition is essential. With the advent of Emergency Medical Dispatch tools and the use of dispatcher protocols, patients with stroke-like symptoms are more easily recognized by 911 operators. However, there is variability in dispatcher ability to recognize stroke symptoms, with correct identification varying between 30 and 83 % [2]. Any patient presenting within a 6–8 h window of symptom onset should still be considered a candidate for acute intervention and appropriate response configurations utilized. Use of protocols clearly helps determine dispatch prioritization, which is critical to potential early interventions [3].

There are many barriers to treatment, primarily related to delays in hospital arrival after symptom onset [4]. Patients that do not use 911 or EMS, have a prior stroke history or mild symptoms, or are ethnic minorities or live in rural communities, all have lower rates of reperfusion treatment [5–7]. Patients are more likely to receive timely treatment if they utilize 911, are transported by EMS, have more severe symptoms, or have a new stroke. Most importantly for prehospital providers, early EMS notification to the receiving hospital makes timely treatment more likely. Identifying and addressing any regional prehospital barriers to care is critical to ensuring optimal care.

Case Presentation: A 911 Call for Ill Person at Wal-Mart

On arrival the EMS personnel find the patient lying on the ground, awake but not talking. A quick assessment shows no imminent issues regarding the patient's airway, breathing, or circulation (ABC's). Her initial vital signs are blood pressure of 175/110 mmHg, pulse rate of 93 and irregular, oxygen saturation of 92 % on room air.

EMS personnel quickly perform the Cincinnati Prehospital Stroke Screen that is positive since the patient is aphasic, has a facial droop on the right and is unable to move her right arm. EMS personnel also ask coworkers about when she was last normal, was she complaining of anything prior to the onset, and if she has any medical problems. EMS asks Wal-Mart staff to bring her purse in which they find medications for diabetes and blood pressure. Given the high suspicion for stroke they quickly prepare the patient for transport to the most appropriate stroke center.

Prehospital Stroke Assessment

As with all initial assessments, the first priorities are the ABCs. The airway should be assessed in standard fashion, but note that stroke patients may have difficulty managing their secretions and could be prone to vomiting. If possible, the head of the stretcher should be elevated to 30°. However, if the patient symptoms worsen with the head of the bed elevated, the patient's head should be placed back to flat since the patient may require the higher blood pressure to perfuse the area of stroke. Typically for most stroke patients, breathing is not substantially altered, but if it is, ventilatory assistance is warranted. Hyperventilation should be avoided unless the patient's presentation suggests impending herniation (i.e., has signs of hypertension, bradycardia, irregular respiratory pattern) and is approved by medical control. Circulatory status is assessed with vital signs and ECG monitoring, as stroke patients are at risk for dysrhythmias. Frequent reassessment of the ABC's is required as the patient's condition may dramatically change en route.

After the primary survey and baseline vitals, performance of a validated stroke assessment tool aids in the recognition of possible stroke. There are a variety of scales that are widely used, but the most common are the Cincinnati Prehospital Stroke Scale (CPSS) and the Los Angeles Motor Scale (LAMS) (Table 2.1) [2]. These screening tools attempt to balance ease of use with accuracy in order to help identify the

Table 2.1 Prehospital stroke scales

Cincinnati Prehospital Stroke Scale [19]		Los Angeles Motor Scale (LAMS) [20, 21]		
Face	Both sides move normally	Face	0	Both sides move normally
	One side is weak or is flaccid		1	One side is weak or flaccid
Arm	Both arms have equal normal strength	Arm	0	Both sides move normally
	One arm is weak or does not move at all		1	One side is weak
Speech	Speech is normal and appropriate		2	One side is flaccid/does not move
	Speech is slurred, inappropriate words or mute	Grip	0	Both sides move normally
If any one of these is abnormal then there is a 88 % sensitivity for anterior circulation stroke			1	One side is weak
			2	One side is flaccid/does not move
		Total	0–5	
		LAMS score closely correlated with full NIHSS. LAMS ≥ 4 carries an over sevenfold increase in risk for large vessel occlusion		

NIHSS National Institutes of Health Stroke Scale

Table 2.2 Conditions with stroke-like symptoms (mimics)

Stroke mimic	Historical features	Clinical features
Bell's palsy	Recent viral illness, history of previous Bell's palsy	Upper and lower facial muscles involved. No other neurologic deficit
Complicated migraine	History of migraines; aura/headache preceding onset of neurologic symptoms	Headache, may have focal neurologic deficits or more global deficits
Conversion disorder/Psychogenic	History of psychiatric disorders; recent stress	No cranial nerve findings; neurologic deficits do not fit a vascular distribution; exam changes with time
Hypertensive encephalopathy	History of hypertension	Hypertension, headache, altered level of conscious, seizure
Hypoglycemia	Known diabetic	Low glucose, decreased level of consciousness
Infection/Abscess	History of IVDA, endocarditis	Altered mental status; fever
Seizures	History of seizures; witnessed seizure	Loss of consciousness; tongue biting
Tumor	Known malignancy	Slow onset of symptoms; seizure at onset

IVDA intravenous drug abuse

presence of neurologic impairment, but they have some limitations. First, the gross motor exams utilized can miss subtle strokes. Conversely, most of these scales fail to grade the severity of the stroke, which may have implications in selecting an appropriate destination facility. Second, these scales may suggest a stroke when another cause of the patient's symptoms exist, conditions termed "mimics" (Table 2.2). Stroke mimics may account for more than 20 % of patients with neurologic symptoms in the prehospital setting being considered as an acute stroke [8]. While it is impossible to exclude all stroke mimics in the prehospital setting, a basic understanding of mimics should prompt providers to ask pertinent questions of the patient or family, which may lead to more effective patient care. Regardless of the stroke tool used, providers should always consider stroke mimics in their differential but should err on the side of treating the patient as a stroke.

The process of stroke identification in the prehospital setting is constantly evolving as stroke treatments become more advanced. Efforts are underway to not only identify patients having a stroke but to consider stroke severity and time from symptom onset in order to triage a stroke patient to the most appropriate receiving facility and to provide important prearrival information to the stroke team. More comprehensive, graded exams may help to identify and quantify specific stroke characteristics that assist the stroke team in determining treatment options. There are also online and smartphone applications that are available for these scales. Unfortunately, these scales are more time consuming and may be more difficult to remember than the earlier stroke assessment tools, but in conjunction with a good patient history, the newer scales can provide a clearer picture of the patient's condition.

The patient's medical history is another crucial part of the assessment. Past medical history, including relevant surgeries, medications, and allergies, are critically important and should be documented appropriately. Particular attention should be paid to potential stroke risk factors, such as atrial fibrillation, hypertension, diabetes, previous strokes, transient ischemic attacks, recent surgeries, and smoking [9]. One of the most important elements of the patient's history is the time of symptom onset, which will dictate many treatment options. The time of onset is based on the last time the patient was known to be "normal" or at their baseline, as

opposed to when the patient was found with the neurologic deficits. It is also important to document the patient's baseline physical and mental state, especially for patients with previous neurologic, physical, or cognitive deficits. To determine last "normal" time, the patient and family members, caregivers or bystanders should be interviewed. If they are unsure about a specific time, inquiry about other time clues such as daily routines, television shows, or recent phone conversations may be helpful [9]. This can help narrow the time window of symptom onset. Other onset factors to consider include activity, headache, trauma, and seizures. These conditions provide clues to the presence of mimics but may also suggest the possibility of intracranial hemorrhage.

Case Presentation: A 911 Call for Ill Person at Wal-Mart

As they prepare for transport the EMS providers follow their "Suspected Stroke" protocol. They initiate an IV in the left antecubital fossa as requested by the local stroke center, assess her blood glucose, which was 150 mg/dL, and provide supplemental oxygen by nasal cannula, to maintain saturation above 94 %. The initial tracing on the cardiac monitor shows atrial fibrillation with a ventricular rate in the 90s. While her repeat blood pressure is 180/107 mmHg they do not initiate any antihypertensive therapies. Since the last known normal time was less than an hour ago, the patient is triaged to the nearest stroke center. En route, EMS personnel contact the receiving hospital and provide preliminary information regarding what they suspect to be a patient suffering a large stroke.

Prehospital Transport

Once the assessment and history are complete, prehospital focus should be on rapid initiation of treatment and transport. On scene time should be less than 15 min whenever possible and the patient should be treated with the same urgency as major trauma or STEMI [9]. The management plan includes frequent reassessment and management of the ABCs, as well as vital signs and cardiac and pulse oximetry monitoring (Table 2.3). Oxygen should be applied to maintain an SpO_2 above 94 %, though supplemental oxygen is not recommended in nonhypoxic patients with acute ischemic stroke [9]. Finger stick blood glucose assessment is essential in all patients with stroke-like symptoms and hypoglycemia should be corrected with intravenous dextrose per protocol.

Other emergent interventions are rarely required in the prehospital setting, unless the patient begins to decompensate with airway or ventilatory compromise, cardiac dysrhythmias or hemodynamic instability. Currently, no evidence exists to support prehospital lowering of blood pressure in hypertensive stroke patients, and in some cases lowering blood pressures to "normal" levels could exacerbate the patient's symptoms. Prehospital administration of aspirin or other antithrombotic agents to potential stroke patients is also not supported by published studies at this time.

Once EMS has assessed the patient and initiated appropriate management, prompt triage and transport to the most appropriate stroke center destination are critical for effective stroke treatment. As previously mentioned, patient outcomes are better if they are treated at a stroke center, though bypassing the closest facility for a higher level of care should not extend transport time more than 15–20 min [4]. In urban areas, this may be easier to achieve, though traffic patterns and distance may still be considerations. Suburban or rural EMS agencies may have more difficulty accessing a stroke center, though this demonstrates why a regional stroke system concept is so important. Use of helicopter transport increases access to thrombolytics for patients residing in communities that lack specialty facilities and should be utilized when necessary [10–12]. If the patient is too unstable for a prolonged transport or a helicopter is not available, transport to the closest facility for rapid assessment, stabilization and preparation for transfer to a stroke center is an appropriate alternative.

Table 2.3 AHA recommendations for prehospital management of potential stroke [9]

Recommended	Not recommended
ABC's—assess and reassess	Do not treat hypertension unless directed by medical command
Perform cardiac monitoring	
Provide oxygen to maintain oxygen saturation >94 %	
Perform blood glucose assessment, treat if <60 mg/dL	Do not treat with oral medication; maintain strict NPO
Establish intravenous access (consider antecubital 18 gauge)	Do not administer excess fluid or glucose containing solutions
Determine last known normal time	
Determine past medical history and any recent events	
Obtain family contact and phone number	
Triage to most appropriate regional stroke hospital	Do not delay transport for interventions
Provide prehospital notification en-route	
Obtain feedback/Quality improvement	

ABCs airway, breathing, circulation, *NPO* nothing by mouth

Regardless of destination facility or mode of transport, early EMS notification of the receiving hospital is critical. Prehospital notification has been clearly shown to reduce ED times to definitive treatment [2]. In addition to customary information, reports should include "last known normal" time, stroke scale results, vital signs, blood glucose, and any other interventions. Close monitoring of patient condition during transport is obviously critical, and significant patient deterioration should prompt consideration of diversion to a closer facility.

Case Presentation: A 911 Call for Ill Person at Wal-Mart
On arrival at the stroke center Emergency Department, EMS providers are met by the Emergency Department physician and members of the stroke team. After a quick verification of the ABC's the EMS personnel go straight to the CT scanner and provide report. As they complete their run report, they are shown the patient's CT scan that demonstrates no sign of intracerebral hemorrhage but there is a hyperdense middle cerebral artery (MCA) on the left, consistent with their suspicion of a large left MCA stroke. Later, the EMS crew returns to the hospital and learns the patient received IV rtPA and intra-arterial thrombectomy with successful reperfusion within 2 h of last known normal time.

Emergency Department Stroke Management

Emergency Department (ED) management of stroke patients parallels prehospital management. With the critical prehospital notification, all the necessary components of the hospital-based stroke team can be at bedside prior to patient arrival. A rapid assessment of the ABCs on arrival allows for most patients to be taken directly to the CT scanner by EMS, significantly reducing imaging delays. Prehospital notification, concurrent physical evaluation, diagnostic testing, and medical history review substantially reduce time to intervention, the so called Door-to-Needle time, to less than the currently recommended 60 min [13]. A recent study of 58,353 patients treated with IV rt-PA clearly demonstrated the importance of lowering time to treatment, finding that "among 1,000 treated patients, every 15-min–faster acceleration of treatment was associated with 18 more patients having improved ambulation at discharge … and 13 more patients being discharged to a more independent environment (including 7 more being discharged to home)" [14].

Interhospital Transfers

Even with aggressive community and EMS education and advanced protocols, patients will present to facilities that are unable to manage acute stroke, or patients may require more advanced stroke care than is available at the original hospital. The "drip and ship" practice—assessing a patient and initiating thrombolytics before transfer to a higher level of care—may be an appropriate treatment choice for patients presenting within the therapeutic window [4]. EMS and transport providers involved in such interhospital patient transfers should carefully monitor vital signs and the neurologic exam. Strict blood pressure control, maintaining blood pressure below 180/105 mmHg, is required after thrombolytics and clinical deterioration may indicate an intracranial hemorrhage. Air medical transport has been shown to be safe and effective, including for those patients who have received thrombolytics [15]. As with field transport of stroke patients, early destination hospital notification is critical. Preplanning of the transfer process is key to minimizing delays when a stroke patient requires transfer to a higher level of care.

Future of Prehospital Stroke Care

Neurologic emergencies will always be time sensitive, and as such, traditional hospital-based strategies are now being evaluated in the prehospital setting, including novel diagnostic tools, directed therapies, and physiologic management. Prehospital traumatic brain injury physiologic management and early treatment of active seizures are examples where field initiation of global and targeted therapies makes a demonstrable difference on patient outcomes [16].

To further minimize delays to treatment, some centers in the USA and Europe are equipping ambulances with mobile CT scanners, video telemetry, and in some cases neurologists, to respond to the scene of a potential stroke. This model employed in a study by Audebert and colleagues in Berlin led to a reduction in call to needle time of 36 min [17]. Similar models are now being studied in Houston, TX, and Cleveland, OH. This high tech, resource intensive approach may not be broadly applicable in more rural areas but demonstrates the growing appreciation for incorporating the prehospital setting into acute treatment paradigms.

No drug or therapy administered in the prehospital setting has been shown to improve patient outcomes, but recent studies show early treatment is feasible. In acute stroke, the recently completed FAST-Mag study of prehospital administration of magnesium failed to show clinical benefit but demonstrated that patients could be appropriately identified as having a potential stroke and a therapeutic agent, magnesium, administered in a safe and timely fashion [18]. Future studies of prehospital interventions may one day produce successful EMS-administered therapies.

Summary

Stroke is a time-dependent emergency and prehospital involvement is crucial for maximizing patient outcomes. Coordinated development of regional resources into a

cohesive stroke system of care is the cornerstone of stroke care. Early EMS activation, stroke identification, prehospital management, and rapid transport and triage to the most appropriate stroke center will give the patient the best chance to make a full recovery.

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Intravenous Thrombolysis and Anti-thrombotics

3

Mahesh P. Kate, Rajsrinivas Parthasarathy, and Ashfaq Shuaib

Case Vignette *An 86-year*-old gentleman arrived to the emergency department at *240 min* after stroke symptom onset. He had a right-side hemiparesis with dysphasia, with a National Institute of Health Stroke Scale Score (NIHSS) of 10. CT of the head showed early ischemic changes in the right insula, CT perfusion showed a favorable mismatch pattern and CT angiogram showed a right middle cerebral artery occlusion (Fig. 3.1). Informed consent was obtained for IV thrombolysis, in light of *ECASS III and IST 3* studies. He received IV thrombolysis at 270 min from the time of onset. The patient improved at 24 h after onset, with a NIHSS score of 4 and CT of the head showed a right caudate infarct. In the hospital, he was noted to have atrial fibrillation on post-thrombolysis continuous cardiac monitoring. He was discharged after 5 days on Dabigatran 110 mg twice daily with an appointment for outpatient rehabilitation. This case vignette highlights the rapidly changing scenario of acute ischemic stroke treatment particularly in relation to use of intravenous (I.V) thrombolysis and antithrombotics.

Introduction

The only medical therapy shown to improve patient outcome in acute ischemic stroke (AIS) is intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) [1]. A thrombolytic agent aids clot dissolution and timely restoration of the blood flow to the ischemic brain tissue thereby preventing death of neurons and leading to clinical improvement (Fig. 3.2). Due to the success of rtPA, a number of new lytic agents are being tested in clinical trials. Despite evidence from randomized control trials and meta-analyses, the IV thrombolysis rates among all acute ischemic stroke patients presenting within 3 h have been poor (7 %) [2]. The primary reasons for under use of rtPA are a narrow therapeutic window and strict inclusion/exclusion criteria.

In the first half of this chapter, we examine the rationale for use of intravenous thrombolysis in acute ischemic stroke management based on contemporary clinical evidence. Further we delineate practical steps for IV thrombolysis in the emergency setting. In the latter half, we discuss the role antithrombotics in AIS.

Rationale for IV thrombolysis

Acute ischemic stroke is caused by complete or partial occlusion of cerebral artery in approximately 80 % of patients [3]. The occlusion is due to in-situ arterial thrombosis or thromboembolism from cardiac or proximal arterial source and occasionally from the venous source when there is PFO or pulmonary AV fistula.

There is sudden and severe reduction in the cerebral blood flow (CBF) to the cerebral tissue distal to the clot. In elegant primate experiments, Astrup et al. [4] demonstrated that the affected arterial territory has varying reduction in the CBF. The territory can be divided into four zones according to the decreasing cerebral blood flow: zone of normal blood flow, zone of oligemia, zone of penumbra, and zone of infarct (Fig. 3.3). The neuronal and supporting cells in the occluded arterial territory die due to the lack of oxygen and glucose in the zone of infarct.

In the zone of penumbra, the CBF is low but has not reached the critical level to cause neuronal cell death. The volume of the penumbra tissue decreases with time. The fate of penumbral tissue is dependent on the triad of adequacy of cerebral collateral circulation, ischemia tolerance of the cerebral tissue and the clot burden. The clot burden (Fig. 3.4)

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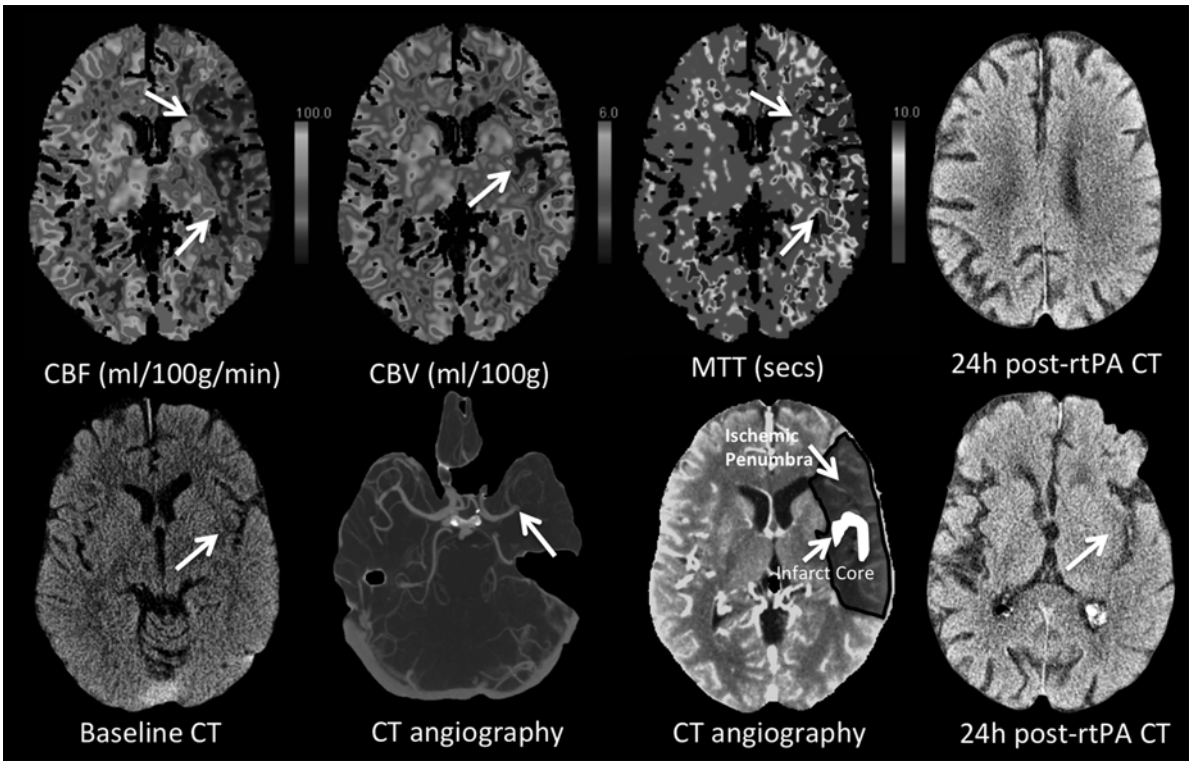

Fig. 3.1 Multimodal CT imaging of acute ischemic stroke patient presenting at 4 h of symptom onset, baseline non-contrast CT scan shows early changes of ischemia in the left insula as loss of great and white matter differentiation, CBF (cerebral blood flow) is reduced and MTT (mean transit time) is prolonged in larger area (*white arrows*) in the left middle cerebral artery (LMCA) territory, CBV (cerebral blood volume) is reduced in small area (*white arrow*) in LMCA territory, CT angiography shows distal LMCA occlusion and CT angiography map at the level of basal ganglia has an schematic area of penumbra and core based on the perfusion imaging. The follow-up CT scan at 24 h shows left insular involvement alone (*white arrow*)

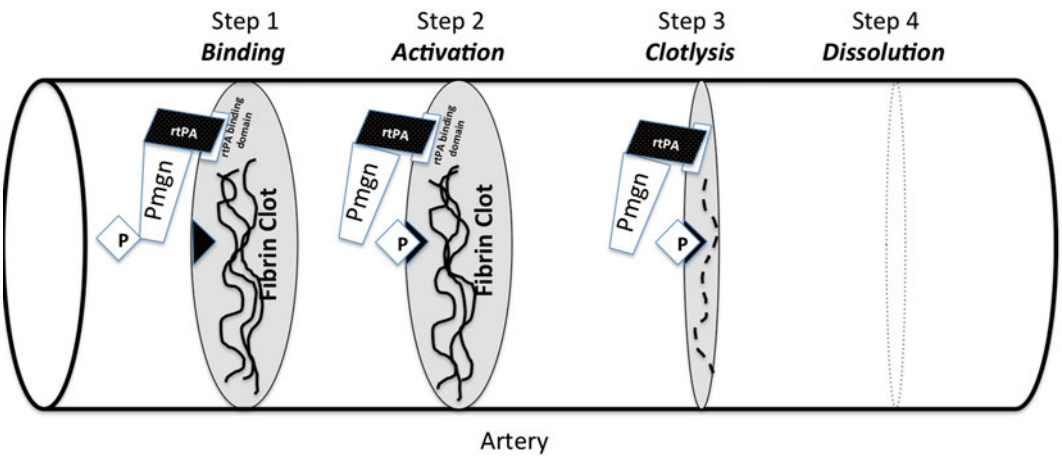

Fig. 3.2 Mechanism of action of recombinant tissue plasminogen activator; Step 1 is binding of rtPA molecule to fibrin clot, Step 2 is activation of fibrin bound plasminogen, leads to cleaving of plasmin (serine protease) from plasminogen, Step 3 is fibrinolysis by activated plasmin and Step 4 is clot dissolution and restoration of blood flow. *rtPA* recombinant tissue plasminogen activator, *pmgn* plasminogen, *p* plasmin

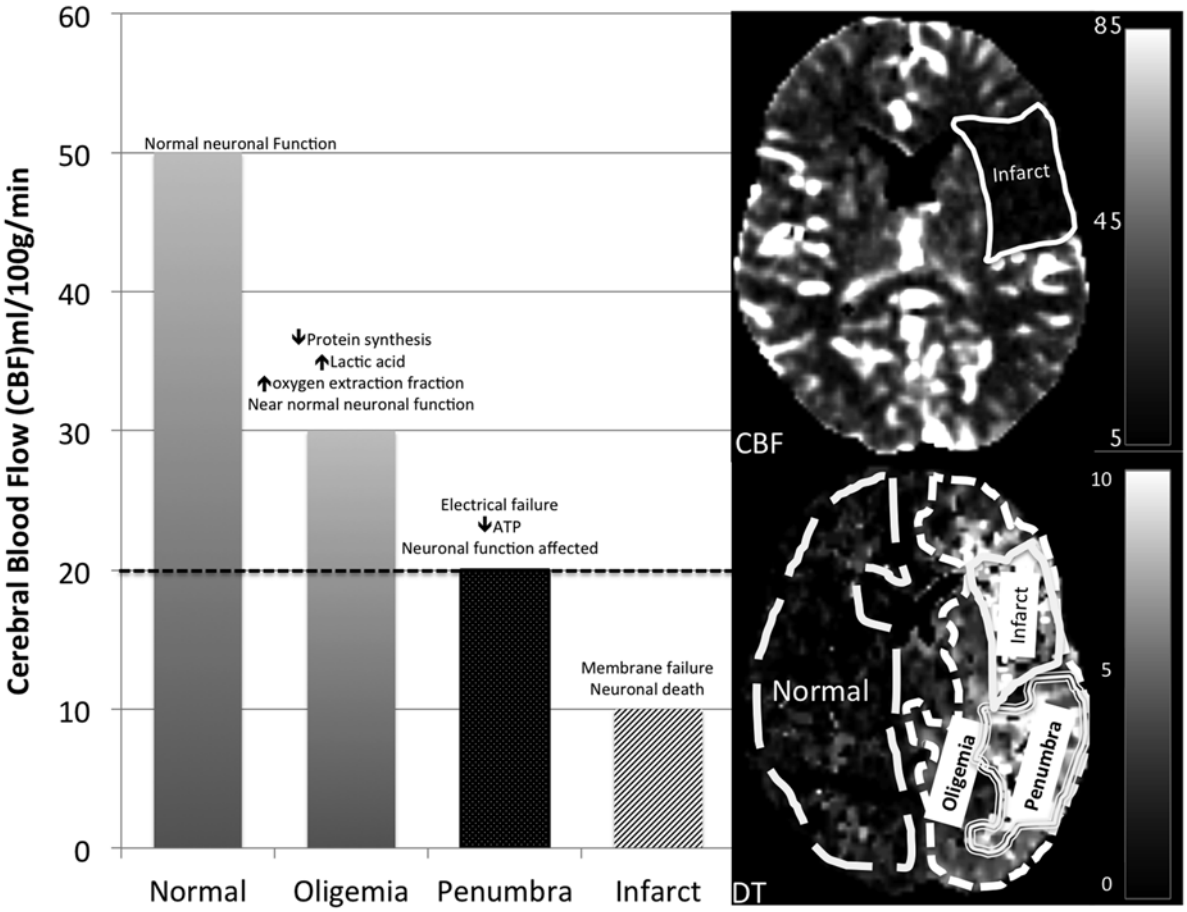

Fig. 3.3 Zones of differential distribution of cerebral blood flow in the ischemic cerebral hemisphere and effect of low blood flow on the cerebral tissue. *CBF* cerebral blood flow map, *DT* delay time map

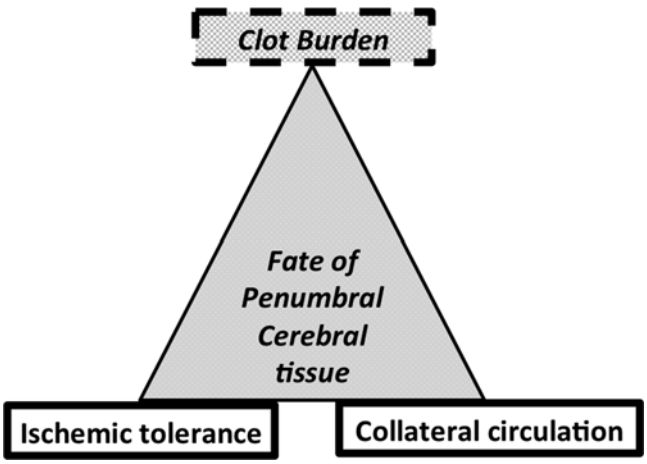

Fig. 3.4 Triad of determinants of fate of penumbral tissue

can be reduced by fibrinolysis and thereby reperfusion to the affected tissue can be achieved. Fibrinolytic agents like streptokinase (ASK [5], MAST-I [6], MAST-E [7] studies), rtPA (NINDS [8], ATLANTIS A [9], ATLANTIS B [10], ECASS [11], ECASS II [12], ECASS III [13]), Tenecteplase (Parson et al.) [14], and Desmoteplase (DIAS [15], DEDAS [16], and DIAS 2 [17]) have been used for stroke thrombolysis.

Evidence for Efficacy

Recombinant Tissue Plasminogen Activator (rtPA)

The recombinant tissue plasminogen activator (rtPA) is a second-generation thrombolytic agent. It is the only thrombolytic agent approved by US FDA, based on results from the NINDS Stroke Study published in 1996 [8]. Twelve randomized clinical trials have been done to date using rtPA (Table 3.1). All the other abovementioned thrombolytic agents or fibrinolytic agents are categorized as experimental (Table 3.2) and are being used as a part of clinical trial only. The use of IV thrombolysis in AIS is time-dependent and the randomized clinical evidence can be divided into three time periods: 0–3, 3–4.5, and 0–6 h.

Table 3.1 Randomized clinical trials of tissue plasminogen activator for acute ischemic stroke according to symptom onset time

Study	Year	*N*	Dose	Time of outcome assessment	Outcome
Symptom onset: 0–3 h					
Haley et al.	1993	27	0.85 mg/kg	3 months	NIHSS
NINDS I	1995	291	0.9 mg/kg (max. 90 mg)	24 h	NIHSS
NINDS II (Pivotal)	1995	333	0.9 mg/kg (max. 90 mg)	3 months	NIHSS, GOS, BI, mRS
NINDS I and II	1995	624	0.9 mg/kg (max. 90 mg)	3 months	NIHSS, GOS, BI, mRS
Symptom onset: 0–6 h					
Mori et al.	1992	34	0.6 mg/kg vs. 0.9 mg/kg	1 month	Reperfusion (A), HSS
JTSG	1993	98	0.6 mg/kg (34 mg)	1 month	Reperfusion (A), HSS
ECASS	1995	620	1.1 mg/kg (max. 100 mg)	3 months	mRS, BI
ECASS II	1998	800	0.9 mg/kg (max. 90 mg)	3 months	mRS 2–6
ATLANTIS A	2000[a]	142	0.9 mg/kg (max. 90 mg)	3 months	mRS 2–6, BI, NIHSS
ATLANTIS B	1999[a]	613	0.9 mg/kg (max. 90 mg)	3 months	mRS 2–6, BI, NIHSS
Wang et al.	2003	100	0.9 mg/kg (max. 90 mg)	3 months	CSS, BI
IST-3	2012	3,035	0.9 mg/kg (max. 90 mg)	6 months	OHS 0–2
Symptom onset: 3–4.5 h					
ECASS III	2008	821	0.9 mg/kg (max. 90 mg)	3 months	mRS 0–1
Symptom onset: 3–6 h					
EPITHET	2008	101	0.9 mg/kg (max. 90 mg)	3 months	Infarct Growth

[a]Stopped prematurely
mRS modified Rankin scale, *BI* Barthel index, *NIHSS* National Institute of Health Stroke Scale, *HSS* hemispheric stroke scale, *GOS* Glasgow outcome score, *CSS* Chinese stroke scale, *OHP* Oxford handicap score

Table 3.2 Randomized clinical trials of other thrombolytic agent for acute ischemic stroke according to symptom onset time

Study	Year	Drug	*N*	Time Window (hours)	Dose	Time of outcome assessment	Outcome
MAST-I	1995	Streptokinase[a]	622	0–6	1.5 mU	6 months	mRS
MAST-E	1996	Streptokinase[a]	310	0–6	1.5 mU	6 months	BI, mRS
ASK	1996	Streptokinase[a]	340	0–4	1.5 mU	3 months	BI > 60
STAT	2000	Ancrod	500	0–3	0.082–0.167 IU/Kg/h	3 months	BI ≥ 95
DEDAS	2006	Desmoteplase	37	3–9	90 μg/kg vs. 125 μg/kg	Early	SICH
DIAS 2	2009	Desmoteplase	186	3–9	90 μg/kg vs. 125 μg/kg	3 months	mRS (0–2), NIHSS ≥ 8, BI 75–100
Parsons et al.	2012	Tenecteplase vs. Alteplase	75	0–6	0.1 mg/kg vs. 0.25 mg/kg (TNK) vs. 0.9 mg/kg (tPA)	24 h	Tissue reperfusion and NIHSS improvement

[a]Stopped prematurely due to harm
BI Barthel index, *NIHSS* National Institute of Health Stroke Scale, *mRS* modified Rankin scale, *tPA* tissue plasminogen activator, *TNK* tenecteplase

0–3 h

The NINDS stroke study was done in two parts. Part 1 aimed to assess the clinical activity of rtPA at 24 h defined as early improvement, with either complete resolution of neurological deficits or an improvement in NIHSS score of 4 or more. Part 2 aimed to assess the persistent effect of rtPA at 3 months, with the hypothesis that a greater proportion of patients treated with rtPA would have minimal or no deficit compared to patients treated with placebo. The inclusion and exclusion criteria were the same for both parts of the study. Part 1 of the study did not show a significant difference in patients treated with rtPA vs. placebo (47 % vs. 39 %, relative risk (95 % CI), 1.2 (0.9–1.6); $p = 0.21$) for the primary outcome. On post-hoc analysis there was a difference in the median NIHSS score (8 (3–17) vs. 12 (6–19); $p < 0.02$) at 24 h.

Part 2 of the study, showed significant differences in several measures of morbidity, with more favorable outcomes in patients treated with rtPA. A modified Rankin scale of 0–1 was observed in 39 % of patients treated with rtPA as compared to 26 % of patients treated with a placebo (Odds Ratio (95 % CI), 1.7 (1.1–2.6); $p = 0.019$). The combined results of part 1 and 2 showed an absolute difference of 12 % (OR (95 % CI), 1.7 (1–2.6); $p = 0.03$), and 20 % (2.4 (1.5–3.7);

$p<0.001$) for favorable outcome as assessed by mRS (0–1) in patients treated with tPA in first 90 min and between 90 min and 180 min, respectively. The *number-needed-to-treat* (*NNT*) to have a Barthel index of 95–100 at 3 months is 6.6 in the first 90 min and 5.8 between 90 and 180 min. The observed beneficial effect of rtPA was irrespective of stroke subtype. Despite this overwhelming difference in disability, there was no difference in mortality at 3 months in patients treated with rtPA (17 %) vs. placebo (21 %, $p=0.30$). Symptomatic intracerebral hemorrhage (SICH) in the first 36 h after treatment was more common in patients treated with rtPA (6.4 %) vs. placebo (0.6 %, $p<0.001$). The *number-needed-to-harm* (*NNH*) was 17. The patients with high admission NIHSS score and persistently elevated blood pressure post thrombolysis were more likely to have SICH.

Further follow-up showed persistent benefit (modified Rankin scale 0–1) in patients treated with rtPA compared to placebo at 6 months (41 % vs. 29 %, OR 1.8 (95 % CI, 1.3–2.5); $p=0.001$) and 1 year (41 % vs. 28 %, OR 1.8 (1.3–2.5); $p=0.001$) [18].

3–4.5 h

The ECASS III trial hypothesized that benefits of IV rtPA could be safely extended up to 4.5 h [13]. A total of 821 patients were enrolled in the study, 418 to the rtPA group and 403 to the placebo group. The inclusion and exclusion criteria were more rigid compared to the NINDS stroke study. Ischemic stroke patients between ages 18–80 years were included; whereas patients with severe stroke based on clinical assessment (e.g., NIHSS > 25) or appropriate imaging (stroke involving >1/3rd of the middle cerebral artery territory), patients with a history of prior stroke and diabetes mellitus and patients on oral anticoagulants (regardless of INR) were excluded.

The study showed that patients with ischemic stroke who had rtPA administered between 3 and 4.5 h of symptom onset had a modest benefit compared to those who received placebo. A total of 52.4 % of patients treated with rtPA had favorable outcome (mRS 0–1) vs. 45.2 % in the placebo group, with absolute improvement of 7.2 % (OR 1.34 95 % CI 1.02–1.76; $p=0.04$). The *NNT* was 13.8 for a favorable outcome. There was no difference in the mortality in patients treated with rtPA (7.7 %) vs. placebo (8.4 %, OR 0.90, 95 % CI 0.54–1.49; $p=0.68$). SICH according to the NINDS stroke study definition occurred in 7.9 % patients treated with rtPA vs. 3.5 % (OR 2.38 95 % CI 1.25–4.52; $p=0.006$) placebo group, the *NNH* is 22.7.

A pooled analysis [19] of data from the NINDS stroke study, ECASS, ECASS II, ATLANTIS A and B, ECASS III and EPITHET [20] studies showed a declining effect size with symptom onset to treatment time ($n=3{,}670$). Adjusted odds of a favorable 3-month outcome were 2.55 (95 % CI 1.44–4.52) for first 90 min after symptom onset, 1.64 (1.12–2.4) for 90–180 min, 1.34 (1.06–1.68) for 181–270 min and 1.22 (0.92–1.61) for 271–360 min in favor of the patients treated with rtPA. Benefit was evident up to 4.5 h but not later. The odds of intra-parenchymal hemorrhage type 2 (post-rtPA hemorrhagic transformation occupying more than two-thirds of the ischemic area and/or with mass effect) was not associated with time, though it was persistently higher in patients treated with rtPA, 3.1 % vs. 0 in the first 90 min, 5.6 % vs. 1 % (OR 8.23 95 % CI 2.4–28.3; $p<0.0008$) for 90–180 min, 4.3 % vs. 1.2 % (3.61, 1.76–7.38; $p<0.0004$) for 181–270 min and 0.9 % vs. 6.8 % (4.3, 2.8–18.9; $p<0.0001$) for 271–360 min. The *NNT* for modified Rankin score of 0 or 1 in the first 90 min was 4.5, 91–180 min was 9, and 181–270 min was 14.1 and 271–360 min was 21.4. The results of this pooled analysis had set the stage for the Third International Stroke Trial (IST-3).

0–6 h

The Third International Stroke Trial (IST-3) [21] was the largest randomized controlled trial involving intravenous thrombolysis in AIS. The primary trial hypothesis was that rtPA given to adult patients of all ages with acute ischemic stroke, within 6 h of symptom onset, increased the proportion of people who were alive and independent at 6 months compared to placebo. It aimed to broaden the inclusion criteria for IV thrombolysis. Patients older than 80 years and severe stroke at presentation were included. At the outset, in the year 2000, researchers planned to recruit 6,000 patients to detect an absolute difference of 3 % in the primary outcome. In the year 2007, the target recruitment was revised to 3,100 patients to detect an absolute difference of 4.7 % in the primary outcome due to slow recruitment. At baseline, 54 % of patients were >80 years of age, one-third of patients were enrolled between 4.5 and 6 h after symptoms onset, 14 % had a NIHSS of >20 and 41 % of patients had signs of acute ischemia on pre-randomization imaging.

The study failed to meet the prespecified end point. At 6 months, 37 % in the rtPA group and 35 % in control group (OR 1.13 95 % CI 0.95–1.35; $p=0.18$) were alive and independent. In subgroup analyses, 3.8 % more patients had favorable outcome in the >80 years group vs. −0.7 % in the ≤80 years group, with an Odds ratio of 1.35 (95 % CI, 0.97–1.88) in favor of rtPA. This was the most significant finding of this study. The odds for favorable outcome for patients treated between 0 and 3 h was 1.64 (95 % CI, 1.03–2.62), 3–4.5 h OR was 0.73 (0.5–1.07) and 4.5–6 h OR was 1.31 (0.89–1.93). The lack of benefit for patients treated with rtPA between 3 and 4.5 h was in contradiction to the ECASS III results and may reflect the different population in this study.

There was no difference in groups with or without possible evidence of early ischemic changes on the pre-randomization imaging. SICH was observed in 7 % patients treated with rtPA vs. 1 % in the control group (OR 6.94, 95 % CI 4.1–11.8; $p<0.0001$), the *NNH* was 16.6. In a subgroup analysis, there was no difference among patients treated with antiplatelet drugs in previous 48 h.

Following IST-3, a systematic review and meta-analysis of all the randomized tPA trials to date including IST-3 was conducted ($n=7{,}012$) [22]. The aim was to assess the overall effect of IV rtPA when given up to 6 h after stroke. The studies were not differentiated according to the onset to treatment or time of follow-up (Table 3.1). The meta-analysis reported favorable outcome (mRS 0–1) in 34.8 % patients treated with rtPA vs. 29.3 % with placebo (OR 1.29 95 % CI 1.2–1.4; $p<0.0001$), with *NNT* of 18.2 for patients treated up to 6 h after symptom onset. SICH was seen in 7.6 % patients treated with rtPA vs. 1.8 % with placebo (3.72, 2.98–4.64; $p<0.0001$), the *NNH* was 17.2. Patient older than 80 years of age treated with rtPA had persistent benefit at 0–3 h with an odds ratio of 1.68 (95 % CI 1.2–2.3) and at 0–6 h with OR of 1.22 (0.98–1.53). The meta-analysis suggests that there may be benefit in treating patients after 4.5 h of symptom onset but careful patient selection is warranted, as the magnitude of benefit was minimal at best. As this was not a pooled analysis, the results should be interpreted with caution.

Other IV Thrombolytics

Streptokinase (SK)

SK is a first generation thrombolytic agent. As the name suggests, it is derived from streptococci bacteria. It binds to plasminogen in a nonspecific manner thus resulting in more widespread fibrin degradation. All the randomized studies associated with SK were stopped prematurely due to increased risk of intracranial hemorrhage [5–7]. The Australian Streptokinase trial (ASK) [5] observed a trend towards unfavorable outcome (Table 3.2) (relative risk 1.08; 95 % CI, 0.74–1.58) and increased symptomatic hemorrhage (12.6 % vs. 2.4 %, $p<0.01$). The authors observed a greater unfavorable outcome in patients treated after 3 h of symptom onset. The Multicentre Acute Stroke Trial—Europe (MAST-E) study [7] noted similar outcomes (mRS ≥ 3 or death) in patients treated with streptokinase vs. placebo (79.5 % vs 81.8 %, $p=0.6$) with increased incidence of symptomatic cerebral hemorrhage (21.2 % vs 2.6 %, $p<0.001$). In this study, both groups received concomitant heparin therapy, which may account for the increased hemorrhage risk. The Multicentre Acute Stroke Trial—Italy (MAST-I) [6] used aspirin with streptokinase in acute ischemic stroke in a 2×2 factorial design. Patients receiving streptokinase with or without aspirin had higher odds 2.7 (95 % CI 1.7–4.3; $p<0.0001$) of 10-day fatality.

There is a recent interest in SK, particularly in the setting of developing countries, due to low cost and possible efficacy [23]. Developing an optimal study design including the application of stringent inclusion and exclusion criteria would be rather challenging.

Tenecteplase

Tenecteplase (TNK), a fibrin specific thrombolytic agent, can be administered as a bolus intravenous injection. Two studies have compared TNK to rtPA in randomized manner. The first study was prematurely stopped due to slow enrollment [24]. One hundred twelve patients with acute ischemic stroke within 3 h of symptom onset were randomized to one of three doses of TNK (0.1 mg/kg, 0.25 mg/kg, and 0.4 mg/kg) vs. 0.9 mg/kg of rtPA. The symptomatic intracerebral hemorrhage rate was highest (15.8 %) with TNK dose of 0.4 mg/kg and this dose assignment was stopped early, but the study was continued with two doses 0.1 and 0.25 mg/kg. The study was inconclusive, had similar outcome at 3 months between the two doses of TNK vs. 0.9 mg/kg rtPA. The symptomatic intracranial hemorrhage occurred 0 % in 0.1 mg/kg and 6.5 % in 0.25 mg/kg doses of TNK and 3.2 % in rtPA group.

The second study by Parson et al. [14] randomized 75 patients to 0.9 mg/kg rtPA vs. 0.1 mg/kg TNK vs. 0.25 mg/kg TNK within 0–6 h of stroke symptom onset. Inclusion criteria required patients to have a perfusion lesion at least 20 % greater than their infract core on CT perfusion. The co-primary end points were reperfusion on a 24 h post-treatment MR perfusion study and extent of clinical improvement on the NIHSS after treatment. The mean (±SD) baseline NIHSS score was high at 14.4 ± 2.6. The median infarct cores were comparable in the groups; 13 ml in rtPA group vs. 8 ml in the 0.1 mg/kg TNK group vs. 11 ml in the 0.25 mg/kg TNK group. The median perfusion deficits were also comparable in the groups, 76 ml in rtPA group vs. 80 ml in the 0.1 mg/kg TNK vs. 79 ml in 0.25 mg/kg TNK dose group. There was an overall significant benefit in the TNK groups in both the imaging end point, defined as mean reperfusion percentage (55.4 % vs. 79.3 %, $p=0.004$), and clinical end point, defined as improvement in mean (±SD) NIHSS score between baseline and 24 h (3 ± 6.3 vs. 8 ± 5.5, $p<0.001$). On comparison of the two TNK dose tiers, the higher dose had better mean percent reperfusion (69.3 % vs. 88.8 %, $p<0.05$) and mean NIHSS improvement (6.3 vs. 9.6, $p<0.05$).

On-going phase III randomized studies are evaluating the role of TNK. NOR-TEST [25] is comparing TNK 0.4 mg/Kg vs. rtPA 0.9 mg/kg in the first 4.5 h with the primary end point of modified Rankin scale of 0–1 at 90 days. ATTEST

[26] is comparing 0.25 mg/kg TNK vs. rtPA 0.9 mg/kg in the first 4.5 h with the primary end point of percentage of penumbral salvage at 24–48 h on CT perfusion study.

Desmoteplase

Desmoteplase is one of newer fibrinolytic agents. It is a highly fibrin-specific plasminogen activator. Desmoteplase has been studied in one phase III study with the aim of extension of the therapeutic time window. In the DIAS-2 study [17], a total of 186 patients with moderate severity ischemic strokes were randomized to three groups within 3–9 h of symptom onset: desmoteplase 90 μg/kg or desmoteplase 125 μg/kg or placebo. The rationale for extension of the therapeutic time window was based on the results two phase II studies, DIAS [15] and DEDAS [16]. All patients in DIAS-2 had at least a 20 % perfusion deficit on CT or MRI. The median baseline NIHSS was 9 and most (63 %) patients were treated within 6–9 h of onset. The efficacy end point was good clinical outcome at 90 days as defined by NIHSS ≤ 1 or improvement in NIHSS by 8 points, modified Rankin scale (mRS) score 0–2 and Barthel index of 75–100. There was no difference in the primary efficacy end point ($p = 0.47$) among the three groups. Major hemorrhagic events occurred in 5 % of the desmoteplase 90 μg/kg group, 8 % in the desmoteplase 125 μg/kg group, and 6 % in the placebo group. The study had an overall 11 % mortality rate and the drug-related mortality was comparable to ECASS III. The DIAS-2 study did nots show any beneficial effect of IV thrombolysis using Desmoteplase between 3 and 9 h after symptoms onset. The explanations provided were that patients in the DIAS-2 study had milder to moderate stroke severity compared to DIAS/DEDAS studies and only 30 % of DIAS-2 patients had proximal vessel occlusions compared to 58 % in DIAS/DEDAS studies.

The ongoing DIAS-3 and DIAS-4 [27] studies are evaluating the safety and efficacy of Desmoteplase at a dose of 90 μg/kg in patients with proximal cerebral artery occlusion or high-grade stenosis (arterial occlusion grade: thrombolysis in myocardial infarction grade (TIMI) 0–1) and presenting within 3–9 h of symptom onset. The presence of perfusion deficit is not an inclusion criterion. DIAS–J is evaluating two doses of Desmoteplase 70 μg/kg vs. 90 μg/kg in Japanese patients with similar inclusion and exclusion criteria.

Sonothrombolysis

Sonothrombolysis is novel approach of augmentation of IV thrombolysis with ultrasound energy. Ultrasound energy leads to microcavity formation and alteration of fibrin structure in the clot thus increasing the penetration of the fibrinolytic agent and clot lysis [28, 29]. Sonothrombolysis can be further augmented with micro-bubbles. Micro-bubbles are gas- or air-filled lipid shell microspheres in the micron size range and when they pass through ultrasound field focused on the clot they oscillate and cause agitation. This potentiates the penetration of rtPA. Typical duration for application of sonothrombolysis is 1–2 h after initiation of thrombolysis.

Pooled analysis of five randomized control phase II studies ($n = 206$) for the primary outcome of death and disability at 3 months showed a significant difference in favor of sonothrombolysis compared to controls (OR 0.50, 95 % CI 0.27–0.91) [30]. There was no difference in the rate of intracerebral hemorrhages in patients who underwent sonothrombolysis vs. no sonothrombolysis. An ongoing phase III study is comparing combined lysis of thrombus with transcranial ultrasound and systemic tissue plasminogen activator (tPA) with standard of care rtPA therapy (Clinical Trials: NCT01098981) for emergent revascularization in acute ischemic stroke in the first 4.5 h of symptom onset. The study plans to enroll 830 patients over 2 years (2013–2015).

Practical Steps for IV Thrombolysis

Time is brain and every minute delay in thrombolysis is associated with loss of 1.9 million neurons [31]. The latest mantra is "Save a minute and save a day" [32]. Thrombolysis in acute stroke entails the swift art of patient management. The epochs associated are *pre-thrombolysis* (first medical contact to decision of thrombolysis), *peri-thrombolysis* (decision of thrombolysis to completion of thrombolysis), and *post-thrombolysis* (post 1 h thrombolysis to 24 h post thrombolysis).

The *pre-thrombolysis* period begins from the time of first medical contact by the paramedic followed by prehospital notification [33], prehospital blood pressure management, prehospital thrombolysis [34], and institution of a prehospital neuro-protection strategy [35]. After arrival at the hospital, a quick neurological assessment is performed and, in patients without any coagulation disorders, only blood glucose levels are checked. This is followed by transfer to Computed Tomography (CT) room and checking of the relevant past medical history. As the patient is being transferred, the treating physician examines the inclusion criteria (diagnosis of ischemic stroke, measureable neurologic deficits, time of onset <4.5 h) and exclusion criteria (Fig. 3.5) for IV thrombolysis [1]. The criteria are stricter for patients presenting between 3 and 4.5 h of symptom onset based on the ECASS III study, with additional exclusion criteria of the following: age > 80 years, NIHSS score > 25, oral anticoagulant therapy, and history of diabetes in patients with a past history of ischemic stroke [13]. According to AHA guidelines, non-contrast CT head (NCCT) is the only imaging required prior to thrombolysis decision-making [1].

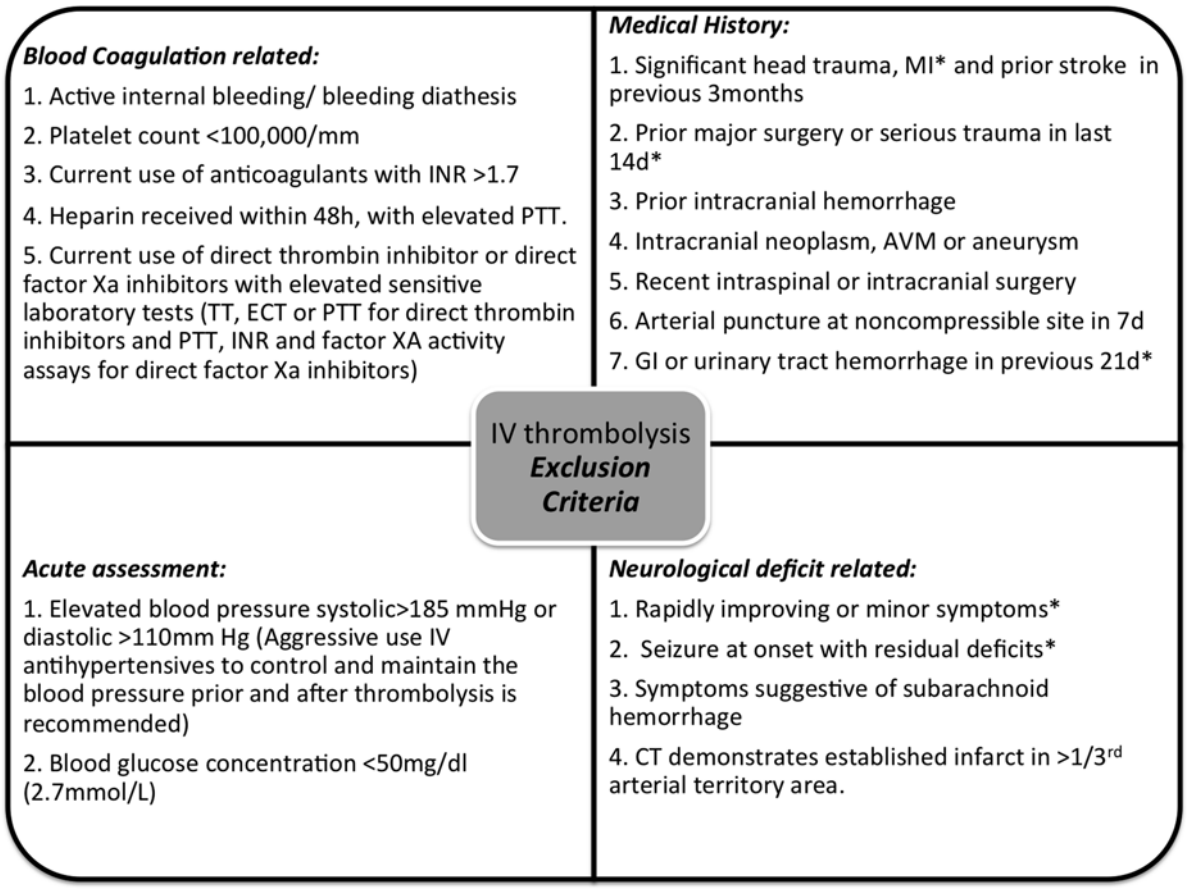

Fig. 3.5 Key exclusion criteria of intravenous thrombolysis with recombinant tissue plasminogen activator

The NCCT head is used to determine early signs of infarct and exclude intracranial hemorrhage. The Canadian Best Practice Recommendations for Stroke Care do not discriminate between patients presenting at 0–3 and 3–4.5 h after onset and allows IV thrombolysis in ischemic stroke patients with a previous history of intracranial hemorrhage if the ICH is >6 months old if the patient otherwise meets all other criteria [36]. The exclusion criteria can be exempted in some circumstances when the risk/benefit ratio is in favor of rtPA according to the opinion of the stroke expert treating the patient and after obtaining informed consent from the patient or patient's family about possible SICH.

The *peri-thrombolysis* stage begins with a brief discussion with the family and mixing of rtPA. Almost simultaneously, one can obtain a CT angiogram of the head and neck (and CT perfusion of the head) in order to enroll eligible patients in mechanical thrombectomy studies if available. The aim should be to administer the iv tPA bolus dose as the patient is being wheeled to the observation unit after imaging. Blood pressure management is a continuum from the prehospital period to the post-thrombolysis period. During peri-thrombolysis period, frequent neurological monitoring is required [1].

The post-thrombolysis epoch continues with hourly neurological monitoring and cardiac telemetry. The post-thrombolysis period ends with repeat neuroimaging (for assessment of infarct size and hemorrhagic transformation) and plan to start anti-thrombotics for secondary stroke prevention.

Case Vignette An 85-years-old lady presented to emergency department after 65 min of last seen well, with left sided weakness, slurred speech, respiratory distress and rapidly declining consciousness. Even before the stroke team could assess the patient she had to be intubated for ventilation. She was recently discharged home recovering from an aspiration pneumonia and sepsis. Her past history was significant for hypertension, chronic obstructive pulmonary disease, osteoarthritis, depression, and partial vocal-cord paralysis. She had a bi-hemispheric stroke 8 years prior with complete recovery and underwent left carotid endarterectomy for secondary stroke prevention. However, she was independent for activities for daily living. On examination by stroke team her NIHSS was 32.

The differential diagnosis was post-stroke seizure vs. new onset stroke. We performed non-contrast CT for head,

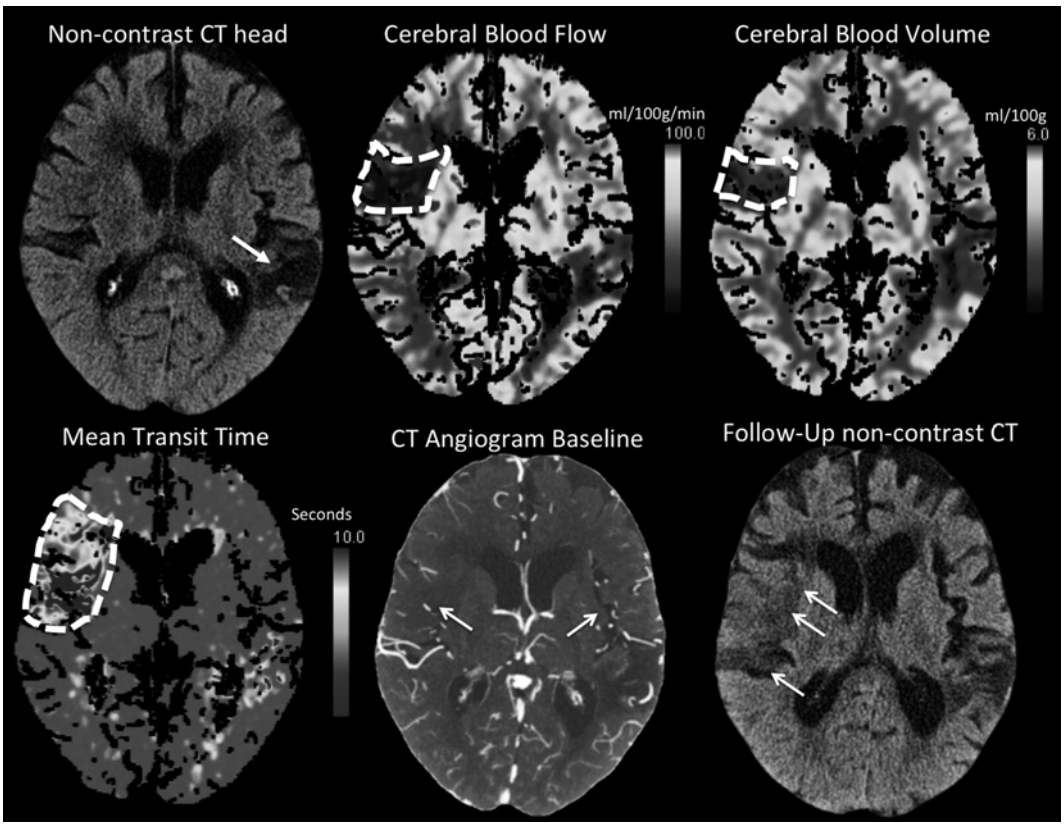

Fig. 3.6 The non-contrast CT head shows old infarcts with encephalomalacia (marked with *white arrow*). The cerebral blood flow map and cerebral blood volume map shows a small area in the frontal cortical-subcortical region with low cerebral blood flow and cerebral blood volume respectively (marked with *dotted lines* to show area of interest). The mean transit time map shows a larger area of delayed flow compared to the cerebral blood flow map and cerebral blood volume map, suggestive of penumbral pattern. The CT angiogram shows normal vascularity in bilateral hemispheres (marked with *white arrow*). The follow-up CT head shows new area of infarct in the right frontal cortical-subcortical region (marked with *white arrow*)

CT angiogram for head and neck, and CT perfusion study for the brain (Fig. 3.6). The non-contrast CT revealed old strokes in the bilateral hemispheres, CT angiogram did not show any large artery occlusion. The CT perfusion was sensitive to new ischemic stroke; the mean transit time (MTT) map demonstrated a new area of delayed flow in the right frontal-temporal region; the cerebral blood flow (CBF) and cerebral blood volume (CBV) was low in smaller area compared to the mean transit time on qualitative assessment. This was suggestive of penumbral pattern (MTT prolonged in a larger area compared to low CBF and CBV in a smaller area). This information was obtained at an additional cost of 4 min. Patient received IV thrombolysis while on the CT table. After 24 h of rtPA infusion patients was extubated and NIHSS was 6. The follow-up CT scan demonstrated a new ischemic stroke in right frontal cortical-subcortical region.

This example reveals utility of multimodality CT imaging within first 3 h of symptom onset in patients who are otherwise ineligible for IV thrombolysis due to lack clinical certainty in diagnosis. This strategy is particularly useful to increase the thrombolysis rates.

Thrombolysis in Anterior vs. Posterior Circulation Strokes

Twenty percent of ischemic strokes are in posterior circulation territory, yet only 5 % of the NINDS study population [8] and 8 % of IST-3 study population [21] had posterior circulation strokes (PCS). Other randomized thrombolysis studies have not reported the proportion of patients with posterior circulation strokes. NIHSS score is not as sensitive for PCS [37]. IV thrombolysis administration in patients with minor symptoms (e.g., ataxia, nystagmus, diplopia, and dysphagia) is variable with very few patients receiving thrombolysis [8]. There was no difference in the outcome of patients with PCS vs. anterior circulation strokes (ACS) in the IST-3 study [21]. An observational study has reported favorable outcome with thrombolysis in

patients with PCS ($n=95$) compared to ACS ($n=788$) as defined by modified Rankin scale of 0–1 (66 % vs. 47 %, $p<0.001$) [38]. PCS also had a lower rate of symptomatic intracranial hemorrhage than ACS (0 % vs. 5 %, $p=0.02$) in the same study. Simultaneous noninvasive vascular imaging with either CT angiography or MR angiography may increase the thrombolysis rates in PCS. Use of MRI DWI imaging may prove an important tool for diagnosis of posterior circulation strokes and increase early thrombolysis decision-making. In future randomized studies with IV thrombolysis, there is a need for attention to ensuring appropriate representation of PCS.

Thrombolysis with Regard to Etiologic Classification of Stroke

In the NINDS stroke study, 44 % patients had a cardioembolic stroke etiology and a beneficial effect was reported in all sub-types of stroke [8]. In the ECASS III study [13], 13 % of patients had known atrial fibrillation and there was no difference in outcomes between patients with or without atrial fibrillation. In the IST-3 study [21], 30 % of patients had atrial fibrillation and there was no difference in outcomes between patients with or without atrial fibrillation. One observational thrombolysis study has noted favorable outcome in small vessel disease ($n=101$) compared to other etiological classifications ($n=856$) after adjusting for baseline parameters (Odds ratio 1.81 95 % CI 1.01–3.23; $p<0.05$) [39]. In the same study, no symptomatic intracranial hemorrhages were reported in any patients with SVD (0 %) compared to patients with strokes of all other etiologies (10.7 %, $p<0.01$). A recent review of the literature [40] also highlights the efficacy of thrombolysis in acute lacunar stroke and emphasizes that the presence of small vessel disease on imaging is not a contraindication for thrombolysis.

Thrombolysis in Special Circumstances

Pregnancy

There is increased risk of acute ischemic stroke during pregnancy and first 12 weeks post-partum [41]. Pregnancy is regarded as a relative contraindication for thrombolysis and was an exclusion criterion for the clinical trials. However, alteplase is not teratogenic in rats and rabbits and it does not cross placental barrier [42]. Data from case series [43] suggest that in carefully selected patients, the benefits of thrombolysis to the mother may outweigh the risks. Use of multimodal MRI also may be useful in deciding appropriate treatment modality in this group of patients [44].

Thrombolysis for Patients on Anticoagulation

The AHA/ASA guidelines permit thrombolysis in patients taking warfarin if the admission prothrombin time, international normalized ration (INR) is ≤ 1.7 [1]. The "Get With The Guidelines" observational study did not find increased risk of symptomatic intracranial hemorrhages (Adjusted OR 0.78, 95 % CI 0.49–1.24) in patients taking warfarin with PT INR ≤ 1.7 at the time of thrombolysis [45]. The thrombolysis decision in patients on direct oral anticoagulants (DOACs) [46] has proven to be challenging. Recent case series have shown that thrombolysis may be reasonable in patients taking dabigatran if the thrombin time <38 s [47]. Although thrombin time is very sensitive to dabigatran level, the authors suggest that it be standardized individually for an individual hospital, as there may be considerable inter-institution variability. Alternatively if a reliable drug history is available and dabigatran has not been ingested for more than 48 h, thrombolysis may be reasonable on individual case basis.

PT/INR is prolonged in patients taking direct factor Xa inhibitors (rivaroxaban and apixaban) but these tests alone are not sufficient for making thrombolysis decisions [48]. The anti-factor Xa activity test is a more sensitive and specific measure of the direct factor Xa inhibitor medication concentration. An absent anti-factor Xa activity test may reliably indicate an absent direct Xa inhibitor medication level. However, the availability of the anti-factor Xa assay in a time sensitive manner in emergency situations is limited. More data is required to establish reliable guidelines for thrombolysis in patients taking DOACs.

Antithrombotics in Acute Ischemic Stroke

The rationale of using antithrombotic agents in acute ischemic stroke is to prevent re-occlusion by inhibiting platelet aggregation and beginning early secondary stroke prevention in the first 48 h [49]. The role of antithrombotic agents (antiplatelet and anticoagulants) in acute ischemic stroke therapy in the first 6 h of symptom onset is however controversial. In this section we highlight results of randomized clinical trials involving early antithrombotic use in the treatment of acute ischemic stroke (Table 3.3).

Aspirin vs. Placebo

The large scale blinded, randomized placebo controlled Chinese acute stroke trial (CAST) [50] assessed the efficacy of aspirin in acute ischemic stroke. A total of 21,206 acute ischemic stroke patients were randomized within 48 h of symptom onset to receive either aspirin or placebo for 4 weeks. The primary end point was either death during the scheduled

Table 3.3 Randomized control trial of glycoprotein IIb/IIIa inhibitors in acute ischemic stroke

Study group	Year	Drugs	*N*	Time window (hours)	Dose	Time of outcome assessment	Outcome
GP IIb/IIIa inhibitors alone							
The Abciximab in Ischemic Stroke Investigators	2000	Abciximab (Dose finding study)	74	0–24	0.15–0.25 mg/kg bolus alone or plus 0.125 μg/kg/min 12 h	0–5 days	Fatal and nonfatal major ICH
AbESTT	2005	Abciximab	400	0–6	0.25 g/kg + 0.125 μg/kg/min (max 10 g/min) for 12 h	Safety: 5 days Efficacy: 3 months	SICH, mRS
AbESTT-II[a]	2008	Abciximab	808	0–5	0.25 g/kg + 0.125 μg/kg/min (max 10 g/min) for 12 h	Safety: 5 days Efficacy: 3 months	SICH, mRS
SATIS	2011	Tirofiban	260	3–22	0.4 μg/kg/min for 30 min + 0.1 μg/kg/min for 48 h	2–7 days	SICH
GP IIb/IIIa inhibitors + rtPA							
CLEAR	2008	Eptifibatide	94	0–3	75 μg/kg bolus + 0.75 μg/kg/min for 2 h (rtPA 0.3 mg/kg or 0.45 mg/kg)	Safety: 0–36 h Efficacy: 3 months	SICH, mRS
CLEAR-ER	2013	Eptifibatide	126	0–3	135/kg bolus + 0.75 μg/kg/min for 2 h (rtPA 0.6 mg/kg)	Safety: 0–36 h Efficacy: 3 months	SICH, mRS

[a]Study terminated early
ICH intracranial hemorrhage, *SICH* symptomatic ICH, *mRS* modified Rankin scale

treatment period or death or dependency on discharge. There were 5.4 fewer deaths from all causes ($p=0.04$), 4.7 fewer recurrent fatal or nonfatal ischemic strokes and 1.9 more transfused nonfatal extracranial bleeds per 1,000 patients allocated to aspirin versus placebo. However, the beneficial effects of aspirin did not reach significance for the primary end point of composite outcome of death and dependency ($p=0.08$).

Aspirin vs. Anticoagulants

In the open labeled International Stroke Trial (IST) [51], 19,436 patients were randomized within 48 h of onset to receive aspirin, subcutaneous unfractionated heparin (5,000 (low-dose) or 12,500 (medium-dose) IU two times daily), both or none for 14 days. Overall there was no significant difference between the heparin and avoid heparin group in the incidence of death or nonfatal strokes in the first 14 days. The reduction in the number of recurrent ischemic strokes was offset by the increase in the number of hemorrhagic strokes in the heparin group. In addition, there were nine more patients who required transfusion or died from extracranial hemorrhage per 1,000 patients in the heparin group. Even in the group of patients in whom atrial fibrillation was thought to be the likely underlying stroke mechanism, the reduction in the risk of recurrent ischemic stroke was offset by an increase in risk of intracranial hemorrhage. In the low dose heparin (5,000 IU twice a day) group there were 15 fewer recurrent ischemic or hemorrhagic strokes, 17 fewer deaths or nonfatal strokes and 14 fewer transfusions or fatal extracranial hemorrhages when compared to the medium dose (12,500 IU twice daily) heparin. In contrast there were 11 fewer deaths or nonfatal strokes per 1,000 patients randomized to the aspirin group at 14 days and 14 fewer patients who were dead or dependent at 6 months. Despite the need for transfusion and fatal extracranial hemorrhages being commoner in aspirin group, there was net clinical benefit in taking aspirin early. In the Aspirin group 13 more patients were likely to be independent at 6 months. However this did not reach statistical significance. A pooled analysis of CAST and IST showed a significant 0.9 % (*NNT*-111) absolute risk reduction for deaths or nonfatal strokes for patients taking aspirin in the first 48 h compared to patients avoid-aspirin group [52].

Glycoprotein IIb/IIIa Antagonist

Abxicimab is a monoclonal antibody that binds to the glycoprotein IIb/IIIa receptor as well as α v β 3 integrin receptor of endothelial and smooth muscle cells. The initial demonstration of abxicimab safety was in an acute ischemic stroke dose escalation study [53] and AbSETT study [54]. This lead to the phase 3 trial, Abciximab in Emergency Stroke Treatment Trial II (AbESTT-II) [55]. AbESTT-II was a randomized trial to assess the efficacy and safety of intravenously administered abxicimab given to patients with acute ischemic stroke (non-thrombolysed) up-to 6 h after symptom onset or within the first 3 h of a wake-up-stroke. The trial was stopped prematurely, after enrolling 808 patients, due to the increased incidence of symptomatic or fatal intracranial hemorrhage in patients treated with abciximab (5.5 % vs. 0.5 %, $p=0.0002$). The study concluded that it is not safe to use intravenous abciximab in acute ischemic stroke patients.

Tirofiban and eptifibatide are non-peptides and are highly selective to GP IIb/IIIa receptors. The Safety of Tirofiban in Acute Ischemic Stroke (SaTIS) trial [56] enrolled 260 moderate severity stroke patients between 3 and 22 h of symptom onset.

The aim of the study was to evaluate the rate of all cerebral hemorrhage occurring in the first week of stroke. The secondary outcomes were early neurological and functional performance. There was no significant difference in cerebral hemorrhages in the Tirofiban group (30 %) vs. the placebo group (26.6 %). The Tirofiban group had significantly lower mortality compared the placebo group (2 % vs. 8 %, $p=0.03$), but there was no difference in early neurological improvement at 1 week or functional outcome at 5 months. The authors suggested that since the primary goal of Tirofiban therapy in acute ischemic stroke is to prevent arterial re-occlusion, it is imperative to use it in tandem with IV thrombolysis or as a bridging treatment prior to intra-arterial therapies. However, phase III studies are needed to address the efficacy and further study the safety.

Combined Antithrombotics and Fibrinolysis

In the Multicenter Acute Stroke Trial-Italy (MAST-I), 622 acute ischemic stroke patients within 6 h of symptom onset were randomized in a 2×2 factorial design to aspirin alone, streptokinase alone, aspirin plus streptokinase, or neither active treatment. This study was underpowered ($n=153$) to detect an effect of aspirin alone and did not show benefit in mortality (aspirin, 10 % vs. control 13 %) or disability (aspirin, 42 % vs. control, 39 %). Patients receiving aspirin plus streptokinase had a significantly higher risk of early death than those given neither (OR 3.5; 95 % CI 1.9–6.5; $p<0.0001$).

Abciximab in combination with rt-PA in acute ischemic stroke has not been studied. Tirofiban has been evaluated in a pilot study of middle cerebral artery occlusion in combination with reduced dose of rt-PA [57]. A total of 19 patients were enrolled in a single arm study and 68 % had recanalization. Patients with recanalization also had good neurological improvement ($p<0.0001$). There was no symptomatic intracranial hemorrhage in any of the treated patients. The median onset-to-treatment was 135 min. No phase II or III studies have been done.

Eptifibatide has been studied in a phase II study to assess safety. Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke-Enhanced Regimen Stroke Trial (CLEAR-ER) [58] enrolled 126 patients within 3 h of symptom onset. Patients were randomized in proportion of 4:1, 4 to epitifibatide 135 mcg/kg bolus followed by a 2 h infusion at 0.75 mcg/kg plus medium dose rtPA (0.6 mg/kg) and 1 to rtPA alone (0.9 mg/kg). The combination group had lower rate of symptomatic intracranial hemorrhage (2 %) compared to rtPA alone (12 %, OR 0.15, 95 % CI 0.01–1.4; $p=0.053$). There was no difference in the functional disability scales at 90 days after adjusting for the age and baseline neurological deficits. There could be a future role of eptifibatide in treatment of acute ischemic stroke but it needs to be assessed in a phase III study.

Conclusion

Intravenous thrombolysis with rtPA is effective in the first 4.5 h of symptoms onset in patients with ischemic stroke. Beyond 4.5 h, the decision of thrombolysis is challenging and patients should be enrolled in experimental studies. The task is to improve thrombolysis rates using novel strategies, like prehospital thrombolysis, simultaneously increasing awareness among the general population for early arrival to the hospital. Antithrombotics in combination with intravenous thrombolysis may have promise and needs to be evaluated in phase 3 randomized studies.

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Intra-arterial Therapy for Acute Ischemic Stroke

4

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Introduction

Acute ischemic stroke remains a leading cause of disability and death worldwide. Occlusion of cerebral arteries is the premier cause of ischemic stroke; and strong correlations between arterial recanalization and better outcomes (improved functional status and reduced mortality) in acute ischemic stroke (AIS) have been demonstrated [1, 2]. Achieving recanalization is associated with a four to fivefold increase in the odds of good functional outcome, with a similar magnitude of reduction in the odds of death [1, 2]. Moreover, the recanalization effect is "dose dependent": the greater the degree of recanalization and reperfusion the higher the likelihood of a good functional outcome [1, 2]. Hence, achieving recanalization by thrombolysis (systemic or local), mechanical retrieval devices, or combinations of these approaches to remove the occlusive cerebral arterial thrombus, is a key therapeutic goal in AIS management.

However, the only approved therapy for AIS is intravenous recombinant tissue Plasminogen activator (IV-rtPA) therapy, which has a modest recanalization effect; and only a relatively small proportion of AIS patients actually receive this proven and efficacious therapy [3–5]. The IV-rtPA requires an effective system of care to be able to deliver this timely therapy to large proportion of AIS patients. In addition, IV-rtPA has been shown to have poor recanalization rates (the main goal in AIS) in larger artery occlusion, such as terminal internal carotid artery (ICA) and proximal middle cerebral artery (MCA) [6, 7]. Extending the IV-rtPA therapeutic window beyond 4.5 h was not shown to be beneficial in subsequent clinical trials [8].

To provide an alternative to patients who cannot receive IV-rtPA or do not have recanalization with IV-rtPA, approaches such as administering local intra-arterial therapy (IAT) of the thrombolytic drug via a micro-catheter or mechanically removing the occlusive clot using retrieval devices have emerged. Due to early limitations in technology, it was more feasible to start with IAT chemical thrombolysis, then subsequently move to mechanical thrombectomy devices as the technology advanced (Fig. 4.1 demonstrates the favorable evolution of clinical evidence corresponding to advances in device technology).

These clinical and technical advances were incorporated into the design of "MR CLEAN" interventional AIS therapy randomized clinical trial [9]. The MR Clean results demonstrated an overwhelming clinical and angiographic efficacy of mechanical approach added to standard of care over standard of care alone when initiated within 6 h from symptoms onset [9].

In this chapter, we provide an overview of intra-arterial AIS therapy [10].

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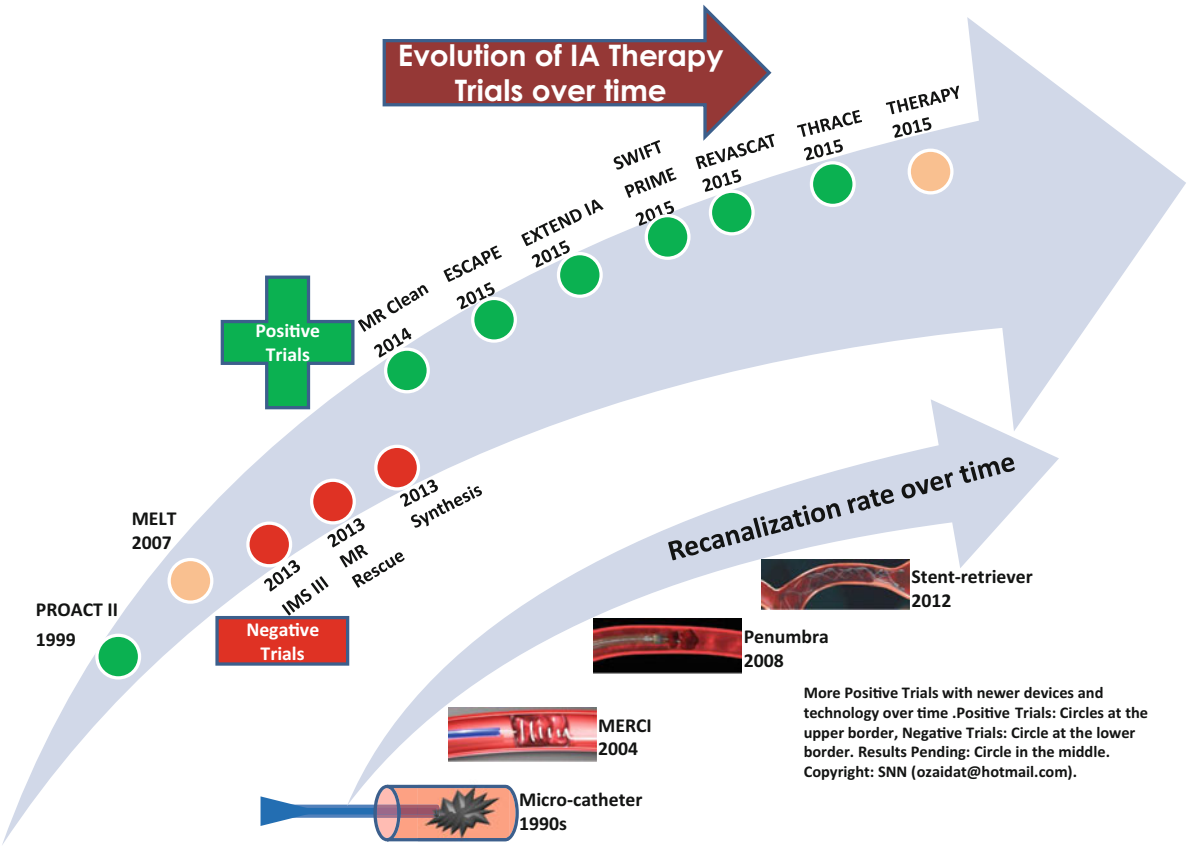

Fig. 4.1 Evolution of IA therapy trials over time. More positive trials with newer devices and technology over time. Positive trials: *Circles* at the upper border, Negative trials: *Circle* at the lower border, Results pending: *Circle* in the middle. Escape results announced to the participating sites investigators as favoring IA without pending the full publication (Endovascular Stroke Trials Halted for Benefit. Can be found at http://www.medscape.com/viewarticle/835040. Last accessed January 7, 2015). Permission from Stroke, Neurointerventional and Neurocritical Care (SNN) research center. ozaidat@hotmail.com

Table 4.1 Pros and Cons of IAT for AIS

Pros	Cons
Superior to IV-rtPA for stroke due to large artery occlusion (MR CLEAN 2014, Escape 2015[a], Extend IA trials[a])	Embolization into new territory
Expanded time window to 6 h from symptoms onset	Downstream distal embolization
Efficacious for large vessel occlusion and fibrinolysis resistant clots	Tortuous anatomy in elderly stroke patients
Smaller dose or no fibrinolytic agents	Access complication and vessel injury
Higher rate of complete recanalization	24/7 specialized team and tertiary care center needs
Faster recanalization time	

[a]Results not yet published or presented but trials prematurely stopped due to reportedly highly favorable benefit of IAT

The Basis for Intra-arterial Therapy

The intra-arterial approach to acute ischemic stroke has emerged as an adjuvant or stand-alone therapeutic modality for AIS. Local intra-arterial therapy (IAT) offers some advantages over systemic thrombolysis (See Table 4.1 for advantages and disadvantages of IAT).

First, it can expand the treatment time window beyond 3 or 4.5 h. The time window has been safely expanded to 8 h and 24 h in anterior and posterior circulation, respectively, using IAT [11–14]. Second, IAT provides faster and more efficient recanalization for clot loads that are large or resistant to enzymatic degradation [15]. One study evaluated the recanalization rate in consecutive IV-rtPA treated AIS patients based on the clot size using ultrathin

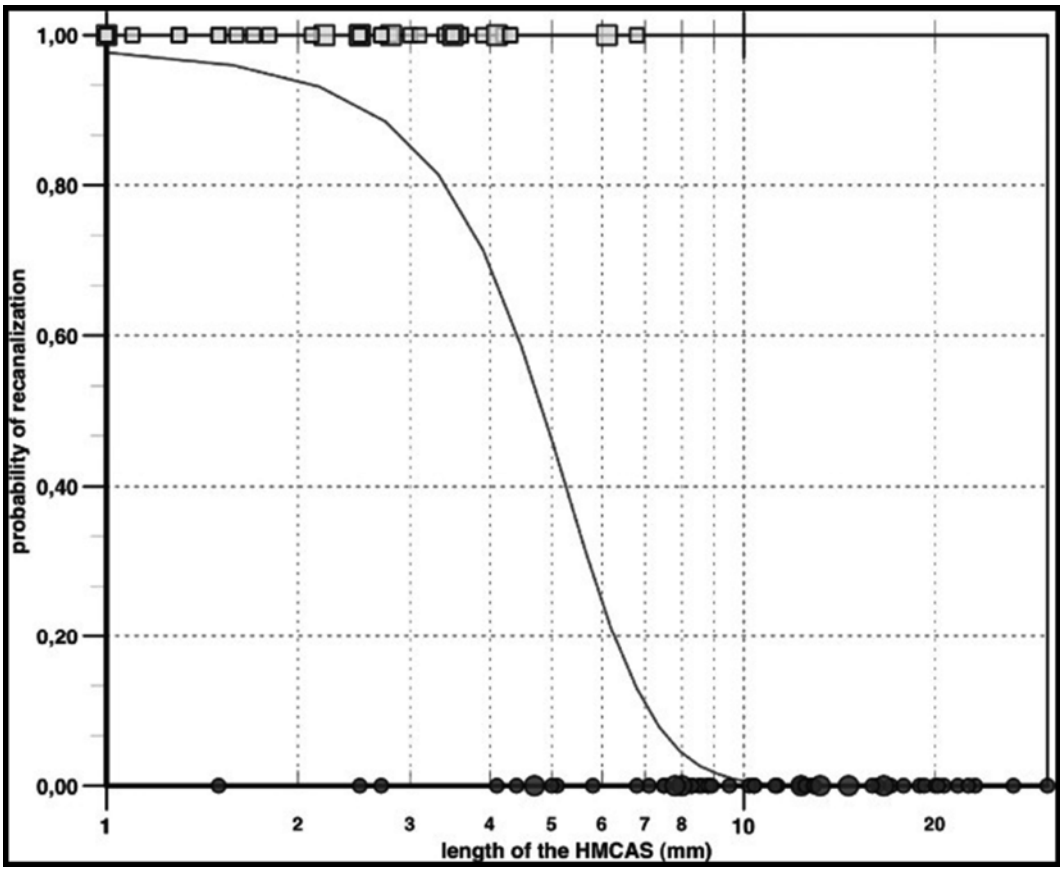

Fig. 4.2 Probability of occluded vessel recanalization by intravenous thrombolysis is very low (<5 %) when thrombus length approaches 8 mm. Reproduced from: Wolters Kluwer Health, Stroke, The Importance of Size: Successful Recanalization by Intravenous Thrombolysis in Acute Anterior Stroke Depends on Thrombus Length, Christian H. Riedel, Philip Zimmermann, Ulf Jensen-Kondering, Robert Stingele, Günther Deuschl, Olav Jansen, Dec 31, 1969, Vol 42, Issue 6

computerized tomography of the head to assess the length of hyper-dense MCA sign (clot size) [15]. The study demonstrated that with IV-rtPA, short clots (length <5 mm) were highly likely to be dissolved completely, whereas for longer clots (8 mm in size or greater), recanalization was very unlikely and was observed in <1 % of cases, as illustrated in Fig. 4.2 [15].

Third, beside the length and size of the clot, its composition such fibrin and platelet rich white clot, or clots rich with calcium or cholesterol crystals may render themselves resistant to both local and system fibrinolysis (versus red clots composed mainly from erythrocytes) and the need for mechanical retrieval devices ensues [16].

Given the above rationale and evidence, IAT became the logical next area of major research emphasis in AIS management to accelerate reperfusion, particularly in patients with large vessel occlusion secondary to large size clot.

Intra-arterial Chemical Thrombolysis Approach

The first attempt of IAT was the use of a local fibrinolytic agent delivered via microcatheter directly into the clot (Fig. 4.1). The pharmacological advances and newer fibrinolytic agents may lead to higher use in the future for both IV and IA thrombolysis. For example, development of a more specific agent that can be administered as a single bolus with more specificity to fibrin may reduce the time required for administration and the risk of intracranial hemorrhage (Fig. 4.3, depicting thrombolysis pathway).

The main advantage of local intra-arterial fibrinolytic therapy is the ability to infuse smaller doses of the thrombolytic drugs locally, within or in a close proximity to the thrombus. In theory, this direct delivery of the thrombolytic agent to the thrombus can increase the chance of recanalization, decrease

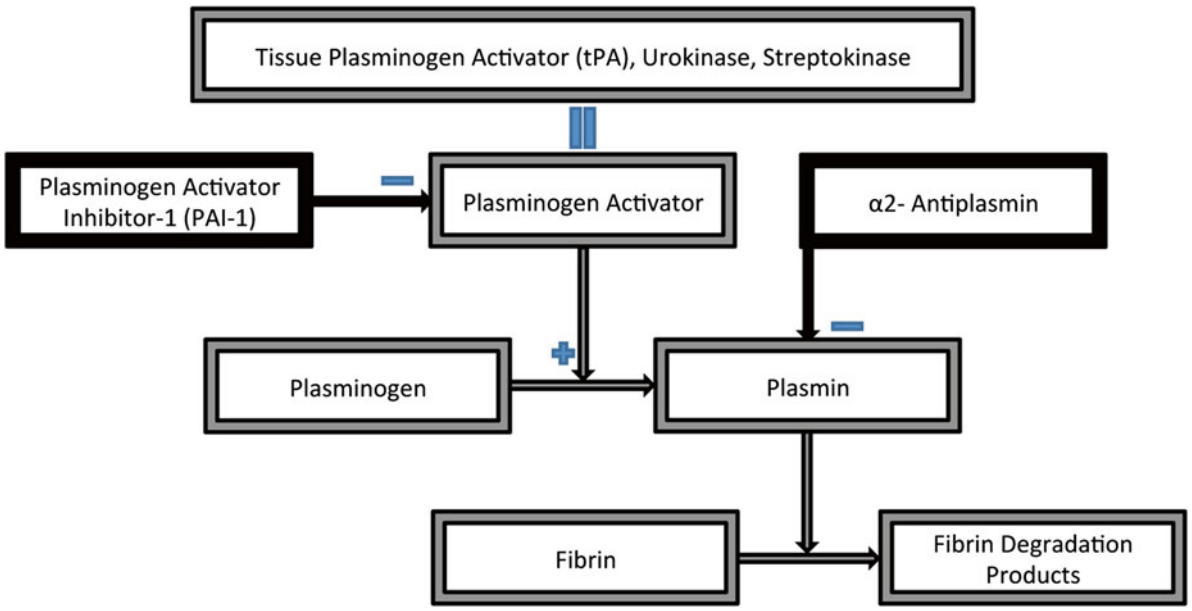

Fig. 4.3 Fibrinolysis pathway

Table 4.2 Thrombolysis in myocardial infarction (TIMI) scale (Established by the national heart, lung and blood institute in 1983 to measure myocardial reperfusion. The scale since then has been widely adopted for use in the cerebral circulation and has been used in the PROACT Trial, MERCI, MULTI MERCI, PENUMBRA PIVOTAL, SWIFT, and the START trials)

TIMI score	Definition
0-Complete occlusion	There is no antegrade flow beyond the point of occlusion.
I-Penetration without perfusion	Perfusion past the initial occlusion, however the is contrast stagnation without distal branch filling.
II-Partial perfusion	Perfusion past the initial occlusion, however the contrast rate of entry or rate of clearance rate delayed when compared to unaffected vessels.
III-Complete perfusion	Full perfusion with filling of all distal branches, contrast material clears as rapid as unaffected branches.

the risk of hemorrhage by providing a higher concentrated dose into the clot and using a smaller total dose. Moreover, in comparison to other IAT technique; it is technically easier to perform (i.e., tracking a soft and small diameter microcatheter to the face of the clot is easier). However, it is less effective than mechanical thrombectomy, and takes longer to complete (due to the slow IA infusion rate).

Different fibrinolytic agents can be used with varying targets, and rates of specificity and sensitivity to thrombus components, for example some are more specific for Plasminogen, versus Plasmin versus fibrin, while others may be more resistant to inhibitory pathways than others (Fig. 4.3). The most commonly used agent for IAT in clinical practice is rtPA. However, Urokinase and Prourokinase have been also used in clinical studies.

The Prolyse in Acute Cerebral Thromboembolism (PROACT Trial) is the first double-blinded, randomized, placebo-controlled study of fibrinolytic agents delivered intra-arterially by microcatheter in AIS and was published in 1998 [17]. The study aimed to test the safety and efficacy of the intra-arterially delivered thrombolytic agent (Prourokinase) versus placebo in AIS patients with angiographically proven proximal middle cerebral artery (MCA) occlusion. Patients who displayed a 0–1 grade MCA occlusion on the Thrombolysis in Acute Myocardial Infarction (TIMI) scale (see Table 4.2 for TIMI scoring) were enrolled in the trial.

The patients were randomized in a 2:1 ratio to receive intra-arterial (IA) prourokinase or placebo infusion within 6 h from symptoms onset. Both groups also received IV heparin infusion. Forty patients were randomized (26 received prourokinase and 14 received placebo). Partial or complete recanalization in the prourokinase group was observed in 15 of 26 patients (57.7 %) compared with 2 of 14 patients (14.3 %) in the placebo group ($p=0.017$). Symptomatic hemorrhagic transformation occurred in 15.4 % and 5.1 % of the prourokinase and the placebo groups, respectively ($p=0.61$). The authors observed higher absolute rates of excellent neurological outcome in the IA cohort (modified Rankin Scale score of 0–1: 30.8 % vs. 21.4 %; Barthel Index score of 9–10: 42.3 % vs. 35.7 %; NIHSS score of 0–1:

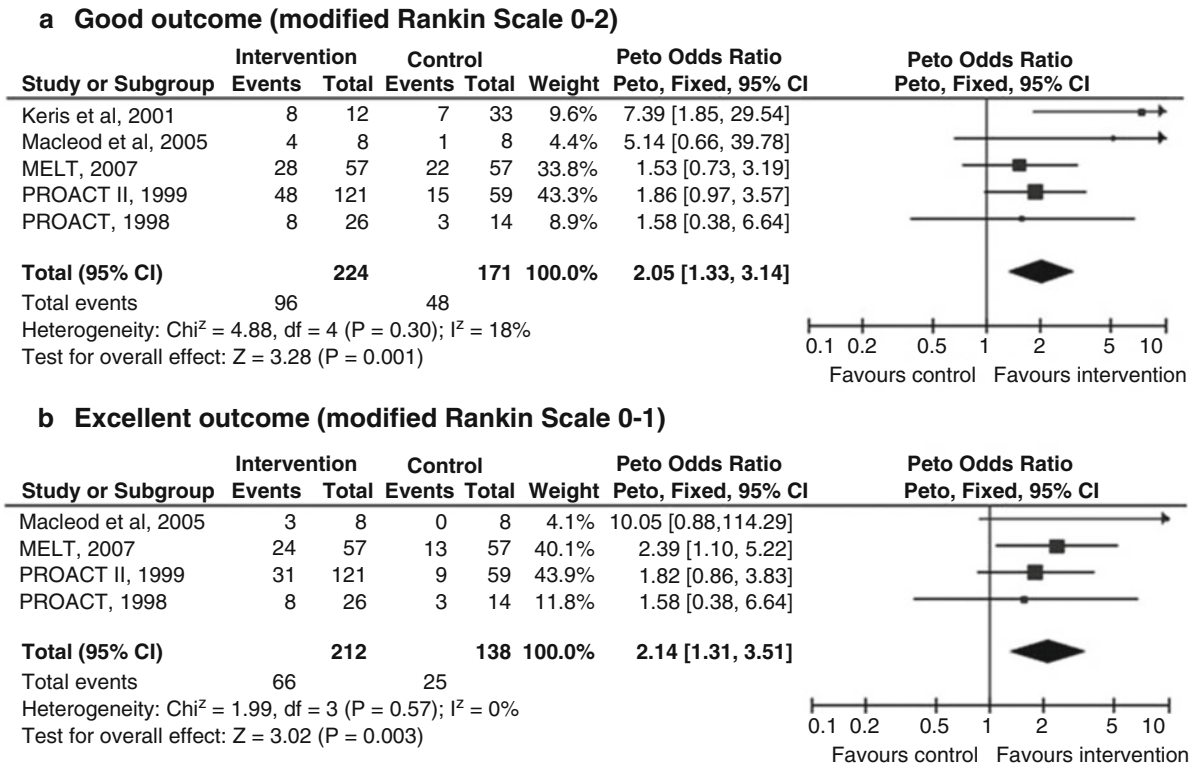

Fig. 4.4 Meta-analysis of intra-arterial chemical thrombolysis clinical studies. (**a**) Good outcome (mRS 0–2) and (**b**) Excellent outcome (mRS 0–1). Reproduced from Wolters Kluwer Health, Stroke, Efficacy of Intra-Arterial Fibrinolysis for Acute Ischemic Stroke: Meta-Analysis of Randomized Controlled Trials, Meng Lee, Keun-Sik Hong, Jeffrey L. Saver, May 1, 2010, Volume 41, Issue 5

19.2 % vs. 7.1 %), but these difference did not reach statistical significance [17].

These encouraging results led to the PROACT II trial, which was published in 1999 [18]. In PROACT II, patients with angiographically proven MCA occlusion were randomized to receive IA Prourokinase plus IV heparin ($n=120$) or IV heparin alone ($n=60$) within 6 h from stroke symptoms onset in a 2:1 ratio. The primary outcome was slight or no disability at 90 days as defined by modified Rankin Scale (mRS) of 2 or less. The total recanalization rate was 66 % in the Prourokinase group and 18 % in the control group. The rate of good neurologic outcome (90 days mRS 0–2) was 40 % for the Prourokinase group vs. 25 % for the placebo group. This was the first clinical trial that demonstrated a benefit of IAT in AIS. However, Prourokinase failed to get FDA approval in the USA and is therefore not available.

Another IAT study with MCA occlusion was done in Japan, and published in 2007 [19]. The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) was halted prematurely in 2005 due to the approval of IV-rtPA in Japan, and further enrollment into a control arm (not receiving IV-rtPA) was considered unethical [19]. In the MELT trial, a total of 114 patients were randomized to receive IA Urokinase versus placebo. Although more patients in treatment group met the primary end point of a mRS 2 or less, the difference did not reach statistical significance (49.1 % vs 38.6 %, $p=0.345$). However, excellent clinical outcome (mRS of 0 or 1), which was a preplanned secondary outcome, was statistically more frequently seen in the Urokinase group than in the control group (42.1 % vs 22.8 %, $p=0.045$).

For posterior circulation AIS, a small randomized study of 16 patients within 24 h of stroke symptom onset was reported [14]. Eight patients were randomized into each arm, with higher stroke severity at baseline in the Urokinase arm. A good functional clinical outcome was observed in four of eight patients who received intra-arterial Urokinase compared with one of eight patients in the control patients [14].

A meta-analysis of chemical IA thrombolysis [20], showed overall favorable outcome with IA therapy over controls, as shown in Fig. 4.4.

Combined IV and IA Therapy

Intravenous thrombolytic therapy has certain advantages over IA therapy; it is more widely accessible, since it can be administered rapidly in the emergency room, and potentially

in a stroke mobile unit ambulance, or via Telestroke across the country. Therefore, the combined (bridging) approach takes advantage of the rapidity by which IV-rtPA can be administered, and the high recanalization efficacy of the IAT. The "bridging" approach is a method by which the patient receives systemic thrombolysis at the field (in a mobile stroke unit), an outside hospital ("drip and ship" to tertiary stroke center), or locally in the receiving hospital; then is transferred immediately to the angiography suite for possible additional local IA therapy. If symptoms resolve, or intervening imaging such CT angiography shows no large vessel occlusion, or angiogram shows no occlusion, then IA therapy is aborted.

The combined IV/IA treatment strategy was initially tested in a small open-label prospective study of 45 patients [21]. A total of 12 patients received IV-rtPA plus IA-rtPA (IV/IA) with either MCA (9) or internal carotid artery (ICA, 3) occlusions versus 33 patients who received IV-rtPA only [21]. In the IV/IA group: good outcome was seen in 67 % and 83 % at 1 month and 12 months, respectively versus 21 % and 33 % in the control groups at 1 month and 10 months, respectively [21]. The randomized combined IV/IA Emergency Management of Stroke (EMS) Bridging Trial was published in 1999 [22]. Seventeen AIS patients were randomized to IV/IA group and 18 patients into the placebo/IA group within 3 h of symptoms onset. There was no difference in the clinical outcome or symptomatic intra-cerebral hemorrhage (sICH) between the two groups. However, there was a better recanalization rate in IV/IA group compared to the placebo/IA group (68 % versus 10 %, respectively; $p=0.03$). This pilot study suggested that combined IV/IA treatment was feasible, safe, and provided good recanalization rates.

The initial Interventional Management of Stroke Study (IMS) [23] was an open-label, single arm study in which patients with moderate to severe stroke who had received IV-rtPA were treated with up to an additional 22 mg of IA-rtPA. Patients in IMS were compared to historical controls from the NINDS IV rt-PA trials who received active treatment (IV-rtPA only comparators) or placebo (no treatment comparators). When compared to patients from the placebo arm of the NINDS IV-rtPA trials, the 3-month mortality was lower but not statistically different (IMS versus Placebo of NINDs trial). The rate of sICH was similar between the IMS patients and the NINDS IV-rtPA treatment group (6.3 % vs 6.6 %, respectively). However, IMS patients had significantly better functional outcome at 3 months than the placebo NINDS group.

The IMS II Study [24] was a phase two trial, with a similar design single arm study; except that patients were treated with only two thirds of the IV-rtPA dose (0.6 mg/kg) within 3 h of symptoms onset, and then received up to an additional 22 mg of IA-rtPA. The results mirrored those of the first IMS Study. In the IMS II study, 81 AIS patients were treated with IV/IA via standard or ultrasound tip microcatheter technique within 3 h of symptoms onset. The 3-month mortality in IMS II was 16 % as compared with the mortality of placebo (24 %) and rtPA-treated patients (21 %) in the NINDS IV Trial. The rate of sICH in IMS II patients (9.9 %) was not significantly different than that for IV-rtPA treated group in the NINDS Trial (6.6 %). IMS II patients had significantly better outcomes at 3 months than NINDS placebo-treated patients for all end points (ORs $\geq$2.7) and better outcomes than NINDS IV-rtPA-treated patients as measured by the Barthel Index and Global Test Statistic [24].

The IMS phase three (IMS III) trial [25] randomized patients with moderate to severe AIS within 3 h from symptoms onset to receive IV-rtPA with an additional mechanical endovascular therapy (based on the interventionalist choice) or IV-rtPA alone in a 2:1 ratio. The trial started in 2005 using the first-generation AIS mechanical thrombectomy MERCI devices (see below), and was halted early because of futility analysis after 656 patients had been randomized [25]. The primary end point of the proportion of subjects with good outcome (mRS 0–2) was not different between the groups (40.8 % for IV/IA group and 38.7 % for IV-rtPA group). The incidence of sICH was similar in both groups (6.2 % and 5.9 %, respectively) [25]. It was unfortunate that the trial was halted (in April 2012) as soon as new-generation AIS thrombectomy devices (Stent retrievers) were approved by the FDA on March 2012 (theses new devices may have contributed to the positive results of MR CLEAN clinical trial [9], please see below).

Mechanical Thrombectomy Devices

The AIS therapy aim is to improve outcome and reduce mortality by rapidly revascularizing large cerebral artery occlusion, thereby limiting the extent of ischemic brain tissue, has been the main force propelling the development of quicker and more reliable thrombectomy devices. The impetus for the iterative development of various mechanical thrombectomy devices originates primarily from these needs, along with the suboptimal use of IVrtPA in clinical practice, as well as less than optimal rate of complete recanalization, and the technical complexity of using the first-generation mechanical thrombectomy devices (see below).

MERCI Retrievers

The first Mechanical Embolus Removal for Cerebral Ischemia (MERCI) device was conceived in 1995. The MERCI Retrievers (MR) are corkscrew-shaped mini devices

attached to micro-wire, that are designed to remove blood clots from large cerebral vessels. They had various diameter and length sizes and housed in constrained format in a small cerebral microcatheter. Once deployed and unsheathed from the microcatheter, the MR becomes coiled in shape to engage and retrieve the clot (Fig. 4.5).

Animal studies began with the device in 1996, and subsequently in humans with a series of MERCI trials, which led to its FDA approval in 2004. The MERCI retriever was the first FDA approved intra-arterial mechanical thrombectomy device for use in humans (Fig. 4.6, MERCI case example).

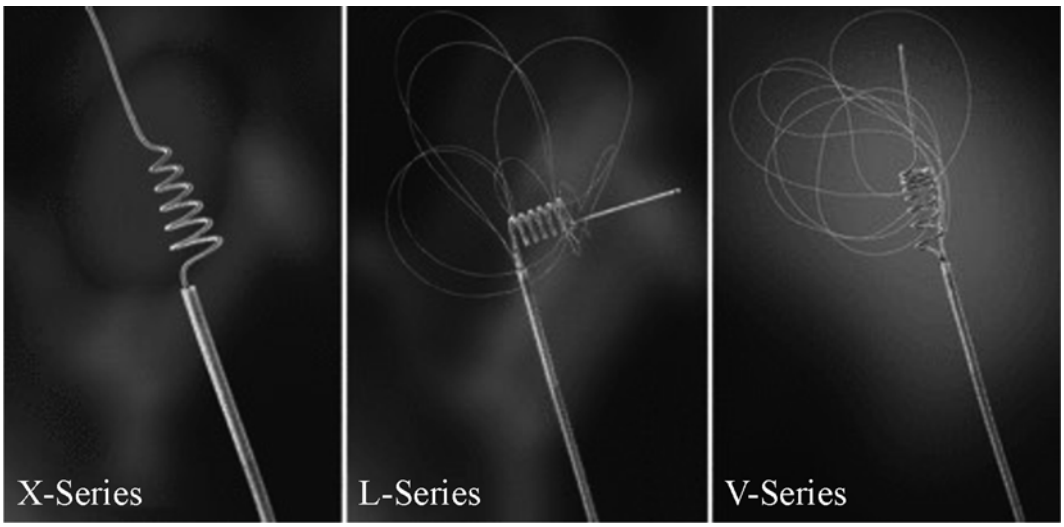

Fig. 4.5 Evolution of the MERCI device. The first-generation X-Series with a tapered design and no filaments. The L-Series with added filaments to provide increased surface area for clot engagement. The V-Series with coil linear configuration and filaments for optimal clot retention

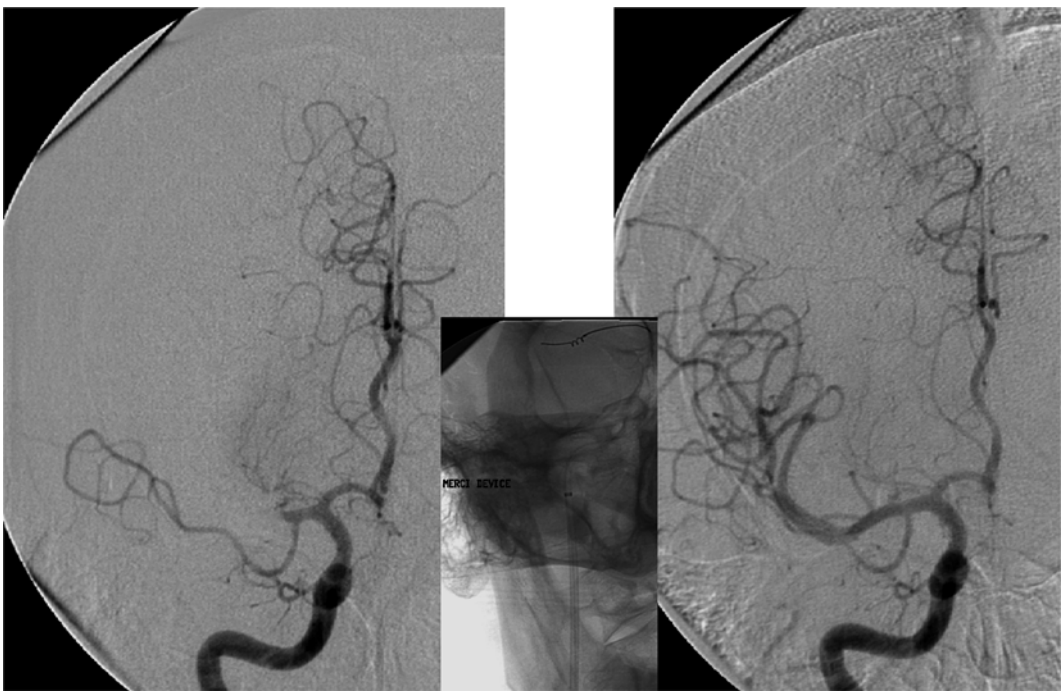

Fig. 4.6 A case example of successful use of the MERCI device in right MCA occlusion

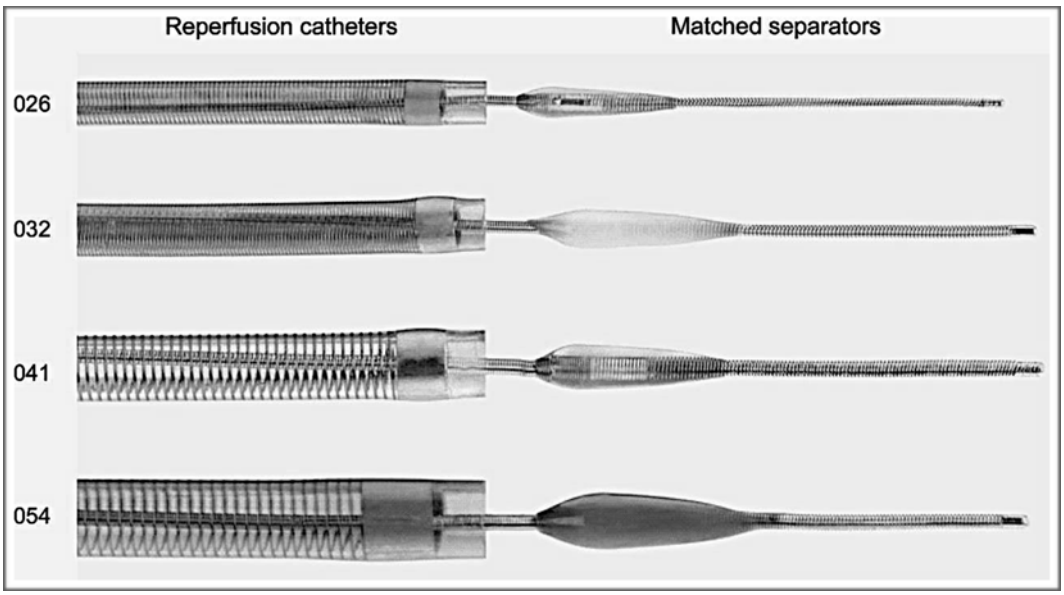

Fig. 4.7 First-generation penumbra system, consisting of both a thromboaspiration suction device and a separator

In the MERCI and Multi MERCI trials [11, 12], the device was tested in patients with moderate to severe strokes (NIHSS ≥ 8) up to 8 h from symptom onset in a prospective, nonrandomized, single arm, multicenter trial. The results demonstrated a successful TIMI scale of 2 or higher recanalization rate of 48 % and 57.3 %, respectively. These rates were significantly higher than the 18 % rate in the placebo group of PROACT II study [18]. The risk of sICH was similar to historical controls in the PROACT II trial [18]. Good functional outcome was defined as an mRS ≤ 2, which was found more frequently in patients with recanalization versus not. These results emphasized the importance of reestablishing blood flow to ischemic brain tissue to improve outcome. However, the rate of complete recanalization or meaningful recanalization was still limited with the MERCI device; and the time to reperfusion (groin puncture time to successful recanalization) was relatively long. Moreover, the introduction of stent retriever and more efficient suctioning devices may have ultimately led to very limited use in current practice.

Suction Thrombectomy

In 2008, the Penumbra system, a form of suction thrombectomy, was FDA approved and launched for commercial use as a new class of neuro-thrombectomy devices. Suction thrombectomy is performed with a catheter tracked into the face of the clot under X-ray fluoroscopy guidance, then attached to negative suctioning machine (vacuum) to aspirate the occlusive intra-vascular clot in AIS. The first-generation Penumbra system utilizes a special micro-wire called a separator that helps break a larger clot into pieces by a back and forth motion under aspiration (Fig. 4.7).

Newer-generation Penumbra systems included more trackable and larger bore distal catheter (MAX and ACE systems).

The device was tested with success in a prospective, multicenter, single-arm study called the Penumbra Pivotal Stroke Trial [13]. In this trial, 125 patients were enrolled with an NIHSS ≥ 8 within 8 h of symptom onset. Patients who presented within 3 h could be enrolled if they were excluded from IV-rtPA treatment for any reason. Of the treated vessels, 81.6 % were successfully recanalized based on TIMI scale (≥2). The rate of sICH was 11.2 %, which was comparable to MERCI 9.8 % and IA PROACT II group of 10 %. Despite the high rate of successful revascularization, a relatively low rate of good outcome (defined as 90-day mRS of 0–2) was reported at 25 %. However, the first post-market experience of the Penumbra system (POST study) showed better functional clinical outcome (41 % of 157 patients enrolled) than the original pivotal FDA study [26]. This is comparable with the good outcome rates of 40 % in the PROACT II trial, and slightly higher than the 36 % achieved with Multi-MERCI trial. The sICH rate of 6.4 % was more favorable than those reported in their pivotal study.

Perhaps to explain differences in neurological outcome with relatively similar recanalization rates, the Stroke Treatment and Revascularization Therapy (START) trial was designed to determine if there was a correlation between pretreatment infarct volume and functional outcome at 90 days [19]. Included in this study was Penumbra's newer-generation

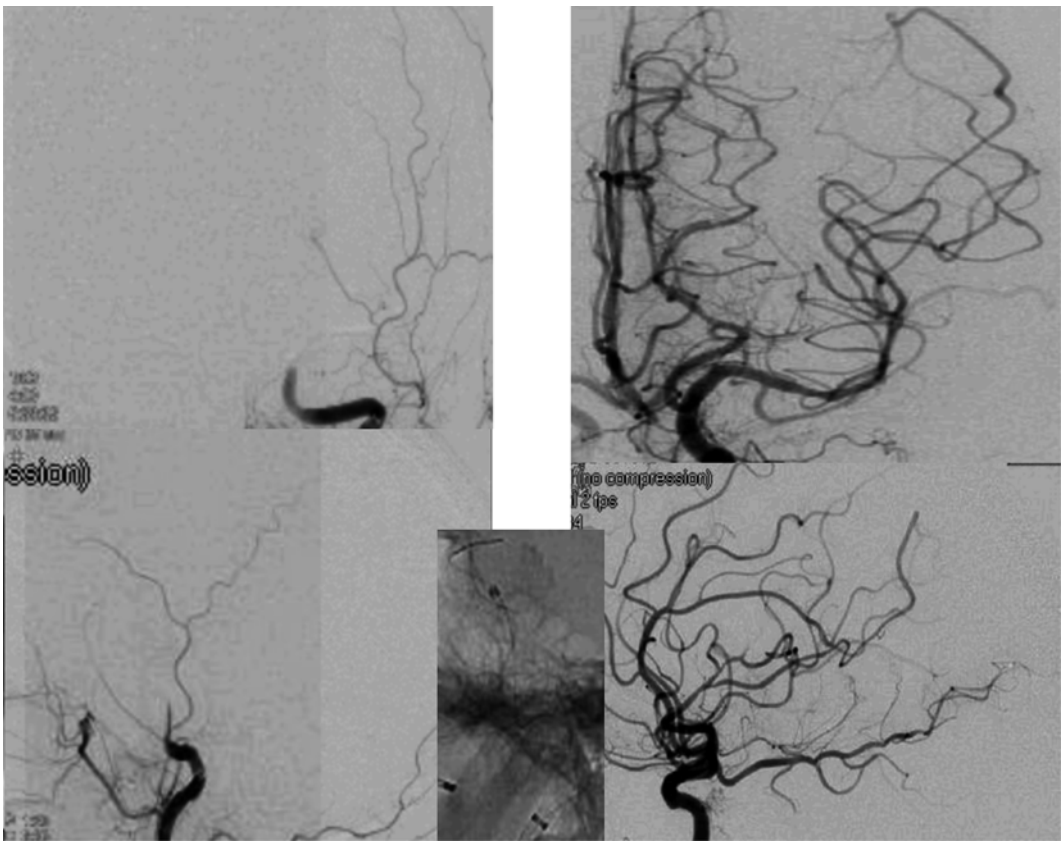

Fig. 4.8 Acute ischemic stroke secondary to a thrombus occluding the left internal carotid artery terminus (T-Occlusion) treated acutely with the Penumbra Aspiration System. Angiogram in AP and Lateral Pre (*left hand* pictures) and post (*right hand* pictures) Penumbra Aspiration System therapy with complete recanalization

device; Max catheter, which was designed to be easier to navigate the cerebral circulation, and to provide a better aspiration than the older-generation Penumbra devices. A total of 77 patients were enrolled with an average NIHSS of 19 (range of 14–24). The imaging methods used to select patients for the study were at each center's discretion and included non-contrast CT, CT angiography, CT perfusion, and MRI diffusion imaging. The overall results of the study showed a good neurological outcome (mRS 0–2 at 90 days) of 48.1 % (37/77). The Alberta Stroke Program Early CT score (ASPECTS) score was used to evaluate core infarcts. The highest percentage of good neurological outcome 64.3 % was seen in the small core infarcts or an ASPECT score of 8–10 patients (Fig. 4.8 is AIS case example treated with Penumbra).

With technical advances, a new approach has been to directly aspirate the cerebral clot with new-generation large bore distal access catheter without breaking it up, thus decreasing the chance of distal and new territory embolization, and potentially reducing procedure time [27–29]. Direct aspiration techniques (example of names used for this technique: FAST, MAT, ADAPT) has been used with different brands of large bore distal catheters (LBDC). When the LBDCs are advanced and placed at the proximal surface of the clot, a negative manual hand pressure (or automatic negative pressure pump machine) is applied by a 20 or 50 ml syringe for approximately 20 s. If no flow through the system is seen, the distal tip of the LBDC is assumed to have engaged the clot and the catheter is slowly withdrawn.

Using this direct aspiration technique, one retrospective single-center study reported outcomes in 57 patients with AIS due to basilar artery occlusion treated with either IA fibrinolysis ($n=25$) or direct aspiration thrombectomy ($n=32$) [27]. Revascularization, in this study, was graded using the modified thrombolysis in cerebral ischemia (TICI, Table 4.3), in which successful revascularization is commonly defined as mTICI 2b/3 [30].

The direct suction thrombectomy group had a shorter procedure time (75.5 min versus 113.3 min, $p=0.016$) and higher successful revascularization rate (88 % versus 60 %, $p=0.017$) than the fibrinolysis group. Fair outcome, defined as a modified Rankin Scale 0–3, at 3 months was achieved in 34 % of patients undergoing direct suction thrombectomy and 8 % of patients undergoing fibrinolysis ($p=0.019$), and

Table 4.3 Modified thrombolysis in cerebral ischemia (mTICI) scale (The scale is recommended as the main scale in AIS trials. It has been used in IMS trials, I, II, and III, in TREVO-2 trials and MR CLEAN trial)

mTICI	Angiographic criteria
0	No perfusion
1	Minimal flow past the occlusion with little to no perfusion
2a	Antegrade partial perfusion of less than half of the downstream ischemic territory
2b	Antegrade partial perfusion of half or greater of the downstream ischemic territory
3	Antegrade complete perfusion of the downstream ischemic territory

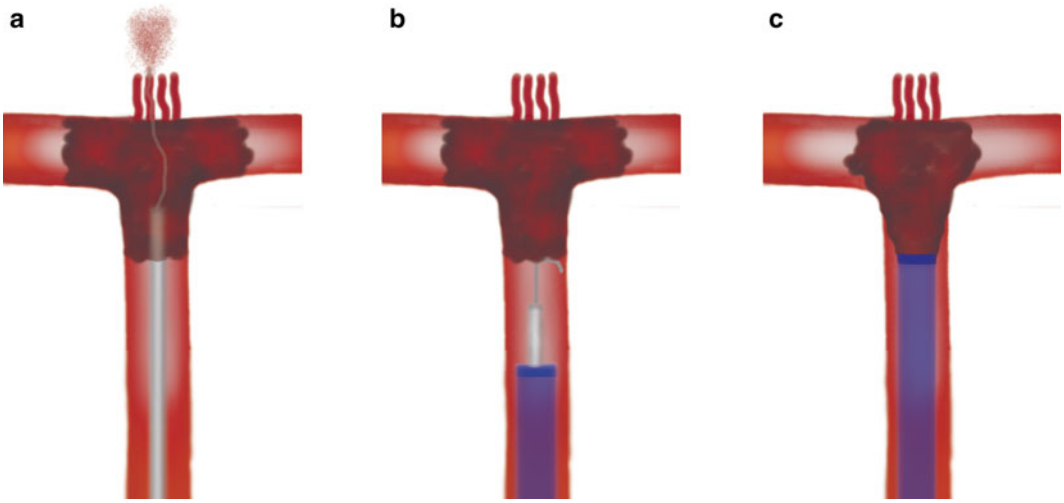

Fig. 4.9 Direct aspiration method (modified Penumbra method): The technique eliminates the need to cross the clot with the micro-wire, which may lead to perforation (as in **a**), in (**b**) and (**c**), the aspiration distal large bore catheter is advanced into the face of clot over the J micro-wire (**b**), and barely embedded into the proximal part of the clot (**c**). *AJNR Am J Neuroradiol*. 2014 Dec;35(12):2354–9. © by American Society of Neuroradiology

the mortality rate was significantly higher in the fibrinolysis group (25 % versus 68 %, $p=0.001$).

Other single arm studies using the direct aspiration technique reported successful recanalization rates (mTICI ≥ 2b) of 59–78 % in all vascular territories, with good clinical outcomes (mRS 0–2 at 90 days) of 40–46 % [28, 29]. This is a promising simple new technique, with preliminary data reporting high successful recanalization rates, and one of the shortest reported recanalization times. However, due to the variability of self-reported data, prospective independently adjudicated data on direct aspiration are needed. Figure 4.9 demonstrated the direct aspiration technique.

Retrievable Stents

The goal of stent deployment in AIS treatment is to entrap a thrombus between the stent and the vessel wall, providing fast recanalization and restoration of antegrade blood flow [31, 32]. However, the complicated post acute stent medical management with required anticoagulation and antiplatelet therapy made its use unfeasible. The stent retriever (SR) technology helped to resolve this issue, because the stent is retrieved and not permanently implanted in the body [33–37]. When the stent is retrieved, the clot is trapped within the stent struts and recanalization ensues. Withdrawing an open stent across the vessel wall into the base guiding catheter, or LBDC has been shown to be effective in achieving rapid recanalization without pathological evidence of vessel damage in animal models [33]. Stent retrievers are self-expanding stents and deployed by unsheathing the small open cell mesh stent attached to a microwire from the housing microcatheter. Once deployed, flow is typically restored and the device is left in place up to 10 min to allow engagement of the thrombus into the stent struts. Once the clot is fully engaged, the SR can then be retrieved with the clot trapped within it, into a proximally placed catheter. To reduce the risk of clot fragmentation and embolization during extraction, a proximal balloon guiding catheter is inflated to occlude antegrade flow while retrieving and aspiration from the side of the guide catheter [38].

The Solitaire device was the first self-expanding stent retriever that was initially designed for stent-assisted coiling of cerebral artery aneurysm (Fig. 4.10).

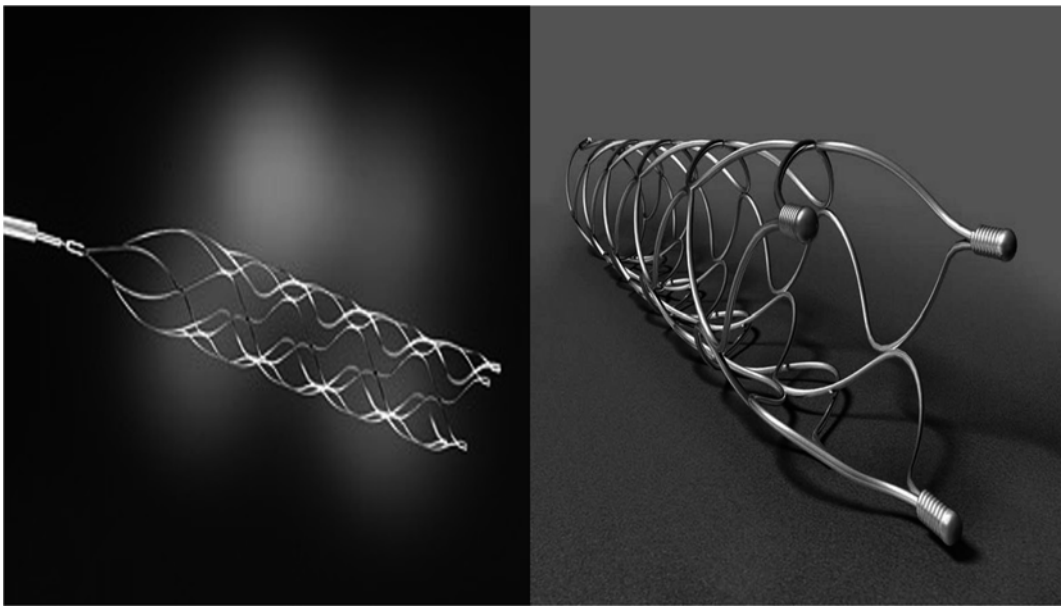

Fig. 4.10 Solitaire stent retriever device

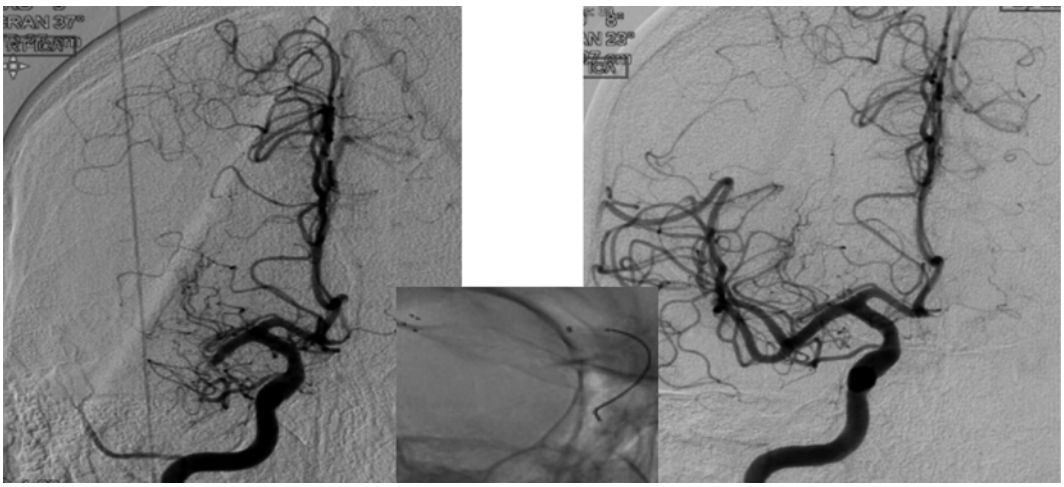

Fig. 4.11 A case example of successful use Solitaire device in right MCA occlusion

Solitaire was used and reported as a mechanical thrombectomy method in pilot studies and earned FDA approval in 2012 after a successful phase two study was reported [35]. The FDA approved this device for AIS patients presenting within 8 h of stroke symptoms who were ineligible for IV-rtPA or who had failed to achieve recanalization with IV-rtPA based on the results of the Solitaire flow restoration device versus the Merci Retriever in patients with acute ischemic stroke (SWIFT) trial [35]. The SWIFT trial randomized 113 stroke patients to either the Solitaire device or the MERCI Retriever device within 8 h of stroke symptoms. The trial was stopped due to the overwhelming positive results in favor of the Solitaire group. The Solitaire group achieved statistically higher rate of successful cerebral recanalization (61 % vs 24 %, p-value = 0.001) without sICH, improved global neurological disability outcomes (58 % vs 33 %, p-value = 0.02), and reduced mortality than the MERCI group (17 % vs 38 %, p-value = 0.02). Figure 4.11 presents an illustrative case of use of Solitaire stent retriever [39].

The second stent retriever, approved first in Europe in 2010, was the TREVO® Retriever. In the USA, the FDA approved it in 2012 based on the results of the Thrombectomy Revascularization of large Vessel Occlusions (TREVO 2) trial [36]. The trial was designed to investigate the safety and efficacy of the TREVO device compared to the MERCI device for removing clots from ischemic stroke patients

within 8 h of symptoms onset. One hundred seventy-eight patients who presented with large vessel occlusions with moderate to severe strokes (NIHSS 8–29) were randomly assigned 1:1 into each arm. The rate of successful recanalization (mTICI ≥ 2) was achieved in 86 % in the TREVO group compared to 60 % in the MERCI group [36].

Intra-arterial Therapy Clinical Trials

The IAT clinical trials have seen a bimodal evolution overtime (Fig. 4.1) from randomized trials looking at chemical IA lysis to single arm prospective mechanical thrombectomy device studies to again randomized clinical trials of mechanical thrombectomy versus standard of care (Table 4.4). The last few years have seen several randomized clinical trials comparing IA therapy plus standard of care versus standard of care alone, with differences in design, patient selection and devices [25, 40–47]. The IMS III was discussed above in the combined IV/IA section of the chapter, and no benefit of IA therapy (mRS 0–2 was seen in IV/IA in 40.8 % versus 38.7 % in the IV only group), similarly no difference was noted in the MR Rescue and Synthesis trials [25, 40, 41]. However, the design (for example not documenting large vessel occlusion prior to IAT, or strict time to groin puncture) and the use of older-generation thrombectomy devices (IA chemical lysis only or MERCI device) may have led to these negative results. Incorporating the newer-generation devices (mainly stent retrievers) and patient selection requiring large vessel occlusion on triage CT angiogram of AIS may have led to the positive results of the MR CLEAN trial [9].

MR Clean trial randomized patients with AIS with NIHSS of 2 or higher and documented large vessel occlusion and failed IV therapy to either standard of care only or added IAT [9]. In the IAT arm, the groin puncture had to start within 6 h of symptoms onset. Greater than 92 % of patients were treated with stent retrievers. The results demonstrated positive results in favor of IAT over medical therapy when administered to patients with within 6 h of symptom onset when comparing 0–1, 0–2, and 0–3 mRS at 90 days between the two groups with ORs of 2.06, 2.05, and 1.89, respectively (Fig. 4.12) [9].

The endovascular group was also associated with significantly lower final NIHSS and smaller infarcted brain tissue (Infarct size: 49 ml endovascular vs 80 ml medical therapy) [9].

Following the positive results from MR CLEAN, two similar trials for endovascular therapy ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke) and EXTEND IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial) have been stopped early for efficacy [43, 44]. In light of these preliminary reports at the time of this writing, the data safety monitoring boards of several ongoing randomized clinical trials comparing the IAT added to standard of care versus standard of care alone (SWIFT PRIME, THERAPY, and REVASCAT trials [45–47]) have recommended suspending enrollment and completion of an early interim analysis.

Since the presentation and publication of the MR CLEAN data; a meta-analysis was performed of the IAT randomized trials using a weighted fixed-effect model to compare the good functional clinical outcome (mRS 0–2) at 90 days between the treatment groups. This analysis showed favorable outcome in patients treated IAT compared to the standard of care as demonstrated in the Forest plot (Fig. 4.13) [42].

Similar to the Forest plot analysis; when comparing the mRS scale, including all the IAT patients enrolled in these 6 trials versus their control groups, there is a clear difference in clinical outcome favoring the IAT group over the control group as depicted in Fig. 4.14.

The positive results for MR CLEAN, ESCAPE, and EXTEND IA suggest that we are moving forward in our IA management of AIS. It is as important to advance our medical practice to develop faster and more reliable ways to improve stroke systems of care, such that eligible AIS patients are treated at the right centers with well established infrastructure and personnel. Moreover, establishing protocols and pathways to guide optimal patient selection, appropriate acute imaging triage modalities, and timely transfer protocols are keys for successful IAT.

Patient Selection for Endovascular Therapy

Although the last few years have witnessed a significant advancement in new recanalization techniques enabling safer, reliable, and faster recanalization, uncertainty still looms over the question of patient selection for endovascular stroke therapy. This may change as new data from the positive trials become available. However, one may deduce several concepts that have repeatedly been demonstrated in stroke trials:

First the best imaging approach to selecting patients for IAT may be plain CT scan of the head and CT angiogram showing large vessel occlusion, as performed in the MR CLEAN protocol. There is no randomized trial data to support more complex perfusion imaging for patient selection at this time. However, there have been two completed trials so far. MRI profile and response to endovascular reperfusion after stroke (DEFUSE-2) study was a multicenter study in which a prospective cohort of patients were selected for endovascular therapy utilizing an automated mismatch analysis program (using a T-max threshold of >6 s identified patients with a target mismatch on MRI) (DWI:PWI ratio of at least 1:1.8) [48]. DEFUSE-2 showed that patients who achieved early reperfusion had less infarct growth and more favorable clinical functional outcomes versus patients without a target [48]. The positive association between reperfusion, favorable clinical response, and attenuation of infarct growth did not diminish as time from onset to therapy progressed [48]. However, MR RESCUE, an IAT study that also used penumbral imaging,

Table 4.4 Summary of the intra-arterial therapy studies

Trial name	Year published	IAT patients enrolled	NIHSS median	Time to treat (h)	Recanalization rate (%)	Good outcome %	Mortality (%)	SICH%
Randomized controlled studies								
PROACT II	1999	121		0–6		40	25	10
MELT	2007	57		0–6		49	5	2
IMS III	2013	415		0–3		41	20	6
SYNTHESIS	2013	181		0–6		42	14	6
MR RESCUE	2013	64		0–8		19	19	4.7
MR CLEAN	2014	233		0–6		33	21	
ESCAPE	2015	316		0–12		53	10	3.6
EXTEND-IA	2015	70		0–4.5		71		0
SWIFT PRIME	2015	191		0–4.5		60	9.2	1
Prospective studies								
MERCI	2005	151	19	0–8	TIMI ≥ 2: 48 TIMI 3: 24	28	44	8
MULTI MERCI	2008	131	19	0–8	TIMI ≥ 2: 57	36	34	10
PENUMBRA PIVOTAL	2009	125	18	0–8	TIMI ≥ 2: 82 TIMI 3:27	25	33	11
SWIFT	2012	58	18	0–8	TIMI ≥ 2: 83+ TICI ≥ 2a: 78 TICI ≥ 2b: 76	58	17	2
TREVO II	2012	88	18	0–8	TICI ≥ 2a: 86 TICI ≥ 2b: 68	40	33	7
TREVO EU	2013	60	18	0–8	TICI ≥ 2a: 92 TICI ≥ 2b: 78	55	20	5
START trial	2012	77	19	0–8	TIMI ≥ 2:85	48	28	5
ADAPT, FAST study	2014	98	17	0–8	TICI ≥ 2b: 78	40	20	0
TOTAL	N/A	788	18	time 0–8		41 %	29 %	6 %
Retrospective studies								
NASA	2014	354		Real life practice (any time)	†TIMI ≥ 2: 83 mTICI ≥ 2a: 88	42	30	10
STAR	2013	202			TICI ≥ 2a: 89 ‡TICI ≥ 2b: 79	58	7	1.5
TRACK	2014	93			TICI ≥ 2a 86 TICI ≥ 2b 66	43	21	8
Retrospective Multicenter of Solitaire FR	2012	141			mTICI ≥ 2b: 85	55	20	4
The POST trial	2010	157			TIMI ≥ 2: 87	41	20	6

All Numbers are rounded to the nearest whole number
– Good neurologic outcome is defined as mRS of ≤2 at 90 days
+69 % determined by core lab, 83 % was determined on-site
ESCAPE trial: The endovascular arm was associated with reduced mortality (10.4 % vs. 19 % in the control)
EXTEND-IA was stopped early after 70 patients had been enrolled because of significant benefit in the endovascular arm

did not validate the findings from DEFUSE-2 (MR Rescue used different thresholds for Tax and allowed both CT and MR perfusion). Randomized trials incorporating the use of perfusion imaging-based selection of patients are still needed.

Second, time from onset to recanalization must be as fast as possible. A 30 min delay to recanalization was associated with a 10–20 % reduction in the number of patients achieving a good clinical outcome at 3 months [49].

Third, successful recanalization, achieving higher grade of revascularization within the shortest duration with no sICH is becoming the target of AIS endovascular therapy. The data from IMS III showed better outcome with higher degree of recanalization (TICI 3 versus TICI 2b or TICI 2a), consistent with data from other studies [1, 2, 25]. Hence, the future goal of recanalization may be moved to newer target such as the rate of TICI 3 versus TICI 2b.

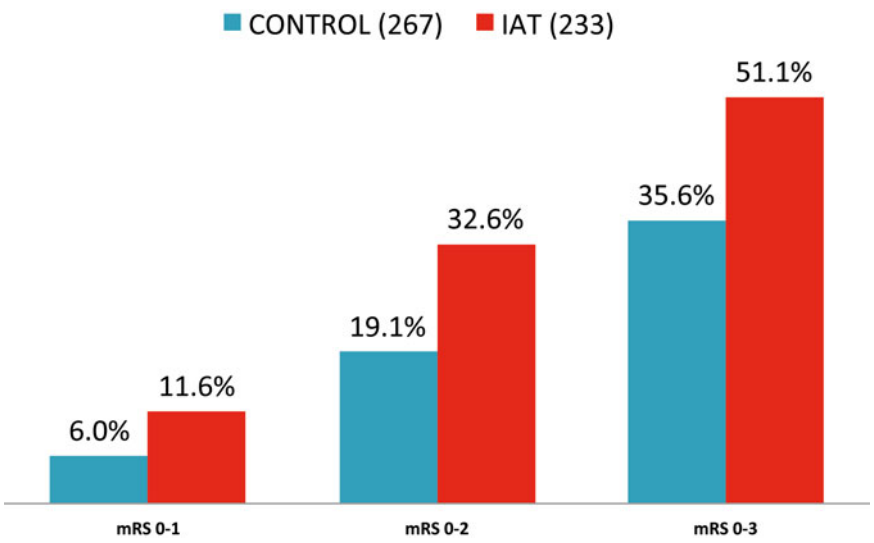

Fig. 4.12 mRS in MR CLEAN trial comparing mRS 0–1, 0–2, and 0–3 between the groups showing significantly better outcome with IAT than standard of care with OR of 2.06, 2.05, and 1.89, respectively

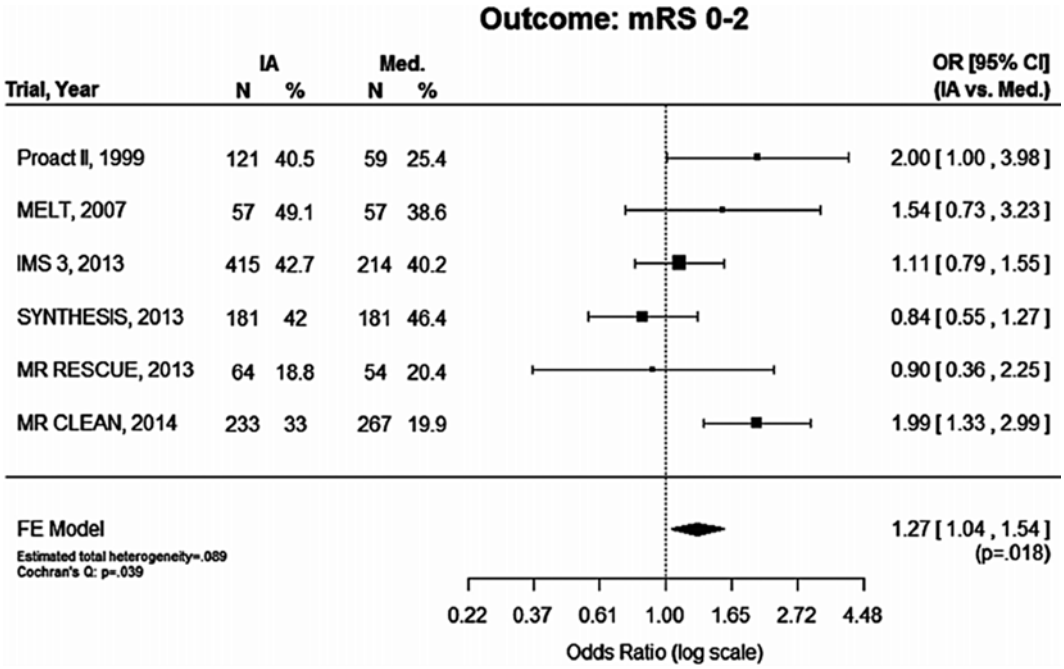

Fig. 4.13 Meta-analysis using weighted fixed-effect model of the randomized clinical trial in intra-arterial therapy (IAT) of acute ischemic stroke. The meta-analysis demonstrated favorable overall outcome of the IAT. Reproduced from Journal of NeuroInterventional Surgery, A meta-analysis of prospective randomized controlled trials evaluating endovascular therapies for acute ischemic stroke Kyle M Fargen, Dan Neal, David J Fiorella, Aquilla S Turk, Michael Froehler, J Mocco, Nov 28, 2014 with permission from BMJ Publishing Group Ltd

Illustrative Case A 72 year old right handed man with history of hypertension who presented with sudden onset of right hemiplegia and aphasia with an initial NIHSS of 18. Time from symptom onset to presentation to an outside hospital was 4 h. Initial blood pressure was 170/90 mmHg. He was started on full dose IV-rtPA (0.9/kg; 10 % as a bolus and 90 % as a continuous infusion over 1 h) and transferred using flight for life directly to the CT scan in our institution. He arrived to our hospital at 5 h from symptoms onset. His initial head CT scan is shown below (Fig. 4.15) and demonstrated hyper-dense left MCA sign with clot length greater than 8 mm. His CT perfusion (standard of care at our

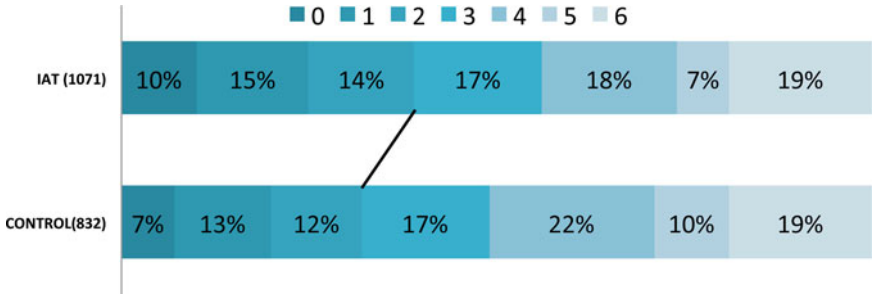

Fig. 4.14 mRS in AIS clinical trials in the active and control (PROACT II, MELT, IMS III, Synthesis, MR Rescue, MR Clean)

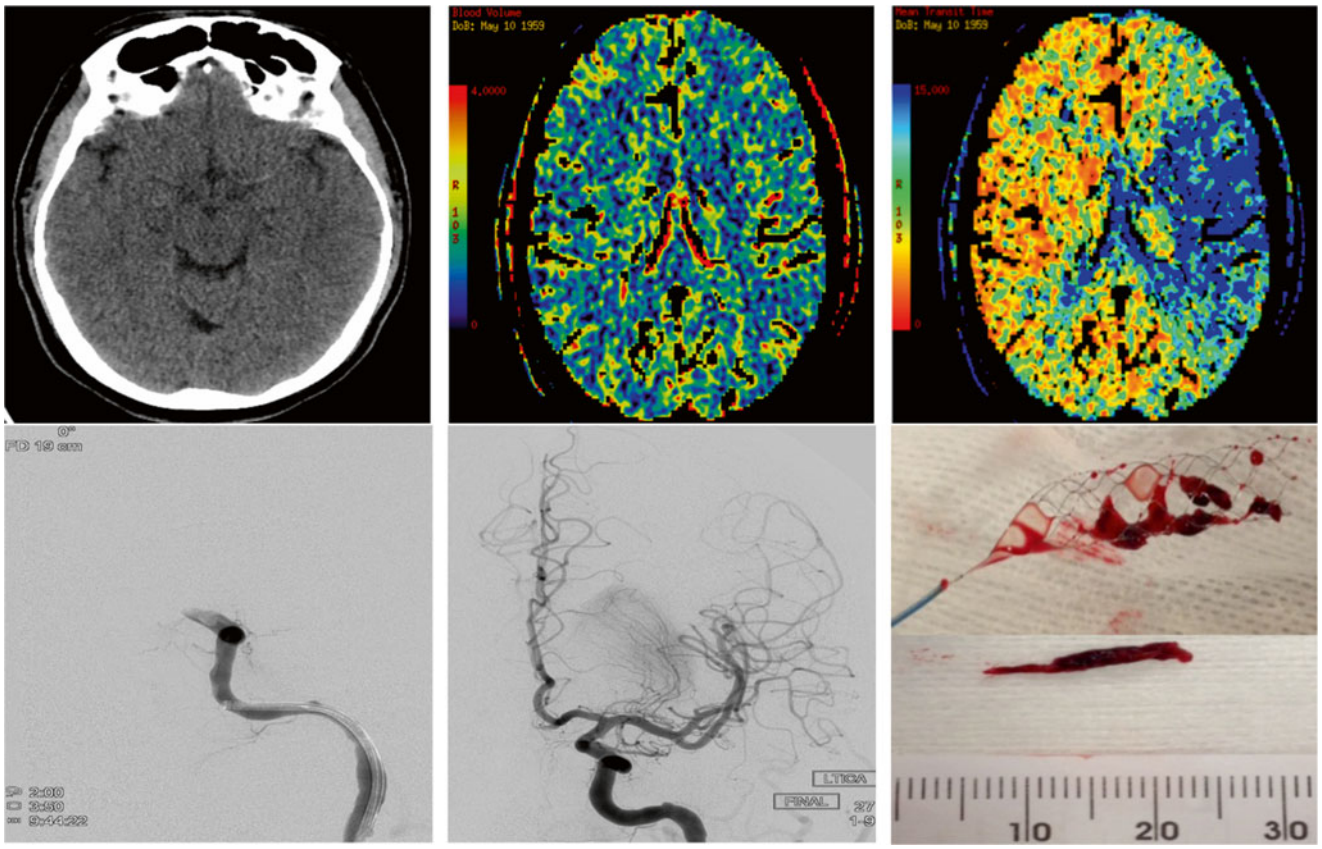

Fig. 4.15 Illustrative case of a patient presenting with left hemispheric syndrome with NIHSS of 18, without improvement with IV-rtPA. CT head showed hyperdense left MCA sign, and CT perfusion with mismatch between CBV (*middle upper panel*) and MTT maps (*right upper panel*). Angiogram demonstrated left ICA terminus occlusion (*left lower*) with complete recanalization (*lower middle*), post stent-retriever thrombectomy and clot removal (*right lower*)

institution at the time) showed significant mismatch between Cerebral Blood Volume map (CBV, middle upper) and Mean Transit Time map (MTT, right hand side). Given the clinical presentation was still consistent with large left hemispheric syndrome, CT head and CT perfusion findings, the patient was taken to the angio-suite directly from the CT scanner. Groin puncture was performed at 5 h and 45 min from symptoms onset and 45 min from repeat imaging. The angiogram AP projection image demonstrated complete ICA terminus occlusion (lower left) with complete recanalization to TICI 3 following single Solitaire stent retriever pass (lower middle), stent retriever with the clot is shown in the lower right panel. The procedure time from groin puncture to complete recanalization was 45 min. Patient was discharged home with NIHSS of 4, 3 days later with mRS of 1 at 90 days follow up.

Future Directions

Technical advances are needed to achieve a higher TICI 3 (complete recanalization) rate than the rate achieved currently, which is less than 50 % after using all devices and 25 % using the first choice device (submitted multicenter data from NASA cohort that is awaiting publication).

However, with positive randomized clinical trials in favor of IAT, future efforts will also need to focus on improving stroke systems of care at the national, regional, and local levels. The time from door to groin puncture and from groin puncture to successful recanalization may become one of the metrics for comprehensive stroke center (CSC) certification. Routing patients with severe strokes and likely large artery occlusions to CSC's (i.e., bypassing hospitals that cannot provide IAT) may become the best approach in the near future.

Final thoughts

One may conclude this chapter with few take-home points:

- IAT has been shown to be effective and superior to standard of care in selected patients with large vessel occlusion.
- Advances in IAT technology may improve on these early positive results even further.
- IAT is not widely available in many regions of the country and changes in systems of stroke care will be needed to provide IAT to patients who may benefit from treatment.

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Hemicraniectomy

5

Brian L. Hoh, Kyle M. Fargen, and Tim O'Connor

Case Presentation A male in his 50s developed sudden onset dysarthria, left facial droop, and arm weakness and presented to a local hospital. CT angiography demonstrated occlusions of the right internal carotid artery and proximal right middle cerebral artery secondary to dissection of the right internal carotid artery. Intravenous tissue plasminogen activator was administered and he was transferred to a tertiary care center. On arrival, the patient was admitted to the intensive care unit and underwent a repeat CT demonstrating a completed right MCA territory infarct. Serial CT scans revealed increasing edema with early subfalcine and uncal herniation (Fig. 5.1).

Despite maximal medical therapy, the patient progressively deteriorated to coma with a fixed and dilated right pupil. After discussion regarding the risks and benefits of surgery with his next of kin, the patient was taken to the operating room for emergent decompressive hemicraniectomy. Several hours postoperatively, the patient was able to follow commands again on the right side. In less than 2 weeks the patient was discharged to an inpatient rehab facility. On follow up evaluation 3 months later, the patient had persistent left face and arm weakness but was ambulating with minimal assistance. He underwent cranioplasty several weeks later. At final follow-up, the patient required assistance with some activities of daily living but he and his family were grateful he had undergone life-saving craniectomy.

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Introduction

The management of acute ischemic stroke (AIS) has evolved significantly over the last several decades, but the devastating consequences of space-occupying hemispheric infarcts present a unique set of challenges. Standard medical therapies such as blood pressure control, barbiturates, hyperventilation, and osmotherapy have been unable to reduce either mortality or disability in intensive care based trials [1–4], and studies suggest that some of these treatments may ultimately reduce survival [3].

As a result of these limitations, decompressive craniectomy (DC) has remained a commonly performed surgical treatment for malignant middle cerebral artery (MCA) and cerebellar strokes. The goal of early surgical intervention is to decompress the affected area and preserve perfusion to viable tissue. Although the core of infarcted tissue is irreversibly damaged, the penumbra around the core can be salvaged by reducing the pressure caused by space-occupying lesions and restoring cerebral blood flow. Furthermore, this procedure may prevent transtentorial herniation leading to irreversible brainstem injury or death. Multicenter randomized controlled trials demonstrate that surgical decompression can improve both survival and functional outcome in patients with early intervention, and follow-up studies document that the majority of patients and their families would choose to undergo the operation again if given a second chance [5–7].

Pathophysiology

Acute occlusion of the internal carotid artery or proximal MCA may result in a large supratentorial infarct encompassing the ipsilateral MCA territory, including portions of the frontal, temporal and parietal lobe. Such infarcts can result in a syndrome of lethal edema and herniation known as a malignant MCA infarct. Within minutes of acute ischemic injury, a decrease in oxygen and glucose causes failure of

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sodium–potassium ATPase, resulting in loss of the membrane potential and dissipation of ionic gradients. The subsequent rise of intracellular sodium ultimately induces cell death and cytotoxic edema. It has been estimated that approximately 1.9 million neurons die during each minute of ischemia [8]. Vasogenic edema then results from disruption of the blood–brain barrier and an increase in hydrostatic and osmotic pressure [9].

Both cytotoxic and vasogenic edema contribute to an increase in intracranial pressure (ICP) following AIS. Although the brain possesses a remarkable ability to maintain blood flow over a broad range of cerebral perfusion pressures, cerebral autoregulation is limited to ranges between 50 and 150 mmHg. Because cerebral perfusion pressure (CPP) is defined as the mean arterial pressure (MAP) minus the intracranial pressure (CPP = MAP − ICP), an increase in ICP from edema eventually reduces perfusion outside the range of autoregulation. In addition, a space-occupying lesion can increase the pressure gradient between the infratentorial and supratentorial compartment, leading to subfalcine and/or transtentorial herniation and a reduction in level of consciousness [10–14].

Malignant MCA infarction is characterized by a continuing cycle of cell death and edema through elevated ICP and diminished CPP. As time progresses and ICP rises, reduction in CPP leads to further cell death and secondary edema, resulting in further elevations in ICP and reduction in CPP. This cycle continues until herniation occurs, resulting in death. The goal of DC in malignant MCA stroke is to decrease intracranial pressure by allowing external expansion of edematous brain tissue into a compensatory space, to reduce the presence of herniation and brainstem compression, and to restore cerebral blood flow [14, 15].

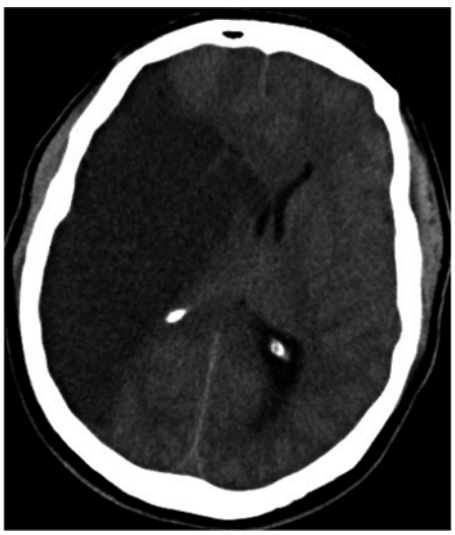

Fig. 5.1 CT of the brain demonstrating significant mass effect and right-to-left midline shift from a completed right middle cerebral artery territory infarct

Clinical Presentation

Malignant MCA strokes occur in up to 10 % of patients with a supratentorial infarct and carry a mortality reaching 80 % in patients treated with standard medical therapy [16]. Patients with malignant MCA strokes present with features consistent with severe hemispheric infarct and space occupying edema that generally manifest between the second and fifth day following ischemic insult (Fig. 5.2) [4, 11, 12, 17–19].

Patients may initially present with reduced level of consciousness and undergo neurological deterioration over the next 1–2 days, often requiring mechanical ventilation

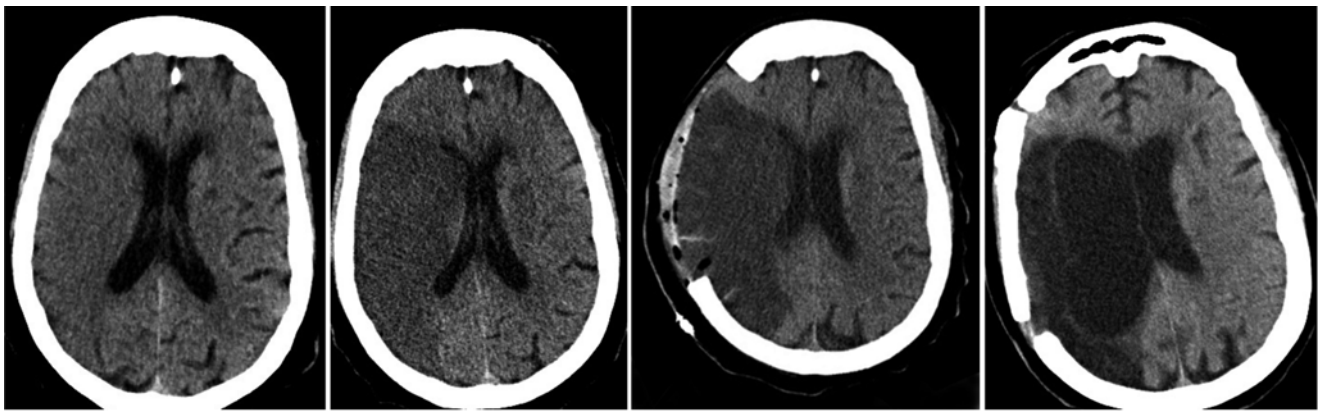

Fig. 5.2 A 63-year-old female presented with sudden onset left hemiparesis and neglect. Noncontrast CT of the head at presentation (*first panel*) and at 24 h (*second panel*) demonstrate the evolution of her right MCA infarct. Noncontrast CT of the head after early hemicraniectomy (*third panel*) and after bone flap replacement 3 months later (*fourth panel*)

secondary to diminished respiratory drive [1, 13, 18]. Other signs and symptoms can include headache, vomiting, pupil asymmetry, papilledema, gaze deviation, dense hemiparesis, and global aphasia. Although the National Institutes of Health Stroke Scale (NIHSS) is generally greater than 15 in these patients, the NIHSS may underestimate the severity of deficit in non-dominant hemisphere infarction [13, 20].

Radiologic Findings

Accumulating radiologic data continue to provide better predictions about the evolution of malignant hemispheric infarcts, but variables such as hemorrhagic transformation, expansion of stroke volume, and spontaneous recannalization of occluded vessels make it difficult to reliably predict malignant MCA infarcts [14, 21]. Images that demonstrate greater than 50 % infarction of MCA territory on CT scan within 18 h have a sensitivity of 58 % and specificity of 94 % for the development of malignant MCA infarcts [22], and infarcts greater than 66 % of MCA territory within the same time span yield a sensitivity of 45 % and a specificity of 100 % [22].

Although CT scans can predict malignant infarcts with a high degree of specificity, their low sensitivity may not reveal patients that are at risk for a malignant MCA stroke. A study by Oppenheim demonstrated that when the initial infarct volume assessed by MRI was greater than 145 cm^3 within 14 h, sensitivity was 100 % and specificity was 94 % [23]. As a result, the National Institute for Health and Clinical Excellence created criteria for consideration of hemicraniectomy that included CT evidence of an infarct greater than 50 % of the MCA territory or infarct volume greater than 145 cm^3 on MRI [24].

Surgical Timing

Patients generally demonstrate improved outcomes when they undergo early surgical decompression before or soon after the development of neurological signs such as pupil asymmetry and/or impaired levels of consciousness. One-third of patients show neurological deterioration 24 h after onset of acute infarct, another third of patients within 24–48 h, and the majority of patients will demonstrate deterioration within 1 week following stroke [21]. Randomized controlled trials suggest that DC is able to reduce mortality and increase functional outcome within 48 h of malignant MCA infarct [4, 15, 25, 26], however more data is needed to determine the efficacy of DC after that time. These findings demonstrate that the timing of DC has a role in influencing outcome. Although data is emerging to allow prediction of malignant MCA infarct with greater accuracy, a combination of neurological signs, radiological findings, and clinical judgment are needed to determine the necessity and timing of decompression.

Surgical Technique of Hemicraniectomy

Decompressive hemicraniectomy was first described by Cushing in 1905 and used in the setting of AIS in 1956 [27, 28]. Surgical decompression allows the infarcted edematous tissue to swell outside the confines of the cranial vault in order to reduce external forces on the brain and decrease ICP. Under general anesthesia, a reverse question mark incision is fashioned and a craniectomy flap at least 12 cm is turned [1, 3, 14]. The dura is then opened widely. Removal of infarcted tissue for internal decompression is controversial due to the possibility of disrupting salvageable tissue around the area [1, 4, 15, 29–31]. However, depending on the degree of swelling, removal of some infarcted tissue may be necessary for adequate decompression. It is not uncommon for the brain to slowly expand out of the dural defect during surgery, which may make skin closure difficult.

Control of carbon dioxide levels using hyperventilation, with a goal pC02 of 30–32, as well as hyperosmolar therapy during surgery, may reduce cerebral herniation through the dural opening during surgery. After completion of the decompression, hemostasis is obtained to prevent postoperative epidural hematoma formation, a surgical drain is often left in place, and the temporalis muscle and skin flap are reapproximated. The bone flap is stored in a tissue bank or in a subcutaneous pocket fashioned in the patient's abdomen.

Post-operative care after DC requires the use of a helmet when the patient is upright or out of bed. This may prevent injury to the exposed brain during falls, a high-risk event due to patient hemiparesis and/or neglect. Based on the degree of functional recovery and patient or family wishes, a cranioplasty may be performed in a delayed fashion. The preserved bone flap is replaced to both restore the normal cranial vault for protective purposes as well as for cosmesis. Bone flap replacement is often performed 6 weeks to 3 months after DC. The risks and benefits of bone flap replacement should be considered strongly in disabled patients as this procedure is associated with complication rates approaching 25 % [32].

Complications

There are limited studies evaluating the complications of decompressive hemicraniectomy, though life-threatening complications are generally uncommon. Along with the expected risk of bleeding and infection following any surgical procedure, hydrocephalus and subdural or epidural

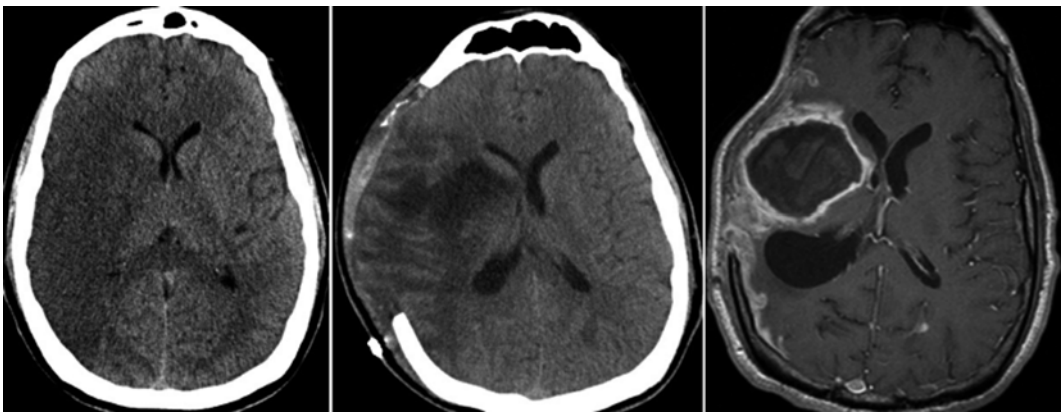

Fig. 5.3 A 48-year-old man presented with a right MCA stroke secondary to enterococcus bacterial endocarditis. Noncontrast CT demonstrating a large right MCA territory infarct was seen at presentation (*left panel*). Noncontrast CT performed after the patient underwent early hemicraniectomy (*center panel*). T1 post-gadolinium MRI demonstrates the persistent hypodensity seen in the center panel evolved into a large enterococcal brain abscess, necessitating evacuation (*right panel*)

hematomas may occur. Sinking skin flap syndrome can occur in a delayed fashion in which midline shift to the contralateral side results in neurological symptoms including seizures, focal deficits, and paradoxical herniation [33–35]. This syndrome may be related to unopposed atmospheric pressure effects upon the skin and underlying brain once the swelling of infarcted tissue diminishes and may be worsened by cerebrospinal fluid diversion. Brain abscess following infarcts related to endocarditis may also be seen (Fig. 5.3). Additionally, bone flap necrosis following reinsertion of the autologous bone graft can appear in over 20 % of patients and may present a challenge during long-term follow-up [36].

A more likely complication arises when the craniectomy is not large enough to allow adequate expansion of edematous tissue, and as a result induces sheer stress at the margins of the bone flap and secondary venous insufficiency [37]. If compression of the swollen brain continues, herniation can occur adjacent to the bone margin. The diameter of the craniectomy should therefore provide adequate space to allow decompression of the infarcted area. Based on the observation that malignant MCA infarcts require an additional volume of at least 80 mL, studies suggest that the craniectomy should be at least 12 cm in diameter to allow sufficient expansion [20, 38].

Outcomes of Decompressive Hemicraniectomy

There are multiple international randomized controlled trials evaluating the outcomes of DC in the setting of space-occupying malignant infarction. Three European randomized control trials, the Dutch HAMLET trial, the German DESTINY trial, and the French DECIMAL trial, compared hemicraniectomy to standard medical treatment [4, 15, 26, 38]. All three were stopped prematurely due to a significant decrease in mortality with DC. HAMLET, DESTINY, and DECIMAL all examined functional outcome as a primary outcome and mortality as a secondary outcome measure due to the emphasis on quality of life following malignant hemispheric infarction.

These trials included a total of 93 patients with an NIHSS of at least 16 and an impaired level of consciousness following a significant MCA stroke. Although they enrolled similar ages, there were slight differences among the three. DESTINY and HAMLET included patients between 18 and 60 years of age, while DECIMAL enrolled patients between 18 and 55 years old. There were also variations in the time to decompression following stroke onset. DECIMAL enrolled patients within 24 h of malignant MCA infarction and performed DC no later than 6 h after randomization. DESTINY mandated that DC be performed within 36 h from the onset of symptoms, and HAMLET enrolled patients that had evidence of space-occupying edema within 96 h of stroke onset.

The modified Rankin Scale (mRS) was used to assess functional outcome after stroke in all three trials (Table 5.1) [39]. The scale ranges from 0 to 6, with a score of 0 representing no symptoms and a score of 6 indicating death. For the purposes of statistical analysis, there is often a distinction made between moderate disability (mRS of 3) and moderately severe disability (mRS of 4) in clinical studies. The European trials initially defined a mRS score ≤ 3 as "favorable", but post-hoc analysis also provided results between groups 0–4 and 5–6. In addition, the pooled analysis of the three trials defined a "favorable" outcome as a mRS ≤ 4.

Table 5.1 Modified Rankin Scale (mRS) [39]

0	No symptoms	
1	No significant disability	The patient has some symptoms but is able to carry out all activities
2	Slight disability	The patient can attend to their own affairs, but they cannot carry out all previous activities
3	Moderate disability	The patient requires some help, but is able to walk unassisted
4	Moderately severe disability	The patient cannot walk unassisted nor can they attend to their own bodily needs without assistance.
5	Severe disability	The patient is bedridden, incontinent, and requires constant nursing care and attention.
6	Death	

The DESTINY trial reported that 47 % of patients receiving surgical treatment and 27 % of patients receiving medical treatment had favorable outcomes (mRS ≤ 3), although the difference was not statistically significant. When the authors included patients with moderately severe disability in the favorable group (mRS ≤ 4), there was a significant difference between surgical and medical therapy (77–33 %).

The DECIMAL trial reported that 50 % of surgical patients and 22 % of medical patients had favorable outcomes (mRS ≤ 3), and a statistically significant difference arose in favorable outcomes when dividing functional outcome between a mRS score of 0–4 and 5–6 (75 % in the surgical group versus 22 % in the medical group). In the HAMLET study, surgery had no effect on functional outcome before the study was stopped, although there was an increase in survival rate in the surgical treatment group.

In the combined analysis of the European studies [25], patients undergoing decompressive hemicraniectomy had an overall greater functional outcome when compared to medical therapy (43.1 % versus 21.4 % with a mRS ≤ 3, 74.5 % versus 23.8 % with a mRS ≤ 4). There was also no significant increase of severely disabled patients in the group undergoing surgical intervention (4 % in the surgical group versus 5 % in the medical group). To achieve survival with a mRS score of less than or equal to 3, the number needed to treat was four. To achieve survival with a mRS score less than or equal to 4, the number needed to treat was two.

The DESTINY, DECIMAL, and HAMLET trials all showed a significant increase in survival both 6 and 12 months after surgery, and the pooled analysis reported a significantly increased survival of 71 % in hemicraniectomy patients compared to 22 % in patients receiving best medical therapy at 12 months. The number needed to treat to increase survival was two.

Although DC significantly reduces mortality and improves functional outcome without increasing the proportion of patients that are severely disabled, the number of patients after DC that have moderate disability is doubled and the number of patients with moderately severe disability is tripled. Recovery may also be complicated by depression and additional interventions such as cranioplasty and shunt implantation [7]. These risks can make it difficult for the clinician to determine which patients are appropriate candidates for DC without taking into account social support, expected prognosis, and ultimately the wishes of the patient and their family regarding what is deemed an acceptable quality of life.

Several studies have investigated whether patients continue to support the decision to undergo DC after their operation. Most patients and their caretakers agreed with the decision to perform DC and would support the decision again if given a second chance [5]. Patient satisfaction is between 80 and 90 %, and 95 % of caregivers retrospectively supported the decision to undergo DC [6, 7]. Although many of these surveys suffer from small sample size and the inherent biases of retrospective studies, they suggest support for DC in the setting of malignant MCA infarcts and may guide clinicians when deciding to pursue surgical intervention.

Factors to Consider Before Hemicraniectomy

Although there is strong evidence supporting DC in middle-aged adults, there are less supporting data for the use of surgical intervention in patients younger than 18 years or older than 60. Smaller studies have suggested that elderly patients might have poorer outcomes following decompression [40, 41]; however, a randomized controlled trial ($n=47$) documented that there was no difference in mortality or functional outcome in elderly patients compared to their younger counterparts [42]. This trial reported that patients up to 80 years old receiving DC had a significantly better functional outcome (31.2 % in the surgical group versus 92.3 % in the medical group had a mRS score between 0 and 4) and survival (81.2 % in the surgical group and 30.8 % in the medical group survived by 12 months) compared to standard medical therapy. Additionally, the Destiny II randomized controlled trial recently released their findings from 112 patients demonstrating that patients 61 years of age or older had increased survival without severe disability following hemicraniectomy, providing the strongest evidence to date of the efficacy of surgical intervention in this age group [43].

Theoretically, younger patients are more at risk from space-occupying hemispheric infarcts because they lack the

atrophy of older patients and as a result have less potential space for the brain to expand. A review of the pediatric literature revealed that young patients respond as well to surgical decompression as older adults, and in addition are able to receive a therapeutic benefit even after the onset of herniation and the involvement of multiple vascular territories [44].

Patients with devastating hemispheric infarcts or multiple comorbidities such as coronary artery disease and liver failure may be suboptimal patients for DC. A study by Slezins et al. found that all patients with cerebral infarct volume greater than 390 cm^3 expired regardless of management, and as a result these patients may not be good candidates for decompressive surgery [16].

The role of DC in patients with dominant versus non-dominant hemisphere infarcts is controversial. Although dominant strokes can cause global aphasia and hemiplegia, there is often a significant improvement in language following the initial recovery [6, 45, 46]. On the other hand, non-dominant strokes can result in debilitating and often lasting hemispatial neglect. Clinicians have traditionally formed opinions on which hemisphere offers a more favorable prognosis by relying on their clinical background and personal experience managing these patients, but a growing body of literature is beginning to objectively assess the implications of dominant and non-dominant malignant space-occupying infarcts.

One study reported there was no difference in functional outcome between right and left hemispheric stokes using the Barthel index and Glasgow Outcome Scale in malignant MCA strokes [47], and other trials have replicated these findings using the mRS and Beck Depression Inventory [7]. Reports confirm that patients with a left-sided stroke often have greater difficulties with language, but multiple studies have demonstrated there are no other significant differences in functional outcome, patient satisfaction, and quality of life between the two groups [7]. Recently, a retrospective review documented that there was no difference in 30-day mortality between dominant and non-dominant malignant MCA infarcts, and clinical outcomes at 6 months were the same [48]. In addition, the majority of patients and caregivers supported the decision to undergo DC irrespective of the side of the infarct [7].

Although more data is needed, accumulating evidence is suggesting that the side of the infarct may not be a useful prognostic indicator for mortality and overall functional outcome in malignant MCA strokes.

Current Recommendations

The 2013 American Heart Association and American Stroke Association guidelines for the early management of patients with acute ischemic stroke recommend that stroke patients should be closely monitored for neurological deterioration, undergo measures to reduce edema, and be transported to a hospital facility with neurosurgical services [49]. These recommendations are Class 1, Level A evidence, indicating a strong benefit-to-risk profile as a result of high-quality data derived from multiple randomized control trials. Decompressive hemicraniectomy for cerebral edema is currently recommended as Class 1, Level B evidence, indicating the recommendation was based on data derived from nonrandomized studies or a single randomized control trial. Decompressive hemicraniectomy is considered potentially life-saving, though factors such as patient age and comorbidities may impact surgical decisions [49].

The utility of aggressive medical intervention for patients with cerebral infarct and edema has not been fully established. Standard medical interventions are recommended as Class IIb, Level C evidence, denoting that these procedures provide a benefit that is greater than or equal to the risk of the treatment itself. Corticosteroid use in this setting is considered Class III, Level A evidence and therefore not recommended, since it may increase the risk of infection without providing further benefit [49].

The National Institute for Health and Clinical Excellence has also provided a set of criteria to help identify candidates for DC [24]. These guidelines recommend that patients be less than 60 years old, exhibit clinical manifestations of an MCA infarct with an NIHSS exceeding 15, demonstrate decreased level of consciousness resulting in a score of 1 or more on the NIHSS on item 1a, and have imaging findings of an infarct at least 50 % of the MCA territory on CT or an infarct greater than 145 cm^3 on MRI [24].

Suboccipital Decompressive Craniectomy

In addition to decompressive hemicraniectomy for malignant MCA infarcts, a suboccipital craniectomy can be performed to relieve malignant posterior fossa hypertension in the setting of cerebellar infarction. Vertebral artery dissection or PICA stroke may lead to a syndrome of progressive mass effect and brainstem compression from cerebellar infarction. Swelling of the cerebellar hemispheres can cause fourth ventricular outflow obstruction resulting in obstructive hydrocephalus, as well as edema leading to transtentorial herniation through downward compression of the cerebellar tonsils into the foramen magnum or upward cerebellar transtentorial herniation. If the swelling is allowed to progress patients may develop coma, cardiorespiratory depression, and death from medullary compression.

Suboccipital decompressive craniectomy (SODC) differs from DC for malignant MCA infarcts in several important ways. First, patients with cerebellar infarcts frequently make excellent neurologic recoveries due to the inherent plasticity

of the cerebellum, unlike those with MCA cortical infarcts who may have lasting and severe deficits. Therefore patients who are candidates for SODC often have an excellent prognosis if adequate decompression can be obtained before irreversible brainstem injury occurs. Second, SODC usually involves placement of an external ventricular drain for management of hydrocephalus either before or during surgery. Third, intraoperative resection of a portion of infarcted cerebellum is commonly performed with an expansion duraplasty to allow outward expansion of edematous cerebellum. Finally, due to the thick overlying occipitocervical musculature, posterior fossa cranioplasty is rarely performed.

Chen et al. detailed a series of 11 patients with cerebellar infarctions that were unresponsive to medical therapy and underwent surgical decompression to prevent further deterioration. All patients treated by SODC survived, and 7 of 11 patients demonstrated neurological improvement within 24 h after surgical intervention [50]. Recently, Tsitsopoulos et al. reported long-term follow-up on 32 patients treated with SODC. The median GCS score was 9 before decompression and increased to 13.6 at discharge. In their study, 77 % of patients had a good outcome (mrs $\leq$ 2) at long-term follow-up (median 67.5 months), and advanced age was not associated with a bad outcome. These results suggest that SODC for cerebellar infarctions can be used effectively in both older patients and patients that are declining at the time of intervention [51].

Conclusion

Decompressive hemicraniectomy is a surgical treatment that can increase survival and functional outcome with early intervention in patients with malignant space-occupying infarcts. Ongoing studies are continuing to evaluate the effects and complications of decompression in malignant MCA stroke and cerebellar infarction, especially in the pediatric and elderly populations. Ultimately, the decision to undergo surgical intervention should include a combined approach that involves the medical team, patients, and their families.

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Supportive Care and Management of Inhospital Complications

6

Aimee M. Aysenne and S. Andrew Josephson

Case Presentation An 81 year old with a history of atrial fibrillation was found in her bed at 8:00 am after last being seen normal the night before at 10:00 pm, outside of the treatment window for IV tPA. She had an expressive aphasia and was mute but followed some simple commands. The right side was hemiparetic wfith her arm affected more than her leg. Her NIHSS score was 16. On arrival, she was afebrile. She was started on aspirin and statin for secondary stroke prevention and enoxaparin for DVT prophylaxis. Her blood pressure was permissively allowed to be elevated. Her stroke workup included a CT showing a hypodense lesion in the left middle cerebral artery territory and a CT angiogram that noted mild atherosclerotic disease with no flow limiting stenosis except a left superior M2 cutoff. Physical, occupational, and speech therapies were consulted for evaluations. Her swallowing was affected and therefore a nasogastric tube administration and was placed for medication nutrition.

On hospital day 4 she became febrile, tachycardic, and tachypneic. She had worsening of her neurologic exam and was lethargic. Her NIHSS score was 22. Blood cultures, urinalysis, and urine cultures were sent. Chest X-ray showed a right middle lobe consolidation, consistent with aspiration pneumonia. She was started on broad-spectrum antibiotics with vancomycin and piperacillin/tazobactam for aspiration pneumonia and acetaminophen for fever control. She required a cooling blanket to achieve euthermia.

She then had a prolonged hospitalization and required a percutaneous tube feeds for nutritional support. Her neurologic exam improved to an NIHSS score of 10 and modified Rankin Sore of 4 prior to discharge to an inpatient rehab facility.

General Concepts

- To understand the basic resuscitation methods used for stroke patients.
- To understand common neurologic complications of stroke and prevention strategies of secondary brain injury.
- To understand the relationship of the cardiovascular system on cerebrovascular disease.
- To understand how to safely manage common medical complications following stroke.
- To understand how to maximize prevention of serious adverse events during hospitalization of stroke patients.

Key Questions

- What is the most important feature of initial assessment of a patient presenting with an acute cerebral infarct?
- What are the most concerning neurologic complications for stroke patients and what are the basic management techniques?
- Are there any special considerations for the medical management of stroke patients while hospitalized?
- What are the most proven strategies for patient safety during hospital admission for acute ischemic stroke?

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Supportive Care Basics

Acute ischemic stroke patients often present to the emergency department. With the education of emergency providers about acute stroke treatment options and education of the general public about the signs and symptoms of stroke, more patients are presenting early in their disease process. As with any patient presenting acutely, basic emergency support should be provided as the evaluation begins. Circulation, Airway and Breathing (C-A-B) is the order in which the American Heart Association recommends for assessing every unstable patient. Circulation refers to a pulse check and blood pressure monitoring. Assessment for airway compromise is especially important for patients with decreased level of consciousness due to neurovascular injuries; some will require intubation for airway protection and aspiration prevention. Breathing includes both oxygenation and ventilation; these are usually preserved in patients with an acute stroke and normal lung function. These concepts are described in more detail in other chapters of this book. With the patient stabilized from a cardiopulmonary perspective, neurologic assessment and treatment may safely begin.

"Neuroworsening"

Patients are monitored closely for neurologic changes after stroke. Approximately one-third of patients admitted with acute ischemic strokes have a neuroworsening in the first 48 h after symptoms onset [1]. Those who have received thrombolytic or endovascular therapy and those with high likelihood of deterioration should have nursing neurologic examinations every hour, usually for at least the first 24 h. Posterior circulation strokes, particularly those affecting the brainstem, and anterior circulation strokes that involve a large volume of brain are most likely to have deterioration and therefore may require longer close monitoring.

Nurses in stroke units or neurointensive care units are trained to detect changes in the neurologic exam. Many studies have used the NIHSS exam as a monitoring tool with varying thresholds for alerting to a clinician to significant worsening [2]. In some studies, a change of greater than or equal to 2 points signifies an alert for investigation while a change of greater than 8 points signifies a major worsening [2, 3].

Stroke symptoms localize to a neurovascular territory at risk. If patients recover quickly, even if there are some small or no residual deficits (as in TIA), they remain at risk for worsening ischemia or infarction. Those that have rapid improvement of symptoms within 24 h have threefold risk of neuroworsening [4]. Improvement may correlate with vessel recanalization, and worsening with reocclusion in some cases and in others, may be dependent on the integrity of collateral circulation providing blood flow to underperfused areas [5–7].

Patients who present with more severe stroke, higher NIHSS score or those with greater than 50 % of the MCA territory infarcted tend to have a higher incidence of stroke progression [8, 9]. Major neurologic worsening has also been associated with hemorrhagic transformation or cervical artery dissection [3]. Less severe causes of worsening include petechial, or smaller, hemorrhagic transformation, cerebral edema, or a new ischemic event. Other etiologies of worsening include metabolic disturbances such as systemic infections, electrolyte changes, or glucose abnormalities. Some clinical findings that predispose patients to worsen include those who on admission have elevated blood pressures, elevated blood glucose or carotid territory involvement. Death occurs in about one third of patients who worsen during admission [1].

Cerebral Edema

Cerebral edema may occur in patients with large vessel strokes, particularly of the middle cerebral artery or carotid territory. Transtentorial herniation and progression to brain death occurs in up to 80 % of patients who experience malignant swelling. The maximum effect is between 3 and 5 days after onset of symptoms [10]. The most accurate monitoring involves serial neurologic exams; since swelling may be localized, ICP monitors may show abnormalities in a delayed fashion.

Aggressive measures should be taken to preserve neurologic function and life in the setting of malignant cerebral edema. Randomized control trials have shown both a morbidity and mortality benefit from decompressive hemicraniectomy for malignant middle cerebral artery syndromes [11], addressed in more detail in Chap. 5. See Fig. 6.1. Large cerebellar infarctions are also treated with posterior decompressive craniectomy. See Fig. 6.2. Osmolar therapies including mannitol and hypertonic saline are often used to treat cerebral edema but have limited data to support the use in stroke patients [12]. Corticosteroids are used to treat other causes of cerebral edema such as mass lesions but are contraindicated in the stroke population [13]. Mild hypothermia has a proven benefit in hypoxic ischemic encephalitis but does not have a proven benefit in stroke patients at this time; one small prospective phase 1 clinical trial reported the safety of mild hypothermia after recannulation therapy [14].

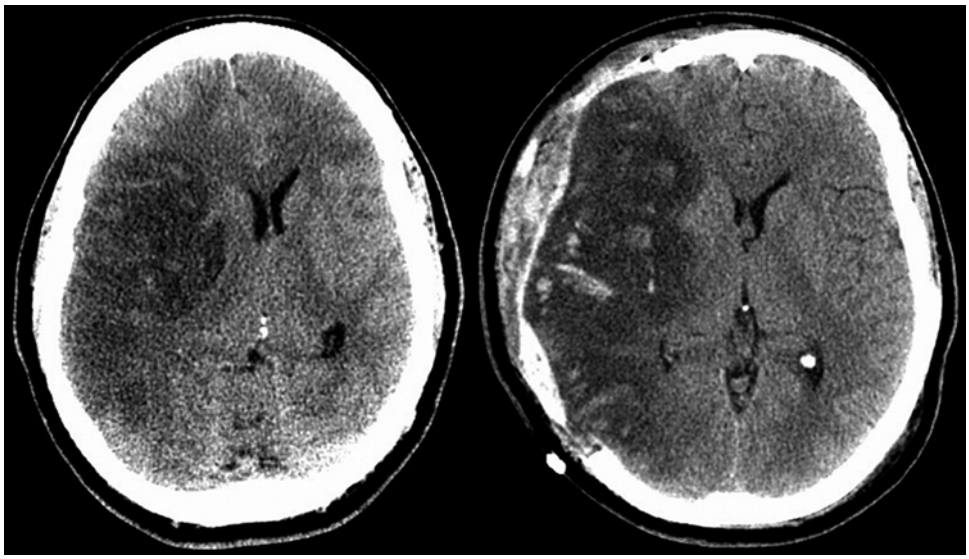

Fig. 6.1 Non-contrast CT scan of the brain showing a large right middle cerebral artery territory infarction in a 38-year-old man with atrial fibrillation both before (*left*) and after (*right*) decompressive hemicraniectomy which took place following signs of early herniation 36 h after stroke onset

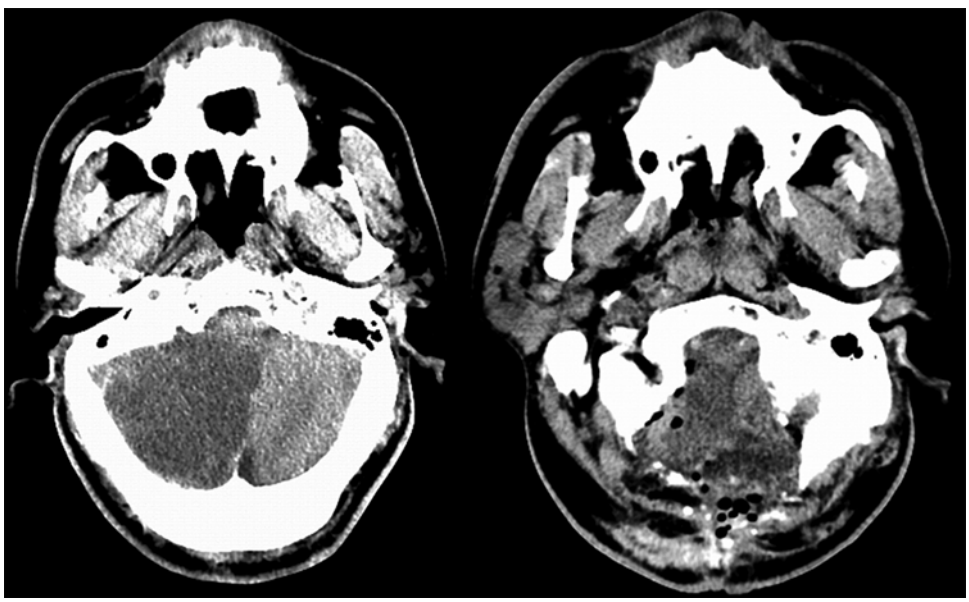

Fig. 6.2 Non-contrast CT scan of the brain showing a subacute right posterior inferior cerebellar infarction before (*left*) and after (*right*) posterior fossa decompression in the setting of increasingly depressed mental status and ventilatory failure

Reperfusion Injury and Hemorrhagic Transformation

During ischemia, the blood–brain barrier is affected and autoregulation is impaired. With its protection compromised, tissue is at risk of damage when blood flow is restored termed "reperfusion injury" [15]. Large hemorrhagic transformation is most severe and worrisome form of reperfusion injury. The most widely accepted grading system for hemorrhagic transformation is based on data from the European Cooperative Acute Stroke Study (ECASS II) [16] (See Table 6.1).

There are several clinical markers that help determine who is at higher risk of for reperfusion injury. More severe strokes with higher NIHSS scores and volume of infarct have higher rates of spontaneous hemorrhage. Patients who have

Table 6.1 Classification of hemorrhagic transformation

Classification	Definition
HT1	Small petechiae along margins of infarct
HT2	Confluent petechiae within infarct but no space-occupying lesion.
PH1	Blood clot in ≤30 % of infarcted area.
PH2	Blood clot in >30 % of infarcted area with substantial space-occupying effect.
Symptomatic ICH	If NIHSS worsened by ≥f NIHSS worse

HT = Hemorrhagic transformation, PH = parenchymal hemorrhage
Larrue et al. [16]

received intravenous tPA are three times more likely to have hemorrhagic transformation than those who have not [16]. Analyses of over 30,000 patients in the Safe Implementation of Treatments in Stroke (SITS) International Registry found nine clinical markers that increase the risk of hemorrhagic transformation and have developed a scoring system to predict this risk; the components of the score include previous use of antiplatelet medications, stroke severity, elevated glucose on arrival, elevated systolic blood pressure, weight and age [17]. It is important to note that even though these findings indicate an increased risk of hemorrhagic transformation following thrombolytic therapy, the overall functional clinical outcome is improved in greater than 30 % patients receiving tPA, and only 3 % have a worsened outcome because of the medication [18, 19].

Some of the radiographic findings that have been used to predict the risk of hemorrhagic transformation include scores measuring the volume of middle cerebral artery infarct on non-contrast head CT, a clot burden score measuring contrast opacification on CT angiography, and scores demonstrating breakdown of the blood–brain barrier on MRI [20].

Seizures and Epilepsy

Strokes are the most common cause of new onset epilepsy in the elderly population and are found in about 30 % of adult patients with first time unprovoked seizures [21]. However, seizure is still a rare complication of stroke; in one study of 675 stroke patients followed for 2 years post stroke, only 1.8 % of ischemic strokes presented with a seizure and less than 10 % had seizures in the first 5 years after stroke. As with most other complications, the likelihood of post-ischemic seizures and epilepsy is related to the size of the infarct. Most post-infarction seizures occur soon after the ischemic event, with one third occurring in the first 24 h after symptom onset; the incidence subsequently decreases with time from the infarct. Those patients with earliest seizures are also more likely to develop epilepsy [22]. Broad-spectrum antiepileptic drugs (AEDs), such as phenytoin, levetiracetam, lacosamide, or valproate, or those that treat focal onset epilepsy, such as carbamazepine or oxcarbazepine, are best for post-stroke seizures. The choice of AED is based on the comorbid factors of the patient and the side effect profile of the medications. The duration of treatment for epilepsy is dependent on a variety of factors including seizure control [23].

Prophylactic use of antiepileptic medications in ischemic stroke patients is not indicated. There is a suggestion based on animal models and observational studies that even a single dose of phenobarbital or phenytoin may slow the motor recovery if given in the first 7 days post infarct [24]. More recent animal models report a neuroprotective effect of newer antiepileptic medications, but this theory has not been tested in human subjects [25].

Psychiatric Effects

Depression

The incidence of depression is reported to be as high as 30 % of stroke survivors [26]. Selective serotonin receptor inhibitors (SSRIs) are the mainstay for treatment of depression and have also been studied for motor recovery in stroke survivors. These trials have reported less disability and neurologic impairment after stroke in both depressed and non-depressed patients treated with SSRIs [27]. Two large prospective randomized control trials are underway to confirm this effect.

Delirium

Delirium is defined as a waxing and waning of attention, often with altered level of consciousness, disorganized thinking, or both. The incidence of delirium in stroke patients ranges from 13 to 48 % in clinical studies [28]. Delirium has been shown to predict worse outcomes including increased mortality in a variety of disease states including stroke [29, 30]. Patients should be screened for delirium daily during their admission; neurologically injured patients present a unique challenge for applying standard delirium scales. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) has been validated in the stroke population and is an easy to administer, well-validated bedside assessment [31]. Some of the factors that predict patients who will develop delirium include older age, previous cognitive impairment, and baseline visual or hearing deficits. Patients with right-sided stroke that experience neglect are also more likely to experience delirium compared with infarcts in other territories [32].

Alcohol withdrawal delirium is common. A recent population based survey found that about a third of elderly patients with chronic medical problems drink alcohol regularly and about 6 % have risky drinking behaviors [33]. This reminds

the clinician to take a complete social history in all patients hospitalized following stroke.

The treatment of delirium is focused on avoiding factors that may increase confusion including avoidance of benzodiazepines and other centrally acting medications, encouraging day and night orientation, early mobility, providing glasses for those with corrective vision problems, and treatment of dehydration and infections [34]. Antipsychotics, particularly haloperidol, can help to treat symptoms of hyperactive delirium but should only be used when patients' behaviors are posing a harm to themselves or staff. Atypical antipsychotics, such as risperidone and olanzapine, have been studied and have a safer side effect profile than haloperidol but have not been directly studied in the stroke population [35]. All antipsychotic agents have an FDA Black Box warning for increased mortality for patients over 65 years old and have known cardiac side effects including prolonged QT and therefore should be used sparingly and in low doses only when necessary.

Secondary Prevention

The most important goals of hospital admission of stroke are prevention of complications and planning for prevention of stroke recurrence. Secondary stroke prevention is covered in detail in other chapters of this book.

Cardiovascular Management of Stroke Patients

Blood Pressure Control

The appropriate acute blood pressure goal in stroke patients is a balance between maximizing cerebral perfusion and protection of the brain and other organs, especially the heart and kidneys, from hyperemia and its complications. The patient's baseline blood pressure, impaired cerebral autoregulation and physiologic compensatory mechanisms make this ideal target individualized and complex. Some data suggest a U shaped curve associated with outcomes in stroke patients, with both hypertension and hypotension on presentation having worsened outcomes [36]. Other studies describe worsened outcomes with elevated blood in a more linear fashion [37].

The current guidelines from the American Heart Association for the treatment of acute ischemic strokes recommend careful lowering of the blood pressure in the acute setting to keep systolic blood pressure less than 220 and diastolic blood pressure lower than 120 unless there is a compelling reason to lower further for the protection of another organ system such as in myocardial ischemia or aortic dissection. If the blood pressure is higher, then reducing it by 15 % in the first 24 h is recommended. For patients who undergo thrombolytic therapies, a lower blood pressure is advised, specifically less than 185/110 [38].

In the acute setting prior to thrombolysis, attention is placed on lowering the blood pressure to less than 185/110. The current AHA/ASA guidelines recommend attempting to treat with intravenous labetalol with two doses prior to initiating a nicardipine infusion based on a safety study of aggressively lowering blood pressure using either agent prior to tissue plasminogen activator (tPA) [39]. Based on a retrospective study, patients treated solely with nicardipine may reach targeted blood pressure with less dose adjustments and faster than those treated with labetalol [40, 41].

When to further control blood pressure after acute ischemic stroke is more controversial, and this debate has being ongoing for more than 30 years. Many stroke patients were on antihypertensive agents prior to their cerebrovascular event. A randomized control trial of stopping or continuing antihypertensive medications was conducted with 4,071 patients in the first 24 h after stroke. There was no difference in neurologic outcomes at 14 days or 3 months after stroke, and the blood pressure was lowered by 9 mmHg systolic in the control group [42].

For the past two decades, there has been emerging evidence that inhibiting the renin angiotensin aldosterone system (RAAS) has benefits on a variety of cardiovascular outcomes in addition to lowering blood pressure [43]. As a result, these agents, or thiazide diuretics are typically the first choice for secondary prevention when an oral agent is to be started.

Hypotension

Hypotension is occurs at presentation in less than 1 % of patients with acute ischemic stoke [36]. Some of these strokes occur when systemic hypotension is present in a patient in the setting of a fixed intracranial or cervical stenosis. The pattern of stroke is often consistent with a watershed distribution [44]. In general, strokes that present with low blood pressure have a much worse prognosis than those that present with elevated blood pressure [36]. The choice for treatment of hypotension is limited to animal data only, and there is no data to recommend vasopressors in this setting. Occasionally hypotension is due to an effect of an underlying condition, such as an arrhythmia or aortic dissection, which is the etiology of stroke.

Arrhythmias

Atrial fibrillation or flutter is the known cause of stroke in about 20 % of patients presenting with acute ischemic infarcts. An additional 25 % of patients have a suspected

embolic source that cannot be identified (i.e., cryptogenic stroke) [45]. Detection of cardiac arrhythmias influences the secondary prevention strategy moving forward and an aggressive search for such rhythms should be part of routine stroke evaluation. An electrocardiogram is standard for all patients being admitted with an acute ischemic event. While some arrhythmias are detected with the initial EKG, paroxysmal atrial fibrillation is more likely to cause a stroke than persistent atrial arrhythmias, necessitating further cardiac telemetry [46]. The presence of paroxysmal supraventricular tachyarrhythmias other than atrial fibrillation are also an independent risk factor for stoke [47]. Observational studies have shown an additional 7 % of patients with idiopathic etiologies are found to have atrial arrhythmias with repeated EKG's up to 48 h from stroke [48]. The incidence of atrial fibrillation was found to be about 30 % of patients with implantable cardiac defibrillators that are capable of monitoring atrial rhythm; patients with cryptogenic stroke have a 15–20 % risk of atrial fibrillation with 21–30 days of cardiac monitoring [49–51]. Another study of patients with recently implanted defibrillators that can detect atrial rates found 10 % of patients had an atrial rate of greater than 160 beats per minute sustained for at least 6 min within 3 months of implanting the device; these patients had a higher incidence of stroke and other embolic events in the subsequent 2 years [52].

Clinicians caring for patients with atrial fibrillation can use the validated CHADS2 scoring system helps clinicians determine stroke risk and potential benefit of antiplatelet or anticoagulation agents. The presence of congestive heart failure, hypertension, or diabetes or age greater than 75 are each worth 1 point in the score, and stroke or TIA is 2 points [53]. Anticoagulation has been recommended for CHADS score of 1 or more and aspirin therapy is recommended in patients with 0. In the age of directed anticoagulation agents for non-valvular atrial fibrillation, there may be expanded recommendations for full anticoagulation [54, 55].

The benefit and timing of therapeutic anticoagulation in ischemic stroke patients remains a source of much debate. The AHA recommends starting all patients with stroke and atrial fibrillation on anticoagulation if there are no contraindications [45]. Starting too early may increase the risk of hemorrhagic transformation; starting too late may increase the risk of further ischemic events. The Heparin in Acute Embolic Stroke Trial (HAEST) randomized 449 patients with acute ischemic strokes and presenting with atrial fibrillation within the first 30 h of symptoms onset to either low molecular weight heparin, dalteparin 100 IU/kg, subcutaneously twice a day or aspirin 160 mg orally for the first 14 days after stroke. The primary outcome was functional neurologic outcome. A secondary outcome was hemorrhagic transformation. There was no difference in the functional outcome at 14 days and 3 months but there was a statically significant increase in larger symptomatic hemorrhages in the group that received low molecular weight heparin [56]. A further meta-analysis with more than 22,000 patients included evaluating the risks or benefits of anticoagulation within the first 14 days of stroke and found no net difference in patients who were started on heparin compared with those who were started on aspirin or placebo [57]. With this knowledge, patients are typically started on aspirin on admission or 24 h after thrombolytic therapy and then anticoagulation with a bridge upon discharge. The aspirin may be stopped after the anticoagulation is at a therapeutic level.

Myocardial Ischemia

Given the similarities in the pathophysiology of cerebral and cardiac ischemia, all patients admitted with cerebral ischemia are at risk for coronary disease. Troponins are used as a marker of cardiac damage but are often elevated in other medical conditions including renal insufficiency, pulmonary embolism, sepsis, hypertensive emergencies, and stroke [58]. About 20 % of patients with acute ischemic stroke have elevated troponins on admission [59]. Older patients and those with larger strokes are more likely to have an elevated troponin as well as serum creatine kinase level, and these markers are associated with an increase in stroke mortality [60].

Determining the clinical significance of elevated cardiac markers can be challenging. One study described 834 consecutively admitted stroke patients with troponins measured at admission; if elevated, an EKG was performed and troponins were measured again 3 h later. The patients were divided into two groups, those with greater than 30 % increase in the troponin level and those levels that remained constant. There were no patients in the constant group that met established criteria for myocardial infarction (MI) but half of the patients with an increase in the troponins did. Of all 834 patients, only 29 (3 %) had concurrent cerebral and cardiac ischemia, consistent with previous studies [58].

Respiratory Management of Stroke Patients

Oxygenation and Ventilation

During a time of decreased cerebral perfusion, hypoxemia is the most rapid cause of cellular death. There is limited data for the appropriate level of oxygenation for patients experiencing a stroke. It is reasonable to keep oxygen saturation greater than 94 % during the time of acute ischemia, which can be achieved in the vast majority of patients with supplemental oxygen administered via nasal cannula [38].

When oxygenation cannot be maintained with less invasive measures, intubation is indicated. Intubation is also indicated for patients who have a decreased level of consciousness

with a Glasgow Coma Scale (GCS) of less than 10 and is required for patients with a GCS of less than 8, as they are unlikely to maintain appropriate ventilation and oxygenation. If the partial pressure of oxygen becomes less than 60 mmHg with supplemental oxygen or if the partial pressure of carbon dioxide becomes greater than 60, intubation is also recommended [38]. For stroke patients who require ventilation based on these needs, there is a 70 % 1-year mortality [61].

Hypercapnic respiratory failure may occur in stroke patients with decreased levels of consciousness and inability to protect their airways. Additionally, obstructive sleep apnea (OSA) is an independent risk factor for ischemic stroke and leads to an elevated CO_2 level at baseline; any structural neurologic damage, including stroke, can worsen the hypercarbia [62]. When the carbon dioxide level rises, the systemic and cerebral vasculature dilates. For patients who are dependent on collateral flow to perfuse an area of tissue experiencing ischemia, this change is particularly dangerous since dilation of normal blood vessels shunts blood away from tissues experiencing ischemia [61]. In one study of patients with a history or reported symptoms of OSA who were admitted with stroke, those treated with noninvasive mechanical ventilation had a 6 % absolute decrease in mortality during the admission [63].

The decision to extubate a neurologically injured patient is often more difficult than the decision to intubate. For patients who were intubated for a primary lung problem, there are studies to support when a patient is likely to be successful extubated. However, there is limited data for neurologically injured patients who are often incapable of following verbal commands. The decision falls on the global impression of the physicians and respiratory therapist. Typically if bulbar functions are preserved, then extubation is attempted. Fifteen to 35 % of intubated stroke patients will fail to wean from the ventilator and require a tracheostomy and long-term ventilation. Some small studies have shown benefit of early tracheostomy, similar to larger studies in the general ICU population [64].

Stroke Associated Pneumonia

One of the most common medical complications of stroke is pneumonia. Aspiration is typically the mechanism, presenting as an opacification of the gravity dependent areas of the lungs on radiographs. See Fig. 6.3. Reported incidences range from 4 to 20 % of stroke patients in the hospital [65]. The presence of pneumonia in a hospitalized stroke patient increases the cost of hospitalization by on average over $27,000, adding an additional $459 million dollars to health care cost in the United States each year [66, 67]. The development of pneumonia increases mortality by five times in acute stroke patients [65].

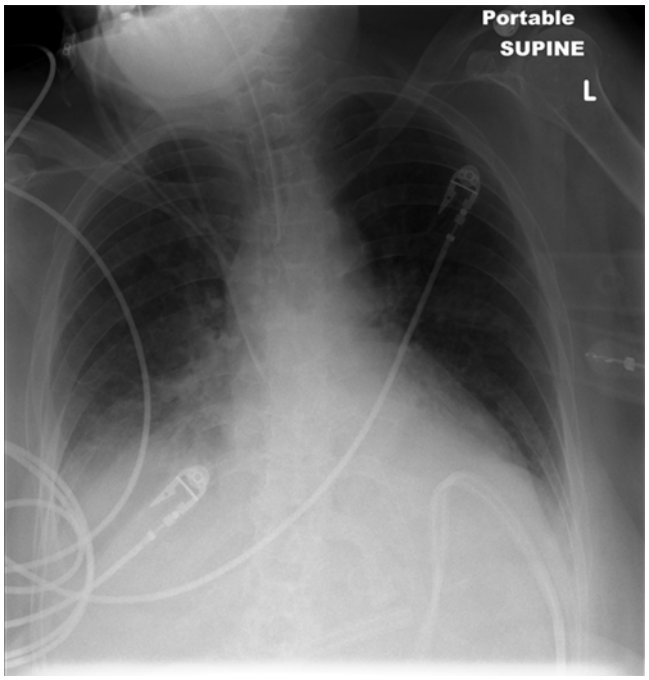

Fig. 6.3 A 62-year-old man with new cough and fever 6 days after left middle cerebral artery stroke. Chest radiograph demonstrates right middle and lower lobe consolidations consistent with aspiration pneumonia

Several studies have described predictors for the development of stroke-associated pneumonias. Pneumonias are associated with older patients and those who have worse strokes, higher NIHSS scores, and those that involve the brainstem [68]. Endotracheal intubation is a major risk for pneumonia, especially when prolonged ventilation is required. Even brief intubations for endovascular procedures have been associated with an increased risk of pneumonia [69].

The presence of dysphagia is the single biggest risk factor for aspiration pneumonia. The AHA's Get With the Guidelines Program has placed an emphasis on screening for dysphasia in all stroke patients prior to any oral intake including fluids or medications [65]. This type of screening has been shown to aid the early identification of patients at risk so that they may undergo modifications to reduce the incidence of aspiration pneumonia, in turn decreasing length of stay, cost, and mortality rates [70]. Any health-care provider may perform and document testing for dysphagia [65]. Even though there is no standard assessment for dysphagia, there are several studies that have looked at key features of the tests including direct observation of patients swallowing water. Other important components of an assessment may include observing for an abnormal volitional cough, an abnormal gag reflex, dysarthria, dysphonia, cough or throat clearing after swallowing, and voice change after swallowing [70]. If there is a suspicion that the patient may not be able to swallow safely, the patient should not take anything orally until further assessed by a speech and language pathologist.

The treatment of stroke patients with aspiration pneumonia is no different than other hospitalized patients. Nasal and oral floras are the most commonly found bacterial pathogens. Empiric antibiotics should cover both Gram positive and Gram-negative organisms [68]. If the patient has been hospitalized for two or more days in an acute care facility within 90 days; lives in a nursing home or long-term care facility; has attended a hospital or hemodialysis clinic, or has received intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of infection, then their pneumonia is considered health care-associated. For these patients, empiric coverage should include antibiotics targeting multidrug resistant organisms according to the local bacterial resistance patterns [71].

Nutrition for Stroke Patients

Nutritional Requirements

Food choices can influence many risk factors for stroke such as hypertension, diabetes and dyslipidemia, and patients who have chronic medical problems are often malnourished. The nutritional status of patients who are admitted with acute ischemic stroke likely changes rapidly.

Once dysphagia is recognized, tube feedings should begin. The result of being underfed after a stroke can have serious consequences including increased infections and bedsores and has an association with worsened neurologic outcome [72]. Nutritionists are charged with the challenge of determining the resting metabolic needs for each patient, and there are a several equations that can be used to determine the appropriate caloric needs in critically ill states. Each disease process uses a corrective factor to help predict the increased demands due to illness. For example, sepsis, malignancy, burns and trauma require remarkable additional nutritional support due to the high catabolic demands of these states. There is very little data on the metabolic needs of patients with acute stroke. One small prospective study of 27 stroke patients found that 40 % of them had a negative nitrogen balance when evaluated using urine nitrogen excretion, suggesting they were being underfed by using a standard equation for calculating nutritional needs [73]. In practice, calculating the nitrogen balance or oxygen consumption is rarely done; nutritionists more often rely on end markers of nutritional status such as serum pre-albumin or C-reactive protein levels.

Long-Term Nutrition

While some patients regain their ability to swallow, others are left with long-standing dysphagia or impaired consciousness and are unable to meet their nutritional needs orally. Patients with higher NIHSS scores, larger infarct size, those who are more critically ill, or require long term ventilator support are more likely to need prolonged nutritional support [74]. For these patients, surrogates are often required to make a decision regard long-term artificial nutrition. Some wish to withhold artificial nutrition and succumb to the stroke; others elect to have a percutaneous endoscopic gastrostomy (PEG) tube placed. This decision-making involved is often complex and reliant on imprecise data regarding long-term recovery prognostication.

Fluid and Electrolyte Management in Stroke Patients

Fluid Choices

When patients are admitted with acute ischemic stroke, intravenous fluids are often quickly administered for a variety of reasons. These patients are not allowed fluid intake by mouth until swallowing function can be assessed and hydration may be desired prior to receiving intravenous contrast dye. Insuring the body has enough intravenous volume can theoretically improve perfusion to the ischemic brain tissue.

In general, isotonic fluids are preferred due to a decreased risk of exacerbating cerebral edema. Animal models suggested albumin administered could in theory decrease infarct size when compared to normal saline. A recent phase-3 clinical trial showed no difference in functional outcome or mortality at 30 and 90 days between the albumin and control groups, but the albumin group had an increased incidence of shortness of breath, complications of fluid overload including congestive heart failure, and symptomatic intracranial hemorrhage compared to those given normal saline [75]. Current clinical studies would support the use of isotonic crystalloid intravenous fluids; 0.9 % saline solution is most appropriate if the electrolytes are normal.

Electrolytes

Hyponatremia has been associated with increased mortality in patients with cardiac, renal, and liver diseases. In the neurologically damaged, hyponatremia can be a result of SIADH or cerebral salt wasting, particularly in those with subarachnoid hemorrhage, in which a worsened outcome has been demonstrated. Recently, two studies evaluated the correlation of hyponatremia (as defined as sodium less than 134 mmol/l) and found an increased mortality at 3 months, 12 months, and 3 years after stroke [76, 77]. The larger and more rigorous of the two studies evaluated 3,585 patients and found hyponatremia was an independent risk factor for higher NIHSS score on admission, further neurological

worsening during admission and an increase risk of all cause mortality at 3 and 12 months following stroke. The mechanisms of these worse outcomes remain largely unexplained. It is possible that osmotically mediated fluid shifts may cause increased cerebral edema, but the association has been shown in both large vessel strokes as well as lacunar strokes, making this a less plausible explanation [77]. It remains unknown if correcting the sodium would improve these outcomes. There is limited data on the impact of hypernatremia in acute ischemic stroke patients.

Magnesium has been a proposed as a neuroprotective agent in variety of conditions. There is a proven benefit in patients undergoing carotid endarterectomy and in those who have hypoxic ischemic encephalopathy [78, 79]. Magnesium is inexpensive, easy to administer and has very few side effects. One randomized clinical trial failed to show a benefit in neurologic outcome when magnesium was administered within 12 h of symptom onset [80]. A larger trial of magnesium administration by first responders in the pre hospital setting also showed no beneficial effect [81, 82]. There is no human data for the effects of calcium or phosphate administration on stroke patients.

Acute Renal Insufficiency

Acute renal insufficiency (AKI) is a frequent complication in many hospitalized patients. The consensus definition of stage 1 AKI includes a relatively small change in serum creatinine of greater than 50 % or 0.3 mg/dl and is associated with worsened outcomes in many disease states; stages 2 and 3 are more severe forms of the disease. The impact on mortality has been demonstrated in conditions as diverse as sepsis, myocardial infarction, congestive heart failure and liver failure [83]. There are few studies that have investigated this relationship in stroke patients. In one retrospective study including 582 acute stroke patients, the incidence of AKI was 14 %. These patients demonstrated a three times greater chance of death during the hospitalization than those without AKI. The only significant differences between the groups with and without AKI were age and NIHSS score. The administration of iodinated contrast dye for CT was not a significant risk factor for AKI [84]. Another prospective study of 390 Swedish patients with acute ischemic stroke found a similar incidence of AKI when following these patients for 4 years [85]. AKI emerged as a strong predictor of death when 2,155 stroke patients were followed for 10 years [86].

Contrast induced nephropathy (CIN) has been evaluated primarily in patients undergoing coronary catheterization where large volumes of intravenous contrast are administered. When evaluating for contrast enhanced CT, the incidence is quite low in general. The presence of chronic renal insufficiency and diabetes increases this risk, but even for the highest risk patient the incidence is less than 10 % [87]. In stroke patients, the incidence of CIN after emergent CT angiography and CT perfusion is likely less than 1–3 % [88–90]. For patients at high risk of CIN, including those with chronic renal insufficiency or diabetes, prophylaxis may be administered prior to scanning; intravenous fluids have been the mainstay for prevention, either sodium bicarbonate or normal saline. *N*-acetylcysteine may also be used; its benefit is questionable, but the risk of treating is low.

Chronic Renal Disease

Chronic kidney diseases and cerebrovascular disease have many of the same risk factors, especially hypertension, diabetes and increasing age. With the common predisposing pathway, the likelihood that a patient with chronic kidney disease would have a stroke is obviously increased. Several studies have tried to disentangle the risk factors while controlling for common variables. A meta-analysis that included 33 prospective studies of 280,000 patients with chronic renal disease found a 43 % greater risk of stroke in patients with an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 [91].

Renal replacement therapies do not decrease the risk of stroke for these patients. In a national prospective cohort study, Choices for Healthy Outcomes in Caring for ESRD (CHOICE), 1,041 patients who began hemodialysis were monitored for cardiovascular and cerebrovascular events that occurred from the time of hemodialysis initiation until transplant or until the 10 year study period ended. Of 165 patients who experienced a stroke, a vast majority were ischemic events, and more than half were the result of cardioembolic phenomena. Patients with chronic renal disease and stroke experienced a delay in the time of symptom recognition on average for 8.6 h [92]. This presents an important opportunity for patient education regarding the risks and presenting symptoms of stroke for patients on hemodialysis. Even in patients who receive thrombolytic therapy, the mortality and hospital complications associated with stroke are increased in patients undergoing hemodialysis [93].

When hemodialysis patients are admitted to the hospital with stroke, some important considerations must be taken into account. The injured brain is particularly sensitive to rapid changes in osmotic gradients and blood pressure as well as to risk of anticoagulants used routinely during hemodialysis. After discussions between the nephrologist and neurologist, it may be best to temporarily hold intermittent hemodialysis in the early ischemic phase or change to a slower form of renal replacement therapy [94].

Infections and Inflammatory Response in Stroke Patients

Fever

Cerebral ischemia is a pro-inflammatory state as evidenced by the leukocytosis, elevated cortisol levels and temperature associated with stroke even in the absence of infection [74, 95, 96]. For the first 12 h after stroke, every 1 °C increase in temperature increases the relative risk of poor outcome by 2.2 (98 % CI: 1.4–3.5) [97]. This temporal relationship between ischemia and elevating temperatures was defined in a small prospective trial that showed the maximum temperature from the inflammatory response peaked at 72 h, the same time that maximum cerebral cytotoxic edema occurs and also found that patients with a higher peak temperatures had worse modified Rankin scores at discharge compared with patients with lower temperatures, even when other markers of poor prognosis were controlled [98]. This impact of hyperthermia on stroke outcome has best been defined by information derived from the Virtual International Stroke Trials Archives (VISTA) database. Hyperthermia is most strongly correlated with worse outcome at 7 days post-stroke, and this association is strongest in the first week [96].

Because of the high risks associated with fever, hyperthermia should be aggressively treated in stroke patients. First line therapy is acetaminophen, if there are no contraindications. Hyperthermia prevention was systematically evaluated with a randomized controlled trial where patients with a temperature between 36 and 39 °C were randomized to either acetaminophen 6 g either orally or rectally or placebo within 12 h of fever onset. There was a trend toward improved outcomes but no significant difference in the two groups. There was no difference in adverse outcomes in the two groups [99]. However, the current FDA recommendations advise that patients should not exceed the acetaminophen maximum total daily dose (4 g/day). Although acetaminophen has been shown to be a safe and effective treatment of stroke patients with elevated temperatures at moderate doses, NSAIDs are typically avoided because of antiplatelet effects and risk of interactions with other medications. Other non-pharmacological methods of lowering temperature can be also used including surface cooling using cool towels, ice packs to the groin and axilla, and cooling blankets. Cold gastric lavage can quickly lower temperatures as can intravenous cooling with intravenous cool saline solutions or various endovascular or surface cooling devices. Because a fever representing an infection can be missed, once aggressive cooling measures are underway, cultures are routinely done at least every other day. There is a risk of deep vein thrombosis associated with intravenous cooling catheters, and patients should be monitored accordingly.

Infections

Neurogenic fever is a diagnosis of exclusion, and patients should be thoroughly evaluated for sources of infection. Workup includes blood cultures, urinalysis and culture, tracheal cultures if intubated, and CSF cultures if there have been any intracranial procedures or hardware introduced. From one cohort of 276 prospectively followed stroke patients, infections occurred in 15 % of patients; about half was pneumonia and a quarter was urinary tract infections. Infections in this study were associated with a worsened outcome [100]. In a different retrospective study of 663 patients, 23 % of patients experienced an infection, typically pneumonia (10 %) or urinary tract infections (13 %); both were associated with a longer hospitalization, but only pneumonia adversely affected outcome [101]. In one retrospective study of 334 patients, infections present on admission to the hospital did not impact outcome but hospital-acquired infections did [102]. If an infection is identified, it should be treated with antibiotics according to available culture results.

For all patients, efforts should be made to reduce the risks of infections. Recommendations for reducing pneumonia are listed above. For urinary tract infections (UTIs), female sex, older age, presence of diabetes, and increased length of hospital stay are all non-modifiable risk factors that have been identified. The only modifiable risk factor for UTI is the presence and duration of Foley catheter placement [103]. Appropriate use of Foley catheters is critical to reducing the risk associated with them. Properly trained health care providers should place Foley catheters with sterile techniques. Daily review of catheter necessity is recommended as part of routine nursing care; these catheters should be removed as soon as they are no longer indicated. It is inappropriate to use Foley catheters solely for urinary incontinence. For patients with neurogenic bladders, intermittent catheterization is recommended over indwelling Foley catheters. Scheduled changing of indwelling catheters is not recommended, but changing in response to infection or obstruction is appropriate. Suprapubic catheters are rarely indicated during hospitalizations [104]. For men, condom catheters are preferred in lieu of urethral catheters due to decreased rates of infection. Indwelling catheters are frequently colonized with bacteria, and therefore determining the significance of a positive urine culture can be difficult. If a patient is symptomatic for a UTI, has greater than 10^3 colony forming units of a typically pathogenic organism, and evidence of systemic inflammation,

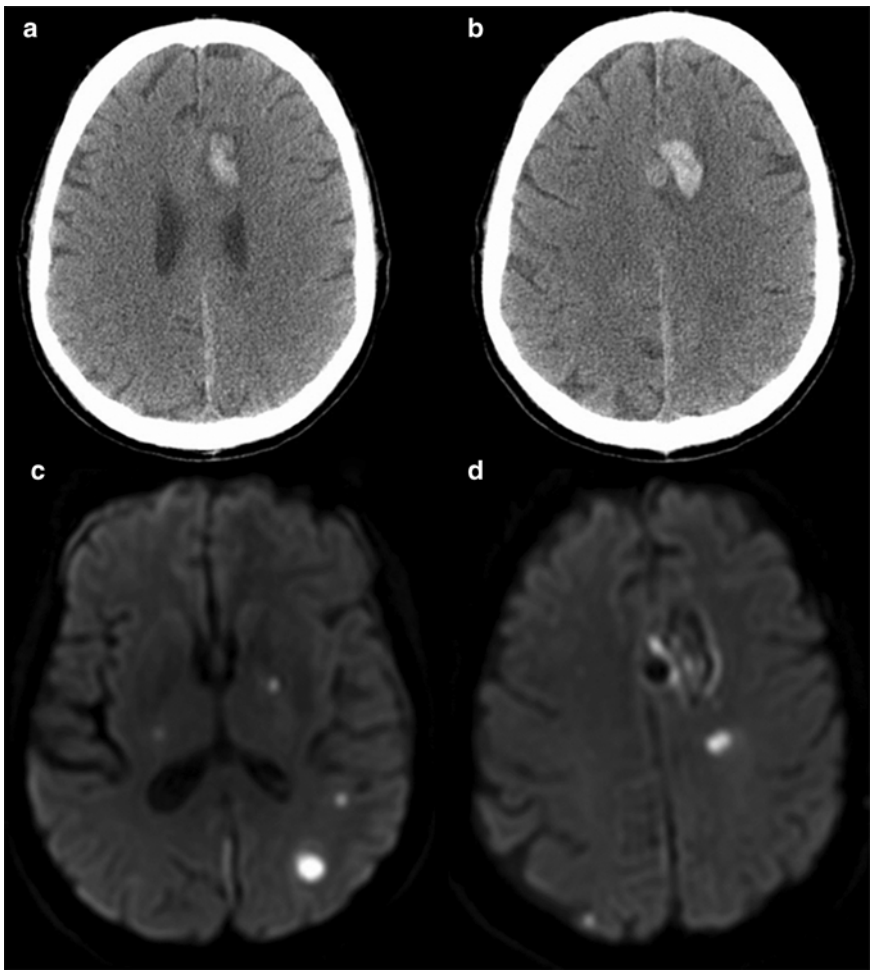

Fig. 6.4 A 54-year-old woman with large mitral valve vegetation who presented with right leg weakness and was found to have a left frontal hemorrhage on non-contrast head CT (**a**, **b**). Diffusion-weighted sequences on MRI show multiple areas of infarction consistent with emboli not appreciated on the CT scan; the left frontal lesion has undergone hemorrhagic transformation

antibiotics are recommended. Treatment should involve removing or replacing the Foley catheter and treatment with antibiotics for at least 7 days [105].

The other major concerning infectious source of stroke patients is endocarditis. Thrombi can form on the valvular vegetation or portions of the vegetation itself can embolize to the brain, leading to ischemic stroke. Infectious emboli are unique because they can also cause mycotic aneurysms and hemorrhages. See Fig. 6.4. There are several case reports and one case series in the literature regarding thrombolysis in the setting of endocarditis, although the risks of hemorrhage are likely higher in these patients post-thrombolysis [106]. The treatment of choice is antibiotics, targeting the sensitivities of the infectious agent. In patients in whom a valvular lesion is present, a careful balance between the urgency of valve repair due to embolic phenomena and the risk of hemorrhage with heparinization required during surgery must be struck. Regardless of treatment, stroke due to endocarditis has a poor prognosis.

Hematologic Considerations for Stroke Patients

Anemia

Red blood cells are primarily responsible for the body's oxygen carrying capacity. During an ischemic event, oxygen delivery is compromised due to decreased blood flow, and anemia may further compromise this delivery. Higher viscosity of blood through stenotic vessels and small collaterals may also compromise tissue at risk of ischemia. The optimal hemoglobin level for patients experiencing stroke is unknown. A large population based cohort study in Taiwan demonstrated an association between iron deficiency anemia and stroke [107]. There are a few retrospective studies describing an increased morbidity and mortality associated with anemia and concurrent stroke but further study is required to establish this association [108, 109].

Transfusion thresholds can be reasonably derived from guidelines from other disease processes where red blood cell transfusions have been associated with an increased mortality of unclear mechanism [110]. A landmark study of medically critically ill patients showed that lower thresholds (<7 g/dl) for red blood cell transfusion were safe and possibly preferred in some patients [111]. More studies are necessary in the stroke population to better target transfusion thresholds but for now, similar low thresholds are likely to be prudent.

Sickle cell disease has a unique mechanism for stroke, particularly in children and young adults with the disease, which is covered in detail in another chapter of this book.

Glucose Management in Stroke Patients

Hypoglycemia

Hypoglycemia can represent a stroke mimic in the acute setting due to recrudescence of a previous brain lesion such as encephalomalacia from an old stroke. More rarely, low glucose can be the primary cause of the deficit and can present with focal symptoms [112, 113]. Capillary blood glucose should be measured as early as possible in acute stroke and hypoglycemia should be corrected rapidly. MRI imaging findings associated with severe and prolonged hypoglycemia have also been described, often affecting the deep grey nuclei or the internal capsule [114]. Acute strokes presenting with low blood glucose have worse NIHSS score at 24 h and 12 months than those with glucose in the normal range [115].

Hyperglycemia

Hyperglycemia presents a management dilemma. From retrospective data sets, patients with stroke who also have elevated blood glucose have three times increased mortality and appropriate glucose control may improve these outcomes [116]. From the medical critical care literature, a randomized control trial of aggressive glucose control to keep capillary blood glucose between 81 and 108 mg/dl versus a target of less than 180 mg/dl showed that patients in the tighter glucose control group had increased mortality than the more liberalized goal which was not an effect of hypoglycemia alone [117]. Some small trials have evaluated the use of intravenous insulin therapy for tighter glucose control in stroke patients. A meta-analysis has found no difference in outcome of patients treated with intravenous insulin versus standard therapies, but there was an increased risk of hypoglycemia [3]. There is an ongoing randomized control trial of IV insulin in acute stroke using computer generated titration scales [118].

Prophylaxis for Stroke Patients

Deep Vein Thrombosis

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are dangerous complications that can arise in any hospitalized patient. Limited mobility after stroke increases the risk of DVT substantially. About 1 % of stroke patients experience a DVT; in about half of those cases, the event is associated with death during that admission [119]. Sequential compression devices (SCDs) are often first line therapy for prevention of DVT, especially if the patient received IV thrombolytic therapy. The effectiveness of these devices was tested in a randomized control trial in acute stroke patients with limited mobility and a 3 % absolute risk reduction was demonstrated but was not statistically significant. While these devices show only a small reduction in DVT, the risk associated with their use is quite rare so they are routinely recommended when other means of prevention are not possible [120].

If there is no radiologic evidence of hemorrhagic transformation 24 h after thrombolysis, pharmacologic DVT prevention should begin. In those not treated with thrombolysis, pharmacologic prevention can be started on admission. A meta-analysis showed that low molecular weight heparin (enoxaparin) decreased the risk of DVT more than prophylactic doses of unfractionated heparin [121]. Enoxaparin 40 mg daily and low dose subcutaneous heparin 5,000 units two to three times daily have been compared in a randomized trial, which showed a 43 % relative risk reduction with enoxaparin, and an absolute risk reduction of 6 %. There was a slightly higher risk of systemic bleeding with enoxaparin but no difference in intracranial bleeding [122].

DVT prevention should be part of every admission plan, but an international study found that only 43 % of ischemic stroke patients underwent appropriate DVT prophylaxis [123]. When evaluating registry data, hospitals that had implemented standard stroke admission orders were more likely to have ordered DVT prophylaxis than those that had not [124].

Stress Ulcer Prevention

While stroke provokes a systemic stress response, the use of stress ulcer prophylaxis in stroke patients has not been directly studied. There are several conflicting rationales for considering starting an H_2 blocker or proton pump inhibitor (PPI) in these patients. Over the past several years, the use of these agents has been associated with more adverse drug reactions than previously thought. In addition to thrombocytopenia with both classes of medications, PPIs have been associated with increased risk of ventilator associated

pneumonias and interact with commonly used stroke medications including clopidogrel [125, 126]. The risk of gastrointestinal bleeding in stroke patients has only been evaluated in two studies in Asia, both of which found an incidence of 5–7 % [127, 128]. With the relatively low risk of gastrointestinal bleeding and the adverse associations of the prophylaxis medications, they are not typically recommended in stroke patients although the benefits may outweigh the risks for those with a history of GI bleeding, mechanical ventilation, use of chronic, high dose steroids, NSAIDS, or dual antiplatelets [129].

Decubitus Ulcers

For patients admitted with decreased mobility, decubitus ulcer prevention is important. Open wounds can become infected and are difficult to treat one they have formed. Relieving the stressed skin of the weight of the body is the best prevention of sores. Most institutional policies require turning immobile patients every 2 h. Evidence supports the use of high quality foam mattresses and specialized air mattresses for those at highest risk [130]. Often physicians are unaware of the work that this prevention routine requires from the nursing staff.

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Post-discharge Complications of Stroke

7

Atif Zafar and Enrique C. Leira

Case Presentation An 82-year-old right handed female presented to the emergency room of a tertiary care hospital (Comprehensive Stroke Center) after a drip and ship from a local rural ER. The patient started having sudden onset of right sided tingling that felt like "fire burning my body down." Since she arrived within 3 h of onset, she was given tPA after blood sugars were reported normal and head CT did not reveal any intracranial bleed. The patient had past medical history significant for HTN, HLD and stroke. She was discharged with small subcortical ischemic stroke mainly involving the basal ganglia and thalamus approximately 6 months ago. Her noticeable deficits were expressive aphasia and mild right-sided weakness. She was gradually recovering from her prior stroke, with compliance to antiplatelet, statin, antihypertensives, and physical therapy when she had this acute event. On arrival to the comprehensive stroke center she was evaluated by the on-call residents and after comparing her presentation to the recent exam performed in clinic visit for routine 3 months stroke follow-up, she was diagnosed with "Thalamic pain syndrome of Déjerine and Roussy". Her sensory exam to pinprick and vibration was not remarkable, but due to overwhelming pain she could not feel light touch as well on the right side, which probably led to the small rural ER physician giving her a diagnosis of new stroke. Patient was started on Gabapentin overnight, and by the time Stroke attending arrived for morning rounds patient had marked recovery of her pain. She was gradually titrated to 600 mg of Gabapentin three times a day and followed up for 24 months with no new reported pain complaints.

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Introduction

Ischemic stroke patients tend to be older individuals, who after suffering from ischemic strokes are even feebler and at increased risk of having complications. Post-stroke complications have been reported in the literature ranging anywhere between from 40 to 96 %. Post-stroke complications include both acute stroke unit complications and post-discharge complications [1]. Due to methodological variability, it is difficult to amalgamate the study results. The large majority of studies focusing on complications have limitations, such as retrospective nature and overlap of ischemic and intraparenchymal hemorrhage patients, and varying diagnostic criteria. A practical estimate is that between one-third and three-fourths of ischemic stroke patients can suffer from complications that might hamper their recovery [2, 3].

Let us consider an example of a patient with ischemic stroke who has hemi-neglect and hemiparesis, making him a high fall risk. Right MCA infarct patients typically lack adequate insight, so they often require supervision in activities of daily living (ADL) like supervision during meals. Long-term prognosis in patients with ischemic stroke depends not only on the severity of the initial deficit [4] and inpatient hospital course, but also whether medical or neurological complications arise (e.g., UTI, pneumonia, fractures from fall, seizure, depression, spasticity, or ulcers) and if they are adequately managed. Patients can have muscular shoulder pain or hip pain, which can reduce their motivation to ambulate. This can contribute to prolonged sedentary lifestyle at home causing malnutrition and even pressure ulcers hampering the anticipated recovery. Relatively delayed complications like central pain syndrome, especially if subcortical thalamic areas were affected from ischemic stroke, can contribute to severe morbidity for the patient. Spasticity in the hemiplegic limbs is also a major hurdle for recovery in post-

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stroke patients. All these issues should be considered before finalizing the disposition plan. In fact, transition of care to the primary health care team or family care physicians at rehabilitation facilities is becoming a significant aspect of comprehensive stroke care management [5–9]. Traditionally, prevention of post stroke complications had been focused in an acute setting while the patient is still in the hospital. However, a more comprehensive and sustainable approach toward preventing complications that includes limiting those problems that occur after discharge from the hospital is needed, since they can all hamper the long-term recovery of patients [10]. The concept of transition of care should include educating other health professionals, such as primary care physicians, on the potential and expected complications, as well as approaches to management. A comprehensive team-effort toward preventing complications would likely benefit the patient during the long recovery phase after ischemic stroke [5]. In the following paragraphs, post-discharge ischemic stroke complications will be discussed. In certain cases, where specific studies and data for post-discharge complications are not available, the best available practice information is shared. The goal is to increase providers' awareness about complications and develop their own checklists for patient encounters. Table 7.1 summarizes the common and uncommon well recognized complications post-discharge in stroke patients.

Table 7.1 Commonly observed sequelae in patients with ischemic stroke

Osteoporosis
Shoulder pain
Falls/fractures
Spasticity
Urinary incontinence
Contractures
Hemiplegic shoulder subluxation
Sexual dysfunction
Seizure
Central post-stroke pain
Deep venous thrombosis
Fecal incontinency
Pressure ulcers
Dysphagia and pneumonia
Urinary infections
Constipation
Depression and/or Anxiety
Emotional versatility
Dementia
Attention focus problems
Memory impairment
Apraxia
Alteration of executive functions
Spatial neglect

Post-stroke Seizures

From a clinical perspective, seizures are more frequently associated with hemorrhagic strokes (HS) than ischemic strokes. Rare cases develop into long-term epilepsy [11]. Post-stroke ischemic seizures can often be characterized as either early onset or late onset. There are no fixed criteria, but some authors made this definition based on whether the post-stroke seizure occurs before or after day 7. Early onset seizures are more common with HS, and can result in prolonged hospital stay as well as increased mortality. On the other hand, late onset seizures have higher likelihood of developing into chronic epilepsy [12]. There are multiple hypothesis for the mechanism of post-stroke seizures including cortical fibrosis, lack of inhibitory neurotransmission after stroke, inadequate or suboptimal reinnervation pattern during recovery, or vascular dysgenesis during later healing phases of stroke. Research is underway and an established mechanism is yet to be determined. Understanding the mechanism of post-stroke seizures may impact how long the treatment with Antiepileptic Drugs (AEDs) is required, which is important from a patient management standpoint.

The incidence of seizure as a complication of ischemic stroke is approximately 2–4 % [13]. In the Oxfordshire Community Stroke project, the calculated actuarial risk of seizure after ischemic stroke was 4.2 % at 1 year, and approximately 10 % at 5 years. Stroke accounts for approximately one-third of all newly diagnosed seizures in patients more than 60 years old. The Oxfordshire Community Stroke project includes intracerebral hemorrhage cases. One recent study in young adults estimated the incidence of epilepsy in ischemic stroke patients to be around 15 % and the numbers are even higher in intracerebral hemorrhage [14] ranging in one study to be as high as 31 % [15]. Epidemiological and imaging data show that characteristics associated with higher risk of seizures post-stroke include cortical infarcts, involvement of the temporal lobe, and higher NIHSS scores can put the patient at higher risk of seizures in the post-stroke life [12, 16]. There is no randomized trial data to accurately guide physicians in the use of antiepileptic treatments to prevent post-stroke seizures. Physicians should balance the benefits of treatment with AEDs, considering the fact that seizures in ischemic stroke patients hinder recovery and are associated with increased morbidity and mortality, with the potential negative effects of AEDs in recovery and cognition. A North American multi-center cohort study highlighted this risk by reporting increased resource utilization, and decreased 1 month and 1 year survival in patients with post-stroke seizures. The development of safer AEDs opens the possibility for lowering the risks of treating these patients. In the past, prophylactic AED use with combined HS and ischemic stroke patients was not advised because the side effect profile of drugs like Dilantin was considerably high. With newer,

safer drugs like Levetiracetam and Lamotrigine available, physicians and pharmacists feel safer in using them in stroke population. The recent debate regarding prophylactic use of AEDs in stroke patients especially after small trials confirmed increased morbidity, mortality for the patient and sizable resource utilization due to seizure in stroke patients, has resulted on the practice of starting patients with HS on AED as a reflex management plan in some emergency rooms [17, 18]. However, there is no evidence supporting this practice and it is not supported by guidelines. In contrast, ischemic stroke patients are less likely to be placed on AEDs until they have a seizure. Some experts advise long term AED only in patients who have late onset post-stroke seizures, as there is higher risk of recurrent seizures in that subgroup. Overall, decisions regarding AED use should be individualized. Factors to consider in that decision include location and size of the ischemic stroke, type of seizure, other metabolic or infectious findings, baseline functional status, EEG findings, age and gender of the patient, and other similar demographics [12, 19, 20]. For example, a young female with gestation potential and a small ischemic stroke may not be the best candidate for AEDs. Similarly, a patient with mild and simple partial seizures can be treated more conservatively compared to a patient with generalized tonic–clonic seizures. Gabapentin, Lamotrigine, and Levetiracetam are considered safer drugs by most neurologists. The first two have Level A evidence in favor of their use in stroke patients [13, 14].

Post-stroke Depression (PSD)

Ischemic stroke frequently leads to depression [21], with an estimated 20–30 % of patients experiencing depression as a complication of ischemic stroke. Some studies have reported the prevalence as high as 65 % [22]. The prevalence of post-stroke depression (PSD) varies depending on the criteria used for diagnosing depression. Some studies classified any patient started on an antidepressant as being depressed, while others required fulfillment of a stricter Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, which reflects this wide range of prevalence reports [22]. In any case, neurologists and general practitioners who follow stroke patients in both the inpatient and clinic setting would agree that depression is a common complication that adversely affects the long-term outcome [23]. There is a strong rationale to screen for depression in stroke patients, since untreated PSD can negatively impact survival, compliance with medications and rehabilitation, functional outcome, and quality of life. In order to identify stroke patients with depression early and improve the long-term outcome, dedicated stroke centers typically use a nursing depression screening scoring system. The most commonly utilized is thePHQ-9 depression screening form. Interestingly, PSD can be identified as late as 6 months and can persist up to 2 years after stroke. Hence, screening for depression should continue even in the outpatient and home nursing setting.

Today's commonly used antidepressants (AD) have improved safety profiles resulting in increased AD utilization. There have been several trials depicting better outcome with timely antidepressant use in stroke patients compared with placebo. Initially, tricyclic antidepressants (TCA) showed benefit in stroke patients from a mood and recovery standpoint, but anticholinergic side effects were the limiting factor in some cases. If tolerated, TCAs can still be a good option, as one study demonstrated that moderate to high dose TCAs are slightly more effective than a Selective Serotonin Reuptake inhibitor (SSRI) [24]. Recent research has paid more attention to SSRIs with most studies showing improvement in depressive symptoms [25]. One placebo controlled randomized trial reported 60–75 % reduction in depression symptoms in PSD patients with Fluoxetine. Paroxetine has more anticholinergic side effects than other SSRIs, and hence, cautious use is advised in the elderly. Fluoxetine for PSD has been tried and tested in multiple RCTs with proven benefit in treating depression and improving long-term outcome. A randomized placebo controlled trial called FLAME (Fluoxetine for motor recovery after acute ischemic stroke) reported that early use of fluoxetine with physiotherapy enhanced motor recovery after 3 months in patients with moderate to severe motor deficits from ischemic stroke [26]. The concept of modulation of spontaneous brain plasticity by pharmaco-therapeutics as the mechanism was endorsed by this study. One study supported the prophylactic use of Duloxetine for depression prevention and improved long-term recovery [27], but has not been replicated. SSRI side effects include dry mouth, insomnia, nausea, somnolence, agitation, cardiac conduction abnormalities, and hyponatremia. Patients with low sodium who are discharged on SSRIs should be advised to recheck a sodium level a few weeks after discharge as a precautionary measure [19, 28].

Pain

Pain related symptoms are common in stroke patients and can hinder not only rehabilitation therapy but also the overall lifestyle of patients. Due to the highly variable inclusion criteria used by different studies, the prevalence of pain that includes articular pain, musculoskeletal pain, pain related to muscle spasms, headache, and central post-stroke pain syndrome (CPSP), ranges from 8 to 74 % [29]. Comparatively, CPSP as a diagnosis is a more straightforward stroke complication and its estimated prevalence ranges from 1 to 12 %. One prospective study reported the incidence of post-stroke pain at 6 months as the following: shoulder pain 16 %, other joint pain 12 %, other pain 20 %, headache 13 %,

hyperesthesia 8 %, possible CPSP 11 %, with a total of approximately 46 % of the total ischemic stroke patients followed up [30]. Another interesting study showed post-stroke chronic pain complaints among 39 % of the stroke patients, only slightly higher than the 30 % in the control group [31].

Among patients complaining of musculoskeletal pain, shoulder pain is the most commonly reported symptom and mostly occurs on the paralyzed side, but can occur on either side depending on the patient's ambulatory or postural dynamics. Headache was another complaint, but no particular type has been identified. CPSP typically occurs a few weeks to months after a thalamic stroke; however, any other location can trigger CPSP for reasons not completely understood. Epidemiological studies show remission of the pain symptoms with time, with one study reporting prevalence of 21 % 12 months after stroke [32, 33].

Management of post-stroke pain, like other chronic pain syndromes, can be challenging. Treatment can vary and should be individualized to the patient. The presence of spasticity in the paretic side should be evaluated as it could influence treatment choices. The type of pain (e.g., musculoskeletal vs. hyperesthesia) and severity can influence treatment choices. Hyperesthesia can theoretically be managed with gabapentin and pregabalin, but no major clinical studies have confirmed its efficacy. Topical creams may be considered for benign, mild superficial pain symptoms. For musculoskeletal post-stroke pain, some experts recommend amitriptyline and lamotrigine (class IIB) as mainstay of treatment and mexiletine, fluvoxamine, and gabapentin as second-line choices. Refractory patients require expert consultation in a pain clinic and some may even go for repetitive transcranial magnetic stimulation (rTMS), typically reserved as a treatment for patients refractory to more conservative treatments [34, 35]. CPSP, which can be a refractory and debilitating problem, is managed with nor-adrenergic inhibitors, antiepileptics and GABAergics like lamotrigine, gabapentin, and pregabalin [34, 35]. Recently, pain cognitive therapy is also being tried.

Post-stroke Spasticity (PSS)

Spasticity after stroke is a well-documented complication interfering with functional recovery of stroke patients. It is often accompanied by stiffness-related muscle pain, which limits the motor activity in patients in addition to weakness. After acute ischemic stroke, there is an acute phase of flaccidity after which the muscle tone reemerges, in some instances, pathologically to more than its pre-stroke level, leading to spasticity. Spasticity after stroke is reported to reach its peak in 1–3 months after stroke. However, as experience has shown, patients can experience spasticity many months after their stroke.

One study reported 19 % of all stroke patients were found to have spasticity 3 months after stroke [36]. Another small study in the UK might have overestimated this prevalence, reporting 23 of their 59 studied stroke patients (39 %) were spastic a year after stroke [37]. However, most studies document the prevalence to be around 20–30 %. One comprehensive study that only included EMG confirmed cases in the results, reported 21 % patients had spasticity 13 months post stroke [38]. In general, upper extremities are more prone to being spastic than lower extremities in stroke patients.

Modified Ashworth Scale (MAS) is one of the many tools utilized to assess the severity and ranges of spasticity in patients with various neurological diseases mostly affecting the upper limbs. Rehabilitation therapists have depended on this tool for years due to its bedside convenience and inter-rater reliability in wrist and elbow flexors [39, 40].

Medications that have been tried for managing spasticity secondary to ischemic stroke include diazepam, dantrolene, baclofen, tizanidine, clonidine, and gabapentin. The first three are the more commonly used oral agents [41–43]. Botulinum toxin is now used widely to counter spasticity and improve functional outcome. One study compared botulinum toxin type A (BoNT A) to Tizanidine with BoNT A inferred to be superior in that randomized trial [44]. Trials for spasticity in lower extremities also showed BoNT A to be effective than placebo [45, 46]. Intrathecal administration of baclofen has been successfully tried in a series of cases [47]. Other effective interventions include physical therapy, occupational therapy, aquatics, splints, and biofeedback. Most of the physicians taking care of post-stroke patients would agree that combination techniques of both pharmacological and non-pharmacological therapies together play an effective role in managing post-stroke spasticity [48]. Table 7.2 summarizes conservative and non-conservative approach to PSS.

Table 7.2 Post-stroke spasticity (PSS) management

Pharmacological (noninvasive)
Diazepam
Baclofen
Tizanidine
Gabapentin
Dantrolene
Clonidine
Others (anticonvulsant etc.)
Pharmacological (invasive approaches)
Botox Type A injections
Intrathecal baclofen
Surgical approaches
Split tendon release
Tendon lengthening
Tendon transfer (e.g., split anterior tibial tendon transfer)

Falls

A large number of patients who return home after stroke have reported falls, with the incidence around 50–70 %. Most falls are relatively minor, but fear of falling can limit activities and further deteriorate quality of life in some patients. In patients discharged on anticoagulation, falls are particularly risky. Falls can also result in serious injury and death, and are an important source of liability for hospitalized patients in stroke units. Limb fractures have been reported in patients discharged home after stroke adversely impacting recovery and rehabilitation of those patients [49, 50].

Some studies have tried to identify predictors for post-discharge falls in stroke patients. As expected, falls occurring during stay in hospital or rehabilitation unit are reliable predictors of future falls after discharge. The Falls efficacy scale and Berg Balance Scale (BBS) along with many other fall prediction scales have been used by therapists in identifying patients at higher risk for falling [51]. These assessment tools assist in deciding whether the patient can be discharged home or if they need home modifications, or gait assist devices before discharge. BBS is elaborated in Table 7.3.

Table 7.3 Berg Balance Scale

Equipment needed: Ruler, two standard chairs (one with arm rests, one without), footstool or step, stopwatch or wristwatch, 15 ft walkway
Scoring: A five-point scale, ranging from 0 to 4. "0" indicates the lowest level of function and "4" the highest level of function. Total Score = 56
ITEM DESCRIPTION SCORE (0–4)
Sitting to standing _____
Standing unsupported _____
Sitting unsupported _____
Standing to sitting _____
Transfers _____
Standing with eyes closed _____
Standing with feet together _____
Reaching forward with outstretched arm _____
Retrieving object from floor _____
Turning to look behind _____
Turning 360° _____
Placing alternate foot on stool _____
Standing with one foot in front _____
Standing on one foot _____
Total _____
Interpretation:
41–56 = low fall risk
21–40 = medium fall risk
0–20 = high fall risk

Constipation

Constipation is a common problem encountered by stroke patients. Since there are many confounding factors, and constipation is a common complaint in the general geriatric population, it has not been adequately studied. Studies report a wide prevalence range from 30 to 60 %, with the reason for this variance likely due to inconsistent methodological considerations [52] Multiple causes and contributory factors have been attributed to post-stroke constipation including lethargy, insufficient fluid or nutrition intake, medication side effects, depression, lack of exercise, and cognitive issues. Eating a high-fiber diet, lifestyle modifications such as increased activity, and bowel regimens work well for most patients [52, 53].

Infections (Pneumonia/Urinary Tract Infection)

Aspiration pneumonia and pneumonitis (APP) is a well-documented complication of stroke patients. Most studies do not separate incidence data for hospital versus post-discharge. Chemical pneumonitis typically develops rapidly following aspiration of gastric contents, while infective aspiration pneumonia usually lags a few days. The two conditions can overlap. The average incidence of APP in stroke patients is 7 % but most of the cases occur while the patient is in the hospital or rehab facility. If ventilator-related or hospital acquired pneumonia in patients in critical units is included, the average incidence is at least 3–4 times higher [54]. APP increases morbidity and mortality in ischemic stroke patients.

The most likely cause of APP in stroke patients is aspiration caused by dysphagia. Special emphasis on swallowing evaluation by nursing in the form of bedside swallow screening has been made an ardent part of primary stroke centers' protocols. Hence, no patient admitted with stroke should be allowed to eat until they pass this screening evaluation. If there is any question or concern, or the patient fails the bedside screen, a speech therapist who specializes in swallowing evaluation should be consulted. In those cases, a formal swallowing test like a Barium Swallow, fiber-optic scope or oropharyngeal motility study are utilized. The head of the bed is often raised up if patient is getting tube feedings to prevent overflow aspiration. The purpose of these measures is to limit the respiratory infection rate. Introduction of modified type of diets depending on patient's swallow evaluation has helped with gradually incrementing oropharyngeal muscle functional abilities [55]. Respiratory muscle exercise to prevent pneumonia incidence in stroke patients is in trial phases and may become part of nursing care in stroke centers in the coming years. Diagnosis of respiratory infection is suspected on clinical grounds, typically by the presence of fever, hypoxia, and leucocytosis in a patient at risk for

Table 7.4 Avoiding aspiration in post-stroke patients with permission for oral intake

Watch over level of consciousness, cough reflex
Sit upright at 90° or as upright as possible
Food in small quantities
Avoid regular liquids in patients with dysphagia and use thickening agents
Cut up food into small portions
Break pills before administration
Keep the bed head raised for 30–45 min after eating
Give the patient a lollipop to suck on and thus foster the strength of the tongue, if there is no contraindication
Observe movements of the patient's tongue when eating
Observe the sealing of the lips and control if there are fatigue signs when eating, drinking, and swallowing.
If there are signs of fatigue, choking, coughing, or vomiting, expertise from speech therapists should be utilized.

aspiration. The diagnosis is typically confirmed by a chest CXR, but portable films are limited in sensitivity and CT of the chest might be needed.

Treatment with antibiotics depends on a multitude of factors and is out of domain of this chapter. Since stroke patients are prone to serious illness, aggressive management for pneumonia is preferred. Table 7.4 lists preventive and precautionary measures recommended in stroke patients discharged with permission for oral intake.

Urinary Tract Infection (UTI)

UTI is considered one of the top three complications in stroke patients. The occurrence is equally high in inpatient and outpatient setting. The incidence rate of UTI in stroke patients is reported to be as high as 40 %. One study reports a conservative estimate, with 13 % of stroke patients suffering an UTI at some point in their care [56]. This was a retrospective study and so the reported incidence rate depends on how thoroughly the patient was screened for UTI. Another study reported the incidence rate during an inpatient rehabilitation stay to be as high as 30 % [57]. Isolated post-discharge epidemiological data are not available.

Recent studies have focused on factors that can predict UTI. Prolonged Foley catheter placement is a well-known cause for UTI in inpatients. Straight catheterization is utilized after discharge, but also carries an increased risk of UTI. Low cognitive function and immobility leading to poor functional status are other associated factors predictive of UTIs [58]. Some studies suggest that a post void residual volume (PVR) of more than 100–150 cm^3 is a predictor of future UTI [59]. Since UTI is one of the factors that can prolong the inpatient stay, rehabilitation facilities frequently pursue the strategy of aggressive nursing care to prevent them. After discharging home, PVR cannot be checked at home so patients are often advised to straight-catheterize themselves in a timely manner to prevent increased post void residual urine acting as a stagnant reservoir for prospective infections [58].

Conclusion

The current emphasis is to start the planning of post-discharge care as soon as the patient is admitted to an inpatient acute setting. Adequate ancillary care results in better stroke outcomes as demonstrated by clinical trials testing the effect of dedicated stroke unit care. This includes basic medical management, prevention of complications, and specialized nursing care. It is important to identify the most likely complications based on patient characteristics in order to minimize risks. A multidisciplinary team of neurologists, physical, occupational, and speech therapists in close coordination with patient's primary care physician (PCP) is needed. PCPs' ability to perform thorough evaluations of recently discharged stroke patients in order to identify and treat these post-discharge complications in a timely manner can assist with negating the impact on recovery in our stroke patients. This is in addition to the responsibility of primary stroke centers to ensure all the post-discharge needs are addressed before the patient goes out of the unit. The anticipated result is relatively better long-term patient outcomes with less health care spending.

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General Concepts: Stroke Mechanisms, Subtyping, and Workup

8

Jong S. Kim

Stroke is a heterogeneous disorder associated with diverse etiologies and pathogenic mechanisms. Understanding these mechanisms is important in determining strategies for treatment or secondary prevention in individual patients. Identifying the stroke mechanism requires appropriate history taking, neurological examinations and laboratory/diagnostic tests.

Careful history taking may provide some insights into stroke etiologies or mechanisms. For example, maximal neurologic deficits at stroke onset in a patient with a history of atrial fibrillation suggest a cardiogenic embolic infarction. Recurrent transient ischemic attacks (TIA) or strokes with the same hemispheric symptoms are suggestive of ipsilateral large artery disease (LAD). Brief, stereotactic TIAs evoked by fatigue or dehydration are signs suggestive of hemodynamic insufficiency. Examination of peripheral pulse, carotid bruits and auscultation of cardiac murmurs further help us to delineate stroke mechanisms.

Chest X ray, electrocardiography, Holter monitoring, echocardiography and laboratory tests, including serum lipid, glucose, homocysteine, and coagulation profiles are usually performed. In addition, neuroimaging assessment has become increasingly important in the diagnosis of stroke as well as the assessment of stroke mechanisms.

Neuroimaging Evaluation to Assess Stroke Mechanisms

Common neuroimaging techniques utilized to diagnose stroke and to delineate stroke mechanisms include computed tomography (CT) and magnetic resonance imaging (MRI).

CT scan is usually the initial procedure of choice due to its wide availability and short scanning time. Moreover, it can rapidly exclude conditions that contraindicate administration of thrombolytic therapy such as hemorrhage, tumor and extensive infarction. However, CT has a disadvantage in that it usually does not delineate tissue injury associated with TIA, acute (within a few hours after onset) brain infarction, and posterior fossa ischemia. On the other hand, MRI is more sensitive and accurately delineates the extent of infarction. Due to relatively long scanning time, however, it is occasionally difficult to get images from agitated patients. MRI is costly, not always available, and cannot be used in patients with cardiac pacemakers or some other metallic objects. Various MRI techniques are nowadays used to assess stroke mechanisms as described below.

Techniques used to assess the status of cerebral vessels include conventional angiography, MR angiography (MRA), CT angiography (CTA), and Doppler ultrasonography. Although conventional cerebral angiography has been considered a gold standard for assessment of steno-occlusive cerebral vessels, it is invasive and associated with small but significant morbidities [1]. Therefore, MRA and CTA are currently more widely used. *SPECT* and *PET* are occasionally used to assess the status of cerebral perfusion. Here, a few recently developed technologies utilized to delineate stroke mechanisms are briefly described.

Diffusion Weighted MRI

Diffusion weighted MRI (DWI) is an MRI technique that measures the random motion of water molecules, the magnetic resonance intensity of which differs according to the characteristics of different tissues. It is performed by the addition of a pair of symmetric, opposing gradient pulses to a standard pulse sequence. DWI can quickly and accurately detect acute ischemic lesions with high sensitivity and specificity [2–4]. It also can (1) detect small cortical or brainstem infarcts that may not be detected on T2-weighted MRI, (2) differentiate between new and old infarcts [5, 6], (3) detect relevant ischemic lesions in approximately half of

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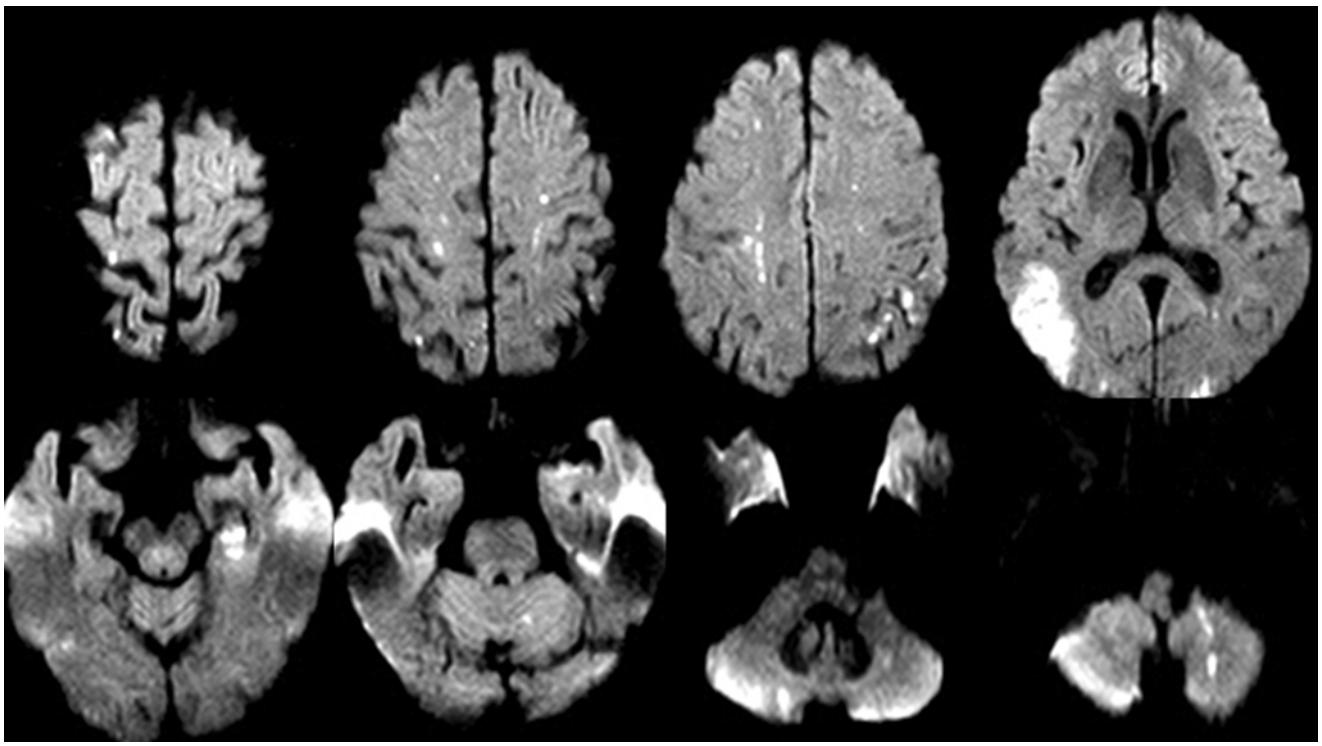

Fig. 8.1 An 83-year-old man without any vascular risk factors developed dysarthria and confusion. DWI showed multiple scattered infarcts in bilateral anterior and posterior circulations. MR angiography, electrocardiography and echocardiography findings were normal. His serum d-dimer level was elevated, and a further workup revealed that he had lung adenocarcinoma. Cancer associated hypercoagulopathy was considered as a stroke mechanism

patients presenting with TIA [7], and (4) detect acute, multiple infarcts, including both asymptomatic and symptomatic ones [8, 9].

DWI lesion patterns may provide clues to understanding the mechanisms of ischemic stroke [8–12]. For example, DWI detection of numerous acute infarcts in multiple vascular territories suggests an embolism from the heart or systemic hypercoagulability [13] (Fig. 8.1).

In patients with significant internal carotid artery (ICA) steno-occlusive disease, DWI lesions occurring in hemodynamic risk zones, along with large perfusion defect suggests the presence of hemodynamic impairment [14] (Fig. 8.2) while ipsilateral territorial infarcts suggest embolic mechanism (Fig. 8.3). In patients with intracranial atherosclerosis (ICAS), ipsilateral territorial, cortical infarcts are also associated with embolic mechanisms (Fig. 8.4), whereas deep perforator infarcts in the territory of perforating arteries suggest branch occlusion as a responsible stroke mechanism (Fig. 8.5) [15, 16].

Because these DWI lesion patterns provide only partial clues, other information such as medical history, findings on neurologic examinations, and vascular and perfusion imaging results should be concomitantly considered to determine stroke mechanisms in individual patients.

Gradient Echo MRI

Gradient echo MRI (GRE) can identify microbleeds as small dark signals, due to the paramagnetic properties of deoxyhemoglobin. The presence of multiple microbleeds indicates that these patients have fragile, hemorrhage prone small vessel disease [17], associated either with advanced hypertension or amyloid angiopathy [18]. In addition, GRE provides information on the composition of thrombi during the acute stage of stroke, by revealing the so-called "GRE susceptibility vessel sign" (GRE SVS) [19–21]. Because red thrombi formed in low pressure areas such as cardiac chambers and are rich in fibrin and trapped red blood cells [22, 23], GRE SVS is more frequently observed in patients with cardioembolic stroke than in those with other stroke subtypes [24].

Perfusion Weighted MRI

Perfusion weighted MRI (PWI) is a set of techniques that creates images depicting hemodynamics at the microvascular level. PWI has an advantage over other tools, such as PET or SPECT, in that it can easily be combined with structural and vascular MRI in a single session. Perfusion

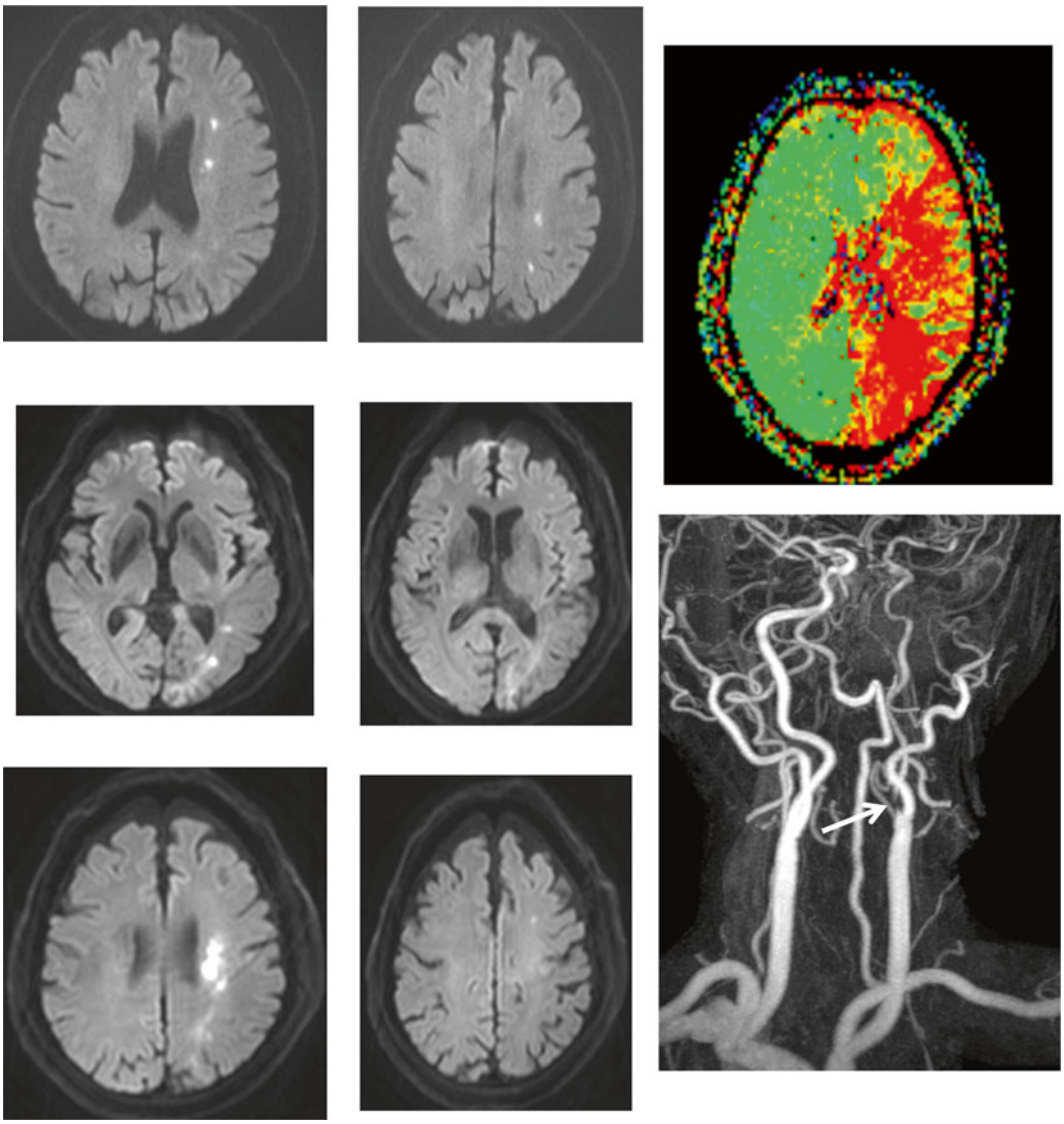

Fig. 8.2 An 85-year-old hypertensive man developed dysarthria, aphasia, and mild right hemiparesis. Initial DWI showed dot like infarcts in the middle cerebral artery–posterior cerebral artery borderzone and internal borderzone areas (*left upper and middle images*). Perfusion weighted MRI (*right upper image*) using regional mean transit time showed hypoperfused areas in the left MCA territory. The symptoms fluctuated and then his limb weakness worsened (MRC grade III) four days later when DWI showed enlarged ischemic lesions (*left lower image*). MR angiography showed severe atherosclerotic stenosis in the left carotid bulb area (*right lower image, arrow*). Angioplasty and stenting procedures were performed, and the patient's symptoms gradually improved

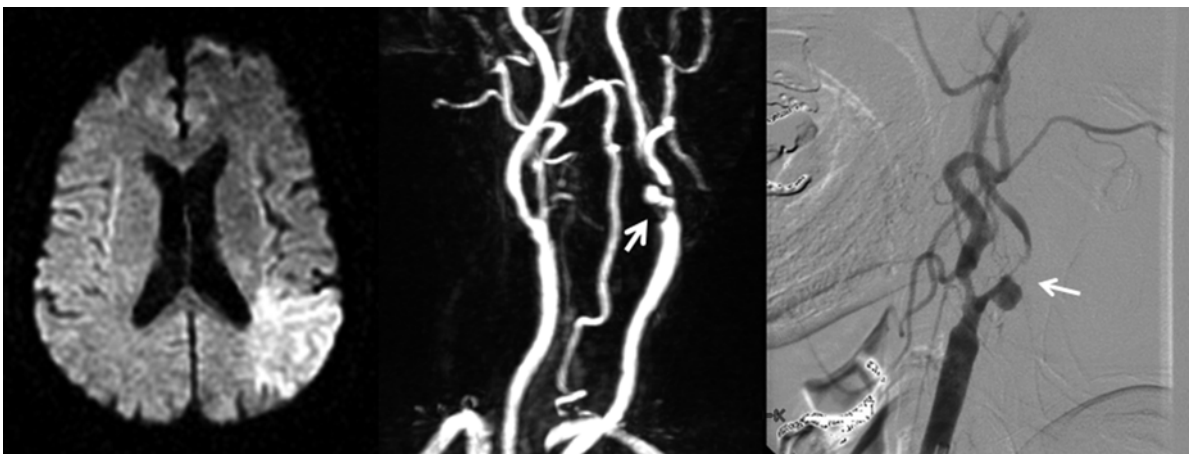

Fig. 8.3 A 76-year-old hypertensive, cigarette smoker developed sudden sensory aphasia and right hemiparesis. DWI showed an infarct in the left parietal area. MR angiography showed focal stenosis with ulceration in the left carotid artery (*middle image*, *arrow*). Conventional angiography showed similar findings (*right image*, *arrow*). The stroke mechanism was considered an artery-to-artery embolism from the ulcerative plaque

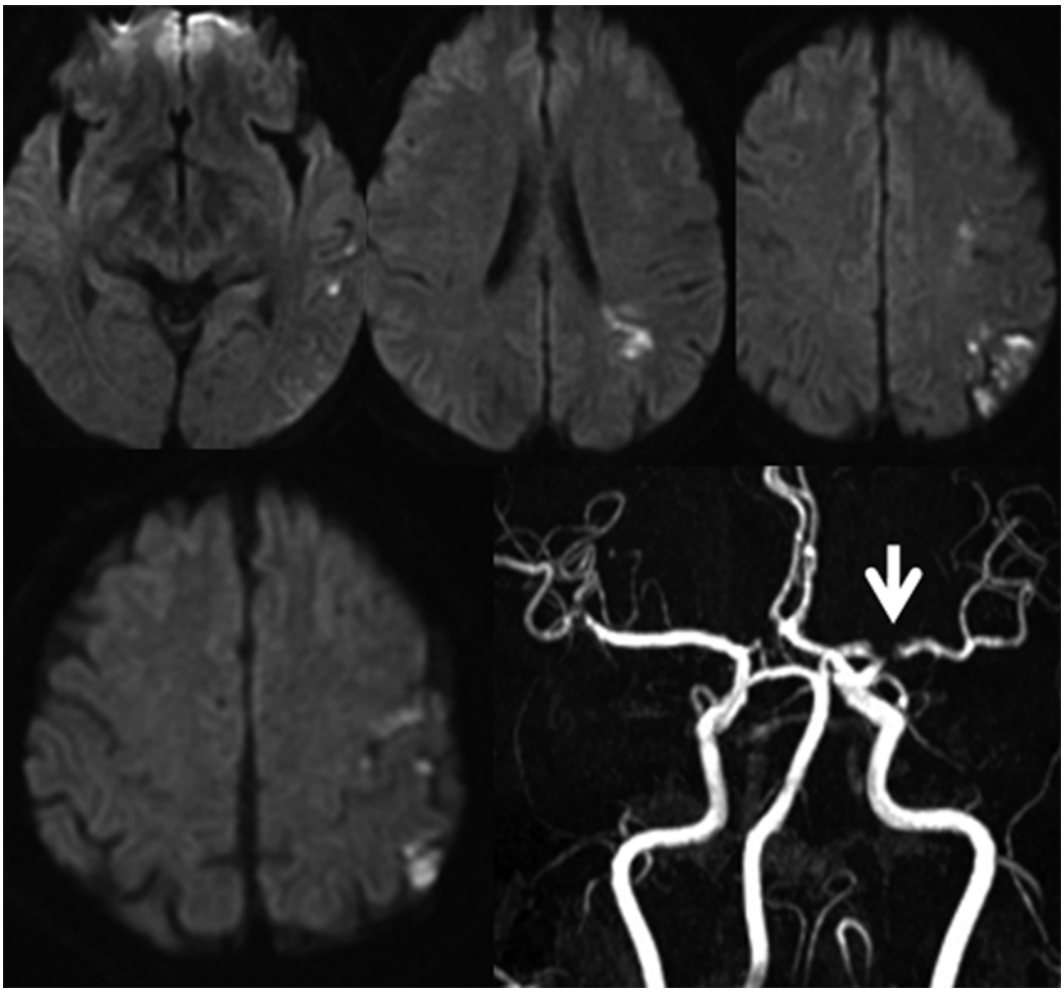

Fig. 8.4 A 62-year-old cigarette smoker developed dysarthria, acalculia, mild left hemiparesis, and paresthesia. DWI showed scattered infarcts in the right frontal, temporal and parietal area. MR angiography showed focal severe stenosis in the M1 portion of the left middle cerebral artery (*right lower image, arrow*). Mild stenosis was also observed in the right distal M1 portion. Five days later, repeat MR angiography showed that the middle cerebral artery stenosis was unchanged (not shown). The stroke mechanism was considered an artery-to-artery embolism from the left M1 atherosclerotic lesion

parameters are most commonly obtained following the intravenous bolus injection of a paramagnetic contrast agent, with perfusion parameters changing as the contrast agent passes through the brain vasculature. This technique generates time-contrast concentration curves, which allow the computation of regional mean transit time (rMTT), time-to-peak (rTTP), cerebral blood volume (rCBV), and cerebral blood flow (rCBF). The most sensitive MRI measure of abnormal perfusion is the rTTP map, which includes benign oligemic tissue as well as the penumbral area. Thus, the abnormal areas detected by rTTP and rMTT images are usually larger than those shown in rCBF and rCBV images.

PWI-DWI mismatches are used to assess potentially salvageable areas in patients with acute stroke and can help in deciding whether to perform recanalization therapy. These mismatches are also useful in identifying hypoperfusion mechanisms in patients with strokes and TIAs (Fig. 8.2, *right upper image*).

High Resolution Vessel Wall MRI

High resolution cross sectional vessel wall MRI (HRMRI) is occasionally used to assess the diseased vessel wall. Unlike other MR images, axial images are acquired based on a localizing two-dimensional time-of-flight MRA technique, focusing on the stenotic segment. HRMRI has emerged as a noninvasive method for identifying the characteristics of carotid plaques, including the state of the fibrous cap, the presence of necrotic lipid cores, and intraplaque hemorrhages [25, 26]. In patients with intracranial artery stenosis, HRMRI can detect atherosclerotic plaques (Fig. 8.5, *right lower image*), and help in determining the other etiologies of

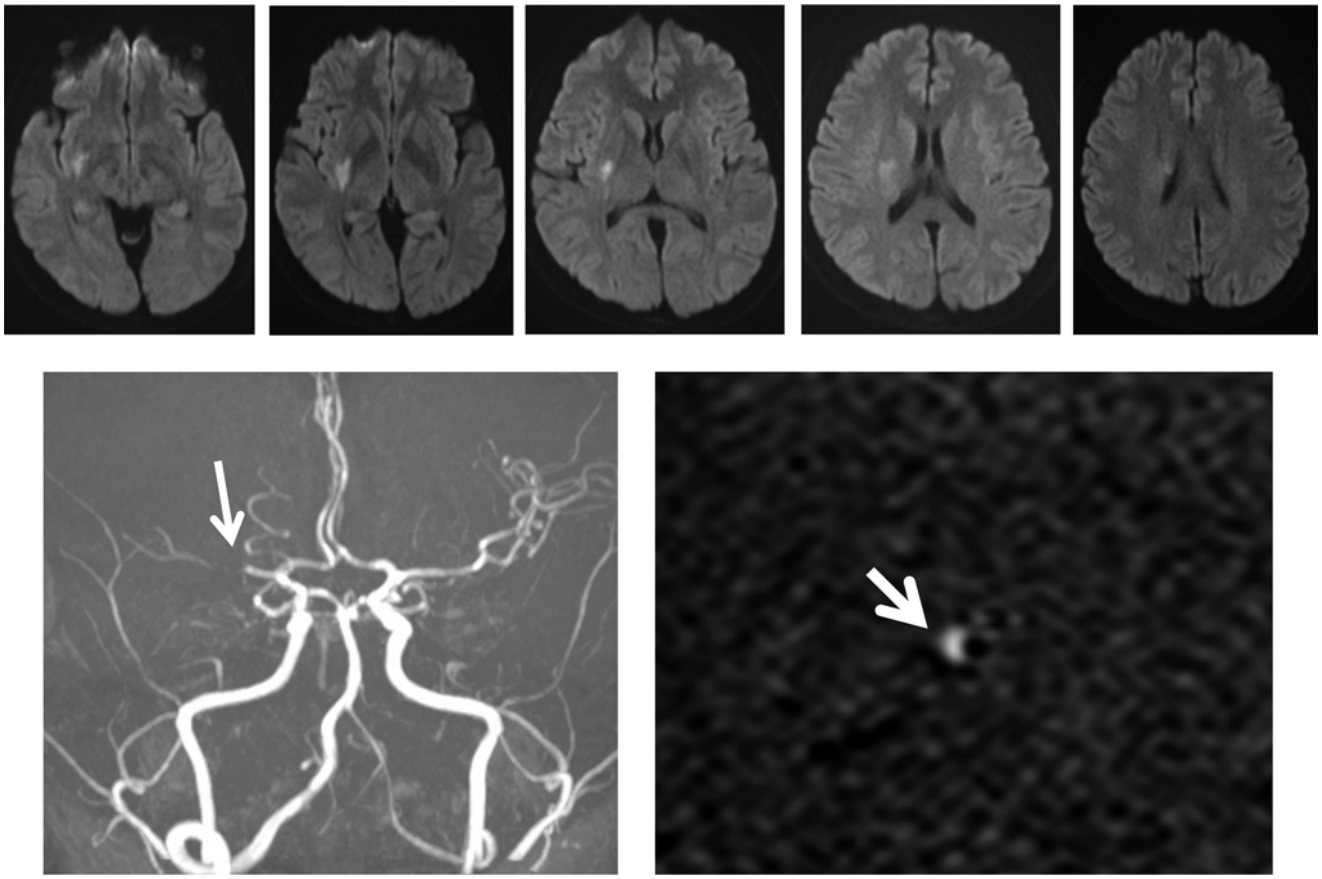

Fig. 8.5 A 52-year-old hypertensive and diabetic woman presented with dysarthria and left hemiparesis. DWI showed an infarct involving the right putamen/internal capsule and corona radiata. MR angiography showed right middle cerebral artery stenosis (*left lower image*, *thin arrow*) that probably induced branch (perforator) occlusion. High resolution vessel-wall MRI showed an eccentric, enhancing lesion, consistent with atherosclerotic plaque (*right lower image*, *thick arrow*)

stenosis (e.g., dissection or moyamoya disease) [27], but is still largely a research tool.

Doppler Ultrasonography

Duplex ultrasonography is a noninvasive method that can detect the stenosis of atherosclerotic vessels and identify the nature of plaques. Doppler findings of ulcerated, heterogeneous plaques suggest that these plaques are associated with a high risk for embolic stroke. Duplex scans in combination with MRA are frequently used to select patients for carotid endarterectomy.

Transcranial Doppler (TCD) imaging is helpful in assessing ICAS, by showing altered blood flow velocity and wave patterns in stenosed vessels. Despite its higher negative predictive value (83 %) TCD has a lower positive predictive value (55 %) than MRA [28]. Therefore, it cannot detect mild stenosis without producing significant hemodynamic alteration. Nevertheless, it can noninvasively identify and monitor the stenosed intracranial artery, and assess the status of collateralization. In addition, microembolic signals (MES) detected by TCD are likely to represent an embolus passing through the insonated artery [29–32] and help in assessing the risk of embolism [33]. Unfortunately, TCD results are dependent on the skills of individual technicians, and Doppler signals cannot be obtained in some elderly women due to temporal window failure [34].

Mechanisms of TIA and Stroke

Large Artery Disease

Large artery disease (LAD) is a major cause of cerebral infarction and TIA. Its main pathology consists of thrombosis superimposed on atherosclerosis. The process of atherosclerosis is complex. Repeated mechanical or toxic injuries to the intima associated with turbulent flow, and vascular risk factors such as hypertension, diabetes, hypercholesterolemia and

cigarette smoking, promote the process of atherosclerosis. Circulating lipids, especially low density lipoproteins, enter the vascular wall and inflammatory processes are initiated. Cholesterol containing macrophages and smooth muscle cells proliferate and result in atheroma formation [35–37].

Atherosclerosis is prone to occur in bifurcation areas, where blood turbulence occurs, which include the carotid bulb, siphon, proximal middle cerebral artery (MCA), proximal vertebral artery, proximal/mid-basilar artery, and proximal posterior cerebral artery (PCA). Although extracranial atherosclerosis (ECAS), especially ICA bulb disease, is the most common form of LAD in Caucasians, ICAS is more frequent than ECAS in Asians, Hispanics, and Blacks [38]. The reason for this ethnic difference is not fully understood [39].

Detailed stroke mechanisms in LAD include artery-to-artery embolism, hypoperfusion, branch occlusion, in situ thrombotic occlusion, and their combinations.

Artery-to-Artery Embolism

Examination of carotid endarterectomy specimens revealed that plaque inflammation, ulceration, erosion and hemorrhages were more common in symptomatic than asymptomatic patients [40–42]. Rupture of this unstable plaque promotes thrombus formation [43, 44], that may be broken up by blood flow and migrate through the bloodstream to occlude distant arteries, resulting in clinical symptoms (artery-to-artery embolism). The plaques can be identified in vivo by CTA, MRA, or conventional angiography (Fig. 8.3). On duplex scans, vulnerable plaques appear as echolucent and heterogeneous, with occasional evidence of intraplaque hemorrhage [45]. MES detected by TCD is also helpful in predicting future embolic stroke [46]. Artery-to-artery embolism is the predominant stroke mechanism in patients with ECAS, and one of the important stroke mechanisms in patients with ICAS (i.e., proximal MCA to distal MCA) [47] (Fig. 8.4).

DWI is useful in assessing the embolic mechanism of stroke, in that it can reliably detect small, scattered, cortical infarcts in the territory of the diseased artery. In many patients, DWI-identified lesions are also located in border zone areas, suggesting that embolism often develops in combination with hypoperfusion. Underlying perfusion deficits may contribute to artery-to-artery embolism by promoting a thrombotic condition and by the impaired clearance of migrated emboli [48].

Although less frequent than in anterior circulation stroke, artery-to-artery embolism also occurs in the posterior fossa. Significant atherothrombosis in the proximal vertebral artery often induces embolization, occluding distal arteries such as the PCA, superior cerebellar artery, posterior inferior cerebellar artery and the tip of the basilar artery [49]. Stenoses in the distal vertebral and basilar arteries may also produce embolism, although they more often cause brainstem infarction by way of branch occlusion [50, 51]. As in the anterior circulation, embolisms seem to occur more frequently in the setting of posterior fossa hypoperfusion caused by bilateral vertebral artery disease or hypoplasia.

Embolisms may develop in more proximal arteries such as the common carotid artery, subclavian arteries, ascending aorta and aortic arch. Transesophageal echocardiography is required to detect plaques in the aorta. Case control studies showed that thick (≥4 mm), mobile atherosclerotic plaques in the aorta are prone to develop recurrent strokes [52], although this argument has not been unanimously agreed [53, 54].

In Situ Thrombotic Occlusion

Extensive thrombus formation in areas of atherosclerotic plaque can ultimately occlude the vessel. In patients with ECAS, the clinical consequences of arterial occlusion are not so grave because of the ample collateral circulations in the circle of Willis. Therefore, total arterial occlusion may remain asymptomatic or produce minor hemodynamic TIAs or strokes. In rare patients with insufficient collaterals or those with previous contralateral ICA occlusion, ICA occlusion may result in devastating infarcts involving whole ICA (MCA and ACA, plus PCA in the presence of fetal circulation) territories [55].

In contrast to ECAS, insitu thrombotic occlusion in patients with ICAS more often produces significant cerebral infarction as the collateral circulation is less sufficient. The resultant infarcts are usually larger than those caused by branch occlusion. However, unlike cardiogenic embolism, in situ thrombotic occlusion rarely produces sudden, whole territory infarction because of the relatively well developed collateral circulation in patients with a chronic atherosclerotic process [56]. In patients with in situ thrombotic occlusion, the initial infarct size frequently grows in following hours or days, accompanied by progressive neurological worsening (Fig. 8.6). Thus, the ultimate size of the infarct varies according to the status of the collateral circulation, the speed of arterial occlusion and hemodynamic stability after the occurrence of stroke. With sufficient collaterals, total thrombotic intracranial occlusion may remain asymptomatic or result in only minor stroke or TIA.

Branch Occlusion

Branch or perforator occlusion is a stroke mechanism unique to patients with ICAS. Atherosclerotic plaques in the intracranial artery can occlude the orifice of the perforators, causing infarcts limited to the subcortical (Fig. 8.5) or brainstem areas [57] (Fig. 8.7). Pathological studies [58, 59] have shown that the pathologic substrates occluding the branching vessel are microdissection, plaque hemorrhage, and platelet-fibrin materials. Branch occlusion is an important, yet so-far neglected mechanism of LAD [57, 60]. It is one of the major

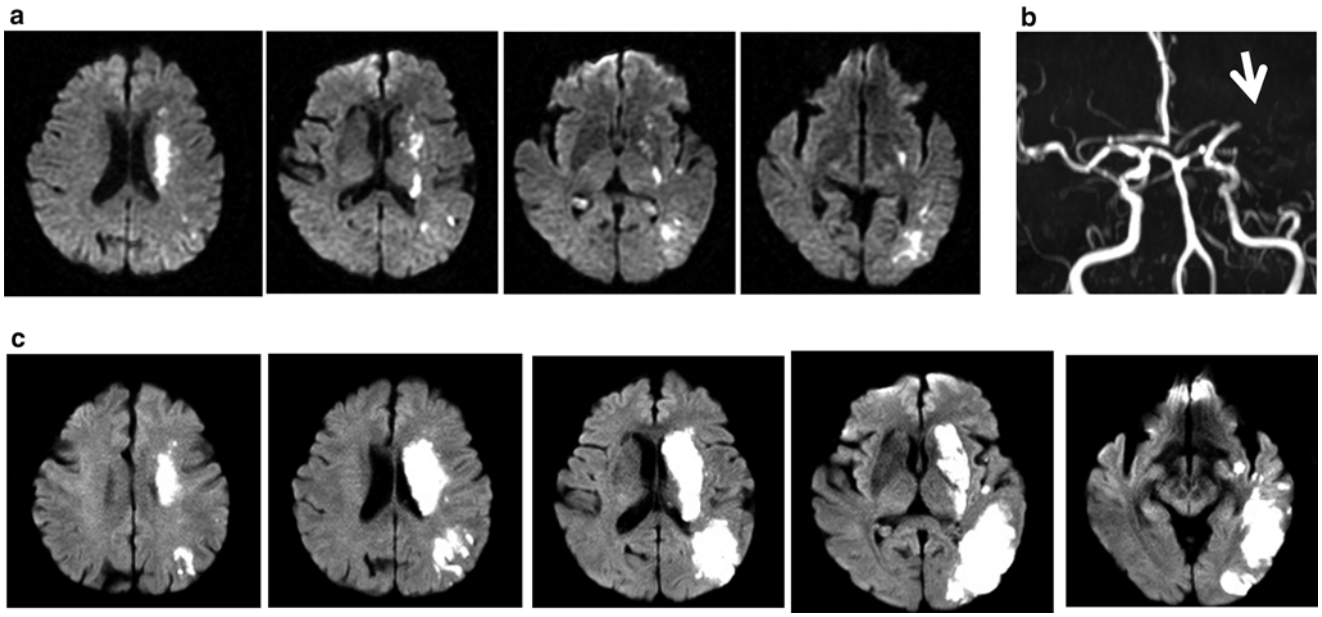

Fig. 8.6 A 64-year-old hypertensive man developed mild right hemiparesis and sensory aphasia. (**a**) DWI at the time of admission showed acute infarcts in the left lenticulocapsular and borderzone areas between middle cerebral artery and posterior cerebral artery. (**b**) MR angiography showed thrombotic occlusion of the left middle cerebral artery. The patient's neurologic symptoms progressively worsened to have severe right hemiparesis and global aphasia. (**c**) Follow up MRI 4 days later showed increased lesion size (from Wong KS CL, Kim JS. Stroke mechanisms In Kim JS, Caplan LR, Wong KS (ed) Intracranial Atherosclerosis, John Wiley & Sons, 2008:57–68, with permission)

mechanisms of brainstem stroke [50, 51, 61, 62]. Branch occlusion is currently easily recognized by imaging methodologies such as MRA and CTA [63–66]. Compared with arterial lesions producing embolism or hemodynamic impairment, branch occlusion is related to milder atherosclerosis [67].

The infarcts associated with branch occlusion do not differ fundamentally from "lacunar infarcts" caused by lipohyalinotic small artery disease (SAD), although their pathologic nature is different. The subcortical infarcts caused by branch occlusion tend to extend to the basal surface (Figs. 8.5 and 8.7), whereas a lacune caused by lipohyalinosis usually produces an island of ischemic tissues within the parenchyma (Fig. 8.8). Although both conditions equally produce lacunar syndromes clinically, the former is more often associated with atherosclerosis in other vascular beds [68], and an unstable and adverse clinical course than the latter [51, 69, 70].

Hypoperfusion

Progressive narrowing of the atherosclerotic vessel leads to hypoperfusion distal to the site of stenosis. Generally, the degree of hypoperfusion depends on the severity of vascular stenosis/occlusion, and there is a correlation between the occurrence of ischemic stroke and the severity of occlusive disease [71, 72]. However, the ischemic event is also influenced by the status of collateral flow, from arteries at the circle of Willis, external carotid artery system and cervicothyroid arteries, etc.

In patients with severe vascular stenosis/occlusion and insufficient collaterals, hemodynamic TIAs can occur. Typically, symptoms such as hemiparesis, aphasia, monocular blindness, limb shaking (in anterior circulation disease) or dizziness, diplopia, and visual disturbances (in posterior circulation disease) occur briefly and stereotypically in patients who are dehydrated or fatigued or at the time they suddenly stand up. Revascularization therapies, such as angioplasty/stenting or bypass surgery, may rapidly relieve these symptoms (Fig. 8.2). When stroke develops, the symptoms may fluctuate widely according to the degree of hydration, blood pressure and the position of the patient's head. With a continued perfusion defect, the symptoms may worsen gradually.

In the anterior circulation, infarcts caused by hemodynamic impairment usually develop in superficial (anterior cerebral artery-MCA, MCA-PCA) and/or internal borderzone areas (areas between superficial MCA pial penetrators and lenticulostriate arteries), the latter being more specifically associated with hemodynamic impairment than the former. Hypoperfusion as a pathogenic mechanism can therefore be recognized by DWI lesion patterns, the degree of vascular stenosis, the status of collateral vessels, perfusion imaging findings and appropriate clinical histories. In the posterior circulation, hemodynamic TIAs and strokes occur following severe steno-occlusive lesions occurring in both vertebral arteries or the basilar artery. Here, DWI patterns of hemodynamic infarction have not been clearly established.

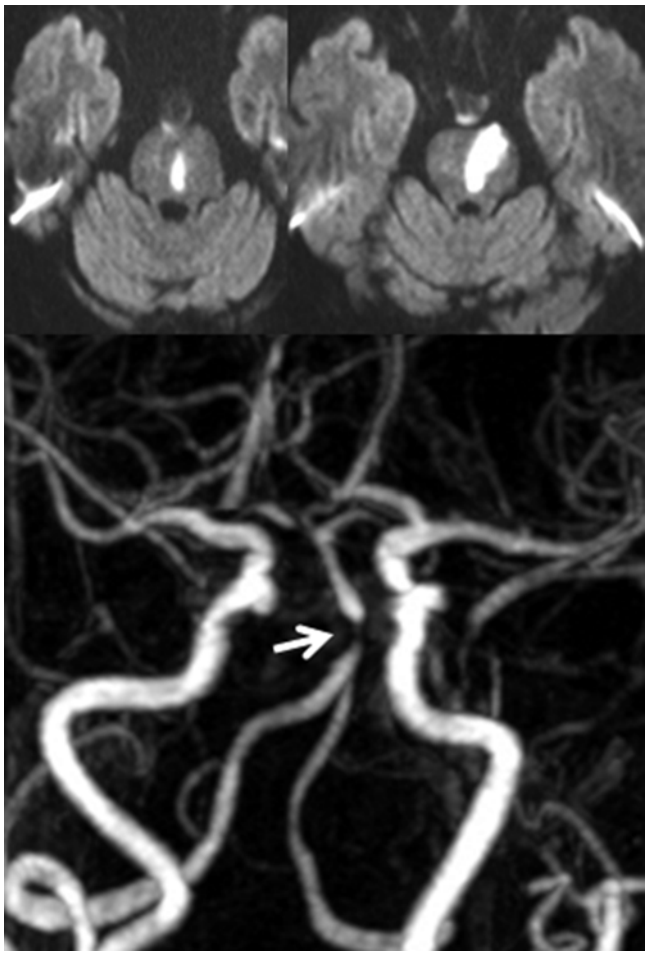

Fig. 8.7 An 81-year-old woman with hypertension and dyslipidemia developed dysarthria, right facial palsy, hemiparesis, and hemiataxia. DWI showed an infarct involving the left paramedian area of the pons. MR angiography showed focal basilar artery stenosis (*lower image, arrow*) that probably resulted in branch (perforator) occlusion

Although hypoperfusion is an important stroke mechanism, strokes caused by hemodynamic failure alone are uncommon in clinical practice. More often, hypoperfusion plays an additive role in the development of stroke, together with other major stroke mechanisms. As discussed earlier, the co-occurrence of hypoperfusion and embolism in patients with severe steno-occlusive vascular diseases is common, due in part to both mechanisms being related to complicated atherosclerotic plaques protruding into the lumen, and in part to ineffective wash out of emboli in hypoperfused areas [48].

Small Artery Disease (SAD)

A single subcortical infarction, traditionally called a "lacunar infarction" usually results from SAD [73]. Its pathological hallmarks include irregular cavities, less than 15–20 mm in size, located deep in the cerebral hemisphere, brainstem, and the cerebellum. Penetrating arteries associated with these lesions have disorganized vessel walls, fibrinoid material deposition and hemorrhagic extravasation through arterial walls, called "lipohyalinosis" by Fisher [59, 73–79] (Fig. 8.8). More benign and common vascular changes include the deposition of collagen replacing smooth muscles cells, with preserved lumen size and overall vascular architecture. Although these simple vascular changes do not produce arterial occlusions, they are associated with reduced vascular distensibility and are probably related to white matter ischemic changes commonly seen in elderly patients and those with vascular risk factors [80].

These vascular changes occur at arteries or arterioles 40–400 μm in diameter, and frequently affect the lenticulostriate branches of the MCA, the thalamoperforating arteries from the PCA and the perforators of the basilar arteries. The resultant subcortical infarcts produce "lacunar syndromes," including pure motor stroke, pure sensory stroke, sensorimotor, dysarthria clumsy hand, and ataxic hemiparesis without cortical symptoms. However, lacunar infarctions are not always caused by non-atherosclerotic lesions. As discussed earlier, single subcortical infarctions may be caused by branch occlusion associated with atherothrombotic lesion in the parental, intracranial artery (Figs. 8.5 and 8.7) These atherosclerotic causes of subcortical infarction have been collectively described as "branch atheromatous disease (BAD)" by Caplan [57]. In addition, subcortical lacunar infarcts, especially large ones, may be caused by embolism from a diseased heart or carotid artery [81, 82].

Cardiac Embolism

Embolism from a diseased heart is the cause of approximately 20–25 % of ischemic strokes [83–85], with the proportion depending on the extensiveness of cardiac workup, such as Holter monitoring or transthoracic/transesophageal echocardiography. A thrombus arising in the heart most frequently travels to the MCA territory. DWI studies have shown that the most frequent pattern of cardiogenic embolic infarctions was territorial and cortical [67]. However, cardiac embolism may affect any part of the brain, including the subcortical and brainstem areas [81, 82].

Infarcts associated with cardioembolism are typically larger than those associated with LAD, partly because the clots are larger and partly because of the insufficiently developed collateral circulation [86]. The onset is usually abrupt, with a gradual progression or fluctuation of symptoms being less common than with LAD. Unlike LAD, multiple vascular territories are often involved.

The occluded vessels are visible when angiography is performed soon after stroke. Although the MCA trunk and/or

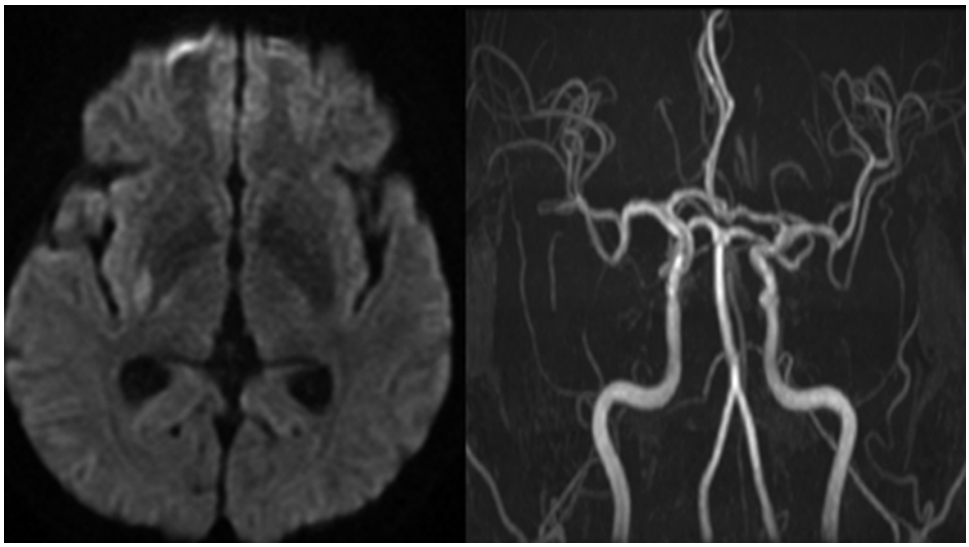

Fig. 8.8 A 54-year-old hypertensive man suddenly developed dysarthria, left hemiparesis, and sensory symptoms limited to the perioral area and the left hand. DWI showed an infarct involving the right putamen and internal capsule. MR angiography findings were normal. The stroke mechanism was considered a perforator occlusion associated with small vessel (lenticulostriate artery) disease

branches are the most frequently affected, larger vessels such as the ICA or common carotid arteries may be occluded. Clinical symptoms vary according to the size and location of the occluded vessels. Generally, cardiogenic embolic infarcts tend to produce more severe clinical symptoms than those associated with other etiologies. However, small cortical infarcts may produce minor or transient symptoms. Signs of peripheral artery occlusion, such as a reddish discoloration of the skin in distal limbs, are suggestive of embolic stroke.

In cardioembolic infarcts, the embolic materials are generally evanescent. Embolic occlusion of vessels has been detected in >75 % of patients evaluated by angiography within 8 h of stroke onset [87], but in only 40 % when angiography was delayed for up to 72 h [88]. Follow-up angiograms occasionally show recanalization of occluded vessels or migration of emboli from proximal to distal vessels. These characteristics may help differentiate embolic from atherosclerotic in situ occlusion [89]. Due in part to large lesion size and in part to frequent recanalization (and reperfusion), hemorrhagic transformation of an infarct is relatively common, which may result in delay in the initiation of anticoagulation therapy (Fig. 8.9). GRE SVS signs are more frequently observed in patients with cardioembolic than atherothrombotic occlusion [24], since mural thrombi formed in the heart chamber generally contain a large amount of trapped red blood cells.

Table 8.1 summarizes the important heart diseases causing embolism. Due to space limitations, only a few etiologies are briefly discussed here, but a more detailed discussion is provided in the following chapters of this section.

Atrial Fibrillation

Atrial fibrillation is the most common cause of embolic infarction in developed countries. Paroxysmal atrial fibrillation, which can be detected by Holter monitoring, is also risky. In patients with atrial fibrillation, the following characteristics are shown to increase the risk of stroke: previous embolic events, advanced age, hypertension, diabetes, and associated cardiac problems such as rheumatic valve disease, left ventricular dysfunction and enlarged atrium. Based on this information, scales have been developed that can predict the stroke risk and identify the patients who need anticoagulation therapy. One of the best validated schemes is the CHADS2 [90] (Table 8.2). The risk of thromboembolism linearly increases as CHADS2 score increases [91]. More recently, another system called the CHA(2)DS(2)-VASc score was introduced that also includes gender as a factor and puts more weight on patient age [92] (Table 8.2). CHA(2)DS(2)-VASc seems to improve the predictive value over the $CHADS_2$ score, as a study comparing CHADS(2) and CHA(2)DS(2)-VASc systems in patients with atrial fibrillation showed that the CHADS(2) score classified 33 % as requiring oral anticoagulation while the CHA(2)DS(2)-VASc score classified 53 % as requiring oral anticoagulation. With CHA(2)DS(2)-VASc system, many older, women patients are reassigned from the low- to high-risk categories [93].

It seems clear that these scoring systems help us predict embolism risks and define patients who need anticoagulation among those with atrial fibrillation. However, as many items are also factors predicting prognosis in patients with non-cardiogenic infarction, the scores may not be specifically valuable for patients with cardiogenic stroke [94].

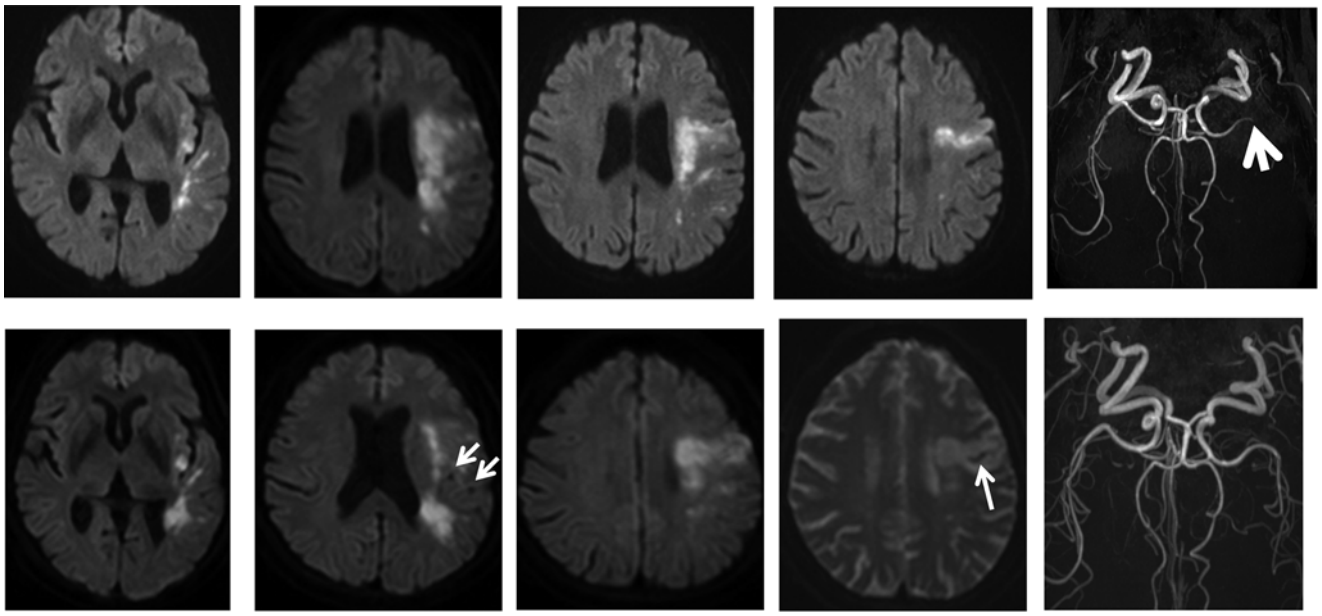

Fig. 8.9 A 75-year-old woman who had had hypertension and atrial fibrillation suddenly developed dysarthria and right hemiparesis. DWI showed an infarct involving the left middle cerebral artery territory (images in the *upper row*). MR angiography showed occlusion of the left middle cerebral artery (*right upper image*, *thick arrow*). Three days later, follow up images (*lower row*) showed recanalization of the vessel (*right image*). The infarct size slightly increased and hemorrhagic transformation (*thin arrows*) is observed. The stroke mechanism was considered a cardiogenic embolism

Table 8.1 Cardiac diseases producing embolic infarction

High risk for ischemic stroke
Sustained atrial fibrillation
Paroxysmal atrial fibrillation
Sick sinus syndrome
Sustained atrial flutter
Recent (<1 month) myocardial infarction
Rheumatic mitral or aortic valve disease
Bioprosthetic and mechanical heart valves
Congestive heart failure (with ejection fraction <30 %)
Dilated cardiomyopathy
Nonbacterial thrombotic endocarditis
Infective endocarditis
Left atrial myxoma
Low or uncertain risk for ischemic stroke
Mitral annular calcification
Patent foramen ovale
Atrial septal aneurysm

Table 8.2 CHADS2 and CHA2 DS2-CASc score

CHADS2		CHA(2) DS(2)-VASc	
*C*ongestive heart failure	1	*C*ongestive heart failure/left ventricular dysfunction	1
*H*ypertension	1	*H*ypertension	1
*A*ge ≥ 75 years	1	*A*ge ≥ 75 years	2
*D*iabetes mellitus	1	*D*iabetes mellitus	1
*S*troke/TIA	2	*S*troke/TIA/Thromboembolism	2
		*V*ascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
		*A*ge 65–74 years	1
		*S*ex *c*ategory (ie female gender)	1

Patent Foramen Ovale

The combination of patent foramen ovale (PFO) and right to left shunting is a potential source of embolism. Postmortem studies have confirmed that thrombi arising in the venous system, usually in the leg or pelvis, travel to occlude cerebral arteries through a right to left cardiac shunt (paradoxical embolism). Therefore, patients with a suspected embolism but without a clear source are usually assessed by transesophageal echocardiography with shunt tests to detect PFO and right to left shunt.

However, the significance of PFO as a cause of stroke remains still unclear; PFO is present in over 25 % of the normal population, and the combination of PFO and right to left shunting does not necessarily indicate causality. Accompanying venous thrombosis is rarely detected [95], and a meta-analysis showed that the rate of recurrent stroke does not differ between cryptogenic stroke patients with and without PFO [96]. Moreover, although previous studies have suggested a significant association between PFO with a large shunt and atrial septal aneurysm and recurrent stroke [97, 98], this was not confirmed by other studies [99].

Nevertheless, a recent study illustrated that PFO is not an incidental finding in approximately 2/3 of the patients with cryptogenic stroke, especially in young patients with atrial septal aneurysm [100]. Another study showed that PFO-related strokes are smaller and more often located in the vertebrobasilar territory than atrial fibrillation-related strokes [101]. These characteristics may be helpful in determining the causality of PFO in a given patient.

Uncommon Causes or Mechanisms of Stroke

Uncommon causes of stroke include dissection, moyamoya disease, arteritis, coagulation abnormality, and CADASIL. Details are described in other chapters. The basic stroke mechanisms in patients with these conditions are similar to those previously described, including artery-to-artery embolism, branch occlusion, hypoperfusion, in situ thrombotic occlusion and SAD. However, certain stroke mechanisms are more prevalent in a particular disease, depending on the nature and the predilection site of each vascular disease.

Cervicocerebral artery dissections occur in 1–2 % of all patients with ischemic strokes, but are one of the major causes (10–25 %) of stroke in younger patients [102]. As in atherothrombotic infarction, extracranial dissection usually produces stroke or TIA via artery-to-artery embolism with occasional hemodynamic impairment, whereas branch occlusion is an important stroke mechanism in intracranial artery dissection. Branch occlusion due to distal vertebral artery dissection is an important mechanism of medullary infarction [50].

Moyamoya disease is characterized by progressive occlusion of the distal ICA or proximal MCA, with the development of fine meshworks of basal collateral vessels. Cerebral hypoperfusion is the predominant stroke mechanism in these patients, and repeated TIAs are observed when patients are dehydrated or hyperventilating (e.g., eating hot noodles or crying). Decreased cerebral perfusion may result in impaired cognition and intelligence in young patients [103]. Less often, cerebral infarction due to embolism or thrombotic occlusion is encountered [104]. Abnormally dilated, fragile collateral vessels or aneurysm formation may lead to intracerebral hemorrhage (ICH) that more often occurs intraventrally than hypertensive ICH [105].

Vasculitis may be caused by infectious (e.g., bacterial, tuberculous, spirochetal, fungal, viral) and immunologic (e.g., lupus, polyarteritis nodosa, Takayasu disease) disorders. Generally, intracranial arteries adjacent to the brain are primarily involved, with the most frequent stroke mechanisms being in situ thrombotic occlusion and branch occlusion. Takayasu disease is an exception in that it primarily involves extracranial arteries, such as the aorta, subclavian arteries and common carotid arteries. Therefore, the main stroke mechanisms in this condition are hemodynamic impairment and artery-to-artery embolism. Subclavian steal syndrome may also develop. These inflammatory/immunologic conditions may involve the renal arteries thereby inducing hypertension. Cardiac involvement may lead to cardiogenic embolism. Chronic inflammatory conditions as well as the drugs used for this condition (e.g., steroid) may induce accelerated atherosclerosis, which can indirectly produce ischemic strokes.

Coagulation disorders such as factor abnormalities, protein C and S deficiencies, and anticardiolipin antibody syndromes are uncommon causes of arterial strokes. Cancers, especially malignant, advanced disease may provoke ischemic stroke via hypercoagulation, non-bacterial thrombotic endocarditis, cancer embolization and chemotherapy- or radiation-induced vasculopathy. Patients with cancer-associated stroke frequently have high serum D-dimer and CRP concentrations, and DWI often shows multiple, scattered lesions in multiple vascular territories [106]. With increase in aging population, cancer associated stroke is now being more frequently observed than before. Physicians have to be alert on this condition as unexplained embolic strokes with the above laboratory and imaging characteristics may allow us to detect previously unrecognized cancers (Fig. 8.1).

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a hereditary disorder characterized clinically by recurrent migraine, stroke episodes, and vascular dementia. Autopsy findings have shown that the cerebral and leptomeningeal arterioles are primarily involved. The media is thickened and smooth muscle cells are swollen and degenerated, resulting in luminal narrowing and occlusion. Thus, CADASIL is essentially an SAD. However, a recent study suggested that LAD may also occur in CADASIL patients [107].

Cryptogenic (Undetermined) Stroke

Cryptogenic stroke, or infarct of undetermined origin, may be defined when there is an incomplete workup, two or more possible mechanisms, or when the cause is undetermined despite adequate workup. Recent advances in imaging technologies have reduced the proportion of cryptogenic stroke, from 30 to 40 % in the late 1980s [83, 108], to <20 % more recently [109–112]. However, there are complex issues in defining and classifying stroke mechanisms, and the proportion of patients with cryptogenic infarction cannot be directly compared among different stroke centers.

Globally, the most important reason for inadequate etiological workup is a lack of resources. Countries in many parts of the world, including Africa, south Asia, and South America, simply do not have resources for an advanced

diagnostic workup, and the stroke subtypes and mechanisms in these countries remain largely unknown. Even in other countries, the extensiveness of etiologic workup depends on the interest of physicians or governmental policies; countries adopting socialized health care systems tend to regulate the use of expensive workup for cost–benefit reasons.

In addition, differences in operating definitions among centers affect the proportions of stroke subtypes. For example, in Western countries, where ECAS and artery-to-artery embolism are predominant, LAD has been defined based on significant (>50 %) large artery stenosis/occlusion, the presence of cortical symptoms, and appropriate duplex scan findings, as shown in classification systems such as TOAST (Trials of Org 10172 in Acute Stroke Treatment) [113] and Stop-Stroke Study TOAST (SSS-TOAST) [114]. However, infarcts caused by branch occlusion are frequently associated with mild (<50 %) ICAS, unassociated with cortical symptoms, and cannot therefore be classified as LAD [115]. Thus, classification of these patients as LAD, SAD or cryptogenic stroke, depending on the policy of the center, would affect the proportion of subtypes. Confusion in subtype classification also occurs in patients with PFO or aortic atherosclerosis. Due to questions regarding their causality, they are generally, though not always, classified as cryptogenic.

Subtype Classifications

The etiologies of ischemic stroke are diverse, making it difficult to include all stroke subtypes within a single classification system [116]. Recent advances in neuroimaging have significantly improved our understanding of the mechanisms of ischemic stroke, allowing treatment strategies to be individualized in accordance with the particular stroke pathophysiology [117].

The Harvard Cooperative Stroke Registry, the first published database on any medical condition, classified stroke patients by clinical findings. In this registry, only 45 % of patients received angiography, and 3 % underwent CT [118]. Ten years later, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) initiated the Stroke Data Bank, and classified stroke subtypes [83]. Although 97 % of the included patients underwent CT scan, nearly half of ischemic strokes were categorized as stroke of unknown cause. The Oxfordshire Community Stroke Project utilized a classification system based on clinical findings. This is a simple system, but the poor reliability in certain neurological signs such as hemianopia ($k=0.39$) and sensory loss ($k=0.15$) influences the reliability [119].

TOAST was the first classification system based on stroke mechanisms, and is still most widely used (Table 8.3). Vascular risk factors [120], early recurrence [121], and long-term recurrence and survival [84] were found to differ according to ischemic stroke subtypes classified by TOAST. However, the TOAST system has several limitations; the inter-rater reliability was only moderate [122], and the criteria for small-vessel occlusions, i.e., subcortical lesions smaller than 15 mm, appear to be too strict. Moreover, only ischemic strokes with stenosis >50 % in the corresponding artery were classified as large-artery atherosclerosis whereas mild stenosis (<50 %) with a potential to generate distal embolization was ignored. Thus, approximately 40 % of ischemic strokes remain in the undetermined category.

To resolve this issue, a new classification system, SSS-TOAST, was proposed [114]. In this system, each causative category is subdivided according to the level of evidence, and algorithms are used to determine the most likely etiology. The criteria for small-vessel occlusion are widened from "less than 15 mm" to "20 mm." Even if a single subcortical infarction is larger than 20 mm, it may be classified as a small-vessel occlusion according to the algorithm if there is no "evident" support for classification into other categories. Additionally, embolic infarctions with corresponding stenosis less than 50 %, with plaque protruding into the vessel lumen, may be classified as large-artery atherosclerosis, in the absence of evidence suggesting other categories.

Table 8.3 TOAST classification

Features	Large artery atherosclerosis	Cardioembolism	Small artery occlusion	Other cause
Clinical				
Cortical or cerebellar dysfunction	+	+	–	+/–
Lacunar syndrome	–	–	+	+/–
Imaging				
cortical, cerebellar, brainstem, or subcortical infarcts >1.5 cm	+	+	–	+/–
Subcortical or brainstem infarct <1.5 cm	–	–	+/–	+/–
Tests				
Stenosis of extracranial internal carotid artery	+	-	–	–
Cardiac source of emboli	–	+	–	–
Other abnormality on tests	–	–	–	+

These algorithms decreased the percentage of strokes designated "of undetermined etiology" to 4 %.

The complex algorithms of SSS-TOAST have been automated in the next web-based Causative Classification System (CCS). If multiple potential causes are present, the patient is automatically assigned to the most likely mechanism, based on the following data: (1) clinical evaluation; (2) neuroimaging (CT or MRI); (3) extra- and intracranial vascular investigations (carotid doppler/transcranial doppler, MRA, CT angiography, or conventional angiography); (4) cardiac evaluation (electrocardiogram, echocardiography, and Holter monitoring); and (5) other workup for uncommon causes of stroke. This new process yielded a high inter-rater reliability, without inflating the unclassified category [123].

Another classification system proposed is the ASCO [124], that stands for atherosclerosis, small-vessel disease, cardiac embolism, and other causes. This system includes all the potential phenotypes of a given patient. According to the level of evidence, each of the four ASCO phenotypes is graded 1, 2, or 3; 1 for "definitely a potential cause of the index stroke," 2 for "causality uncertain," or 3 for "unlikely a direct cause of the index stroke (but disease is present)." When the disease is completely absent, the grade is 0; when grading is not possible due to insufficient workup, the grade is 9. For example, a patient with 70 % ipsilateral symptomatic stenosis, leukoaraiosis, atrial fibrillation, and platelet count of 700,000/mm can be classified as A1-S3-C1-O3. Thus, the ASCO system assigns a level of likelihood to each potential cause and chooses the most likely etiology, but without ignoring other unrelated vascular conditions. The system may be utilized flexibly according to the purpose of physicians. For example, a patient's treatment can be adapted to the most likely etiology (e.g., grade 1 in one of the four ASCO phenotypes), while enrollment of patients in clinical trials may allow several of these four phenotypes (e.g., patients with A1 or A2). Recently, ASCO phenotyping was slightly revised and upgraded to include "D" for dissection (ASCO-D) [125]. The ASCO or ASCO-D system has a merit in that no information is neglected from a given patient, but the many possible combinations can generate confusion.

Because these systems are still incomplete, further research is needed worldwide to establish standardized definitions and classifications of strokes. At present, each center should establish its own consensus opinion on standardized etiologic workup and operating definitions. Since stroke mechanisms are often unclear in many patients, establishment of mechanism and subtype classifications should be made by the consensus of teams of physicians who confer regularly after reviewing and discussing all available information on a given patient [85, 112].

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Traditional Stroke Risk Factor Treatment

9

Shelly Ozark and Bruce Ovbiagele

Introduction

The greatest opportunity for decreased stroke incidence and mortality is through stroke prevention [1]. While the focus for every patient should be on the primary prevention of stroke, for many patients the need for true risk factor modification doesn't become obvious until their first stroke has already occurred. For these patients, secondary prevention of stroke is crucial—the underlying pathophysiological mechanisms to which they are susceptible are already in progress, and now clearly manifesting clinically. However, despite studies suggesting that stroke can be prevented in 50–80 % of patients, this promising opportunity to reduce the burden of stroke is not broadly being realized [1]. Use of evidence-based therapies for the prevention of ischemic stroke in patients receiving conventional care remains inadequate, despite the available data and the current national guidelines that support their use [2]. A comprehensive discussion of this issue can be found in the sections detailing stroke systems of care.

The importance of early diagnosis and aggressive initiation of secondary prevention strategies for patients with acute ischemic cerebrovascular syndromes [3] is reinforced by community-based data that confirm a much higher early risk of subsequent stroke than was previously appreciated in patients with transient ischemic attacks (TIAs) or minor stroke [4]. The initiation of proven secondary prevention strategies is most effective when implemented early (before disabling stroke occurs), monitored frequently, and maintained long term after an index cerebrovascular event [5, 6]. As such, secondary prevention must start when the patient is admitted for stroke work-up and must be adapted to the individual's needs. Fortunately, longitudinal epidemiologic studies have identified several modifiable stroke risk factors including hypertension, cardiac disease, diabetes mellitus, hyperlipidemia, cigarette smoking, alcohol abuse, physical inactivity, carotid stenosis, and prior stroke or transient ischemic attack [7].

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Large Artery Atherosclerotic Disease—Which Patients Need Revascularization?

During work-up following ischemic stroke, it is common to find atherosclerotic plaque buildup in the extracranial carotid arteries. For these patients it is not always clear what, if any, intervention should be performed on the newly discovered stenosis and when it should be performed. For most patients with symptomatic extracranial high-grade carotid stenosis, there is a clear benefit to carotid endarterectomy (CEA) over carotid stenting (CS). However, the decision of whether or not to intervene rests on the answers to the following questions: (1) Does the stroke represent symptomatic stenosis, that is, was the stroke likely caused by the stenosis? (2) How severe is the stenosis? And (3) what are the patient's other comorbidities and reasons for stenosis?.

Typically the answers to questions one and two are very much related. To make these assessments, one must consider the patient's diagnostic images. Co-existing acute infarcts in other vascular territories should deflect blame from the stenotic vessel and refocus attentions towards more central or cardiogenic etiologies such as atrial fibrillation. However, even in these instances, a classic border zone appearance of infarcts on the corresponding side of the stenosis should still raise the question of a symptomatic stenosis in addition to possible cardiogenic process.

Once carotid stenosis is established as the causative mechanism, treatment may be guided by the principles discussed in

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the chapter on large artery atherosclerosis. If not causative and no other sources of stroke are identified, the risk factor modification discussed below should be implemented.

Lipid Modification

The need for adequate control of serum lipid levels for secondary prevention of stroke in patients with heterogeneous causes of stroke or TIA was illustrated by the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study [8]. SPARCL randomized 4,731 patients with ischemic or hemorrhagic stroke and no history to heart disease to atorvastatin 80 mg vs. placebo. During a median follow-up of almost 5 years, 11.2 % of patients receiving atorvastatin and 13.1 % receiving placebo had a fatal or non-fatal stroke (5-year absolute reduction in risk, 2.2 %, NNT = 45; adjusted hazard ratio, 0.84; 95 % confidence interval, 0.71–0.99; $P = 0.03$; unadjusted $P = 0.05$). SPARCL also showed that aggressively lowering low density lipoprotein (LDL) levels to <70 resulting in a 28 % reduction of subsequent ischemic stroke. For those patients who were able to achieve a reduction of 50 % from their baseline LDL, a 35 % decrease in the rate of stroke was seen. For this reason, the current AHA/ASA Secondary prevention of stroke guidelines recommend the use of high-dose statin medications for stroke patients following stroke thought to be due to atherosclerosis. For those thought to be due to a different etiology, moderate dose statins are recommended [1]. There is insufficient evidence to recommend the use of fibrates or niacin for secondary stroke prevention; however, in patients unable to tolerate statins, these medications may present a reasonable therapeutic option. There is some suggestion from the SPARCL and other trials that the use of statins may increase the risk of intracranial hemorrhage, and as such, some experts avoid use of statins in patients with ICH without known atherosclerotic cardiovascular disease.

Statins, however, have been shown to convey a multitude of beneficial effects beyond just lowering cholesterol which many feel outweigh any additional ICH risk that they may convey. These effects include improved endothelial function through antioxidant activity [9], plaque stabilization through reduction in inflammation and metalloproteinase activity [10], and inhibition of platelet deposition and thrombus formation on damaged vessel walls [11].

Discussion of Case Vignette 1

Key features of this case are the patient's history of insulin-dependent diabetes, prior myocardial infarction, elevated LDL cholesterol and low HDL cholesterol levels. Based upon the history of coronary heart disease (CHD) and diabetes, the patient has established symptomatic atherosclerotic cardiovascular disease and a coronary heart disease risk equivalent (diabetes), regardless of whether his underlying stroke mechanism is determined to be atherosclerotic in nature. As such, we would recommend the use of high-dose statin therapy, typically atorvastatin 80 mg, which was used in the SPARCL trial, or Rosuvastatin 20 mg daily (another high-dose statin regimen). Aiming for an LDL cholesterol level <70 mg/dL may be appropriate based on a post hoc analysis of the SPARCL trial showing that recent stroke and TIA patients with an average LDL cholesterol of <70 mg/dL had significantly lower recurrent vascular events than those with LDL cholesterol levels >100 mg/dL [1]. If the patient is unable to tolerate the 80 mg dose, down titration to a lower dose (e.g., 40 mg of atorvastatin daily) with or without the addition of a non-statin lipid modifier agent (ezetimibe 10 mg daily). Low HDL cholesterol levels are associated with a higher risk of stroke, and boosting HDL cholesterol levels above 40 mg/dL in men has been recommended as a secondary lipid therapeutic target (after LDL cholesterol) in patients at high vascular risk. So far, HDL-boosting medications have either been ineffective or possibly harmful, so the main recommendation at this time (based on the best available evidence) for raising HDL cholesterol levels is advising the patient to engage in regular exercise accompanied by weight loss [1]. Additional efforts should be made to identify and mitigate other potential vascular risk factors in this patient, such as atrial fibrillation.

Blood Pressure Lowering

Hypertension is one of the most important risk factors for stroke, with the risk of first stroke increasing directly with blood pressure. But does this play as important a role in secondary stroke prevention, and if so, what are the best agents to use?

The Poststroke Antihypertensive Treatment Trial (PATS) and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial proved the importance of blood pressure reduction in secondary stroke prevention, but also suggested that certain medication classes, namely diuretics and ACE inhibitors, may play a greater role in this fight than other drug classes. Many providers may mentally classify ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) as being similar classes of drugs, switching a patient from an ACE-I to an ARB in cases of drug-related cough for example. However, for secondary stroke prevention these medication classes are far from equivalent. While ACE-I have been shown to be effective in not only lowering blood pressure but also reducing the incidence of secondary stroke, the Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) [12] and the Prevention Regimen for Effective Avoiding Secondary Strokes (PRoFESS) [13] studies clearly illustrated that ARBs do not appear to confer additional benefit for stroke prevention beyond their blood pressure lowering

properties when used as a secondary prevention mechanism for the prevention of stroke. In the PRoFESS trial, patients were randomized to the use of telmisartan 80 mg daily vs. placebo within an average of 15 days following stroke. After a mean follow-up of 2.5 years, no additional reduction in the rate of stroke, cardiovascular event, or diabetes was seen. Thus, it is not merely blood pressure lowering but the mechanism by which such lowering is attained that is important.

The degree of blood pressure control necessary for optimal secondary stroke prevention remains unclear, but current guidelines [14] suggest that the goal should be systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure <90 mmHg. This has been illustrated by studies comparing targets of SBP <120 mmHg and SBP <140 mmHg, which showed no reduction in rate of stroke for those randomized to stricter blood pressure control [15]. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial for the prevention of lacunar strokes randomized patients following recent lacunar or small vessel strokes to two blood pressure targets, <150 systolic blood pressure (SBP) or <130 SBP. Though there was an overall reduction in the number of strokes and cardiovascular events seen in patients assigned to SBP <130 mmHg group, there was no significant difference seen in the rate of recurrent stroke or other cardiovascular events between the two groups [16].

Glycemic Control

Insulin resistance and progressive destruction of insulin-secreting beta-islet cells of the pancreas are hallmarks of diabetes mellitus, which is defined as having a hemoglobin A1c of ≥6.5 %. Prediabetes, defined as impaired glucose tolerance, impaired fasting glucose, and moderate elevations in hemoglobin A1c (HgbA1c 5.7–6.4 %), is its precursor. Diabetes is highly prevalent in the US population and as many as 8 % of ischemic strokes may be directly attributable to poorly controlled diabetes [17]. By some estimates over 77 % of patients who have had a stroke are either prediabetic or diabetic [18], and the results of the Cardiovascular Health Study have implicated diabetes in causing as much as a 60 % increased risk of recurrent ischemic stroke [19].

A lack of studies specifically targeting diabetes control in stroke secondary prevention limits the ability to discuss the efficacy of interventions in this population; however information can be extrapolated from studies in non-stroke populations. There is no convincing evidence that intensive control of impaired glucose intolerance alters the incidence of larger vessel (so-called macrovascular) events. However, both lifestyle interventions and the use of metformin may prevent progression from a prediabetic state to frank diabetes mellitus, by 58 and 31 % respectively according to the Diabetes Prevention Program Trial [20]. The avoidance of progression to diabetes or reduced duration as a diabetic may have microvascular implications over time by limiting its role in the development of lipohyalinosis.

Lifestyle Modification

While lifestyle modification has never been formally tested in a randomized controlled clinical trial, it would make sense that modifying lifestyle risk factors shown to influence primary risk for stroke may have a role in mitigating risk for recurrent stroke as it has for other medical risk factors such as hypertension. Smoking cessation, improvements in diet, and alterations in level of physical activity seem the highest yield targets for lifestyle modification given the incidence of such risk factors within the stroke patient population.

Smoking

Smoking substantially increases the risk of both first and recurrent strokes, the latter being proven most substantially in elderly populations for whom there was a twofold increased risk of recurrent stroke in the Cardiovascular Health Study [19]. Secondhand or passive exposure to tobacco smoke has also been implicated in the increased risk of first stroke. As such, smoking cessation and the avoidance of secondhand smoke should be encouraged of all patients who have had a stroke. For those who do smoke, nicotine replacement products and counseling may greatly assist patients in quitting.

Dietary Changes

While some health benefits have been seen with low to moderate alcohol consumption [21], including lower risk for first time ischemic stroke, patients should be counseled against heavy or binge-type alcohol consumption due to the well-known risks of cardiomyopathy, atrial fibrillation, and liver disease that may result from long-term heavy use.

The role for modification of specific micro- and macronutrients in the prevention of stroke is limited in evidence; however both reduced dietary vitamin and potassium levels have been implicated in the increased risk for stroke [22, 23], though studies of supplementation of these nutrients for secondary prevention purposes have not been performed. Similarly, diets rich in folic acid may offer an 18 % reduced risk of initial stroke occurrence [24]. The only micronutrient supplementation studies that have occurred involved the supplementation with B vitamins following stroke and these studies indicated that B vitamin supplementation failed to

offer any statistically significant protection against secondary stroke, except in a small subset of patient with hyperhomocysteinemia and low B12 levels [25].

For the average American diet, however, much of the focus for dietary modification is on reduction of nutrients harmful in excess rather than supplementation. This included the recommendation to reduce dietary sodium intake to less than 2.4 g/day, with even greater benefits seen for reduction in blood pressure for those who reduce their sodium intake to as little as 1.5 g/day [26].

While specific diets have not been proven to reduce secondary stroke, there is some evidence that following a traditional Mediterranean diet rich in fruits, vegetables, fish, nuts, and olive oil may reduce the incidence of first stroke [27], and as such, this diet may offer benefit in secondary prevention.

Physical Activity

Less than 50 % of adults achieve the 40 min of moderate to vigorous physical activity 3–4 times weekly recommended by the American Heart Association. Despite several studies implicating the benefits of exercise in improvements of other cardiovascular risk factors including control of insulin resistance and lipid metabolism as well as reductions in blood pressure and endothelial dysfunction, there have been no studies directed towards the use of exercise protocols in secondary stroke prevention. Despite this, meta-analyses of lifestyle interventions including increased physical activity showed greater benefit in secondary stroke reduction than several key drug therapies including aspirin and anticoagulation, with an odds ratio of 0.09 vs. anticoagulation and 0.10 vs. antiplatelets. Following stroke, a patient's ability to engage in any substantial degree of physical activity may be severely limited. Lingering deficits in strength, balance, and coordination may prevent a patient's use standard exercise programs following stroke. However, for those who are physically able to do so, either independently, or with the help of a rehabilitation professional, patients should be counseled to exercise moderately for at least 40 min three times per week, the amount recommended by the American Heart Association for all adults [28]. Structured programs geared towards the specific needs of patients post-stroke may have greater impact than counseling alone by healthcare providers about the importance of exercise.

Discussion Case Vignette 2

The keys features of this patient's history include her active smoking, status as a prediabetic (hemoglobin A1c of 5.9 %), and mild hypertension (blood pressure 146/88 mmHg). As she has multiple vascular risk factors, the patient demands a multifactorial approach to secondary prevention. Stopping smoking may halve her risk of a recurrent stroke compared to similar patients who continue to smoke, and so counseling her about the continued risk of smoking as well as providing her with smoking cessation options including a patch or medications will be crucial [1]. Avoiding a transition from the prediabetic to a frank diabetic state will be key to this patient's risk reduction as well, and as such recommending therapeutic lifestyle changes including regular exercise and a healthy diet, along with weight loss if appropriate, is important. For certain high-risk patients with prediabetes (morbidly obese, strong family history of diabetes), initiating metformin on top of encouraging positive lifestyle changes may be indicated [1]. Starting a low-dose antihypertensive agent to bring the patient to a blood pressure goal of less than 140/90 mmHg will assist in controlling the premier modifiable risk factor for recurrent stroke prevention. Any antihypertensive agent class can be used in this situation although available clinical trial evidence centered on thiazide-diuretic-like based (indapamide +/− angiotensin converting enzyme inhibitor [ACE] inhibitor) regimens. No antihypertensive agent class has so far shown a benefit in preventing recurrent stroke beyond blood pressure lowering effects. If the patient had frank diabetes, then a modulator of the angiotensin system (ACE inhibitor or angiotensin receptor blocker) would be indicated given the proven nephroprotective benefits of these agents.

Conclusion

Secondary stroke prevention remains a dynamic field of study, with several upcoming trials that will continue to inform about the best therapies for preventing additional stroke. The Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke in Hypertensives (ESH-CHL-SHOT) Trial is one such trial which hopes to identify optimal blood pressure and LDL goals, using all open label, approved antihypertensive and statin medications to see if values lower than current guideline recommended targets further reduce secondary stroke incidence. Current questions about optimal risk factor management will be answered by ongoing studies including Treat Stroke to Target (TST), which seeks to determine if there is an increased therapeutic benefit if the goal of lipid management is LDL <70 mg/dL instead of LDL 100 mg/dL, and the Insulin Resistance Intervention After Stroke Trial (IRIS) which seeks to determine if the use of insulin resistance modifying agents following stroke reduces the occurrence of future strokes. Also the concept of a singly polypill that contains the 3 main therapeutic class of secondary prevention drugs is being tested in clinical trials of patients at high vascular risk [29–31].

A recent observational study suggested that optimal combination of secondary prevention medication classes after a recent noncardioembolic stroke is indeed associated with a significantly lower risk of stroke, major vascular events, and death [32], but dedicated clinical trials are required to convincingly support this premise. Despite the aging population and the higher frequency of stroke in such a population, few studies have tackled questions of secondary prevention in the very elderly, those over 80 years of age, leaving much work to be done in the field of stroke secondary prevention research.

This chapter sought to address basic therapeutic strategies that most providers need to know to help their patients prevent a secondary cerebrovascular event, especially for their patients with atherosclerotic strokes. For more in-depth discussion of less common stroke risk factors, other chapters in this book are recommended for further reading.

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Heterogeneous Causes of Stroke: Antithrombotics

10

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Case Presentation A 65-year-old male with multiple risk factors for cerebrovascular disease presents to the hospital with several days of dizziness, vertigo, and headache. He is admitted to the hospital and a thorough work-up reveals multifocal strokes in the territory of the right posterior-inferior cerebellar artery, the basilar artery perforators, and right posterior-cerebral artery. The left vertebral artery is calcified and completely occluded. The right vertebral artery is >50 % occluded in its intracranial portion on CT angiogram. The basilar artery has a near complete occlusion in the mid-section with evidence of acute perforator strokes in the pons. The patient is admitted to the neurological intensive care unit for close monitoring. Physical examination reveals an awake and oriented patient with weakness in the left upper and lower extremities, left visual field deficit, and a skew deviation. The patient also has moderate dysphagia and dysarthria. The cause of stroke is determined to be secondary to an artery-to-artery stroke and after a prolonged and complicated hospitalization, the patient undergoes tracheostomy and feeding tube placement and is discharged on a combination of aspirin and clopidogrel for secondary prevention against stroke.

Indications

Anti-platelet agents can be used for the recurrence of ischemic stroke in patients who do not suffer from atrial-fibrillation [1–3]. The most recent American Heart Association (AHA)/American Stroke Association (ASA) guidelines for secondary prevention of stroke recommend the following treatment in patients with heterogeneous causes of stroke [4]:

1. Acute non-cardioembolic ischemic stroke or TIA (Class I; Level A recommendation): Aspirin (50–325 mg/day) monotherapy (Class I; Level of Evidence A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B) is recommended as initial secondary prophylaxis. Clopidogrel (75 mg) monotherapy is a reasonable alternative (Class IIa; Level of Evidence B), especially for patients who are allergic to aspirin. A combination of aspirin and clopidogrel can also be initiated within 1 day of a minor ischemic stroke or TIA and continued for 90 days (Class IIb; Level of Evidence B).
2. In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin (50–150 mg/day) is reasonable after the first trimester of pregnancy (Class IIa; Level of Evidence B).

Antiplatelet Agents Used in the Secondary Prevention of Stroke/Transient Ischemic Attacks (TIA)

Aspirin

Aspirin is the antiplatelet agent that has been most extensively studied in stroke and TIA prophylaxis. Several studies have reported that aspirin prevents recurrent ischemic events. Lower doses of aspirin have been shown to be as effective as higher doses, especially between 75 and 1,500 mg [1, 5, 6]. Although efficacy data is limited for doses less than 75 mg, higher doses do tend to have higher toxicity risks [1, 7–10]. Doses as low as 30 mg of aspirin per day have been shown to be effective in preventing strokes and TIA, as shown in the Dutch TIA trial [10]. The UK-TIA

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study also reported favorable results in 2,435 patients taking aspirin (300 mg or 1,200 mg) compared to placebo, after from suffering a minor stroke [9]. In this randomized placebo-controlled study, participants were followed for a maximum of 6 years. The odds of suffering a vascular event, including a major stroke, were 15 % less in both of the aspirin groups compared to the placebo group [9]. Similarly, a meta-regression analysis of 11 randomized, placebo- controlled trials that included 5,228 patients treated with aspirin also concluded that aspirin doses from 50 to 1,500 mg/day uniformly decreased the risk of stroke by about 15 % (risk ratio, 0.85; 95 % CI, 0.77–0.94) [5].

Aspirin is recommended for secondary prophylaxis beginning immediately after an acute stroke. A Cochrane review of 12 trials involving 43,041 participants [mostly from the International Stroke Trial (IST) [11] and Chinese Acute Stroke Trial (CAST) [12] concluded that with aspirin treatment there was a significant decrease in death or dependency at the end of maximum follow-up of 6 months (odds ratio, 0.95; 95 % confidence interval, 0.91–0.99) [13]. This review placed the number needed to treat to reduce the risk of early recurrent ischemic stroke and improve long-term outcome at 79 despite there being a small increase in hemorrhagic complications [13]. Recent guidelines strongly recommend aspirin administration (325 mg) in the first 24–48 h after an acute stroke [14, 15]. At the present time, the AHA/ASA guideline for the early management of patients with acute ischemic stroke does not recommend clopidogrel, tirofiban, eptifibatide, or glycoprotein IIb/IIIa receptor inhibitors as substitute for aspirin early after stroke.

In the Canadian cooperative study, 585 patients were treated with an antiplatelet agent and observed for approximately 26 months for subsequent ischemic events. The patients taking aspirin had a 19 % reduction in the risk of continuing ischemic attacks, stroke, or death compared to patients taking oral placebo or sulfinpyrazone ($P<0.05$) [16]. In the Warfarin–Aspirin Recurrent Stroke Study (WARS), the effect of warfarin (dose adjusted to achieve INR of 1.4–2.8) was compared to that of aspirin (325 mg/day) in 2,206 patients randomized equally between the two groups. The primary end point of death or recurrent ischemic stroke at 2 years was observed in 17.8 % in the warfarin group and 16.0 % in the aspirin group ($P=0.25$), with the hazard ratio being 1.13 (95 % CI, 0.92–1.38) [17].

To assess the efficacy of antiplatelet agents in preventing recurrent strokes in the African American population, the investigators of the African American Antiplatelet Stroke Prevention Study (AAASPS) randomized 1,809 patients to receive either Aspirin or Ticlopidine. Although no difference was found in the primary outcomes of a vascular event (including strokes) between the two groups, the Kaplan-Meier curves for time to the secondary outcome of fatal or nonfatal stroke approached a statistically significant reduction favoring aspirin ($P=0.08$). The investigators concluded that aspirin was better than ticlopidine for the prevention of vascular events in the studied population [18].

A Cochrane review of antiplatelet therapy for acute ischemic stroke (12 trials, $N=43,041$) recommended the use of aspirin within 48 h versus no aspirin at all. This analysis demonstrated a relative risk ratio (RRR) of 12 % (95 % CI, 3–21), adjusted risk ratio (ARR) of 0.5 %, and NNT of 200 (over 2–4 weeks) [13, 19]. In terms of annual protection against stroke, myocardial infarction, or vascular death with aspirin (versus no aspirin), the RRR, ARR, and NNT are 13 % (95 % CI, 6–19), 0.9 %, and 111 per year respectively.

Clopidogrel

This platelet ADP receptor antagonist has been studied as a single agent, and in comparison to aspirin and a combination of aspirin plus dipyridamole. Limited data is available in the setting of an acute stroke and hence clopidogrel may not be recommended in this setting [14]. The reader should also be cautioned that clopidogrel takes 3–7 days to provide effective platelet inhibition when given at standard doses (75 mg/day) and therefore will not provide immediate recurrent stroke prevention unless a bolus dose (300 mg) is given [20].

A double-blind, active and placebo-controlled study known as the prevention regimen for effectively avoiding second strokes (PRoFESS) trial investigated the preventive effects of antiplatelets and the angiotensin II receptor antagonist telmisartan. Patients with an ischemic stroke were randomly assigned to receive either 25 mg aspirin plus 200 mg extended-release dipyridamole twice a day or 75 mg clopidogrel once a day, and either 80 mg telmisartan or placebo once per day. Median follow-up duration was 2.4 years for 20,332 patients with a mean age of 66 years. Nine percent of patients in each group had a recurrent stroke and modified Rankin scores (mRS) were not statistically different in patients with recurrent stroke who were treated with aspirin plus dipyridamole group versus clopidogrel ($p=0.38$) [21].

In the MATCH (management of athero-thrombosis with clopidogrel in high-risk patients) study, 7,599 high-risk patients with recent ischemic stroke or TIA and at least one additional vascular risk factor were randomized to receive clopidogrel 75 mg plus either aspirin (75 mg/day) or placebo [22] . At the end of the follow-up period of 18 months, the composite end point (which included recurrent stroke) in the aspirin plus clopidogrel group showed a relative risk reduction of 6.4 % (95 % CI, −4.6 to 16.3] and an absolute risk reduction of 1 % (95 % CI, −0.6 to 2.7) compared to clopidogrel alone. The risk of major bleeding was higher in the combination antiplatelet group (absolute risk increase 1.36, 95 % CI 0.86–1.86; $p<0.0001$) but there was no change in mortality. Life-threatening bleeding was higher in the

group receiving aspirin and clopidogrel versus clopidogrel alone (absolute risk increase 1.3 %, 95 % CI 0.6–1.0; $p<0.0001$). As a result of MATCH study, the AHA/ASA Guideline for the prevention of stroke in patients with stroke or transient ischemic attack was updated to include caution regarding the routine long-term use of dual antiplatelet therapy for stroke and TIA prevention.

The CHANCE trial (clopidogrel in high-risk patients with acute nondisabling cerebrovascular events) randomized 5,170 patients within 24 h after the onset of minor ischemic stroke or high-risk TIA to clopidogrel (300 mg initially followed by 75 mg daily for 90 days) and aspirin (75 mg/day for the first 21 days) or to placebo plus aspirin (75 mg/day for 90 days) [23]. Each patient received open-label aspirin at a clinician-determined dose of 75–300 mg on day 1 after the event. At 90 day follow-up, recurrent stroke occurred in 8.2 % of patients in the clopidogrel–aspirin group, as compared with 11.7 % of those in the aspirin group (hazard ratio, 0.68; 95 % CI, 0.57–0.81; $P<0.001$). Moderate to severe hemorrhage rates in both groups were similar. This study however only included Chinese participants. The ongoing POINT trial (Platelet-oriented inhibition in new TIA and minor ischemic stroke) will test the efficacy of clopidogrel plus aspirin versus aspirin taken <12 h after TIA or minor ischemic stroke symptom onset in preventing major ischemic vascular events at 90 days in the high-risk western population [24].

CAPRIE (clopidogrel versus aspirin in patients at risk of ischemic events) was a randomized, blinded, international trial designed to assess the relative efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in reducing the risk of a composite outcome of ischemic stroke, myocardial infarction, or vascular death [25]. A total of 19,185 patients were followed for 1–3 years. Patients treated with clopidogrel had a 5.32 % risk of ischemic stroke, myocardial infarction, or vascular death compared with 5.83 % with aspirin ($p=0.043$) with a relative risk reduction of 8.7 % in favor of clopidogrel (95 % CI, 0.3–16.5). The overall safety profile of clopidogrel was found to be at least as good as that of aspirin. The annual RRR, ARR, and NNT for clopidogrel are 7 % (95 % CI, −6 to 19), 0.6 %, and 167, when compared to aspirin alone [19, 25, 26].

For early recurrence of stroke (~3 months), a combination of clopidogrel and aspirin has an RRR, ARR, and NNT of 30 % (95 % CI, 18–41), 3.3 %, and 30 respectively, when compared with aspirin alone [20, 23, 27]. Versus clopidogrel, the RRR, ARR, and NNT over 18 months are 17 % (95 % CI, −93 to 64), 0.8 %, and 125 respectively [19, 27]. A recent review by Hankey summarizes effective strategies to prevent recurrent stroke [19].

In a subgroup analysis of CLAIR study, early dual therapy with clopidogrel and aspirin reduced microembolic signals (MES) in patients with minor ischemic stroke or transient ischemic attack, without causing significant bleeding complications [28]. Patients with ≥1 microembolic signals at baseline were randomized to receive dual therapy (aspirin 75–160 mg daily and clopidogrel 300 mg day 1 then 75 mg daily) or monotherapy (aspirin 75–160 mg daily) for 7 days. At the end of the study, 9 of 29 patients in dual therapy group and 18 of 34 patients in monotherapy group had ≥1 MES (adjusted relative risk reduction 41.4 %, 95 % CI, 29.8–51.1; $P<0.001$) with the median number with MES on day 7 being 0 in dual therapy group and 1 in monotherapy group ($P=0.046$) [28].

Mono vs. Dual Antiplatelet Therapy

As discussed above, there are several studies that have attempted to evaluate the efficacy of dual antiplatelet therapy in the secondary prophylaxis after a stroke or TIA.

In a recent article, Wong et al. reviewed the efficacy and safety of dual versus mono antiplatelet therapy in the secondary prevention of stroke [27]. In their meta-analysis, they included 14 randomized, controlled trials including 9,012 patients who had therapy initiated within 3 days after an acute noncardioembolic ischemic stroke or TIA. Their results found that dual antiplatelet therapy significantly reduced risk of stroke recurrence (risk ratio, 0.69; 95 % CI, 0.60–0.80; $P<0.001$) and the composite outcome of stroke, TIA, acute coronary syndrome, and all death (risk ratio, 0.71; 95 % CI, 0.63–0.81; $P<0.001$) when compared with monotherapy. The risk of major bleeding was increased with dual therapy but this was not found to be significant (risk ratio, 1.35; 95 % confidence interval, 0.70–2.59, $P=0.37$). All of the studies reviewed included aspirin in combination with dipyridamole or clopidogrel (except for one study which administered cilostazol). Seven studies were double-blinded.

In a review by Lee et al., the authors evaluated the risk-benefit profile of long-term (greater than 1 year) dual versus single antiplatelet therapy among patients with ischemic stroke [29]. The seven studies that were included in the analysis were randomized, controlled studies ($N=39,574$) which primarily looked at recurrent stroke and intracranial hemorrhage (ICH) as outcome measures. The risk of recurrent stroke risk did not differ between patients receiving dual therapy and those receiving aspirin alone (relative risk, 0.89; 95 % CI, 0.78–1.01) or clopidogrel (relative risk, 1.01; 95 % CI, 0.93–1.08). The risk for ICH also did not differ between the groups. Those patients that received dual therapy had a relative risk of 0.99 (95 % CI, 0.70–1.42) as compared to those taking aspirin alone. The relative risk of ICH in patients taking dual therapy versus clopidogrel was found to be greater (relative risk, 1.46; 95 % CI, 1.17–1.82) in this study.

There remains continued interest in assessing the usefulness of multiple antiplatelet agents in the secondary prophylaxis of stroke. The ongoing POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke, ClinicalTrials.gov Identifier: NCT00991029) trial is assessing the safety and efficacy of clopidogrel (75 mg qod after a loading dose of 600 mg) plus aspirin (50–325 mg qod) versus aspirin alone (50–325 mg qod) for reducing risk of major ischemic vascular events at 90 days [24]. Prophylaxis will be given to 5,840 patients with TIA or minor stroke within 12 h of symptom onset in this randomized, double-blinded study.

The TARDIS (Triple Antiplatelets for Reducing Dependency after Ischemic Stroke, ClinicalTrials.gov Identifier: NCT01661322) trial compares the safety of a combination of three antiplatelet therapy (aspirin, clopidogrel, and dipyridamole) versus aspirin and dipyridamole, or clopidogrel alone [30]. This study will include 4,100 patients with acute stroke/TIA.

Dipyridamole and Aspirin Plus Dipyridamole (DP-ASA)

Dipyridamole is a phosphodiesterase inhibitor that also augments prostacyclin-induced inhibition of platelet aggregation. The efficacy of dipyridamole in secondary stroke prevention has been largely studied in combination with aspirin.

The European stroke prevention study (ESPS-1) randomized 2,500 patients with a diagnosis of a recent stroke/TIA to receive either dipyridamole 75 mg plus aspirin 325 mg (DP-ASA, $N=1{,}250$) or placebo ($N=1{,}250$) thrice daily. The results showed that 16 % on DP-ASA and 25 % in placebo group had a recurrent stroke or death at the end of 24 months [1, 31]. The relative risk reduction was 33 % ($p<0.001$). The number of patients who died was higher in the placebo group ($p<0.01$).

ESPS-1 was followed by ESPS-2, a randomized, placebo-controlled, double-blinded trial ($N=6{,}602$) to investigate the safety and efficacy of low-dose aspirin (25 mg twice daily), extended-release dipyridamole (200 mg twice daily), and the two agents in combination (25/200 mg twice daily) [32]. Primary end points were stroke, death, and stroke or death together and the secondary end points were TIA and other vascular events. Patients were followed for 2 years. In comparison with placebo, stroke risk was reduced by 18 % with aspirin alone ($p=0.013$), 16 % with dipyridamole alone ($p=0.039$), and 37 % with combination therapy ($p<0.001$). Risk of stroke or death was reduced by 13 % with aspirin alone ($p=0.016$), 15 % with dipyridamole alone ($p=0.015$), and 24 % with combination therapy ($p<0.001$). When compared with aspirin alone, combination therapy reduced the risk of stroke by 23 % ($P=0.006$) and stroke or death by 13 % ($P=0.056$) [1, 32].

According to a meta-analysis, dipyridamole without aspirin will reduce stroke recurrence in patients with previous ischemic cerebrovascular disease with an odds ratio of 0.82 (95 % CI, 0.68–1.00) [33]. However, the combination of aspirin plus extended-release dipyridamole is more effective than aspirin alone in preventing stroke and other serious vascular events in patients with minor stroke and TIA. Another meta-analysis reported that with aspirin plus extend-release dipyridamole the relative risk for a recurrent stroke is 0.76 (0.65–0.89) and for a composite secondary vascular outcome (including stroke, myocardial infarction, or vascular death) the relative risk is 0.82 (0.73–0.92) [34].

In the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), patients with a stroke or TIA of presumed arterial origin were randomized to receive either aspirin (median 75 mg daily; range 30–325 mg) with dipyridamole ($n=1{,}363$) or without dipyridamole ($n=1{,}376$; 200 mg twice daily) within 6 months of the event [35]. Primary outcome events (composite of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication, whichever happened first) arose in 173 (13 %) patients on aspirin and dipyridamole and in 216 (16 %) on aspirin alone (hazard ratio, 0.80; 95 % CI, 0.66–0.98). The absolute risk reduction with combination therapy was 1.0 % per year (95 % CI, 0.1–1.8).

According to a recent meta-analysis, the extended-release dipyramidole and aspirin combination was found to have a nonsignificant RRR, ARR, and NNT of 36 % (95 % CI, −10 to 63), 2.6 %, and 38 over 3–28 months when compared to aspirin for prevention of recurrent stroke. When compared to clopidogrel, the combination (DP-ASA) has a nonsignificant RRR, ARR, and NNT of 44 % (95 % CI, −17 to 73), 1.8 %, and 56 over 3 months for prevention of recurrent stroke [27]. However, according to another meta-analysis, the annual RRR, ARR, and NNT for DP-ASA versus aspirin are 22 % (95 % CI, 10–32), 2.3 %, and 43 over 2.6 years for prevention of recurrent stroke [36].

As discussed above, the PRoFESS trial did not show any statistically significant difference in modified Rankin Score (mRS) or major hemorrhage in patients receiving a combination of aspirin plus dipyridamole versus clopidogrel [1, 20]. There was also no statistically significant difference in the Barthel index or mini-mental state examination (MMSE) in the patients with recurrent stroke who had a good outcome [21].

Cilostazol

Cilostazol inhibits phosphodiesterase 3, increases cyclic adenosine monophosphate (cAMP) concentrations, has vasodilatory activity, inhibits vascular smooth muscle proliferation, and protects the vascular wall and endothelium [37].

The second Cilostazol Stroke Prevention Study (CSPS 2) was conducted to establish noninferiority of cilostazol versus aspirin for prevention of stroke and to compare the efficacy and safety of cilostazol and aspirin in patients with noncardioembolic ischemic stroke [37]. Patients (aged 20–79 years) who had had a stroke or TIA within the previous 26 weeks were administered cilostazol (100 mg twice daily, $N=1,379$) or aspirin (81 mg once daily; $N=1,378$) for 1–5 years. The first recurrent stroke occurred at annual rates of 2.76 % ($n=82$) in the cilostazol group and 3.71 % ($n=119$) in the aspirin group (hazard ratio, 0.743; 95 % CI, 0.564–0.981; $p=0.0357$). Hemorrhagic complications were lower in the cilostazol arm of the study (0.77 %, $n=23$) than in the aspirin arm (1.78 %, $n=57$; 0.458, 0.296–0.711; $p=0.0004$).

The cilostazol versus aspirin for secondary ischemic stroke prevention (CASISP) trial aimed to compare the efficacy and safety of cilostazol with that of aspirin for the long-term prevention of the recurrence of ischemic stroke [38]. In this prospective, multicenter, double-blinded, randomized study, patients (mean age = 60.2 years, SD 9.86) who had had an ischemic stroke in the previous 1–6 months were administered cilostazol ($N=360$) or aspirin ($N=360$). An MRI was performed on all participants at the beginning and the end of the study. The primary end point (ischemic stroke, hemorrhagic stroke, or subarachnoid hemorrhage) was reported in 12 patients in the cilostazol group and in 20 patients in the aspirin group. The estimated hazard ratio was 0.62 (95 % CI, 0.30–1.26; $p=0.185$). Cerebral hemorrhage events were more common in the aspirin group than in the cilostazol group (7 vs. 1, $p=0.034$). The above studies suggest that cilostazol may be more effective and safer for secondary prevention of stroke as compared to aspirin. Although cilostazol is available in the United States, it is not currently approved for stroke prevention and prescribing practices of physicians may be influenced by the presence of a black box warning for use of cilostazol in patients with congestive heart failure.

Ticlopidine

Ticlopidine is a thienopyridine derivative, similar to clopidogrel, and is an adenosine diphosphate (ADP) receptor inhibitor.

The Canadian American Ticlopidine Study (CATS) was a randomized, double-blinded, placebo-controlled trial to assess the effect of ticlopidine in reducing the rate of subsequent occurrence of a composite end point (stroke, myocardial infarction, or vascular death) in 1,072 patients who have had a recent thromboembolic stroke [39]. Patients were entered in the study between 1 week and 4 months after their event and were followed for up to 3 years (mean = 24 months). Primary end point was observed in 15.3 % in the placebo group and 10.8 % in the ticlopidine group. The relative risk reduction with ticlopidine was (23.3 %, $p=0.020$). A Cochrane review of the studies comparing ticlopidine with aspirin for efficacy and safety showed that ticlopidine was at least as effective as aspirin for the prevention of stroke and heart attacks [26]. However, it's use may be limited by its ability to cause serious side effects like bone marrow suppression and is rarely used for stroke prevention.

Conclusion

Antiplatelet agents are strongly recommended for patients with ischemic stroke events due to noncardiogenic sources. These agents can be given within 24–48 h after onset of stroke and have demonstrated efficacy in prevention of recurrent strokes in both early and late phases after an initial stroke. Despite easy availability of these agents (especially in developed nations), recurrent strokes continue to comprise a significant percentage of all strokes. This is likely due to inadequate implementation of other secondary prevention strategies such as blood pressure control, lipid reduction, and lifestyle changes. Inadequate implementation of healthcare policies may also contribute to negating the effects of antithrombotics. Of toxicity when using antiplatelet agents, the more common clinically important ones are bleeding and gastrointestinal side effects for which therapy should be tailored accordingly. Recent studies have attempted to maximize the antiplatelet activity after stroke by using dual (and even triple) agents. The risk-benefit of such combination therapy over traditional single-agent therapy remains to be determined.

Disclaimer The opinions expressed herein belong solely to the authors. They are neither those of nor endorsed by the Uniformed Services University of the Health Sciences, Department of Defense, or any other agency of the federal government.

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Heterogeneous Causes of Stroke: Select Emerging Risk Factors

11

Kazunori Toyoda

Abbreviations

CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CARASIL	Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy
CI	Confidence interval
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
FLAIR	Fluid-attenuated inversion recovery
GFR	Glomerular filtration rate
HTRA1	HtrA serine protease 1
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes

Chronic Kidney Disease and End-Stage Kidney Disease

Case Presentation (#1)

A 74-year-old woman with hypertension and a 15-year history of maintenance hemodialysis for diabetic nephropathy suddenly developed motor aphasia and gaze disturbance to the right side soon after completion of her routine hemodialysis. Emergent head CT revealed a small hematoma in the right pontine tegmentum, and magnetic resonance imaging (MRI) revealed a fresh infarct in the left inferior frontal gyrus. On carotid echogram and magnetic resonance angiography (MRA), the left internal carotid artery was occluded, with an intact left middle cerebral artery presumably via the anterior communicating artery. She was diagnosed as showing simultaneous onset of hemorrhagic and ischemic strokes immediately after hemodialysis. The complete details of this case have been described elsewhere [1].

Possible mechanisms of stroke unique to hemodialysis are shown in Fig. 11.1 based on the medical records during hemodialysis of Case #1. High blood pressure in the morning before starting hemodialysis and heparin use during hemodialysis might enhance bleeding. On the other hand, the diminished vascular responses due to diabetic autonomic neuropathy and advanced arteriosclerosis appear to explain an abrupt decrease in blood pressure during hemodialysis; this might cause hemodynamic ischemic stroke.

Risk of Stroke in Chronic Kidney Disease Patients

Stroke is common in patients with end-stage kidney disease (ESKD), both in patients undergoing hemodialysis [2] and those undergoing peritoneal dialysis [3]. The risk of stroke in dialysis patients has been found to be four to ten times higher than that in the general population [4]. In addition to the point that ESKD is a typical end result of arteriosclerosis, special characteristics unique to dialysis, including drastic hemodynamic change and consequent high variability of blood pressure, dialysate, anticoagulants, vascular access, dialysis amyloidosis, vascular calcification, and dialysis vintage can be triggers of both ischemic and hemorrhagic strokes [5]. In addition, milder chronic kidney disease (CKD) not requiring dialysis therapy also contributes to the risk and severity of stroke [6, 7].

CKD is primarily defined as a reduced glomerular filtration rate (GFR) or the presence of proteinuria [8]. Kidney disease and stroke share traditional cardiovascular risk factors, such as aging, diabetes, hypertension, dyslipidemia,

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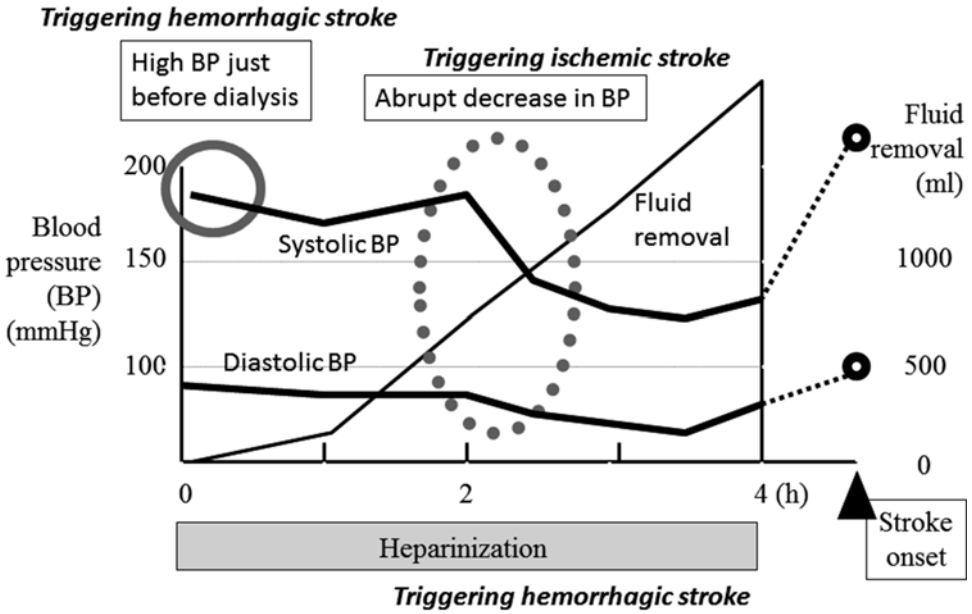

Fig. 11.1 Possible mechanisms of stroke based on the medical records of Case #1

Table 11.1 Risk factors common to stroke and kidney disease

Traditional risk factors: aging, hypertension, diabetes, dyslipidemia, obesity, smoking
Risk factors unique to chronic kidney disease that increase stroke risk: chronic inflammation, asymmetric dimethylarginine, oxidative stress, sympathetic nervous system overactivity, thrombogenic factors, extravascular coagulation, hyperhomocysteinemia, maladaptive arterial remodeling
Risk factors unique to advanced chronic kidney disease: uremic toxins, fluid retention, anemia, malnutrition, $Ca^{2+}$and PO_4^{2-} abnormalities, hyperparathyroidism, decreased Klotho protein expression
Risk factors unique to end-stage kidney disease and dialysis procedures: drastic hemodynamic changes, dialysate, anticoagulants, vascular access, dialysis amyloidosis, vascular calcification, dialysis vintage

obesity, and smoking. Both the kidney and brain are known to be target organs of arteriosclerotic insults. However, large-scale meta-analyses have demonstrated that CKD is a risk factor for stroke independent of known cardiovascular risk factors [9, 10]. In a meta-analysis including 284,672 people experiencing 7,863 stroke events, the risk of incident stroke increased by 43 % (95 % confidence interval [CI] 31–57 %) in subjects with an estimated GFR (eGFR) below 60 mL/min/1.73 m^2 [9]. In 11 of 33 studies included in the meta-analysis, the risk estimate after adjustment for sex, age, and other cardiovascular risk factors was 1.45 (95 % 1.26–1.68). In a meta-analysis involving 140,231 people experiencing 3,266 stroke events, subjects with proteinuria had a 71 % (95 % CI 39–110 %) greater risk of stroke compared to those without proteinuria [10]. The risk remained significant after adjustment for known cardiovascular risk factors. These findings indicate the existence of nontraditional risk factors as contributors to the excess risk of stroke in CKD patients [6, 7] (Table 11.1). In addition, CKD is strongly associated with subclinical cerebrovascular abnormalities, including white matter lesions, silent infarcts, cerebral microbleeds, and carotid atherosclerosis, as well as cognitive impairment [7, 11–14].

CKD is also indicative of stroke severity and poor clinical outcomes after stroke. In the Fukuoka Stroke Registry involving 3,778 patients with first-ever ischemic stroke, of whom 1,320 (34.9 %) had CKD, CKD patients had a 49 % (95 % CI 17–89 %) greater risk of neurological deterioration during hospitalization, defined as a ≥2 point increase in the National Institutes of Health (NIH) Stroke Scale score, a 138 % (95 % CI 61–257 %) greater risk of in-hospital mortality, and a 25 % (95 % CI 5–48 %) greater risk of a modified Rankin Scale (mRS) score of 2 or more at discharge than non-CKD patients, after adjustment for potential confounding factors, including initial stroke severity [15]. The Fukuoka Stroke Registry also showed a 73 % (95 % CI 3–190 %) greater risk of recurrence of non-cardioembolic stroke in CKD patients [16]. In a post hoc analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Trial, involving 18,666 patients with recent ischemic stroke, patients with reduced eGFR below 60 mL/min/1.73 m^2 had a 16 % (95 % CI 4–31 %) greater risk of

recurrent stroke after multivariate adjustment for confounders [17]. Studies of intracerebral hemorrhage showed that renal dysfunction (eGFR below 60 mL/min/1.73 m^2, proteinuria, or serum creatinine ≥1.5 mg/dL) was associated with larger baseline hematoma volume, lower tendency to direct discharge to home and a high percentage of discharge to nursing homes, and death or disability at 1 year [18–20].

Management of Stroke in Chronic Kidney Disease Patients

Limitations of stroke therapies in CKD patients seem to be a reason for the poor stroke outcomes of CKD patients. The dilemma is that CKD patients have both high thromboembolic risk and high bleeding risk, and it is often difficult to maintain the balance of the risk and benefit of antithrombotic therapy in CKD patients. For example, in the Danish national registries involving 132,372 patients with nonvalvular atrial fibrillation, patients with non-end-stage CKD, as well as those with ESKD, had an increased risk of stroke and an increased bleeding risk compared with patients with normal renal function [21]. Thus, special care to prevent bleeding complications is needed for anticoagulation in patients having both CKD and atrial fibrillation. There is conflicting evidence on the benefit of stroke prevention from warfarin, especially in dialysis patients. In the above Danish national registries, warfarin significantly decreased the risk of stroke and significantly increased the risk of bleeding for both patients with non-end-stage CKD and those with ESKD. In contrast, other studies reported that warfarin increased all of bleeding risk, ischemic stroke risk, and mortality in atrial fibrillation patients on dialysis [22, 23]. Warfarin for dialysis patients also increases vascular calcification [22]. Thus, routine use of warfarin in ESKD patients seems to be often limited to those at very high risk for stroke and is performed with close monitoring of the international normalized ratio. Although non-vitamin K antagonist oral anticoagulants (otherwise, novel oral anticoagulants) may be safer and more beneficial for patients with nonvalvular atrial fibrillation than warfarin, they are contraindicated for patients with advanced renal dysfunction due to reduced clearance.

Although intravenous thrombolysis for hyperacute ischemic stroke is not contraindicated for patients with ESKD or advanced CKD, renal dysfunction seems to affect clinical outcomes after thrombolysis [24, 25]. In a meta-analysis of three studies involving 344 patients with reduced eGFR and 504 patients without, reduced eGFR was significantly associated with early symptomatic intracerebral hemorrhage, high mortality, and low percentage of patients with mRS score 0-2 at the subacute or chronic stage [26, 27]. Similarly, revascularization by endovascular therapy for CKD patients has several problems, such as limited use of contrast agents and difficulty in catheterization due to carotid calcification.

Emerging Risk Factors

Case Presentation (#2)

A 53-year-old, normotensive, ex-smoker developed 3 strokes over 5 months, and he was admitted to our hospital for the third stroke. After the death of his wife 4 years previously, he lived alone and often dined on box lunches and noodles. The first stroke was an ischemic event in the left corona radiata, with resulting right hemiparesis. One month later, he noticed right hemiparesis again due to an infarct in the left basal ganglia. Oral aspirin was started after the first stroke, and ticlopidine was added after the second. Four months after the second stroke, he noticed dysesthesia of the right side of his body. MRI revealed a fresh hematoma in the left thalamus. MRA did not show stenosis of any arteries. Blood tests showed an increased level of homocysteine (22.5 μmol/L). Among the serum vitamins, B12 (320 ng/L) and folate (3.3 μg/L) were within normal levels, and B6 was slightly decreased (5.9 μg/L). Methylenetetrahydrofolate reductase TT genotype was documented on polymerase chain reaction DNA amplification using whole blood lymphocytes. Oral supplementation of vitamin B6, vitamin B12, and folate brought the homocysteine level down to normal. The complete details of this case have been described elsewhere [28].

Young-Onset Strokes and Causes for Premature Atherosclerosis

Stroke in young adults is often associated with risk factors other than the traditional vascular risk factors. The differential diagnosis of ischemic stroke in young adults is listed in "Caplan's Stroke" [29]. Here, the table is revised with some additional diseases (Table 11.2). The pathologic states in the table are indicative of uncommon causes of stroke, and stroke patients with such pathologic states are sometimes diagnosed as having cryptogenic stroke because these states are often underdiagnosed. Some of the causes are introduced in other chapters of this textbook.

In this chapter, causes of premature atherosclerosis are discussed. In addition to traditional risk factors for cardiovascular disease, including dyslipidemia, hypertension, diabetes, and smoking, emerging risk factors such as hyperhomocysteinemia, sleep disorders, insulin resistance, and metabolic syndrome are briefly introduced.

Homocysteine is a sulfurous amino acid that is an intermediary biosynthesized during the conversion of methionine to cysteine. A high serum level of homocysteine results from vitamin deficiencies due to lifestyle factor-related insufficiencies and wasting diseases, as shown in Case #2, CKD (vitamin deficiencies), and hereditary abnormalities of the metabolism of methionine (homocystinuria). Homocysteine

Table 11.2 Causes of ischemic stroke in young adults

Migraine
Arterial dissection
Drugs, especially cocaine and heroin
Premature atherosclerosis: dyslipidemia (familial hyperlipidemia), hypertension, diabetes, smoking, sleep disorders, insulin resistance, metabolic syndrome, hyperhomocysteinemia
Female hormone-related (oral contraceptives, pregnancy, puerperium): eclampsia, dural sinus occlusion, peripartum cardiomyopathy, peripartum vasculopathy
Hematologic: deficiency of antithrombin III, protein C, protein S, factor V Leiden, prothrombin gene mutations, fibrinolytic system disorders, deficiency of plasminogen activator, antiphospholipid antibody syndrome, increased factor VIII, cancer, thrombocytosis, polycythemia, thrombocytopenic purpura, disseminated intravascular coagulation
Rheumatic and inflammatory: systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, Sjögren's syndrome, scleroderma, polyarteritis nodosa, cryoglobulinemia, Crohn's disease, ulcerative colitis
Cardiac: intra-atrial septal defect, patent foramen ovale, mitral valve prolapse, mitral annulus calcification, myocardiopathies, arrhythmias, endocarditis
Penetrating artery disease (lacunes): hypertension, diabetes
Genetic: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), Fabry's disease, homocystinuria (hyperhomocysteinemia)
Others: Moyamoya syndrome, Behçet's syndrome, neurosyphilis, Takayasu's disease, Sneddon's syndrome, fibromuscular dysplasia, Cogan's disease

Modified from Caplan LR, eds. Caplan's Stroke: a clinical approach (3rd ed). Boston; Butterworth Heinemann; 2000

causes endothelial cell injury and initiates the process of premature atherosclerosis. Meta-analyses indicate the association of hyperhomocysteinemia with an increased risk of ischemic stroke [30, 31]. Hyperhomocysteinemia predisposes to large-artery atherosclerosis stroke subtypes, including carotid stenosis [32, 33]. However, patients with small-artery infarction are also reported to have higher serum homocysteine levels than control patients [33]. Methylenetetrahydrofolate reductase serves as an enzyme for conversion of dietary folate to 5-methyltetrahydrofolate, and a methyl donor requires the remethylation of homocysteine to methionine in vivo. Methylenetetrahydrofolate reductase TT genotype seems to be an independent risk factor for silent brain infarction and white matter lesions in the general Japanese population [34]. Hyperhomocysteinemia may be a potential risk factor for stroke including small-artery infarctions and hemorrhage for relatively young patients with lifestyle factor-related insufficiencies. Hyperhomocysteinemia is a treatable disorder, but the effectiveness of lowering serum homocysteine for stroke prevention is not yet proven. In the Vitamin Intervention for Stroke Prevention (VISP) trial involving 3,680 patients with ischemic stroke, mean 2 μmol/L more reduction of serum homocysteine level by administration of high-dose folic acid, pyridoxine, and cobalamin as compared to low-dose administration did not decrease recurrent stroke during 2-year follow-up [35]. Similarly, daily administration of B vitamins did not reduce major vascular events including recurrent stroke as compared to placebo in the VITAmins TO Prevent Stroke (VITATOPS) trial [36].

Obstructive sleep apnea results from partial or complete closure of the upper airway and causes blood oxygen desaturation and sleep fragmentation [37, 38]. Obstructive sleep apnea has close relationships with hypertension, diabetes, obesity, patent foramen ovale, and arrhythmias; these are all risk factors for stroke. However, several studies demonstrated that obstructive sleep apnea increases the risk of stroke independent of known risk factors including hypertension [39, 40]. Continuous positive airway pressure is the first-line treatment, and it decreases the risk of cardiovascular events [41]. On the other hand, central sleep apnea, characterized by repetitive cessation of ventilation during sleep resulting from loss of ventilatory drive, seems to be a consequence rather than a cause of stroke.

Besides diabetes mellitus, hyperinsulinemia or insulin resistance is reported to increase stroke risk, although some have refuted the relationship [42, 43]. Metabolic syndrome, also known as the insulin resistance syndrome, is a constellation of central obesity, dyslipidemia, elevated blood pressure, and impaired glucose tolerance [44]. Metabolic syndrome increases the risk of ischemic stroke; the adjusted risk ratios for ischemic stroke associated with the metabolic syndrome in prospective studies have ranged between 2.10 and 2.47, and a hazard ratio as high as 5.15 has been reported [43]. Individual components of the metabolic syndrome should be treated appropriately.

Genetic Risk Factors

Case Presentation (#3)

A 49-year-old ex-smoker visited our clinic. He described a 3-year history of episodes of unilateral throbbing headache preceded by dizziness, right-sided weakness, sensory symptoms,

and dysarthria. His neurological and cognitive examinations were normal. Transesophageal echocardiography revealed a patent foramen ovale. Brain MRI performed at the ages of 46 and 49 years showed progressive leukoencephalopathy without involvement of the anterior temporal poles and an increasing number of silent lacunar infarcts. A diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was confirmed by point mutation (C222S) in exon 4 of the Notch3 gene. The complete details of this case have been described elsewhere [45].

Stroke with Genetic Etiologies

CADASIL is a typical monogenic disorder caused by mutations of the neurogenic locus notch homolog protein 3 gene, located on chromosome 19 [46]. Common symptoms other than cerebral ischemia are migraine with aura, dementia, seizure, apathy, and mood disturbance. Since patients with CADASIL have been reported to have a high incidence of patent foramen ovale [47], as in Case #3, migraine in CADASIL patients may have some causal association with patent foramen ovale. Patients usually develop recurrent lacunar strokes by the age of 50 years. On brain MRI, multifocal and bilateral fluid-attenuated inversion recovery (FLAIR)/T2 hyperintensities in the periventricular and deep white matter, with white matter lesions mainly affecting the anterior temporal pole, frontal and parietal lobes, external capsule, pons and basal ganglia, as well as lacunar infarcts and sometimes cerebral microbleeds, are typically demonstrated. In particular, white matter lesions in the anterior temporal poles are helpful in the diagnosis of CADASIL, although it is not always identified, as shown in Case #3.

In patients with cryptogenic stroke, monogenic disorders should also be considered. While CADASIL is well known, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and Fabry's disease should also be considered.

CARASIL is caused by mutations in HtrA serine protease 1 (HTRA1) gene localized on chromosome 10q encoding HTRA1 that represses signaling mediated by the transforming growth factor-β family [48]. CARASIL has been reported mainly from Japan, with some cases from China [49]. The main clinical manifestations of CARASIL are recurrent ischemic stroke or stepwise deterioration of motor ability, progressive dementia, alopecia, and acute lumbago or spondylosis deformans/disk herniation. On brain MRA, diffuse white matter changes and multiple lacunar infarctions in the basal ganglia and thalamus are identified.

Fabry's disease is an X-linked lysosomal storage disorder resulting from deficiency of α-galactosidase A activity that predominantly affects the central and peripheral nervous systems, skin, heart, kidneys, and eyes [50, 51]. It is an important cause of stroke in young adults. Lacunar stroke is a well-known stroke subtype associated with Fabry's disease, since deposition of glycosphingolipids occurs in the vascular endothelium and smooth muscle cells. Since enzyme replacement therapy with recombinant human α-galactosidase A reduces accumulation of globotriaosylceramide, the therapy should be initiated before the onset of end organ failure [52].

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Secondary Prevention After Cardioembolic Stroke

12

Mark N. Rubin, W. David Freeman, and Maria I. Aguilar

Case Presentation A 63-year-old man with a mechanical aortic valve (see Fig. 12.1) on chronic anticoagulation with wafarin presents to the emergency department with 30 min of difficulty with speech. The patient is otherwise asymptomatic and his National Institute of Health Stroke Scale (NIHSS) score is 5, scoring 1 point for right facial droop, 2 points for aphasia, and 2 points for dysarthria. His partner mentions that the patient has been off of his warfarin for the last 5 days in preparation for an upcoming dental procedure. Emergent computed tomography (CT) scan of the brain was unremarkable and specifically did not show hemorrhage or early ischemic changes. Point-of-care International Normalized Ratio (INR) is 1.4 and the remainder of his routine acute stroke laboratory screen is unremarkable. Reexamination after CT demonstrates neurologic decline, with worsening of his aphasia and the development of a right arm drift, and a NIHSS of 7. His medical chart and partner were interrogated for thrombolysis contraindications, and none were identified, and thus the patient and his partner were counselled as to the benefits, risks, and alternatives to systemic thrombolysis. Verbal assent was ascertained from the patient's partner and systemic intravenous thrombolysis was infused per acute stroke guidelines. As the thrombolytics were infused, the patient underwent emergent multiparametric magnetic resonance imaging (MRI) of the brain and blood vessels of the head and neck to screen for large artery occlusive disease given the early neurologic decline. The study was most remarkable for multifocal restricted diffusion including a wedge-shaped region in the left frontal lobe and scattered punctate lesions in the right frontoparietal lobe (see Fig. 12.2). No large artery occlusion was noted in the cervical or intracranial vasculature and the only perfusion deficit matched the left sided area of restricted diffusion. The patient was admitted to the hospital for routine guideline-based post-thrombolytic acute stroke care, including no antithrombotics or anticoagulation for 24 h. Repeat CT neuroimaging the next day demonstrated subacute ischemic changes commensurate with the restricted diffusion seen on MRI the day prior with no hemorrhage in the infarct bed or elsewhere.

The multifocality in different vascular distributions of the brain, most likely the bilateral carotid artery ("anterior circulation") in this particular patient, suggests a cardio-aortic source of embolism ("cardioembolic source") versus the less likely scenario of bilateral internal carotid or middle cerebral artery embolic disease. The head and neck vessel imaging performed in the emergent setting did not suggest cervical or intracranial arterial sources of embolism, making a cardioembolic source that much more likely. The patient has a known thrombogenic device in his aortic valve and his INR was subtherapeutic, and this is the likely source of embolism. Other considerations include intracardiac thrombus with or without occult atrial fibrillation, both of which would be medically managed with anticoagulation, and ascending aortic arch atherosclerosis, of which management is more controversial with anticoagulation or antiplatelet medication. These other structural considerations on the differential diagnosis were screened for by transesophageal echocardiography, which only demonstrated some small thrombotic remnants attached to the aortic end of the mechanical prosthetic. In light of these findings, a low-intensity unfractionated heparin infusion (goal activated partial thromboplastin time [aPTT] 50–70 s) with no bolus was initiated for maximal secondary prevention of stroke. Warfarin was restarted at the same time with a goal INR of 2.0–3.0, avoiding the temptation to intensify the degree of anticoagulation in light of a major arterial thromboembolism because this event happened with an INR out of the therapeutic range.

The patient was still aphasic at the time of anticoagulation but his right arm drift had improved and his NIHSS was 5. His acute hospitalization and rehabilitation were otherwise

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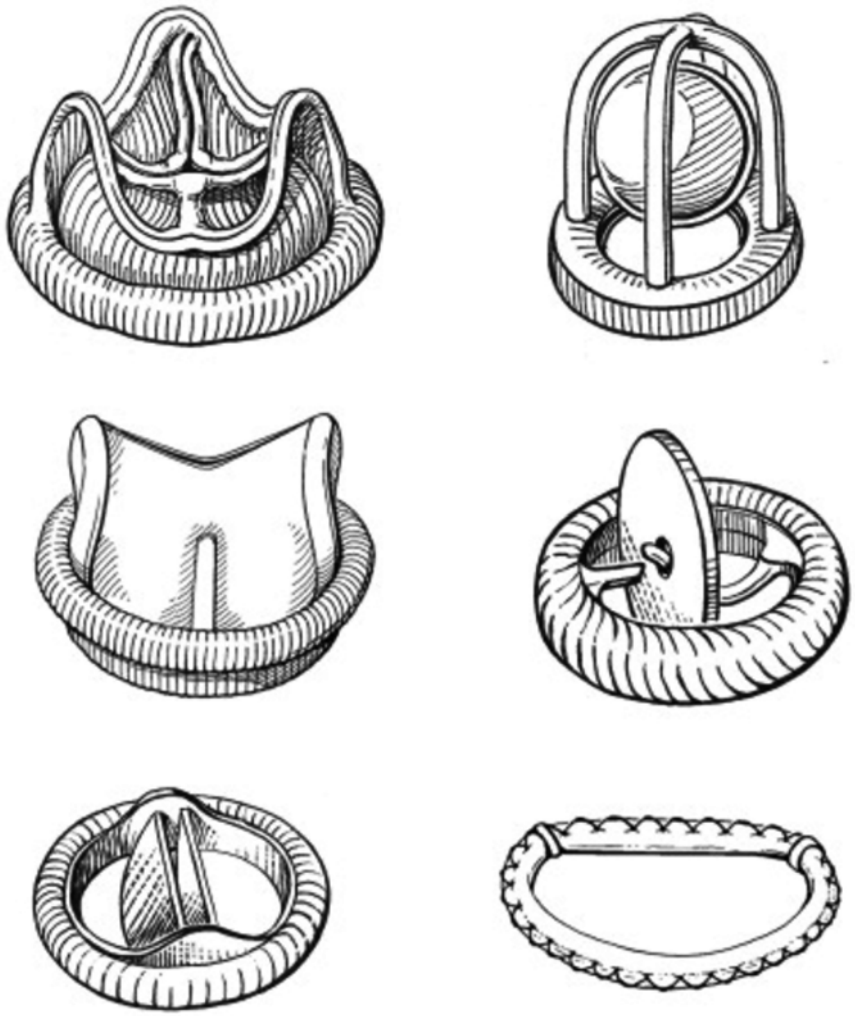

Fig. 12.1 Valve prostheses. Different prosthetic heart valves. Bioprosthetic valve (*top left*). Prosthetic bileaflet (*top middle* and *bottom left*). Ball in cage prosthesis (*middle right*). Annuloplasty ring (*bottom right*). *By permission of Mayo Foundation for Medical Education and Research. All rights reserved*

uneventful as he transitioned from unfractionated heparin to warfarin alone once his INR was therapeutic. At 3 months this previously high-functioning patient would notice some word finding difficulty when very tired but was otherwise working full time and able to go about all his activities as desired.

Epidemiology

Cardiac embolism causes up to 30 % of all ischemic strokes [1–4] with an incidence ranging from 20 to 40 per 100,000 in the US population. Cardioembolic stroke is disproportionately more disabling and potentially fatal than nonembolic-mechanism stroke, due to occlusion of larger intracranial arteries and larger ischemic brain volume [5]. Atrial fibrillation (AF) remains the most common cause of cardioembolic stroke (Fig. 12.3) and has a steep age-related increase in incidence. AF accounts for 1.5 % of strokes among patients in their 50s but increases to 23.5 % among patients in their 80s [2, 3, 5, 6]. However, there are a variety of other causes of cardioembolic stroke, which include acute myocardial infarction (AMI), ventricular thrombus (20 %), structural heart defects, cardiac tumors (15 %), and valvular heart disease (15 %) (see Table 12.1) [3]. Cardioembolic stroke affecting the posterior circulation accounts for ≤25 % of all posterior circulation ischemic events in some registries [7–15].

Clinical and Radiographic Features

The clinical presentation of cardioembolic stroke is typically indistinguishable from other clinical strokes, namely a sudden neurologic deficit with maximal symptomatology at

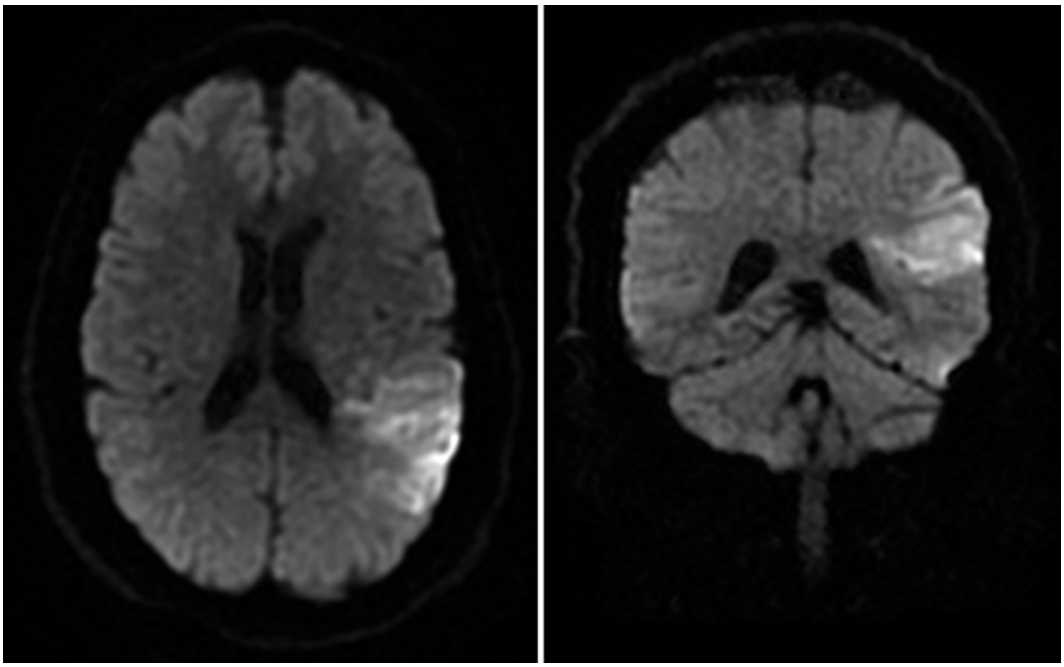

Fig. 12.2 Typical MRI neuroimaging pattern of cardioembolic stroke. Diffusion-weighted images of two slices of a patient with mitral valve endocarditis and subsequent cardioembolic infarcts. The left frontal infarct has a distal cortical "wedge" appearance typical of cardioembolic or embolic infarcts that travel to the distal cortical arteries. There is also a right parietal infarct, which is often seen with cardioembolism (different vascular territories, anterior left and right and/or posterior circulation). The left-sided image is at a lower slice cut than the right image, which is higher (more cephalad). *With kind permission from Springer Science and Business Media*

onset [16, 17]. However, clinical predictors of cardioembolic stroke include rapid or "dramatic" improvement of a major neurologic deficit [18], a maximal deficit from onset [16, 17], simultaneous ischemic strokes in different vascular territories (especially anterior and posterior circulation), and hemorrhagic transformation of an ischemic infarct that suggests recanalization and reperfusion injury. Patients with cardioembolic stroke are less likely to have had a transient ischemic attack (TIA) as a harbinger of their stroke than patients with another high-risk mechanism, large-vessel (e.g., carotid artery) atherosclerosis [16]. Also, cardioembolic strokes may present with a "stuttering" or fluctuating pattern of neurologic deficits, especially those that display features of alternating right or left hemisphere or anterior and posterior circulatory localization. Cardioembolic ischemic stroke may occlude a larger-sized intracranial artery (e.g., proximal middle cerebral artery [M1] segment occlusion) compared to small vessel disease or perforator vessel disease and so the former stroke type tends to often come with greater neurological symptom severity [16, 19]. Seizures are more likely to occur from embolism to distal cortical brain tissue as compared to small vessel disease infarcts in deep locations [20]. Thromboembolic events may also exhibit a characteristic distal cortical wedge-shaped pattern of infarction on CT or MRI (Fig. 12.2) [21]. Embolic events also typically have a scattered pattern of infarction that suggest an embolus fractured or shattered into several pieces before traversing the downstream vascular territory [17, 18]. It should be noted that these radiographic patterns are not pathognomonic for cardiac embolism, per se, as these patterns can occur with emboli arising from other sources including aortic or cervical arterial atherosclerosis that travel through the intracranial circulation.

Diagnostic Approach to Cardioembolic Stroke

The clinical approach to cardioembolic stroke patients is systematic but not algorithmic. As with all neurologic evaluations, it hinges on a detailed history and physical examination. It also includes neuroimaging, cardiac rhythm monitoring, laboratory and echocardiographic data. The history should screen for symptomatic palpitations, unexplained bradycardic or tachycardic episodes, assessment of the patient's history of cardiac disease or heart failure, and family history of cardiac disease or arrhythmias. Asymptomatic patients should be screened during routine annual examinations for risk factors for cardiac embolism by cardiac auscultation for murmurs and assessment for an irregular heart rhythm [22].

The history and physical examination may disclose a potential risk factor or cause for cardioembolic stroke, such

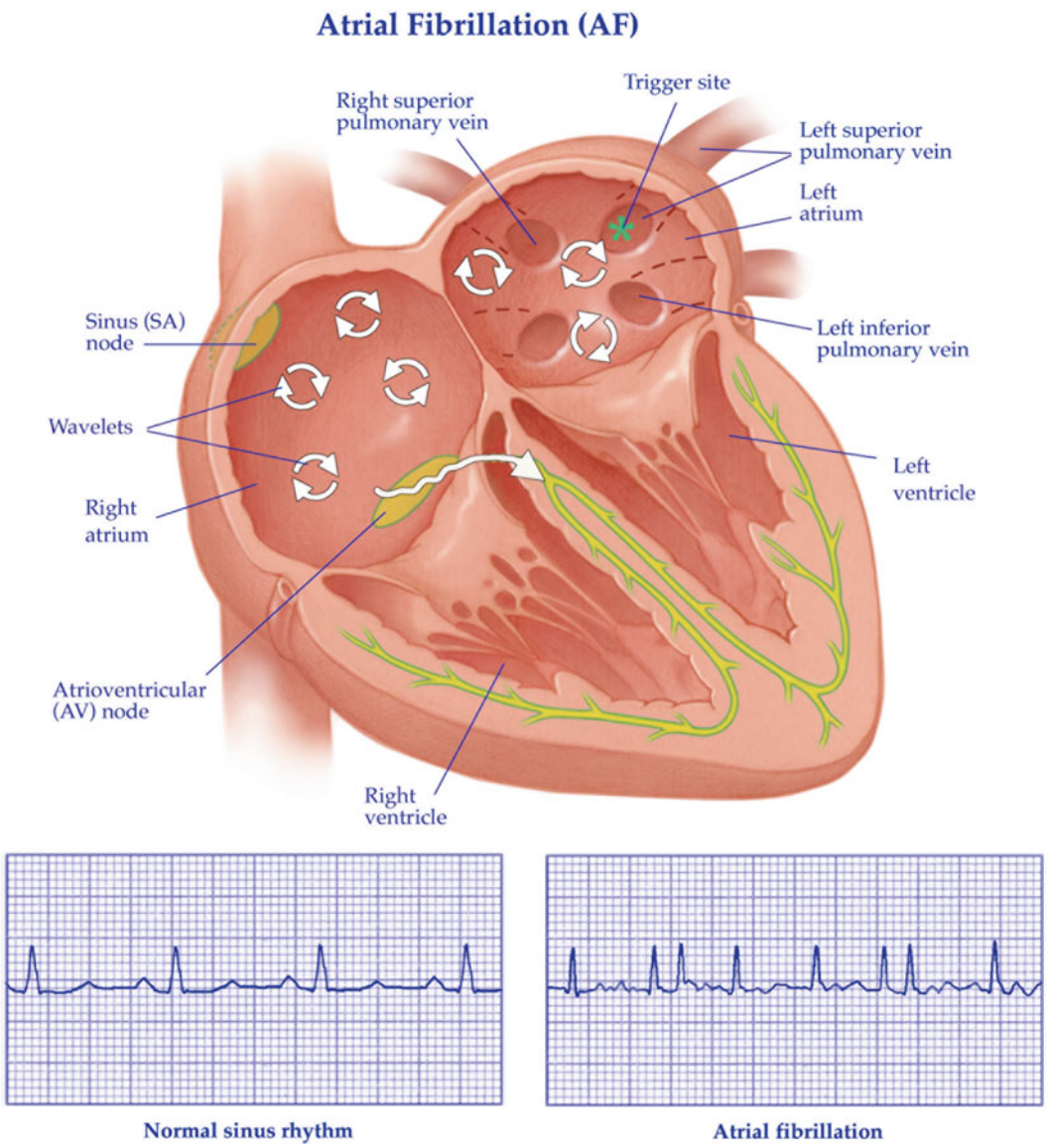

Fig. 12.3 Atrial fibrillation. Atrial fibrillation, abnormal electrical excitation pathways that lead to irregular cardiac rhythm, stagnant blood flow in the left atrium, which predisposes to clot formation and potential subsequent embolism. *With kind permission from Springer Science and Business Media*

as AF. However a substantial number of patients who present with stroke will not display AF during the inpatient setting, even on telemetry, but may require prolonged monitoring, such as Holter monitoring or event monitoring to detect occult AF. In such patients for whom a clinician has a high degree of clinical suspicion for arrhythmia, a 12-lead electrocardiogram, inpatient telemetry, or outpatient Holter monitor [23] or event recorder may be necessary to capture intermittent paroxysmal AF or sick sinus syndrome. Prolonged outpatient Holter monitoring up to 7 days after an index cerebrovascular event can also be considered for patients with unexplained cerebral ischemia, which has a higher yield of occult AF detection compared to 24 or 48 h Holter monitoring (12.5 % compared with 4–6 %) [24]. Long-term continuous electrocardiographic monitoring or 30-day event recorders show a 9–23 % detection rate of occult AF among those without known AF or with previously diagnosed cryptogenic stroke [25–27]. A recent meta-analysis of trials and observational studies focused on the utility of prolonged outpatient cardiac telemetry suggested an overall rate of detection of AF at 11.5 %, noting higher rates in selected vs. unselected patients [28]. Furthermore, the use of automated detection algorithms is preferred over patient-triggered detection because AF is often asymptomatic [29]. The results of the CRYptogenic STroke and underlying Atrial Fibrillation (CRYSTAL AF) trial, which tested

Table 12.1 Causes of cardioembolic stroke

Biology		Ischemic Stroke Risk
Arrythmias		
	Coexisting AF	2–18 % per year
	Sick sinus syndrome	3.5 % per year, 5–10 % per year with coexisting AF
Cardiomyopathy		
	Acute MI without AF	1–2 % in 3 months
	LVEF 35–45 % without AF	2–4 % per year
	LVEF <35 % without AF	1.6 % per year
	LVEF dysfunction with AF	2–18 % per year
	LV thrombus	15 % within 3 months
Valvular disorders		
	Aortic stenosis	Variable
	Aortic regurgitation	Variable
	Aortic bioprosthetic valve	Variable
	Aortic mechanical valve	≥12 % per year
	Mitral rheumatic	5 % per year
	Mitral rheumatic with AF	>5 % per year
	Mitral valve prolapse	1 % per year
	Endocarditis	variable
	Non-mitral valve prosthesis/replacement without AF	0.4–1.9 % per year
	Mitral valve—bioprosthesis	1–2 % per year
	Mitral valve—mechanical	22 % per year
PFO (age 18–55)		
	PFO without ASA	2.3 % per year
	PFO with ASA	15.2 % per year

AF = atrial fibrillation, MI = myocardial infarct, LVEF = left ventricular ejection fraction, PFO = patent foramen ovale, ASA = atrial septal aneurysm

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an implantable monitor (REVEAL XT, Medtronic, Minneapolis, MN) vs. standard monitoring (as described above) in a randomized fashion for detection of occult AF of greater than 30 s within 6 months of randomization, were reported at the 2014 International Stroke Conference [30]. The investigators reported that the primary end point, which was time to first detection of atrial fibrillation lasting more than 30 s, was reached in 8.9 % of patients with the implanted device vs. 1.4 % of control patients. The end points for longer monitoring were even more robust with detection rates of 12.4 % vs. 2 % and 30 % vs. 3 % for implanted vs. control subjects at 12 months and 36 months, respectively. The expense and current clinical heterogeneity of cardiac monitoring to detect atrial fibrillation has some physicians questioning the utility of monitoring in general and instead advocating for empiric anticoagulation with NOACs, which have similar bleeding rates as antiplatelet agents (the latter antithrombotic agents being more typically used if cardioembolism is suspected but a source is not found) [31].

Stroke onset after Valsalva (e.g., cough, sneeze, bowel movement) is suggestive of intracardiac or intrapulmonary right-to-left shunt such as large patent foramen ovale or other cardiac septal (atrial or ventricular) defects. In such cases, echocardiogram with a bubble study or alternative means of detecting shunt physiology may disclose this source of potential cardiac embolism. Standard laboratory investigations include complete blood cell count with platelets, prothrombin time, and aPTT [22]. B-type natriuretic peptide (BNP) elevation rises to >76 pg/mL at stroke admission has a greater association with cardioembolic stroke as compared to other stroke types (odds ratio [OR] 2.3, confidence interval [CI], 1.4–3.7; $p = 0.001$), and BNP elevation was highest in the cardioembolic stroke cohort (as high as 410 pg/mL) among all stroke subtypes [32, 33].

Young patients without vascular risk factors who experience cardioembolic stroke or especially TIA, and who have a family history suggestive of thrombophilia, should undergo a prothrombotic workup. A standard prothrombotic laboratory workup for younger patients includes Prothrombin G20210A (prothrombin gene) mutation, factor V Leiden mutation, protein C or S deficiency, anti-thrombin III deficiency, and anti-phospholipid antibodies (e.g., anticardio-

lipin antibodies, beta-2 glycoprotein antibodies, and the lupus anticoagulant), and serum homocysteine. Recently, hypercoagulable blood testing has come into question, given recent meta-analyses showing a weak association with arterial stroke [34]. However, this may be considered in young patients with no other cause of stroke.

In patients with incident stroke, echocardiography is advised to evaluate the source of cardioembolism. Transesophageal echocardiogram (TEE) remains the diagnostic "gold-standard" to evaluate cardiac structural sources of stroke [22, 35, 36]. TEE has been shown to be superior to transthoracic echocardiography (TTE) in detecting cardiac sources of embolism [36]. Some clinicians prefer to perform TTE first, and if positive for cardioembolic stroke proceed with treatment, depending on the cause. However, if TTE is negative and TEE is not obtained, it is possible to fail to identify the source of cardiac embolism as a TEE can identify high-risk structural abnormalities including intracardiac thrombus (particularly in the left atrial appendage), high-grade aortic plaque and valvular sources of embolism that cannot routinely be identified with TTE [37, 38]. The risks of TEE include local irritation or injury to the oropharynx and esophagus and respiratory decompensation, especially in those with poor cardiopulmonary status (e.g., end-stage cardiopulmonary disease). The hypopnea from sedating medications and Valsalva can increase intracranial pressure, perhaps dangerously in patients who are at risk such as those with large space-occupying intracranial lesions. Structural changes such as wall hypokinesis, septal aneurysm, valvular masses and atrial abnormalities are of particular interest. The presence of left atrial enlargement, although it is nonspecific, is typically seen in patients with atrial fibrillation and one series suggested a greater than sixfold difference in presence of left atrial enlargement in patients with cardioembolic stroke than patients with small vessel disease [39]. The sensitivity for both TTE and TEE in detecting right-to-left shunting can be greatly enhanced by intravenous injection of saline mixed with air (e.g., the saline bubble study or agitated saline study) as compared to detection by color flow imaging alone [40]. Saline bubble study transcranial Doppler ultrasonography can also detect right-to-left shunting with great sensitivity and specificity when intravenous microbubbles are detected as they pass through the middle cerebral artery segment (M1) [41–44]. In addition, paradoxical embolism should be considered in stroke patients with a known right-to-left shunt in whom deep vein thrombosis (DVT) is detected.

Cardiac CT and MRI are emerging diagnostic tools and have identified sources of cardioembolism missed by conventional echocardiography [45, 46], especially for left atrial thrombi. However, cardiac MRI is not typically utilized in routine practice, because it is not widely available, knowledge among physicians with regard to its approved indications is limited, and it so far it has received poor reimbursement [45]. Current guidelines [45, 47] provide the following indications for cardiac MRI: (1) TTE study is questionable for the presence of left ventricular thrombus; (2) a cardiac mass suspected on TTE requires further evaluation; (3) patients cannot tolerate TEE and/or cannot undergo TEE secondary to medical reasons; (4) the TEE study was inconclusive; and (5) suspected false-negative TEE results, in which a cardiac MRI can adequately image potentially missed sources of embolus, such as left ventricular thrombus, cardiac masses, aortic plaque, or left atrial appendage thrombus.

Neuroimaging of cardioembolic stroke is typically performed acutely via noncontrast head CT for patients presenting to the emergency room. Noncontrast head CT has wide availability, quick turnaround time, and an ability to exclude intracranial hemorrhage which is why it is typically used in the decision making process regarding eligibility for intravenous tissue plasminogen activator (tPA) for patients who present within 3–4.5 h of symptom onset [22]. However, patients who present with subacute to chronic stroke symptoms or TIA, or when CT is nondiagnostic, MRI is often used. MRI with diffusion-weighted image sequences has superior sensitivity in detecting small areas of ischemia or infarction that are often missed on initial CT, particularly in the posterior fossa. The neuroimaging pattern of a cardioembolic infarct is typically a cortical or a cortical-subcortical pattern of ischemia on diffusion-weighted imaging, if within roughly 2 weeks of the event. In comparison, small deep penetrator infarcts of the lenticulostriate or brainstem (<1 cm in size) are typically not cardioembolic in origin and most likely relate to small vessel (≤100 μm in diameter) disease processes, such as lipohyalinosis secondary to hypertension or diabetes. However, reports of migratory cardioembolic events that occlude penetrating vessel ostia are reported, but their parenchymal involvement is typically greater than 1 cm in size.

Atrial Fibrillation

AF is the most common source of cardiac embolism (~45 %) and has an incidence that increases with age [6, 48–50]. Approximately 2.3–3.2 million people are currently affected in the USA, and based on epidemiologic data from Olmsted County in Minnesota, the USA, the future projections of patients with AF could exceed 12 million by 2050 [48], which has tremendous potential to impact societal and healthcare costs attributed to stroke. According to the American College of Cardiology, the American Heart Association, and the European Society of Cardiology [49], AF is classified into different forms: (1) paroxysmal AF (PAF), a self-terminating or intermittent form that generally last less than 7 days and usually less than 24 h; (2) persistent

AF, which fails to self-terminate and lasts longer than 7 days; and (3) permanent AF, which lasts for more than 1 year. However, it is important to note that the ischemic stroke risk is similar for persistent, sustained, and PAF based on data within the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) [51, 52] and anticoagulation is recommended for patients with both chronic and PAF. Detection of PAF can be particularly elusive and sometimes it is first detected during embolic stroke. AF causes ineffective atrial contractions, which lead to stagnation of blood within the left atrium and within the left atrial appendage, which later embolizes to the brain and sometimes viscera. Another classification for AF is either "valvular" or "nonvalvular" AF. Valvular AF refers to AF in the setting of mitral valve disease (e.g., rheumatic mitral valve stenosis) or prosthetic valve [49]. Nonvalvular AF refers to AF without any underlying structural valve disease or prosthetic valve. Nonvalvular AF occurs in approximately 0.7 % of the general population and incidence increases steeply with age [6, 50, 53, 54].

AF ischemic stroke risk is stratified by concomitant independent risk factors, including age (>75 years), history of prior transient ischemic attack or stroke, hypertension, diabetes, and heart failure. Multiple studies have identified these risk factors for stroke in patients with AF. These include the Atrial Fibrillation Investigators (AFI), the Boston Area Anticoagulation Trial of Atrial Fibrillation Investigators (BAATAF) [55], Stroke Prevention in Atrial Fibrillation (SPAF) [56, 57], Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) [58], Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study (AFASAK) [59], and Canadian Atrial Fibrillation Anticoagulation (CAFA) study [60]. Several stroke risk stratification schemes have been proposed [61, 62], and one scheme has not been definitely proven superior to another scheme or 100 % predictive of ischemic stroke risk. For clinical purposes, we find the $CHADS_2$ risk stratification scheme [62] easy to use in patients identified with AF. "CHADS" is an acronym of the particular risk factor and is weighed for each to estimate the annual ischemic stroke risk (Table 12.2). The letters stand for Congestive heart failure, Hypertension, Age >75 years, Diabetes, and Stroke or transient ischemic attack. All facets of the score count for a single point toward the total score except the stroke/TIA component which confers 2 points, for a possible total of 6 points. We find the $CHADS_2$ scale simple and easy to use, especially when discussing the risk-benefit ratio of anticoagulation therapy. There are several other, more clinically nuanced scales that were designed to add granularity for individual patients, but a recent comparison [63] suggested that no one scale was superior to another

Table 12.2 Estimating stroke risk using $CHADS_2$ and CHA_2DS_2-VASc scores with ACCP recommendations for antithrombotic therapy

$CHADS_2$ Score	Annual stroke risk (95 % CI)	2012 ACCP recommendations
0	1.9 (1.2–3.0)	No therapy is safer than antithrombotic therapy (2B) If antithrombotic therapy is selected, use ASA or combo (2B)
1	2.8 (2.0–3.8)	OAC outweighs no therapy (1B), ASA, or combo (2B)
		If OAC is not selected, combo is better than ASA (2B)
2	4.0 (3.1–5.1)	OAC outweighs no therapy (1A), ASA, or combo (1B)
3	5.9 (4.6–7.3)	Dabigatran is OAC of choice, rather than VKA (2B)
4	8.5 (6.3–11.1)	If OAC is not selected, combo is better than ASA (1B)
5	12.5 (8.2–17.5)	
6	18.2 (10.5–17.4)	
CHA_2DS_2-VASc Score	Adjusted annual stroke risk	2010 ESC recommendations
0	0	No therapy is safer than antithrombotic therapy
		If antithrombotic therapy is selected, use ASA
1	1.3	OAC or ASA is recommended, but OAC is preferred
		OAC recommendation: VKA or dabigatran
2	2.2	OAC is recommended: VKA or dabigatran
3	3.2	
4	4	
5	6.7	
6	9.8	
7	9.6	
8	6.7	
9	15.2	

ASA aspirin, *CI* confidence interval, *combo* aspirin plus clopidogrel, *ESC* European Society of Cardiology, *OAC* oral anticoagulant, *VKA* vitamin K antagonist (warfarin)

for risk prediction in high-risk patients, although the CHA_2DS_2-VASc [64] score was the best at clarifying low risk, which is important for deciding for or against oral anticoagulation for stroke prevention. The American Academy of Neurology recently published an evidence-based guideline for evaluation and management of non-valvular (e.g., not in association with rheumatic heart disease or other valvular defects) atrial fibrillation, and the contents of this section are informed by that publication [29].

Antithrombotic Therapy for Stroke Prevention with AF

Several large prospective trials and meta-analyses have demonstrated the superiority of oral vitamin K antagonist anticoagulation (predominately warfarin in the USA) compared to antiplatelet (chiefly aspirin internationally) therapy in reducing stroke for high-risk AF patients. Overall, the optimal therapy for each patient is individualized based on ischemic stroke risk factors against hemorrhage risks, such as prior intracranial hemorrhage or gastrointestinal bleeding. Review of all data supporting this assertion comparing warfarin to antiplatelet agents will not be fully outlined, but references and a table (Table 12.3) are provided to the reader [65–79].

The ACTIVE A trial [80] and ACTIVE W trial [51] investigated the role of aspirin and clopidogrel against AF-related thromboembolic events and hemorrhagic events. The ACTIVE A trial studied 7,554 patients with AF at risk for stroke who were unsuitable for warfarin anticoagulation randomized to clopidogrel (75 mg daily) or a placebo in addition to aspirin (75–100 mg daily). The primary outcome measure was a composite end point of stroke, myocardial infarction (MI), extra-cerebral embolic events, and vascular death. The combination of aspirin and clopidogrel reduced the risk of ischemic stroke (relative risk [RR], 0.68; 95 % CI, 0.57–0.80; $p<0.001$; number needed to treat [NNT] 111) and myocardial infarction (RR, 0.78; 95 % CI, 0.59–1.03; $p=0.08$; NNT 500), but also increased the risk of major bleeding in the clopidogrel group (2.0 % per year) compared to aspirin-placebo group (1.3 % per year) (RR, 1.57; 95 % CI, 1.29–1.92; $p<0.001$; number needed to harm [NNH] 143). The ACTIVE W trial randomized more than 6,600 patients with AF with at least 1 risk factor for stroke to aspirin (75–100 mg daily) plus clopidogrel (75 mg daily) or dose-adjusted warfarin (target INR, 2.0–3.0). The primary outcome measure for the study was incident stroke, extracerebral embolic event, MI, and vascular death. The study was stopped early due to the findings of superiority of oral anticoagulation compared to the aspirin plus clopidogrel group in preventing primary events (RR, 1.44; 95 % CI, 1.18–1.76; $p=0.0003$), and less major bleeding with oral anticoagulation therapy (RR, 1.30; 95 % CI, 0.94–1.79; $p=0.03$). These data from the ACTIVE studies suggest clopidogrel and aspirin reduces ischemic stroke and MI (2.4 % stroke rate per year for clopidogrel plus aspirin vs. 3.3 % for aspirin alone), but at the cost of increased bleeding events compared to aspirin alone (2.0 % had major bleeds per year for clopidogrel and aspirin vs. 1.3 % for aspirin alone). Also the combination of aspirin and clopidogrel increases bleeding risk compared to warfarin (major bleeds, 2.42 % vs. 2.21 % per year, respectively) and is inferior to oral anticoagulation in preventing ischemic stroke (2.1 % vs. 1.0 % per year, respectively).

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial [81] is another recent important study. BAFTA studied 973 elderly patients (aged 75 years or older) with AF, which is significant given that, broadly speaking, an older cohort has more medical comorbidity and increased risk of hemorrhage [82]. The study randomized patients to either low-dose aspirin (75 mg/day) or dose-adjusted warfarin (target INR, 2.0–3.0). The primary end point was ischemic stroke, fatal or disabling hemorrhagic event (such as intracranial hemorrhage [ICH]), or clinically significant arterial embolic event. The mean period of follow-up was 2.7 years in a primary care setting in the UK. The primary event rate was 3.8 % per year in the aspirin group compared to 1.8 % per year in the warfarin group (RR, 0.48; 95 % CI, 0.28–0.80; $p=0.003$). The annual absolute risk reduction using warfarin compared to aspirin was only 2 % (95 % CI, 0.7–3.2). However, it is important to note this study included all AF patients, regardless of stratified risk (e.g., $CHADS_2$ or other scale). The findings demonstrate a "net clinical benefit" ("fatal or disabling stroke" regardless of ischemic or hemorrhagic origin) in older patients (48 % RR reduction) in overall stroke events treated with warfarin compared to aspirin. The annual risk of extracranial bleeding was not significantly different between the groups (e.g., 1.6 % in the aspirin group compared to 1.4 % in the warfarin group [RR, 0.87; 95 % CI, 0.43–1.73]).

Table 12.3 Pre-NOAC antithrombotic trials in AF

AC vs. placebo/NT	AntiPLT vs. placebo/NT	AC vs. AntiPLT
AFASAK I [56]	AFASAK I [56]	AFASAK I [56]
SPAF I [53]	SPAF I [53]	AFASAK II [72]
BAATAF [52]	EAFT [66]	SPAF II [185]
CAFA [57]	ESPS II [186]	SPAF III [78]
SPINAF [55]	UK-TIA [187]	PATAF [73]
EAFT [66]	LASAF [188]	ATAFS [75]
	JAST [189]	WASPO [76]
	SAFT [190]	SIFA [191]
		NASPEAF [77]
		ACTIVE-W [48]
		EAFT [69]
		Vemmos et al. [74]

NOAC = novel oral anticoagulant, AF = atrial fibrillation, AC = anticoagulation, NT = no treatment, AntiPLT = antiplatelet

The National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) trial studied various antithrombotic modalities for stroke risk reduction. Patients deemed high risk (previous embolism, >60 years of age and/or mitral stenosis, $n=495$) were randomized to anticoagulation with INR goal of 2.0–3.0 ($n=259$) or a combination of the antiplatelet medication triflusal (600 mg daily) plus moderately dose anticoagulation (INR goal 1.40–2.40, $n=236$). Patients considered to be of intermediate risk (not meeting criteria for high or low risk by SPAF III [83] criteria), were randomized in a 1:1:1 fashion to triflusal (600 mg daily) alone ($n=242$), anticoagulation with target INR 2.0–3.0 ($n=237$), or combination triflusal (600 mg daily) with moderate anticoagulation (target INR 1.25–2.00, $n=235$). The primary outcome was a composite of vascular death and nonfatal stroke or systemic embolism. Median follow-up was 2.76 years. The primary outcome was lower in the combined therapy than in the anticoagulant arm in both the intermediate- (HR 0.33 [95 % CI 0.12–0.91]; $p=0.02$) and the high-risk group (HR 0.51 [95 % CI 0.27–0.96]; $p=0.03$). The primary outcome plus severe bleeding was lower with combined therapy in the intermediate-risk group but not the high risk group. Interestingly, the nonvalvular and mitral stenosis patients—two groups not often included in the same trial—had similar embolic event rates during anticoagulation therapy. This study demonstrated that combined antiplatelet therapy and moderate anticoagulation was effective in reducing vascular events and death in patients with nonvalvular AF and was safe as compared to standard anticoagulation or antiplatelet medication alone [77]. That said, it is not the authors' practice nor impression of guideline-based care that utilization of dual antiplatelet therapy and lower-intensity anticoagulation be used routinely in this setting.

A single multicenter placebo-controlled trial (Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontané; FFAACS) demonstrated that the risk of hemorrhagic complications was increased in the dose-adjusted vitamin K antagonist plus aspirin group as compared with the vitamin K antagonist alone group (risk difference 14.6 % [95 % CI 5.5–24.8 %]). The study lacked the power to detect important differences in the risk of thromboembolic events. Overall, in patients with nonvalvular AF, the combination of low-dose aspirin and dose-adjusted vitamin K antagonist therapy probably increases the risk of hemorrhagic complications without necessarily favorably affecting the risk of ischemic stroke or other thromboembolic events [84].

The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) trial by Singer et al. [85] demonstrated a net clinical benefit of warfarin anticoagulation in older patients (age > 85) with AF, despite hemorrhagic events. There were 13,559 adult patients with nonvalvular AF who were involved in both retrospective and prospective components of the study. The ATRIA study used the $CHADS_2$ score to estimate embolic stroke risk. A net clinical benefit was assessed by determining the annual rate of ischemic strokes and systemic emboli prevented by warfarin minus ICH attributable to warfarin, multiplied by an impact factor. An impact factor of 1.5 was used for ICH. The study demonstrated a net weighted benefit of warfarin in AF patients increasing with $CHADS_2$ score, starting from 0 and increasing to 6, even when accounting for ICH and in older patients. Controversy exists, however, given a more recent retrospective review of spontaneous intracranial hemorrhage in anticoagulated patients that suggests the risk of anticoagulation may approach if not outweigh any benefit in the very elderly or those with other clinical risk factors for hemorrhage [82]. It remains the authors' recommendation to *not* consider advanced age a strict contraindication to anticoagulation but perhaps another clinical variable for which a stroke provider must account. The recent American Academy of Neurology guideline on nonvalvular AF suggests the benefit of anticoagulation for stroke prevention likely extends to the elderly based on two Class I studies [29].

Another population of concern is those with AF and chronic kidney disease (CKD). Among patients with CKD participating in the SPAF III trials [86], adjusted-dose warfarin (INR target 2.0–3.0) reduced ischemic stroke and systemic embolism in patients with CKD and a high risk of stroke (relative RR 76 % [95 % CI 42 % – 90 %]) as compared with aspirin or low-dose warfarin, with no difference in major hemorrhage rates. For patients with stage 3 CKD [87], apixaban as compared with aspirin significantly reduced stroke and systemic embolism event rates (HR 0.32 [95 % CI 0.18–0.55], $p<0.001$) without an increase in major bleeding (absolute rate apixaban 2.5 % vs. aspirin 2.2 %). So, overall, the benefits of anticoagulation for AF extend to patients with CKD, in spite of the known increased bleeding rates in that population [88].

Ximelagatran, a direct thrombin inhibitor, was studied in Stroke Prevention using Oral Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III and V trials, but had complications of hepatic dysfunction and was not approved for use by the US Food and Drug Administration [89–91]. The drug was not inferior to warfarin in reducing ischemic stroke in AF patients and had a relatively low incidence of bleeding similar to warfarin. In the SPORTIF trials, ximelagatran had similar rates for major hemorrhage (gastrointestinal and soft tissue) as compared to warfarin, approximately 2.5 % per year.

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RELY) trial [92] studied dabigatran (Pradaxa, Boehringer Ingelheim, Rhein, Germany), another oral direct thrombin inhibitor in AF patients. The study randomized 18,113 patients with AF at risk for ischemic stroke to either dabigatran (fixed doses of 110 or 150 mg twice a day in blinded fashion) or dose-adjusted warfarin (unblinded). Nearly 20 % of the patients in each treatment arm had

experienced a stroke or transient ischemic attack prior to enrollment (19.9 % in dabigatran 110 mg arm, 20.3 % in dabigatran 150 mg arm, 19.8 % in warfarin arm). The primary outcome was stroke or systemic embolism. The median duration of follow-up was approximately 2 years. The primary outcome occurred in 1.69 % per year in the warfarin group compared to 1.53 % in the dabigatran group (with 110 mg) (RR with dabigatran, 0.91; 95 % CI, 0.74–1.11; $p<0.001$ for non inferiority) and 1.11 % per year in the dabigatran group (with 150 mg) (RR, 0.66; 95 % CI, 0.53–0.82; $p<0.001$ for superiority). Major bleeding was reported in 3.36 % per year in the warfarin group compared to 2.71 % in the dabigatran group (with 110 mg) ($p=0.003$), and 3.11 % per year in the dabigatran group (with 150 mg) ($p=0.31$). ICH occurred at a rate of 0.38 % per year in the warfarin group compared to 0.12 % per year in the dabigatran group (with 110 mg) ($p<0.001$), and 0.10 % per year in the dabigatran group (with 150 mg) ($p<0.001$). The data suggest the dabigatran group (with 110 mg dose) was not inferior to the dose-adjusted warfarin for stroke prevention, and had less major bleeding complications, particularly ICH (0.38 % warfarin vs. 0.12 % with 110 mg). The higher dose of dabigatran (with 150 mg) was superior to warfarin in ischemic stroke prevention, and had less ICH than warfarin (0.38 % per year with warfarin vs. 0.10 % per year with 150 mg oral dabigatran), but it had similar rates of extracranial major hemorrhage (3.36 % per year with warfarin vs. 3.11 % per year with 150 mg dabigatran). Dabigatran needs to dose-adjusted with renal function and interacts with amiodarone (a P-gp inhibitor), which is commonly used in AF patients. Other P-gp inhibitors ketoconazole, verapamil, quinidine, and clarithromycin do not require dose adjustments. The drug is also a category C in regard to pregnancy. The effects of dabigatran are reduced by rifampin which is a P-gp inducer. The dose used for patients with a creatinine clearance of greater than 30 mL/min is 150 mg orally twice daily, whereas in patients with a creatinine clearance of 15–30 mL/min the suggested dose is 75 mg orally, twice daily [93]. The half-life of dabigatran is approximately 12 h, and there is no known "antidote" to reverse its effects if life-threatening bleeding occurs. Dabigatran was approved by the US Food and Drug Administration in 2010 for use in AF patients for stroke prevention [94], and it was available for prescription by mid-November to December 2010. The drug has been approved and available for use in Europe (prior to approval in the USA) for venous thromboembolism prevention after knee replacement (at a dose of 110 mg, twice a day), which was not for stroke prevention.

Dabigatran prolongs the aPTT. In patients with bleeding, the aPTT test may determine if the drug is present or not, or to assess drug compliance. In areas that in which it is available, a thrombin time or ecarin clotting time may be more sensitive in evaluating, and with the anticoagulant effects of the drug. The prothrombin time (PT) is also prolonged by this drug, but is less sensitive than ecarin clotting time and is not deemed suitable for assessing the anticoagulation effect of the dabigatran. The drug can be dialyzed, and as mentioned there is no antidote to reverse its effects. The manufacturer suggests providing sufficient intravenous fluids to maintain diuresis because the drug has a renal elimination route [93].

Dabigatran was the first of a new line of oral anticoagulants to compete with warfarin for stroke prevention in AF, which has been the anticoagulation mainstay for the past 50 years. However, other newer anticoagulants have either recently been approved or are being actively investigated in trials [95]. These include the recently FDA-approved oral anti-Xa drugs apixaban and rivaroxaban, as well as the drugs still under investigation which include edoxaban [96], darexaban [97], betrixaban [98], and the pro-drug AZD0837 (Table 12.4), which converts into a select and reversible direct thrombin inhibitor (AR-H067637). These drugs have "-xaban" in the name to indicate their mechanism of action (factor Xa inhibition). Edoxaban is the only drug of those still in investigatory phases that has undergone a randomized trial in a large number of patients and has been shown to be non-inferior to warfarin for prevention of stroke in non-valvular AF with significantly less hemorrhagic complication [96]. These newer anticoagulants may provide a wider array for AF patients and ischemic stroke prevention, depending on the results of these trials, which include at least 1 risk factor for stroke, and looking at embolic events both central nervous system (CNS) and non-CNS events, and bleeding.

The results of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial are important to highlight [99]. Rivaroxaban is a direct, competitive factor Xa inhibitor with a half-life of 5–13 h and has hepatic metabolism (CYP 450) and one third renal clearance. Rivaroxaban has once-daily dosing without the need for coagulation monitoring. The ROCKET AF trial randomized patients to either rivaroxaban (20 mg orally, once daily except for patients with creatine clearance of 30–49 ml/min, which received 15 mg daily), or warfarin (INR target, 2.0–3.0) in a double-blind, double-dummy fashion. The primary end point was stroke or non-CNS systemic embolism, and major bleeding events. The multicenter, international study enrolled 14,264 patients with baseline AF and $CHADS_2$ score of ≥ 2 in 45 countries and 1,178 sites ($n=7,131$ rivaroxaban and $n=7,133$ warfarin). A key difference between this study and RE-LY is that many of the patients had experienced systemic or cerebral embolism prior to randomization: 54.9 % in the rivaroxaban arm and 54.6 % in the warfarin arm. The annualized stroke or systemic embolism event rate in the rivaroxaban group

Table 12.4 Comparison of the new anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of Action	DTI	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
FDA-approved indication(s)	Reduction of stroke and systemic embolism in patients with NVAF	Reduction of stroke and systemic embolism in patients with NVAF Treatment and prevention of thromboembolism	Reduction of stroke and systemic embolism in patients with NVAF	Not FDA approved
Dosing for NVAF	150 mg orally bid	20 mg orally once a day	5 mg orally bid	60 mg orally once a day
	75 mg orally bid in renal impairment (CrCI 15–30 mL/min)	15 mg orally once a day in renal impairment (CrCI 15–50 mL/min)	2.5 mg orally bid in patients with at least 2 of the following: renal impairment (SCr ≥ 1.5 mg/dL), age ≥ 80 years, weight <60 kg	30 mg orally once a day in renal impairment
Bioavailability (%)	3–7, not affected by food	66 (in fasted state) and higher with food	56, not affected by food	50[a], not affected by food
Time to peak (h)	1–2, delayed when taken with food	2–4	1–3	1–2

ADRs = adverse drug reactions, BID = twice per day, CrCl = creatinine clearance, CYP450 = cytochrome P450, FDA = US Food and Drug Administration, Vd = volume of distribution

[a]Based on animal studies

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was 1.71 % compared to 2.16 % in the warfarin group (HR 0.88, 95 % CI, 0.79; 0.66–0.96; with a p value for noninferiority of <0.001). The event rate of hemorrhagic stroke was 0.26 in the rivaroxaban group vs. 0.44 in the warfarin group ($p = 0.024$), and ischemic stroke rates of 1.34 and 1.42, respectively among the groups ($p = 0.581$). However, the rate of fatal bleeding was lower in the rivaroxaban group (0.24) compared to the warfarin group (0.48), which was significantly different ($p = 0.003$). The data suggest that rivaroxaban was not inferior to warfarin for prevention of stroke and non-CNS embolic events, and by intention to treat analysis not superior to warfarin. Rivaroxaban had a similar rate of bleeding, but less fatal and intracranial bleeding than warfarin. Rivaroxaban was approved for use in prevention of thromboembolism in non-valvular atrial fibrillation (among other indications) in July of 2011; therefore, rivaroxaban represents another alternative to warfarin for stroke prevention in patients with AF.

Apixaban is another Factor Xa inhibitor that has been approved by the FDA recently (12/2012) for stroke prevention in the setting of non-valvular atrial fibrillation with support from two trials, namely Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) [100] and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) [101]. In AVERROES, 5,599 patients with AF were randomized to either apixaban (5 mg orally, twice a day) or aspirin (81–325 mg) and the primary end point was stroke and other embolism. Mean follow-up was approximately 1 year, but the study was terminated earlier due to clear benefit of apixaban compared to aspirin. Apixaban was superior to aspirin in stroke prevention for the primary end point of stroke (1.6 % per year among apixaban patients and 3.7 % per year with aspirin). Major bleeding rates were similar (1.4 % per year in the apixaban group and 1.2 % per year in the aspirin group), with similar rates of intracranial hemorrhage (0.3 % on apixaban, and 0.4 % on aspirin). ARISTOTLE compared the same dose of apixaban (5 mg twice daily) to warfarin with the targeted INR of 2.0–3.0 for the prevention of stroke in 18,201 patients with non-valvular atrial fibrillation and at least one major risk factor for stroke. Only 19 % of the patients had experienced a prior stroke, transient ischemic attack or systemic embolism (19.2 % in the apixaban arm, 19.7 % in the warfarin arm). The primary outcome was the combined end point of stroke (of any type) or systemic embolism. Patients were followed for a median of 1.8 years and the annual rate of the primary outcome was 1.27 % in the apixaban group versus 1.6 % in those taking warfarin (HR 0.79, 95 % CI 0.66–0.95; $p < 0.001$ for non-inferiority, $p = 0.01$ for superiority). Parsed out by stroke subtype, the annual rate of ischemic or uncertain type of stroke was 0.97 % with apixaban and 1.05 % with warfarin. The annual rate of major bleeding of any kind was 2.13 % in the apixaban group compared to 3.09 % with warfarin, with the annual rate of intracranial bleeding at 0.24 % with apixaban and 0.47 % with warfarin. These favorable results led to the approval of apixaban as another option for stroke prevention in patients with atrial fibrillation.

A newer drug named tecarfarin (ATI-5923), recently studied by Ellis et al. [102], is an oral vitamin K antagonist similar to warfarin. However, tecarfarin is a vitamin K epoxide reductase antagonist, which is metabolized by carboxylesterases and not the cytochrome P450 (CYP450) system involved

Table 12.5 Considerations with warfarin and dabigatran

Drug	Advantages	Disadvantages
Warfarin	Cheap, generic antidotes known[a]	Multiple drug–substance interactions
		Frequent blood draws to monitor (costs)
		Long half-life (~40 h)
		Adjustments based on hepatic and other interactions
Dabigatran	Little to no monitoring	Expensive, but may offset long-term laboratory costs
	Lower bleeding risks (compared to warfarin)	No generic
		Interacts with amiodarone
		Half-life (12-h)
		Adjusted for renal function and moderate hepatic impairment
		No known bleeding antidote

[a]Warfarin reversal antidotes include discontinuation of the drug, vitamin K, and in emergencies fresh frozen plasma, prothrombin complex concentrates, and possibly recombinant factor VIIa
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in the metabolism of warfarin. Nonetheless, the drug acts like warfarin by elevating the INR, and it can be monitored in a similar fashion as warfarin. This difference in metabolism can also decrease many potential drug, herbal, and dietary interactions seen with warfarin due to the broad use of the CYP450 system. The drug may not involve the CYP450-2C9 gene polymorphisms, and this may lead to more stable anticoagulation control, especially in patients with those genetic polymorphisms. However, the study by Ellis et al. is limited in that it was only an open-label study whose primary outcome was time in the therapeutic range. A phase II clinical trial of tecarfarin in patients with atrial fibrillation and valvular prosthesis and/or renal dysfunction was initiated shortly after their initial publication in 2009 but, as of 2014, no data has been reported and the status of the trial is unknown according to ClinicalTrials.gov (www.clinicaltrials.gov). Nevertheless, the drug provides insight into other pharmacotherapeutic options in the research and development pipeline for patients with AF.

Direct thrombin inhibitors (DTI, Factor II inhibition) and Factor Xa inhibitors (collectively referred to as NOACs) have some advantages in comparison to warfarin, which includes the lack of frequent blood draws to monitor levels (as seen with patients on warfarin) and avoidance of the many drug interactions that warfarin has with other substances (herbal and dietary) (Table 12.5). Some health insurance companies may not cover NOACs initially, especially if warfarin is cheaper, although the long-term costs of frequent blood testing may offset the cost of the drug. A recent cost analysis comparing warfarin, dabigatran, rivaroxaban, and apixaban suggested that the adjusted costs and quality-adjusted life years favor the NOACs as equivalent or better than warfarin [103]. The drug also may be preferred in some patients in which there is concern of potential ICH, given its lower annual risk (0.1–0.2 %) than dose-adjusted warfarin (0.3–0.4 % per year). The dilemma of starting or restarting anticoagulation after ICH, and whether restarting warfarin or a NOAC is preferable, is an ongoing conundrum without much in the way of an evidence base to guide recommendations. Decisions regarding selection of anticoagulation therapy should be made based on the individual patient characteristics and best judgment by an expert provider.

The treatment approach for AF patients between aspirin and warfarin anticoagulation should be individualized based on the patient's ischemic stroke risk, hemorrhagic risk, and other factors. A number of anticoagulation-related hemorrhage risk prediction scores exist, perhaps the most commonly used in the clinical and research setting being the HAS-BLED, which was designed to assist in clinical decision-making and trial design by estimating 1-year risk of hemorrhage with anticoagulation [104]. Consensus guidelines for treatment are shown in Table 12.6. However, "one size fits all" model does not apply to many patients. For example, a 75-year-old patient with AF who had no other risk factors may not be recommended anticoagulation by current consensus, but results from the BAFTA trial suggest a small absolute benefit (absolute risk reduction, 2 %) over aspirin. Another example is a 76-year-old patient with AF, hypertension, diabetes, prior TIA, and no congestive heart failure would have a $CHADS_2$ score of 4 or annual ischemic stroke risk of approximately 8.5 %. This patient's estimated ICH risk is approximately 0.3–1 % annually [81, 85, 89–92, 105]. This patient's "risk-benefit ratio" favors anticoagulation with either warfarin or a NOAC over aspirin (or clopidogrel-aspirin combination) for ischemic stroke prevention based on the aforementioned trials.

Surgical or interventional options are described for AF. These include the MAZE procedure, which involves surgical alteration of left atrial anatomy to disallow fibrillation and aberrant impulse conduction to the ventricles. It can be

Table 12.6 Cardioembolic stroke therapy

Cardioembolic etiology	Therapy and evidence level
AF	Aspirin therapy: 22 % relative risk reduction Warfarin: 54–77 % relative risk reduction and superior to aspirin level I–II NOACs: 73 % relative risk reduction vs. aspirin (apixaban), 9.5–21 % relative risk reduction vs. warfarin
Reduced LVEF (<35 %)	Aspirin provides a 56 % relative risk reduction in patients who have reduced ejection fraction with no AF or other embolic risk factors; level II
Stroke risk increases 18 % for each LVEF decrease of 5 percentage points (relative risk, 1.18; 95 % CI, 1.02–1.36; $p=0.03$); stroke risk when LVEF ≤28 % is double LVEF ≥35 %	
Women who have reduced LVEF are at higher risk than men with reduced LVEF (Studies of Left Ventricular Dysfunction [SOLVD])	Warfarin reduces risk for stroke for patients who have reduced LVEF and AF. embolic events, or left ventricular thrombus and effect only slightly inferior to aspirin (level II–III)
Acute myocardial infarction	Anticoagulation[a], level II
Left ventricular thrombus	Anticoagulation[a], level II
Valvular disease	
Mitral: rheumatic	Aspirin, anticoagulation[a] or valve repair level II
Mitral: prolapse	None, antiplatelet[b], unless AF then anticoagulation[a], level II
Endocarditis	Antibiotics, level II
	Controversy regarding antiplatelet[b] or anticoagulation[a]
Prosthetic valves	Level II
Mitral: bioprosthetic	Dependent on valve type and AF
Mitral: mechanical	INR 2.5–3.5 and 81–100 mg aspirin
Aortic: bioprosthetic	Antiplatelet[b]
Aortic: mechanical	Anticoagulation[a]
	INR 2.5–3.5 (most valves). Ball in cage (higher INR)
Valvular strands	Unclear if therapy needed; level V
Nonbacterial thrombotic endocarditis	Heparin; level IV
PFO and cryptogenic stroke	Aspirin for TIA/stroke; level I–II
PFO + ASA and cryptogenic stroke	Aspirin first, anticoagulation[a] if antiplatelet[b] fails; level I–II

AF = atrial fibrillation, NOAC = Novel Oral Anticoagulant, LVEF = left ventricular ejection fraction, PFO = patent foramen ovale, ASA = atrial septal aneurysm, INR = international normalized ratio

[a]Anticoagulation: heparin [short-term], warfarin [long-term]

[b]Antiplatelet: aspirin, aspirin-dipyramidole combination, clopidogrel, or ticlopidine

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done in an open or thoracoscopic minimally invasive fashion. Single-center longitudinal series suggest it is a relatively safe procedure and offers long-term stroke risk reduction without anticoagulation, but this has never been trialed in a randomized fashion [106]. Another surgical approach to stroke prevention in patients with AF is occlusion of the left atrial appendage that, as previously described, is implicated in cardioembolic stroke risk as a place where an intracardiac clot may form. A series of trials known as the Left Atrial Appendage Occlusion Studies (LAAOS) [107–109] test the hypothesis that surgical amputation of the left atrial appendage while undergoing other on-pump cardiac surgery is a safe and effective alternative therapy for stroke prevention in patients with AF as compared to standard therapy with anticoagulation. The first two trials demonstrated apparent safety and feasibility and the third installment, currently recruiting, is designed to be the definitive trial for this promising hypothesis.

The WATCHMAN [110, 111], PLAATO [112, 113], and Amplatzer [114] devices are endovascular (e.g., transvenous, trans-septal) tools used to occlude the left atrial appendage [115, 116]. These devices are typically used in AF patients who cannot tolerate prolonged anticoagulation therapy. These devices also carry initial surgical or endovascular risks not seen with medical therapy. Although these interventions have shown feasibility, their long-term superiority to medical management remains a matter of debate. It appears to make sense that exclusion of the left atrial appendage and subsequent thrombus formation may reduce ischemic stroke risk. However, at the present time we encourage enrollment in clinical trials to help to scientifically determine whether these surgeries or procedures are superior to medical management. The WATCHMAN device (Boston Scientific, Natick, MA) has the best evidence for use in the form of a non-inferiority trial as compared to warfarin for stroke prevention in patients with atrial fibrillation, published in *The*

Lancet in 2009. The PLAATO (ev3, Plymouth, MN) device showed promising results in early phase trials and small series, but the latest series demonstrated some substantial perioperative risks and development of the device was discontinued over complicated market concerns [117]. The Amplatzer Cardiac Plug (St. Jude Medical, Minneapolis, MN) is best known for its use for occlusion of septal defects including a patent foramen ovale (to be discussed in a subsequent section) but has been used in an early phase trial for left atrial appendage occlusion. Patients who cannot tolerate or have a strict contraindication to long-term anticoagulation may be considered on a case-by-case basis for such surgical or interventional devices in clinical trials [118].

A summary of the evidence-based practice guidelines [29] for stroke prevention in nonvalvular AF is provided in Table 12.6.

Ischemic Cardiomyopathy

Acute myocardial infarction (MI) and ischemic cardiac disease are the leading cause of death in the USA. Cardioembolic strokes may occur within 24 h after MI. Approximately half of cardioembolic strokes occur within the first week, although stroke risk remains high for as many as 3 months post-MI before decreasing gradually [119]. Myocardial infarction that involves the anterior myocardial wall carries a higher stroke risk than inferior wall myocardial infarction (25 % vs. 5 %) [120–126]. TTE is the preferred test for detecting left ventricular wall and apical thrombi. However, TEE may be used if TTE has a suboptimal transthoracic view. Patients who have experienced MI from coronary artery disease are often treated with heparin, which also reduces the risk of ventricular wall thrombus formation [121–123, 126]. Patients with anterior wall MI with ventricular wall thrombus should be treated with warfarin, with the goal of attaining an INR of 2.0–3.0 for as many as 6 months. Subsequently, aspirin therapy may be used if ejection fraction is preserved and AF is absent. The Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial [122] demonstrated reduced stroke risk of as much as 40 % during a 3-year time span in patients treated with prolonged anticoagulation after myocardial infarction, although bleeding risk was increased. If AF develops after myocardial infarction, anticoagulation may be considered indefinitely, depending on other risk factors, as assessed by the $CHADS_2$ score [126]. If stroke occurs after MI despite antithrombotic therapy, the patient's stroke mechanism and risk needs to be reevaluated, especially to ensure that adequate medical prophylaxis is used. For example, the severity of left ventricular ejection fraction (<35 %), the presence of ventricular wall thrombus, whether anticoagulation was therapeutic or not, and the presence of AF or another cause of the patient's stroke, such as carotid disease, need to be considered. Discovering the mechanism of a stroke after MI should lead to appropriate therapeutic intervention assuming there is no contraindication (e.g., AF after MI and stroke leads to anticoagulation).

Heart Failure and Reduced Left Ventricular Pump Function

Dilated cardiomyopathy is associated with various different etiologies (ischemic and nonischemic, infectious and infiltrative). Among patients older than 55 years, 3.9 % have heart failure [127]. When heart failure occurs, stroke risk increases almost threefold by 5 years [119]. The Survival and Ventricular Enlargement (SAVE) trial [128] showed every decrease of 5 percentage points in left ventricular ejection fraction (LVEF) was accompanied by an 18 % increase in stroke risk. More than 50 years ago, experts discovered that warfarin reduced the risk for pulmonary embolism (PE), which was a major cause of death in patients who had heart failure [129–131]. However, these patients also had a high prevalence of atrial fibrillation and more deep venous thrombosis (DVT) and PE risks. Patients who had an LVEF of 28 % or less had almost double the risk for stroke compared with those who had an LVEF greater than 35 %. Cerebrovascular reactivity also decreases linearly with decreasing LVEF [132], and reduced regional cerebral blood flow foci seen in patients who had heart failure [133] may be a factor predisposing to stroke. Reduced cerebrovascular reactivity and regional cerebral blood flow in these patients may also signify intracranial atherosclerotic disease, which also may be a risk factor. Both warfarin and aspirin are effective in reducing stroke risk, but warfarin is associated with more bleeding complications, especially when used with aspirin. However, decreasing LVEF is associated with increased stroke risk [119, 134, 135]. Oral anticoagulation (INR intensity, 2.0–3.0) is recommended in those who have atrial fibrillation, previous episodes of thromboembolism (stroke, systemic or pulmonary embolism), or documented left ventricular thrombus [136]. Whether antiplatelet or anticoagulant therapy is more beneficial for stroke prevention in patients who have heart failure and without the aforementioned risk factors remains uncertain.

A retrospective subgroup analysis of the multicenter, prospective, placebo-controlled treatment trial Study of Left Ventricular Dysfunction (SOLVD) [137] elucidated the relationship between embolic stroke risk and worsening ventricular function. Increased stroke risk was seen only in women (2.4 events per 100 patient-years compared with 1.8 events per 100 patient-years in men). In this study, warfarin and aspirin were associated with a lower rate of death or hospitalization for heart failure than aspirin, but only warfarin

reduced death from worsening heart failure. Although embolic stroke risk doubles when LVEF declines below 28 % compared with 35 %, patients also benefit from aspirin alone (56 % relative risk reduction in SAVE [128]), without the bleeding complications. This stands in contrast with the Warfarin/Aspirin Study in Heart Failure (WASH) [138] and Heart failure Long-term Antithrombotic Study (HELAS) [139] trials that argue against the use of antithrombotics in heart failure without atrial fibrillation or documented intracardiac thrombus, so controversy exists about whether antiplatelet or anticoagulation therapy should be used [128, 137, 140, 141]. The Warfarin and Aspirin Therapy in Heart Failure trial (WATCH) [142] was designed to compare aspirin 160 mg/day, clopidogrel 75 mg/day, and warfarin (INR, 2.5–3.0) in 4,500 patients who had poor left ventricular function. However, the trial was terminated 18 months prematurely (June 2003) by the VA Cooperative Study Program because of poor enrollment. Results published in 2009 [143] showed that warfarin reduced nonfatal stroke compared with aspirin and clopidogrel ($p<0.05$), but the combined end point of nonfatal myocardial infarction or stroke and death did not reach statistical significance. The Warfarin Versus Aspirin in Patients With Reduced Cardiac Ejection Fraction (WARCEF trial) [144] was a randomized, double-blind, multicenter trial studying the efficacy of warfarin (INR, 2.0–3.5) versus aspirin (325 mg/day) on all-cause mortality and stroke (both ischemic and hemorrhagic) in patients who have LVEF of 35 % or less. The study randomized 2,305 patients who were followed up for a mean of 3.5 years. The rate of the primary outcome was 7.47 per 100 patient-years in the warfarin group and 7.93 in the aspirin group (HR with warfarin, 0.93; 95 % CI 0.79–1.10; $p=0.40$) demonstrating no significant overall difference between the treatment groups. This is the best evidence to date that argues against the use of anticoagulation in the setting of heart failure and sinus rhythm, although it should be noted that the combined end point used was inappropriate as ischemic and hemorrhagic strokes should not be "clumped," nor should be intracranial and systemic hemorrhages which have very different clinical implications. It remains to be seen if NOACs will be studied for this indication.

Patent Foramen Ovale

A patent foramen ovale (PFO) remains a controversial cause of cryptogenic and cardioembolic stroke due to its widespread prevalence in the population of approximately 20–25 % [47]. A PFO is a hole between the left and right atria and allows passage of blood between the atria depending on the size of the PFO and physiological variables, such as Valsalva, which increases intrathoracic pressure. The PFO remains controversial because of its high prevalence and because common physiologic stressors frequently occur that do not result in immediate ischemic stroke. Nonetheless, the association of a PFO with atrial septal aneurysm (ASA) has been suggested in prospective trials of patients with cryptogenic stroke (e.g., mechanism not certain after exhaustive evaluation) (Table 12.1). The ASA is a mobile structure that bows back and forth around the PFO and is hypothesized to be a nidus for clot formation, although it is rarely substantiated on echocardiogram [47, 145–147]. For patients with incident stroke and PFO detected on echocardiogram and no other identifiable cause (e.g., lacunar disease mechanism or large vessel atherosclerosis) with a cryptogenic stroke classification, we advise evaluation for ASA on echocardiogram and use of aspirin or other antiplatelet initially, along with risk factor modification. For patients who fail this approach, we recommend enrollment in a clinical trial studying medical management vs. endovascular PFO closure.

Recently, the Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale (CLOSURE I) trial results have been published [148, 149]. The CLOSURE I trial was a prospective, multicenter study of closure of the PFO using the STARFlex PFO occluder device, combined with the best medical therapy, compared to best medical therapy alone in patients with TIA or stroke who had known PFO. The study enrolled 909 patients and required a 2-year follow-up. The primary end point of the CLOSURE I trial was a 2-year incidence of stroke or TIA, all-cause 30-day mortality, and neurologic mortality from 31 days of follow-up, which was adjudicated by a panel of physicians who were blinded of treatment allocation. The primary end point was reached in 5.5 % of the closure group and 6.8 % of the medical arm (adjusted HR, 0.78; 95 % confidence interval, 0.45–1.35; $p=0.37$). The rates were 2.9 and 3.1 % for stroke ($p=0.79$) and 3.1 and 4.1 % for TIA ($p=0.44$). The results of the CLOSURE I trial suggest the PFO occluder device was not superior to the best medical therapy for prevention of recurrent stroke or TIA.

Randomize Evaluation of recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) is another PFO occlusion trial (Amplatzer AGA Medical, Plymouth, MN) whose results have been recently reported [150]. The study randomized 980 patients to either best medical therapy (heterogenous: single or dual antiplatelet in 75 %, warfarin in 25 %) or PFO closure and tracked recurrent stroke rates. Over the course of a median of 2.1 years of follow-up per patient, 9 patients in the closure group and 16 in the medical-therapy group had a recurrence of stroke in the intention-to-treat cohort (HR with closure, 0.49; 95 % CI, 0.22–1.11; $p=0.08$). The between-group difference in the rate of recurrent stroke was significant in the prespecified per-protocol cohort (6 events in the

closure group vs. 14 events in the medical-therapy group; HR 0.37; 95 % CI, 0.14–0.96; $p=0.03$) and in the as-treated cohort (5 events vs. 16 events; HR, 0.27; 95 % CI, 0.10–0.75; $p=0.007$). These results are a bit ambiguous; some suggest that there is perhaps some role for PFO closure in patients similar to those enrolled in this study and that the procedure is relatively safe but the NNT for the primary outcome was 67 and NNH only 23 for serious device or procedure-related adverse events. Another recent trial using the Amplatzer device, the PC-Trial [151], published contemporaneously with the RESPECT trial, also failed to show the superiority of PFO closure over medical management, further weakening the indication to perform the procedure.

The CLOSE trial (NCT00562289 [152]) is a three-arm trial comparing antithrombotic therapy (antiplatelet vs. anticoagulation) vs. PFO closure to determine which is best in preventing recurrent stroke, and recruitment is planned through 12/2016 with a target enrollment of 900 patients. Gore-REDUCE trial (NCT00738894 [153]) is another randomized clinical trial evaluating PFO closure plus antiplatelet vs. antiplatelet alone in secondary stroke prevention with an estimated study completion date of 1/2018. The results of these studies will be very important for patients with PFO and stroke and their providers.

It is also important to note PFO may be a culprit in "paradoxical embolism," which is arterial circulation embolism from venous clots, such as from DVT. The stroke in these cases can occur from a venous thrombus that crosses through a PFO and, instead of causing pulmonary emboli, causes arterial embolic events that resemble cardioembolic stroke. A high degree of clinical suspicion should exist in patients with apparent arterial embolic stroke and who have DVT and PFO. Given the high risk of DVT development after stroke in paretic limbs, the timing of the discovery of DVT and PFO should occur as soon as possible. A paradoxical stroke mechanism should not be attributed when there is obvious mechanism, such as AF. However, in patients with cryptogenic or undefined stroke mechanism, who have a large-sized PFO with shunting on bubble study proving right-to-left sided physiology, and with early detected DVT, paradoxical embolism is sometimes considered. However, there is considerable controversy as to whether paradoxical embolism mechanism exists and how to treat it, especially with a PFO [154, 155]. In young patients with a PFO, a shunt on an echocardiogram, and proven DVT, hypercoagulability workup should be considered. In patients with a proven hypercoagulable state, a cerebral embolic event, and a proven early diagnosed DVT and PFO, paradoxical embolism can be considered. Treatment is controversial, but patients are often treated with anticoagulation once safe from a cerebrovascular standpoint and the abnormality causing hypercoagulability is defined.

Aortic Arch Atherosclerosis

An overlooked but potentially serious source of embolic stroke is the aortic arch, especially when proximal aortic atheromatous disease is present [156]. Aortic embolic events may be misclassified as cryptogenic unless adequate transesophageal echocardiography or angiography of the aorta is performed. Aortic embolic disease manifests in different forms, including mobile and ulcerated plaques, aortic dissection, and aneurysms (Fig. 12.4). Ascending aorta or proximal arch plaques of 4 mm thickness were seven times more likely to be identified in patients with cerebral infarction than controls in a prospective registry (14.4 % versus 2 %; $p<0.001$) [156, 157]. The authors have observed mobile or unstable aortic atheromatous plaques in some patients after coronary artery bypass, cerebral angiography, cardiac catheterization, and intra-aortic balloon pump placement when consulted for stroke (level V evidence). Whether the aortic plaque formed de novo after the procedure or was present preprocedure remains unknown, because most did not have a preprocedure aortic evaluation and multiple atherosclerotic risk factors. For nonmobile aortic plaque, statin therapy may be protective in preventing stroke (level II evidence [158]), whereas uncertainty remains about whether aspirin or warfarin is the optimal antithrombotic. However, mobile aortic plaques may be treated with warfarin anticoagulation (target INR, 2–3) [159].

Valvular Disease

Clinically symptomatic cerebral embolic events are uncommon in calcific aortic valve stenotic disease (Fig. 12.5) unless concomitant atrial fibrillation, reduced LVEF, or mitral valve disease is present [160–164]. Calcific emboli to the retina occurring spontaneously (e.g., asymptomatic emboli) or after valvuloplasty are reported [162, 165]. Antiplatelet therapy may be initiated in patients who have TIA and bicuspid calcific aortic stenosis, but anticoagulation is generally not recommended unless atrial fibrillation or another high-risk factor for embolism echocardiographic abnormality is detected [160–162, 166].

Mitral valve stenosis from rheumatic heart disease with or without AF is an indication for warfarin anticoagulation, with INR ranging between 2.0 and 3.0, to prevent thromboembolic events (cerebral and systemic) [167, 168]. Anticoagulation is recommended in some patients who have mitral valve stenosis without atrial fibrillation and have evidence of spontaneous echo contrast ("smoke") within a large left atrium (>5.5 cm). In these patients, valvuloplasty may be attempted after an adequate period of anticoagulation.

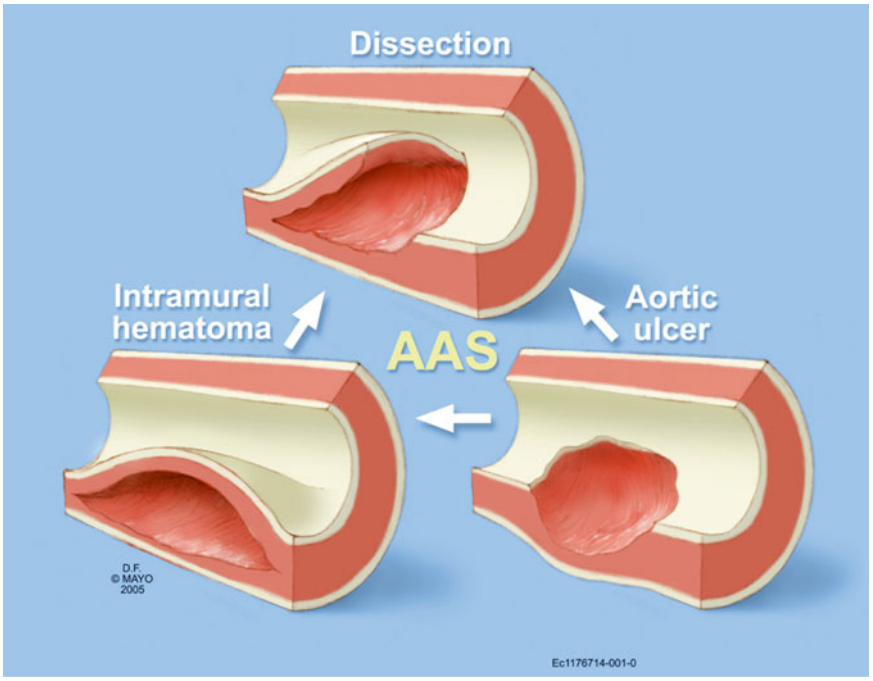

Fig. 12.4 Aortic plaque as a source of cardioembolic stroke. Aortic atherosclerosis. Aortic atherosclerosis mechanisms, including aortic ulcer (*bottom right*), followed by intramural hematoma (*bottom left*), which is a raised structure creating reduced caliber to the aortic lumen. Similarly, although it is not shown, aortic atheromata narrow the aortic lumen and may lead to local thrombus formation and embolization. The top shows aortic luminal dissection. *By permission of Mayo Foundation for Medical Education and Research. All rights reserved*

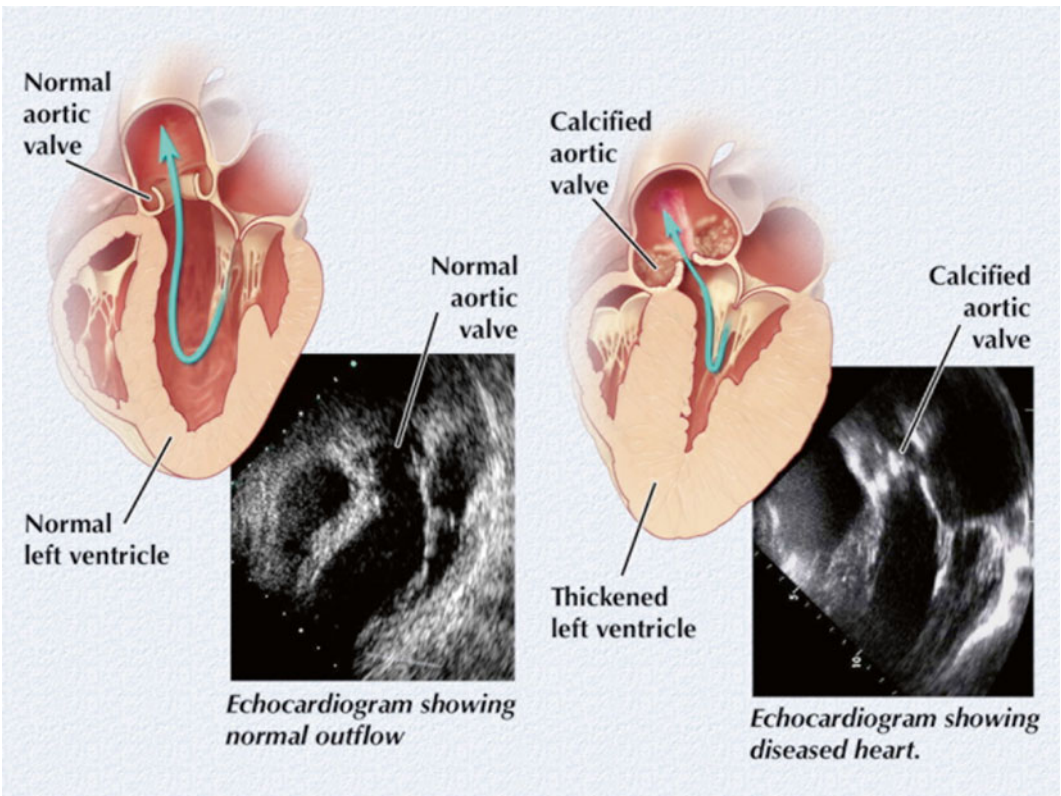

Fig. 12.5 Aortic stenosis as a source of cardioembolic stroke. Normal and calcific aortic valves. Normal aortic valve and ventricle on the *left upper diagram*, with normal aortic valve appearance and ventricle (*bottom left*). *Top right* (diagram) and *bottom right* (echocardiogram) showing a calcified aortic valve that leads to aortic stenosis, increased resistance to outflow, and resultant thickening of the ventricular wall. *By permission of Mayo Foundation for Medical Education and Research. All rights reserved*

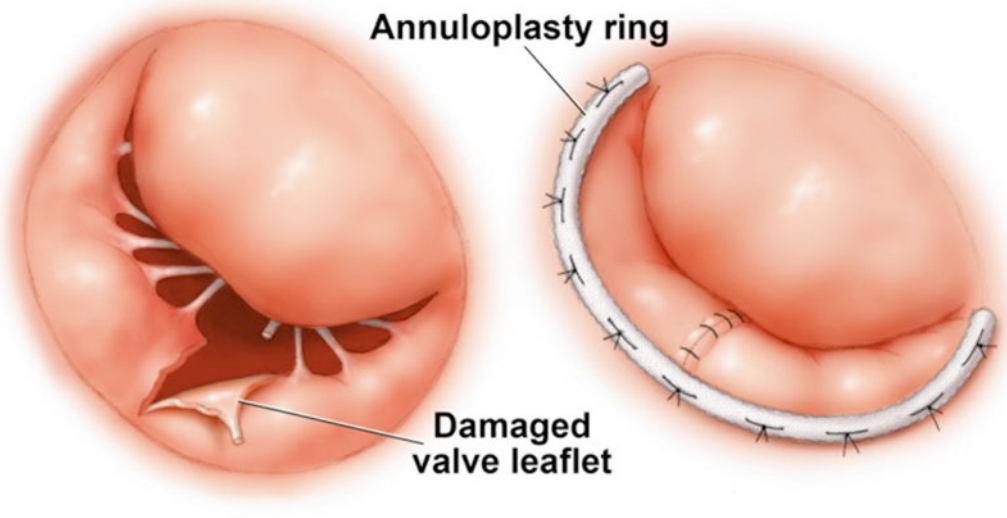

Fig. 12.6 Mitral valve repair. Mitral valve annuloplasty. Mitral valve annuloplasty (*right*) repairing damaged mitral valve leaflet (*left*). *By permission of Mayo Foundation for Medical Education and Research. All rights reserved*

Mitral annular calcification (MAC) does not denote simply calcification of the mitral annulus, but rather a syndrome characterized in elderly patients by a calcified mitral annulus, mitral stenosis or regurgitation, aortic stenosis, conduction disturbances, embolic phenomenon, and even endocarditis. Antiplatelet agents are reasonable first-line therapy, but if recurrent embolic events occur or atrial fibrillation develops, anticoagulation or valvular repair (Fig. 12.6) should be considered [161, 162].

Mitral valve prolapse (MVP) is the most common valvular echocardiographic finding in normal individuals (4–6 %). If symptomatic, palpitations or chest pain may be present. MVP is typically a benign echocardiographic finding and not associated with increased stroke risk unless it occurs in combination with mitral annular calcification, mitral regurgitation, or AF. MVP is being studied in cerebrovascular disease, with some studies showing denudation of the mitral endothelium and platelet-fibrin thrombi, which may embolize. Antiplatelet agents remain first-line therapy, but anticoagulation is considered for recurrent cerebral ischemic events or MVP associated with atrial fibrillation or another embolic risk factor [161, 162].

Regarding valve prostheses, antithrombotic therapy depends on the type and location of the prosthetic valve (Fig. 12.1) and the presence of AF [161]. For metallic valves ("ball in cage" and "caged-disc," see Fig. 12.1, top right and middle-right), warfarin anticoagulation is typically recommended to attain a target INR ranging from 2.5 to 3.5. A single trial of a NOAC (the DTI dabigatran) [169] vs. warfarin for thromboembolic protection against mechanical aortic or mitral valves was halted prematurely due to excess bleeding in the dabigatran cohort, and thus warfarin remains the mainstay of anticoagulation in this setting for now. Prosthetic valves in the mitral position are associated with a higher thrombotic risk than those in the aortic position. Patients who have a bileaflet aortic valve (see Fig. 12.1, middle left and bottom left) without atrial fibrillation or left ventricular dysfunction should receive warfarin to attain a target INR ranging from 2.0 to 3.0 [170]. For high-risk patients, aortic bileaflet valves, mitral bileaflet, or caged disc location with concomitant atrial fibrillation, warfarin with INR intensity of 2.5–3.5 and aspirin, 81–100 mg/day, may be given. Patients who have aortic bioprosthetic valves are typically managed with aspirin (325 mg/day) monotherapy, assuming no atrial fibrillation, whereas those who have mitral bioprosthetic valves may require warfarin for the first 3 months before converting to aspirin monotherapy. Bioprosthetic valves complicated by thrombus formation, atrial fibrillation, or thromboembolism failing antiplatelet therapy may require warfarin anticoagulation with an INR ranging from 2.0 to 3.0 [160, 170].

Giant Lambl's excrescence (GLE) are valvular abnormalities that have a frond-like appearance and a stalk-like attachment that arise mostly from left-sided valvular surfaces (aortic more than mitral) and are of unclear cause (neoplastic, hamartomatous, or reparative). Embolic risk is difficult to quantify for GLE, but seems directly proportional to size and mobility. Initial medical therapy typically involves an antiplatelet agent; if recurrent cerebral ischemic events occur, anticoagulation or surgical resection are considered for large (>1 cm) mobile lesions [171–173].

Valvular strands [171, 174] are common small filiform projections (<1 mm wide and <1 cm long) arising near valve

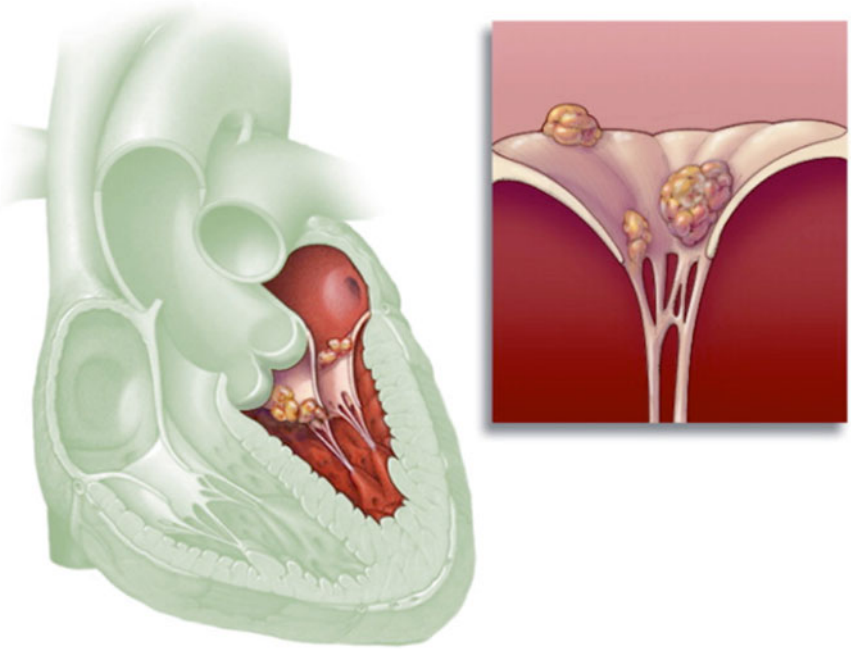

Fig. 12.7 Endocarditis. Mitral valve endocarditis. Mitral valve endocarditis, showing the valvular vegetations on the surface of the mitral valve. *By permission of Mayo Foundation for Medical Education and Research. All rights reserved*

closure lines (mitral more than aortic) that result from traumatic abrasions of the valve surface. Risk factors for valvular strands include age and valvular disease (e.g., rheumatic valve disease). Antiplatelet therapy is recommended for patients who have cerebral ischemic events attributable to valvular strands. Whether anticoagulation is superior to antiplatelet therapy for stroke prevention in this condition is unclear; however, administering antiplatelet therapy is reasonable [126, 174].

Nonbacterial thrombotic endocarditis (NBTE), or marantic endocarditis, is a noninfectious process affecting normal or degenerative cardiac valves caused by fibrin thrombotic deposits in patients who have hypercoagulable states associated with adenocarcinomas of the lung, colon, or pancreas that produce mucin [162]. Patients who have NBTE may present with arterial and venous thromboembolism and disseminated intravascular coagulation. Heparin may be beneficial for stroke risk reduction [175]. Libman–Sacks endocarditis is a noninfectious valvular abnormality associated with autoimmune disorders, such as systemic lupus erythematosus and the antiphospholipid antibody syndrome. No large-scale randomized trials exist to provide evidence-based data, but some experts recommend anticoagulation with warfarin as primary treatment to prevent stroke [3].

Infectious seeding of heart valves (Fig. 12.7) or endocarditis before the advent of antibiotics was associated with a very high cerebral embolic rate (70–90 %), which decreased (12–40 %) in the era of antibiotics. Specific antibiotic therapy for endocarditis remains first-line treatment based on blood culture results, whereas anticoagulation remains controversial or contraindicated given the early rates of cerebral hemorrhage and the fact that anticoagulation does not reduce the incidence of embolism in native valve endocarditis. Patients who have mechanical prosthetic valves, however, may be at higher risk if anticoagulation is discontinued [137]. Exceptions to this rule include patients who have infected aortic bioprosthetic valves and those on antibiotics and in normal sinus rhythm. Controversy remains about the duration and intensity of anticoagulation in patients who have prosthetic valve endocarditis, given the risk for embolism versus intracranial hemorrhage [162, 176–181]. Embolism to the brain may also occur in these patients, and they may develop an infected microscopic nidus (especially in the presence of *Staphylococcus aureus*) or microaneurysm that may be prone to cerebral hemorrhage. Prosthetic valve endocarditis may be considered an anticoagulation dilemma, because patients have equal risks for ischemic stroke and cerebral hemorrhage. The authors recommend carefully considering the patient's valve type, location, and presence of atrial fibrillation in weighing the ischemic and hemorrhagic risks. For example, if the patient had a large ischemic stroke from endocarditis, anticoagulation presents higher risk for brain hemorrhage and may need to be delayed or not administered. Surgical removal or repair is considered for patients who have congestive heart failure, cardiac abscess, or persistently positive blood cultures despite antibiotic treatment.

Infective endocarditis with large vegetations and/or causing heart failure warrants early surgical consultation [182]. Timing of surgery is otherwise nebulous outside of the setting of uncontrolled infection, large vegetations and/or heart failure because of the conflicting results of uncontrolled studies. Surgical replacement of an infected prosthetic valve presents a high risk for morbidity and mortality, especially for mitral position valves. Early surgery is also warranted in fungal endocarditis.

Cardiac Tumors

Primary cardiac tumors are rare (<0.2 % in unselected autopsy series), and most are benign (50 % myxomas and papillary fibroelastoma) but associated with a high frequency of embolic events [183]. Myxomas commonly occur in the left atrium and arise from the interatrial septum. They may embolize to the systemic circulation, particularly to the brain when tumor pieces break off or secondary thrombus formation occurs. TEE is invaluable in defining tumor location, size, and morphology. Surgical resection of the tumor is recommended in all cases of myxomas to prevent embolization [126, 172, 173, 183].

Papillary fibroelastomas are benign tumors that tend to originate on cardiac valves as single or multiple masses. Embolic events are typically the first clinical manifestation, because they are present on highly mobile valve leaflets. The embolic mechanism is the same as myxomas, caused by tumor fragmentation or secondary thrombus generation. Surgical resection is also indicated for fibroelastomas [126, 172, 173, 183].

Metastatic tumors to the heart are 20–40 times more frequent than primary cardiac tumors, which are rare (e.g., angiosarcoma, rhabdomyosarcoma) [126, 184]. Cerebral embolization can also occur from these tumors. Surgical treatment can be offered but depends on the underlying tumor type and prognosis.

Summary

Cardioembolic stroke is highly incident and prevalent, is often disabling, and has myriad causes each with different treatment(s). The diagnostic approach hinges on a comprehensive history and physical examination, complemented by electrophysiologic, serologic and imaging diagnostics as appropriate. Many cardioembolic strokes are associated with AF and stroke risk can be drastically reduced when patients with AF and other risk factors receive anticoagulation with warfarin or a NOAC. A judicious clinician must keep an open mind diagnostically if an embolic pattern of infarction is noted but no AF detected. Evidence-based guidelines for primary or secondary prevention of stroke by the various non-AF-related cardioembolic stroke mechanisms are lacking, and antithrombotic medication choices must be carefully individualized.

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Secondary Prevention After Ischemic Lacunar Stroke

13

Raffaella Valenti and Leonardo Pantoni

Case Presentation A 70-year-old woman affected by hypertension presented to the emergency department for sudden onset of right-hemisensory loss. Brain CT-scan excluded hemorrhage and revealed mild leukoencephalopathy. The patient was on aspirin 100 mg per day for previous myocardial infarction.

At this point, the treating physicians discussed the appropriate therapy for secondary prevention of stroke. Doctor 1 proposed to increase the dose of aspirin up to 300 mg per day. Doctor 2 proposed to replace aspirin with clopidogrel, while doctor 3 proposed to start double antiaggregation with aspirin 100 mg plus clopidogrel 75 mg daily. All the doctors agree upon the introduction of atorvastatin. An MRI examination performed 10 days after the event showed a hyperintense lesion in left thalamus on Fluid Attenuated Inversion Recovery (FLAIR) sequences representing a lacunar infarct and numerous hypointense lesions on gradient echo sequences compatible with diffuse hemosiderin deposits. Which of the 3 proposed drug regimens is the most appropriate? Does the presence of cerebral microbleeds affect in some way the decision?

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Introduction

Definitions

The term cerebral small vessel disease (SVD) refers to a group of pathological processes with various etiologies that affect the small arteries, arterioles, venules, and capillaries of the brain [1]. The most common forms are age- and hypertension-related SVD and cerebral amyloid angiopathy [1]. The consequences of SVD on the brain parenchyma are mainly lesions located in the subcortical structures such as lacunar infarcts, white matter lesions, large hemorrhages, and microbleeds. Unlike large vessels, small vessels cannot be currently visualized in vivo; therefore, the parenchyma lesions that are thought to be caused by these vessel changes have been adopted as the marker of SVD, and the term SVD is frequently used to describe these brain parenchyma lesions rather than the underlying small vessel alterations [1]. Of note, the definition of small vessel is not uniform: in one survey, there was less than 50 % agreement among leading neuropathological centers on its definition [2].

Currently, there is an incorrect tendency to use the term SVD to describe only the ischemic component of the SVD process (i.e., lacunar infarcts and white matter lesions) [1, 3]. Instead, a broader view of SVD should be maintained, particularly when considering preventive and therapeutic aspects, because patients with SVD also have an increased risk of hemorrhage [1].

In a recent consensus paper the definition of SVD was extensively revised [4]. According to this new classification, there are at least 6 types of SVD. This consensus position is mainly based on neuroimaging. As a result, the hemorrhagic component of SVD is restricted to microbleeds, and large hemorrhages are not contemplated.

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Clinical Correlates

SVD has an important role in cerebrovascular disease in both acute and chronic phases. Lacunar strokes are the cause of about one fifth of all strokes, [5] and SVD is a major contributor of cognitive decline, [6] psychiatric disorders, [7] and functional loss in older people [8, 9]. SVD is the most common cause of vascular dementia, [9] and a major contributor to mixed dementia [10, 11]. Lacunar infarcts and white matter lesions are associated with specific cognitive deficits such as psychomotor retardation, deficits of attention, planning, and set-shifting, and dysexecutive syndrome [12]. There is a correlation between progression of white matter lesion load and decline in cognitive performance [13].

Patients with SVD have also other relevant functional deficits. Gait is frequently affected and patients with SVD have an increased risk of falls [14–17]. Mood disturbances, particularly depressive symptoms and apathy, [18, 19] are also frequent, and urinary disturbances may be present [20]. Patients with severe white matter lesions had more than double the risk of transition to disability than patients with mild lesions, independent of many other predictors of disability [8, 21].

Patients with a lacunar infarct usually present with one of the classical lacunar syndromes (pure motor hemiparesis, pure sensory syndrome, sensorimotor stroke, ataxic hemiparesis or dysarthria-clumsy hand); a number of less frequent lacunar syndromes have been described [22].

SVD ischemic strokes are overall less severe than other types of stroke during the acute phase, and are characterized by lower risk of early mortality and better functional outcome on hospital discharge. However, recurrence rates and mortality reach convergence with that of other stroke subtypes over a longer follow-up period [23, 24]. Risk rate of recurrent stroke 1 year after lacunar stroke is 5–10 % in hospital-based studies, [25–27] and 6–11 % in community-based studies [28]. In clinical trials, the annual recurrent lacunar stroke rate ranges from 3 to 10 % [29–32]. One recent study with a 12-year follow-up reported a higher mortality rate in patients with small vessel occlusion than other stroke subtypes [26]. However, the long-term outcome of these patients is not benign in terms of functional impairment [33, 34]. For this reason, lacunar stroke should be regarded as a potentially severe condition rather than a relatively benign disorder and, therefore, lacunar stroke patients require appropriately rigorous management and timely follow-up.

Another relevant point to outline is that many lacunar infarcts are clinically "silent," i.e., not overtly and temporally associated with clear cut neurological symptoms. Despite being initially silent, these lesions are associated with an increased risk of dementia and stroke [35, 36].

Pathophysiological Aspects

The pathophysiological mechanisms of SVD are largely unknown, and therefore knowledge on prevention and treatment measures is still limited. For example, it is still unclear how disease of the small vessel relates to the parenchyma lesion. Moreover, as stated above, given the frequent coexistence of different forms of SVD, all the relevant lesion types should be taken into account [1]. According to a classical view, most lacunar infarcts result from disease of small penetrating arteries. However, any etiology of brain ischemia (e.g., atherothrombosis, cardioembolism) may cause a lacunar infarct, [37–40] for example, lacunar infarcts in the pons may be caused by atherosclerosis of the basilar artery involving penetrating branches [41]. Consequently, it may be challenging to manage patients with lacunar strokes who have other potential etiologies when it is unclear if the association is simply coincidental or not.

Because it is assumed that SVD strokes have underlying pathogenic mechanisms different from those of atherosclerotic or cardioembolic strokes, one would expect distinct therapeutic and preventive approaches. However, no specific treatment for stroke caused by SVD has yet been proposed; on the other hand, there are no data that an approach with recognized evidence-based efficacy for strokes in general is not efficacious lacunar strokes in particular.

Stroke caused by SVD has rarely been the specific object of trials for secondary prevention of ischemic stroke, which generally have enrolled participants with heterogeneous stroke subtypes. Many secondary stroke prevention studies, however, have included a significant proportion of patients with SVD and some provided subtype post-hoc analysis (usually without neuroimaging verification) [42]. These data will be discussed in the following sections.

As stated above, SVD includes ischemic and hemorrhagic lesions; thus, a correct approach should consider both aspects of this pathology. Nevertheless in this chapter, because a paucity of specific data about the hemorrhagic component, we focus exclusively on secondary prevention of small vessel ischemic stroke, i.e., lacunar stroke, not including major hemorrhages and microbleeds.

Vascular Risk Factor Control in Patients with Previous Lacunar Stroke

Blood Pressure Control

Hypertension is the most prevalent and powerful modifiable risk factor for small vessel stroke and stroke in general, with an attributable risk between 35 and 50 % [43]. Reduction of blood pressure has consistently been shown to reduce stroke

occurrence in multiple primary prevention studies. Lowering systolic blood pressure by 10 mmHg is associated with a 40 % reduction in stroke occurrence [44–46]. Similar benefits of blood pressure reduction are seen in secondary prevention trials. A meta-analysis of seven randomized controlled trials, including 15,527 patients with TIA or stroke randomly allocated to treatment group within 1–14 months after the event, showed that long-term blood pressure reduction reduces stroke by about 28 % [47].

One of the largest randomized placebo-controlled trials included in the meta-analysis, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), enrolled nearly 6,105 patients with stroke and TIA, 35 % of whom had lacunar strokes. The study demonstrated that a mean reduction of 9 mmHg of systolic blood pressure resulted in 28 % risk reduction in stroke (achieved systolic pressure in the active group was 138 mmHg, but the optimum target for blood-pressure control was not established) with the combination of perindopril and indapamide compared to placebo [48, 49]. In this trial, the effects of blood pressure lowering on the risk of different types of stroke were also investigated [49]. Possibly because of the smaller sample sizes within subtypes, a statistically significant effect was seen only for large artery infarction prevention, while only a trend for the active treatment to reduce the risk of lacunar stroke was outlined (23 % reduction; 95 % CI: −7–44 %) [49].

In the PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial the effect of blood pressure-lowering, initiated early after a stroke, was evaluated [50]. The study used a two-by-two factorial design to compare four regimens: a combination of aspirin and extended-release dipyridamole compared with clopidogrel, and telmisartan (80 mg daily) compared with placebo. On enrollment, 52 % of patients had SVD strokes. The primary outcome of first recurrent stroke occurred in 880 SVD stroke patients (8.7 %) in the telmisartan group, as compared with 934 patients (9.2 %) in the placebo group (HR 0.95; 95 % CI: 0.86–1.04; $p=0.23$). Also the type of recurrent stroke was evaluated together with the predictors of stroke recurrence, including index stroke [50]. Considering the 10,578 patients with SVD ischemic stroke at baseline, recurrent stroke was of the same subtype in 48.7 % of patients, while 19.4 % had a large artery stroke and, of note, 10.0 % had a cerebral hemorrhage [51]. In the multivariable analysis, the predictors of stroke recurrence in the SVD group were older age, male sex, previous stroke, previous transient ischemic attack, hypertension, diabetes, and tobacco use [51]. Having an index SVD stroke together with older age, previous stroke, and the association treatment with aspirin and dipyridamole, was a significant predictor of cerebral hemorrhage (OR 1.71; 95 % CI: 1.20–2.45) [51].

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial was the first secondary stroke prevention trial designed specifically to assess therapeutic interventions in patients with symptomatic lacunar infarcts [52]. It was designed to categorically address cerebral SVD and, so far, it is the only randomized trial that included a homogeneous cohort of patients with recent lacunar stroke [52, 53]. The study was a randomized, multicenter trial performed in 81 centers in North and Latin America and Spain between March 2003 and April 2011. Eligible participants had symptomatic lacunar infarcts without severe carotid stenosis or major cardioembolic disease. Patients with prior cortical or hemorrhagic stroke were not included. In this study, 3,020 participants were randomized at least 2 weeks after the index stroke, with a mean time to randomization of 62 days. The treatment was open label; in a two-by-two factorial design, patients were randomized to two interventions: a) antiplatelet treatment (aspirin 325 mg vs. aspirin 325 mg + clopidogrel 75 mg) and b) two target levels of systolic blood pressure control ("higher" 130–149 mmHg vs. "lower" <130 mmHg) [52, 53]. The primary outcomes of the study were the prevention of recurrent stroke (including ischemic strokes and intracranial hemorrhages) and a reduction in cognitive decline frequency. Secondary endpoints were reductions in acute myocardial infarction, need for acute admission to hospital for a major vascular event, and death classified as vascular, nonvascular, or unknown. Analysis was by intention to treat. Patients with SVD were defined on the basis of criteria from the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [54] supplemented by MRI data. The study was of particular interest because it also took into account a cognitive outcome measure [55].

The blood pressure arm of the trial used a prospective, open-label, blinded evaluation (PROBE) design, and investigators were able to use any antihypertensive agents or combination of agents to meet the assigned targets. 1,519 patients with symptomatic lacunar infarct were allocated to the "higher" target group and 1,501 to the "lower" group [52, 53]. After 1 year, mean systolic blood pressure was 138 mmHg (95 % CI: 137–139) in the higher-target group (75 % had blood pressures within the assigned target ranges) and 127 mmHg (95 % CI: 126–128) in the lower-target group (with only 65 % of patients in the target ranges). After a mean follow-up of 3.7 years, nonsignificant rate reductions were seen for all strokes (HR 0.81; 95 % CI: 0.64–1.03; $p=0.08$), disabling or fatal stroke (HR 0.81; 95 % CI: 0.53–1.23; $p=0.32$), and the composite outcome of myocardial infarction or vascular death (HR 0.84; 95 % CI: 0.68–1.04; $p=0.32$) in favor of the lower target. A nonsignificant 13 % reduction in the rate of recurrent lacunar stroke was seen in the lower-target group (HR 0.87; 95 % CI: 0.62–1.22; $p=0.41$) compared with higher-target. Serious side effects of blood pressure therapy were infrequent (3 %) and did not differ between the two target groups.

The nonsignificant results of the SPS3 trial might be the result of good blood-pressure control in both treatment

groups, the frequent use of statins, and high adherence to antiplatelet therapy. Moreover, the assignment to blood pressure targets was not masked, which could have potentially introduced a bias [52, 53]. Intracerebral hemorrhage was however reduced significantly by 63 % (HR 0.37; 95 % CI: 0.15–0.95; $p=0.03$) [53]. This result is consistent with the known association between hemorrhage and hypertension. These data indicate that the patient number needed to treat (NNT) to prevent one intracerebral hemorrhage at 4 years (roughly the average follow-up in SPS3) would be 175. Although the difference in the primary end point was not statistically significant, the study hints at a reduction in stroke recurrence in the lower-blood pressure group [53].

Though the overall results of the SPS3 study did not reach statistical significance, in the context of previous trials demonstrating a benefit for stroke reduction with blood pressure treatment, the SPS3 significant reduction of intracerebral hemorrhage in the lower-target group, and the low rate of major side-effects of blood pressure lowering in both blood pressure groups, it might seem appropriate to target blood pressure reduction to a systolic pressure of 130 mmHg in patients with lacunar stroke [52, 53, 56]. At present, there is no evidence to support the preferential use of one particular antihypertensive agent or combination of agents in lacunar stroke.

Some authors argue that reducing blood pressure to lower levels may delay progression of the cerebral SVD but blood pressure levels slightly higher may sustain cerebral blood flow and potentially improve cognition. In an ongoing trial, the authors are comparing the reduction of blood pressure with usual targets and are carrying out an MRI study to assess the amount of brain damage and blood flow to the brain. The aim is to see whether one of the two treatment regimens is better at reducing brain damage and increasing blood flow to the brain to reduce cognitive problems over a 2 years period [57].

Another question is whether blood pressure should be lowered more aggressively in lacunar stroke patients with diabetes. This question has never been explored in any clinical trials. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study, [58] the efficacy and safety of setting systolic blood-pressure targets lower than 120 mmHg in 4,733 patients with diabetes were explored. No differences in outcomes in patients allocated to target <120 mmHg systolic compared with those treated to <140 mmHg systolic was detected [58, 59]. In this population, the annual rates of stroke (a prespecified secondary outcome) were 0.32 and 0.53 % in the two groups, respectively (HR=0.59; 95 % CI: 0.39 to 0.89; $p=0.01$). However these results were based on only 100 events.

Lipid Control

Observational studies have shown a modest association between elevated total cholesterol and low-density lipoprotein cholesterol and increased risk of ischemic stroke [60, 61]. However, also for this risk factor, studies specifically addressing possible differences across stroke subtypes do not exist. It would be expected that the association and response to therapy will be stronger in patients with atherosclerotic stroke mechanisms [62, 63].

In The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, 4,731 patients with stroke or TIA and without known coronary heart disease were randomized to atorvastatin 80 mg daily or placebo [31]. The SPARCL primary end point was fatal or nonfatal stroke. In the overall population, patients allocated to atorvastatin had a significant reduction in the primary outcome (HR 0.84; 95 % CI: 0.71–0.99; $p=0.03$). Regression models testing for an interaction with treatment assignment were used to explore potential differences in efficacy, based on stroke subtype [31]. In a post-hoc analysis, there was no evidence that one stroke subtype benefited selectively from statin therapy with regard to reduction of stroke or other major vascular events [64]. In particular, 29.8 % of patients ($n=1,409$) were classified as having SVD, and in this patient group the primary end point occurred in 13.1 % in those treated with atorvastatin and in 15.5 % of placebo group; this difference was not statistically significant. The study showed an increased risk of hemorrhagic stroke in the group with lacunar stroke as entry event (HR 4.99; 95 % CI: 1.71–14.61) and in the overall population (HR 1.6; 95 % CI: 1.09–2.59). In the multivariate regression analysis however, risk factors for hemorrhage were male sex, increased age and stage 2 hypertension, while there was no evidence that patients with lacunar strokes faced a selectively higher rate of intra-cerebral hemorrhage when treated with atorvastatin [31, 65]. In conclusion, the SPARCL trial does not provide definitive information about the benefit of treatment with statin in SVD patients, nor does it conclusively point to harm from this treatment.

Until further studies examine the association among lacunar infarcts, hyperlipidemia, and response to statins, patients should be treated following the current recommendations on the basis of available data from the American Heart Association/American Stroke Association (AHA/ASA) [66]. Statin therapy with intensive lipid-lowering effect is recommended for secondary prevention among patients with ischemic stroke (or TIA) who have evidence of atherosclerosis, a low-density lipoprotein cholesterol-level ≥100 mg/dL, and who are without known coronary heart disease [66].

A multicenter, open-label randomized controlled trial, whose aim is to examine the role of pravastatin in the secondary prevention of stroke in Japanese patients is ongoing [67]. A total of 1,578 patients with non-cardioembolic ischemic stroke (lacunar, atherothrombotic, and infarction of undetermined etiology) were enrolled. More than 60 % of patients were included because of a lacunar infarction. This study will also evaluate the effect of pravastatin on the recurrence of each stroke subtypes [67]. Follow-ups of patients are in progress [67].

Antiplatelet Therapy for Secondary Stroke Prevention

Although the presence of thrombosis in cerebral small vessels leading to lacunar strokes has not been clearly documented, the process that results in occlusion of a small vessel might also involve platelet aggregation and thrombi formation. It is thus assumed that antithrombotic agents are beneficial in preventing stroke recurrence in lacunar stroke patients. In fact, the benefit of antiplatelet therapy in lacunar stroke patients for secondary prevention is supported by existing evidence from randomized controlled trials. As reviewed by Nakajima et al. [68], some secondary stroke prevention randomized trials, performed between 1983 and 2012 and published before the SPS3, investigated different antithrombotic agents and classified the index event by stroke mechanism [29, 69–78]. These studies provide data about secondary prevention of lacunar infarcts in 28,244 patients [68]. Despite some methodological shortcomings, such as the absence of rigorous stroke subtype definition and the lack of statistical power, the results outline a global superiority of antiplatelet therapy in comparison with placebo in preventing recurrent stroke.

Four studies have compared treatment with different antiplatelet drugs and placebo. The Canadian American Ticlopidine Study (CATS) trial compared ticlopidine with placebo in patients who had suffered from a stroke [69]. After a mean of 24 months of follow-up, the primary endpoint stroke was less frequent with ticlopidine, although not significantly (relative risk reduction (RRR) = 50 %; 95 % CI: 0.76–76.0), in the 275 lacunar stroke patients [69]. Results from the Chinese Acute Stroke Trial (CAST) study, comparing aspirin and placebo for early secondary prevention (30 days after stroke), showed a nonsignificant (RRR = 10 %; 95 % CI: −0.5–1.1) in the subgroup of patients with stroke caused by SVD (n = 6,102) [70]. In the Accidents, Ischemiques Cerebraux Lies a l'Atherosclerose (AICLA), trial of aspirin plus dipyridamole versus placebo, out of 604 cerebral ischemic event, a small group of 98 (16 %) were lacunar [71]. In this group, the active treatment resulted in a RRR = 29 % (95 % CI: 2–34) [71]. In the Cilostazol Stroke Prevention Study, 1,095 patients with noncardioembolic ischemic cerebrovascular events were enrolled, and 74 % (n = 810) had a lacunar stroke. Treatment with cilostazol, a phosphodiesterase 3 inhibitor, was associated with a reduction of the risk of stroke also in lacunar stroke patients (RRR = 42 %; 95 % CI: 9.2–62.5) [72].

Six other randomized controlled trials compared different antiplatelet strategies for secondary prevention of lacunar stroke. The African American Antiplatelet Stroke Prevention Study (AAASPS) enrolled 1,809 black patients with a recent non-cardioembolic ischemic stroke, of whom 1,221 (67 %) had lacunar stroke, and randomized them to receive ticlopidine (500 mg/daily) or aspirin (650 mg/daily) [73]. The study was halted after about 6.5 years when futility analyses revealed a <1 % probability of ticlopidine to be superior to aspirin. In the ticlopidine arm the recurrent stroke was of the lacunar type in 36.2 % of cases, while in the aspirin arm the lacunar subtype accounted for 47.1 % of recurrences (p = 0.12) [73].

In the European Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), patients were assigned to aspirin (30–325 mg daily) with or without dipyridamole (200 mg twice daily) within 6 months of a transient ischemic attack or minor stroke [74]. In patients with lacunar stroke (n = 1,377), combination therapy was not superior to aspirin alone [74].

In the antiplatelet arm of the PRoFESS trial, 10,500 patients with lacunar stroke were randomized to receive aspirin (50 mg/daily) combined with extended-release dipyridamole (400 mg/daily) or clopidogrel alone [50, 75]. The two treatments did not differ in terms of the effects on functional outcome, recurrence, death, bleeding, or serious adverse events either in the total sample or in the lacunar stroke group (OR 0.97; 95 % CI: 0.79–1.19) [75].

In the second Cilostazol Stroke Prevention Study (CSPS 2) patients with a cerebral infarction within the previous 26 weeks were allocated to receive 100 mg cilostazol twice daily or 81 mg aspirin once daily for 1.5 years [76]. In the 1,473 lacunar stroke patients there was a trend for the primary endpoint (cerebral infarction, cerebral or subarachnoid hemorrhages) to occur less in the cilostazol group (HR 0.75; 95 % CI: 0.54–1.04) [76]. Hemorrhagic events (cerebral or subarachnoid hemorrhages, or hemorrhage requiring hospital admission) were significantly fewer in patients on cilostazol than on aspirin (HR 0.46; 95 % CI: 0.30–0.71; p = 0.0004). Although a specific subgroup analysis for hemorrhagic events was not provided, it is likely that this safety issue applied particularly to SVD patients who accounted for more than two thirds of the total sample [76].

The more recent PERFORM trial (Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic strOke or tRansient ischeMic attack) compared the role of selective thromboxane-prostaglandin receptor antagonist terutroban (30 mg/daily) with aspirin (100 mg/daily) in the prevention of cerebral and cardiovascular ischemic events in patients with a recent non-cardioembolic cerebral ischemic event [77]. Eight-hundred and fifty-six patients with lacunar stroke were randomized to terutroban and 877 to aspirin. The primary endpoint of fatal or nonfatal ischemic stroke was 54 (6 %) in the terutroban group vs. 61 (6 %) in the aspirin group, among patients with the lacunar stroke subgroup (HR 0.90, 95 % CI 0.62–1.31) [77].

In the second European Stroke Prevention Study (ESPS-2), 2,600 patients with SVD and a previous TIA or ischemic stroke were randomized to aspirin, dipyridamole, their combination, or placebo [78]. While the use of the single drugs, compared with placebo, was associated with only a trend for

a reduction of vascular events or stroke in the SVD patient group, the two combined drugs offered a significant benefit in comparison with placebo (HR = 0.56, 95 % CI: 0.40–0.78; NNT = 13.7) or with aspirin alone (HR 0.68; 95 % CI: 0.48–0.97; estimated NNT = 22.7) [78].

The SPS3 was the first secondary stroke prevention trial designed specifically to assess therapeutic interventions with aspirin compared with aspirin plus clopidogrel in patients with symptomatic lacunar infarcts. The antiplatelet arm was double-blinded and enrolled 3,020 participants [52, 53, 56]. Patients were randomly assigned to receive 75 mg of clopidogrel or placebo daily; both groups received 325 mg of aspirin daily (1,503 patients were in the group treated with aspirin plus placebo and 1,517 in the group treated with aspirin plus clopidogrel). The primary outcome was any recurrent stroke, including ischemic stroke and intracranial hemorrhage. The primary safety outcome was major extracranial hemorrhage. The antiplatelet agent comparison aim of the trial was stopped prematurely due to lack of benefit and excess in mortality in patients assigned to combination therapy. After a mean follow-up of 3.4 years the annualized rate for recurrent stroke was 2.5 % in those on dual therapy vs. 2.7 % in those assigned to aspirin (HR 0.92; 95 % CI: 0.72–1.16). There was no effect on ischemic strokes alone or disabling stroke (HR 1.06; 95 % CI: 0.69–1.64) or in the composite outcome of stroke, myocardial infarction, or death from vascular causes (HR 0.89; 95 % CI: 0.72–1.11). Major hemorrhages were doubled in the combination group (2.7 % per year) as compared with aspirin (1.1 % per year, $p < 0.001$). More than two-thirds (71 %) of recurrent ischemic strokes were of lacunar type. Mortality (all-cause) was significantly increased in those assigned to dual antiplatelet therapy (HR 1.52; 95 % CI 1.14–2.04; $p = 0.004$); however, this difference was not accounted for by fatal hemorrhages [52, 53, 56].

The results of the SPS3 trial have generated some discussion. It has been suggested that the low rate of recurrent stroke in patients taking aspirin alone (2.7 % per year) might have been caused by the wide use of statins by the study participants and the good blood pressure control achieved by the majority of patients. It has also been noted that dual antiplatelet therapy was associated with a trend toward a reduction in recurrent strokes attributed to atherosclerosis but not to recurrent lacunar strokes. This result supports the hypothesis that the role of platelets is different in different types of ischemic stroke. Finally, attention has been drawn to the higher dose of aspirin (325 mg daily) in the SPS3 trial in comparison with that used in other trials testing a combination therapy [52, 53, 56]. Exploratory analyses in one study suggested that when combined with clopidogrel, higher doses of aspirin could be less efficacious than lower doses for the prevention of vascular events [79–81].

Data from a recent large Korean Stroke Registry including more than 9,000 patients with small vessel stroke, confirmed that antiplatelet combination therapy (aspirin plus clopidogrel or cilostazol in most cases) did not have benefits over monotherapy [82].

In summary, the evidence reviewed above concerning secondary prevention of lacunar stroke seems to suggest that: (1) aspirin is effective; (2) cilostazol is equally effective to aspirin but potentially safer in terms of hemorrhagic risk; (3) the combination of dipyridamole and aspirin is superior to aspirin alone; (4) the combination of aspirin and clopidogrel is not superior to aspirin and is associated with an increased risk of non-cerebral hemorrhage.

Anticoagulation as Secondary Prevention in Lacunar Stroke

There is no evidence to support the use of oral anticoagulants in patients with lacunar stroke who do not have also a major-risk cardioembolic source. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) compared the efficacy of adjusted-dose warfarin (INR 1.4–2.8) with that of aspirin (325 mg/day) in terms of recurrent ischemic stroke or death within 2 years [83]. Patients with clear cardioembolic sources were excluded, and 1,237 (56 %) patients had lacunar stroke. In this latter group, anticoagulation was not superior to aspirin in the primary outcome (HR 1.15; 95 % CI: 0.88–1.52; $p = 0.31$) [83].

At present, risk stratification for patients with atrial fibrillation considers the presence of stroke history but no evidence is available regarding the stroke subtype in terms of benefit or harm. However, one study has shown that warfarin was superior to aspirin in preventing cardioembolic but not lacunar recurrence in stroke patients with atrial fibrillation, and that the recurrence rate in aspirin-treated patients who presented at baseline with lacunar stroke and atrial fibrillation was similar to that seen in patients receiving warfarin (8.8 % vs. 8.9 %) [84]. In the Korean Stroke Registry, the risk of death was higher with anticoagulants therapy in patients with SVD-related stroke [HR 1.44; 95 % CI: 1.06–1.97] [82].

Moreover, an increased risk of hemorrhage has been reported in patients with ischemic stroke of arterial origin treated with warfarin if they also have neuroimaging evidence of SVD (leukoaraiosis) [85]. In the Stroke Prevention in Reversible Ischemia Trial (SPIRIT), leukoaraiosis was (together with age >65 years) the only independent predictor of major bleeding during anticoagulation started after cerebral ischemia (OR 2.7; 95 % CI: 1.4–5.3) [86]. These data were confirmed by another study that reported leukoaraiosis as an independent risk factor for warfarin-related intracranial hemorrhage [87].

The current state of knowledge, however, does not preclude the use of anticoagulation in patients with SVD (leukoaraiosis or brain microbleeds on neuroimaging) if they are clear candidates to this treatment. Further studies are needed to quantify the hemorrhagic risk associated with these neuroimaging features and to test whether the novel oral anticoagulants may be better suited for this group of patients.

Carotid Stenosis Endarterectomy and Lacunar Stroke Secondary Prevention

Symptomatic carotid stenosis may occasionally be responsible for lacunar strokes and data show that ipsilateral carotid stenosis is present in 3–39 % of lacunar stroke patients [88, 89]. Because many studies have failed to demonstrate a causal relationship between carotid disease and lacunar stroke, some authors consider this finding coincidental [90, 91].

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) studied patients with TIA or minor stroke and an ipsilateral carotid stenosis of 50 % or more. The NASCET data showed a clear benefit from surgery in patients with symptomatic carotid stenosis >70 %; the 2-year risk of ipsilateral stroke was 9 % in the surgical group and 26 % in the medical group with an absolute risk reduction of 17 % [92]. Patients with less severe stenosis (50–69 %) have less benefit from surgery [93].

Stroke in patients entering the NASCET were classified as nonlacunar, possible lacune (symptoms without CT lacunae), or probable lacune (symptoms with CT lacunae) [94]. Among 1,158 participants in the NASCET, 493 (42.6 %) had clinico-radiologic features of lacunar stroke. Lacunar stroke occurred more commonly in patients with milder (<50 %) degrees of internal carotid artery stenosis ($p = 0.003$). Patients with "probable" lacunar stroke in the medical treatment group had a higher recurrence rate of ipsilateral lacunar stroke (9.2 % in 3 years) than those with non-lacunar (2.9 %) or those with "possible" lacunar stroke (4.2 %) during a follow-up period of 3 years. Among patients with "probable" lacunar event and with >50 % carotid stenosis, the absolute risk reduction of carotid endarterectomy was 9.0 % (from 25.5 to 16.5 %) [94]. For patients with "probable" lacunar stroke and moderate-to-severe (50–99 %) internal carotid artery stenosis, the RRR in stroke from carotid endarterectomy was lower (35 %) than in those in whom the presenting stroke was non-lacunar (61 %). Patients presenting with a possible lacunar stroke had a 53 % RRR [94]. Therefore, patients with probable lacunar infarcts who have ipsilateral carotid stenosis >50 % should be considered for carotid intervention, being the NNT = 11.1 [95].

The same study also showed that severe leukoaraiosis, another expression of SVD, is associated with a threefold higher risk of stroke and death during the perioperative period (30 days) [96]. These results suggest that the presence of leukoaraiosis predicts a reduced benefit from the treatment, but should not be taken as a contraindication to surgical treatment.

Conclusions

Intervention for secondary prevention in patients with lacunar ischemic stroke remains inadequately defined. However, our review outlines that a certain amount of data are present in the literature. These data derived from studies including different types of stroke and providing subtype post-hoc analysis (usually without neuroimaging verification), and from the large, and specifically addressed, SPS3 trial. The evidence reviewed seems to suggest that: (1) lowering of blood pressure after SVD stroke is desirable although the target remains to be further specified; (2) anti-aggregation (aspirin, cilostazol, and association of aspirin and dipyridamole) is efficacious while the association of aspirin and clopidogrel is associated with increased hemorrhagic risk without advantages; (3) lacunar stroke does not represent a contraindication to statin use despite this stroke subtype exposes to a moderate increased risk of hemorrhage, (4) a correct approach should consider also the hemorrhagic aspect of SVD.

Because SVD and its various manifestations are associated with a three-time increased risk of stroke and death, early implementation of preventive measures and administration of treatments appropriate to the underlying cause are relevant. Studies specifically focused on lacunar stroke prevention are needed to implement the evidences in clinical practice.

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14 Secondary Prevention After Symptomatic Large Artery Extracranial Disease

Chrysi Bogiatzi and J. David Spence

Case Presentation A 72-year-old retired high school principal was referred because the auscultation of a right carotid bruit at a routine examination led to a carotid ultrasound study. She was otherwise well, with a past history of a cholecystectomy at age 48, well-controlled hypertension, and a previous history of smoking (a 20-pack-year history; she stopped smoking 10 years earlier). She had no symptoms to suggest transient ischemia in the territory of the carotid stenosis.

Her examination was normal, with the exception of a right carotid bruit. Her blood pressure in the higher of the two arms was 138/86, with a heart rate of 77/min. There were no murmurs, no signs of congestive heart failure, and no indication of an abdominal aneurysm on palpation. The neurological exam was normal, with no findings to suggest ischemia in the right carotid territory. Ophthalmoscopic examination did not reveal any Hollenhorst plaques.

The carotid ultrasound exam revealed a peak frequency of 247 cm/s in the right internal carotid, with a ratio >2 (the peak velocity in the common carotid was 100 cm/s), indicating a 70 % stenosis. There was no significant stenosis elsewhere. She had a high total plaque area (TPA) of 180 mm^2, which put her in the top quartile of TPA, with a 5-year risk of stroke, death, or myocardial infarction of 19.5 % [1].

In order to determine if she might benefit from endarterectomy or stenting, she underwent 1 h of transcranial Doppler embolus detection, which revealed no microemboli. This put her in a low-risk category, with a 1-year risk of stroke of only 1 %, well below the risk of endarterectomy or stenting. Accordingly she was advised to follow a Mediterranean diet and was provided with recipes and advice to help her do so; she was advised to exercise regularly (30 min per day of brisk walking or equivalent) and consume alcohol in moderation (<9 standard drinks per week). She was also prescribed clopidogrel 75 mg daily and acetylsalicylic acid 80 mg daily (with advice to reduce the ASA to alternate days if bruising was excessive), perindopril 4 mg daily, rosuvastatin 10 mg daily, and ezetimibe 10 mg daily.

A year later she was well, and her carotid total plaque area had regressed to 147 mm^2. She was advised to continue with her present regimen, and scheduled for follow-up in another year.

Introduction

Among ischemic stroke subtypes, transient ischemic attack (TIA) or minor stroke due to large artery disease carries the highest risk of early recurrence [2].

Intensive risk factor reduction is required for all patients with carotid stenosis, or even patients with a high carotid plaque burden in the absence of stenosis. Apart from the risk of stroke, patients with carotid stenosis have a higher coronary risk than do patients with coronary artery disease [3]. Spence et al. showed in 2002 [1] that patients in the top quartile of carotid plaque burden, assessed as total plaque area, had a 19.5 % 5-year risk of stroke, death, or myocardial infarction [1]. Among patients with asymptomatic carotid stenosis, the risk of stroke on medical therapy has declined markedly since 2005 [4–6]. It is now clear that most patients with asymptomatic carotid stenosis are better served by intensive medical therapy. There are ways to identify high-risk asymptomatic carotid stenosis, and new approaches are being developed. Even in symptomatic carotid stenosis, some patients at lower risk of stroke or higher risk of surgery may be better served by intensive medical therapy; that question will need reevaluation [7].

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Intensive Risk Factor Reduction

Intensive medical therapy is warranted in patients with large artery disease. This includes lifestyle modification, antiplatelet therapy, angiotensin-converting enzyme inhibitors, lipid-lowering therapy, control of diabetes, and blood pressure control. Achieving all these reduces the risk of recurrent stroke by 80 % or more [8]. Among patients with asymptomatic carotid stenosis, Spence et al. found that more intensive medical therapy based on measurement of carotid plaque burden reduced the 2-year risk of stroke from 8.8 to 1 %, and reduced the 2-year risk of myocardial infarction from 7.6 to 1 %. The intensive risk factor reduction program used to achieve that is described below, and was recently reviewed [9, 10].

Lifestyle

A healthy lifestyle is much more important than most physicians or patients suppose. In the US Health Professionals study, participants who followed all five healthy lifestyle choices had an 80 % reduction of stroke risk compared to those who followed none [11]. These choices were the following: not smoking, maintaining a healthy weight, following a healthy diet, exercising daily for 30 min, and consuming a moderate intake of alcohol. What patients can do for themselves is at least as important as what their doctor can do for them, as described in the book "How to Prevent Your Stroke" [12].

Diet

Probably the best diet for stroke prevention is the Mediterranean diet. In a retrospective article, Ancel Keys, who was the principal investigator of the Seven Countries Study that recognized the benefit of this diet, described what he called "the good Mediterranean diet" as follows: "The heart of this diet is mainly vegetarian, and differs from American and northern European diets in that it is much lower in meat and dairy products and uses fruit for dessert." It is high in beneficial oils such as olive oil and canola, with 40 % of calories from such sources of fat, whole grains, fruits, vegetables, lentils, beans, and other legumes and nuts, and much lower in animal fat and cholesterol.

The first trial to compare this diet to a low-fat diet was the Lyon Diet Heart Study [13]. Survivors of myocardial infarction were randomized to a Cretan Mediterranean diet, substituting canola margarine for butter, vs. a diet called a "prudent Western diet" that mounted to the Step 1 diet of the National Cholesterol Education Program (NCEP). The intake of red wine was not different in the two diets, but the intake of cholesterol was lower and that of beneficial oils higher on the Mediterranean diet. The result was a greater than 60 % reduction of stroke or myocardial infarction on the Mediterranean diet. The results were largely disbelieved, perhaps because there was no significant reduction of fasting cholesterol levels, and the results seemed too good to be true. However, in a recent Spanish study in primary prevention [14], a Mediterranean diet supplemented with olive oil or nuts reduced cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) by 30 %; the Mediterranean diet supplemented by nuts reduced stroke by 46 %.

Fasting cholesterol has little to do with what the person ate the previous day; it is mainly determined by how much cholesterol is synthesized by the liver overnight. Diet is really about the postprandial state: for about 4 h after a high-cholesterol meal, there is oxidative stress, with nearly a 40 % increase in oxidized LDL, endothelial dysfunction, and vascular inflammation [15].

Some foods, such as egg yolks, may be particularly harmful for patients at risk of vascular disease. The yolk of a single 65-g egg contains 237 g of cholesterol, more than the 200 mg daily that is recommended for patients at risk of vascular disease (and more than a 12-oz Hardee's Monster Thickburger). However, the harm from egg yolks is not just due to the very high cholesterol content. The recent recognition of the role of metabolic effects of the intestinal microbiome has further explained the harm from egg yolk [16]. Hazen's group have shown, first in an animal model [17], and then in patients referred for coronary angiography [18], that phosphatidylcholine (lecithin) is converted by intestinal bacteria to trimethylamine, which in turn is oxidized in the liver to trimethylamine *n*-oxide (TMAO). Coronary angiogram patients in the top quartile of TMAO levels after consuming two hard-boiled eggs had a 2.5-fold increase in the 3-year risk of stroke, death, or myocardial infarction. L-Carnitine (mainly from red meat) is also converted by intestinal bacteria to TMAO [19, 20].

Although it might be argued that a vegan diet may be even better than a Mediterranean diet, it is unlikely that many North American patients would adopt it. A Mediterranean diet, reducing the intake of animal flesh to approximately 4 oz every other day (or 2 oz a day), with no egg yolks, is probably the best diet for patients with large artery disease [9].

Smoking Cessation

Smoking increases the risk of stroke sixfold, and passive smoking increases stroke risk 1.8-fold [21]. Smoking is very hard to quit: it is not only a powerful addiction; it is also a social activity, habit, and psychological crutch, and probably has other holds on its victims. Quitting smoking is therefore very difficult. It is important that physicians be nonjudgmental and understanding and offer help. Medications such as

bupropion and varenicline, in combination with liberal use of nicotine replacement and counselling, are important [22–24].

Blood Pressure Control

Approximately 90 % of strokes occur among patients with resistant hypertension [25]. An important problem in the management of hypertension therapy is cookbook therapy, blindly following guidelines that assume that all patients are the same. In patients with resistant hypertension it is important to identify the underlying cause, and treat it specifically. This is particularly important in patients of African origin, who are more likely to have hereditary causes of hypertension related to salt and water retention [26, 27]. Howard et al. [28] found that in the USA, black patients were more likely to have their hypertension detected, more likely to be treated, more likely to be treated more intensively, and less likely to be controlled.

Approximately 20 % of resistant hypertension is due to primary aldosteronism [29]. It is increasingly recognized that much of primary hypertension is due not to unilateral adenomas, but due to bilateral adrenocortical hyperplasia [30], so mainly treated medically [31]. An important cause of resistant hypertension that is more common than is usually recognized, and which requires specific therapy, is mutations of the renal tubular sodium channel (variants of Liddle's syndrome) causing salt and water retention. This was reported in 5 % of black patients in London [32], UK; 6 % of patients in South Africa [33]; 20 % of the Khoi San people (indigenous people of the Kalahari desert) [34]; and 6 % of patients in a Veteran's Hospital clinic in Missouri [35]. The specific treatment for Liddle's variants is amiloride [32].

In patients with resistant hypertension, after excluding rare causes such as pheochromocytoma, adult coarctation of the aorta, and licorice, the underlying physiological cause of hypertension can be identified, and specific treatment selected, by measuring plasma renin and aldosterone [36–38]. In patients with low renin and high aldosterone (primary hyperaldosteronism), the best medical therapy is aldosterone antagonists (spironolactone or eplerenone), which are better not only for control of hypertension, but also for the adverse cardiac and vascular effects of aldosterone [30, 39]. In patients with low renin and low aldosterone levels, the best treatment is amiloride, for presumed Liddle's syndrome. In patients with high renin and high aldosterone levels (secondary hyperaldosteronism), renal investigation is warranted to exclude renal obstruction and renal artery stenosis, and the best medical therapy is with an angiotensin receptor blocker or a renin antagonist. Some patients with primary aldosteronism may need adrenalectomy for control, some patients with renal obstruction may need a ureteric stent or other procedure to relieve obstruction, and some with renal artery stenosis may need revascularization. Rare cases may need interventions such as renal denervation or stimulation of the carotid sinus. In most cases, however, identifying and treating the physiological drivers of the hypertension can achieve control of hypertension.

Lipid-Lowering Therapy

Patients with carotid stenosis should all receive intensive lipid-lowering therapy. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed greater benefit from atorvastatin among patients with carotid stenosis [40], and Spence's group showed significant reduction of carotid plaque volume within 3 months of initiating atorvastatin 80 mg daily [41]. It seems likely that plaque regression also resulted in improvement in plaque vulnerability, since intensive therapy also reduced the proportion of patients with asymptomatic carotid stenosis who had microemboli on transcranial Doppler, a strong predictor of stroke risk [42]. Among patients with asymptomatic carotid stenosis, the proportion with microemboli dropped from 12.6 to 3.7 % after initiation of a program of intensive medical therapy based on measurement of plaque burden [6]. Events dropped in parallel with the reduction of microemboli: the 2-year risk of stroke dropped from 8.8 to 1 %, and the 2-year risk of myocardial infarction dropped from 7.6 to 1 %. Based on those results, it is probably desirable to aim to lower the LDL cholesterol as much as possible, not being content with consensus targets based on coronary disease. The maximum tolerated dose of statin should probably be used, and in patients whose LDL level remains above target levels despite the maximum tolerated dose of statin, it is useful to add ezetimibe, which is synergistic with statins. Concerns about ezetimibe based on studies in which intima-media thickness did not respond to ezetimibe were probably misplaced [43].

An important issue is poor adherence with statins, which is often due to misplaced concern about mythical adverse effects. Statins probably do not cause hepatotoxicity, intracerebral hemorrhage [44], impaired renal function, or cognitive impairment. Increased levels of liver enzymes are not usually due to statin therapy, but due to fatty liver [45–48]. Statins also do not cause most of the symptoms listed in long lists of all symptoms known to humankind (headache, fatigue, dizziness, nausea, diarrhea, constipation, etc.). The causally related adverse effects of statins—myopathy and an increase in the risk of diabetes—are probably due to depletion of ubiquinone.

In patients with muscle problems from statins it may be helpful to add supplements of ubiquinone. It probably is useful to give supplements of CoQ10 [49, 50]. However, the doses required may need to be higher than in most of the

clinical trials (200–300 mg twice a day, or perhaps more). Although it is commonly stated that the effects of CoQ10 supplementation are contradictory and unproven [51], this is probably an issue of the dose of CoQ10. Higher doses of ubiquinone such as 300 mg twice daily are more effective in improving muscle fatigue [52, 53]. The negative trial of Bookstaver et al. [54] used only 60 mg twice daily. Fedacko et al. [55] found a significant improvement of statin myopathy with CoQ10 200 mg daily in a factorial designed trial in which selenium was not efficacious. Ubiquinone does improve mitochondrial function in an animal model of statin myopathy [56].

There is evidence that in diabetics, L-carnitine not only prevents the rise in blood sugar due to statins, but also reduces insulin resistance [57], improves lipid values [58], and may improve myopathy [59]. However, recent evidence that carnitine is converted by intestinal bacteria to trimethylamine, leading to increased levels of trimethylamine *n*-oxide (TMAO), which is harmful to the arteries [16, 19], will require further evaluation of the potential use of L-carnitine to mitigate adverse effects of statins.

Antiplatelet Therapy

The first randomized trial to show that acetylsalicylic acid (ASA, Aspirin) reduced the risk of recurrent stroke was the Canadian study by Gent and Barnett et al. [60]. Low-dose ASA is more efficacious than higher doses [61], probably because only a very low dose of ASA is needed to permanently acetylate platelet thromboxane in circulation platelets. Having no nuclei, platelets in the circulation are unable to recover from the effect of ASA. In contrast, higher doses of ASA, which cause higher levels of ASA to persist longer, have a greater effect on production of prostacyclin by endothelial cells.

The controversial issue of "aspirin resistance" may be due to "pseudoresistance," resulting from enteric coating of ASA. Fitzgerald et al. [62] found that up to 49 % of study participants had apparent resistance to enteric coated ASA, but none was resistant to uncoated ASA.

The benefit of clopidogrel alone over ASA was only marginal; in the CAPRIE trial [63] the absolute risk reduction was only 1.7 %, giving an NNT of more than 50. Although use of dual-antiplatelet therapy has been limited since the MATCH trial [64], which showed an excess of bleeding with combined ASA and clopidogrel, there are good reasons to regard dual-antiplatelet therapy as more efficacious. Dual-antiplatelet therapy, though associated with an increased risk of bleeding, is clearly more efficacious in coronary artery disease [65–67], and in the MATCH trial only 34 % of the patients had large artery disease. Although results were not presented separately for that group, the forest plots for that study suggest greater efficacy among patients with coronary artery disease or peripheral vascular disease. By blocking more than one pathway, combined therapy should further impair platelet aggregation and adhesion to endothelial surfaces. In the coronary literature dual-antiplatelet therapy is clearly more efficacious, and dual-antiplatelet therapy reduces the occurrence of microemboli on transcranial Doppler in patients with symptomatic carotid stenosis [68].

A recent trial in China [69] showed that combination of ASA and clopidogrel reduced the risk of recurrent stroke by 32 %, with no increase in bleeding, in the first 3 months after the initial TIA or minor stroke. It is thus likely that dual-antiplatelet therapy is indicated for most high-risk patients with large artery disease. Risk of intracerebral hemorrhages can be minimized by controlling hypertension, and risk of gastrointestinal hemorrhages can be minimized by treating infections with *Helicobacter pylori*.

Several new antiplatelet agents are in use in acute coronary syndrome, and in clinical trials in secondary stroke prevention. An important problem with clopidogrel is that it is a prodrug, which needs to be metabolized by several cytochrome isoforms to the active form [70]. There are significant interactions with many drugs, and possibly some foods such as grapefruit, that reduce efficacy of clopidogrel. This is a particular problem with proton pump inhibitors, with the possible exception of pantoprazole [71]. Similarly prasugrel requires hydrolysis by an esterase followed by a CYP-dependent oxidation step, which is not an issue for ticagrelor [70].

Treating Arteries Instead of Treating Risk Factors

In 2002, Spence et al. reported that carotid plaque burden strongly predicted the risk among 1,686 patients attending cardiovascular prevention clinics [1]. After adjusting for age, sex, cholesterol, blood pressure, diabetes, homocysteine, and treatment of blood pressure and cholesterol (i.e., much more than a Framingham risk score), patients in the top quartile of total plaque area (TPA), above 119 mm^2 of plaque, had 3.4 times higher 5-year risk of stroke, death, or myocardial infarction. The prediction of risk was a nice step function by quartile of risk—approximately 5, 10, 15, and 20 % 5-year risk by quartile. That this was a 5-year risk of events meant that the study population was at very high risk—there were as many events as in the first 10 years of the Framingham study—so although relatively small, it was powerful. Patients with plaque progression by more than the median change of 5 mm^2 during the first year of observation had twice the risk of events, after adjusting for the same panel of risk factors,

and it was half the patients who had progression. This meant that treating patients according to guidelines was failing half the patients. As a result, the group implemented a new approach, "treating arteries instead of treating risk factors" [72]. The result of this change was that the proportion of patients with progression vs. regression (half vs. a quarter) was reversed [72], and among patients with asymptomatic carotid stenosis, the risk was markedly reduced [6]. The rate of carotid plaque progression declined significantly, the proportion of patients with microemboli on transcranial Doppler (a strong predictor of stroke risk [42]) declined from 12.6 to 3.7 %, and the risk of events declined remarkably. The 2-year risk of stroke dropped from 8.8 to 1 % and the 2-year risk of myocardial infarction declined from 7.6 to 1 % [6]. This approach appears to be very promising, but will require validation in a multicenter randomized trial comparing usual therapy according to guidelines, vs. the new imaging-based approach, before widespread adoption would be justified. The approach is already being used in prevention clinics across Argentina, and in Switzerland.

Diagnosis of Extracranial Carotid Disease

Carotid stenosis is often diagnosed initially by ultrasound, which may be ordered because of a bruit or other reason to suspect carotid disease. Although the US Preventive Services Task Force recommended against screening for carotid stenosis [73], the American Medical Association approved a Category 1 reimbursement code for carotid IMT and plaque scanning. These seemingly contradictory decisions were both rational: it is not appropriate, as discussed below, to search for patients with asymptomatic carotid stenosis for the purpose of identifying cases for endarterectomy or stenting; on the other hand measurement of carotid plaque burden identifies patients at high risk of cardiovascular events, who would benefit from intensive medical therapy. Patients with a high plaque burden are at high risk, even after adjustment for coronary risk factors: patients in the top quartile of carotid total plaque area (above 119 mm^2 of plaque) have a nearly 40 % 10-year risk of stroke, death, or myocardial infarction [1], so intensive medical therapy is warranted in such patients. Measurement of carotid plaque burden is superior to measurement of intima-media thickness, both for risk stratification and for management of patients [74, 75].

Severity of stenosis can be assessed by Doppler peak velocity on ultrasound, CT angiography, and MR angiography; the gold standard is conventional angiography with digital subtraction. A key problem for assessment of degree of stenosis is distal collapse with approaching near occlusion [76], which may lead to underestimation of the degree of stenosis.

Symptomatic Carotid Stenosis

Carotid Endarterectomy

Endarterectomy is a surgical procedure that involves isolating the carotid bifurcation by dissection, clamping the artery distally and proximally, incising the artery in the axis of flow, dissecting the stenosing plaque off the deeper layers, and removing it surgically. Then the artery is flushed to remove debris, sewn up carefully, and the clamps removed. Sometimes a distal shunt is placed to provide flow distal to the clamped artery, and sometimes a patch is inserted to enlarge the artery. Whether distal shunting, patching, or general or local anaesthesia is used is the individual preference of the surgeon that does not seem to materially affect outcomes.

Several randomized trials established clearly that patients with severe carotid stenosis clearly benefited from carotid endarterectomy (Table 14.1). In the North American Symptomatic Carotid Artery Surgery Trial (NASCET) [77] the number needed to treat to prevent one stroke in 2 years was only 6 for severe stenosis in patients below age 75, 3 for symptomatic severe stenosis above age 75, and 15 for patients with moderate stenosis [78]. Benefits were similar in the European Carotid Surgery Trial (ECST) [79]. It should be noted that women benefit less from endarterectomy [80].

Importance of Early Endarterectomy

With medical therapy the risk of stroke declines fairly rapidly, so that the benefit of endarterectomy is highest early. In NASCET, the risk of patients randomized to medical therapy declined quickly, becoming equal to that of surgical therapy in 18 months in patients with moderate stenosis, and after 30 months in patients with severe stenosis [77]. As medical therapy has improved, this time has been compressing, so that patients benefit most from surgery done within 2 weeks or less, and the benefit is marginal if done more than 3 months after the sentinel stroke or TIA [81].

Carotid Stenting

Carotid stenting involves placement of a metal sheath into the narrow segment of the artery by catheterization (often from the femoral artery). Sometimes the stent is dilated by balloon angioplasty; an alternative is self-expanding stents. This approach seems intuitively attractive, but has important problems that result from the difficulty of passing a catheter through a tortuous craggy artery. Table 14.2 summarizes trials comparing carotid endarterectomy to stenting.

Table 14.1 Carotid endarterectomy or stenting vs. medical management

Study name	*n*	*n*	Results
	CEA	Medical	
(a) Carotid endarterectomy (CEA) in symptomatic patients			
Shaw et al. 1984 [116]	20	21	Early death, stroke, TIA (within 1 month): 45 % CEA vs. 0 % Medical
			Late death (after 1 month): 7 % CEA vs. 10 % Medical
			Late stroke (after 1 month): 1 % CEA vs. 5 % Medical
			Late TIA (after 1 month): 0 % CEA vs. 11 % Medical
NASCET 1991 [117]	328	331	Ipsilateral stroke (at 2 years): 9 % CEA vs. 26 % Medical ($p<0.001$)
			Any stroke or death (at 2 years): 15.8 % CEA vs. 32.3 % Medical ($p<0.001$)
NASCET 1998 [77]	1,108	1,118	5-year rate of ipsilateral stroke with ICA stenosis 50–69 %:
			15.7 % CEA vs. 22.2 % Medical ($p=0.045$)
			5-year rate of ipsilateral stroke with ICA stenosis <50 %:
			14.9 % CEA vs. 18.7 % Medical ($p=0.16$)
ECST 1998 [79]	1,807	1,211	Major stroke or death: 37 % CEA vs. 36.5 % Medical ($p>0.05$)
			Major stroke or death with ICA stenosis ≥80 % at 3-years follow-up:
			14.9 % CEA vs. 26.5 % Medical ($p<0.05$)
(b) CEA in asymptomatic patients			
CASANOVA 1991 [118]	206	204	3-year stroke, death: 10.2 % CEA vs. 11.3 % Medical (odds CEA:Medical 0.94, $p=0.486$)
VA 1993 [119]	211	233	Overall stroke, death: 41.2 % CEA vs. 44.2 % Medical ($p>0.05$)
ACAS 1995 [94]	825	834	Overall stroke, death: 5.1 % CEA vs. 11 % Medical ($p<0.001$)
ACST 2004–2010 [95, 120]	1,560	1,560	5-year stroke, death: 6.4 % CEA vs. 11.7 % Medical ($p<0.001$)
			10-year stroke, death: 13.4 % CEA vs. 17.9 % Medical ($p=0.009$)
Study name	*n*	*n*	
	Stenting	Medical	
(c) Stenting versus medical management in symptomatic patients			
SAMMPRIS 2011 [121]	224	227	30-day stroke or death: 14.7 % CAS vs. 5.8 % Medical ($p=0.002$)

CEA carotid endarterectomy, *Medical* medical management

In contrast to coronary intervention, the purpose of carotid endarterectomy or stenting is not to increase blood flow to the brain, but to prevent embolization of atheromatous debris into the brain (Fig. 14.1). Furthermore, the purpose of intervention is to prevent ipsilateral stroke due to large artery disease, not to prevent contralateral stroke, lacunar infarction, or myocardial infarction. In our personal opinion, physicians should not be distracted by the finding in CREST [82] that stenting carried a lower risk of myocardial infarction, nor by the lower risk with stenting in patients at high risk for surgery [83], most of whom were not good candidates for carotid revascularization [84].

Carotid revascularization with stenting is often, even usually, complicated by procedure-related embolization. This problem is illustrated in Fig. 14.2. The Calgary stroke group [85] performed MRI scans after deployment of stents, with transcranial Doppler embolus detection during the stenting procedure, in 30 patients, 23 % of whom were asymptomatic. They divided emboli into malignant and nonmalignant emboli according to signal intensity. The median embolic signal count was 212.5. The embolic signal count was highest during stent deployment, followed by deployment of the protection device. New diffusion-weighted imaging (DWI) lesions were found in 80 % of the patients after stenting, with a median of four new DWI lesions (interquartile range 7). Two of 30 (6.7 %) had new or worsening clinical deficits post-CAS.

As a result, with carotid stenting the risk of stroke is approximately double that with carotid endarterectomy. The myocardial infarctions in CREST, many of which were "biochemical" myocardial infarctions identified by elevations of troponin levels, impaired quality of life much less than did strokes. A major stroke impaired quality of life three times more than did a minor stroke, and a myocardial infarction only reduced quality of life 2/3 as much as did a minor stroke [82]. Furthermore, a year after the intervention, an endpoint stroke had large adverse effects on physical function, role functioning, and vitality (energy/fatigue); endpoint myocardial infarctions and cranial nerve palsies had quantitatively smaller and not statistically significant effects [86, 87].

Table 14.2 Carotid endarterectomy vs. carotid stenting

Study name	#CEA	#CAS	Results
(a) Symptomatic patients			
CAVATAS 2001 [122]	253	251	30-day death or any stroke: 10 % CEA vs. 10 % CAS ($p>0.05$)
SAPPHiRE 2004 [83]	167	167	30-day stroke, MI, death: 9.3 % CEA vs. 2.1 % CAS ($p=0.18$)
			1-year stroke, MI, death: 16.5 % CEA vs. 16.8 % CAS ($p=0.95$)
SAPPHiRE 2008 [123]	111	143	Death, stroke, MI, or ipsilateral stroke between 1 and 3 years:
			21.7 % CEA vs. 32 % CAS ($p>0.05$)
			Stroke between 1 and 3 years: 8.7 % CEA vs. 6 % CAS ($p>0.05$)
EVA-3S 2006 [124]	262	265	30-day stroke and death: 3.9 % CEA vs. 9.6 % CAS ($p=0.01$)
			Any stroke or death within 6 months: 6.1 % CEA vs. 11.7 % CAS ($p=0.02$)
EVA-3S 2008 [125]	262	265	Hazard ratio (for CAS vs. CEA): 1.97 (95 % CI 1.06–3.67; $p=0.03$)
SPACE 2008 [126]	601	613	30-day ipsilateral stroke or death (intention-to-treat analysis):
			6.45 % CEA vs. 6.92 % CAS ($p=0.09$)
CREST 2010 [82]	1,251	1,271	4-year stroke, death, MI: 35 % CEA vs. 45 % CAS ($p=0.3$)
			4-year stroke, death: 21 % CEA vs. 40 % CAS ($p=0.02$)
(b) Asymptomatic patients			
Sherif et al. 2007 [127]	421	525	1-year stroke, death: 9 % CAS vs. 13 % Medical
			3-year stroke, death: 20 % CAS vs. 26 % Medical ($p=0.0036$)
			5-year stroke, death: 29 % CAS vs. 38 % Medical
SAPPHiRE 2004 [83]	167	167	30-day stroke, MI, death: 10.2 % CEA vs. 5.4 % CAS ($p=0.20$)
			1-year stroke, MI, death: 21.5 % CEA vs. 9.9 % CAS ($p=0.02$)
SAPPHiRE 2008 [123]	111	143	Death, stroke, MI, or ipsilateral stroke between 1 and 3 years:
			29.2 % CEA vs. 21.4 % CAS ($p>0.05$)
			Stroke between 1 and 3 years: 9.9 % CEA vs. 10.3 % CAS ($p>0.05$)
Tang et al. 2008 [128]	206	120	30-day stroke, MI, death: 2.4 % CEA vs. 4.2 % CAS ($p=0.41$)
			30-day stroke, death: 1 % CEA vs. 2.5 % CAS ($p=0.34$)
CREST 2010 [82]	1,251	1,271	4-year stroke, death, MI: 21 % CEA vs. 21 % CAS ($p=0.96$)
			4-year stroke, death: 8 % CEA vs. 15 % CAS ($p=0.15$)
You et al. 2013 [129]	36,524	6,053	Perioperative stroke and death: 1.8 % CEA vs. 4.1 % CAS ($p<0.001$)

CEA carotid endarterectomy, *CAS* carotid stenting, *MI* myocardial infarction

Possible Benefit of Trans-cervical Stenting with Reverse-Flow Shunt

Direct surgical placement of stents into carotid arteries, with shunting of flow to prevent emboli [88], is a promising approach to carotid stenting that may carry a lower risk of stroke [89]. This warrants further investigation.

Carotid Intervention in Patients Scheduled for Coronary Bypass

Although it may seem intuitive that opening a carotid stenosis before performing coronary artery bypass grafting (CABG) should reduce the risk of stroke during the CABG, and this practice is rather widespread, the approach is misguided. The brain is well protected by the Circle of Willis, so the purpose of endarterectomy is to prevent embolization of atheromatous debris, not to improve blood flow. There is little or no evidence that preoperative (or intraoperative) revascularization of the carotid arteries in patients scheduled for CABG will reduce the risk of stroke [90].

Most strokes during CABG are not from reduced blood flow to the brain, but from emboli related to the embologenic events such as clamping of the aorta and circulatory bypass. In the Lehigh Valley study [90, 91], the authors reported the following: "Clinically definite stroke was detected in 1.8 % of patients undergoing cardiac operations during the same admission. Only 5.3 % of these strokes were of the large-vessel type, and most strokes (76.3 %) occurred without significant carotid stenosis. In 60.0 % of cases, strokes identified via computed tomographic head scans were not confined to a single carotid artery territory. According to clinical data, in 94.7 % of patients, stroke occurred without direct correlation to significant carotid stenosis. Undergoing combined carotid and cardiac operations increases the risk of postoperative stroke compared with patients with a similar degree of carotid stenosis but who underwent cardiac surgery alone (15.1 % vs. 0 %; $p=0.004$)."

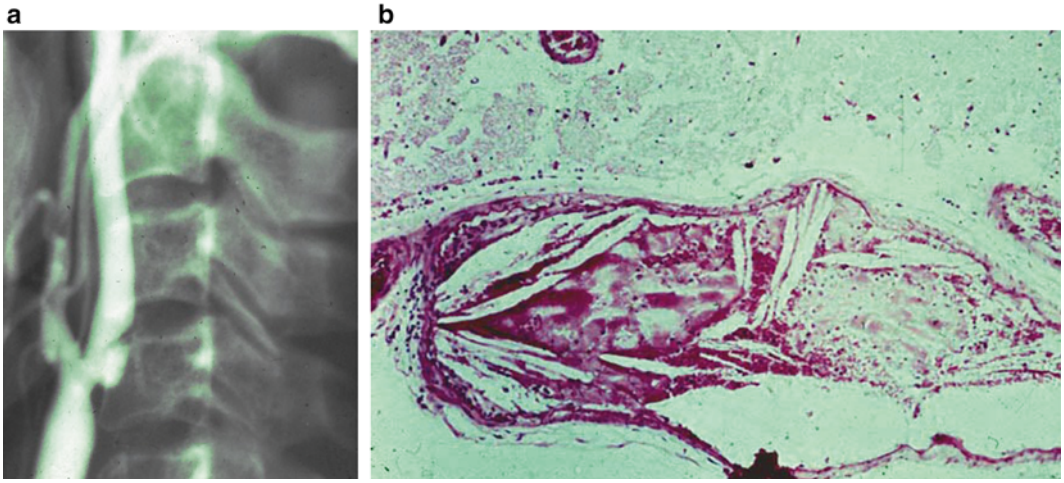

Fig. 14.1 The purpose of carotid intervention is mainly to prevent embolization of atheromatous debris. The figure at left is an angiogram of a carotid artery, with a large ulcer. The figure at right shows the kind of atheromatous debris that would have embolized into a brain artery when the plaque ruptured. Angiogram courtesy of Dr. Henry JM Barnett and Dr. John Allcock; histology slide courtesy of Dr. Joseph Gilbert. Reproduced by permission from: Spence JD, Pelz D, Veith FJ. Asymptomatic Carotid Stenosis: Identifying Patients at High Enough Risk to Warrant Endarterectomy or Stenting. Stroke 2014;45(3):655–7 [84]

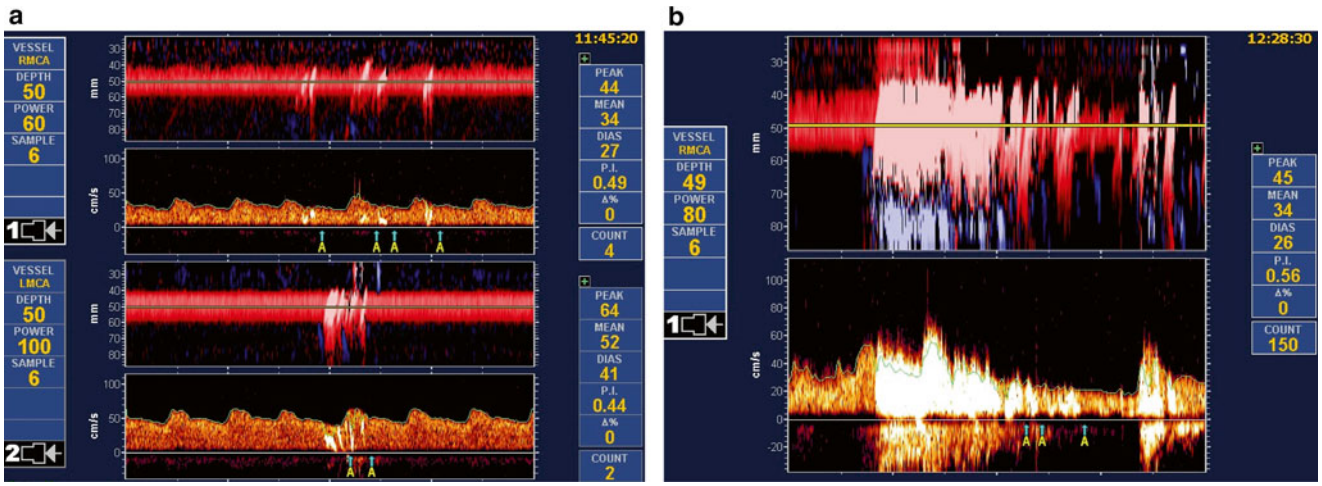

Fig. 14.2 Microemboli during carotid stenting. Showers of emboli of atheromatous debris occur commonly (even usually) during carotid stenting, and can be observed by transcranial Doppler. The *upper row* on each side is the M-mode image from the middle cerebral artery; the *lower* shows high-intensity transit signals in the Doppler channel. Panel (**a**) shows microemboli in both middle cerebral arteries (4 on the right and 2 on the left), while the aortic arch was being crossed; Panel (**b**) shows 150 microemboli in the right middle cerebral artery during stenting of the right internal carotid artery, during one cardiac cycle and the beginning of the next (courtesy of Dr. Claudio Muñoz)

Asymptomatic Carotid Stenosis

In the USA, more than 90 % of carotid interventions are for asymptomatic stenosis [92], even though the evidence discussed below now indicates that 90 % of patients with carotid stenosis would be at lower risk with medical therapy alone [93]. This is being justified by historical data that no longer pertain (Table 14.3). When the Asymptomatic Carotid Artery Surgery trial (ACAS) [94] was carried out there were essentially no patients on statins; during the later years of the European Asymptomatic Carotid Surgery Trial (ACST) [95] there were some patients on low-dose statins, but very few (if any) on high-dose statins. It is therefore not legitimate to justify carotid stenting on the basis of the Carotid Revascularization with Endarterectomy or Stenting Trial (CREST) [82], which had no concurrent medical arm [93]. Fortunately the CREST 2 trial and the recently initiated European carotid stenosis trial will compare endarterectomy, stenting, and best medical therapy, so this issue should be sorted out within a few years.

Table 14.3 Endarterectomy in symptomatic vs. asymptomatic patients

Study name	*n* Symptomatic	*n* Asymptomatic	Results
Roubin et al. 2001 [130]	241	287	30-day stroke, death: 8.2 % symptomatic vs. 6.3 % asymptomatic ($p=0.47$)
Kastrup et al. 2005 [131]	170	129	30-day TIA, stroke, death: 15.9 % symptomatic vs. 3.1 % asymptomatic ($p<0.001$)
BEACH 2006 [132]	189	558	30-day stroke, MI, death: 7.9 % symptomatic vs. 5 % asymptomatic
			30-day stroke: 7.4 % symptomatic vs. 3.4 % asymptomatic
			30-day death: 0.1 % symptomatic vs. 1.6 % asymptomatic
BEACH 2008 [133]	112	368	1-year stroke, MI, death: 7.7 % symptomatic vs. 4.7 % asymptomatic
			1-year stroke: 7.7 % symptomatic vs. 3.5 % asymptomatic
			1-year death: 1 % symptomatic vs. 1.7 % asymptomatic
ARCHeR 2006 [134]	138	443	30-day stroke, MI, death: 13 % symptomatic vs. 6.8 % asymptomatic
			30-day stroke, death: 11.6 % symptomatic vs. 5.4 % asymptomatic
CASES-PMS 2007 [135]	322	1,158	30-day stroke, MI, death: 6.2 % symptomatic vs. 4.7 % asymptomatic
CAPTURE 2 2011 [136]	721	4,337	30-day stroke, MI, death: 6 % symptomatic vs. 3 % asymptomatic
			30-day stroke, MI, death, age < 80: 4.5 % symptomatic vs. 2.9 % asymptomatic
			30-day stroke, MI, death, age ≥ 80:10.7 % symptomatic vs. 3.3 % asymptomatic
			30-day stroke, death: 5.7 % symptomatic vs. 2.8 % asymptomatic
			30-day stroke, death, age < 80: 4.2 % symptomatic vs. 2.7 % asymptomatic
			30-day stroke, death, age ≥ 80:10.7 % symptomatic vs. 3.2 % asymptomatic
Tulip et al. [137]	17	23	DWMRI new acute cerebral emboli: 7 symptomatic vs. 10 asymptomatic ($p=0.9$)
Tulip et al. 2012 [137]	17	23	Ipsilateral TCD microemboli detection:
			313 symptomatic vs. 285 asymptomatic ($p=0.6$)
			Ipsilateral TCD microemboli showers:
			25 symptomatic vs. 26 asymptomatic ($p=0.68$)

TIA transient ischemic attack, *MI* myocardial infarction, *TCD* transcranial Doppler

In CREST, the procedural (30-day) risk of stroke or death for asymptomatic patients was 2.5 % for stenting and 1.4 % for endarterectomy; the 4-year risk was 4.5 % with stenting and 2.7 % with endarterectomy [82]. The 2011 report of Wang et al. [92] documents in Medicare patients a 1-year risk of stroke or death of 16.7 % for stenting and 11 % for endarterectomy. It is now clear that stenting carries a higher risk of stroke than does CEA and a higher risk than that with intensive medical therapy [96].

Lower Risk with More Intensive Medical Therapy

Intervention with CEA or CAS in asymptomatic stenosis is based on the historical risk of stroke in patients randomized to medical therapy in ACAS and ACST, which were approximately 2 % per year. However, as shown in Fig. 14.3, the annual risk has declined since 2005 to approximately 0.5 %. This was shown in a population-based study in the UK [5], a stroke prevention clinic population in Canada [6], and in meta-analyses [4]. The consequence of this change is that most patients with asymptomatic stenosis (approximately 90 %) would be better off with medical therapy.

Patients with symptomatic carotid stenosis are also at lower risk now than at the time the randomized trials were carried out. Surgical risk has been declining, as has the risk with more intensive medical therapy. Some have objected that the risk with medical therapy is higher in patients with more severe stenosis, but Naylor has recently shown that this is not the case [97].

Low-Risk Groups Who Benefit Less from Endarterectomy

Women, patients with less severe stenosis [81], and patients with only retinal TIAs [98] benefit less from endarterectomy. Patients with chronic ocular ischemia, who may benefit from revascularization, represent a special case.

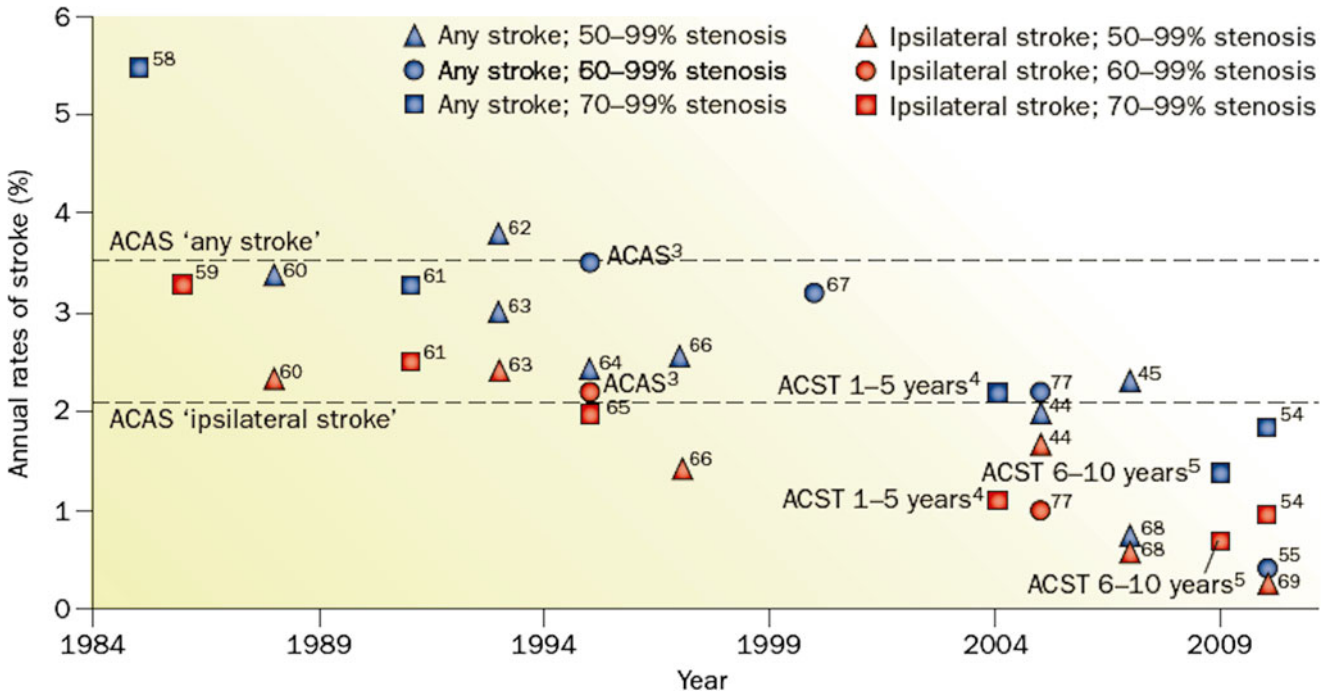

Fig. 14.3 Decline in risk of asymptomatic carotid stenosis with medical therapy, regardless of severity of stenosis. Annual rates of stroke in medically treated patients with asymptomatic carotid stenosis stratified for year of publication and baseline severity of stenosis. A sustained decrease in the annual rates of ipsilateral and any stroke has occurred over the past two decades. This decline is evident in both randomized and nonrandomized studies. Reproduced by permission of Nature Publishing Group from: Naylor AR. Time to rethink management strategies in asymptomatic carotid artery disease. Nature Reviews Cardiology 2012;9:116–24 [97]

That there are lower risk patients with symptomatic stenosis, and that risks are declining both with medical and surgical therapy, has led to calls for randomized trials of medical vs. surgical therapy, not only for asymptomatic carotid stenosis, but also for symptomatic stenosis [7].

The challenge, therefore, is how to identify the few who might benefit from CEA or CAS.

Identifying High-Risk and Low-Risk Subgroups

Approaches to identifying patients with high-risk carotid stenosis were reviewed in 2012 [99]. These include evaluation of clinical characteristics [100], transcranial Doppler (TCD) microemboli [42, 101], ulceration on 3D ultrasound [102], plaque composition/texture on ultrasound [103–105], neovascularization on ultrasound [106], intraplaque hemorrhage on MRI [107], juxtaluminal black plaque [108, 109], and plaque inflammation on PET/CT [110–112]. Plaque roughness on ultrasound and ulcer volume on 3D ultrasound are in development.

Extracranial Vertebral Artery Disease

Stenosis of a vertebral artery, usually at the origin from the subclavian, may cause atheroembolic events in the vertebrobasilar territory. Although there are many reports of endovascular therapy for this condition, there is little or no evidence that such therapy is beneficial. The only randomized controlled trial we could find was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), in which there were eight patients randomized to medical therapy and eight to endovascular therapy, with no benefit shown for endovascular therapy [113]. A systematic review [114] and a Cochrane review [115] concluded that more studies were needed.

Conclusions

Patients with large artery atherosclerosis are at high risk of stroke or myocardial infarction. Intensive medical therapy, including lifestyle changes, is warranted in all patients with

carotid stenosis, and can markedly reduce risk. In the face of the increasing effectiveness of intensive medical therapy, carotid endarterectomy and stenting are now less beneficial than in the past. In making decisions about which patients should be treated with endarterectomy or stenting, it is increasingly important to identify which patients are at high risk of stroke, and to balance the risks of intervention against the potential benefit.

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Secondary Prevention After Symptomatic Large Artery Intracranial Disease

15

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Case Presentation A 64-year-old African-American female with a past medical history of diabetes mellitus, hypertension, hyperlipidemia, and tobacco abuse presents to the emergency department with a chief complaint of right arm weakness and numbness and mild word finding difficulties 12 h from the last known normal. Her exam reveals some mild word finding difficulties and right upper extremity decreased strength and sensation. Her initial non-contrasted CT scan reveals scattered small hypodensities in the left frontal parietal region. The patient is admitted to the stroke unit for stroke evaluation. An MRI of the brain reveals acute ischemic infarcts throughout the left hemisphere in the middle cerebral artery distribution. MRA of the brain reveals a moderate to severe stenosis of the left middle cerebral artery territory in the M1 region. The blood pressure is 167/85, LDL cholesterol is 170 mg/dL, and the HbA1c is 11.2 %. The patient is started on aspirin 325 mg daily, clopidogrel 75 mg daily, statin therapy, insulin therapy, and blood pressure medications including HCTZ and Lisinopril.

Antithrombotic Therapy

Antiplatelet Agents Versus Anticoagulants

The use of anticoagulation for the prevention of stroke in patients with symptomatic ICAS was reported in the literature as early as 1955 [5] and was considered the standard of care by many neurologists. A retrospective study in 1995 suggested that warfarin was superior to aspirin for secondary stroke prevention in patients with ICAS [6]. Following this retrospective analysis, a randomized clinical trial to compare antithrombotic medications for stroke prevention in patients with symptomatic ICAS was undertaken. The Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial was a multicenter randomized double-blind, placebo-controlled trial comparing aspirin 1,300 mg/day to dose-adjusted warfarin (target INR 2–3) in patients with TIA or stroke within 4 months attributed to 50–99 % stenosis of a major intracranial artery [1]. Data from WASID showed that there was no significant benefit of warfarin over aspirin for prevention of stroke and vascular death in patients with symptomatic ICAS. In addition, WASID showed that aspirin was safer than warfarin, with a reduced rate of death and major hemorrhage. The WASID results lead to a change in the clinical management of patients with symptomatic ICAS, with significantly fewer neurologists prescribing warfarin for stroke prevention [7]. WASID subgroup analyses also confirmed that certain groups that were thought to be more responsive to anticoagulation, such as patients with vertebrobasilar stenosis [8], severe (70–99 %) stenosis, or previous stroke symptoms on antithrombotic therapy (medical failures) [9], had no significant benefit from warfarin over aspirin. Furthermore, WASID showed that patients with symptomatic ICAS remained at high risk for recurrent stroke whether taking aspirin or warfarin, with up to 18 % of patients having recurrent strokes in the territory of a 70–99 % stenosis after 1 year.

Dual Antiplatelet Agents

While aspirin was shown to be as effective in lowering stroke recurrence and even safer than warfarin for stroke prevention in patients with symptomatic ICAS in the WASID trial, newer antiplatelet regimens were being studied in patients with heterogenous causes of stroke, some of whom had ICAS. The Management of Atherothrombosis with

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Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) trial compared dual antiplatelet therapy with aspirin and clopidogrel versus clopidogrel alone for prevention of major vascular events in high-risk patients with recent ischemic stroke or transient ischemic attack (TIA) and at least one vascular risk factor [10]. This study included patients with non-cardioembolic causes of ischemic stroke, but only about 1/3 were determined to be strokes secondary to large artery atherosclerosis (i.e., ICAS and extracranial carotid disease). The results revealed that there was no significant benefit for stroke prevention in the dual antiplatelet therapy group over clopidogrel alone in this heterogeneous group. Additionally, there was an increased risk of major hemorrhage in the dual antiplatelet therapy arm beyond the third month of treatment [10]. Later, the Clopidogrel plus Aspirin for Infarction Reduction (CLAIR) [11] and the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) [12] studies suggested that the use of *short-term* dual antiplatelet therapy (aspirin and clopidogrel) may be effective at lowering the early risk of stroke recurrence in patients with stroke due to large artery atherosclerosis. In the CLAIR study, patients with recently symptomatic (≤7 days) ICAS or extracranial carotid stenosis who were treated with dual antiplatelet agents (clopidogrel and aspirin) had significantly lower rates of microembolic signals detected by transcranial Doppler (TCD) on days 2 and 7 after randomization compared with patients treated with aspirin monotherapy [11]. In a weighted analysis, the recurrent stroke events of CLAIR combined with the events from the CARESS study (limited to patients with recently symptomatic >50 % extracranial carotid stenosis), showed significantly more recurrent stroke events on aspirin alone compared with aspirin and clopidogrel combined [11, 12]. These studies provided a rationale for including short-term dual antiplatelet (aspirin plus clopidogrel) use in future studies of ICAS.

The use of short-term dual antiplatelet therapy (aspirin plus clopidogrel) for recently symptomatic ICAS is also supported by results from the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) Trial [4]. In SAMMPRIS, patients with 70–99 % ICAS of the major intracranial arteries who had had a stroke or TIA in the territory of the stenosis within the preceding 30 days were randomly assigned to either aggressive medical therapy plus percutaneous transluminal angioplasty and stenting (PTAS) or aggressive medical therapy alone [13]. Aggressive medical therapy included aspirin 325 mg/day during the entire follow-up period, clopidogrel 75 mg/day for 90 days after enrollment, and protocol-driven intensive medical management (described in detail later in the chapter). SAMMPRIS began recruitment in November 2008, but the National Institute of Neurological Disorders and Stroke (NINDS) stopped SAMMPRIS enrollment early due to the high rate of periprocedural stroke in the stenting arm [4]. The 30-day rate of stroke or death was 14.7 % in the PTAS group (nonfatal stroke, 12.5 %; fatal stroke, 2.2 %) and 5.8 % in the medical-management group (nonfatal stroke, 5.3 %; non-stroke-related death, 0.4 %) ($p=0.002$). For comparison, patients in the WASID trial (with the same entry criteria as SAMMPRIS) who were given aspirin (1,300 mg/day) or warfarin (target INR 2-3) and usual blood pressure and LDL management had a 30-day rate of stroke or death of 10.7 %. The lower rate of stroke at 30 days in SAMMPRIS compared to WASID may be driven by the early use of dual antiplatelet treatment in SAMMPRIS, since the effects of aggressive risk factor and lifestyle modification on stroke recurrence at 30 days might not likely be apparent.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) also provides support for the use of short term dual antiplatelet therapy in patients with ICAS. CHANCE was a randomized trial conducted in China that compared short-term dual antiplatelet therapy versus aspirin monotherapy for the prevention of subsequent stroke at 90 days in patients with non-cardioemoblic minor stroke or high-risk TIA [14]. The primary outcome was a new stroke event (ischemic or hemorrhagic) at 90 days. A total of 2,584 patients were randomly assigned to the clopidogrel-aspirin group and 2,586 to the aspirin group. Overall, CHANCE showed that the addition of clopidogrel to aspirin within 24 h after symptom onset reduced the risk of subsequent stroke by about 32 % as compared with aspirin alone [14]. However, a subgroup analysis reported that 55.83 % of patients in CHANCE had ICAS, suggesting some of the benefit of dual antiplatelet therapy may have been due to a benefit in ICAS patients. CHANCE patients with ICAS had a higher rate of recurrent stroke (12.47 % vs. 5.43 %, $P<0.0001$) and poor outcome (mRS 0-2) (89.1 % vs. 97.02 %, $P<0.0001$) at 90 days than the patients without ICAS. The primary end point rate was lower in ICAS patients treated with dual antiplatelets compared with aspirin only, but was not significant (11.26 % dual vs. 13.60 % aspirin; hazard ratio [HR] 0.79, 95 % CI 0.47–1.32). However, the authors concluded that the benefits of dual antiplatelet therapy tended to be more apparent in patients with ICAS than in patients without ICAS [15].

The current AHA/ASA guidelines for secondary stroke prevention [16] indicate that for patients with recent stroke due to 70–99 % intracranial stenosis, the addition of clopidogrel 75 mg/day to the use of aspirin for 90 days is reasonable, largely based on the results of the SAMMPRIS trial.

Other Antiplatelet Agents

Other antiplatelet agents such as cilostazol (a phosphodiesterase inhibitor) have been studied in patients with ICAS. Kwon et al. randomized 135 patients with ICAS (MCA or basilar) to cilostazol (200 mg/day) plus aspirin (100 mg/day) or placebo

plus aspirin (100 mg/day) and measured progression of ICAS by magnetic resonance angiography (MRA) and transcranial Doppler (TCD) at 6 months [17]. Progression of atherosclerosis was significantly lower in the cilostazol group than in the placebo group ($p=0.008$) and there were no reported strokes or TIAs in either group. A subsequent trial [18] randomized 457 patients with symptomatic middle cerebral or basilar artery stenosis to cilostazol (100 mg twice daily) plus aspirin (75–100 mg/day) or clopidogrel (75 mg/day) plus aspirin (75–100 mg/day) to determine the number of new ischemic lesions on MRI at 7 months. There was no statistically significant difference in new ischemic lesions (18.7 % vs. 12.0 %, $p=0.078$) or hemorrhagic events (0.9 % vs. 2.6 %; $p=0.163$) between the cilostazol and clopidogrel groups [18].

Overall, there is no published data for the equivalence or superiority of other antiplatelet agent regimens such as monotherapy with extended release dipyridamole, clopidogrel, cilostazol or the combination of dipyridamole and aspirin for stroke prevention in patients with symptomatic ICAS.

Risk Factor Modification

Secondary stroke prevention trials in patients with heterogenous causes of stroke focusing on lowering of LDL cholesterol (e.g., the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study) or blood pressure (e.g., the Perindopril pROtection aGainst Recurrent Stroke Study (PROGRESS) study) showed significant reductions in recurrent stroke risk in stroke patients treated with statins and angiotensin-converting-enzyme (ACE) inhibitors [19, 20]. However, prior to the SAMMPRIS trial, an aggressive multimodal approach to risk factor control in patients with stroke-related atherosclerosis was not being incorporated into clinical trials. Evidence from WASID showed that poorly controlled vascular risk factors (particularly SBP and LDL) in patients with ICAS were associated with a higher risk of major vascular events [21, 22]. This prompted inclusion of aggressive management of vascular risk factors in the SAMMPRIS trial [23]. SAMMPRIS aggressive medical management primarily targeted systolic blood pressure (SBP) ≤140 mmHg (≤130 mmHg if diabetic) and low-density lipoprotein cholesterol (LDL) <70 mg/dL. The study neurologist and coordinator at each site implemented risk factor management for both primary and secondary targets (primary: LDL, SBP; secondary: non-HDL, hemoglobin A1c (HbA1c), smoking, weight management, physical activity) and were assisted by an evidence-based, educational, lifestyle modification program (INTERxVENT) that was administered at regularly scheduled times to all patients throughout the study [23].

The final results of SAMMPRIS [3] revealed that the early benefit of aggressive medical management over PTAS for high-risk patients with ICAS persisted over the extended follow-up (median duration of follow-up in all patients was 32.4 months). The occurrence of primary end points in the medical group versus PTAS group was 12.6 % versus 19.7 % at year 1 ($p=0.0428$), 14.1 % versus 20.6 % at year 2 ($p=0.07$), and 14.9 % versus 23.9 % at year 3 ($p=0.0193$). Secondary end points, specifically the rates of any stroke (19 % vs. 26 %, $p=0.0468$) and any major hemorrhage (4 % vs. 13 %, $p=0.0009$) were significantly lower in the medical group versus PTAS group.

Compared to similar patients treated with usual management of risk factors in the WASID trial, patients in SAMMPRIS had substantially better risk factor control and reduction in stroke risk (5.8 % at 30 days and 12.2 % at 1 year in SAMMPRIS versus 10.7 % at 30 days and 25 % at 1 year in WASID) [4]. In SAMMPRIS, within the first 30 days, mean SBP decreased by over 5 mmHg and mean LDL decreased by over 20 mg/dL, with both of these primary risk factor measures continuing to improve at 1 year [23]. Improvements in secondary risk factor targets were also seen, with significantly better control of non-HDL cholesterol and HbA1c, weight loss, improved exercise, and smoking cessation compared to baseline [23]. Although historical comparisons between WASID and SAMMPRIS patients do not prove that the SAMMPRIS aggressive medical management strategy improved outcomes, these improvements in risk factor control very likely contributed to better-than-expected outcomes in the medical management arm of SAMMPRIS. Successful "real world" implementation of the lifestyle modification program used in SAMMPRIS was also demonstrated in a single-center study of 22 patients with an ischemic stroke or TIA secondary to 50–99 % intracranial stenosis [24].

Surgical Therapy

Initial reports of surgical treatment for intracranial stenosis or occlusion were described in the 1970s [25, 26]. Surgical therapy for stroke prevention in ICAS has been explored for both anterior and posterior arterial stenosis and occlusion. Surgical bypass for carotid occlusive disease has been studied in two large randomized trials. The EC/IC Bypass trial randomized 1,377 patients with symptomatic extracranial carotid occlusion, intracranial carotid occlusive disease, or middle cerebral artery (MCA) stenosis to receive best medical care (typically aspirin 325 mg QID and blood pressure control) versus medical care plus extracranial–intracranial anastomosis surgery (superficial temporal artery to middle cerebral artery anastomosis) [27]. Stroke occurred earlier and more frequently in the surgery group during the mean follow-up of 55.8 months and patients with MCA stenosis actually did worse with the surgery than with medical therapy. The Carotid Occlusion Surgery Study (COSS) attempted to improve patient selection for EC/IC bypass by targeting

patients with carotid occlusion and recent hemodynamic ischemic symptoms, but was terminated after enrollment of 195 patients due to futility [28]. The primary end point was any stroke or death within 30 days or ipsilateral stroke within 2 years, which occurred in 21.0 % of patients in the surgical group and 22.7 % in the nonsurgical group. Extracranial to intracranial bypass has since been abandoned as a treatment for stroke prevention in patients with symptomatic anterior circulation ICAS. Surgical bypass for vertebrobasilar disease has not been systematically studied although there are a few small case series and case reports of surgical bypass for vertebrobasilar disease [29–31].

While direct bypass of intracranial stenosis has been unsuccessful for stroke prevention, encephaloduroarteriosynangiosis (EDAS) is another surgical procedure designed to deliver flow beyond an intracranial stenosis. With EDAS, indirect revascularization is achieved by a network of collaterals, which forms between the donor artery and the adjacent brain vessels without a surgical anastomosis. In a small study of 13 patients with intracranial stenosis who had failed medical management, 85 % of patients had complete resolution of ischemic symptoms over a median follow-up of 54 months [32]. EDAS has several advantages over EC-IC bypass because it requires no clamping or manipulation of the diseased artery, it does not induce sudden hyperemia since collaterals develop over time, it has a shorter surgical time than bypass, and it provides revascularization only where needed. However, further studies are needed to determine if EDAS has benefit over medical therapy. Surgical Indirect Revascularization For Symptomatic Intracranial Arterial Stenosis (ERSIAS) is a phase II NIH funded study that aims to determine if EDAS revascularization combined with aggressive medical therapy warrants further evaluation in a subsequent pivotal trial as an alternative to aggressive medical management alone for preventing the primary end point of stroke or death in patients with symptomatic intracranial arterial stenosis (clincaltrials.gov NCT01819597).

Endovascular Therapy

In the 1980s, endovascular treatment emerged as a potential option for stroke prevention in patients with ICAS [33]. Angioplasty alone was typically reserved for severe ICAS in patients with recurrent TIA or stroke despite medical therapy. The outcome data have been reported in many retrospective studies, but the 30-day rate of stroke or death has varied widely (4–40 %) [34], with restenosis rates after angioplasty between 24 and 50 % [35–38]. One review in 2006 found an overall periprocedural stroke or death rate of 9.5 % (95 % CI 7.0–12.0 %) in 79 reports with at least 3 cases of angioplasty treatment for intracranial stenosis [39]. Another retrospective series of 4 centers and 74 patients showed a 30-day stroke and death rate of 5 % (95 % CI, 1.5–13 %) and a 3 months stroke or death rate of 8.5 % (95 % CI, 3.1–17.5 %) [40]. To date, there is still little or no prospective data or studies comparing angioplasty alone verses medical therapy in ICAS.

Although angioplasty is considered to be technically easier to perform than stenting, stenting became the preferred endovascular treatment for ICAS because of the limitations of angioplasty (e.g., risk of dissection, recoil and post-procedure residual stenosis [41]) and the success of stenting in the coronary circulation. Percutaneous angioplasty and stenting (PTAS) was initially performed using stents designed for the coronary vasculature and used off-label to treat intracranial atherosclerosis. The Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) [42] was the first multicenter, non-randomized prospective trial using a balloon expanding bare metal stent, Neurolink, in patients with ICAS. Of the 61 patients enrolled, 43 had ICAS. In the first 30 days, 4 patients (6.6 %) had strokes and no deaths occurred. Beyond 30 days to 1 year, the stroke rate was 7.3 %. There was a restenosis rate of 35 % and 39 % of those patients with restenosis were symptomatic.

The Wingspan self-expanding Nitinol stent is the only FDA approved stent for ICAS and became commercially available in 2005 under a humanitarian device exemption (HDE) approval for "treatment resistant intracranial atherosclerotic disease" in patients with TIA or stroke secondary to 50–99 % stenosis of a major intracranial vessel. The initial study that led to FDA approval was based on the results of a European and Asian study of 45 patients with 50–99 % stenosis where the technical success rate was 98.8 % and the 30-day stroke and death rate was 4.5 % [43]. Subsequently, 2 large registries, the US Wingspan Registry [44] and the NIH Wingspan Registry [45] reported data on the use of this stent in the US. Data from these registries suggested that PTAS with Wingspan might be considered a safe, effective option for stroke prevention in patients with 70–99 % stenosis when compared to patients treated with usual medical therapy in WASID.

As a result, the SAMMPRIS trial was undertaken to compare PTAS to medical management (design described previously). SAMMPRIS showed that aggressive medical therapy was superior to PTAS with the Wingspan stent in the treatment of patients with 70–99 % stenosis of the intracranial arteries. At the time enrollment was stopped, stroke or death within 30 days occurred in 33 patients in the stenting group and in 13 patients in the medical therapy group (14.7 % vs. 5.8 %, $p=0.002$) [4]. Final results from SAMMPRIS, during a median follow-up period of 32.4 months, revealed that the early benefit of aggressive medical management over PTAS with Wingspan persisted over an extended time period [3]. In other words, even if the high periprocedureal complica-

tion rate from PTAS could be reduced, PTAS would still not be superior to aggressive medical therapy for prevention recurrent stroke in high-risk patients with ICAS.

In an effort to understand the high periprocedural stroke and death rate in SAMMPRIS, analyses of these early events in the PTAS arm have been performed. The majority of periprocedural ischemic strokes were perforator occlusions and the symptomatic hemorrhages were roughly an equal mix of intracerebral hemorrhages ($n=7$) and subarachnoid hemorrhages ($n=6$) [46]. Perforator occlusions in the PTAS arm in SAMMPRIS were seen more commonly in the treated basilar arteries [47]. Operator inexperience was not associated with an increased risk of periprocedural complications, as more experienced interventionists (i.e., more than 10 Wingspan cases submitted for credentialing prior to study entry) tended to have higher rates of 30 day events (19.0 % vs. 9.9 %) than those with less experience (less than 10 Wingspan cases submitted for credentialing) [48].

Several non-randomized case series and registries using the Wingspan stent have been reported since the SAMMPRIS trial started in 2008 and have also shown high periprocedural complication rates similar to the 14.7 % rate in SAMMPRIS [49–52]. These findings suggest that the periprocedural complication rate seen in SAMMPRIS was well within the range of other contemporary reports of periprocedural complications with Wingspan.

Another randomized industry-sponsored trial, the Vitesse Intracranial Stent Study for Ischemic Therapy for Symptomatic Intracranial Stenosis Trial (VISSIT), evaluated the safety and efficacy of the Pharos Vitesse stent (balloon-mounted stent) plus medical therapy versus medical therapy alone for preventing stroke in patients with high-grade symptomatic ICAS (≥70 %) [53]. Medical therapy included clopidogrel (75 mg/day) for 90 days after enrollment and aspirin (81 mg or 325 mg/day) for the duration of the study as well as statin therapy to achieve an LDLc ≤100 mg/dL, antihypertensive medication, diet modification and smoking cessation. Clinical follow-up was performed at 30 days, 90 days, 180 days, and 1 year. Primary end points of the study were stroke in the same territory as the presenting event within 12 months of randomization and "hard TIA" in the same territory as the presenting event from day 2–12 months post randomization. Secondary end points included technical success, in-stent restenosis, and comparison of NIHSS and mRS between the treatment arms. Enrollment in VISSIT was stopped early and preliminary results demonstrating no benefit of stenting over medical therapy were presented at the combined 6th International Conference on Intracranial Atherosclerosis and 6th Annual Society of Vascular and Interventional Neurology Meeting in October, 2013 [54]. However at the time of this writing, the final results have not been published.

Based on recommendations by an FDA advisory panel meeting convened in March 2012, the FDA implemented additional restrictions for the use of Wingspan under the HDE, which limit use to patients with 70–99 % stenosis and "a very specific group of patients with severe intracranial stenosis and recurrent stroke despite continued medical management…" [55]. However, the characteristics of patients who are still indicated for treatment with the device is unclear, as the definition of stroke "despite continued medical management" is not clearly limited to failure of antithrombotic therapy or intensive risk factor management. Furthermore, the assumption that patients who fail antithrombotic therapy are higher risk of recurrent stroke was disproven by a WASID analysis that showed no difference in recurrent stroke risk between patients who were on antithrombotic agents at the time of their qualifying event versus those who were not [9] as well as a preliminary SAMMPRIS analysis showing similar results [56].

Treatment Based on Pathophysiology

There are multiple mechanisms of stroke due to ICAS including atherosclerotic plaque extension over perforating artery ostia (branch atheromatous disease), thrombus formation with distal embolization (artery-to-artery embolization), and hypoperfusion. Theoretically, one could argue that optimal stroke prevention in patients with ICAS should focus on the stroke mechanism. For example, hypothetical stroke due to hypoperfusion may be best treated with revascularization whereas stroke due to artery-to-artery embolization secondary to plaque rupture may be best treated with antiplatelet agents and statins. However, a WASID post-hoc analysis suggested that the mechanism of the index stroke does not necessarily predict the mechanism of a subsequent stroke, since patients who presented with lacunar strokes in WASID were not more likely to have recurrent lacunar strokes during follow-up compared to patients who presented with non-lacunar strokes at study entry [57]. More studies are needed to better understand the pathophysiology of stroke secondary to ICAS in order to design potential prevention strategies specific to stroke mechanism.

Current Treatment Recommendations

Overall, medical management and lifestyle modifications including increasing physical activity, heart healthy diet and smoking cessation are recommended for patients with ICAS. Medical management recommendations, based on the results of SAMMPRIS, for recently symptomatic severe ICAS include combination antiplatelet therapy of clopidogrel (75 mg per day) plus aspirin (325 mg per day) for 90

days followed by aspirin (325 mg per day) and intensive risk factor modification with goal SBP ≤140 mmHg and LDL ≤70 mg/dL. Patients with symptomatic moderate ICAS or patients that have experienced an ischemic event more than 30 days previously (regardless of degree of stenosis) should take aspirin (325mgs per day) and intensive medical management of risk factors including goal systolic blood pressure (SBP) ≤140 mmHg and LDL ≤70 mg/dL. (Dual antiplatelet therapy beyond 90 days from initial treatment is not recommended due to the increased risk of major hemorrhage.) There is insufficient data to recommend the usefulness of other antithrombotic strategies such as clopidogrel alone, combination of aspirin and dipyridamole or cilostazol alone.

Stenting is not recommended for symptomatic patients with moderate ICAS because of the low rate of stroke recurrence on recommended medical management strategies and the high periprocedural risk of endovascular treatments. Stenting is also not recommended as first line therapy for patients with symptomatic severe stenosis even if the event occurred while taking antithrombotic medication. The usefulness of other stents (e.g., not Wingspan) and angioplasty alone is not known and is investigational in patients with symptomatic severe ICAS. There are no data supporting the use of stenting or angioplasty in patients with severe ICAS who have recurrent stroke or TIA while already on combination aspirin and clopidogrel and who have achievement of recommended risk factor targets.

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Secondary Prevention After Non-atherosclerotic Cerebral Vasculopathies

16

Rima M. Dafer

Abbreviations

ABRA	Amyloid β-related angiitis
ACA	Anterior cerebral arteries
CNS	Central nervous system
CAA	Cerebral amyloid angiopathy
CSF	Cerebrospinal fluid
CCAD	Cervicocephalic arterial dissection
FMD	Fibromuscular dysplasia
GCA	Giant cell arteritis
ICA	Internal carotid artery
MCA	Middle cerebral artery
NAV	Non-atherosclerotic vasculopathy
PRES	Posterior reversible ischemic encephalopathy syndrome
PACNS	Primary angiitis of the CNS
RCVS	Reversible cerebral vasoconstriction syndrome
SAH	Subarachnoid hemorrhage

Case Presentation A 35-year-old woman developed a severe headache associated with nausea and vomiting. She had history of migraine with aura and generalized anxiety disorder, treated with propranolol and fluoxetine respectively. She took multiple doses of sumatriptan over a period of 48 h with minimal relief. On day 3, she presented to the emergency department with persistent intractable headache, altered mental status, and intermittent tingling of the right arm and face. She was disoriented to time and place, but had no focal neurologic deficit. Ancillary blood tests were normal. A CT scan of brain showed a cortical left frontal subarachnoid hemorrhage (SAH). Cerebrospinal fluid examination showed elevated red blood cell count with normal white blood cells count and slightly elevated protein level. A magnetic resonance angiogram (MRA) showed segmental narrowing in the middle cerebral arteries (MCAs), anterior cerebral arteries, and posterior cerebral arteries bilaterally, a finding confirmed by catheter cerebral angiogram. MR venogram was normal. Extensive vasculitis workup was non-contributory. The diagnosis or reversible vasoconstriction was made. She received intravenous magnesium sulfate, nimodipine, and topiramate. Despite overall improvement, she continued to complain of constant waxing and waning headaches for two consecutive weeks. On day 21, a CT scan of brain showed resolution of the SAH, with persistent vasoconstriction of the vessels of the circle of Willis bilaterally on CT angiogram (CTA). At 12 weeks, a repeat CTA showed resolution of vasoconstriction and normalization of vessels caliber in the MCAs, ACAs, and PCAs. At 12 months, she was asymptomatic except for occasional migraine attacks.

Introduction

Uncommon causes of stroke represent up to 5 % of all ischemic strokes [1]. Non-atherosclerotic vasculopathies (NAVs) account for a minority of strokes and are of particular importance in children and young adults, accounting for 14–25 % of strokes in patients under the age of 50. NAVs comprise a great variety of diseases with various underlying mechanisms including immunological, infective, collagen vascular, and hematological conditions. Increased availability of multimodal brain imaging and improved quality of noninvasive angiographic imaging has allowed more accurate and timely diagnoses, as well as better differentiation among such vasculopathies, resulting in appropriate management and enhanced outcomes. Arterial dissection, both traumatic and spontaneous, is the most common of the NAVs. Dissection is often interlinked with other arteriopathies including fibromuscular dysplasia and collagen vascular disorders. Other NAVs are being increasingly recognized, including reversible cerebral vasoconstriction syndrome, unilateral intracranial

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arteriopathy of childhood, moyamoya disease, post-radiation vasculopathies, and cerebral vasculitides. Mechanisms of stroke in NAVs vary from traumatic vessel injury to inflammation and infection, often in the setting of an underlying genetic predisposition. This chapter reviews the clinical manifestations, diagnosis, and management of the most common NAVs.

Cervicocephalic Arterial Dissection

Cervicocephalic arterial dissection (CCAD) is the most common of the NAVs accounting for 2.5 % of all ischemic strokes and for 15–20 % of cerebral infarctions in young adults [2–6]. CCAD usually involves the extracranial pharyngeal and distal segments of the internal carotid artery (ICA), at times extending to its petrous or supraclinoid segment [7, 8]. Dissection affecting the vertebral arteries accounts for one third of all CCADs [7, 8]. Vertebral artery dissections usually involve the distal third segment of the vessel, with intracranial extension occurring less frequently [5, 7, 8]. Intracranial dissections may follow closed head trauma or basilar skull fracture. A subintimal tear in a cervicocephalic carotid or vertebral artery occurs, followed by formation of an intramural hematoma within the layers of the tunica media [7, 9]. Longitudinal extension of the hematoma subsequently leads to tapering, luminal narrowing, focal stenosis, or occlusion of the affected vessel [7, 9]. When the intramural hematoma extends between the medial and adventitial layers, a false lumen or pseudoaneurysm may form [4, 5, 7]. Bilateral involvement is seen in 5–10 % of patients and usually raises the suspicion of underlying genetic component [10, 11]. The etiopathogenesis of CCAD remains unknown. Impaired endothelial-dependent vasodilatation occurs following a trivial trauma or when another precipitating event is present [9]. Hereditary, environmental, infective, and intrinsic factors may increase the risk of CCAD [11–14]. Abrupt cervical manipulation, in particular neck rotation and extension such as during contact sports or chiropractic manipulation, as well as minor neck extension (beauty parlor syndrome) may increase the risk of dissection (Table 16.1) [14–18]. Spontaneous dissection may occur, although patients often report a history of antecedent trivial trauma or strenuous effort such as during labor [7, 11, 12, 19, 20]. Patients with heritable connective tissue disorders and underlying arteriopathy such as FMD and collagen vascular disorders are in particular prone to arterial dissections [21–27]. Other conditions associated with increased risk of CCAD include migraine, preceding infections, arterial hypertension, MTHFR mutation, and homocysteinuria (Table 16.2) [28–32].

The clinical diagnosis of CCAD can be challenging. CCAD is often an asymptomatic incidental finding on MRI and CTA. Ipsilateral headache is the most common clinical presentation, with retro-orbital and retro-auricular pain often described in patients with carotid and vertebral artery dissections respectively [3, 5, 7, 33]. Other neurological symptoms resulting from direct compression by the dissecting aneurysm or vessel occlusion include partial Horner's syndrome, cranial nerve palsies, pulsatile tinnitus, dysgeusia, and ocular

Table 16.1 Traumatic causes of extracranial arterial dissection

Direct blow to the head and neck
Chiropractic neck manipulation
Strangulation
Atlanto-axial sublaxation
Elongated styloid process
Cervical spine fracture
Basal skull fracture
Excessive head banging
Beauty parlor syndrome
Labor and delivery
Prolonged cell phone use
Excessive coughing or retching

Table 16.2 Conditions associated with cervicocephalic arterial dissections

Fibromuscular dysplasia
Marfan syndrome
Ehlers–Danlos syndrome type IV
Alpha-1 antitrypsin deficiency
Alport syndrome
Extreme vessel tortuosity
Type 1 collagen point mutation
Osteogenesis imperfecta
Pseudoxanthoma elasticum
Adult polycystic kidney disease
Fibrocystic dysplasia
Other connective tissue disorders
Takayasu's disease
Moyamoya disease
Coarctation of the aorta
Reticular fiber deficiency
Menkes disease
Accumulation of mucopolysaccharides
Elevated arterial elastase content
Atherosclerosis
MTHFR 677TT mutation
Pharyngeal infections
Homocystinuria
Migraine
Oral contraceptives
Tobacco use
Hypertension
Meningovascular syphilis

symptoms. Focal neurologic deficits due to retinal and hemispheric ischemia may occur (Table 16.3) [5, 7, 33, 34]. In the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) Study Group, the presence of occlusive cervical artery dissection, multiple cervical artery dissections, and vertebral artery dissection were associated with an increased risk for delayed stroke [35]. Intracranial extension of arterial dissection may result in SAH. When CCAD is suspected, noninvasive studies such as Doppler ultrasonography, MRA or multisectional CTA head and neck are recommended. CTA and MRA are minimally invasive techniques that can provide high-resolution and high-contrast images of the arterial lumen and wall, with good sensitivity and specificity [36]. MRA and CTA have replaced conventional angiography, thereby facilitating early diagnosis and rapid treatment. Findings may include pseudoaneurysmal formation, intimal flap with double lumen (Fig. 16.1), vessel stenosis, or total arterial occlusion (Figs. 16.2 and 16.3). Fat suppression MRI techniques may reveal the presence of the intramural hematomas within the vessel wall [36] (Fig. 16.4). Conventional angiography has historically been the gold standard for the diagnosis of arterial dissection; its use however should be limited to selective cases where MRA or CTA is inconclusive. In patients with recurrent dissection, family history of dissection, or associated intracranial aneurysms, further workup to exclude FMD and collagen vascular disorders may be indicated [26].

Table 16.3 Clinical manifestations of CCADs

Headache
Orbital pain
Neck pain
Pulsatile tinnitus
Horner's syndrome
Visual symptoms
Visual scintillations
Amaurosis fugax
Central retinal artery occlusion
Anterior ischemic optic neuropathy
Posterior ischemic optic neuropathy
Cranial neuropathies
Dysgeusia
Transient ischemic attack
Focal neurological deficits

In the absence of randomized clinical trials to compare various treatment options, the choice of stroke prevention therapy remains controversial. Treatment is usually aimed at preventing intramural extension, thrombus formation, and artery-to-artery embolization. Treatment options include intravenous or intra-arterial thrombolysis in patients eligible for alteplase. Optimal secondary prevention strategies in CCADS remain controversial. Options include antithrombotic therapies with either antiplatelet agents or anticoagulants; endovascular and surgical interventions are considered in selected patients with recurrent symptoms despite antithrombolytic therapies [37–43].

Intravenous thrombolysis with tissue plasminogen activator should be considered within the 4.5 h of the onset of symptoms when acute ischemic stroke is suspected [44, 45]. In the Cervical Artery Dissection and Ischemic Stroke (CADISP) registry, 68 of 616 patients received thrombolysis, majority of which in the intravenous route (55 patients) [46]. The use of thrombolysis was not associated with increased risk of bleeding [46]. Similar results were reported by Georgiadis et al. in 33 patients with acute ischemic stroke treated with intravenous thrombolysis without clinical deterioration, increased risk of SAH, pseudo-aneurysm formation, or arterial rupture [47].

Early preventive strategies should be initiated as the risk of recurrent ischemic events is highest within the first few weeks of the dissection. Anticoagulation with heparin followed by

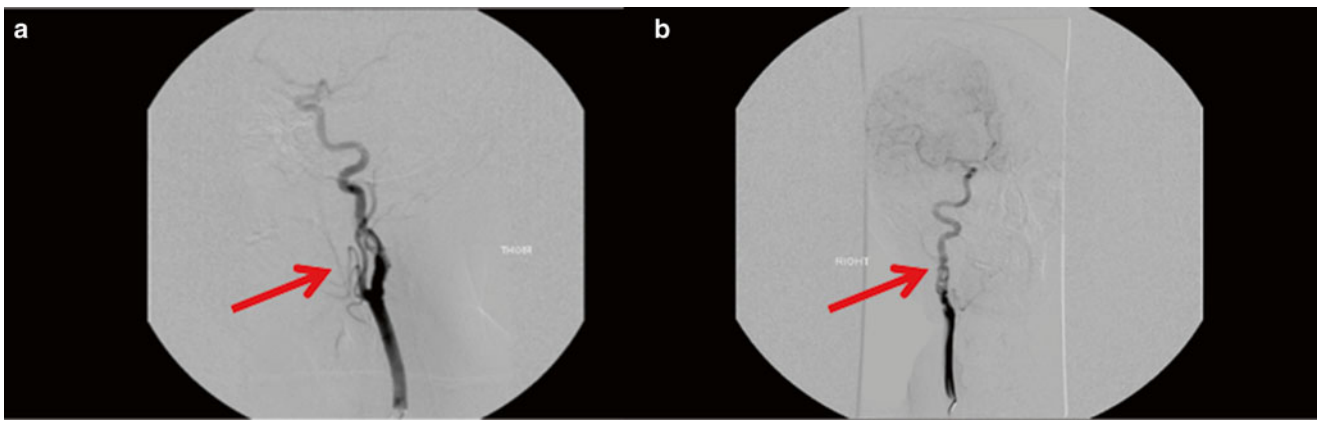

Fig. 16.1 Cerebral angiogram showing cervical ICA dissection with (**a**) double lumen with intimal flap, and (**b**) pseudoaneurysmal formation

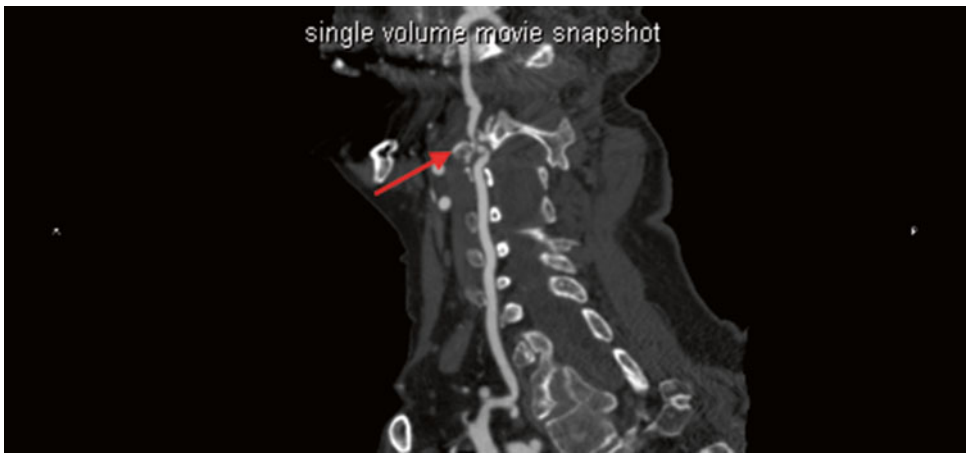

Fig. 16.2 CTA of the neck showing distal vertebral artery dissection secondary to cervical fracture

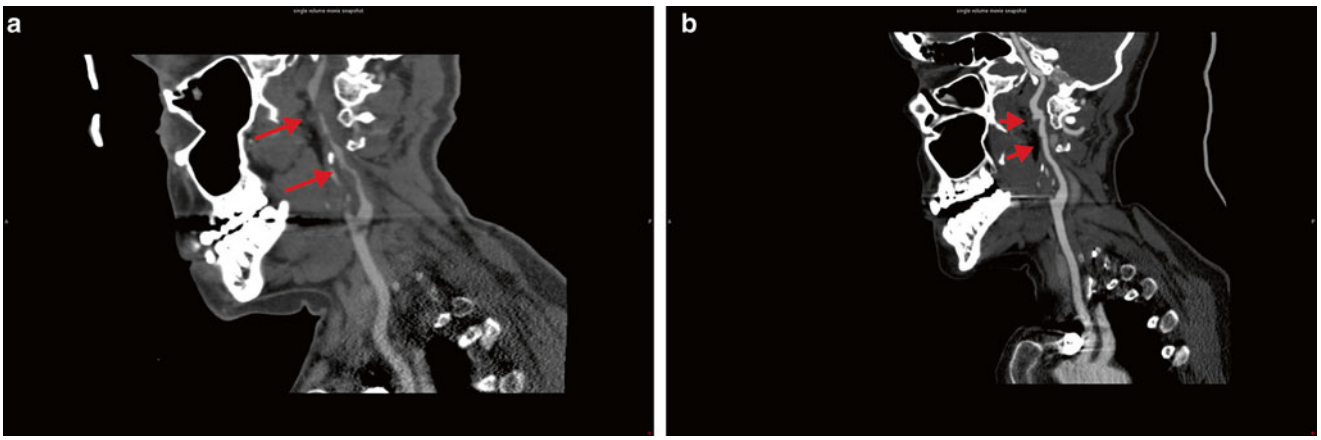

Fig. 16.3 (**a**) CTA neck showing a long segment of beaded focal stenosis in the left ICA suggestive of dissection extending into the petrous segment in a young woman with severe migraine following the use of triptans; (**b**) healing of the previously noted ICA dissection at 2 month follow-up

warfarin for 3–6 months has been empirically recommended except when intracranial extension is suspected [37, 47]. However, the value of anticoagulation in extracranial CCAD has not been established [43]. Data from a Cochrane review comparing antiplatelets with anticoagulants across 36 observational studies with 1,285 patients showed no differences in the odds of death or the occurrence of ischemic stroke between the two treatment modalities [38]. The results of the non-randomized arm of the Cervical Artery Dissection in Stroke Study (CADISS) which compared anticoagulation and antiplatelets for the prevention of recurrent stroke in carotid and vertebral dissection showed no difference between the two treatment arms [39]. The prospective multicenter randomized open label-controlled part of CADISS is ongoing [40]. Treatment should be customized based on acuteness of symptoms, clinical characteristics, symptom-recurrence, and imaging findings. Anticoagulation should be avoided when intracranial dissection is suspected due to increased risk of SAH [41]. Antiplatelets are often prescribed in patients with asymptomatic stenosis with subacute or late presentation. In contrast, the presence of thrombus in the dissected artery favors the use of anticoagulation [7, 37]. Surgical and endovascular interventions with angioplasty and stenting should be reserved to patients with recurrent symptoms who fail medical therapy [48–51]. The majority of CCADs heal spontaneously and outcome is usually favorable. Recurrence dissection in the involved vessel is very rare, often occurring within the first 2 months after the initial event [52, 53].

Fibromuscular Dysplasia

FMD is a non-atherosclerotic non-inflammatory segmental non-inflammatory vascular disease of unknown etiology affecting the medium and small sized arteries of virtually every arterial bed, predominantly the renal and extracranial

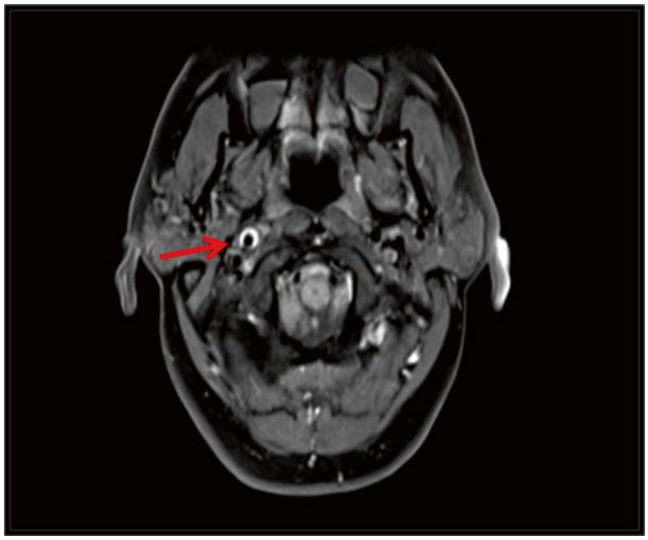

Fig. 16.4 MRI brain with fat suppression shows right cervical ICA dissection with narrow eccentric flow-void surrounded by hyperintense crescent shaped intramural hematoma

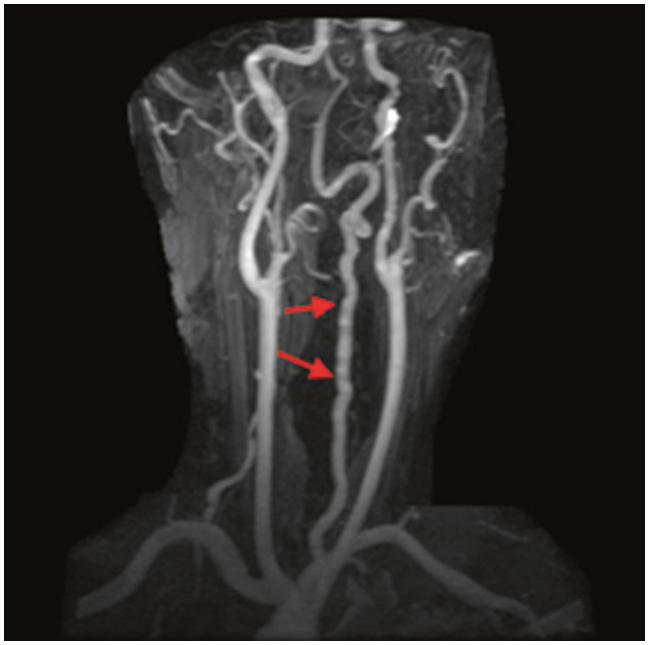

Fig. 16.5 String of beads in the left vertebral artery and left ICA in a patient with fibromuscular dysplasia

segment of the ICA [54]. FMD may result in arterial stenosis, occlusion, aneurismal formation, or vessel dissection. While the prevalence of the disease is unknown, FMD is increasingly being diagnosed due to advances in neuroimaging. FMD is more common in young women between the ages of 30 and 50 years, especially in individuals with a history of migraines, thus hormonal factors have been postulated [54]. The disease is uncommon in children. Genetic susceptibility has been suggested in subsets of patients with autosomal mode of inheritance [55–57]. Histologically, medial fibroplasia accounts for 95–99 % of cases. Involvement of the intima and the adventitia is rare (<1 %) [58]. Angiographic characteristics observed in 80–90 % of cases of FMD include multifocal short segment of arterial stenoses with alternating mural dilatations and constriction giving the classic appearance of "string of beads", predominantly in the mid- and distal portion of the internal carotid and vertebral arteries (medial fibroplasia or type 1) [54, 58] (Fig. 16.5). Less commonly, a unifocal concentric or band-like tubular stenosis may occur due to intimal fibroplasia (type 2). Rarely, adventitial involvement or medial hyperplasia may exit (type 3) [54, 58]. Clinical symptomatology is variable and nonspecific. Majority of cases are asymptomatic incidental findings on neuroangiographic studies. Symptoms may include headaches, pulsatile tinnitus, and blood pressure changes. Arterial dissections and cerebral aneurysms occur in 7–20 % of cases. Although often asymptomatic, these may be responsible for cerebral ischemia or subarachnoid hemorrhage [59, 60].

When arterial dissection occurs, around 20 % of patients may develop transient ischemic symptoms or cerebral infarction [35]. FMD should be suspected in patients with bilateral CCADs, especially when intracranial aneurysms are present. Patients with hypertension, migraine, and history of cigarette smoking are more predisposed to FMD. The condition may coexist with other collagen vascular disorders such as cystic medial necrosis, Ehlers–Danlos syndrome (type IV), Marfan's syndrome, Alport syndrome, and vasculitic conditions such as Takayasu's disease [21, 60, 61]. Management of FMD is similar to that of CCAD. There are no randomized controlled trials of revascularization versus medical therapy in patients FMD. Medical management should always be the first choice of therapy, with percutaneous or surgical intervention reverted to patients with recurrent symptoms and cerebral aneurysms [62].

Moyamoya Disease

Moyamoya disease is an idiopathic progressive non-inflammatory intracranial occlusive arteriopathy of unknown etiology. It is characterized by vaso-occlusive changes involving the circle of Willis, typically the ICA terminus or proximal anterior cerebral arteries (ACA) and middle cerebral arteries (MCA), resulting in a complex network of collateral net-like tuft of vessels corresponding to the lenticulostriate and thalamoperforate arteries [63, 64]. Moyamoya disease

predominantly affects children and young adults in the first or third decades of life with female preponderance. Moyamoya disease was first described by Suzuki and Takaku in 1969 in Japanese patients with abnormal net-like vessels in the base of brain appearing as "something hazy just like a puff of cigarette smoke drifting in the air" (moyamoya in Japanese) [63]. It has since been reported in every ethnic group. Histologically, there is excentric intimal hyperplasia with fibrosis of the cerebral arterial trunks, thinning of the media, and endothelial thickening leading to stenosis or occlusion of the lumen in the internal carotid terminus, ACAs and MCAs, without an obvious underlying inflammatory response [64–66]. The internal elastic lamina of the affected arteries is often tortuous; the adventitia is usually spared. Cerebral aneurysms are common [64]. Immuno-histochemical studies showed aberrant expression of IgG and S100A4 protein in vascular smooth muscle cells of the intracranial vascular wall, suggesting an underlying immune reaction [67, 68].

The pathogenesis of primary moyamoya disease is unclear, with genetic predisposition suggested. Genetic link to telomeric region of 17q25.3 was reported in Japanese family with autosomal dominant pattern [69]. Familial occurrence has also been reported in various ethnic groups in particular among identical twins [68, 70–77].

Clinical manifestations include headaches, cognitive impairment, mental retardation, encephalopathy, seizures, involuntary movements, transient neurological deficits, SAH, and focal neurological impairment secondary to ischemic or hemorrhagic strokes [64, 66, 78–81]. Moyamoya disease should be differentiated from secondary conditions associated with similar intracranial vascular stenotic pattern known as moyamoya syndrome (Table 16.4) [82].

In the absence of hematological, biochemical, and serologic findings, diagnosis is usually based on clinical presentation and neuroradiological and angiographic findings. Cerebral CT and MRI scans may reveal multiple infarctions or hemorrhages, often bilateral, in the distribution of the ACAs, MCAs, and watershed zones. Microbleeds are common. Cerebral atrophy is present in patients with recurrent symptoms due to progressive disease [83–87].

Angiographic findings include multiple mid-sized arterial irregularities and focal arterial stenoses or occlusion (Fig. 16.6) at the terminal portion of the ICAs bilaterally with distinct collateral channels formation at the base of the brain (Fig. 16.7). Except for the occlusion of the posterior cerebral arteries, the vertebrobasilar system is rarely involved. Six angiographic stages have been described: (1) bilateral suprasellar ICA narrowing, (2) collateral channels or moyamoya vessels at the base of the brain, (3) progressive ICA fork stenosis and prominent moyamoya vessels, (4) occlusion of the main arteries of the circle of Willis and extracranial collaterals, (5) further progression of stage 4 with prominent extracranial collaterals and disappearance of moyamoya vessels, and (6) complete absence of moyamoya vessels and major cerebral arteries with predominantly extracranial collaterals [63]. Intracranial aneurysms are common [80, 86]. The optimal treatment of moyamoya disease and timing of neurovascular intervention in symptomatic patients remain unclear. Medical therapy includes antiplatelet agents, vasodilators, and when seizures occur, antiepileptic agents. Patients with symptomatic progressive moyamoya disease are usually referred for neurovascular surgical intervention, with the goal to improve cerebral perfusion thereby halting disease progression, and thus reducing risk of stroke and clinical deterioration [87]. Surgical approaches include direct bypass with extracranial–intracranial anastomosis such as superficial temporal artery to middle cerebral artery (STA-MCA) bypass, indirect bypass such as encephalomyo-

Table 16.4 Moyamoya mimics

Cranial radiotherapy
Intracranial arteritides
Sickle cell disease
Arteriosclerosis
Neuro-oculo-cutaneous syndromes
Neurofibromatosis type 1
Tuberous sclerosis
Sturge–Weber syndrome
Hypomelanosis of Ito
Phakomatosis pigmentovascularis type IIIb
Connective tissue disorders
Systemic lupus erythematosus
Polyarteritis nodosa
Infections
Tuberculous meningitis
Bacterial meningitis
Post-varicella vasculitis
Leptospirosis
Collagen vascular disorders
Pseudoxanthoma elasticum
Fibromuscular dysplasia
Marfan syndrome
Alport syndrome
Miscellaneous
Oral contraceptive use
Brain tumor
Turner's syndrome
William's syndrome
Sneddon's syndrome
Homocystinuruia
Type I glycogenosis
Sarcoidosis
Hirschsprung's disease
Down syndrome
Ulcerative colitis

synangiosis, encephaloduroarteriosynangiosis, encephalomyoarteriosynangiosis, omental pedicle transposition, durapexy, multiple cranial burr holes, multiple cranial burr holes with vessel synangiosis, or combined revascularization approaches [78, 82, 87–94]. Given the rarity of the disorder and of lack evidence-based guidelines, best surgical treatment options remain unknown. Intraoperative video angiography using indocyanine green is a promising technique to assess bypass graft patency in patients undergoing direct bypass with STA-MCA anastomosis [95].

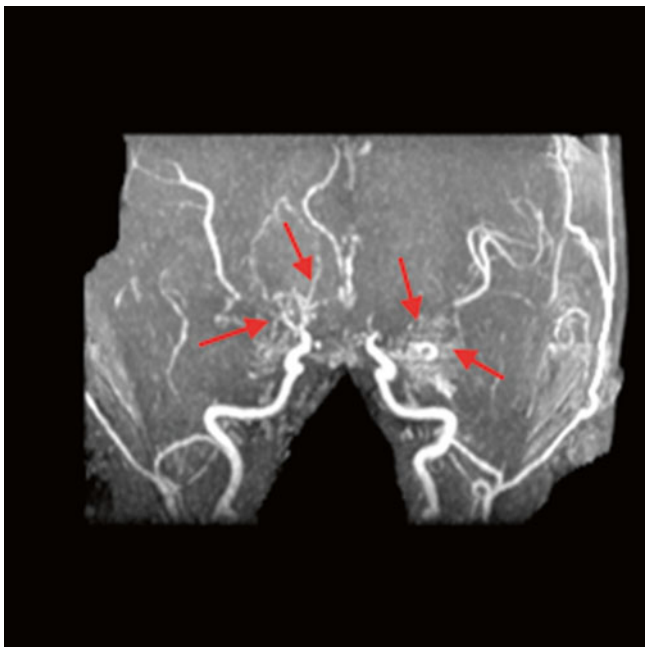

Fig. 16.6 MRA showing high-grade stenosis or occlusion of the supraclinoid ICA with subtle increased vascularity noted at the base of the skull adjacent to the cavernous sinus due to moyamoya collateral vessels

Radiation Induced Vasculopathy

Radiation-induced vasculopathy is a common late complication of cranial radiation therapy. The condition is of particular importance in children treated with intracranial radiation for parasellar brain tumors and craniopharyngiomas [96–99]. Radiation-induced vasculopathy may develop months to years after radiotherapy, a risk persisting until adulthood (Fig. 16.8). The mechanism by which vasculopathy occurs after cranial irradiation remains unclear. Small and medium arteries are primarily affected, with progressive luminal narrowing due to endothelial thickening and medial fibrosis. Radiation injury to the large vessels is rare, usually occurring following radiation therapy for vascular malformations and pituitary tumors (Fig. 16.9). Head and neck radiation for the treatment of epithelial cancers or lymphomas is associated with delayed carotid atherosclerosis. Higher brain radiation with doses exceeding 50 Gy confers increased risk of radiation-induced vasculopathy leading to progressive cerebral arterial occlusive disease mimicking moyamoya syndrome [98, 100].

Clinical manifestations include encephalopathy, seizures, and focal neurological deficits secondary to cerebral ischemia. Hemorrhages from radiation-induced vascular

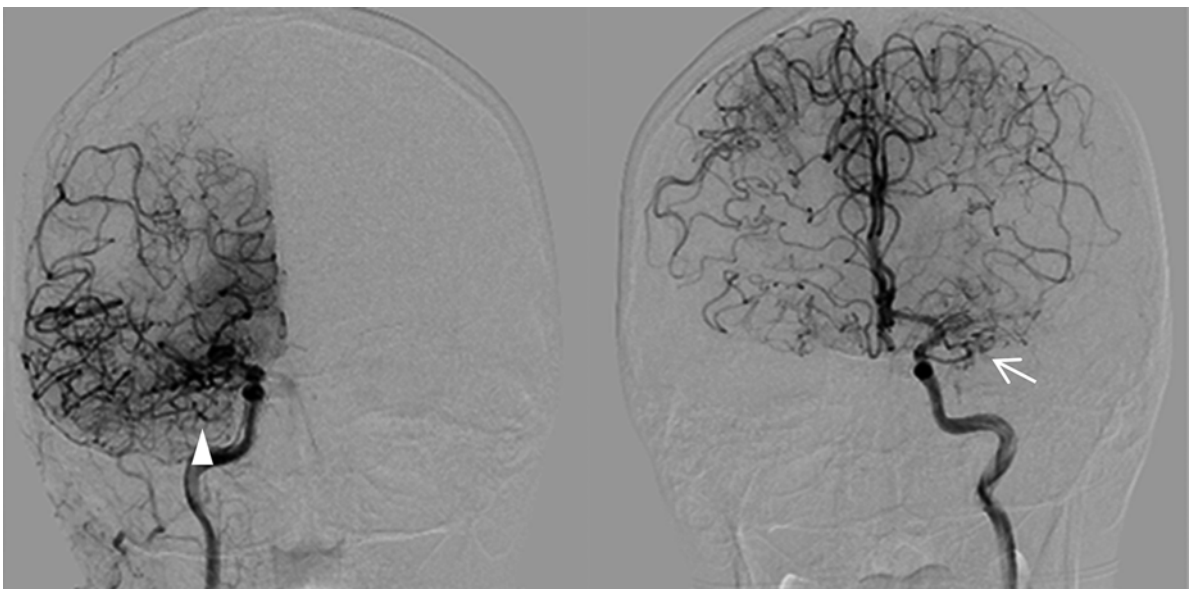

Fig. 16.7 Bilateral supraclinoid ICA stenosis/MCA occlusion (*arrow*) on cerebral angiogram with extensive collaterals through lenticulostriates and thalamoperforates collaterals (*arrowhead*) consistent with moyamoya disease

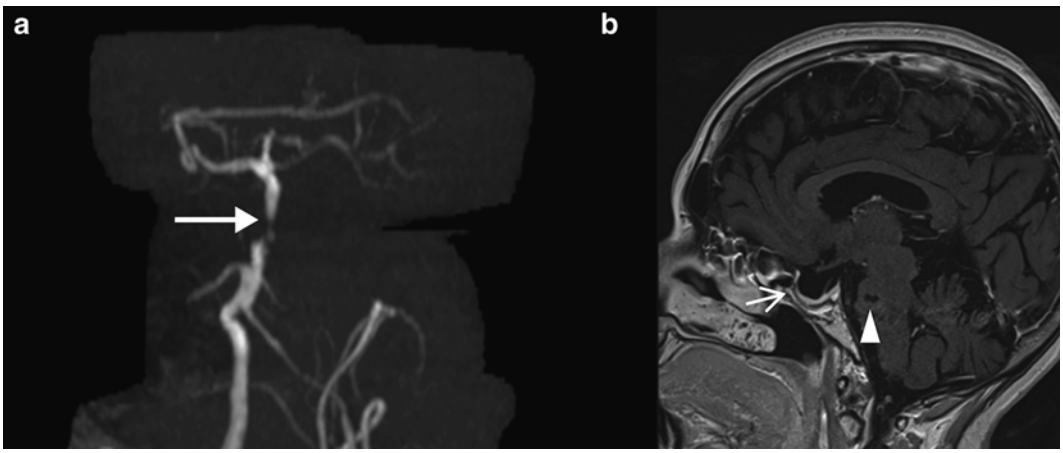

Fig. 16.8 (**a**) Radiation induced basilar artery stenosis and PCA stenosis on MRA head in a patient with cranial radiation for pituitary macroadenoma. (**b**) Post-surgical changes in the pituitary fossa (*arrow*), with hypodensity in the basis pontis due to ischemic changes (*arrowhead*) on sagittal gadolinium enhanced MRI brain

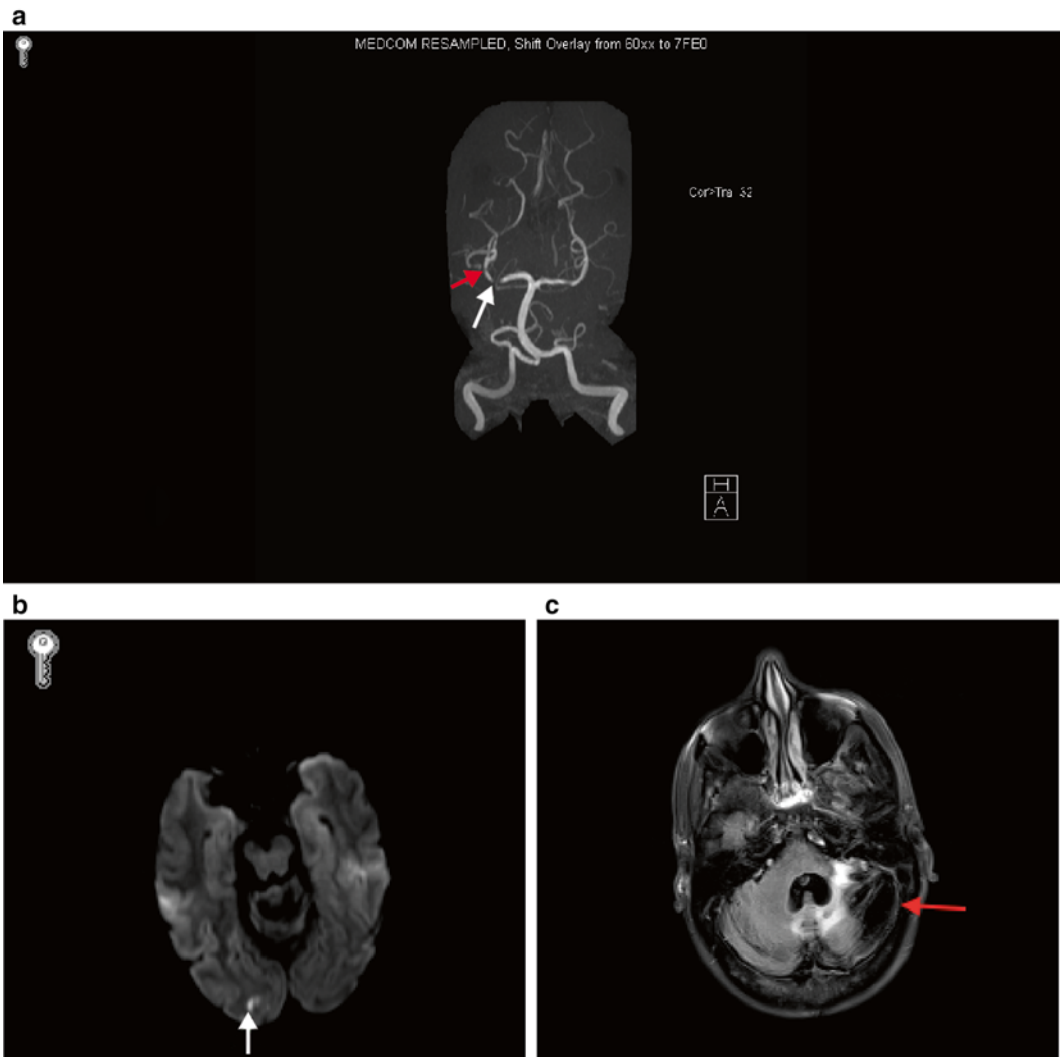

Fig. 16.9 (**a**) Radiation-induced vasculopathy changes on MRA head with irregular stenosis of the PCAs bilaterally in a 49-year-old woman with visual field defects and focal seizures. She had a medulloblastoma resected 25 years ago followed by cranial radiation therapy. (**b**) DWI shows area of restricted diffusion in the right occipital lobe. (**c**) Post-surgical changes are noted in left cerebellum on FLAIR sequence

abnormalities are rare, often instead resulting from a chemotherapy effect on hemostatic system [98, 101, 102].

There is no effective treatment for radiation-induced vasculopathy. Physicians should focus on reducing radiation doses. The benefit of antiplatelet agents has not been established. Revascularization surgery may be considered in patients' progressive arteriopathy (moyamoya syndrome) and recurrent neurological symptoms. In radiation-induced symptomatic carotid artery stenosis, surgical treatment with carotid endarterectomy may be equally effective as in non-irradiated carotid atherosclerosis [101, 102].

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by thunderclap headaches, usually severe, with or without seizures or other neurologic symptoms, and segmental constriction of cerebral arteries, which resolves spontaneously within 3 months (Table 16.5) [103–105]. RCVS is also known as Call-Fleming syndrome, CNS pseudo-vasculitis, postpartum angiopathy, idiopathic thunderclap headache with reversible vasospasm, isolated benign cerebral vasculitis, and migraine angiitis. RCVS may occur in susceptible patients such as postpartum women, even without preeclampsia or eclampsia, due to transient failure of regulation of cerebral arterial tone with sympathetic overactivity [103, 106, 107]. Migraineurs with aura are more susceptible to the disease, especially when using vasoactive drug such as triptans or ergot-alkaloids. Other precipitants include nasal decongestants containing pseudoephedrine and ephedrine, illicit drugs including cannabis, cocaine, lysergic acid diethylamide, methamphetamine, selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors, catecholamine-secreting tumors, and intravenous immunoglobulin therapy (Table 16.6) [103, 107, 108]. RCVS is more common in women in the mid-40s, although it has been reported in children and in adults in every age group [104]. RCVS is often underdiagnosed with an unknown incidence. While relatively benign, serious ischemic and hemorrhagic events may occur in 5–10 % of patients, thus resulting in permanent neurological deficit [105, 108, 109]. Posterior reversible ischemic encephalopathy syndrome (PRES) may occur [103, 105–107].

The most common presentation includes recurrent severe rapidly escalating thunderclap headache (Table 16.7). Unlike in SAH, the headaches in RCVS are short-lived, lasting minutes to days, often recurrent, and gradually dissipating within 3 weeks of symptom-onset [103, 108, 110]. Patients typically endorse some form of exertional activity as a trigger prior to the onset of headaches. Seizures may occur especially when PRES develops. Transient neurological symptoms in particular visual disturbances mimicking migraine aura are common. When persistent focal deficit lasts beyond 1 h, stroke is suspected. In the absence of cerebral ischemia or ICH, neurological examination is usually normal [103, 108]. A surge in blood pressure may often occur due to the pain intensity.

Table 16.5 International Headache Society Diagnostic Criteria for Reversible Cerebral Vasoconstriction Syndrome

Headache, with or without focal deficits and/or seizures with 'strings and beads' appearance
Headache on angiographic studies' with either or both of the following characteristics
Recurrent during ≤1 month, and with thunderclap onset
Triggered by sexual activity, exertion, Valsalva maneuvers, emotion, bathing and/or showering
No new significant headache occurs >1 month after onset

Adapted from The International Classification of Headache Disorders, 3rd edition (beta version)

Table 16.6 Conditions associated with increased risk of reversible cerebral vasoconstriction syndrome

Postpartum period
Migraine with aura
Vasoactive drugs
Migraine specific medications (e.g., triptans and ergot-alkaloids)
Nasal decongestants (e.g., phenylpropanolamine, pseudoephedrine, ephedrine)
Recreational drugs (e.g., cannabis, cocaine, LSD, methamphetamine)
Other drugs
SSRIs and SNRIs
Intravenous immunoglobulin therapy
Immunosuppressants
Others
Pheochromocytoma
Sexual activity
Porphyria
CSF hypotension

LSD lysergic acid diethylamide, *SSRIs* selective serotonin reuptake inhibitors, *SNRIs* serotonin–norepinephrine reuptake inhibitors, *CSF* cerebrospinal fluid

Table 16.7 Causes of thunderclap headache

Subarachnoid hemorrhage
Intraparenchymal hemorrhage
RCVS
CCAD
Cerebral dural venous sinus thrombosis
Aseptic or infective meningitis
Colloid cyst
Pituitary apoplexy
Spontaneous intracranial hypotension
Primary thunderclap headache
Coital headache

Blood workup including ancillary laboratory tests with complete blood count (CBC), metabolic panel, and vasculitis panel is noncontributory. Cerebrospinal fluid (CSF) analysis is typically normal, sometimes with slightly elevated lymphocytic white blood cell (WBC) count.

MRI brain is usually normal. SAH, ICH, and cerebral infarction may occur. PRES-like findings are encountered in 10 % of patients (Fig. 16.10) [103, 104, 109]. Neuroangiographic studies with MRA or CTA usually show diffuse vasoconstriction in the various arteries of the circle of Willis, both in the anterior and in the posterior circulation distribution (Fig. 16.11). Resolution of vasoconstrictive changes of the affected vessels and new constriction in previously normal vessels is not uncommon, with maximum changes seen within 2 weeks of initial onset of symptoms. Complete or substantial normalization of arteries is observed on follow-up angiographic studies within 12 weeks of clinical onset. Differential diagnosis includes aneurismal SAH, ICH, CCAD, meningitis, cerebral dural venous sinus thrombosis (CDVST), pituitary apoplexy, colloid cyst of the third ventricle, primary angiitis of the central nervous system (PACNS), and idiopathic primary thunderclap headache. The diagnosis of RCVS is made by exclusion when all other conditions are ruled out. RCVS is usually a uniphasic and self-limiting condition.

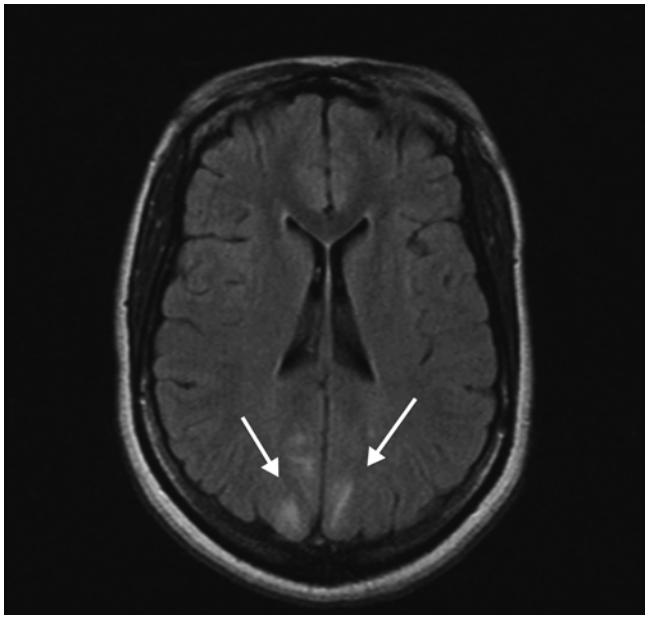

Fig. 16.10 MRI FLAIR sequence demonstrates moderate signal intensity changes in the occipital lobes bilaterally typical of PRES

In the absence of randomized clinical trials, treatment for RCVS remains conservative, aiming at alleviating symptoms and preventing complications. Analgesics and antiepileptic agents are often administered to alleviate headaches and to prevent seizure recurrence. Prophylactic use of antiepileptic drugs is not advocated [103, 108]. Early administration of calcium channel blockers such as nimodipine or verapamil, and magnesium sulfate is often recommended. While short courses of glucocorticosteroids may help alleviating the cephalgic pain, they do not seem to prevent clinical deterioration in RCVS and thus should be avoided, in particular in patients with ischemic and hemorrhagic strokes [103, 107]. In refractory cases with rapidly deteriorating symptoms, intra-arterial administration of milrinone,

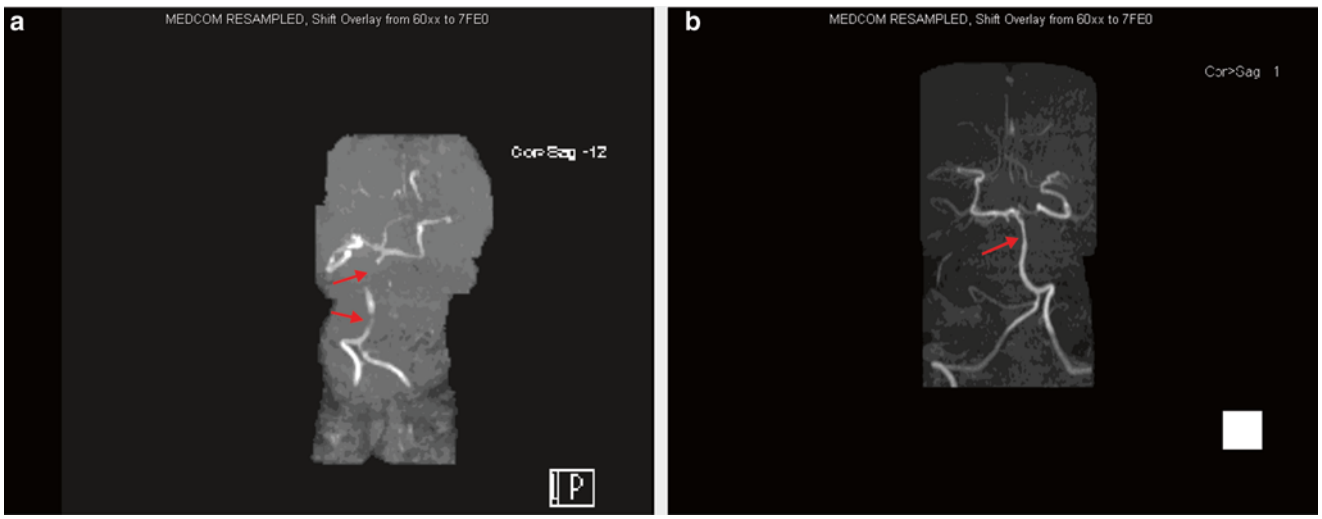

Fig. 16.11 (**a**) MRA brain shows areas of severe vascular narrowing in the mid and distal basal artery (*arrow*) and the posterior cerebral arteries (*arrowheads*) in a 42-year-old woman with intractable migraine with aura and hyperemesis gravidarum. (**b**) Follow-up study at 3 months interval demonstrates near normalization of vessel caliber and contour

verapamil or nimodipine may be considered [111, 112]. Intra-arterial balloon angioplasty should be restricted to patients with rapid clinical progression when all other treatment measures have failed [113, 114].

Unilateral Arteriopathy of Childhood

A vasculopathy unique to children is unilateral arteriopathy of childhood. Also known as transient cerebral arteriopathy (TCA), this condition is a non-progressive, often reversible, unilateral vasculopathy characterized by infarction in the lateral lenticulostriate artery territory due to non-progressive unilateral arterial disease affecting the supraclinoid ICA and its proximal branches. The hallmark of TCA is normalization or significant improvement of initial arterial stenotic changes on follow studies at 3–6 months interval. The pathophysiology of TCA is not well understood. A transient inflammatory process has been implicated, and a history of chickenpox preceding the ischemic event has been reported in 44 % of patients [115, 116]. The condition should be suspected in children with acute ischemic stroke especially with recurrent symptoms when other etiologies of cerebral infarctions are excluded [117, 118]. Vascular imaging reveals unilateral subcortical infarctions affecting the basal ganglia and internal capsule, with unilateral multifocal or segmental narrowing in the arterial wall of the distal ICA, proximal ACA or MCA [117, 118]. Transient worsening of the arterial lesions may occur up to 6 months from the initial symptom-onset in 20 % of patients, making differentiation from other intracranial causes of vasculopathies such as moyamoya disease and cerebral vasculitis a challenging process to the treating physician [119].

Despite its reversible course, children with TCA are left with focal neurological deficits due to the cerebral infarctions. Poor functional outcome tends to be more frequent in patients with initially progressive arteriopathy. Treatment includes antithrombotic agents, sometimes in combination with antiviral drugs [120].

Central Nervous System (CNS) Vasculitides

CNS vasculitides are uncommon cause of strokes in children and young adults leading to neuropsychiatric manifestations and devastating neurological deficits. They consist of a heterogenous group of systemic disorders, which include infection-related vasculitides, non-infectious inflammatory systemic vasculitides, autoimmune vasculitides, drug induced vasculitis, and the rare PACNS (Table 16.8).

Table 16.8 Classification of cerebral vasculitides

Primary angiitis of the CNS
Amyloid β-related angiitis
Systemic vasculitides
Large vessel (e.g., GCA, Takayasu's)
Medium vessel (e.g., Kawasaki, polyarteritis nodosa)
Small vessel (e.g., ANCA-associated vasculitis, Churg–Strauss)
Hypersensitivity vasculitis (e.g., Henoch–Schönlein purpura, drug-induced)
Vasculitis associated with connective tissue disorders (e.g., SLE, Sjogren's)
Others (e.g., Behçet's disease, neurosarcoidosis, Kohlmeier–Degos syndrome)
Infectious vasculitides
Fungal (e.g., aspergillosis, mucormycosis, candidiasis, coccidiomycosis)
Bacterial (e.g., meningitis)
Viral (e.g., HIV, varicella zoster)
Spirochetal (e.g., syphilis)
Rickettsial (e.g., cat scratch disease, Rocky Mountain spotted fever)
Mycobacterial (e.g., tuberculosis)
Parasitic (e.g., amebiasis)

Primary Angiitis of the Central Nervous System

PACNS is a rare vasculitic disorder involving the small and medium leptomeningeal arteries, with an annual incidence of 2.4 per one million persons per year. Since first described by Cravioto in 1959, the condition has been increasingly recognized as a devastating cause of recurrent stroke in young adults [121–123]. The disease is more common in men in the fourth decade of age, and solely affects the brain and spinal cord. Neurological manifestations include chronic nonspecific headaches, behavioral abnormalities, cognitive dysfunction, seizures, meningeal inflammation, multifocal neurological deficits, and recurrent strokes [121, 123–125].

Serological workup and lumbar puncture analysis are usually non-diagnostic. CSF analysis is necessary to exclude infective etiologies and other systemic conditions that may mimic PACNS. Findings are nonspecific, with mild pleocytosis in 80–90 % of patients, normal glucose and CSF protein. Diagnostic criteria include the presence of an unexplained neurologic deficit, in the absence of systemic vasculitides, and angiographic or histopathologic CNS arteritic process [121, 124].

Findings on MRI of brain are nonspecific with multiple infarctions of various ages in both cortical and subcortical distributions. Angiographic findings are also nonspecific, with a low sensitivity and specificity of less than 25 %. In the appropriate clinical scenario, the findings of multiple

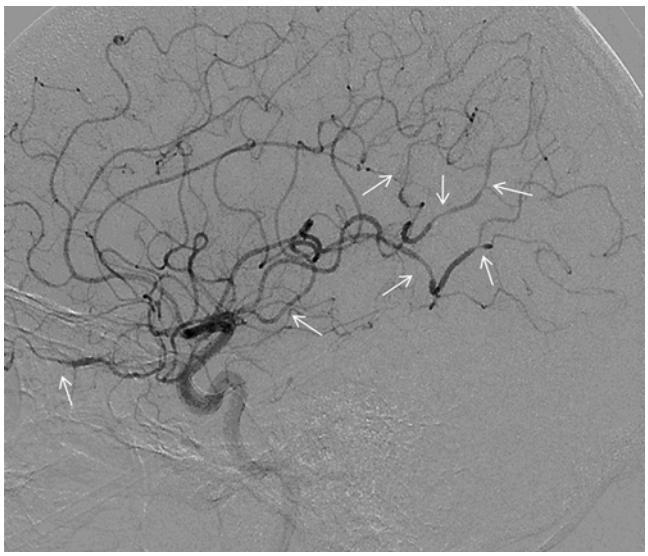

Fig. 16.12 Cerebral angiogram showing multiple irregularities in the MCA and ACA branches in PACNS

subcortical and cortical infarcts on CT or MRI brain, together with the presence of arterial beading, is suggestive of the condition (Fig. 16.12). Brain biopsy with sampling of the leptomeninges is the gold standard, but also carries a low yield. A negative brain biopsy does not preclude the diagnosis [125, 126].

Differential diagnosis includes RCVS and secondary causes of cerebral vasculitis. Early recognition is crucial as treatment with corticosteroids with or without cytotoxic drugs can often prevent serious outcomes [126]. The disease if often progressive; if untreated, prognosis is poor.

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is characterized by amyloid β deposition in the media and adventitia of leptomeningeal and cortical vessels [127, 128]. Amyloid β-related angiitis (ABRA) is a rare complication of CAA resulting from a granulomatous inflammatory response to beta amyloid (Aβ) deposition in the vessel walls [129–131]. The condition should be differentiated from PACNS, and from the perivascular non-destructive inflammatory infiltration or CAA-related inflammation (CAA-RI). Clinical symptomatology includes acute or subacute cognitive decline, headaches, seizures, uveo-meningitis, and focal neurological deficits [127, 132]. Unlike PACNS, ABRA often affects people of older age group usually in the seventh decade, without gender predilection [129]. Except for elevated erythrocyte sedimentation rate (ESR), serological markers of inflammation are usually normal. CSF abnormalities are common but nonspecific, including mild pleocytic lymphocytosis, elevated protein, and rarely oligoclonal bands. CSF tau and Aβ 41 are usually normal. APOE4 may be present in 70 % of patients [130, 131]. MRI characteristics include hyperintensities on T2-weighted image or fluid-attenuation inversion recovery (FLAIR) with minimal gadolinium-enhanced leptomeninges. The presence of microbleeds at the cortico-subcortical junction is often seen on susceptibility-weighted images. Cerebral infarcts may occur. Unlike non-inflammatory CAA, ICHs are uncommon [129, 133]. Brain biopsy is the gold standard with findings of transmural granulomatous vasculitis changes superimposed on CAA histological characteristics. Majority of patients with ABRA responds well to steroids and immunosuppressant agents such as cyclophosphamide [128, 129, 131].

Systemic Vasculitides

CNS vasculitis may occur secondary to idiopathic systemic and hypersensitivity vasculitis, autoimmune conditions, collagen vascular disorders, and various CNS infections. Clinical manifestations are diverse; fever, generalized malaise, weight loss, and fatigue are common. There is usually multi-organ involvement with renal, cardiac, arthropathic, dermatological, ocular, and pulmonary manifestations. The spectrum of neurological symptoms is broad and nonspecific. Headaches, cognitive disturbances, psychiatric manifestations, meningoencephalitis, myelopathy, myopathy, peripheral neuropathy, TIA-like symptoms, and recurrent ischemic or hemorrhagic strokes may occur. Large vessel arteritides are more commonly associated with cerebrovascular events. These include giant cell arteritis (GCA) and Takayasu's disease.

GCA is a chronic granulomatous vasculitis mainly affecting the aorta and its branches, in particular the cranial arteries derived from the extracranial carotid arteries. It is the most common systemic vasculitis among women in the fifth decade of age, with an incidence of 3.5 per 100,000 per year [134, 135]. A dull temporal headache is reported in 90 % of patients, followed by visual symptoms, jaw claudication, weight loss, and fatigue. Other systemic manifestations may include fever, anorexia, night sweats, and muscle aches and stiffness due to polymyalgia rheumatica. Scalp tenderness and temporal artery swelling may occur. Visual loss, cerebral ischemia, and tongue infarction are the most feared complications. Cerebral infarctions occur in 3–4 % of patients with GCA. They are often due to occlusion of an extracranial segment of the vertebral or carotid arteries or their branches. Occlusion of the short posterior ciliary artery leading to choroidal ischemia results in anterior ischemic optic neuropathy (AION), the most common cause of GCA-related permanent visual loss [135, 136]. The diagnosis is straightforward in the presence of headache, visual loss, and elevated ESR. Temporal artery biopsy remains the gold standard for the diagnosis. Ultrasonography may play a role in selecting

biopsy site [135, 137]. MRI and positron emission tomography may help detect any ischemic and active inflammatory changes. Despite the absence of good evidence from clinical trials, high doses corticosteroids therapy (40–60 mg of prednisone) is the treatment of choice and should be initiated even when ESR is normal or when biopsy results are inconclusive. Alternatively, steroids-sparing drugs such as methotrexate should be considered in patients intolerant to steroids or who require prolonged steroids therapy [134, 136]. Combination therapy with methotrexate and steroids is a safe alternative to steroids-only treatment [138].

Takayasu's arteritis or pulseless disease is a chronic granulomatous large vessel panarteritis predominantly affecting the aortic arch or its branches [139]. Unlike GCA, the condition usually affects young women under the age of 40. Clinical symptoms include renovascular hypertension due to renal artery stenosis, intermittent claudication, decreased peripheral pulses, headaches, visual disturbances, focal neurologic deficits, cerebral ischemia, and rarely PRES-like clinical manifestations and imaging findings [139–141]. Laboratory workup is nonspecific, often revealing a normochromic or hypochromic anemia, leukocytosis, elevated ESR, and impaired renal function. Angiographic findings may include renal artery stenosis, as well as narrowing of and wall thickening within the aortic arch and its major branches. Medical treatment includes steroids and immunosuppressant therapies with methotrexate, mycophenolate mofetil, or azathioprine. Endovascular intervention should only be considered in patients with progressive symptoms refractory to conventional treatment. As a general rule, endovascular intervention should be avoided during the active phase of the disease due to a very high rate of arterial restenosis [142].

Kawasaki disease is a multisystemic vasculitis affecting the medium and small vessels, more commonly in infants and young children [143–148]. The disease manifests as an acute febrile mucocutaneous inflammation, with lymphadenitis, coronary artery inflammation, and widespread aneurismal formation. Cerebral infarctions are uncommon [149].

Polyarteritis nodosa is an uncommon systemic necrotizing pan-arteritis of small and medium-sized arteries, which may be associated with pseudo-aneurysmal formation. It affects the heart, kidneys, skin, and gastrointestinal tract. The cerebral vessels are rarely involved. Intraparenchymal and SAH may occur [143].

While neuropsychiatric symptoms and peripheral nervous system involvement are common in systemic lupus erythematosus (SLE), true immune complex-mediated CNS vasculitis and lupus cerebritis are uncommon. When cerebral ischemia occurs, it often results from cardiac embolism associated with Libman–Sacks endocarditis, or due to the presence of circulating antiphospholipid antibodies leading to thrombotic arterial occlusion [150–152]. Cerebral venous and dural sinus thrombosis may occur [149].

Small vessel vasculitides such as ANCA-associated small vessel vasculitis, microscopic polyangiitis, granulomatous polyangiitis, and Cogan's syndrome rarely affect the CNS.

Sjogren syndrome is a chronic inflammatory autoimmune condition with multiorgan involvement including sicca symptoms, peripheral and cranial neuropathy, and myelopathy. CNS is rarely involved when cerebral dural venous sinus thrombosis occurs. Cerebral ischemia is rare [144].

Behçet's disease is a multisystem inflammatory disease affecting the arteries and veins, characterized by relapsing oral and genital ulcerations, recurrent uveitis, iritis, and synovitis [153, 154]. Small vessel arteritis, thromboangiitis, cutaneous vasculitis, and cerebral aneurysms may occur [155, 156]. Clinical manifestations include headaches, cranial neuropathies, vestibulopathy aseptic meningitis, seizures, and cerebral venous thrombosis. Cerebral arterial vasculitic involvement and ischemic strokes are rare [153, 154, 157].

Sarcoidosis is a rare granulomatous disease of unknown etiology with multi-organs involvement. It primarily affects the eyes, skin, and lungs. Neurosarcoidosis with involvement of the brain parenchyma, hypothalamic–pituitary pathway, meninges, cranial nerves, and cerebral vasculature is not uncommon. Cerebral infarctions and transient ischemic attacks (TIAs) may rarely be the initial presenting manifestations of the disease [156]. ICH has been reported in <0.6 % of cases of neurosarcoidosis [158].

Kohlmeier–Degos, or malignant atrophic papulosis, is a rare systemic thrombo-obliterative vasculopathy of the medium and small size vessels, characterized by cutaneous, gastrointestinal, and neurological involvement [159]. Thrombosis of the cerebral arteries and intracerebral hemorrhage may occur due to coagulopathy or primary endothelial dysfunction [160]. Death usually occurs within 2–3 years from the onset of systemic involvement.

Other rare causes of CNS vasculitis include Henoch–Schönlein purpura, infectious etiologies and toxicity related to cancer treatment [161–163]. Chemotherapy agents associated with CNS vasculopathies and dural sinus thrombosis include, but are not limited, to L-aspariginase, methotrexate, BCNU, cisplatin, cyclophosphamide, cyclosporine, and tacrolimus [162, 164–166].

Various infectious etiologies may be associated with increased risk of ischemic and hemorrhagic strokes through various mechanisms including thrombophlebitis, vessel invasion, and cardioembolism [163, 167–175]. Of particular interest is syphilitic arteritis, an obliterative endarteritis involving the large and medium-sized vessels (Heubner arteritis), and less frequently the small cerebral arteries of the brain, meninges, and spinal cord (Nissl arteritis). Meningovascular syphilis occurs 5–10 years after the onset of untreated syphilis. Early manifestations are not uncommon in patients with human immunodeficiency virus (HIV) infections [35, 174]. Neurological symptoms include behavioral

changes, seizures, and focal neurological deficits. When cerebral ischemia occurs, it most commonly affects the MCA and its branches. CSF pleocytosis and elevated protein, together with a reactive serology is suggestive. Cerebral angiography often demonstrates a diffuse angiopathy with concentric narrowing of the large vessels, and focal narrowing and dilatation of the small vessels. Aortic dissection may occur secondary to aortitis. Penicillin remains the drug of choice for neurosyphilis.

In summary, the differential diagnosis of CNS vasculitis is diverse. The diagnosis is based on clinical presentation with progressive neurological deficit, presence or absence of multisystem involvement, serological testing, neuroimaging studies with CT scans and MRI brains, and cerebral angiographic findings (Table 16.9). Neurological manifestations are broad and nonspecific. Serological findings are often nonspecific. CSF may be normal or may demonstrate nonspecific changes consistent with an inflammatory process, including mild lymphocytic pleocytosis and increased protein. CSF analysis and detailed serological and hypercoagulability testing are however necessary to exclude infective etiologies and secondary causes of vasculitis including systemic and connective tissue disorders. Accurate diagnosis is essential to prevent disease progression and to initiate management strategies and to secure precise treatment decisions. Advances in neuroimaging techniques have helped distinguish inflammatory from non-inflammatory vascular lesions. Digital subtraction angiography often shows segmental narrowing affecting multiple intracranial vessels. Tissue diagnosis with brain and leptomeningeal biopsy remains the gold standard.

Management of patients PACNS or multisystem secondary vasculitis is aimed at halting the inflammatory process and thus the disease progression. Combination of corticosteroids and immunosuppressant agents (mainly cyclophosphamide) has been shown to produce favorable clinical outcome. Other agents such as methotrexate, azathioprine, and rituximab have been used with variable results. While antiplatelet agents may be considered in patients with ischemic strokes, their use remains arbitrary in the absence of randomized clinical trials.

Table 16.9 Suggested workup for suspected CNS vasculitis

Ancillary blood tests, including CBC, BMP, and LFT
ESR and hsCRP
Serum complements
Anticardiolipin antibodies, β_2 glycoprotein-1 antibody, lupus anticoagulant
Serum and urine electrophoresis
Hepatitis panel
Haptoglobulin
Thyroid function tests
Connective tissue workup (RF, ANA panel, c-and pANCA, MPO-ANCA; anti-SSA and anti-SSB, anti-endothelial antibodies, anti-glomerular basement membrane)
Urine drug screen
Infectious screening (blood cultures, HIV, mycoplasma PCR and serology, syphilis serology, herpes simplex virus, varicella zoster, Epstein-Barr virus cytomegalovirus)
CXR
CT chest and tissues
Lumbar puncture and CSF analysis (cell count, protein, sugar, gram stain, cultures, ACE level, FTA)
MRI brain with gadolinium enhancement
MRA or CTA intracranial vasculature
Cerebral angiogram
Brain biopsy
Corresponding tissue biopsy (temporal artery, skin, bronchial, renal, sural nerve)

CBC complete blood cell count, *ESR* erythrocyte sedimentation rate, *hsCRP* high sensitivity C-reactive protein, *BMP* basic metabolic panel, *LFT* liver function tests, *LDH* lactate dehydrogenase, *RF* rheumatoid factor, *ANA* antinuclear antibody, *ANCA* antineutrophil cytoplasmic antibodies, *MPO* myeloperoxidase, *ACE* angiotensin converting enzyme, *HIV* human immunodeficiency virus, *PCR* polymerase chain reaction, *CSF* cerebrospinal fluid, *FTA* fluorescent treponemal antibody

Anatomical Vascular Anomalies

Common anatomic variations in the configuration of the circle of Willis and its branches have been linked to the increased risk of ischemic or hemorrhagic strokes. These include but are not limited to vessel fenestration and duplication, hypoplasia and agenesis, coiling, tortuosity, elongation, and kinking. While asymptomatic in the majority, such anatomical variations may increase the risk of stroke thought different mechanisms including compression, dilatation of vascular channel, and intracranial aneurismal formation [175, 176].

Agenesis and hypoplasia of one or both internal carotid arteries is a rare, usually asymptomatic developmental anomaly that occurs during the early phase of embryonic development. Initially reported by Verbiest in 1954, ICA hypoplasia is detected in less than 0.01 % of the population [176, 177]. Flow to the anterior circulation is achieved through collateral pathways of the circle of Willis via dilated basilar artery and posterior communicating arteries, or through transcranial anastomosis between the extracranial and intracranial carotid systems, or through persistent embryonic vessels. Failure of collaterals, arterial compression, or dilated vascular channels may lead to cerebral ischemia. Associated intracranial aneurysms occur in 25–35 % of patients and are often responsible for intraparenchymal and subarachnoid hemorrhages [178].

Duplicates or fenestrations of the intracranial arteries are rare congenital anomalies. Unlike the anterior circulation vessels, fenestration is more common in the vertebrobasilar system, with basilar artery fenestration observed in around

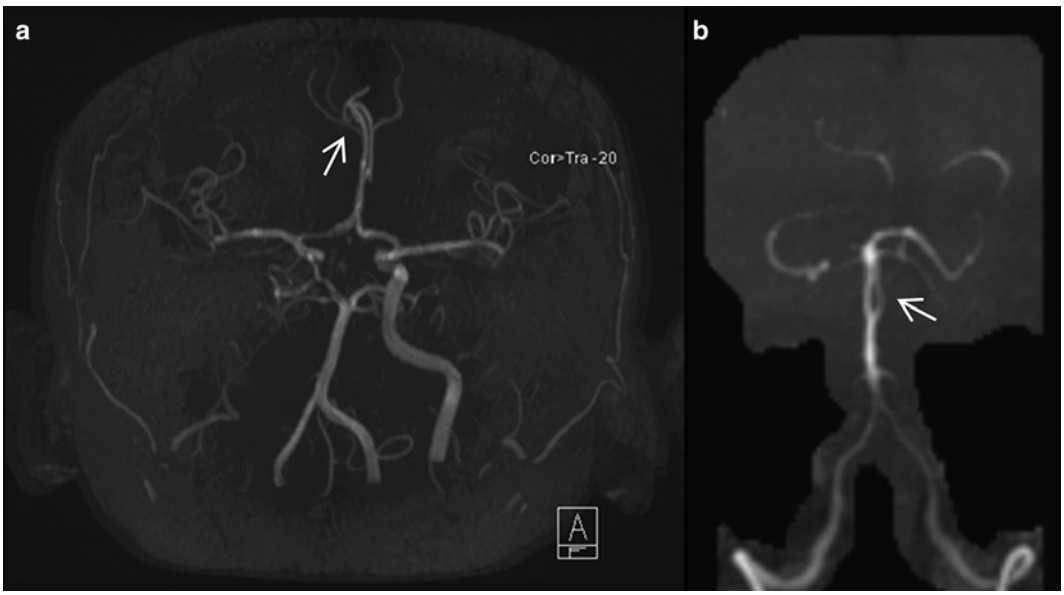

Fig. 16.13 MRA head showing (**a**) fenestrated ACA, and (**b**) basilar artery

5 % of the general population [179] (Fig. 16.13). Arterial fenestrations are usually asymptomatic. When saccular aneurysms form at the site of the fenestration or duplication, subarachnoid hemorrhage may occur [178].

Conclusion

Several non-atherosclerotic vasculopathies are responsible for ischemic strokes in particular in children and young adults. CCADs are among the most common non-atherosclerotic vasculopathies. Other conditions such as radiation-induced vasculopathy, moyamoya disease, and cerebral vasculitis are rare but potentially treatable conditions that should be considered in particular in young patients with recurrent cerebral ischemic events. Accurate diagnosis is necessary to initiate the appropriate treatment, to slow disease progression, and to improve outcome.

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Secondary Prevention after Ischemic Strokes due to Hypercoagulable States

17

Salvador Cruz-Flores

Case Presentation A 38 year-old woman presented to the hospital with a severe headache that started 24 h before her arrival to the emergency room. On the day of her visit, she was found confused at home complaining of visual problems, especially in the left side of her field of vision. Her past medical history was significant only for repeated miscarriages and a deep vein thrombosis that was treated with warfarin, although she stopped this medication several months prior to presentation. On her initial exam, she was awake and had normal speech, but was disoriented to place and time. She had a left homonymous hemianopia, and the rest of her exam was unremarkable. A brain MRI demonstrated right medial temporo-occipital infarction which extended to the right thalamus. CT angiography of the head and neck showed attenuated flow in the right posterior cerebral artery, but no areas of arterial stenosis or occlusion. A transesophageal echocardiogram was normal. Results of a hypercoagulable panel revealed that anticardiolipin antibodies IgG and anti β2 glycoprotein were elevated.

Typical questions to ponder in a case such as this include:

1. When should we suspect a hypercoagulable state as the cause of a stroke?
2. What is the appropriate timing/setting for hypercoagulable testing and what type of prothrombotic investigations can be justified in a patient with an ischemic stroke?
3. What is the impact of various tests on the treatment plan?
4. How should this patient be treated to prevent stroke recurrence?

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Introduction

Coagulation disorders are the cause of up to 4 % of all ischemic strokes, and the prevalence is likely higher among patients <40 years old or patients without conventional vascular risk factors such as hypertension, diabetes, hypercholesterolemia, or smoking [1]. The coagulation cascade with its intrinsic and extrinsic pathways and their interaction with the endothelium form a complex system that can have abnormalities at different levels, resulting primarily in thrombophilia, and secondarily in the manifestation of thromboembolic events. While most of these abnormalities are associated with venous thromboembolism, some like the antiphospholipid antibody syndrome are linked to arterial thrombosis [1–3]. It is worth noting that systemic thromboembolism could also increase the risk of stroke in the presence of a patent foramen ovale [4, 5].

Hypercoagulable states can occur as inherited or primary disorders such as Protein C deficiency or Factor V Leiden mutation, or as secondary conditions in the context of a systemic illness, i.e., cancer, nephrotic syndrome, among others (Table 17.1). In this chapter the most common hypercoagulable disorders causally associated with ischemic stroke are reviewed.

Protein C Deficiency

Protein C, protein S, and antithrombin are key regulatory proteins in the coagulation cascade. Protein C is a vitamin K-dependent serine protease that is expressed in the endothelial cells and is activated when thrombin binds to thrombomodulin. The activated Protein C (APC) in turns inactivates factors Va and VIIa inhibiting thrombosis. As such, Protein C controls the generation of prothrombin. In addition, Protein C inhibits plasminogen activator inhibitor-1 (PAI-1). Protein C abnormalities are the result of a deficient quantity (type 1) or deficient function (type 2) [5, 6].

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Table 17.1 Hypercoagulable states[a]

Primary hypercoagulable states	Secondary hypercoagulable states
Protein C deficiency	Antiphospholipid antibody syndrome (Hughes syndrome)
Protein S deficiency	Protein C deficiency
Factor V Leiden mutation	Protein S deficiency
Prothrombin gene 20210A mutation	Myeloproliferative disorders
Antithrombin deficiency	Cancer
Elevated thrombin activatable fibrinolysis inhibitor	Pregnancy
Elevated factor VIII	Oral contraceptives
Elevated factor IX	Iron deficiency anemia
Fibrinogen disorders	Hemoglobinopathies
Methylenetetrahydrofolate reductase gene mutation (MTHFR)	Paraproteinemia
	Disseminated intravascular coagulation
	Nephrotic syndrome

[a]Not fully inclusive list of frequent hypercoagulable disorders

Primary protein C deficiency is an autosomal dominant disorder that is present in about 0.2 % of the general population [7]. Homozygous protein C deficiency is not compatible with life and usually manifests as neonatal purpura fulminans [8]. The heterozygous form is associated with recurrent thrombosis, relatively younger persons, and most of the thromboembolic events emanate from the venous system …. The majority of patients with primary protein C deficiency present with thrombotic events before age 45 years. Secondary causes of protein C deficiency include liver disease, disseminated intravascular coagulation (DIC) in severe infections, acute respiratory distress syndrome, and administration of L asparaginase or methotrexate [6].

Protein S Deficiency

Protein S is a glycoprotein that is also vitamin K-dependent. Its function is that of a catalyst or cofactor for the APC. Protein S (PS) in the circulation is present as a free form that is biologically active and bound to C4b complement protein. Primary protein S deficiency occurs as type I characterized by low free PS levels and normal PS bound levels; type IIa has low levels of both free and bound PS; and type IIb has normal levels of both free and bound PS, but functionally deficient PS. Either the quantitative or qualitative/functional deficiency forms can result in thrombosis. The inherited form of PS deficiency is transmitted as an autosomal dominant trait and the homozygous form results in death. The heterozygous form behaves similarly to the protein c deficiency producing primarily venous thromboembolic events. Case control studies and an extensive review found no association to ischemic stroke [9]. Acquired cases of PS deficiency have also been described associated with pregnancy, infection, DIC, oral contraceptives, HIV infection, and nephrotic syndrome among other disease states [6, 10–15]. It is worth noting that during pregnancy the C4b binding protein increases resulting in a lower amount of free PS levels normally therefore altering the range of reference making the diagnosis of PS deficiency more challenging during pregnancy. Under these circumstances is recommended to retest no less than 6 weeks postpartum [10, 16].

The prevalence of protein C or protein S deficiencies in patients with venous thrombosis is low at 2–10 %, in fact prior to 2000 there were no prevalent protein C or S deficiencies reported [5, 9]. Case series initially brought attention to these deficiencies in the thrombin pathway however an extensive review of the literature that included six case-control studies of cases of ischemic stroke found that cases and controls had similar rates of protein deficiencies (0–21 % vs 0–20 % respectively) and therefore no causal association [10].

Factor V Leiden Mutation

A single point mutation in the factor V gene (factor V R506Q) results in activated protein C (APC) resistance, Factor V Leiden (FVL) mutation, and explains 90–95 % of cases of APC resistance and is the most common genetic risk factor for thrombosis [17–19]. The prevalence of the heterozygous form of FVL mutation varies among different ethnic groups and races. The higher prevalence is among whites at 5.3 % while among Hispanics is 2.2 %, Native Americans 1.3 %, African Americans 1.2 %, and Asian Americans 0.5 % [17]. The relative risk for thrombotic events among homozygous is 80 as compared to heterozygous in whom the relative risk is only 7 [18]. The thromboembolic events are venous. Since the mutation is not fully penetrant, only about 5–10 % of heterozygous patients will develop venous thromboembolism [18]. In a large review of 16 case control studies of FVL mutation or prothrombin

mutation, the authors the authors did find an association between the mutation and ischemic stroke in 14 of those studies [9].

Prothrombin Gene Mutation

The gene variant G20210A is a point mutation in the prothrombin (PT) gene that leads to high prothrombin levels. The mutation has a 7 % prevalence among whites and is very uncommon among other racial and ethnic groups [20]. Homozygous patients have higher risk of venous thromboembolism. Acquired AT deficiency is associated with liver disease, DIC, oral contraceptives, sepsis, among others. This mutation has no conclusive association with ischemic stroke [6, 20, 21].

Antithrombin Deficiency

Antithrombin (AT) is a glycoprotein that is not a vitamin K-dependent. AT inhibits serine proteases and lyses thrombin and factor Xa. This disorder is autosomal dominant and its prevalence in the general population is 1 in 2,000–5,000 [22]. The most frequent gene mutation is A384S which is seen among whites [23, 24] and it presents with venous thromboembolism.

Antiphospholipid Antibody Syndrome (APS)

APS is an autoimmune disorder that has been positively associated with venous and arterial thromboembolism. It characteristically presents with deep venous thrombosis or arterial thrombosis (typically ischemic stroke), thrombocytopenia and in women with recurrent spontaneous miscarriages usually before the tenth week of pregnancy [3, 25]. Current diagnostic criteria are in Table 17.2.

Antiphospholipid antibodies (aPL) include lupus anticoagulant (LA) and anticardiolipin antibodies (aCL). aPL are a group of polyclonal antibodies directed against several phospholipids including cardiolipin, phosphatidylcholine, and phosphatidyl serine [26–29]. There is a group of aPL that are associated with infections and are not pathogenic and a second type that binds to phospholipid-binding proteins, such as the β2 glycoprotein I or prothrombin, which are bound to injured endothelial cells [26, 30]. Usually patients with underlying autoimmune disease such as systemic lupus erythematous (SLE) with aCL are at particular high risk of thromboembolic complications [26, 30]. The risk of thromboembolic events varies with the type of immunoglobulin isotype (higher with IgG and IgM as compared with IgA), titer and specificity (higher with aCL antiphosphaditylethanolamine or antiphosphatidylserine) [26, 30].

Table 17.2 Revised criteria for antiphospholipid syndrome [43]

Clinical criteria
Vascular thrombosis
One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by imaging, Doppler studies or histopathology with exception of superficial venous thrombosis
Pregnancy morbidity
One or more unexplained deaths of a morphologically normal fetus at or beyond tenth week of gestation with normal fetal morphology documented by ultrasound or examination, or
One or more premature births of morphologically normal neonate before the 34th week of gestation because of preeclampsia or severe placental insufficiency, or
Three or more unexplained consecutive spontaneous abortions before the tenth week of gestation with maternal anatomic or hormonal abnormalities and exclusion of paternal and maternal chromosomal abnormalities
Laboratory Criteria
Anticardiolipin antibody of IgG and/or IgM isotype and measured by standardized enzyme-linked immunosorbent assay or anti-β2-glycoprotein I of IgG and/or IgM isotype in blood, present in medium or high titer, on two or more occasions 12 weeks or more apart.
Lupus anticoagulant present in plasma on two or more occasions 12 weeks or more apart and detected according to the guidelines of the International Society on Thrombosis and Haemostasis in the following steps:
Demonstration of a prolonged phospholipid-dependent coagulation screening test, i.e., activated partial thromboplastin time, Kaolin clotting time, dilute Russell viper venom time, dilute prothrombin time, Texarin time.
Failure to correct the prolonged screening test by mixing with normal platelet-poor plasma
Shortening or correction of the prolonged screening test by addition of excess phospholipid.
Exclusion of other coagulopathies as appropriate, i.e., factor VIII inhibitor, heparin.

The prevalence of aPL has been reported in as many as 10–30 % of unselected patients with stroke and 4–46 % of young stroke patients as compared with 2–12 % of controls [2, 31, 32]. The prevalence of aPL among SLE patients is 40 % [33]. The presence of aPL has been positively associated as an independent risk factor for stroke [31, 34]. While the presence of aPL does not reliably predict recurrent ischemic strokes, a systematic review and meta-analysis showed higher odds for recurrence for those older than 50 years as compared to all ages (5.8 vs 2.5). It is worth noting that the titers of aPL can fluctuate and therefore positive results should be confirmed with repeat testing several weeks later [34].

From the clinical standpoint, patients with ischemic stroke suspected of having APS may present with a history of DVT, thrombocytopenia, and miscarriages, and they can also present with:

- Sneddon's syndrome that is characterized by livedo reticularis
- Vascular dementia
- Atypical migraine
- Chorea
- Cardiac valve lesions
- Pulmonary hypertension

Homocysteine

The association of high levels of serum homocysteine with stroke and cardiovascular disease has been extensively studied. The metabolism of homocysteine is dependent on nutritional and genetic factors although it might be influenced by the presence of factors such as cigarette smoking or vitamin B6 or B12 deficiencies [35]. The metabolism of homocysteine lead to the formation of methionine and therefore genetic disorders affecting the enzymes involved in the metabolic change can lead to accumulation of homocysteine. There are two genetic mutations on the gene coding for the methylenetetrahydrofolate reductase (MTHFR) associated with hyperhomocysteinemia, a homozygous mutation C677T and a heterozygous C677T/A1298C mutation. MTHFR is involved in the folate metabolism that is important in the remethylation of homocysteine [6]. The prevalence of these genotypes in patients with ischemic stroke is 1.4 % and 31.88 % respectively [6, 36, 37]. Acquired causes of homocysteinemia include vitamin folate and B12 deficiency, vitamin B6 deficiency, and renal failure to mention some. It is thought that the accumulation of homocysteine leads to vessel wall injury and atherosclerosis. To diagnose hyperhomocysteinemia, a level has to be measured at baseline and after a methionine load. The reason is that a fasting homocysteine level does not reflect its metabolism [6, 38]. Despite the association of homocysteinemia with ischemic stroke in observational studies, at least two clinical trials failed to show any recurrent stroke preventive benefit from therapies aimed at lowering the homocysteine level with the administration of vitamins [39, 40].

Approaches to Key Questions That Arise in Clinical Practice

1. *When should we suspect a hypercoagulable state as the cause of a stroke*?
   Considering the low prevalence of primary coagulopathies even among patients with ischemic stroke [2, 9] it seems reasonable to try to increase the yield of testing by increasing the pretest probability of the disease and selecting those patients that are at particularly higher risk [5, 41], but consider the impact of the diagnosis on changing treatment, prognosis, or counseling [41].
   Factors that should be considered include:
   - Patients younger than 45 years
   - Stroke of undetermined cause
   - History of venous thrombosis
   - Multiple miscarriages
   - Recurrent thromboembolic events
   - Family history of thromboembolic events
2. *What is the appropriate timing/setting for hypercoagulable testing and what type of prothrombotic investigations can be justified in a patient with an ischemic stroke*?
   The literature indicates that about 30 % of ischemic stroke patients were tested for at least one thrombophilic disorder, 30 % of those were tested inappropriately as the setting or timing was not appropriate for interpretation. Moreover, 75 % of diagnoses were not confirmed with follow-up testing [42]. Prior to proceeding with testing, it is important to understand the rationale, yield and impact on treatment. Table 17.3 illustrates common tests performed. Suggested tests are shown in Table 17.4.
3. *What is the impact of various tests on the treatment plan*?
   As previously discussed, hypercoagulable states have a low prevalence even among patients with ischemic stroke. The yield can be increased by considering those patients with the features suggesting a higher risk for a hypercoagulable state. More importantly, analyses of larger sets of patients with matching controls raise questions about whether a true causal association exists between coagulation abnormalities and ischemic strokes. Moreover, the financial costs associated with these tests are high. Finally, the benefit of treating these hypercoagulable conditions to prevent recurrent stroke is not well established given a paucity of randomized clinical trial evidence to support this treatment approach for stroke risk reduction. Taken as a whole, the aforementioned factors suggest that hypercoagulable testing, with few exceptions (those at high risk and recurrent thromboembolism), may be of low yield, is

Table 17.3 Common hypercoagulable conditions and methods of testing

	Type of assay	Confirmation required	inheritance
Hereditary coagulation defects			
Antithrombin	Functional	Yes, repeat 2–3 months.	Autosomal dominant
Protein C	Functional	Yes, repeat 2–3 months.	Autosomal dominant
Protein S	Functional and free antigen	Yes, repeat 2–3 months.	Autosomal dominant
Genetic polymorphisms			
Activated protein C resistance	APCR screen (APTT based)	Yes, PT based, APCR screen, FVL genotype	Autosomal dominant
Prothrombin gene mutation	G20210A genotyping	No	Autosomal dominant
Acquired coagulopathies			
Anticardiolipin antibodies	ELISA	Yes	NA
Lupus anticoagulant	APTT, DRVVT, KCT, TTI	Yes, mixing tests, confirmation of phospholipid dependence and HPP and/or PNT	NA

APCR activated protein C resistance, *APTT* activated partial thromboplastin time, *DRVVT* dilute Russell viper venom, *HPP* hexagonal phase phospholipid, *KCT* Kaolin clotting time, *PNT* platelet neutralization test, *TTI* tissue thromboplastin inhibition test
From: Current Atherosclerosis, Screening for hypercoagulable syndromes following stroke, Cheryl Bushnell MD, MHS, January 1, 2003, Volume 5, Issue 4. With kind permission from Springer Science and Business Media

Table 17.4 Hypercoagulable panel

Protein C functional
Protein S functional and S antigen (total and free)
Antithrombin
Anticardiolipin antibodies (IgG and IgM)
Lupus anticoagulant
B2 Glycoprotein I antibodies (IgG and IgM)
Factor V Leiden mutation or activated protein C resistance
Methylenetetrahydrofolate reductase (MTHFR) mutation
Homocysteine level

expensive, and unproven, and therefore should be selectively done based on solid rationale.

4. *How should these patients be treated to prevent stroke recurrence*?

   For most of these patients, stroke prevention will involve appropriate risk factor management of all traditional vascular risk factors identified. Although it is recommended at a low level of evidence, some patients will require long-term anticoagulation, specifically those with recurrent thromboembolic events associated with the Protein C and thrombin pathway abnormalities or patients with antiphospholipid antibody syndrome. For all other patients with a single arterial event and no other factors suggesting high thrombotic risk, antiplatelet agents seem to be a reasonable choice.

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General Concepts: Therapies for Rehabilitation and Recovery

18

Robert Teasell and Norhayati Hussein

Stroke is the world's second leading cause of death and is one of the most burdensome diseases, as measured by disability-adjusted life-years (DALYs) lost [1–3]. The impact of stroke on the general well-being of stroke survivors and their caregivers is often underestimated [4]. It has been reported 36 % of stroke survivors have a discernable disability 5 years post-stroke [5] while 42 % of survivors are still dependent for performing basic activities of daily living 6 years post-stroke [6]. Caregivers of stroke survivors also are impacted with an increase in their physical demands [7], a decrease in health-related quality of life [8, 9], and greater risk of experiencing psychological distress [10, 11].

Prevention and Acute Care

One of the challenges of stroke care is trying to strike the right balance between prevention, acute care, and rehabilitation with each having its own proponents. However, there is a growing realization that despite significant investments in prevention and acute care, the number of strokes requiring rehabilitation continues to increase for a number of reasons including an aging population and a greater number of stroke patients surviving their stroke.

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Prevention. Hypertension is described as the single most effective primary and secondary measure to reduce stroke risk; however, additional medical conditions (diabetes, high cholesterol) and lifestyle factors (smoking, alcohol consumption, physical activity, and diet) are targeted factors [12] although these factors are either controversial [13–19] or require difficult behavioral modifications. For instance, only 5 % of adults participate in the recommended amount of physical activity to obtain health benefits [20]. Despite a reduction in age-specific stroke incidence in developed countries, the overall burden of stroke continues to rise with an aging population and a global rise in obesity, diabetes, and smoking levels [21, 22].

Thrombolysis. Even in those countries with strong thrombolytic programs, less than 10 % of patients with stroke are treated within the allotted time frame [23] and, of these only 20–30 % will benefit [24]. These factors highlight that thrombolytics offer, at best, a positive impact on about 2 % of all strokes, and for most countries that percentage is much less.

The Growing Burden of Stroke. Overall, the number of stroke survivors who also have a number of disabilities is rising and these patients need rehabilitation.

Stroke Recovery

Peak neurological recovery from stroke occurs within the first 3 months. A number of studies have shown that recovery may continue at a slower pace for at least 6 months; with up to 5 % of patients continuing to recover for up to 1 year. The latter is especially true with patients who are severely disabled at the time of initial examination [25–30]. Progress towards recovery may plateau at any stage of recovery with only a very small percentage of those with moderate to severe strokes (about 10 %) achieving "full recovery."

The return of motor power is not synonymous with recovery of function; function may be hampered by the inability to perform skilled coordinated movements, apraxias, sensory deficits, communication disorders, as well as cognitive

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impairment. Functional improvements may occur disproportional to neurological recovery [31, 32]. Functional recovery (the ability to do activities despite limitations) and improvement in communication may continue for months after neurological recovery appears to have plateaued.

Rehabilitation Triage

The best predictor of stroke outcome is the initial clinical assessment of stroke severity [33]. As a general rule, the severity of the initial deficit is inversely proportional to the prognosis for recovery and correlates with the length of time to maximal neurological and functional recovery. The second most important factor is age, with younger patients making the greater recovery.

Levels of Severity of Stroke Rehab Patients

Garraway et al. [34, 35] first proposed the concept of **three bands** of stroke patients based upon stroke severity in determining expected rehabilitation needs and prognosis. *Milder* stroke patients do not require inpatient rehabilitation, make limited rehabilitation gains (due to a ceiling effect) although many fully recover, and mild stroke patients are most efficiently rehabilitated in a community/outpatient setting. *Moderately severe* stroke patients tend to benefit the most from an inpatient stroke rehabilitation unit, demonstrating marked improvements in all areas although they are often still partially dependent in many areas at the time of discharge. Over 85 % are discharged to the community [36]. *Severe* stroke patients have profound neurological deficits or serious medical comorbidities and are unlikely to achieve functional independence, regardless of treatment, unless they are younger. Severe stroke patients have the longest rehabilitation stays as well as a smaller likelihood of community discharge [36]. However, these patients do make significant functional gains in rehabilitation, although the focus is as much on limiting post-stroke complications and discharge planning as it is on functional gains. The presence of a caregiver is very important to discharge planning in severe strokes [37].

Impact of Age on Recovery/Rehabilitation

The second predictor of functional outcome following stroke is age, although it is a lesser factor and much more controversial than stroke severity. Age has a small but significant effect on the speed and completeness of recovery [38]. However, because older stroke patients do recover, albeit at a slower rate, and the overall impact of age is relatively small, age in and of itself is not always a good predictor of functional recovery after stroke [39].

Assessment and Triage

A screening examination for rehabilitation should be performed as soon as the patient's medical and neurological condition permits, by a person experienced in rehabilitation [40]. Threshold criteria for admission to a comprehensive rehabilitation program include medical stability, the presence of a functional deficit, the ability to learn, and enough physical endurance to sit unsupported for at least 1 h and to participate actively in rehabilitation [40]. Admission to an interdisciplinary program should be limited to patients who have more than one type of disability and who therefore require the services of two or more rehabilitation disciplines.

Stroke Recovery and Neuroplasticity

Training and rehabilitation has been shown to increase cortical representation with subsequent functional recovery, whereas a lack of rehabilitation or training decreases cortical representation and delays recovery. In animal studies, it appears that the key factors promoting neurological recovery include *increased activity* and *a complex and stimulating environment*.

The Earlier the Better

There is a growing literature on the benefits of early admission to rehabilitation. Biernaskie et al. [41] using a rat model established the beneficial effect of early timing of rehabilitation post-stroke on outcomes. Schallert et al. [42] noted that the brain appears to be "primed" to recover early following stroke and it is at this point rehabilitation therapies will be the most effective. Several studies have suggested that stroke rehabilitation is most effective when initiated early [43–46]. The recent A Very Early Rehabilitation Trial (AVERT) Phase II studied randomly assigned stroke patients less than 24 post-stroke onset to standard care or standard care + very early mobilization (VEM) until discharge or 14 days. The VEM group did not demonstrated improved motor recovery and functional independence at 3 months when compared to the standard care group [47].

Intensity of Rehabilitation Therapies

When attempting to determine factors that contribute to improved functional outcomes that are associated with specialized stroke rehabilitation, the intensity of rehabilitation therapies is often cited as an important element. The total amount of time that a patient spends engaged in rehabilitation activities varies considerably, between units, institutions, and

countries. Lincoln et al. [48] observed that patients on a stroke rehabilitation unit were engaged in interactive behaviors for only 25 % of their time. The AVERT [49, 50] observed a cohort of 58 patients in five acute stroke units in Australia and found patients were engaged in moderate or high levels of activity for only 12.8 % of their therapeutic day while 53 % of the time, patients spent their time in bed and were alone 60 % of the time. Kalra and Langhorne [51] have noted that "*there is evidence from neuroimaging studies showing that increased intensity of rehabilitation therapies results in greater activation of areas associated with the function towards which this therapy is directed*". While a universally accepted definition of the term "intensity" does not exist, it is usually defined as number of minutes per day of therapy or the number of hours of consecutive therapy. Duncan et al. [52] reviewed all RCTs and meta-analyses published to date examining the effect of intensity on improved functional outcome and concluded that there was weak evidence of a dose–response relationship. The authors suggested that all subsets of patients may not benefit equally and could not recommend specific guidelines about the intensity or duration of rehabilitation therapies.

Organized Stroke Care: Stroke Rehabilitation Units

The most recent clinical practice guidelines [52] endorsed by the American Heart Association recommend that stroke rehabilitation care should be provided by a multidisciplinary team and delivered in a setting that is formally coordinated and organized. The authors also acknowledged the need for a flexible approach and were unable to identify a universally applicable "best practice" approach applicable to all stroke patients. The Canadian Stroke Strategy Guidelines note the need for stroke rehabilitation to be formally coordinated and organized, to have a specialized stroke rehabilitation team on a geographically localized unit, for the team to be interdisciplinary and experienced in stroke rehabilitation care, with standardized assessments and at least weekly interdisciplinary team meetings [53].

Foley et al. [54] in a recent systematic review identified 12 RCTs which compared the effectiveness of stroke rehabilitation units to an alternative form of care, usually a general medical ward or a neurology ward [54]. Patients included in the review were admitted to either a subacute unit, after receiving their initial care on an acute stroke unit, or a combined acute/subacute stroke rehabilitation unit immediately following their stroke. Compared to the alternative form of care, the results from pooled analyses indicated a clear benefit of specialized care; the odds of death, the combined outcome of death and dependency, and the need for institutionalization were all significantly reduced. Length of hospital stay was also significantly reduced (Table 18.1).

Table 18.1 Pooled analyses for stroke rehabilitation unit outcomes compared to general rehabilitation units [54]

Outcome	Result from pooled analyses: OR (95 % CI) or weighted mean difference (95 % CI)
Death	0.79 (0.65, 0.98)
Death and dependency	0.59 (0.49, 0.71)
Need for institutionalization	0.69 (0.54, 0.87)
Length of stay	−16.4 (−31.2,−1.6)

When combined meta-analyses of stroke rehabilitation units are performed, there is improvement for the outcomes of combined death/dependency, functional outcomes, mortality, need for institutionalization, and length of hospital stay. Best evidence points to specialized stroke rehabilitation units as achieving optimal outcomes in those patients needing rehabilitation.

Outpatient/Community-Based Rehabilitation

As Health Care Systems attempt to improve efficiencies and reduce costs, there has been increasing emphasis on outpatient rehabilitation care. Outpatient care is much less expensive because it avoids the high nursing and hoteling costs associated with inpatient rehabilitation. Post-acute care has been evaluated by the Outpatient Rehabilitation Trialists [55], the Early Supported Discharge Trialists [56], and others assessing home-based rehabilitation [57]. Outpatient Service Trialists data demonstrated the positive impacts of post-hospital care. Patients who received rehabilitation after being discharged to their home experienced a reduction in poor outcomes or death (OR 0.72, 95 % CI 0.57–0.92, $p=0.009$) and an improvement in Activities of Daily Living (ADL) (OR 0.67, 95 % CI 0.46–0.97, $p=0.03$) compared to those receiving no intervention or routine care. Moreover, in comparison to inpatient rehabilitation, outpatient rehabilitation is relatively inexpensive.

Building on the evidence for outpatient care, Early Supported Discharge (ESD) was introduced to expedite a patient's discharge back into the community through the provision of timely home-based support. Three forms of ESD were identified in the literature: a hospital-based team managing the entire continuum of care for a patient, a team involved in predischarge planning followed by referral to an existing community-based team, and finally, no ESD team, but the availability of multidisciplinary care once a patient was discharged to the community. The comparison groups were patients recruited from an organized stroke unit, neurological unit, or general ward. Findings indicated that ESD services reduced patient duration in hospital ($P<0.0001$), improved patient outcomes with a decreased odds of death or dependency (OR 0.80, 95 % CI 0.67–0.97), and increased

patient satisfaction with care (OR 1.60, 95 % CI 1.08–2.38) compared to no ESD team. When analyses were performed separately for each ESD model of care, only the model involving the hospital-based team managing the entire continuum of care (discharge planning and delivery of community-based care) demonstrated significant improvements in patient outcomes. Compared to conventional care, the ESD model of care decreased odds of death or institutional care (OR 0.65, 95 % CI 0.45–0.93), decreased odds of death or dependency (OR 0.71, 95 % CI 0.55–0.91), and increased odds of satisfaction with care (OR 1.74, 95 % CI 1.13–2.67).

While the ESD concept remains theoretically popular, uncertainties regarding the appropriate length of ESD care [58] and the relevance of ESD for patients with severe stroke [58] still exist. The success of ESD is dependent on the immediate availability of community resources for patients upon discharge. ESD is an attempt to "pull" patients out of expensive inpatient beds and therefore one of the biggest challenges is in ensuring that no waiting lists for these services exist.

ESD is but one form of outpatient therapy. Once discharged to the community to an outpatient program, the question becomes where to provide care. Location of care is dependent on level of functioning, availability of services, and presence of a caregiver. Hiller and Inglis-Jassiem [57] completed a systematic review of the literature comparing home-based care to center-based care for stroke rehabilitation. Eleven RCTs were reviewed, most based on studies from the UK. Interventions were home-based therapy (multidisciplinary team or a select discipline such as PT or OT) and, except for Anderson et al. [59] who made comparisons between disciplines, the comparison groups were individuals receiving center-based or usual care. Patients receiving home-based care experienced significant improvements compared to controls in the Barthel Index at 3–6 months post-intervention ($P=0.03$). However, at 6 months, patients in the intervention group did not show significant differences in the Barthel Index compared to controls ($P=0.27$). There was insufficient evidence to draw conclusions about caregiver outcomes and the differences in outcomes according to type of intervention. Further evidence is needed to assess the efficacy of home-based rehabilitation services.

The Future of Stroke Rehabilitation

Challenges in Knowledge Translation, Reducing the Gap between Research and Practice

In medicine, outcomes are optimized when clinical practice reflects the latest research findings. However, studies of health care delivery have found that only 55–67 % of patients actually receive care that is based on best evidence [60, 61] and 20–30 % of patients receive care that is contradicted [62]. Translating research evidence into clinical practice is challenging and stroke rehabilitation is no exception.

Insufficient time has been cited as the most significant barrier to knowledge translation by occupational therapists [63]. Lack of evidence in the field and lack of skills and knowledge in evidence-based medicine are other notable barriers [63]. However the large majority of those who noted barriers also agreed on the value of current research for informing patient care. Stroke rehabilitation is interdisciplinary in nature and nurses, physiotherapists, occupational therapists, and managerial staff vary with respect to perceived barriers of Evidence-Based Medicine (EBM) [64]. Barriers may include lack of time and insufficient knowledge, training, and skills in EBM [64, 65] although all disciplines cite time as the most widely cited barrier for bringing best available evidence into practice [64].

The development and maintenance of a sustained research synthesis, the Stroke Rehabilitation Evidence-Based Review (www.ebrsr.com) has had a substantial impact on knowledge translation within the area of stroke rehabilitation, both nationally and internationally. It offers a multidisciplinary, methodologically sound, timely and regularly updated review of evidence in stroke rehabilitation. In the context of the knowledge to action process proposed by Graham et al [66], it is an effective mode of knowledge synthesis and is invaluable in informing the surrounding phases of the model.

The Role of Technology

Functional Electrical Stimulation (FES) in Hemiparetic Upper and Lower Extremities

FES of the common peroneal nerve has been used to enhance ankle dorsiflexion during the swing phase of gait. Although weak ankle dorsiflexion with plantar flexion hypertonicity is typically corrected by an ankle foot orthosis, FES may be a suitable alternative for highly motivated patients who are able to walk independently or with minimal assistance. FES combined with gait training improves hemiplegic gait [67]. Systematic reviews [68, 69] have both shown a benefit for walking speed. There is strong evidence FES and gait retraining results in improvements in hemiplegic gait. FES has also been studied in a number of RCTs examining the hemiparetic upper extremity [70, 71]. There is strong evidence that FES treatment improves upper extremity function in acute stroke (<6 months post onset) and chronic stroke (>6 months post onset).

Robotics in Rehabilitation of Upper Extremity Post-stroke

Electromechanical and robotic-assisted therapy are being increasingly utilized in stroke motor rehabilitation, although they account for a very small amount of therapy provided. Theoretically, robot-assisted therapies are able to provide an alternative to labor-intensive therapist-assisted interventions, thus fulfilling the stroke rehabilitation principles of high intensity and task specificity. However, the potential benefits have not yet been fully apparent in research and clinical practice, with studies showing mixed outcome results. There is strong evidence that sensorimotor training with robotic devices improves upper extremity functional outcomes, and motor outcomes of the shoulder and elbow [72, 73] as well as ambulation [74–77]. There is strong evidence that robotic devices do not improve motor outcomes of the wrist and hand [72, 73]. As the technology improves, robotics are going to gain an increasing role.

Virtual Reality in Stroke Rehabilitation

There is strong evidence that virtual reality treatment can improve motor function in the chronic stage of stroke [78, 79]. It is useful as an adjunct to other interventions as it enables additional opportunities for increasing repetition, intensity and provide task-oriented training.

The Long-Term Management of Stroke

Changing views and emerging scientific evidence over the past decades have questioned the presumed 6-month recovery plateau [80, 81]. A growing body of literature, including over 350 randomized controlled trials, have focused on rehabilitation during the chronic (6 months or more post) stroke period [82]. While this work was primarily conducted due to the stable deficits exhibited during this stage, this body of research provides particularly strong evidence for effective functional motor gains from a variety of interventions such as exercises, functional electrical stimulation, and constraint-induced movement therapy [80]. The impact of these interventions on patients who are at least 6 months post-stroke demonstrates the efficiency and potential for true gains with rehabilitation during the chronic stroke stage. These gains are largely due to the fact that, while spontaneous recovery does occur, neuroplasticity is about learning or relearning abilities and can, thus, occur at virtually any time [83].

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Botulinum Toxin for Post-stroke Limb Spasticity

19

Rong Chen and Wuwei Feng

Case Presentation A 67-year-old Caucasian female with a long standing history of hypertension suffered an acute left pontine infarct in June, 2012 (Fig. 19.1 shows an acute ischemic infarct with left Pons).

Her initial stroke presentation was dense right hemiparesis, including face, arm, and leg, as well as dysarthria. The etiology of stroke is likely small vessel disease due to long exposure to hypertension. She was hospitalized for 4 days before she was discharged to acute rehabilitation facility. At the time of hospital charge, she had only trace movement with arm but has horizontal movement with leg, her facial palsy improved and her speech was much better but still dysarthric, her muscle tone increased, and reflex started to be brisk.

After 34 days of acute rehabilitation, she was able to walk with an ankle foot orthosis (AFO) and tripod, and she has partial movement with her arm with most movement in the proximal muscles, her face paralysis was almost gone, and her speech was nearly normal. Spasticity was noticed with increased muscle tone, her reflex was exaggerated, and non-sustained clonus can be induced. She was transitioned to outpatient physical therapy and occupational therapy; however, the recovery process was slow due to increasing spasticity and pain with her arm and leg. She was prescribed with Baclofen but could not take it due to side effect of somnolence and inability of participating in therapy; later on switched to tizanidine, but she became hypotensive, somnolent, and had to discontinue it.

She was seen in the post-stroke spasticity clinic around 80 days after the indexed event; her neurological exam revealed that she had an internally rotated shoulder, flexed elbow, pronated forearm, flexed wrist, and clenched fist. Her gait demonstrated a classic hemiparetic gait with adducted thigh, flexed knee, and crawled toes. Her spasticity was much worse and she had a sustained clonus lasting 24 s. She complained moderate pain and discomfort with both arm and leg not relieved by pain medication; especially she was unable to fit her foot into the AFO well due to crawled toes. There was skin breakdown with her toes. Subsequently, she received Botulinum Toxin type A (Botox®) in the arm first time, then arm and leg in the following visit. She experienced no side effect with injection except a minor transient ache after procedure. Her spasticity was significantly reduced and pain was completely relieved. Her arm function was not significantly improved but she felt much confident with self-esteem; she said that "she feels better when she goes to restaurant or church." Her crawled toes improved and fit better with AFO, and her gait was better with simultaneous physical therapy. She has been received Botox® injection every 3–4 months for 2 years now.

Introduction

Stroke mortality has declined to the fourth leading cause of death with improved risk factors control and better coordinated acute stroke care in the United States [1]. On the other hand, stroke remains a leading cause of disability. An increasing number of individuals are surviving with a variety of residual physical and cognitive deficits [2, 3]. Of these deficits, post-stroke limb spasticity (PSLS) generally occurs with motor impairment, as a frequent sequela after stroke. Current prevalence estimates of PSLS, from several studies with different sample sizes at varying post-stroke phases, range from 4 to 43 % [4]. PSLS is considered a major post-stroke complication with a substantial impact on post-stroke motor recovery and overall quality of life. Spasticity frequently develops weeks or months after strokes and is a major barrier to survivors achieving good motor recovery or independence in the performance of activities of daily living

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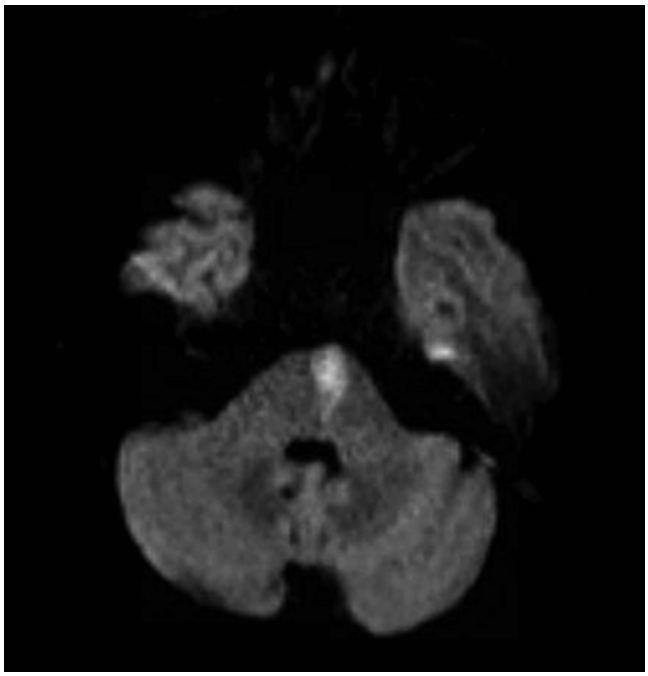

Fig. 19.1 An acute ischemic infarct with left Pons

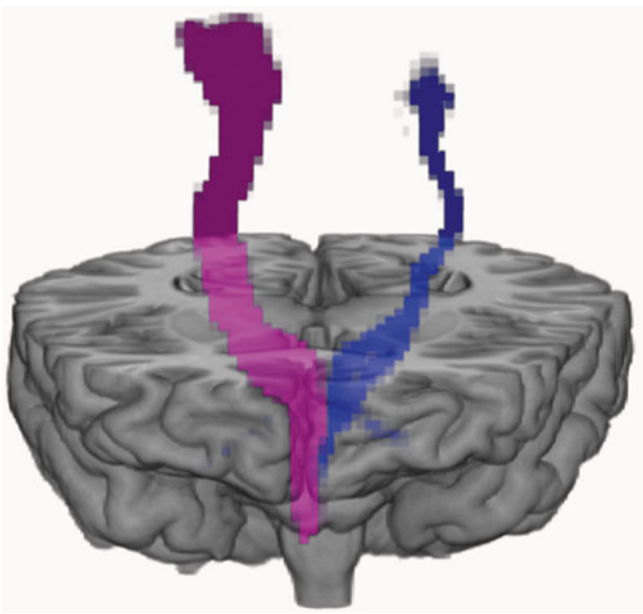

Fig. 19.2 A patient with left pontine infarct exhibits moderate-to-severe post-stroke spasticity affecting both right upper and lower extremities

(ADLs). In recent years, several treatments have become available for spasticity treatment, including botulinum toxin.

This chapter will narratively review the pathology, anatomy, presentation of PSLS, and evaluation of botulinum toxin as a therapy.

Pathophysiology and Anatomy

The term spasticity was defined by Lance in the 1980s [5] as *"*a motor disorder characterized by a velocity-dependent increase in tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting hyper-excitability of the stretch reflex as one component of the upper motor neuron syndrome (UMNS).*"* Muscles affected by UMNS frequently exhibit weakness, loss of reciprocal inhibition, decreased movement control, and spasticity.

The stroke lesion generally affects the cortex and/or subcortical regions. It is considered to be an "upper motor neuron syndrome" if it affects the areas controlling motor strength and muscle tone. For example, the corticospinal tract (CST) is the dominant descending motor pathway connecting the motor cortex to the limbs through the spinal cord to control limb strength and voluntary movement. There are other nondominant subcortical tracts as well. For example, the vestibulospinal tract receives excitatory input from vestibular organs and deep cerebellar nuclei, subsequently synapses on ipsilateral interneurons that excite alpha motor neurons to the limb and trunk muscles, and excites the extensors to regulate posture and balance. The reticulospinal tract is another subcortical tract receiving input from both cortices and ascending sensory input from spinoreticular tract neurons. It innervates interneurons that excite motor neurons to limbs muscles, and mainly excites flexors, thereby facilitating the regulation of voluntary movements. Although we do not know the exact anatomic correlation of PSLS, the injury from stroke affecting the corticospinal tract or other subcortical tracts likely contributes to hemiparesis as well as spasticity [6, 7] (Fig. 19.2 shows this highlighted patient suffered a left pontine infarct and injured the left corticospinal tract; the patient exhibits moderate-to-severe spasticity with both upper and lower extremities after stroke).

Presentation and Evaluation

Limb spasticity is a common complication after stroke and is frequently associated with pain, contractures, fatigue, functional limitations, diminished self-image, poor gait, increased falls, pressure sores, skin breakdown, etc. Spasticity should be comprehensively assessed at the level of impairment and its corresponding impact on function. The spasticity and impairment level can be assessed using the Ashworth Spasticity Scale (or the modified Ashworth) and Tardieu Scale. The Ashworth spasticity scale [8] measures the resistance to stretching when a limb is passively moved. It is a 6-point scale that provides information on the severity of spasticity and can be used to indicate responses to treatment. The Tardieu scale [9] measures spasticity that takes into account resistance to passive movement at both slow and fast speeds. Impact on function can be assessed using the modified Rankin Scale,

Table 19.1 Common presentation associated with PSLS

	Clinical presentation	Muscles (affected)
Upper extremity	Adducted and internally rotated shoulder	Latissimus Dorsi; Pectoris Major; Subscapularis; Teres Major
	Flexed elbow	Biceps Brachii; Brachialis; Brachioradialis
	Pronated forearm	Pronator Teres; Pronator Quadratus
	Flexed wrist	Flexor Carpi Radialis; Flexor Carpi Ulnaris; Palmaris Longus
	Clenched fist	Flexor Digitorum Profundus; Flexor Digitorum Superficialis; Flexor Pollicis Brevis; Flexor Pollicis Longus
	Intrinsic plus hand	Lumbricals
	Thumb in palm	Adductor pollicis; Flexor Pollicis Brevis; Flexor Pollicis Longus
Lower extremity	Adducted thigh	Adductor Longus; Adductor Brevis; Adductor Magnus; Adductor Gracilis
	Flexed hip	Iliacus; Psoas; Rectus Femoris
	Stiff extended knee	Rectus Femoris; Vastus Lateralis; Vastus Medialis; Vastus Intermedius
	Flexed knee	Gastrocnemius; Hamstrings; Tensor Fascia Lata
	Flexed toe	Flexor Digitorum Longus; Flexor Digitorum Brevis; Flexor Hallucis Longus
	Hyperextended toe	Extensor Hallucis Longus

Barthel index, and Functional Independence Measurement and Disability Assessment Scale (DAS). The DAS [10] is a scale specially designed to assess disability linked to upper extremity spasticity, while the other three scales assess overall disability from spasticity. Pain usually accompanies spasticity. Therefore, pain scale, such as the numeric pain rating scale (NPRS), which is an 11-point scale (0 is no pain and 10 is worst pain imaginable), is also used for assessment.

Spasticity can occur in either a single muscle or a group of muscles in both arms and legs. Typical manifestations of spasticity in stroke patients are shown below (Table 19.1).

Treatment and Botulinum Toxin

Management of spasticity requires a multidisciplinary effort, including the patient and/or caregiver, stroke neurologist or physiatrist, occupational therapists, physical therapist, and psychologist. The focus of treatment is usually tailored to the specific needs or goals of the patient and/or caregiver. Spasticity management should be aimed at reducing the effects of disability on daily activities, including limb position, hygiene, dressing, walking, and a healthy self-image. The treatment is also crucial for the caregiver because stroke survivors require various degrees of assistance from the caregiver for dressing, hygiene, walking, and other ADLs. Generally speaking, spasticity reduction, functional improvement, pain relief, self-image enhancement, and reduction of caregiver burden are common goals for both patients and caregivers.

The key element of treatment is spasticity reduction. There are several treatment options for PSLS, including pharmacological agents [11], such as baclofen (oral or intrathecal), tizanidine, or benzodiazepine; rehabilitation therapy (muscle stretching or muscle strength training), electric stimulation [12], and chemodenervation approaches [13], including botulinum toxin regional muscle injection, phenol injection, and alcohol injection. Most of the pharmacological agents carry significant central nervous system related side effects, which can be intolerable to some stroke patients. For example, tizanidine is an effective antispasmodic agent, but it easily causes somnolence, sleepiness, hypotension, and bradycardia. As a result, Botulinum toxin has emerged as the first-line treatment for focal PSLS due to the fact that it has no cognitive side effect.

Botulinum Toxin

Botulinum toxin is a biological toxin produced by the *bacterium clostridium botulinum*. Botox works by inhibiting acetylcholine release into the neuromuscular junction, thus blocking muscular contraction and thereby reducing muscle tone and spasticity. Botulinum toxin was first used for strabismus and has now expanded to many disease conditions, including muscle spasticity. Three forms of this toxin type A (onabotulinumtoxinA/Botox® by Allergan Inc.; abobotulinumtoxinA/Disport® by Ipsen Limited; and IncobotulinumtoxinA/Xeomin® by Merz Pharmaceuticals) and one form type B (rimabotulinumtoxinB/Myobloc by Solstice Neuroscience Inc.) are commercially available for medical or cosmetic use. The potency varies by product. Only OnabotulinumtoxinA/Botox® is approved by FDA to "treat focal spasticity in the flexor muscles of the elbow, wrist, and fingers in adults" after neurological injuries.

An early small study supported the safe and effective use of botulinum toxin for upper limb spasticity in chronic stroke patients [14]. The favorable results prompted a phase-3 multicenter study, in the United States, formally evaluating the definitive efficacy of this toxin. Brasher et al. [15] completed

a clinical trial that recruited 126 stroke subjects who were 6 months post-stroke with focal spasticity at the wrist and finger level (a score of Ashworth Spasticity Scale ≥3 for wrist flexor and ≥2 higher at finger flexor). Subjects were randomly assigned to a treatment group with 200–400 units of botulinum toxin A (Botox) or placebo (Botox vehicle with no active component). Specifically the trial required that 50 units were injected into each of four wrist and finger flexors (Flexor Carpi Radialis, Flexor Carpi Ulnaris, Flexor Digitorum Superficialis, and Flexor Digitorum Profundus); patients also had an option to receive 20 units for each of two thumb muscles (Flexor Pollicis Longus and Adductor Pollicis). The primary outcome was functional disability measured by a four-point Disability Assessment Scale (DAS) at week 6. The secondary outcomes were muscle tone measured by a five-point Ashworth Scale and global outcome measured by the Global Assessment Scale (GAS). Safety and neutralizing antibodies were measured as well. At week 6, 62 % in the treatment group had improvement in the principal target of treatment compared with only 17 % in the placebo group. 83 % of subjects had at least a one-point improvement in the score on the DAS vs. 53 % in the placebo group. Muscle tone was significantly reduced in the treatment group ($P<0.0001$ for all muscles) with maximal effects noted at week 4 (rather than week 6) at both wrist and finger flexors. The GAS score rated by physicians was higher in the treatment group at all of follow-up visits. Only one subject (out of 93 subjects) had positive neutralizing antibody detected. Overall, adverse effects were comparable between the two groups except there was more muscular weakness in the treatment group.

In addition to the two studies described above, two more randomized placebo-controlled studies with Botulinum toxin type A (Botox®) [16, 17] further demonstrated its efficacy for treatment of upper extremity spasticity. Another botulinum toxin type A (Dyport®) [18–20] was also evaluated for upper extremity spasticity and it was demonstrated to be effective at 1,000 units. Botulinum toxin type B (Myobloc) [21] was tested as well but no efficacy was shown.

The efficacy of botulinum toxin for treatment of lower extremity spasticity is not proven yet. There have been at least five placebo-controlled randomized studies assessing the efficacy of Botox® injection in stroke patients [22–26], which showed mixed results in spasticity reduction and safety profiles.

The side effects from the botulinum toxin injection are generally very mild and the majority of them are peripheral effects related to site of injection, such as minor bleeding, ache, infection, and muscle weakness. However, in rare reports from post-marketing surveillance, the toxin spreads beyond the injection site, resulting in dysphagia, dysphonia, or breathing difficulty. Side effects occur hours to weeks after injection. The breathing and swallowing difficulties can be life threatening. Overall, in comparison with other oral antispasmodic drugs, botulinum toxin is safe without the systemic toxicity frequently seen in drugs. The main drawback is high cost associated with the drug and the injection procedure. Additionally, the effect is transient and it requires repeated injection approximately every 3 months. Repeated injection can be considered when the effect from the last injection fades away, but generally the second injection should not occur sooner than 12 weeks to prevent formation of antibodies.

Dosage in the initial and subsequent visits should be tailored to the individual based on the size, number, and location of muscles involved, severity of spasticity, and the patient's response to the previous injection. Doses from 75 to 360 units were tested in clinical trials: Biceps Brachii (100–200 units divided into 4 sites); Flexor Carpi Radialis (12.5–50 units in 1 site); Flexor Carpi Ulnaris (12.5–50 units in 1 site); Flexor Digitorum Profundus (30–50 units in 1–2 site); and Flexor Digitorum Superficialis (30–50 units in 1–2 sites). Localization of the target muscle can be assisted by neuroanatomy, electromyographic guidance, nerve stimulation technique, or ultrasound technique.

The American Academy of Neurology [27] made a recommendation that Botulinum toxin should be offered as a treatment option for the treatment of spasticity in adults and children (Level A). The international consensus statement also supports class I evidence and recommendation Level A for "reduction in pain and deformity, improvement in washing and dressing the upper limb and a reduction in caregiver burden" [28]. The detailed recommendation is summarized in Table 19.2.

Table 19.2 Expert consensus about botulinum toxin use in adults with spasticity

American Academy of Neurology	Strong evidence supports (Level A)	Use of Botulinum toxin as a treatment option to reduce muscle tone and improve passive function
	Good evidence supports (Level B)	Consideration of Botulinum toxin to improve active function
	Insufficient evidence supports (Level U)	Optimum techniques for muscle localization at the time of injection
International Expert Consensus	Class I evidence, Recommendation A	Reduction in pain and deformity, improvement in washing and dressing the upper limb, and a reduction in caregiver burden
	Class III evidence, Recommendation C	Improvement in function performed by active movement of the affected upper limb
	Class IV, Recommendation U	An individually based approach to treatment and outcome measurement is preferred

Conclusion

Post-stroke limb spasticity is a common and burdensome complication after stroke. It causes functional impairment as well as physical deformity. While there are several treatment options for spasticity, botulinum toxin type A is now a mainstream treatment for PSLS. It effectively reduces muscle tone, but the effect is transient and repeated injections are required. Injection to the upper extremity muscle is a well-established practice, but injection to the lower extremity muscles still needs more research before it becomes standard of care.

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Selective Serotonin Reuptake Inhibitors

20

Ali Saad, Patrick Nguyen, and Samir R. Belagaje

Case Presentation *A 60-year-old female admitted to a hospital for an acute ischemic stroke due to a cardioembolic etiology. As a result of the stroke, the patient has hemiparesis. While in the hospital, therapists working with the patient report decreased participation in their sessions and minimal gains. Nurses caring for the patient report that she is sleeping more and complaining of neuropathic pain in her affected limb. The patient's family reports poor engagement and change in personality. Is there a medication or class of medications that can help address the patient's symptoms?*

Introduction

Selective serotonergic reuptake inhibitors (SSRIs) are a class of medications used ubiquitously by a variety of providers. First approved by the US Federal Drug Administration in 1987, they have been used in a variety of conditions including psychiatric disorders, sexual dysfunction, and pain syndromes. In addition, they are used frequently to address issues related to stroke and post-stroke recovery. Health care providers who care for stroke patients will need to familiarize themselves with their general indications as well as possible risks in stroke patients. In particular, they should be aware of key data on SSRIs pertaining to overall recovery, post-stroke depression (PSD), motor recovery, and pain syndromes.

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Pharmacology

SSRIs, as their name implies, work by selectively inhibiting the reuptake of the neurotransmitter, serotonin. Consequently, they increase the local concentration of serotonin and make it more available to bind to receptors. In a typical synaptic transmission, the axons of a given neuron release neurotransmitters that travel across the synaptic cleft and bind to receptors in the dendrites of another neuron to induce an effect on that neuron. The magnitude of that effect is associated with several factors including the concentration of neurotransmitters in that area and the binding affinity to the receptor.

The aforementioned principles hold true for serotonergic neurons. The presynaptic neuron that releases serotonin has membrane proteins, called serotonin transporters (SERT) that allow the serotonin to be taken back by the neuron and thereby regulate the effect of serotonin. When SSRIs are used, they block the SERT and increase the local concentration of serotonin. As a result of the increased serotonin in the synaptic cleft, there is a decrease in the selectivity of the postsynaptic receptors and downregulation in the production of the presynaptic receptors. It is this downregulation that is thought to promote this medication class' main effect and explains the delay in actual clinical effects [1]. Despite their selectivity for serotonergic reuptake inhibitors, they are not 100 % selective and some of the medications in this class, by the nature of their chemical structures, will also block other monoamine neurotransmitters such as dopamine and norepinephrine. Differences among medications of this class are a reflection of varying selectivity and affinity for the SERT.

In addition, SSRIs differ by their half-lives and bioavailability. These differences account for the variety in dosing, frequency, titration schedules, and risks of discontinuation syndromes. SSRIs can inhibit the cytochrome P450 system

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in the liver. As this system is one of the major pathways by which drugs are metabolized, SSRIs can lead to some drug-drug interactions. Examples of major drug-drug interactions include those with monoamine oxidase inhibitors (MAOIs) and warfarin.

Clinical Indications

When first introduced into the market, SSRIs were approved for the treatment of major depression. They have indications for other psychiatric disorders as well including anxiety disorder, bipolar disorder, and post-menstrual syndrome. Some SSRIs are also being used in the treatment of pain syndromes including fibromyalgia, certain headache disorders, and neuropathies.

Side Effects

In general, SSRIs can cause sexual dysfunction, weight gain, and nausea/vomiting. SSRIs can cause drug-drug interactions, most notably, the serotonin syndrome. This syndrome is classically associated with a triad of altered mental status, autonomic dysfunction, and hyperreflexia. It can be seen with high doses of SSRIs or combination with tricyclic antidepressants. SSRIs can also inhibit platelet function and lead to a small increased risk of bleeding.

Overall Functional Improvement

Stroke treatment occurs across a spectrum consisting of various phases. One of these phases is the rehabilitation phase, where the primary focus is to optimally recover from stroke and improve quality of life. SSRIs are most frequently used in this setting to accomplish the goals of this phase. The physiatrist will evaluate the patient's functional capabilities and with a team that includes therapists and nursing staff, they will execute a comprehensive plan for recovery. This plan must prioritize the deficits for the most efficient integration to society while monitoring for any medical complications.

Administration of SSRIs to stroke patients has been shown to improve their overall mortality. This was first demonstrated in a study by Jorge et al. In that study, they enrolled 104 patients who were randomly assigned to receive a 12-week double-blind course of the nortriptyline (tricyclic antidepressant), fluoxetine (SSRI), or placebo early in the recovery period after a stroke [2]. Mortality data were obtained from the patients for 9 years after initiation of the study and analyzed using Kaplan-Meier survival curves. Of the 53 patients who were given full-dose antidepressants, 36 (67.9 %) were alive at follow-up, compared with only 10 (35.7 %) of 28 placebo-treated patients, a significant difference. Logistic regression analysis showed that the beneficial effect of antidepressants remained significant both in patients who were depressed and in those who were nondepressed at enrollment after the effects of other factors associated with mortality (i.e., age, coexisting diabetes mellitus, and chronic relapsing depression) were controlled [2]. Based on these results, the authors concluded that treatment with fluoxetine or nortriptyline for 12 weeks during the first 6 months post-stroke significantly increased the survival of both depressed and nondepressed patients.

Along similar lines, a more recent study has demonstrated improvement in overall disability. Mikami et al. enrolled 83 post-stroke patients in a double-blind randomized trial, which examined the efficacy of antidepressants in treating depressive disorders and reducing disability. Subjects were given one of the three interventions: fluoxetine, nortriptyline, or placebo. The modified Rankin scale (mRS) was used to evaluate the disability of patients and activities of daily living impairments were assessed by the Functional Independence Measure (FIM). In the study, patients who received fluoxetine or nortriptyline had significantly greater improvement in mRS scores compared to patients who received placebo [3]. This effect was independent of depression, suggesting that antidepressants may facilitate the neural mechanisms of recovery in patients with stroke. It is also important to note that the recovery in subjects given antidepressants continued throughout the 12 months, despite cessation of treatment at 3 months; this continued recovery was not seen in subjects who received placebo.

The exact reasons for the improvement are unclear but there are some possible explanations. At first glance, one might explain the findings through PSD. As will be discussed later, PSD is quite prevalent and can adversely affect recovery and impair quality of life. Thus by placing stroke victims on antidepressants, physicians treat PSD and indirectly improve outcomes in this method. However this does not explain all the findings. A key point to highlight in these studies is that even stroke survivors who were not diagnosed with depression still received benefit from these medications.

Other possible mechanisms of post-stroke recovery include neuroplastic mechanisms. There is a large amount of literature on the role of neuroplasticity on functional reorganization and recovery following stroke [4–7]. Yet another proposed mechanism is through inhibition of the microglial production of proinflammatory cytokines by SSRIs [8]. Further research is required to elucidate the exact mechanisms by which SSRIs improve functional outcomes and mortality following a stroke. The antidepressant effects and its role will be discussed in more detail below.

Post-stroke Depression Treatment

PSD is unfortunately common and impedes stroke survivors' path to recovery. The average prevalence is 30 %, although it has been found to be up to 63 % across individual studies [9, 10]. Half of these diagnoses represent major depressive disorder. A pooled observational study found that this rate remained relatively constant averaging 33 % when examined at 1 month, 1–6 months, and greater than 6-month intervals [11]. Another study found prevalence to vary over time, peaking at 3–6 months with a subsequent decline at 1 year to about 50 % of initial rates. This study also suggested that depressive symptoms can be classified into post-stroke major depressive disorder, which tends to remit spontaneously and post-stroke dysthymia which tends to persist at 1–2 years [12]. This subclassification phenomenon has not been reproduced in subsequent studies. Notably, these studies followed the natural history without the administration of any interventions. This demonstrates that PSD is highly prevalent and often remits spontaneously despite treatment, but persists in a significant portion of patients.

The underlying mechanism in the development of PSD is multifactorial. Possible mechanisms include increased activity in the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic stimulation, proinflammatory cytokine levels, diminished adherence to medical treatment, neglect of self-care, inactivity, poor diet, and substance use [13]. Most current studies focus on the pathological changes caused by injury to neural networks as well as poor adjustment to new disability.

Risk Factors for Developing Post-stroke Depression

There has been debate, but no consensus, on whether PSD is more common when stroke is located in certain parts of the brain. The Framingham study and a recent cross-sectional study noted no difference in left- versus right-sided lesions in subanalyses [14]. The only meta-analysis of this topic in 2004 found a weak relationship between PSD and right lesion location [15]. A systematic review in 2000 found no correlation [16].

Pre-morbid depression has been found to be a risk factor for the development of stroke independent of other comorbidities [17, 18]. The Framingham study found a history of depressive symptoms to increase the risk of stroke fourfold in patients under age 65 [19]. Primary and comprehensive stroke centers are now required by The Joint Commission guidelines to screen for depression along with cognitive disability in patients admitted with a diagnosis of acute stroke.

Effect on Outcomes

Depression has an adverse effect on post-stroke outcomes. Studies have shown that the severity of depression was directly correlated with the level of physical, cognitive, and functional impairment [20–23]. In addition to physical impairments, depression impairs the rehabilitation process with increased length of stays and slower progress to rehabilitation goals [24, 25]. Moreover, significant functional improvement at 3 and 6 months was noted in stroke survivors with depression if that severity was reduced by 50 % [26]. Earlier initiation of treatment is associated with the improvement on outcome [27]. These studies highlight the importance of diagnosing PSD and treating it as soon as possible.

Primary Prevention

Several agents have been studied in the primary prevention of PSD including venlafaxine and sertraline [28, 29]. A meta-analysis in 2007 of studies using multiple different agents showed that rates of PSD in the interventional and control groups were 12.54 % (14/327) and 29.17 % (91/312), respectively (number needed to treat = 6, $p = 0.05$) [30]. This study was the first meta-analysis to demonstrate evidence for PSD prophylaxis with use of any SSRI. It is consistent with another meta-analysis of six trials showing the efficacy of fluoxetine in reducing the rate of occurrence of PSD (OR = 0.25, 95 % CI = [0.11, 0.56]), but not in reducing symptom scores at the end point [31]. The largest PSD preventive trial was reported in 2008 by Robinson et al. demonstrating a significant reduction in the frequency of incident PSD as well as severity of depression following the preventive use of escitalopram compared with placebo [32]. The evidence to date suggests that antidepressant use for the primary prevention of PSD is effective and safe and choice of agent does appear to influence that effect. Fluoxetine, citalopram, and nortriptyline appeared to be effective, but sertraline did not reach statistical significance.

Treatment of Depression

Once PSD develops, it can be treated with SSRIs. Citalopram at a dose of 20–40 mg/day has been shown to be superior to placebo in treating PSD (number needed to treat = 22–24 depending on whether one looks at the Hamilton Depression Scale or the Melancholia scale, respectively) [33]. In another study, sertraline did not show any difference compared to placebo for the treatment of depression as measured by the Montgomery-Åsberg Depression Rating Scale but the improvement in quality of life was greater in the sertraline arm of the study [34].

There are conflicting results regarding the use of the fluoxetine. While earlier studies did not show improvement, subsequent trials have shown that fluoxetine improves depression symptoms when followed up sooner [35–38]. In a study of head-to-head comparison between fluoxetine and the SNRI, venlafaxine, stroke survivors in both arms showed similar rates of reduction in depressive symptoms but venlafaxine improved symptoms of emotional awareness [39].

Use of SSRIs and Other Antidepressants

A 2006 meta-analysis assessed treatment effects of antidepressants in PSD and demonstrated that antidepressants improved symptoms of depression, but not neurological improvement or recovery of ADLs [40]. There is a paucity of studies in the literature comparing SSRIs to one another or to other drug classes.

An observational study of European prescribing practices reflects the positive but limited evidence currently available on post-stroke rehabilitation and the absence of convincing data comparing agents [41]. SSRIs and SNRIs were most frequently prescribed for pharmacological enhancement of post-stroke rehabilitation primarily in patients with aphasia or paresis with accompanying depressive symptoms. This study did not demonstrate any difference in prescribing practice based on age, sex, or ischemic versus hemorrhagic stroke. Stroke location and clinical syndrome were not examined. The largest cohort study comparing SSRIs to tricyclic antidepressants examined 20,000 patients in Taiwan to look at incident stroke risk. The analysis showed a hazard ratio (HR) of 0.67 favoring SSRIs, but the population was not well matched with the SSRI patients having a 50 % higher incidence of depression at baseline as well as poorly matched antiplatelet use and history of cerebrovascular disease to highlight the most salient features [42].

Psychotherapy Plus Pharmacotherapy

SSRIs are best used in combination with other modalities of depression-targeted treatment including talk therapy and social support. In addition to pharmacological therapies, there is evidence that patients actively enrolled in inpatient rehab programs have lower rates of PSD [23, 43].

One study compared antidepressant use to antidepressant plus psychosocial-behavioral intervention for the treatment of PSD [44]. Patients in the treatment group were found to have a greater reduction in mean depression scores at 9 weeks and 1 year compared to controls. The PSD remission rate was higher in the active treatment group compared to the control group, significantly so at the first three time points (9 weeks—47 % vs. 19 %; 21 weeks—46 % vs. 22 %; 1 year—48 % vs. 27 %), but not at 2 years (65 % vs. 46 %). This study did not control for type of antidepressant use, although SSRIs as a class were more commonly prescribed than the tricyclics.

Another study randomized patients with stroke to escitalopram, problem-solving therapy (PST), or placebo and followed them for PSD prevention over 12 months [32]. Placebo recipients were significantly more likely to develop major or minor depression (22.4 %) than were patients treated with either escitalopram (8.5 %) or PST (problem-solving therapy) (11.9 %). The hazard ratios (HR) for depression with placebo were 4.5 compared to escitalopram and 2.2 compared to PST (number needed to treat, 7.2 and 9.1, respectively). A stricter analysis assumed that all 27 patients who dropped out before beginning treatment had developed depression; this showed that only escitalopram remained superior to placebo (HR, 2.2). Adverse events and functional outcomes (assessed quarterly) did not differ by group.

Limitations

The diagnosis of depression in neurologically impaired patients is a difficult and at times an uncertain one. Some stroke patients may experience abulia, aphasia, or apathy as a direct result of injury to certain areas of the brain. The diagnosis of clinical depression in such patients can be trying and at times impossible. Such patients are typically excluded from the majority of these pharmacological trials. However, it is conceivable that these patients might also benefit from pharmacotherapy and dedicated studies in such populations remain to be seen.

Other limitations include the open-label design in most studies and paucity of head-to-head trials due to the small sample sizes and heterogeneity of cases. Another intrinsic limitation in the assessment of reduction in depression is the fact that it is based on qualitative questionnaires. This stands in stark contrast to the traditional quantitative outcome measures assessed in the areas of secondary stroke prevention using antithrombotics.

Data regarding long-term benefit for treatment of PSD beyond a year is lacking in the current studies. This may be due to early data showing spontaneous remission of depression after a year in many patients. It may still be worthwhile to know whether there is sustained benefit and better define the time period of statistically significant efficacy for PSD prevention and treatment. It is unclear whether lifelong prophylactic therapy is indicated and whether patients with a history of stroke should be placed on an SSRI indefinitely along with an antiplatelet agent and statin.

Most of the cohort studies are small; thus several meta-analyses have been done to strengthen the power of the data. Despite data pooling, the power remains small compared to the larger, more widely accepted studies examining the use of antiplatelet agents in stroke.

Several psychotropics have been examined for their use in the prevention and treatment of PSD. SSRIs have been the most studied and thus the preferred drug class to target both neuroplastic and behavioral mechanisms of disease. Choice of agent depends on side effect profile, cost, compliance, and interactions. In the treatment of PSD, the data has shown evidence for benefit in those with no pre-existing depression as well as those with a new diagnosis after their stroke [30, 31].

Conclusion

PSD occurs in one-third of stroke patients and persists beyond a year in a third of those who develop it. SSRIs appear to moderately reduce the rate of depressive symptoms and, to a lesser extent, disability post-stroke in some patients. Fluoxetine is the most widely studied SSRI and given the common drug class and lower rate of side effects, this data is extrapolated to the use of escitalopram and citalopram. The low rate of side effects and number needed to treat make the risk-to-benefit ratio favorable and safe. Larger trials with more homogenous populations and controlled treatments are needed to demonstrate which subpopulations would benefit the most. Currently the evidence based largely on meta-analyses suggests that those who benefit the most are patients who are depressed at the start of treatment and those with motor deficits in cortical regions. Some practitioners advocate the routine use of SSRIs in most patients for their antidepressant properties alone to assist in the global recovery after stroke [45]. Evidence supporting this practice is Level B, Class IIa.

Neuroplasticity and Post-stroke Motor Recovery

Neuroplasticity

Neuroplasticity is defined as the ability to adapt neuronal functions and connections at the molecular, cellular, or functional level [46]. This can happen in perilesional or mirrored contralateral areas. The "rewiring" process begins as functional plasticity in the form of altered neuronal connections, excitability, and synaptic efficacy. This begins within hours of symptom onset and gives way to heightened use-dependent functional plasticity and relearning. In animals, these processes are maximally active around 1 week after stroke, and seem to reach a plateau by 3–4 weeks, although they can be modulated in the chronic stage using appropriate intervention [5].

Post-stroke recovery is associated with growth-factor-induced neurogenesis in the subventricular zone of the hippocampus as well as exercise-induced growth in the dentate gyrus [47]. Depression symptoms in rodent models reduced this neurogenesis, a reduction, which was subsequently reversed by citalopram administration.

FLAME Trial

Several trials have suggested the utility of SSRIs in post-stroke recovery [48–51]. They have demonstrated motor cortex excitability in patients treated with fluoxetine using fMRI and transcranial magnetic stimulation measures. In addition, they showed improvement in various outcomes. This culminated in the seminal study, namely the FLAME (fluoxetine in motor recovery of patients with acute ischemic stroke) trial, the largest double-blinded, randomized controlled trial to date [52]. Subjects were prescribed fluoxetine 20 mg daily starting 5–10 days post-stroke and continued for 3 months. The primary outcome was improvement in the Fugl-Meyer motor score demonstrating a 10-point increase. In the fluoxetine group, improvements were seen in both the upper and lower extremities, with the upper limbs demonstrating a greater recovery than the lower limbs, but both were statistically significant. The treatment group also had less disability at 3 months with an mRS of two or less. Patients with a history of prior or current depression were excluded. Most notable side effects in the treatment group were GI upset and digestive disorders, but fluoxetine was otherwise found to be safe.

A key point of this trial is that fluoxetine is specifically useful in recovery of motor function. The study population was small and further studies are needed to reproduce and validate the FLAME trial. The total NIHSS at 3 months was not significantly different between the two groups, although the motor component was. Importantly, the motor recovery was independent of a history of depression, another key aspect of the trial. This reinforces the findings of Jorge et al. demonstrating cognitive recovery independent of a history of depression using escitalopram [53].

The findings of FLAME have ushered in an exciting new area of research. An animal model of stroke, mice given citalopram 24 h post-stroke and then daily, demonstrated improvement in both regeneration of neurons and functional recovery. This effect was seen at both 1 and 4 weeks post-stroke, but was not studied thereafter [54]. However the study used a dose of 10 mg/kg, much higher than the typical 10–40 mg dose prescribed in adults. A dose greater than 40 mg now has a block box warning for cardiac arrhythmias and therefore unlikely to become a standard treatment.

Limitations

One limitation of the available trials is that the mean age group was 51–75 years. Clear data do not exist on whether SSRIs would also be of benefit in younger or older patients, although SSRIs are routinely prescribed to ages outside the studied age bracket. The ideal choice of SSRI depends largely on patient comorbidities, side effect profile, and

drug-drug interactions as there is no clear evidence for the superiority of one over the other. Other limitations are similar to those described in the section on PSD.

Conclusions

The principles that guide the use of SSRIs for post-stroke motor recovery are essentially the same as those for the use in PSD. Direct pathological evidence for SSRIs and neuroplasticity will be limited to animal models and extrapolated to human subjects. Evidence supporting the use of SSRIs in post-stroke motor recovery is Level B, Class IIa.

Pain Management

While SSRIs were primarily developed to treat depression, there is some evidence that they can be used to moderate pain, especially neuropathic pain. In the rehabilitation setting, stroke survivors commonly complain of pain. This is frequently caused by direct injury to the central nervous system (i.e., neuropathic pain). However, pain from musculoskeletal disorders is also common, typically by changes in posture or increase in fall frequency after a stroke. Post-stroke pain can be caused by bladder disorders (e.g., urinary tract infections, retention), constipation, or pressure ulcers. Stroke survivors may even develop post-stroke headaches, sometimes recalcitrant to medical therapy.

Neuropathic pain is usually described as a burning or tingling sensation that is not aggravated with motion. Most of the time, this pain is either allodynic or hyperalgesic in nature. Central post-stroke pain (CPSP) is defined as a constant or intermittent pain in the areas where the body has abnormal sensation from the stroke. It was first noted by Wallenberg in 1895 and further described by Dejerine and Roussy as *thalamic syndrome* (slight hemiplegia, disturbance of superficial and deep sensation, hemiataxia, hemistereoagnosia, choreoathetoid movements, and intolerable pain). Unfortunately, the pathophysiology is not well understood and inductive theories stem from medications used to treat it, which are typically tricyclic antidepressants, NMDA blockers, GABA agonists, and non-pharmacologic approaches such as transcutaneous electrical nerve stimulation. In essence, CPSP mechanisms include neuroplastic changes in sensory cortex via glutamate-NMDA receptor system, reduced intracortical or spinal GABA inhibition, reduced noradrenergic modulation of altered afferent pain pathways, or alteration of sympathetic activity peripherally [55].

SSRIs and their related SNRIs can be primarily used in two different arenas in the management of post-stroke pain. The first is in the management of neuropathic pain. The proposed mechanism for the benefit of SSRIs in controlling neuropathic pain can be explained by Melzack and Wall's gate theory. The gate theory attempts to account for mechanisms where cutaneous stimuli and emotional states alter the level of pain [56]. In theory, activity in large myelinated afferent fibers activates dorsal horn interneurons that inhibit cephalad transmission in small unmyelinated primary afferent nociceptive fibers and the secondary transmission cells in the lateral spinothalamic tracts. In other words, pain signals can be blocked at the level of the spinal cord before being transmitted to the thalamic region of the brain. Melzack and Casey later explained that the pain experience can affect motivation, affect, and cognitive aspects. Some also believe that controlling the descending cortical pathways could block the nociceptive signals at the dorsal horn leading to a behavioral induced reduction of pain. The opposite may be true where depression "opens" gate mechanism leading to increased pain signaling.

Based on this mechanism, one can understand how chronic pain and depression can have a strong association. Chronic pain patients usually have a long history of pain before developing depression and predictors of depression with chronic pain patients include pain intensity, number of painful areas reported, and frequency of severe pain. Thus one possible explanation for SSRI's benefit in stroke patients is modulating pain as well as preventing depression secondary to chronic pain [57].

While SSRIs are used in pain management, the evidence for their role in post-stroke syndromes is not robust. In a study of 31 patients with post-stroke pain, the SSRI fluvoxamine was administered and pain was assessed using a visual analog scale (VAS). In this study, a significant reduction in pain was found (VAS 7.7 ± 2.2–6.0 ± 3.4 ($p < 0.01$)) [58]. This improvement was significant in patients whose stroke was within 1 year, but not in those who had experienced a stroke greater than a year ago. The limitations of this study include it lacking blinding and a placebo arm. Further studies are needed to determine the optimal dose, SSRI, and timing of the medications.

The other role of SSRIs/SNRIs is in the management of chronic pain in stroke patients. As mentioned above, there are several causes of pain from stroke. Many of these conditions are seen in the non-stroke population. In this population, SSRIs have demonstrated benefit in treatment of chronic neuropathic pain including headache [59, 60]. Consequently, when these conditions are present in stroke patients, they can be used for the same indications. In fact, they may be preferred to other pain medications in stroke patients. In contrast to opioids, they have a lower risk of sedation, addiction, and hindrance of neuroplasticity. Compared to NSAIDs, they may be a better alternative as many stroke survivors are on antiplatelet or anticoagulation agents. When combined with NSAIDs, there may be an increased risk of bleeding events. Other advantages of using SSRIs and SNRIS is that they are

well tolerated, are generally safe, are of extremely low risk of abuse, and do not require close monitoring in the outpatient setting.

Summary

SSRIs can play an important role in the management of stroke. Their therapeutic role is most prominent in the rehabilitation phase of stroke treatment. Evidence exists regarding their utility in treating PSD, improving motor recovery, enhancing overall functional status, and mitigating post-stroke pain syndromes. Health care providers who care for stroke patients should be aware of such conditions and consider SSRIs as part of their treatment plans.

This chapter began with a general review of the SSRI class of medication with a focus on the pharmacology as well as its indications in non-stroke-related conditions. Data for overall improvement in stroke uses, role in the treatment and prevention of PSD, motor recovery, pain syndromes, and neuroplasticity was highlighted.

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Constraint-Induced Therapies

21

Heather M. MacKenzie and Ricardo Viana

Case Presentation Mr. S. is a 68-year-old gentleman who sustained a right middle cerebral artery ischemic infarct in December of 2012 secondary to undiagnosed atrial fibrillation. As a result, he had weakness of the left face and upper extremity more than the lower extremity. He also presented with left-sided neglect.

He was admitted for 1 month to a specialized inpatient rehabilitation facility and participated fully in a traditional rehabilitation program with a focus on physiotherapy and occupational therapy. He subsequently returned home with his wife. Following his discharge, a physiotherapist and occupational therapist provided therapy to him on several occasions in his home. He learned compensatory strategies and demonstrated improvement in terms of his left-sided neglect. He also developed mild left-sided lower extremity spasticity, which facilitated his return to ambulation with the assistance of a single-point cane.

However, 9 months later he remained unsatisfied with the level of dysfunction in his left upper extremity. Following reassessment by a physical medicine and rehabilitation physician, he received botulinum toxin injections to better manage his wrist and finger flexor spasticity as well as a referral to a local outpatient hospital-based therapy program.

At the time of his intake assessment he was able to initiate slight active wrist and finger extension. Mr. S. stated that his goals were to increase independence with self-feeding and dressing. The occupational therapist felt that he would be a good candidate for a modified protocol of constraint-induced movement therapy. She had him engage in 1-h sessions of repetitive task-oriented training 2 days per week for a total of 8 weeks. She provided him with a mitt to be worn on the right hand for 2 h per day and taught him exercises to be done at home for 1 h each day. He demonstrated gradual improvements in his ability to maneuver utensils with the left hand at meal times and he developed independence with upper extremity dressing.

Background

Constraint-induced movement therapy (CIMT) is an approach to upper extremity rehabilitation originating from Taub's basic science research on monkeys with deafferented forelimbs [1]. The original protocol specifies a 2-week intervention where the less affected upper extremity is restricted using a mitt or sling for 90 % of waking hours, which includes therapy times. The participant then engages in repetitive task-oriented training with the more affected upper extremity for 6 h per day 5 days per week. CIMT also relies on the principles of shaping whereby progressively more difficult activities are introduced as the participant's performance gradually improves (Table 21.1) [2].

Enrollment in traditional CIMT has been limited to participants with at least 20° of active wrist extension, 10° of active extension at all metacarpophalangeal and interphalangeal joints of the affected upper extremity, and the ability to repeat these movements at a rate of at least three times per minute [3]. The participant must also be able to stand independently without upper extremity support for at least 2 min and transfer independently from sitting to standing and from the toilet with the restraint in place. Individuals have also typically been excluded from studies due to concurrent cognitive impairment, major medical comorbidities, or significant pain in the paretic extremity [4].

The clinical feasibility of CIMT from both the patient and therapist perspective has been questioned; as a result, various modified protocols (mCIMT) with shortened restraint and training periods have evolved (Table 21.2). Most commonly, the protocol continues to be 2 weeks in duration but the

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Table 21.1 Core components of CIMT protocol

Core components of CIMT
1. Restraint of the less affected upper extremity
2. Intense task-specific training and shaping therapy of the more affected upper extremity

Table 21.2 Comparison table examining the differences between traditional CIMT, modified CIMT, and forced-use protocols

	Traditional CIMT	Modified CIMT	Forced use
Duration	2 weeks	2–3 weeks	Variable
Restraint of the less affected upper limb	90 % of waking hours	Up to 6 h per day	Variable
Therapy of the more affected upper limb	6 h per day for 10 days	2–3 h per day for 10 days	No specific therapy

intensity is adjusted such that the restraint is worn for approximately 6 h per day and therapy is administered for 2–3 h per day. These mCIMT protocols require fewer resources and have been shown to yield similar outcomes when compared with the traditional protocol [5–9]. A distributed protocol providing the same total number of therapy hours as the original protocol but distributing them over twice as many days appears to be a promising alternative as well [10].

Mechanism of Action

Learned Nonuse

It is common following stroke for persons to direct their attention towards and rely heavily on their less affected upper extremity to complete tasks, effectively ignoring their paretic limb. The concept of learned nonuse states that a portion of the post-stroke functional deficit is not directly related to structural damage but rather occurs due to learned suppression of movement [11]. This behavior is acquired and reinforced during the acute phase following neurologic injury when attempts to use the paretic limb result in failure and compensation with the less affected limb is successful. CIMT forces the participant to use the affected upper extremity and is believed to overcome this phenomenon.

Neuroplasticity

It has also been hypothesized that processes of neural plasticity and reorganization form the basis for motor recovery following stroke. The utilization of functional magnetic resonance imaging (fMRI) has facilitated our understanding of how the brain changes in response to rehabilitation techniques. While the cortical area representing the affected upper extremity has been shown to shrink in size following stroke [12], the literature suggests that CIMT is associated with both functional and structural brain reorganization [13].

In a randomized controlled trial (RCT) by Lin et al., the clinical improvements seen in the distributed CIMT group were accompanied by a significant increase in activation of the contralesional hemisphere during movement of the affected and unaffected hand [14]. This suggests that recovery in the affected upper extremity may occur through the establishment of an ipsilateral motor pathway [14]. Interestingly, different fMRI activation patterns were seen between the intervention and control groups of the study by Lin et al., which indicates that the type of cerebral reorganization may in fact be specific to the rehabilitation technique being employed. For example, the control group receiving dose-matched traditional therapy based on neurodevelopmental techniques showed a decrease in ipsilateral sensorimotor cortex activation during performance with the affected hand [14].

In addition, a longitudinal fMRI study by Murayama et al. showed that affected limb movement in post-stroke patients before receiving CIMT was associated with contralateral cerebellar activation on fMRI. When they were reassessed post-CIMT there was a change towards bilateral cerebellar activation. Subsequently, at 3 months post-CIMT there was a trend towards increasing ipsilateral cerebellar activation. Following CIMT, brain activation patterns of post-stroke patients developed to more closely resemble those seen in healthy controls [15].

Transcranial Doppler sonography (TCD) is another way of studying the brain functionally. Interpretation of TCD is based on the assumption that increased blood flow velocity within an artery is an indicator of increased regional brain activity [16]. In a study by Treger et al., post-stroke patients at baseline demonstrated reductions in mean blood flow velocity (MFV) within the middle cerebral artery (MCA) of the affected hemisphere when compared to that of the unaffected hemisphere. In healthy controls, the MFV was similar in both hemispheres at baseline. When performing motor tasks with the non-dominant hand, healthy controls showed a slight increase in MFV in both hemispheres and there was no significant change when the dominant hand was restrained. However, in post-stroke patients, restraint of the less affected upper limb while performing motor tasks with the affected side resulted in near normalization of MFV in the MCA of the affected hemisphere [17].

Relative Importance of Protocol Components

There is uncertainty regarding which component(s) of the CIMT protocol—restraint, mode of training, or therapy intensity—are most responsible for its therapeutic benefit. Studies comparing groups receiving the same therapy with and without a restraint found that all participants improve

from baseline with no significant differences in outcomes between groups [18, 19]. Furthermore, extended use of the restraint after completion of the protocol does not appear to augment treatment outcomes [20]. Overall, restraint use does not appear to be a critical component of the protocol as participants make equal gains with and without it.

Conversely, the beneficial effects of CIMT appear to be more closely related to the mode of therapy as well as therapy intensity. When trying to determine whether the effectiveness of CIMT is attributable to intensity alone, it is important to look at studies with a control group receiving focused therapy of the affected upper extremity matched for intensity and duration. In the literature to date, there appears to be a trend towards non-inferiority of CIMT when compared with alternative high-intensity therapies focusing on the affected paretic limb [21]. Similarly, studies have shown CIMT to have a similar effect on upper extremity motor function when compared with intensity-matched bimanual therapy [22, 23]. Furthermore, a systematic review with meta-analysis performed by Stevenson et al. concluded that CIMT produced superior improvements in indicators of upper limb function in adult stroke survivors when compared with control interventions of equal dose and duration [24].

Clinical Applications

A Cochrane review by Sirtori et al. concluded that CIMT was associated with a moderate reduction in disability at the end of the treatment period when compared with traditional rehabilitation [25]. However, this review did not support a persisting benefit months after completion of the therapeutic protocol based on two RCTs [25]. A systematic review and meta-analysis repeated by Corbetta et al. in 2010 included four new studies [26]. This updated analysis showed no significant benefit of CIMT on disability. However, it is important to note that both reviews were limited by the heterogeneity that exists within the literature. Many of the available studies are underpowered due to their small sample size and large RCTs are required to better understand the potential benefits of CIMT.

Overall, the literature associates CIMT with significant gains in function of the hemiparetic upper limb post-stroke as well as increased use of that limb for daily activities [27–31]. In addition, long-term follow-up studies have shown that these improvements are maintained even years after completing the therapeutic protocol [32–34]. Recently some researchers have incorporated a "transfer package" designed to facilitate carryover of functional gains following completion of CIMT and encourage increased spontaneous arm use during real-world activities. The "transfer package" includes practices such as a behavioral contract, home diary, as well as problem-solving strategies to overcome perceived barriers. While initial studies have shown a benefit, research is ongoing [35, 36].

Timing

Traditionally, neurorecovery of the hemiparetic upper extremity is thought to occur predominantly during the first 3 months following stroke [37], though improvement has been shown to continue well beyond this period [38]. However, it is important to note that motor recovery in the upper extremity is notorious for lagging behind that in the lower extremity [39]. Originally, CIMT research focused on the chronic phase post-stroke. However, recent studies turned their attention to the acute and subacute phases.

The literature suggests that CIMT introduction within the first 14 days following stroke is safe. Pilot studies during this period show a trend towards greater improvements in affected limb function and use with CIMT when compared with traditional therapies [40–42]. The VECTORS trial compared traditional therapy with dose-matched mCIMT and high-intensity mCIMT. mCIMT was as effective as the intensity-matched control group during the acute phase following stroke. However, the high-intensity CIMT group showed less improvement in upper extremity function at 90 days; during the acute phase following stroke, there appears to be a threshold in terms of therapy intensity above which there is no added benefit and poorer outcomes may be observed [43].

The EXCITE trial also studied patients in the subacute phase and found that CIMT produced improvements in upper limb function that were both statistically and clinically significant when compared with customary care in patients 3–9 months post-stroke. Furthermore, these benefits were maintained upon reassessment at 1 year [4].

McIntyre and colleagues conducted a systematic review and meta-analysis of the evidence on the use of CIMT among stroke survivors more than 6 months following stroke [38]. They examined 16 RCTs and found that CIMT was associated with a significant benefit in terms of function as measured by the amount of use and quality of movement subscales of the Motor Activity Log, Fugl Meyer Assessment, and Action Research Arm Test. They concluded that for patients during the chronic phase post-stroke, CIMT is a beneficial therapy [38]. Similarly, the EXCITE trial concluded that regardless of whether CIMT was implemented 3–9 months or 15–21 months following stroke, patients reached the same level of affected upper limb function 2 years after their neurologic event [44].

Applications in Special Populations

Despite the prerequisites for participation described previously, CIMT has been used successfully in a variety of patient populations who do not fully meet these criteria.

Siebers et al. implemented a 2-week mCIMT protocol in a group of 20 outpatients with spastic hemiplegia and found

improvement in functional upper limb use and reduction in spasticity as measured using the Modified Ashworth Scale that were maintained at the 6-month follow-up [45]. Sun et al. published a case study of a male patient 4 years post-stroke with severe flexor spasticity and nonuse of the dominant upper limb that did not meet the minimum motor requirements for participation in CIMT. He received botulinum toxin A injections targeting the elbow, wrist, and finger flexors followed by a 4-week mCIMT protocol and a 5-month home exercise program. He showed improvements in muscle tone as well as function and use of the affected upper limb [46]. Similarly, chronic post-stroke patients with plegic fisted hands at baseline have been shown to benefit from CIMT combined with conventional rehabilitation techniques [47].

In addition, Wu and colleagues demonstrated that a distributed 3-week CIMT protocol was well tolerated by elderly stroke survivors with considerable nonuse of their affected upper limb and resulted in significantly greater improvements in function when compared with traditional rehabilitation [48]. Similarly, Boe et al. determined that while patients with cognitive impairment required extra therapist attention, they still showed significant motor gains following 2 weeks of CIMT [49].

Barriers to Implementation

Despite the gains in motor function and increased use of the upper extremity in daily activities after CIMT, it has not become standard practice. A variety of barriers have been identified that continue to limit its routine use in stroke rehabilitation (Table 21.3) [21].

Table 21.3 Barriers to the routine implementation of CIMT

Barriers to CIMT implementation	
1. Generalizability	• Strict mobility requirements • Studies focus on patients with mild to moderate stroke severity
2. Resource intensity	• Cost of restrictive device is minimal • The original protocol requires one-on-one therapy for 6 h per day, 5 days per week, for 2 weeks • Therapists require specialized training • Requires dedicated clinical space
3. Therapist factors	• Challenging to develop a novel 6-h therapy program each day • Highly demanding of therapist time • Less available time for other patients on the therapist's caseload
4. Patient factors	• Low interest in wearing restrictive device • Low motivation to participate in lengthy therapy sessions • Possible exacerbation of pain and/or fatigue

Generalizability

The prerequisites for participation restrict enrollment to a small subset of stroke survivors. Only two trials—EXCITE and VECTOR—reported on the number of potential participants screened in order to obtain their study sample; the study sample represented only 6.1 % and 10.8 % of the screened population, respectively [4, 43].

The mobility requirements for CIMT result in the exclusion of most patients with severe stroke. Patients previously included in CIMT trials would be categorized as mild to moderate stroke severity and have relatively preserved upper limb function. Studies have however been completed using less restrictive inclusion criteria allowing patients with moderate to severe stroke to participate in CIMT. Using a 3-week mCIMT program, patients with chronic moderate severity upper extremity paresis showed improvements in both therapist-rated and patient-rated measures of upper extremity function immediately following the conclusion of therapy [50]. These gains were maintained at 1 and 6 months following the active treatment period [50].

Resource Intensity

While the cost of the restrictive device is minimal, the principal cost of CIMT relates to the resource-intensive therapeutic protocol. The original protocol requires 6 h per day of one-on-one therapy 5 days per week for 2 weeks. This intensity of therapy is generally not available within a publicly funded healthcare system. When asked via self-report questionnaire, 74 % of therapists in the Northeastern USA felt that their facilities did not have the resources necessary to administer CIMT [51]. Therapists also expressed concerns regarding space limitations at their clinics as well as the need to receive specialized training in advance of administering the program [51].

Therapist Factors

Many therapists are reluctant to adopt CIMT into their practice. On the questionnaire administered by Page et al., 68 % of therapists reported that CIMT would be "very difficult" or "difficult" to administer specifically because of the need to develop a challenging and engaging 6-hour therapy program each day [51]. Many therapists also cited safety concerns with the use of a restrictive device in patients with balance problems as a barrier to the routine use of CIMT [51]. Furthermore, therapists were concerned about the extraordinary demands CIMT would put on their schedule and how it might impact upon the treatment time available for the remainder of their patient caseload [51]. Similarly, in response

to an online survey in the UK, 62.9 % of occupational and physical therapists reported that they had not used CIMT [52]. The two main barriers identified by therapists in this study were lack of both resources and training [52].

Patient Factors

Patients are not necessarily enthusiastic about the use of a restraint and, in some cases, they are perceived to be unable to tolerate the degree of therapy intensity required for CIMT. Page et al. also surveyed stroke survivors and found that 68 % of patients said that they would not participate in CIMT due to concerns regarding intense restrictive device use and long therapy hours [51]. Furthermore, 65 % of patients said that they were "somewhat unlikely" or "not at all likely" to wear the restrictive device as prescribed. 54 % of patients indicated that they were "somewhat unlikely" or "not at all likely" to make all the therapy sessions and more than 50 % of this group said that they would be "somewhat unmotivated" or "extremely unmotivated" during the 6-h sessions [51]. Underwood et al. studied patient tolerance to therapy in a subgroup analysis of the participants enrolled in the EXCITE trial and concluded that CIMT could be administered without exacerbating symptoms of pain and fatigue, even in the early phase of recovery post-stroke. Pain and fatigue scores actually remained low throughout the 2-week treatment period in this group of patients with mild to moderate stroke severity receiving CIMT during either the subacute or chronic phase post-stroke [53]. However, it is important to note that participants were carefully selected for the EXCITE trial and were excluded if they had "excessive pain in any joint of the paretic extremity" or if they had "insufficient stamina to participate" [4].

Alternative Methods of Delivery

In an effort to take advantage of the therapeutic benefit of CIMT without straining resources, alternative methods of therapy delivery have been investigated. For example, administering CIMT in a small group format with two to four patients per therapist appears to be a feasible alternative to the original one-on-one design [20, 54, 55]. In addition, Hosomi et al. examined a protocol composed of 60 % self-training and 40 % direct therapist supervision for a total of 5 h of therapy per day for 10 weekdays. This protocol resulted in significant gains in affected upper limb function and provides further evidence that patients do not seem to require constant therapist supervision [56].

Remote, home-based CIMT interventions are also being investigated. Barzel et al. provided both the patient and his or her family member with a 1-day training session by a physiotherapist and they then performed 2 h per day of therapy at home using shaping techniques for 4 weeks (20 therapy days). A restraint was worn for 60 % of waking hours. The physiotherapist visited the home once per week to provide supervision. This protocol was found to be as effective as the original CIMT protocol described by Taub [57].

Lum and colleagues have developed the Automatic Constraint Induced Therapy Extension (AutoCITE) workstation, which delivers the task practice component of CIMT without the need for one-on-one therapist supervision. Studies have shown functional gains with AutoCITE similar to those seen with traditional supervised CIMT [58–60].

Conclusion

CIMT continues to be a controversial therapeutic technique for the hemiplegic upper extremity. Overall, the available evidence supports its use during the acute, subacute, and chronic stages post-stroke. However, it is not routinely used within rehabilitation programs due to various barriers. Nevertheless, the future for CIMT remains promising as research is ongoing and new protocols are emerging that may enable it to be successfully implemented in a more widespread fashion.

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Virtual Reality in Stroke Rehabilitation

22

Gustavo Saposnik

Abbreviations

AMPS	Assessment of Motor and Process Skills
BBT	Box and Blocks Test
BESTest	Balance Evaluation Systems Test
C	Control group
CO	Cable orthosis
CR	Conventional rehabilitation
FIM	Functional Independence Measure
FM	Fugl-Meyer Arm Scale
JTHF	Jebsen Test of Hand Function
MFT	Manual Function Test
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MSA	Modified Ashworth Scale
PE	Physical environment
PO	Pneumatic orthosis
RA	Recreational activities
RCT	Randomized controlled trial
SIS	Stroke Impact Scale
VE	Virtual environment
VR	Virtual reality
WMFT	Wolf Motor Function Test

Case Presentation Mrs. K is a 73-year-old woman who was admitted with a left hemiparesis and slurred speech. Past medical history was remarkable for recent diagnosis of atrial fibrillation and hypertension. An MRI of the brain revealed a right frontal ischemic stroke involving a branch of the right middle cerebral artery. The stroke mechanism was presumed cardioembolic. Anticoagulation therapy was initiated for secondary stroke prevention.

She was discharged from an acute care facility to a rehabilitation institution with a moderate left arm weakness (Medical Research Council scale = 4 proximal and 3 distal) and mild dysarthria. Mrs. K was able to touch with her left arm her chin and contralateral knee. She was assessed by the stroke rehabilitation team who proposed a conventional rehabilitation program. Mrs. K also asked if any novel neurorehabilitation strategies were available as she heard that conventional stroke rehabilitation was boring and labour intense.

This chapter reviews the current evidence available on the application of virtual reality in stroke rehabilitation. Other innovative rehabilitation strategies are discussed in different chapters.

Background

Stroke is a devastating disease for patients and their families and a leading cause of adult disability. Up to 85 % of stroke patients experience hemiparesis immediately after stroke, and between 55 and 75 % of survivors continue to experience motor deficits, associated with diminished quality of life [1, 2]. The risk of stroke increases steeply with age; thus with the aging of the population, an increase in the prevalence of stroke is expected. Consequently, we are expected to face the challenge of managing more patients with functional impairments [3]. Rehabilitation services are an increasingly large and important aspect of health care, especially following a stroke. Generally speaking, conventional rehabilitation after stroke usually consists of 1–2 h of physiotherapy and occupational therapy per day (excluding weekends) [3, 4]. The comparison of different conventional techniques (e.g., neurodevelopmental technique, Bobath, proprioceptive neuromuscular facilitation, or motor relearning) has shown no significant differences in functional outcomes [5–7].

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Limitations of Conventional Rehabilitation

Traditional stroke rehabilitation has several limitations (Table 22.1): it is time consuming, labor and resource intense, dependent on patient adherence, and limited in its availability depending on geography. While conventional rehabilitation (i.e., physiotherapy and occupational therapy) helps improve motor function after stroke, the magnitude of its benefit is suboptimal [3, 7, 8]. Moreover, some patients only perceive modest and delayed effects, so the benefits of conventional rehabilitation are not often fully appreciated by stroke survivors [4, 8].

What Is Virtual Reality?

Virtual reality (VR) is a computer-based technology that allows users to interact with a multisensory simulated environment and receive "real-time" feedback on performance.

Most current VR systems are primarily visual experiences, using either a computer screen or special stereoscopic 3D screens (e.g., virtual reality room). Additional sound information is provided through speakers or headphones. Some advanced VR systems include haptic feedback technology that takes the advantage of the sense of touch by applying forces, vibrations, or motions to the user providing tactile information [9–12].

VR has been used in a wide variety of applications, including aeronautic and military training, architecture, sports, entertainment, art, and medicine. In the medical field, VR is being applied in rehabilitation, laser eye surgery, training for performing medical procedures (e.g., endoscopic or endovascular), and behavioral education (cognitive behavioral therapy) [9, 10, 13, 14].

VR applies relevant concepts in stroke rehabilitation, such as high repetition, high intensity, and task-oriented training of the paretic extremity [7, 15]. VR applications range from non-immersive to fully immersive depending on the degree to which the user is isolated from the physical surroundings when interacting with the virtual environment [15].

Table 22.1 Limitations of conventional rehabilitation for stroke

Time consuming
Modest effect (e.g., initially not appreciated by stroke survivors)
Resource and therapy intensive
Limited compliance/adherence
Transportation to a rehabilitation facility
Availability
Coverage vs. out-of-pocket costs

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Also classified as VR are a variety of non-immersive video-game systems developed by the entertainment industry for home use, making this technology less costly and more accessible to clinicians and individuals. Several of these games have been adopted by clinicians as rehabilitation interventions even though they have not been especially designed to meet rehabilitation goals, nor validated in large randomized clinical trials.

Neurobiological Principles in Virtual Reality Applied to Stroke Rehabilitation

Recovery depends on learning new strategies and motor patterns. Three important principles may be involved in motor recovery using virtual reality technologies: (1) brain plasticity, (2) "mirror-neuron system," and (3) the "brain reward system."

The presence of a hemiparetic limb may result in suppression of the cortical representation of the affected limb (i.e., hand) and further inhibit its spontaneous use [16]. Motor improvement can be achieved by the brain's own ability to relearn and readjust. Repetitive, intensive, and task-specific functional training are the current paradigms applied in neurorehabilitation after stroke to facilitate motor relearning and consequently improvement of function [17, 18]. This is possible due to cortical reorganization and rewiring in the injured brain (brain plasticity) [16, 18]. Intense training and the observation, practice, and representation on the screen of task-specific activities can facilitate cortical reorganization. This is possible by engaging the "mirror neuron system" and/or long-term potentiation effects. The use of virtual reality showed practice-dependent enhancement of the affected arm through the facilitation of cortical reorganization using functional MRI [19]. These observations were also consistent with previous studies using transcranial magnetic stimulation and functional MRI that have demonstrated decreased ipsilateral cortical activation and increased contralateral activation as functions of intensive practice of the affected limb [20, 21]. A learning by imitation has been suggested to induce an imitation-dependent organization around the motor cortex through "mirror" neural networks [22]. Similarly, participants who received sensory feedback during the VR training learned the motor pattern by imitation. This might have facilitated use-dependent cortical plasticity, which was primarily reorganized at the supplementary motor cortex [19].

For example, a study including 154 healthy teenagers revealed morphological changes (e.g., thickening of grey matter) and activation of the ventral striatum using functional MRI among frequent (defined as more than 9 h per week) video-game players. The association of video-game playing with higher left ventral striatum volume could reflect altered reward processing and represent adaptive neural plasticity [23].

VR gaming technology has all the advantages of virtual reality systems including the provision of multisensorial (visual, auditory, and tactile) feedback, affordability, and easy implementation. Moreover, VR may engage the "brain reward system," thus improving performance by optimizing or increasing patients' motivation.

The brain reward system is a group of dopamine-mediated mesolimbic structures (nucleus accumbens and orbitofrontal circuits) that may be activated when participants play a video game. Some studies suggest an improvement of patients' attitudes toward chemotherapy in healthy individuals immediately after the interactive gameplay. Using functional MRI, researchers found increased activation in several brain regions including a subregion of the left parahippocampal cortex. Another study including 18 health males found two different stimuli for the reward circuits: (1) reward-specific and (2) reward nonspecific networks. The anterolateral orbitofrontal cortex processes monetary gains, whereas the posterior lateral processes more basic erotic stimuli. Further studies may be needed to validate these findings [24].

The Current Evidence

Two large meta-analyses evaluating the use of virtual reality revealed the potential benefits of VR [25, 26]. Saposnik et al. evaluated the benefits of VR in the upper extremity after stroke. They initially found 35 studies, but only 12 studies (five RCTs and seven observational) met the inclusion/exclusion criteria comprising 195 participants (on average, less than 20 patients per study). Age ranged from 26 to 88 years old. Two-thirds ($n=8$) of the interventions used non-immersive VR systems (Virtual teacher, Cyberglobe, VR Motion, Pneumoglobe, Wii). Eleven of 12 studies showed a significant benefit toward VR for the selected outcomes (Table 22.2). Among the RCTs, there were three studies using immersive VR (e.g., Glasstrom, IREX, Playstation EyeMotion) and two applying non-immersive systems (e.g., VR Motion, Wii). In the pooled analysis of all five RCTs, patients randomized to VR were five times more likely to improve motor function (OR 4.89; 95 % CI 1.31–18.3) (Fig. 22.1). Interventions were delivered within 4–6 weeks with an average of 1-h duration for each session (range 30 min–2.5 h/session) in most of the studies [25].

The Cochrane review included 19 studies with a total of 565 participants [26]. Virtual reality was found to be significantly more effective than conventional therapy in improving upper limb function (standardized mean difference (SMD) 0.53, 95 % confidence intervals [CI] 0.25–0.81) based on seven studies ($n=205$ patients), and activities of daily living (ADL) function (SMD 0.81, 95 % CI 0.39–1.22) based on three studies. No statistically significant effects were found for grip strength (based on two studies) or gait speed (based on three studies) [26]. They also found a benefit whether the intervention was using specially designed games or commercially available games (Fig. 22.2).

Following these meta-analyses, there have been only two small studies ($n=26$ and $n=33$) showing that VR may potentially improve arm function [27, 28]. One of the studies using kinematics (analysis of movement patterns) revealed that VR training led to improvement in the mild group and less compensation in the moderate-to-severe group likely related to a better sensorial feedback provided by VR systems [28]. Another study comparing three different modalities of VR [e.g., rehabilitation gaming system alone ($n=16$), with exoskeleton (assisted outer limb) ($n=14$), or with tactile feedback technology ($n=14$)] in chronic stroke patients revealed that all groups similarly improved with respect to most standard clinical evaluation scales [29]. These findings suggest that VR itself may lead to benefits irrespective of the specific device [29].

Do We Need Multicenter Clinical Trials Testing VR for Stroke Rehabilitation?

According to the meta-analyses and despite the promising results, most studies have included a small sample size and only seven were RCTs and most were conducted in a single center [25, 26]. Some studies specifically focused on motor recovery of the upper limb, whereas others included more general outcomes after stroke, such as memory retraining, gait stance, and balance. Despite the observed benefit, the heterogeneity in the design, VR systems, population target, control group, and the outcome measures constitute a limitation to draw valid conclusions. The authors concluded, "'*Virtual reality appears to be a promising approach however*, *further studies are required to confirm these findings*'. *Unfortunately*, *whether VR is an effective strategy to improve motor function for activities of daily living after stroke remains unknown*" [26].

As a result, there is a clear need for properly designed large, multicenter, randomized clinical trials to establish the efficacy and safety of virtual reality gaming systems as therapeutic alternative in patients with stroke. Well-designed RCTs will provide the highest level of evidence by reducing bias. By carrying out the study at multiple sites, RCTs will help determining that the results are generalizable to any rehabilitation population and/or setting.

Lessons Learned from Previous VR Studies

In summary, previous VR studies have shown that (1) studies using VR are feasible and largely safe; (2) the target population (recent stroke within 3 months or thereafter within

Table 22.2 Systematic review on virtual reality in neurorehabilitation of the upper extremity after stroke

Author	Design	*N*	Time since stroke onset	Type VR	Intervention	Outcome	Conclusion
Holden et al. (2002)	Pre-Post	9	>6 months	Non-immersive (virtual teacher)	1 h/day, 3 days a week × 20–30 sessions	FM, WMFT	Significant improvement in FM and WMFT
Boian et al. (2002)	Pre-Post	4	1–4 years	Non-immersive (CyberGlove and a Rutgers Master)	2 h/day, 5 days a week, 3 weeks	JTHF	Significant improvement in computerized measure of thumb range, finger speed, fractionation, and JTHF
Piron et al. (2003)	RCT	VR = 12 CR = 12	<3 months	Non-immersive (VR Motion)	1 h/day, 5 days a week, 5–7 weeks	FM, FIM	Small difference between VR and conventional therapy groups in FM and FIMTM
Piron et al. (2005)	Pre-Post	50	>6 months	Non-immersive (VR Motion)	1 h/day, 5 days a week, 4 weeks	FM, FIM	Significant improvement in FM and FIMTM
Jang et al. (2005)	RCT	VR = 5 Control = 5	>6 months	Immersive (IREX)	1 h/day, 5 days a week, 4 weeks	FM, BBT, MFT	Significant difference between VR and no therapy groups in FM, BBT, and MFT
Merians et al. (2006)	Pre-Post	8	1–4 years	Non-immersive (CyberGlove and a Rutgers Master)	2–2.5 h/day, 13 days, 3 weeks	JTHF	Significant improvement in computerized measure of thumb range, finger speed, fractionation, and JTHF
Broeren et al. (2007)	Pre-Post	5	>6 months	Immersive (Reaching APE and Crystal Eyes)	45 min/day, 3 days a week, 5 weeks	Kinematics, BBT, AMPS	Significant improvement in motor performance. No difference in BBT and AMPS
Fischer et al. (2007)	RCT	CO = 5 PO = 5 Control = 5	1–38 years	Immersive (Glastrom/CAVE)	60 min, 18 sessions, 6 weeks	WMFT, FM, BBT	Significant improvement in WMFT. Trend favoring PO in FM and BBT
Yavuzer et al. (2008)	RCT	VR = 10 Sham VR = 10	<12 months	Immersive (Playstation EyeToy)	30 min/day, 5 days a week, 4 weeks	Brunnstrom, FIM	Significant difference in motor performance and DIM
Kamper et al. (2010)	Pre-Post	VR + device = 7 VR control = 7	>6 months	Non-immersive (PneuGlove)	60 min × 3 days a week, 6 weeks	FM, BBT	Significant improvement in FM and BBT
Yong et al. (2010)	Pre-Post	16	<3 months	Non-immersive (Nintendo Wii)	30 min × 6 sessions within 4 weeks	FM, MFT, MAS	Feasible. Significant difference in FM and MFT
Saposnik et al. (2010)	RCT	VR + CR = 10 RA + CR = 10	<3 months	Non-immersive (Nintendo Wii)	60 min × 8 sessions within 2 weeks	WMFT, BBT, SIS	Feasible, safe, and significant improvement in WMFT, BBT
Kwon et al. (2012)	RCT	VR + CR = 13 CR + CR = 13	<3 months	Non-immersive (IREX)	30 min × 5 days per week within 4 weeks	FM, MFT	Feasible, safe, and significant improvement in FM in VR and CR
Subramanian et al. (2013)	RCT	VE = 16 PE = 16	6–60 months	Immersive (CAREN)	12 sessions over 4 weeks	FM, RPS, WMFT	VE training led to motor improvement compared to PE

AMPS Assessment of motor and process skills, *CR* conventional rehabilitation, *CO* cable orthosis, *PO* pneumatic orthosis, *BBT* Box and Blocks Test, *FIM* Functional Independence Measure, *FM* Fugl-Meyer Arm Scale, *JTHF* Jebsen test of hand function, *MSA* Modified Ashworth scale, *MFT* Manual Function Test, *RCT* randomized controlled trial, *SIS* Stroke Impact Scale, *VR* virtual reality, *RA* recreational activities, *WMFT* Wolf Motor Function Test, *VE* virtual environment, *PE* physical environment

Wolters Kluwer Health, Stroke, Virtual Reality in Stroke Rehabilitation: A Meta-Analysis and Implications for Clinicians, Gustavo Saposnik, Mindy Levin, for the Stroke Outcome Research Canada (SORCan) Working Group, May 1, 2011, Volume 42, Issue 5

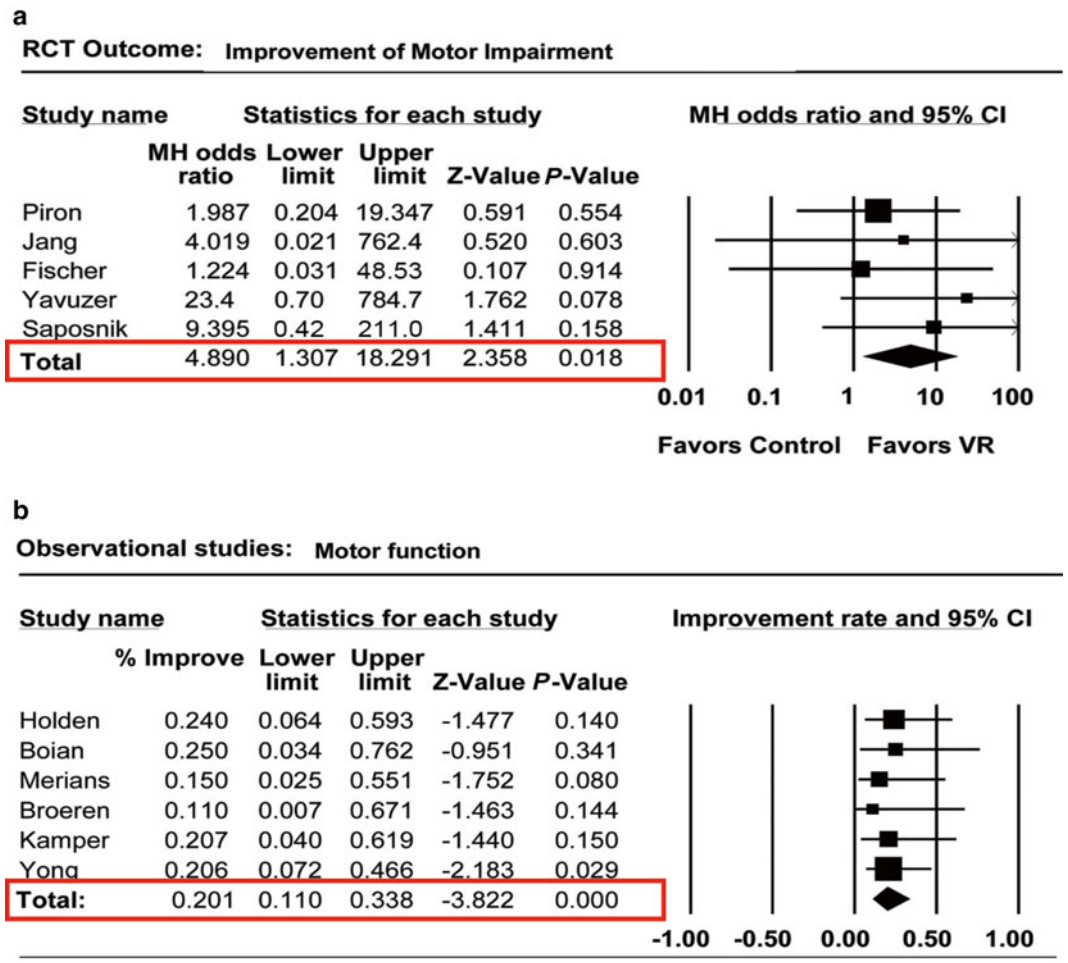

Fig. 22.1 (**a**) Benefits of VR in RCTs (with permission from Saposnik et al.). Stroke patients randomized to VR were nearly five times more likely to achieve a motor improvement compared to controls (**a**). (**b**) Benefits of VR in observational studies (with permission from Saposnik et al.). In observational studies (**b**), patients receiving VR had a mean 20 % improvement compared to their baseline performance [25]. *Wolters Kluwer Health*, *Stroke*, *Virtual Reality in Stroke Rehabilitation*: *A Meta-Analysis and Implications for Clinicians*, *Gustavo Saposnik*, *Mindy Levin*, *for the Stroke Outcome Research Canada* (*SORCan*) *Working Group*, *May 1*, *2011*, *Volume 42*, *Issue 5*

1–2 years) seems appropriate; (3) elderly patients appear to be compliant with the interventions; (4) overall, results from meta-analysis revealed an approximately 4–5 times higher likelihood of benefits for patients randomized to VR technology or 20–30 % improvement in motor function when compared before and after the intervention; (5) scales for functional assessments can be completed within 1 or 2 h; (6) novel VR devices are inexpensive and could be set up in hospitals or patients' homes; and (7) the small sample size (on average 30 patients per study; the largest study had 48 participants), mostly conducted in single centers, was underpowered to make definitive conclusions. Large randomized clinical trials are needed.

Ongoing Clinical Trials Using VR in Stroke Rehabilitation

Overall, there are seven ongoing RCTs, all of them using single blinding (source: ClinicalTrials.gov accessed April 23, 2014) (Table 22.3). A common issue in the design and implementation of RCTs in rehabilitation is the inability to double blind the trial. A potential solution to ameliorate this issue is implementing a blinded assessor (the outcome assessor is blinded to the received intervention). Only three of them have a sample size larger than 100 patients. Prior to 2010, most of the RCTs targeted subacute or chronic stroke

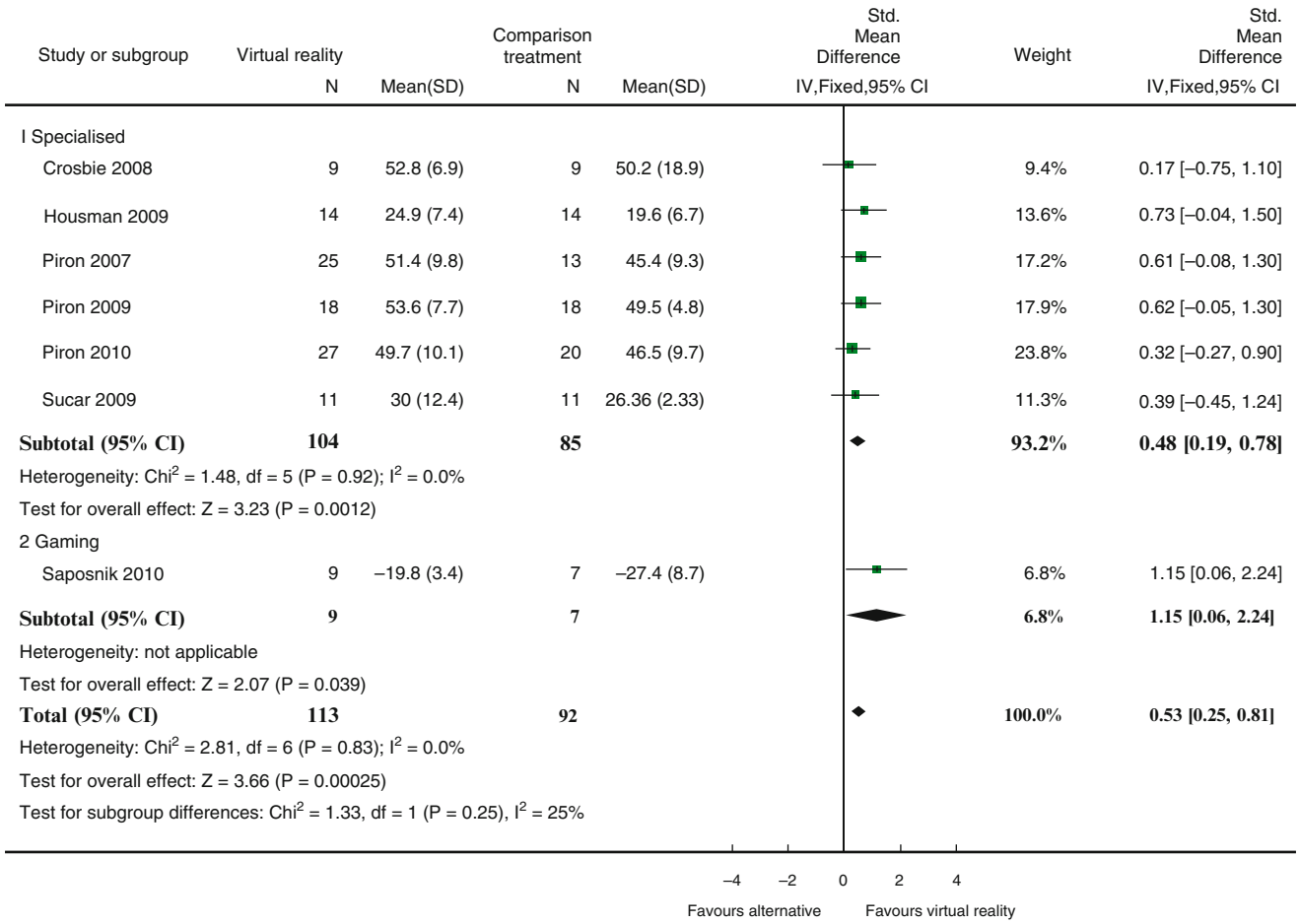

Fig. 22.2 Comparison between specialized and commercially available VR gaming. Most studies have used specialized games. However, small studies suggest that both seem to be effective in improving motor function for stroke rehabilitation [26]. *Cochrane Database of Systematic Reviews*, *Virtual reality for stroke rehabilitation*, *Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons*, *Ltd*, *Kate E Laver*, *Stacey George*, *Susie Thomas*, *Judith E Deutsch*, *Maria Crotty*, *Sep 7*, *2011*, *Fig. 2.2*, *2.3*

patients. One of the earliest studies targeting stroke patients within 3 months from symptom onset (*E*ffectiveness of *V*irtual *R*eality *E*xercises using Wii gaming technology in *ST*roke rehabilitation—EVREST) found that VR was feasible, safe, and potentially effective in improving motor function. Participants in the VR arm had a significant improvement in mean motor function of 7 s (Wolf Motor Function Test (WMFT), 7.4 s; 95 % CI, −14.5, −0.2) after adjustment for age, baseline functional status, and stroke severity compared to recreational therapy. Following the initial EVREST pilot publication, there has been an increasing interest in randomizing patients to VR technologies early after stroke (within the first 3 months) [40].

Despite the wide variety of outcome measures, the primary end-points for most of the previous and ongoing studies include the use of Fugl-Meyer, Wolf Motor Function, and/or Box and Block tests. Kinematics or cognitive improvements are secondary outcome measures in some studies (Table 22.2).

Based on the characteristics of previous studies using VR in stroke rehabilitation, the ideal trial should include a larger sample size, randomized design, multicenter, and multicountry with a comprehensive number of sessions (five times a week, at least 30–60 min each) over a reasonable period of time (2–6 weeks) using a blind assessor for outcome assessment and an active control group.

Table 22.3 Ongoing clinical trials

Author (Country)	*n*	Target population	Design	Intervention	Time	Primary outcome	Expected results
Laffont (France)	62	>18	RCT, S	Dedicated adaptative video games vs. C	<6 weeks	FM, WMFT, ARAT, BBT, MRI	March 2014
Zucconi (Italy)	122	>18	RCT, S	Reinforced feedback in VE (RFVE) vs. C	<12 months	FM, FIM, kinematics	Dec 2016
Kiper (Switzerland)	60	>18	RCT, S	VR (YouGrabber) vs. C	>6 months	BBT, CMM, CAHAI	Dec 2015
Yee (Singapore)	30	25–99	RCT, S	VR + L-Dopa vs. C + L-Dopa	<3 weeks	FM, ARAT, FIM	Aug 2014
Piemonte (Brazil)	40	18–65	RCT, S	VR vs. C	<6 months	FM, BESTest, MoCA	Dec 2015
Saposnik (Canada)	140	18–85	RCT, S	VR games vs. RA	<2 months	Wolf Motor Function, BBT, SIS	Aug 2015
Brunner (Norway)	120	18–80	RCT, S	VR (YouGrabber) vs. C	<3 months	ARAT, BBT, FIM	August 2016

BESTest balance evaluation systems test, *MoCA* Montreal Cognitive Assessment, *C* control, *BBT* Box And Blocks Test, *FIM* Functional Independence Measure, *FM* Fugl-Meyer Arm Scale, *JTHF* Jebsen test of hand function, *RCT* randomized controlled trial, *S* outcome assessor is single blind, *SIS* Stroke Impact Scale, *VR* virtual reality, *RA* recreational activities, *ARAT* action research arm test, *WMFT* Wolf Motor Function Test, *VE* virtual environment, *PE* physical environment, *RFVE* reinforced feedback in virtual environment

Some questions to be answered by these RCTs include the following: (1) Does VR technology improve motor function relative to an active control (e.g., recreational activities) in patients with a recent/chronic stroke independently or as adjunct therapy with conventional rehabilitation? (2) Is VR safe in patients with a recent stroke? (3) Does VR technology help improving quality of life compared to other interventions? (4) What is the motor improvement pattern for participants randomized to VR technologies? (5) Is bimanual training using VR more effective than the training using the affected arm?

Measuring Outcomes in Rehabilitation Studies

There are a wide variety of scales, functional outcomes, and quality-of-life measures. A recent study revealed the disparity of outcomes reported among stroke rehabilitation studies [30]. Some focused on single rather than multiple dimensions (e.g., motor impairment, activities, or social participation and quality of life). For instance, the main outcome measure was motor function using WMFT [31] or Box and Block Test (BBT) [20, 32] in 6/12 studies included in the meta-analysis [25], and only one included social participation/quality of life using the Stroke Impact Scale (SIS) [33]. Improvement in activities of daily living (e.g., Barthel index) (0/12 studies) or social participation/quality (1/12 studies) of life was not included in the majority of the studies. Cognitive assessments mostly use the Montreal Cognitive Assessment (MoCA) [34], which has been validated and translated into several languages. The Functional Independence Measure (FIM) is routinely used to measure functional abilities [35]. The Hospital Anxiety and Depression Scale (HADS) and Intrinsic Motivation Inventory (IMI) are brief, self-administered, and validated tools used to screen for the presence of depression and anxiety and motivation, respectively [36, 37]. Kinematics can be measured either using video recording for subsequent analysis or by using the Reaching Performance Scale (RPS) for assessing compensatory movements for upper extremity reaching [38].

Ideally, RCTs should include different outcome measures to account for multiple dimensions, including motor function (e.g., WMFT, BBT), impairment (e.g., WMFT, Chedoke-McMaster), activities of daily living (e.g., Barthel index), and social participation/quality of life (e.g., SIS). All these scales are commonly used to specifically measure outcomes in neurorehabilitation after stroke [30].

Further details on these and other scales commonly used in stroke rehabilitation can be found at www.medicine.mcgill.ca/strokengine-assess/.

Practical Implications and Relevance

It is expected that in the next 2–3 years, the results of larger RCTs using VR would provide answers on how to best utilize new promising therapeutic opportunities for stroke recovery. For example, EVREST Multicenter (which follows EVREST Pilot) was designed with the hypothesis that VR may provide an affordable, enjoyable, and effective alternative

to intensify treatment and promote motor recovery after stroke [39, 40].

The use of a novel, simple, wireless, and widely available 3D virtual reality technologies may allow the implementation of proven concepts in stroke rehabilitation (repetitive, high-intensity, and task-specific activities) to improve motor function even for home use. The results of the ongoing RCTs will advance knowledge about the optimal rehabilitation strategy for patients with a disabling stroke. At the patient level, there is an opportunity for a new, exciting mode of stroke rehabilitation that may be undertaken in various clinical and non-clinical settings. Further, they may facilitate adjuvant rehabilitation at home, thus revolutionizing current post-stroke rehabilitation practices.

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Transcranial Magnetic Stimulation

23

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Suzete Nascimento Farias da Guarda

Case Presentation A 62-year-old man with a history of arterial hypertension presented sudden complete left hemiparesis (MRC 2 in left arm and leg). He was examined 12 h after the ictus and the NIHSS score was 8 (facial palsy—1, left arm paresis—3, left leg paresis—3, and dysarthria—1). MRI showed an acute infarct in the posterior limb of the right internal capsule. He was not eligible for intravenous thrombolysis. Could treatment with transcranial magnetic stimulation (TMS) facilitate motor recovery, or response to rehabilitation in this case? Could rTMS worsen motor impairments? Would rTMS be safe for this patient?

Introduction

Observations about possible effects of magnetic or electric fields on the nervous system were made as far back as 2000 years ago [1]. However, transcranial magnetic stimulators were publically presented for the first time in 1985. Since then, TMS has emerged as a powerful tool to investigate mechanisms of plasticity, and also as a potential adjuvant therapy for stroke rehabilitation. At the time this chapter is written, repetitive TMS (rTMS) is considered an experimental noninvasive brain stimulation (NIBS) intervention, not approved by the US Food and Drug Administration for clinical use in stroke rehabilitation. In the past decade, research about potential benefits of TMS in stroke has advanced enormously. This chapter reviews key studies that evaluated the effects of rTMS on motor function, language, neglect, and depression in individuals with stroke. Safety aspects are also discussed. The integration between rTMS, other neurophysiology techniques, and structural and functional neuroimaging is a promising strategy to target key networks involved in stroke recovery.

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Basic Principles

In TMS, neurons in the brain are noninvasively depolarized through electromagnetic induction. A high-intensity electric current flows quickly through a coil, inducing a magnetic field perpendicularly to the coil (Fig. 23.1). The rapid change in the magnetic field induces an electric field near the coil. Rather than the absolute intensity of the magnetic field, its rate of change determines the intensity of the induced electric field [2–4].

When the coil is placed on the head, the electric field can reach neurons located at distances that vary according to the type of coil and the intensity of stimulation. Figure-of-eight coils are typically more focal than round coils. Round and figure-of-eight coils typically are able to stimulate cortical neurons at a depth of about 2–3 cm, while H-coils are able to induce currents in deeper structures [5, 6].

Techniques

When a single TMS pulse is applied, neuronal stimulation is short-lived. For instance, if the sensorimotor cortex is stimulated, a movement can be elicited contralateral to the stimulation. This movement occurs because either cortical interneurons projecting to corticospinal neurons are depolarized or corticospinal neurons are directly depolarized by the induced electric field (Fig. 23.2). Action potentials are then induced in axons of the corticospinal tract, leading to depolarization of motor neurons in the spinal cord and hence to activation of motor units and movement.

Depending on the coil position on the head, proximal or distal muscles in the contralateral upper or lower limbs can be activated.

When surface electrodes are placed on the target muscles, motor-evoked potentials (MEPs) can be recorded. A

B. Ovbiagele, T.N. Turan (eds.), *Ischemic Stroke Therapeutics*, DOI 10.1007/978-3-319-17750-2_23

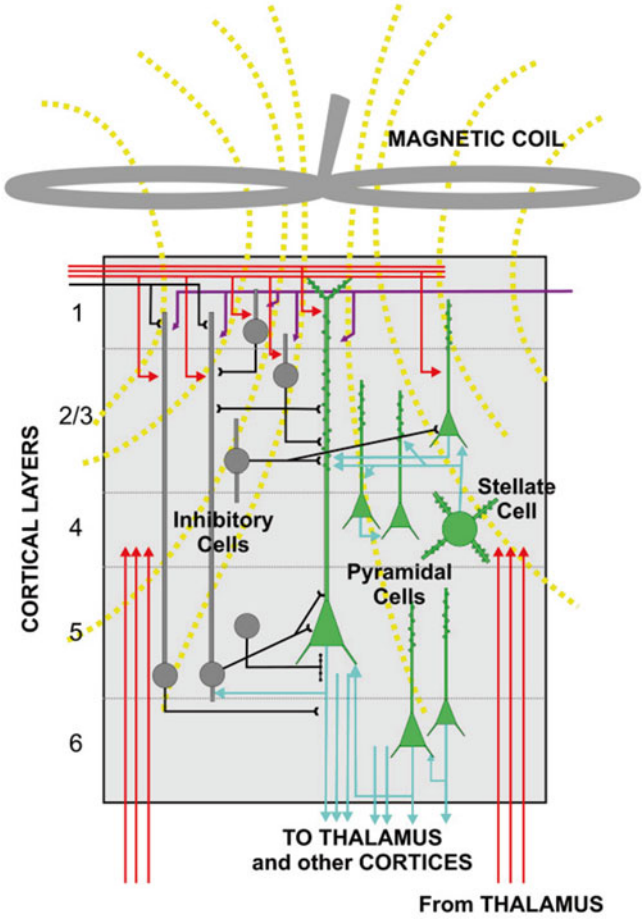

Fig. 23.1 Basic principles of transcranial magnetic stimulation. The magnetic coil, represented as a figure-of-eight device, is placed on top of the cerebral cortex and pulses a magnetic field that induces electrical currents across the six layers of the cerebral cortex (indicated by *numbers at left*). The excitatory cells (*green with blue axons*) and the inhibitory cells (*gray with black axons*) have the potential to be activated at the level of their axons, which contain the highest density of ion channels. The incoming axons from other cortical areas and the thalamus (indicated in *red*) are also activated. The end result of the magnetic pulse is the synaptic activation of a chain of neurons, which generate feed-forward and feedback loops of excitation and inhibition. *Source: Huerta PT and Volpe B. Transcranial magnetic stimulation, synaptic plasticity and network oscillations. Journal of NeuroEngineering and Rehabilitation 2009, 6:7 doi:10.1186/1743-0003-6-7. Creative Commons License CC-BY*

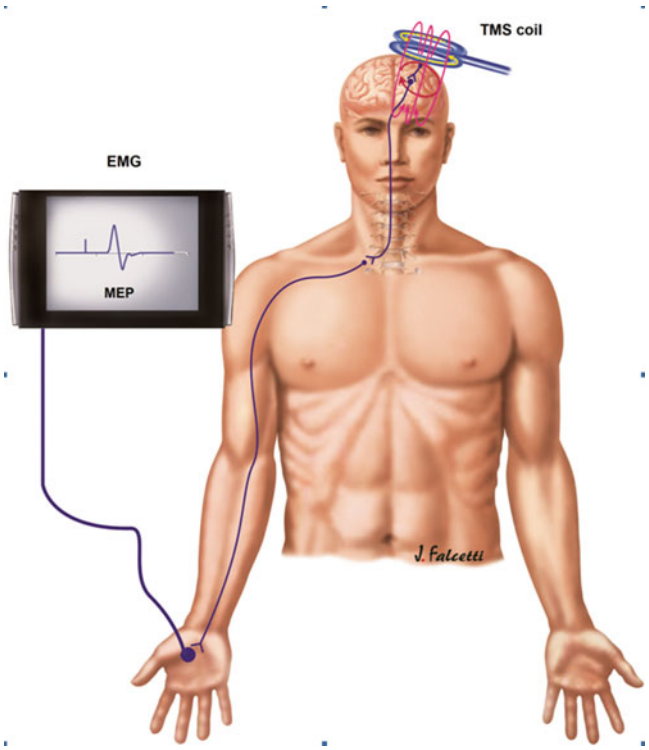

Fig. 23.2 Transcranial magnetic stimulation of the primary motor cortex. Electric currents induced by a changing magnetic field (*in pink*) depolarize interneurons (*in blue*). Excitation of cortical neurons in the motor cortex leads to depolarization of axons in the corticospinal tract and activation of motor units in the spinal cord. Motor-evoked potentials are registered with surface electrodes in target muscles contralateral to the stimulated hemisphere. *EMG* electromyography, *MEP* motor-evoked potential, *TMS* transcranial magnetic stimulation

number of measures of excitability can be obtained by analysis of MEPs after administration of one pulse (single-pulse TMS) or two pulses (paired-pulse TMS), among other paradigms. These measures can aid in understanding changes that occur in the brain after lesions such as stroke [7–9]. In addition, the motor threshold, a measure obtained by analysis of MEPs, is often used to individualize doses of TMS in rTMS studies [10].

The motor cortex is the area most frequently targeted by single-pulse TMS, because evoking and analyzing MEPs are objective and straightforward procedures. However, other areas can be stimulated. TMS of the visual cortex can induce phosphenes, and administration of single pulses to non-motor areas during cognitive tasks can induce "noise" in neuronal activity, leading to transient disruption in task performance when the targeted neurons are relevant to the task [7]. This way, the functional relevance of different brain areas can be evaluated.

Another strategy to transiently disrupt task performance is by the use of rTMS pulses at specific frequencies. Typically, rTMS is administered over several minutes. In contrast with single pulses that only lead to immediate effects, rTMS can down- or up-regulate neuronal excitability. The duration of the change in excitability produced by rTMS can outlast the stimulation period. When several sessions of rTMS are administered over days or weeks, cumulative effects lasting for weeks or months may be observed.

Typically, low-frequency ($\leq$1 Hz) rTMS leads to inhibition, and high-frequency (>1 Hz) rTMS leads to excitation. However, these effects can be state dependent; that is, different outcomes may be observed after rTMS is delivered to neurons that have different levels of baseline excitability. Cortical excitability can be changed by administration of drugs such as calcium- or sodium-channel blockers, and also by lesions. Therefore, rTMS can promote dissimilar alterations of excitability in healthy subjects and in patients [11, 12].

In 2005, a particular paradigm named theta-burst stimulation (TBS) was presented [13]. In TBS, three pulses at 50 Hz are administered in trains that are repeated every 200 ms (5 Hz). These trains can be delivered continuously (cTBS), usually leading to inhibition of corticomotor excitability or intermittently (iTBS), resulting in excitation. These patterned TBS paradigms are based on animal models of long-term potentiation (LTP) and depression (LTD). Shorter durations of TBS (20–190 s) can modulate excitability to an extent comparable to that produced by "traditional" rTMS paradigms delivered over 15–25 min.

In summary, single-pulse and paired-pulse TMS are examples of techniques used to evaluate changes in excitability and mechanisms of plasticity after stroke, while rTMS and TBS are used to modulate neural function. RTMS and TBS are promising therapeutic strategies for stroke rehabilitation. We will review results of studies about the effects of these NIBS interventions on motor function, language, neglect, and depression.

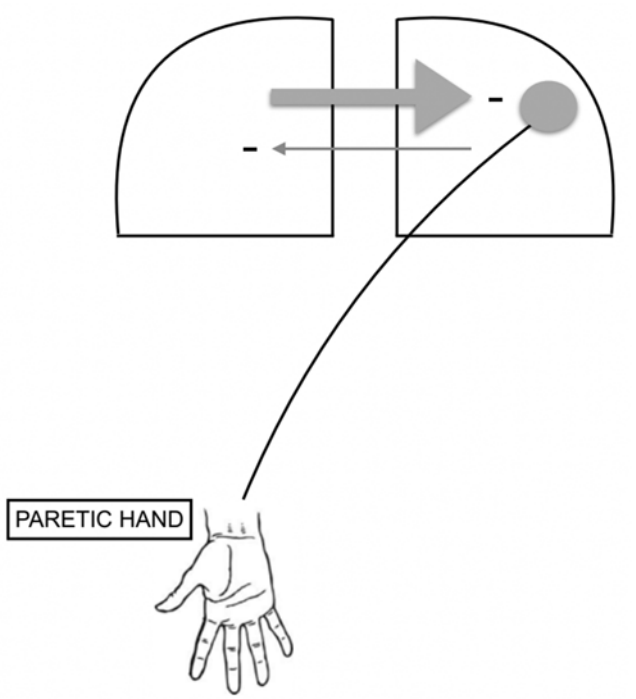

Fig. 23.3 Schematic representation, hypothesis of imbalance in interhemispheric inhibition after stroke. A lesion (*left*) would lead to decreased interhemispheric inhibition of the unaffected hemisphere by the affected hemisphere (*right*). The disinhibited unaffected hemisphere would then excessively inhibit the affected hemisphere. Motor dysfunction in the paretic hand (*right*) would then depend not only on the affected motor cortex or corticospinal tract, but also on excessive inhibition of surviving motor neurons by the unaffected hemisphere through interhemispheric connections

Potential Therapeutic Applications of rTMS and TBS

Motor Function

Upper Limb

Upper limb paresis is very common and significantly contributes to disability after stroke [14, 15]. Most studies devoted to the use of rTMS to enhance stroke recovery have focused on upper limb motor function. The rationale behind the use of NIBS to improve motor function has mainly concentrated on the hypothesis of modulation of interhemispheric inhibition [4, 16]. According to this hypothesis, excessive inhibition of the affected hemisphere by the unaffected hemisphere may worsen performance of the paretic hand, as a form of maladaptive plasticity after stroke (Fig. 23.3). This hypothesis bloomed after the observation that, in well-recovered patients, motor performance of the paretic hand worsened after low-frequency rTMS of the affected but not the unaffected hemisphere [17]. Later, abnormally increased inhibition from the motor cortex of the affected hemisphere by the unaffected hemisphere was documented [18].

Either downregulation of excitability of the motor cortex of the unaffected hemisphere or up-regulation of excitability of intact neurons of the affected hemisphere might improve motor function of the paretic upper limb. Along this line, inhibition of the unaffected hemisphere with low-frequency rTMS (Table 23.1) or excitation of the affected hemisphere with high-frequency rTMS (Table 23.2) have been performed in a number of studies. In some of them, rTMS was applied as an add-on therapy to motor training/physical/occupational therapy while in others, it was the only intervention administered.

Other strategies include bilateral stimulation [47, 52, 53], TBS [54–57], and sequential administration of low- and high-frequency rTMS to the same hemisphere [58]. The combination of rTMS and levodopa has also been investigated [59]. Research has mostly focused on adult patients, but a small trial reported preliminary evidence in favor of low-frequency rTMS in hemiparetic children after stroke [60].

Many reports about the effects of rTMS in patients with stroke did not intend to demonstrate clinical benefits of this intervention but rather to preliminarily evaluate safety or potential beneficial effects of rTMS or TBS in proof-of-principle designs. There is limited follow-up information on the duration of benefit with these treatments, hindering meaningful conclusions about their clinical usefulness at the moment.

Characteristics of patients, study designs, and outcomes have varied. Few studies included patients with severe motor

Table 23.1 Low-frequency repetitive magnetic stimulation (rTMS)

First author, reference	*n*	Time from stroke	Lesion location	Severity of motor impairment	Number of sessions	Associated intervention	Design	Main outcome(s)	Main result(s)
Early stage									
Pomeroy [19]	27	7–85 days	CS, S	Mild to moderate	8	VMC	Randomized SB SC	Muscle function, ARAT	No difference
Liepert [20]	12	<14 days	S	Mild	1	None	Crossover DB SC	NHPT, grip	Active>sham (NHPT)
									No difference in grip
Grefkes [21]	11	1–3 months	S	Mild	1	None	Crossover SC	Frequency of fist closure	Active>sham
Chang [22]	28	7–26 days	S	Mild to severe	10	PT, OT	Randomized SC	BBT, MI-A, FMA-UL, GS	Active>sham
Conforto [23]	30	5–45 days	CS, S	Mild to severe	10	PT	Randomized DB SC	JTT, force	Active>sham
Seniow [24]	40	≤90 days	CS, S	Moderate (plegic were excluded)	15	PT	Randomized DB SC	WMFT, FM-M, NIHSS	No difference
Chronic stage									
Takeuchi [25]	20	≥6 months	S	Mild	1	Motor training	Randomized DB SC	Pinch acceleration	Active>sham
Fregni [26]	15	>12 months	CS, S	Mild to moderate	5	None	Randomized DB SC	JTT, RT, NHPT	Active>sham
Mally [27]	64	>5 years	CS	Not reported	10	Not reported	Not reported	"Expenditure and detection" of movements, spasticity	↑ "motor performance"
							No sham		↓ spasticity (post>pre)
Takeuchi [28]	20	>6 months	S	Mild to moderate	1	Motor training	Randomized DB SC	Pinch force, acceleration	Active>sham
Kakuda [29]	5	>12 months	S	Mild	10	Intensive OT	No sham, UB	WFMT, FM, TST	Post>pre

Kakuda [30]	15	>12 months	CS, S	Mild to moderate	22	Intensive OT	No sham, UB	WFMT, FM	Post > pre
Avenanti [31]	30	>6 months	CS, S (M1-)	Mild	10	PT	Randomized DB SC	Dexterity, force	Active > sham if rTMS before PT
Kakuda [32]	204	>1 years	NS	Mild to moderate	22	Intensive OT	No sham, UB	WFMT, FM	Post > pre
Etoh [33]	18	>5 months	CS, S	Mild to moderate	10	Motor training	Randomized DB SC	FM, ARAT, STEF, spasticity	Active > sham (except for spasticity)
Higgins [34]	11	>3 months	NS	Mild to severe	8	Task-specific training	Randomized DB SC	BBT, WMFT, MAL	No difference
Early and chronic stages									
Mansur [35]	10	<12 months	CS, S	Mild	1	None	Crossover DB SC	RT, NHPT	Active > sham
Nowak [36]	15	4 weeks to 4 months	S	Mild	1	None	Crossover SC	Kinematics	Active > sham
Dafotakis [37]	12	>1 months	S	Mild	1	None	Crossover SC	Grasping and lifting	Active > sham
Emara [38]	60	>1 months	CS, S	Mild to moderate	10	PT	Randomized DB SC	FT, AI, MRS	Active > sham
Theilig [39]	24	2 weeks to 58 monhts	CS, S	Severe	10	Motor training	Randomized DB SC	WMFT, spasticity	No difference

Studies that applied low-frequency rTMS (1 Hz) of the unaffected motor cortex to enhance motor function of the paretic hand in patients at different stages after stroke. Only behavioral outcomes are described. Results are reported as changes in performance in active compared to sham interventions, except for studies that only compared performances before and after active treatment. The *number of sessions* refers to the number of active *or* sham sessions

AI activity index, *ARAT* Action Research Arm Test, *AS* Ashworth scale, *BBT* Box and Block Test, *BI* Barthel index, *CS* cortical, *DB* double blind, *FM-M* Fugl-Meyer; motor score for the upper limb, *FM-UL* Fugl-Meyer; total score for the upper limb, *FT* Finger tapping, *JTT* Jebsen-Taylor test, *M1* lesion-sparing M1, *MAL* motor activity log, *MI* motricity index, *MRC* Medical Research Council, *MRS* Modified Rankin scale, *NHPT* nine-hole peg test, *NIHSS* National Institutes of Health Stroke Scale, *NS* not specified, *OT* occupational therapy, *PT* physical therapy, *RT* reaction time, *S* subcortical, *SB* single blind, *SC* sham controlled, *STEF* simple test for evaluating hand function, *TST* ten-second test, *VMC* voluntary muscle contraction, *WMFT* Wolf Motor Function test

Table 23.2 High-frequency repetitive transcranial stimulation (rTMS)

First author, reference	*n*	Time from stroke	Lesion location	Severity of motor impairment	Number of sessions	Associated intervention	Design	Main outcome(s)	Main result(s)
Early stage									
Khedr [40]	52	5–10 days	CS, S	Severe (plegic)	10	Physical therapy	Randomized DB SC	NIHSS, BI	Active > sham
Khedr [41]	36	7–20 days	CS, S	Not specified, excluded flaccid hemiplegia	5	Physical therapy	Randomized DB SC	NIHSS, BI	Active > sham
Khedr [42]	48	5–15 days	CS, S	Mild to moderate	5	Physical therapy	Randomized DB SC	HSSMP, NIHSS, mRS	Active > sham
Chronic stage									
Richards [43]	39	>6 months	NS	At least 10° of extension—wrist, fingers, and thumb	10	CI-therapy	Randomized DB SC (secondary analysis)	WMFT, MAL	Not superior to CI-therapy + donepezil
Kim [44]	15	>3 months	CS, S	Mild to moderate	2	Motor practice	Crossover SC SB	MA, MT	Active > sham
Lomarev [45]	7	1–5 years	CS, S	Mild to moderate	5	None	Crossover SC	PF	No difference
Malcolm [46]	19	>1 years	NS	At least 20° of wrist extension, 10° of finger extension	10	CI therapy	Randomized DB SC	WMFT, MAL	No add-on effect to CI therapy
Takeuchi [47]	30	>6 months	S	Mild	1	Motor training	Randomized DB	PF, acceleration	No difference
Yozbatiran [48]	12	>11 weeks	CS, S	Moderate to severe	1	None	UB, active only	BI, FM, ARAT, GS, ROM, NHPT, NIHSS	Post > pre (GS, RM, NHPT, FM)
Koganemaru [49]	9	>5 months	S	Moderate to severe	1 (SC) 12 (UB)	Motor training, FES	Crossover DB SC UB, active only	ROM, GP	Active > sham Post > pre
Chang [50]	11	>3 months		Mild	10	Motor training	Randomized UB	MA	Active > sham
Early and chronic stages									
Ameli [51]	29	1–88 weeks	CS, S	Mild to moderate	1	None	Crossover SC DB	FT, mRS, ARAT, MRC, NIHSS	Active > sham (S lesions)
Emara [38]	60	1–36 months	CS, S	Mild to moderate	10	Physical therapy	Randomized SC DB	FT, AI score, mRS	Active > sham

Studies that applied high-frequency rTMS of the affected hemisphere to enhance motor function of the paretic hand in patients at different stages after stroke. Frequencies ranged from 3 to 25 Hz across studies. Only behavioral outcomes are described. Results are reported as changes in performance in active compared to sham interventions, except for studies that only compared performances before and after active treatment. The number of sessions refers to the number of active *or* sham sessions

AI activity index, *ARAT* Action Research Arm Test, *BBT* Box and Block test, *BI* Barthel index, *CI* constraint induced, *CS* cortical or corticosubcortical stroke, *DB* double blind, *FES* functional electrical stimulation, *FT* finger tapping test, *FM* upper limb score of Fugl-Meyer assessment, *GS* grip strength, *HSSMP* hemispheric stroke scale for motor power, *MA* movement accuracy, *MAL* motor activity log, *MRC* Medical Research Council, *mRS* modified Rankin scale, *MT* movement time, *NIHSS* National Institutes of Health Stroke Scale, *NHPT* nine-hole peg test, *NS* not specified, *PF* pinch force, *ROM* range of motion, *S* subcortical, *SB* single blind, *SC* sham controlled, *UB* unblinded, *WMFT* Wolf Motor Function test

impairments. There is preliminary evidence that low-frequency rTMS of the unaffected hemisphere early after stroke may boost the effects of rehabilitation in patients with hand plegia [23], but this observation must be replicated by larger studies before firm conclusions can be drawn.

While some studies focused on ischemic strokes with subcortical locations, others included hemorrhagic or ischemic stroke at various locations. Etiologies, volumes, and time after stroke have also been heterogeneous. Lesion site and volume can be crucial, as demonstrated by the lack of motor improvement in patients with extensive involvement of the motor cortex after high-frequency rTMS of the affected hemisphere [51]. Indeed, it would be surprising to expect changes after high-frequency rTMS of the affected hemisphere with a figure-of-eight coil, in the absence of intact cortical neurons amenable to be targeted by such intervention.

Also, it seems that increased activity in primary or secondary motor areas in the unaffected hemisphere may not be always maladaptive, and may have a favorable functional role in patients with extensive lesions of the corticospinal tract [61, 62]. Therefore, in some patients, inhibition of the unaffected hemisphere may not be an optimal strategy. Finally, the ideal timing for administration of rTMS to up- or downregulate cortical excitability at different stages after lesion onset in individual patients remains to be determined.

While some studies employed laboratory-based outcomes, others evaluated the effects of rTMS on clinically meaningful scales. Some of the reported beneficial effects on upper limb motor function were statistically but not clinically significant. And a single paradigm can lead to opposite outcomes, as illustrated by worsening in performance in the Action Research Arm Test, while grip strength of the paretic upper limb improved after continuous ("inhibitory") TBS of the unaffected hemisphere compared to sham TBS [56]. It has been suggested that effects of TBS may be task specific, and it is reasonable to expect that this property applies to effects of "traditional" rTMS protocols as well.

Finally, sample sizes have been relatively small. Exciting results were reported in a multicenter study that applied 22 sessions of low-frequency rTMS of the unaffected hemisphere and intensive occupational therapy to 204 inpatients [32]. However, the lack of a control group and blinded evaluation of outcomes limit conclusions about the observed improvements in motor function. In double-blind, randomized trials, the largest sample sizes include 52 patients (divided in two groups: active high-frequency rTMS of the affected hemisphere or sham rTMS; [40]) and 60 patients (divided in three groups: active high-frequency rTMS of the affected hemisphere, low-frequency rTMS of the unaffected hemisphere, or sham rTMS; [38]).

Systematic reviews or meta-analyses have reached conflicting conclusions. While statistically significant benefits were reported with fixed-effect models of analysis of 18 studies related to improvement of the paretic upper limb [63], or of three studies related to enhancement of function of the paretic hand [64], a Cochrane systematic review, analyzing results of four trials with a random-effect model, concluded that the available data do not support a significant effect of rTMS on motor function in patients with stroke [65].

Lower Limb

The paucity of reports about the effects of rTMS on motor function of the paretic lower limb may relate to a technical issue: with round or figure-of-eight coils, it is more difficult to induce electric fields in lower limb muscle representations more medially located in the precentral gyrus, compared to upper limb representations. Still, ten sessions of low-frequency rTMS of the unaffected hemisphere, when associated with task-oriented training, were shown to improve gait symmetry in patients in the chronic phase after stroke [66]. Using a double-cone coil to stimulate lower limb representations bilaterally with high-frequency rTMS, it was showed that a single session [67] or 20 sessions [68] of active treatment led to improvement in gait velocity, compared to sham treatment. The rationale behind bilateral high-frequency stimulation relates to a hypothesis of bi-hemispheric control of foot representations.

Pilot data suggested that use of the H-coil, capable of stimulating the brain at a distance of 3–5 cm from the skull, is likely to overcome the technical barriers for rTMS studies related to lower limb motor function. High-frequency rTMS of leg representation areas of both cerebral hemispheres, delivered over 11 sessions through an H-coil, was associated with significant improvement in motor performance of the paretic lower limb, compared to sham stimulation [69].

Spasticity

Reported incidences of spasticity after stroke vary widely across studies, from 1 to 60 % [70]. Research about benefits of rTMS on spasticity is justified by unsatisfactory results or side effects of current pharmacological treatments. Ten sessions of active inhibition of the unaffected hemisphere with low-frequency rTMS applied before physical therapy were associated with improvement in upper limb spasticity in patients in the chronic phase after stroke. There was a trend in favor of a difference in spasticity between the two groups immediately after treatment, but not 1 month later [71].

Another study reported improvement in upper limb spasticity after inhibition of the unaffected motor cortex followed by occupational therapy over 15 days [72]. However, because this study did not include a control group, it is not possible to rule out that the improvement may have been due to occupational therapy alone.

Dysphagia

Oropharyngeal dysphagia increases the risk of pneumonia and mortality after stroke [73]. In patients with dysphagia up to 2 weeks after stroke affecting one cerebral hemisphere, active high-frequency (3 Hz) rTMS of the affected motor cortex for 10 min over 5 days was associated with significant improvement of dysphagia scores after treatment, while sham rTMS did not lead to significant changes in this outcome [41]. The difference between the two groups persisted up to 2 months after treatment. In this study, the coil was positioned over the esophageal cortical area of the affected hemisphere, defined as the side from which MEPs could be evoked on proximal striated esophageal muscles with ring electrodes attached to a catheter, or from the symmetrically opposite area in the unaffected hemisphere. Intensity of stimulation was determined by stimulating the unaffected hemisphere.

In 22 patients with lateral medullary infarcts or other brainstem infarcts, similar results were reported after five sessions of 3 Hz rTMS of the esophageal cortical area of both the affected and unaffected hemispheres, compared to sham stimulation [42]. This strategy was chosen because representation of esophageal motor function is bilateral in humans. It was hypothesized that up-regulation of excitability in both hemispheres would strengthen excitation of brainstem nuclei through corticobulbar projections. In patients with unilateral medullary lesions, enhancement of excitability in contralateral nuclei might compensate for the loss of function and improve swallowing. Some patients with bilateral lesions in the group of other brainstem infarcts also improved, possibly due to changes in excitability in other pathways.

Further studies are necessary to confirm these findings, to investigate benefits of associating rTMS with specific speech therapies, and to better select patients for this kind of treatment.

Language

Up to 38 % of patients with stroke are faced with aphasia that may have an enormous impact on disability and social participation [74]. Aphasia may affect predominantly comprehension, naming, repetition, or expression, depending on the damage of complex networks in the dominant hemisphere (typically the left, in right-handed subjects). Because each area may be part of overlapping networks, multiple deficits may be observed after lesion of a single area, and lesions from different areas can lead to similar deficits. Symptoms are dynamic and recovery can be substantial, particularly over the first weeks and months. However, after 1 year, significant improvements are less frequent. There is a great need of evidence-based interventions to treat aphasia. RTMS has emerged as a potential adjuvant intervention to speech/language therapy, in order to accelerate recovery or to promote enhancement of language capabilities in chronic patients.

The diverse and dynamic nature of symptoms in stroke represents a major challenge to design and interpretation of rTMS studies in this patient population. Recovery may occur through activity of unaffected areas located in the hemisphere affected by stroke, or in the contralesional hemisphere. In some patients, activity in the contralesional hemisphere may be maladaptive, as it may excessively inhibit areas that are functionally relevant to recovery (for reviews, see [75, 76]). The activation of areas in a functional pattern similar to patterns of healthy subjects in the dominant hemisphere is associated with better language performance, while recruitment of areas in the nondominant hemisphere is typically associated with less effective language output, but may be the only avenue for compensation in some patients [75].

Brodmann's area 45 in the inferior frontal gyrus has been a frequent target of NIBS in aphasic patients. According to the theory of interhemispheric inhibition, it might be possible to enhance language by inhibiting the homolog area (usually the right inferior frontal gyrus) or by stimulating the perilesional cortex in patients with nonfluent aphasia caused by strokes involving the left inferior frontal gyrus [77–80]. However, it has been demonstrated that worsening in language output may occur after inhibition of the right hemisphere in patients with aphasia after stroke. Because of the complexities in patterns of rewiring in aphasic patients, the combination of structural or functional neuroimaging and rTMS (neuronavigated rTMS) has become a frequent strategy to define optimal areas for neuromodulation in individual subjects (Fig. 23.4).

In the past years, low- and high-frequency rTMS were administered mainly to the nondominant hemisphere over 10–15 days, with or without associated speech therapy, with encouraging results [77, 80–83]. Later, improved fluency was reported after intermittent TBS was delivered to the dominant hemisphere in two studies [84, 85], and improvement in naming was observed after an H-coil was used to target the right inferior frontal gyrus [86].

Outcome measures have been quite heterogeneous, varying from reaction times in naming tasks to performance in batteries such as the Western Aphasia Battery and the Aachen Aphasia Test. The absence of control groups in some reports limits interpretation of rTMS effects versus spontaneous recovery, or improvement in performance due to learning effects elicited by repetition of tests. In many studies, the types of aphasia were not specified, or a single protocol was applied to patients with predominantly fluent or nonfluent aphasias.

An individualized approach was chosen by a study in which 1-Hz rTMS was applied over 10 days to areas defined

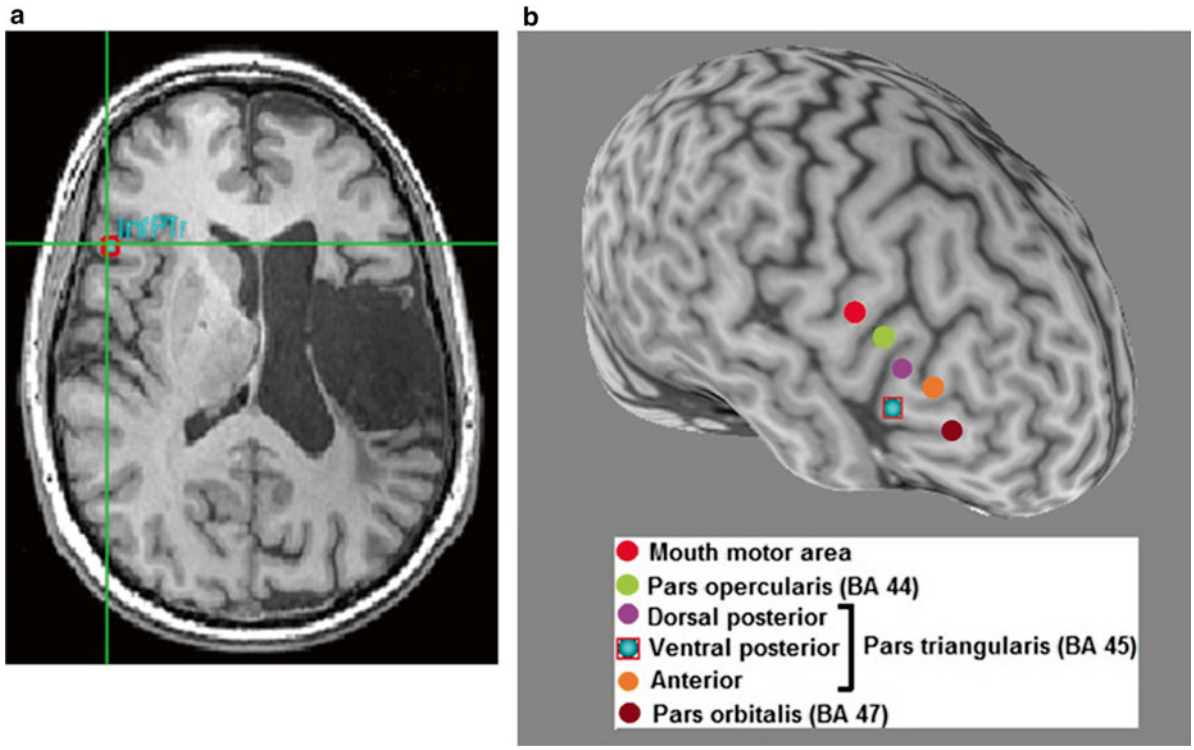

Fig. 23.4 Optimal site finding among right hemispheric homolog areas and rTMS in a left hemisphere stroke patient with aphasia. (**a**) Among several right hemispheric sites, an optimal site is identified on the subject's high-resolution anatomical scan (*red square*; optimal site is the one that exhibits better transient language improvement compared to other sites). Most patients respond optimally to the right inferior pars triangularis. (**b**) A 3-dimensional reconstruction of the subject's high-resolution anatomical scan with the six sites of interest highlighted in different colors in the right hemisphere. Optimal site for this patient in the ventral posterior inferior pars triangularis. *Source: Shah PP, Szaflarski JP, Allendorfer J, Hamilton RH. Induction of neuroplasticity and recovery in post-stroke aphasia by non-invasive brain stimulation. Front Hum Neurosci 2013; 7:888. doi: 10.3389/fnhum.2013.00888. Creative Commons License CC-BY*

according to the type of aphasia and to functional magnetic resonance imaging (fMRI) activation patterns [87]. The inferior frontal gyrus was targeted in patients with predominantly nonfluent aphasia, while the superior temporal gyrus was chosen in patients with predominantly fluent aphasia. This strategy was associated with improvements in fluency in the former group, and in comprehension in the latter group. However, this study was not placebo controlled.

In a double-blind, randomized protocol that tailored treatment according to clinical features, 30 patients with nonfluent aphasia, within 1–12 weeks after stroke, were included. After ten sessions of low-frequency rTMS of the right inferior frontal gyrus combined with high-frequency rTMS of the left inferior frontal gyrus administered before speech/language training, improvements in language were noticed after active treatment, when compared to sham rTMS. The observed benefit persisted for at least 2 months [88].

Overall, results of rTMS in stroke have been encouraging but preliminary, with sample sizes ≤30 [76]. Understanding mechanisms of recovery in different patients and using relevant clinical information are likely to have a substantial impact on the potential clinical use of rTMS in aphasia. The duration of possible beneficial effects also deserves further exploration.

Neglect

Neglect is defined as failure "to report, respond, or orient to novel or meaningful stimuli presented to the side opposite a brain lesion" [89]. It is reported in up to 30 % of patients, affects mainly victims of right hemisphere strokes, and can improve quickly and spontaneously, but may also have a tremendously negative impact on overall disability and rehabilitation outcomes.

The rationale behind the use of rTMS to treat neglect is the imbalance of interhemispheric inhibition. This imbalance may lead to excessive inhibition of frontoparietal networks related to visuospatial attention in the affected hemisphere, by the unaffected hemisphere. In particular, networks in the posterior parietal cortex seem to be often involved. Considering this hypothesis, either low-frequency

rTMS of the unaffected hemisphere or high-frequency rTMS of the affected hemisphere, or both, might ameliorate neglect.

So far, most studies focused on low-frequency rTMS of the unaffected hemisphere [90–95], leading to exciting preliminary results. Still, some of the studies lacked control groups, and durations of effects or follow-ups were limited in most of the reports.

Because it is believed that TBS has LTP-like effects, this intervention was also used to treat neglect with long-lasting improvements. Inhibition of the left posterior parietal cortex with TBS over ten sessions led to improvements that persisted for 1 month and were not observed in the control group [96].

Depression

Depression may occur because of major changes in life due to post-stroke disabilities, or because of disruption of neural circuits involved in mood regulation. Depression negatively impacts recovery and survival [97].

Many patients with depression do not respond well to medical treatment. High-frequency rTMS of the left dorsolateral prefrontal cortex is an FDA-approved alternative to electroconvulsive therapy (ECT) in patients with major depression, based on studies in non-stroke populations [98–101]. There are limited safety data about treatment of post-stroke depression with ECT. In contrast to ECT, rTMS does not involve general anesthesia or produce cognitive dysfunction. RTMS improves the functional status and quality of life in patients who have pharmaco-resistant major depression without stroke [101]. This intervention is based on the hypothesis that decreased activity in the left dorsolateral prefrontal cortex is a mechanism involved in depression.

In a pilot ($n=20$) randomized, double-blind study of ten sessions of active high-frequency rTMS of the left dorsolateral prefrontal cortex or sham treatment in patients with post-stroke depression [102], antidepressants were discontinued prior to enrollment. A significant decrease in Hamilton Depression Rating Scale scores was observed in the active compared to the sham group. Improvement significantly correlated with frontal gray and white matter volumes. Adverse events (transient headaches, local discomfort) were mild and infrequent.

In a later study [103], 92 patients with depression and stroke were randomized to active treatment at two different doses (total treatment, 12,000 pulses over 10 sessions, or 18,000 pulses over 15 sessions). Hamilton Depression Rating Scale scores improved after treatment with both doses compared to sham rTMS, but response and remission rates were significantly better after active treatment only at the highest rTMS dose. Older age correlated negatively with responsiveness, while higher frontal gray matter volumes correlated positively with effects of active treatment.

These findings encourage future studies of rTMS in depressed patients after stroke. Potential advantages of rTMS compared to drug treatments are its safety profile, with mild and infrequent adverse events, and the possibility to avoid interactions between antidepressants and other medications used by patients with chronic conditions. Besides obvious clinical implications, this therapy may aid in clarifying biological mechanisms of depression after stroke and of responsiveness to rTMS in depressed patients [104].

Safety

The only absolute contraindication to TMS/rTMS is the presence of metallic hardware (such as cochlear implants, or an internal pulse generation, or medication pumps) near the discharging coil [105]. Guidelines that suggest safe frequencies, stimulus intensities, and inter-train intervals for rTMS protocols have been published [105, 106]. Conditions of increased or uncertain risk include novel paradigms that do not follow these guidelines, central nervous system lesions (such as stroke), use of drugs that decrease seizure thresholds, pregnancy, implanted brain electrodes, and severe or recent heart disease. TMS has been considered safe in individuals with cardiac pacemakers, as long as the TMS coil is not activated near the components located in the neck or chest [105].

Seizures are the most serious acute adverse event related to rTMS. The risk of seizures after high-frequency rTMS was estimated to be 1.4 % in patients with epilepsy, and 1 % in healthy subjects. Seizures are rare after low-frequency rTMS [105]. After the publication of safety guidelines, few seizures were reported overall and were limited to patients taking drugs that decrease seizure thresholds or after sleep deprivation. None of the reported seizures happened in patients with stroke. In addition, no other serious adverse events of rTMS were reported in patients with stroke [107].

Medications that may lower seizure threshold should be thoroughly scrutinized before enrolling patients in rTMS protocols. More research is necessary to define characteristics of patients that may have enhanced rTMS-related risk, and the best way to monitor subjects during treatment to avoid the risk of seizures [65].

Mild adverse events include headache, dizziness, tingling, anxiety or tiredness, and other minor complaints [23, 65, 107]. Reports of adverse events have been highly heterogeneous across studies. Systematic evaluation of such events has not been mentioned in many manuscripts. There is a need to standardize how adverse events are evaluated, and how they are described in rTMS protocols in general, and in studies related to stroke in particular.

Cost-Effectiveness

Whether rTMS is cost effective is still under debate [108]. It has been suggested that, as an adjuvant tool for inpatient or outpatient rehabilitation, NIBS may be cost effective, but data from randomized clinical trials are still lacking [109]. Currently, TMS machines are heavy and require an intact ground connection. Due to these characteristics, it is not practical to transport TMS machines around a hospital, or apply it at home. Portable TMS are being studied and may have an important role in spreading this technique [110].

The global burden of disability from stroke in an ageing world population is extremely high. It will be necessary to demonstrate that the effects of rTMS are of sufficient magnitude to impact disability or quality of life, and that they last long enough, before cost-effectiveness of this intervention in stroke can be confirmed.

Future Perspectives

One of the biggest challenges for the clinical use of NIBS in stroke rehabilitation is how to match the right patient to the right treatment. Understanding the mechanisms underlying plasticity in different patients with various types, volumes, and clinical or subclinical lesions will be necessary to design effective therapeutic strategies [21, 86, 111].

For instance, the extent of corticospinal tract involvement by a stroke strongly influences motor outcomes. Motor cortex excitability and interhemispheric inhibition, when combined with the degree of corticospinal tract damage, were shown to account for more than 80 % of the variance in functional impairment [112]. Future studies should investigate optimal rTMS strategies, according to these variables as well as other potential biomarkers of responsiveness to NIBS [113].

In studies that involve language or other higher functions, functional neuroimaging can provide crucial information so that appropriate targets for stimulation can be selected. Furthermore, the concept that not particular brain areas but rather key networks should be targeted by NIBS has steadily evolved [21, 111]. The combination of neuronavigated NIBS and connectivity tools is likely to sharpen knowledge about neural correlates of recovery after stroke, and allow selection of interventions according to networks involved in adaptive and maladaptive plasticity processes.

Conclusions

Stroke is a major cause of disability worldwide. Noninvasive interventions that capitalize on beneficial mechanisms of plasticity may reach clinical practice in the near future. The combination of rTMS with other NIBS techniques such as peripheral stimulation and transcranial direct stimulation may bring additional benefits for rehabilitation [4, 111, 114]. Technical advances such as the availability of coils for deep brain stimulation may also provide novel, more effective stimulation paradigms.

Due to the heterogeneous nature of stroke, it is unlikely that "magic bullets," able to enhance recovery in all patients, will be readily available. Careful selection of patients, as well as close interactions between clinicians and researchers, is expected to advance the use of rTMS and contribute to minimizing disability from stroke.

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General Concepts: Management of Asymptomatic Cerebrovascular Disease

24

Philip B. Gorelick

Abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
CEA	Carotid endarterectomy
CI	Confidence interval
c-IMT	Carotid intima-media thickness
CNS	Central nervous system
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial
MRC ACST	Medical Research Council Asymptomatic Carotid Surgery Trial
NASCET	North American Symptomatic Carotid Endarterectomy Trial
PET	Positron emission tomography
TCD	Transcranial Doppler
US	United States
VA	Veterans Affairs
Vs.	Versus

Introduction and Definitions

The concept of asymptomatic brain disease has expanded and evolved over time. The term *asymptomatic cerebrovascular disease* now brings to mind vascular entities such as "asymptomatic carotid artery stenosis or bruit," "silent or unexpected brain infarction," and "subclinical" cerebrovascular disease. According to a report commissioned by the National Institute of Neurological Disorders and Stroke in 1990, the term was used to designate a category of patients who had cerebrovascular disease but no referable cerebral or retinal symptoms [1]. More recently we have become aware that asymptomatic cerebrovascular disease is accompanied by subclinical manifestations and that so-called silent or unexpected strokes are common but may not be so silent. For example, it is estimated that "silent" strokes outnumber clinically manifest ones by a factor of greater than 5 to 1 [2]. Based on the Framingham Offspring Study, approximately 1 in 10 persons in the community who are on average 62 years of age have a "silent" stroke, and the latter strokes track with the Framingham Stroke Risk Profile [3]. Furthermore, in persons without a history of stroke or dementia, substantial *subclinical* cerebrovascular disease is believed to be associated with worse cognitive function [4].

The aforementioned findings have led to a reexamination of the definition of stroke and TIA [5]. For stroke, the definition of *central nervous system* (*CNS*) *infarction* not only includes traditional clinical evidence of cerebral, spinal cord, or retinal focal ischemia based on clinical symptoms lasting for ≥24 h or until death, but now also includes consideration of pathological, imaging, or other objective evidence of focal ischemic injury in a defined vascular territory. Furthermore, the definition of *silent CNS infarction* includes neuroimaging or neuropathological evidence of CNS infarction in the absence of a history of acute neurological dysfunction caused by the lesion. In addition, *silent cerebral hemorrhage* is defined as a focal collection of chronic blood products within the CNS based on neuroimaging or neuropathological examination in the absence of trauma and a history of acute neurological dysfunction attributable to the lesion [5]. Similarly, the new definition of *TIA*, a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia in the absence of acute infarction, also emphasizes neuroimaging findings and thus a tissue-based approach [6].

Therefore, our understanding of "asymptomatic" cerebrovascular disease has evolved from a clinically based definition to one that encompasses neuroimaging and neuropathological examination to elucidate evidence of ischemic or non-traumatic hemorrhagic CNS tissue injury in the absence of clinical

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symptoms. By taking into account evidence of tissue-based injury in persons with ischemic or hemorrhagic disease in the absence of clinical symptoms, we can more precisely begin to elucidate stroke mechanism, pathogenesis, and prognosis in persons at risk. Finally, a tissue-based emphasis of stroke injury in persons without clinical symptoms elevates "*subclinical*" vascular disease (e.g., carotid artery plaque, carotid intima-media thickness, aortic arch atheroma, brachial endothelial reactivity) and brain injury (e.g., white matter hyperintensities, "silent" cerebral infarcts, cerebral microbleeds) to a higher hierarchical level as we further elucidate stroke pathogenesis and pathophysiology [7].

Asymptomatic Carotid Artery Stenosis and Carotid Bruit: Prevalence and Significance

Management of asymptomatic carotid artery stenosis has been a long-standing controversy [8]. "Noises" in the neck (i.e., carotid bruit) have engendered concern about stroke and coronary artery disease risks that have been tempered over time [9]. In 1982, investigators from the Mayo Clinic reported the results of a survey of carotid artery bruits [10]. The prevalence of asymptomatic, localized carotid arterial bruits increased with age and was higher in women. It was 0.9 % at 45–54 years; 2.1 % at 55–64 years; 3.8 % at 65–74 years; and 5 % at 75 years or older. Overall prevalence was 4.4 % in women and 1.6 % in men. In landmark observational studies, one from a population survey in Evans County, Georgia [11], and another from the Framingham Study [12], it was shown that although carotid bruit was an indicator of heightened stroke and systemic vascular disease risk, it was not a good indicator whereby local asymptomatic carotid artery stenosis was the mechanism for subsequent cerebral infarction. In addition, these studies substantially challenged the value of diagnostic procedures or surgical remediation of underlying asymptomatic extracranial carotid artery stenosis. Later, an important referral-based study was published on 659 patients with asymptomatic neck bruits who were followed by clinical and Doppler examinations for up to 4 years (mean: 23.2 months). In this study, asymptomatic cervical bruits were associated with an absolute higher risk of cardiac ischemic events than stroke at 1 year (cardiac ischemia: 7 %; cerebral ischemia: 6 %; and death: 4 %) [13]. The incidence of stroke at 1 year was 1.7 % (1 % without prior TIA) but was 5.5 % in those with severe carotid artery stenosis (>75 %), and occurrence of cerebral ischemia was associated with severity of carotid artery disease, progression of the disease, history of heart disease, and being a man.

Overall, the aforementioned epidemiologic study results led to calls for conservative diagnostic and treatment paradigms for asymptomatic carotid stenosis and bruit management [14, 15]. In fact, some advocated at the time that it might not be indicated to perform neck auscultation as it might lead to unnecessary testing and therapy. Thus, in the 1980s, detection of a carotid bruit was recognized as a risk for myocardial infarction and cardiovascular death [16], but the available evidence did not support a definitive recommendation for use of carotid endarterectomy (CEA) in asymptomatic patients [17]. Clinical trials would be needed to bridge the knowledge gap about proper management of asymptomatic carotid artery stenosis to end the state of clinical equipoise [18].

History of Carotid Artery Surgery and Angioplasty and Stenting

Carotid artery reconstructive surgery was carried out as early as 1916 whereby resection and end-to-end anastomosis were used when there was aneurysm or local cancer [19]. Anastomotic techniques were developed over time when portions of the common and internal carotid arteries had to be sacrificed in the presence of local cancer. Thrombosis of the carotid artery had been described as early as 1881, and it was well known that atherosclerosis had a predilection for the carotid artery bifurcation and siphon in the 1900s. C. Miller Fisher's landmark article in 1951 recognized the importance of collateral blood flow, downstream embolism, and high-grade carotid artery stenosis in the genesis of stroke and prophesized that surgical intervention might be possible [20]. Carotid reconstruction for cerebrovascular disease was reported by Carrea and colleagues [21] and Eascott and colleagues [22], and Debakey claimed to have performed the first successful carotid endarterectomy [23]. Finally, thrombectomy was popularized in the French literature in the 1940s [19].

Endovascular therapy applied to the cervical carotid artery bifurcation with balloon angioplasty was reported as early as 1980 [24]. Protection devices to catch embolic debris and stent technology were also developed.

Brief Overview of Carotid Endarterectomy in Asymptomatic Stenosis

A long-standing concern about performance of CEA was the morbidity and mortality associated with the procedure [25]. In the past decades it became clear that morbidity and mortality rates associated with CEA were quite variable and were not negligible [26, 27]. Three landmark studies in this area focused primarily on direct surgical intervention. Whereas "best" medical management was advocated, these trials were undertaken prior to the more recent period of medical management advances in the treatment of hypertension, dyslipidemia, and other stroke nonsurgically modifiable or potentially

modifiable factors. The largest of the US-sponsored trials was the Asymptomatic Carotid Atherosclerosis Study (ACAS) [28]. ACAS showed an approximate absolute reduction of the primary endpoint (ipsilateral stroke, perioperative stroke, or death) by 1.2 %/year in favor of the CEA treatment arm and a 53 % risk reduction. The findings may be interpreted as a modest benefit of CEA over medical therapy alone and emphasize the importance of achievement by the surgical team of a target CEA perioperative morbidity and mortality rate of <3 %. Otherwise, CEA could prove harmful to the patient [29].

Another US trial, the Veterans Affairs (VA) Cooperative Study, randomized 444 men who had ≥50 % asymptomatic extracranial carotid artery stenosis confirmed by selective carotid arteriography [30]. In this trial, the primary endpoints were TIA, transient monocular visual loss, and stroke. The combined 30-day perioperative risk including angiographic complications, stroke, and death was 4.7 % in the surgical treatment arm versus 2.1 % in the medical treatment arm. However, in this study of modest sample size, there were no significant differences between the treatment groups when all strokes and deaths were taken into account.

The Medical Research Council (MRC) Asymptomatic Carotid Surgery Trial [31] included randomization of 3120 patients with ≥60 % diameter reduction of the carotid artery predominantly based on noninvasive testing. Patients were randomized to immediate or deferred CEA according to the principle of equipoise whereby both the doctor and patient were uncertain whether immediate CEA should be carried out or deferred. Immediate CEA approximately halved the net 5-year stroke risk (12 to 6 %), and about half of the benefit involved disabling or fatal strokes. There was no association with the degree of asymptomatic carotid artery stenosis and benefit from CEA, and the benefit for ischemic stroke reduction was greater for men than women; however, there were overlapping confidence limits in the latter analysis [32]. In a 10-year follow-up of the ACST cohort (ASCT-1), excluding perioperative events and non-stroke mortality, when comparing immediate versus deferred CEA for stroke risks, there were 4.1 % versus 10.0 % at 5 years for a gain of 5.9 %, and 10.8 % versus 16.9 % at 10 years for a gain of 6.1 %, respectively [33]. The authors concluded that successful CEA for asymptomatic carotid artery stenosis in patients younger than 75 years of age reduced the 10-year stroke risks with about half of the benefit resulting from reduction of disabling and fatal strokes. There were net benefits for most subgroups including both men and women up to 75 years of age, though not for older patients.

Finally, in the Mayo Asymptomatic Carotid Endarterectomy Study, a comparative effectiveness trial of CEA versus low-dose aspirin, the trial was terminated early because there was a higher risk of myocardial infarction and TIAs in the CEA treatment group [34]. The increase in risk of the cardiovascular events was linked primarily to the absence of aspirin administration in the CEA group rather than to perioperative surgical events.

Brief Overview of Angioplasty and Stenting in Asymptomatic Carotid Stenosis

Beyond registries and smaller clinical trials, of two large-scale trials comparing carotid artery stenting with CEA [35, 36], the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) included patients with asymptomatic and symptomatic carotid artery stenosis [36]. About 47 % of entrants had asymptomatic arteries. There was no significant difference for treatment effect for the primary endpoint (stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization) based on symptomatic status ($p=0.84$) or sex ($p=0.34$).

Guidelines and Management of Asymptomatic Carotid Artery Stenosis

According to the American Heart Association/American Stroke Association guidelines for first stroke prevention, in addition to medical management CEA may be beneficial for select patients with high-grade asymptomatic carotid artery stenosis (i.e., >70 % stenosis of the internal carotid artery), if the risk of perioperative stroke, myocardial infarction, and death is <3 % [37]. Prophylactic carotid artery stenting may be considered as an alternative to CEA in highly select asymptomatic patients with a minimum of 60 % carotid artery stenosis by angiography and 70 % by validated Doppler ultrasound; however, its effectiveness when compared to medical therapy alone is not well established. Furthermore and similar to other screening recommendations, the American Heart Association/American Stroke Association [37] and the US Preventive Services Task Force recommend against screening for asymptomatic carotid artery stenosis in the general adult population [38].

In summary, there is only modest benefit of CEA over medical management in asymptomatic carotid artery stenosis, and modest changes in perioperative morbidity and mortality rates can shift the scenario against CEA or angioplasty and stenting [29]. Some experts believe that advanced medical management may be non-inferior or possibly superior to surgical or endovascular interventions in asymptomatic patients, especially in those with midrange degrees of carotid artery stenosis (e.g., 50–69 %). This hypothesis remains to be formally tested [39].

Diagnosis and Predictive Value of the Carotid Plaque

The carotid artery plaque has continued to be of clinical and pathologic interest. At a time period when CEA was being carried out frequently, Imparato et al. characterized the pathologic findings of carotid bifurcation plaque in association with cerebral ischemia [40]. They found fibrous thickening, intra-plaque hemorrhage, atheromatous debris, and least often luminal thrombus with or without ulceration. Ulceration occurred in about 1/3 of plaques whether they were symptomatic or asymptomatic. The authors concluded that carotid plaques originated as fibrointimal thickening and evolved into other findings of which intra-plaque hemorrhage was a prominent finding. In the Athero-Express Study, a longitudinal biobank program that included atherosclerotic plaques of persons undergoing primary CEA with assessment by duplex ultrasound, a focus was the relationship between atherosclerotic plaque histology and occurrence of restenosis after CEA [41]. The main finding of the study was that restenosis after CEA was associated with atherosclerotic plaques with low macrophage infiltration, and small or absent lipid core. Based on select studies in the author's file, Table 24.1 provides a summary of key studies of plaque morphology and carotid stenosis [42–52].

Future Directions

Future directions in the field of asymptomatic cerebrovascular disease encompassing primarily carotid artery stenosis will need to address means whereby proper technology assessments of new risk stratification schemes to identify patients who will be best served by CEA and endovascular interventions as compared to medical therapy are carried out. Such proof will require large efficacy and effectiveness data resources, new technology to identify and localize carotid plaque morphology, new risk stratification schemes, and plausible means to successfully apply comprehensive and aggressive medical management options in populations. As it currently stands based on a systematic review and meta-analysis, major CEA studies for asymptomatic carotid artery stenosis may no longer be applicable according to contemporary medical practice, and no major trial has reported a comparison of carotid artery stenting to medical therapy alone [53]. We await the implementation and subsequent results of CREST-2, a US National Institutes of Health funded trial, to address medical therapy compared to CEA and stenting [54].

According to an international meta-analysis of individual participant data of carotid intima-media thickness (c-IMT) progression, after adjustment for multiple factors mean

Table 24.1 Select studies and relationship between carotid artery stenosis and plaque morphology or direct plaque histological examination

Study: Key findings
1. European Carotid Surgery Study [42]: In addition to degrees of carotid artery stenosis, angiographic plaque surface irregularity was associated with increased risk of ipsilateral ischemic stroke in *symptomatic* carotid artery stenosis
2. Academic Medical Centers Consortium data source [43]: Among members of the Academic Medical Centers Consortium from which 100 carotid endarterectomies from each site were randomly selected during the years 1988–1990, the rate of postoperative stroke or death was not significantly impacted by the presence or absence of angiographically recognized ulceration or intraluminal thrombus among *asymptomatic* patients
3. NASCET [44]: Among *symptomatic* carotid artery stenosis patients, ipsilateral irregular or ulcerated plaque detected by angiography predicted 30-day perioperative stroke or death
4. Case series data source [45]: In a case-based series, morphologic plaque characteristics based on color duplex ultrasonography determination included echolucent plaques and progressive lesions that affected symptom occurrence
5. Review of the vascular biology of the symptomatic carotid plaque [46]: Unstable plaques were characterized by surface ulceration and plaque rupture in both symptomatic and *asymptomatic* plaques, thinning of the fibrous cap, and infiltration of the cap by macrophages and T cells
6. Registry data source [47]: Complex carotid ulcers were associated with a higher risk of subsequent stroke in *asymptomatic*, non-stenosing carotid artery bifurcation lesions
7. ACAS and NASCET data source [48]: Symptomatic patients more commonly had carotid artery ulceration regardless of the side of carotid symptoms, and thrombus was associated with plaque ulceration and symptom laterality
8. Oxford Plaque Study [49]: In patients with *symptomatic* carotid artery stenosis, with increasing age plaque calcification and size of the large lipid core increased, the fibrous tissue decreased, and lymphocyte infiltration and inflammation decreased
9. Participants of cohort studies/trials at a single academic center [50]: Among persons with carotid stenosis >50 %, occlusion or unstable carotid plaque who had TCD monitoring for 1 h within 48 h of clinical presentation, Power M-mode TCD identified persons with malignant microembolic signals associated with larger baseline infarcts, a higher occurrence of intraluminal thrombus or ulcerated carotid plaque, and worse clinical outcome
10. Stroke Prevention Clinic of the London Health Sciences Center data source [51]: Among patients with *asymptomatic* internal carotid artery stenosis ≥60 % based on Doppler evaluation and who had 3D ultrasound, those with ≥3 carotid artery ulcers were more likely to have a stroke or death within 3 years regardless of ulcer side; those with microemboli had a higher risk of stroke or death within 3 years; and the annual ipsilateral stroke rate was only 0.8 %. The authors advocated for medical management until there was development of symptoms, ulcers, or emboli
11. Asymptomatic Carotid Embolic Study (ACES) [52]: Among those *asymptomatic* patients participating in an international multicenter study of embolic signals and ultrasound plaque morphology, the combination of embolic signal and plaque echolucency morphology provided a greater degree of prediction of ipsilateral stroke risk than either measure alone. The authors advocated possible use of these measures for selection of asymptomatic patients for CEA

c-IMT of two ultrasound scan recordings remains robustly associated with cardiovascular risk [55]. Furthermore and based on another meta-analysis, advances in neuroimaging have improved the prospects that noninvasive studies could replace conventional cerebral angiography and its inherent risks in the measurement of high-grade (70–99 %) carotid artery diameter stenosis though the accuracy remained uncertain for 50–69 % carotid stenosis [56]. New imaging techniques to localize and identify ruptured and high-risk atherosclerotic plaques, such as 18 F-sodium fluoride positron emission tomography-CT, are now being tested and could provide a new pathway to improve management and treatment of patients at risk for complications from asymptomatic atherosclerosis [57].

Given the aforementioned challenges, asymptomatic intracranial atherosclerosis is probably the most prevalent form of cerebral atherosclerosis and deserves the same attention that asymptomatic carotid artery stenosis receives [58]. Reduction of subclinical brain lesions (silent strokes, white matter disease) within the continuum of asymptomatic cerebrovascular disease could lead to cognitive vitality and better general brain health [59].

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Asymptomatic Carotid Artery Stenosis

25

Pratik Bhattacharya and Seemant Chaturvedi

Case Presentation An 84-year-old man was referred for left carotid stenosis, which was detected by his internist after a carotid bruit was heard. Carotid duplex revealed 80–99 % stenosis. CTA was interpreted as showing 70–80 % stenosis. The patient was on aspirin 325 mg/day, atorvastatin 80 mg/day, ramipril 10 mg/day, and a diuretic. Blood pressure was 136/78. Low density lipoprotein was 51 mg/dl.

Case 2 comment: The patient was counseled regarding the uncertain benefit of revascularization in his age group. He continued on aggressive medical therapy and has been symptom-free for 3 years. This type of patient could be considered for enrollment in a clinical trial such as CREST-2 (described below).

Prevalence of Asymptomatic Carotid Artery Stenosis

Cervical (extracranial) carotid artery atherosclerosis is a well-established risk factor for ischemic stroke. About 7 % of all ischemic strokes are attributed to extracranial carotid stenosis. However, the burden of asymptomatic carotid disease is much larger. The majority of carotid revascularization procedures performed in the USA is in asymptomatic carotid stenosis.

Numerous epidemiological studies have defined the prevalence of carotid stenosis in the general population. Most studies use Doppler ultrasound as the screening tool, and defined significant carotid stenosis as 50 % or greater. In the Framingham study cohort of 1116 subjects aged 66–93 years, the prevalence of significant carotid stenosis was 7 % in women and 9 % in men. Older age, cigarette smoking, higher systolic blood pressure, and high cholesterol were independent predictors of carotid atherosclerosis [1]. Contemporary prevalence estimates can be judged from individual patient data meta-analysis of four large asymptomatic population based cohorts: The Malmo Diet and Cancer Study, Tromso, Carotid Atherosclerosis Progression Study, and Cardiovascular Health Study. This analysis of 23,706 participants showed that the prevalence of carotid stenosis varies by age and sex. [2] The prevalence of *moderate* (50–69 %) carotid stenosis ranged from 0.2 % in men under 50 years to 7.5 % in men over 80 years and the prevalence among women ranged from 0 % under 50 years to 5.0 % over 80 years. The prevalence of *severe* stenosis ranged from 0.1 % in men under 50 years to 3.1 % over 80 years and among women the prevalence ranged from 0 % under 50 years to 0.9 % over 80 years [2]. A systematic review and meta-regression analysis of 40 population based studies on asymptomatic subjects, noted a pooled prevalence of moderate stenosis of 4.2 % and severe stenosis of 1.7 % [3]. Among subjects under 70 years, the prevalence estimate for moderate stenosis was 4.8 % in men and 2.2 % in women. Among those over 70 years, the prevalence increased to 12.5 % in men and 6.9 % in women [3] (Table 25.1).

Similar prevalence estimates were noted across different populations across the globe. The prevalence of significant carotid stenosis $\geq$ 50 % in an asymptomatic Egyptian series of 617 subjects was 6.3 % [4]. The Suita study randomly sampled asymptomatic men and women aged 50–79 years in urban Japan. The prevalence of significant stenosis was 4.4 % (7.9 % in men and 1.3 % in women) [5]. The Korean Longitudinal Study on Health and Aging evaluated carotid intimal–medial thickness (IMT) among asymptomatic elderly

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Table 25.1 Asymptomatic carotid stenosis[a] according to age and sex

	<70 years	≥70 years
Men	4.8 %	12.5 %
Women	2.2 %	6.9 %

[a]Moderate stenosis of >50 %

patients >65 years. The prevalence of subclinical atherosclerosis, defined as carotid IMT>0.8 mm was 39.2 % [6].

The prevalence of Carotid stenosis is higher in subsets of asymptomatic patients with traditional atherosclerotic risk factors. Ultrasound screening of a population of 766 asymptomatic subjects with multiple atherosclerotic risk factors, revealed significant stenosis in 14.2 % of subjects with diabetes and dyslipidemia and 29.6 % in patients with 4 risk factors [7]. In a series of 440 young (25–50 years) North Indian asymptomatic subjects, carotid atherosclerosis (IMT>0.9 mm) was noted in 21.6 % of subjects satisfying the criteria for metabolic syndrome. A large proportion of patients with carotid atherosclerosis (71.5 %) had 4 or more components of the metabolic syndrome [8]. Compared to nondiabetics, subjects with type 2 diabetes are three times more likely to develop asymptomatic carotid stenosis. In subjects with carotid stenosis, type 2 diabetics are more likely to develop severe stenosis [9]. In an East German population of 1632 asymptomatic adults, nonsmoking subjects with poor physical activity and unhealthy diet were at higher odds (OR: 2.68) of developing severe carotid stenosis compared to nonsmokers with physical activity and optimal diet. Diet and activity did not seem to influence risk of stenosis among smokers [10]. In a Japanese series, the prevalence of significant carotid stenosis was significantly greater among rural subjects (9.6 %) compared to urban subjects (4.6 %); this difference was attributed to long standing hypertension [11].

As atherosclerosis is a systemic disease, patients with symptomatic atherosclerosis elsewhere are more likely to also have carotid stenosis. This includes patients with peripheral arterial disease (PAD) and coronary disease. A meta-analysis of 19 studies with 4573 patients with symptomatic PAD, found moderate stenosis in 25 % of subjects and severe stenosis in 14 % [12]. In a series of asymptomatic, elderly patients (60–80 years) with two or more cardiovascular risk factors, a low Ankle Brachial index (ABI) <0.9 predicted the presence of significant carotid stenosis (14.3 % vs. 4.7 % among patients with normal ABI) [13]. Doppler screening of 162 patients with PAD in the SMART (Second Manifestations of ARTerial disease) cohort revealed significant asymptomatic carotid stenosis in 14 % [14]. About two-thirds of the PAD patients with significant asymptomatic carotid stenosis have concomitant coronary artery disease, several of them fulfilling indications for coronary revascularization [15]. The screening for carotid stenosis among patients going for coronary artery bypass grafting (CABG) is a common practice in many institutions. Among 643 patients undergoing CABG, 7.7 % had severe carotid stenosis and the presence of a cervical bruit, PAD or aortic aneurysm predicted significant carotid disease [16]. In another series of 757 patients with CABG, the prevalence of ≥50 % stenosis was 26.4 % and ≥70 % stenosis was 8.6 %. High plasma levels of ApoB/ApoA1, lipoprotein(a), and homocysteine predicted carotid stenosis in this population [17]. Among patients with abdominal aortic aneurysms, severe asymptomatic carotid stenosis was found in 10.8 % [18].

Pathophysiology of the Asymptomatic Carotid Plaque

Carotid atherosclerosis is well established as an inflammatory process [19] in which the vascular endothelium plays a dynamic role [20]. Inflammation is responsible for the initiation, progression, and vulnerability of the atherosclerotic plaque. [20] Normal endothelium is quiescent and in an anti-inflammatory state, with excess production of nitric oxide, which is regarded as protective for the endothelium. Hypertension, diabetes, oxidized low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, smoking, homocysteine, certain infections, and the mechanical shear stresses in the region of the carotid bulb convert the anti-inflammatory endothelial cell into a pro-inflammatory state [20]. The pro-inflammatory state results in excess production of oxygen-derived free radicals such as superoxide and peroxynitrites. One of their major effects is the oxidation of LDL cholesterol.

Oxidized LDL results in activation of leucocytes and intimal smooth muscle cells. It induces production of endothelium adhesion molecules, which attract monocytes to the area. It activates monocytes into macrophages, which engulf oxidized LDL molecules resulting in foamy macrophages. Oxidized LDL also reduces the expression of nitric oxide synthase, decreasing the production of protective nitric oxide [20]. Another effect of oxidative stress is the increased expression of matrix metalloproteinase 9 (MMP 9). MMP 9 results in deterioration of the extracellular matrix, promoting migration of leukocytes and smooth muscle cells into the subendothelial area. In the fully developed plaque, MMP 9 may weaken the fibrin cap, resulting in plaque rupture [20].

The various stages of atherosclerotic plaque evolution have been classified by the American Heart Association, starting with an initial lesion with activated macrophages [21]. The next stage is the fatty streak where foamy macrophages are formed. This progresses to the intermediate lesion, where foamy macrophages increase in number, and some of them die resulting in extracellular lipid formation. Plaques are usually asymptomatic up to this stage [21].

As the extracellular lipid increases in quantity, the plaque is now called an atheroma. This progresses to a fibroatheroma with a defined lipid necrotic core and a fibrous cap [21]. When sufficient amount of necrotic lipid accumulates, it may crystallize into cholesterol crystals. The jagged crystals may cause a rupture of the fibrous cap or may rupture the vasa vasorum of the artery resulting in intraplaque hemorrhage. Such a complicated lesion is the setting for initiation of thrombosis. Once a necrotic lipid core begins to form, the patient is prone to develop clinical symptoms [21].

Pathological studies on plaques removed during endarterectomy suggest that the asymptomatic plaque in patients who have never experienced symptoms have increased smooth muscle content, increased calcification and less frequent intra-plaque hemorrhage [22]. Genetic studies in the elderly patients with asymptomatic carotid plaque have identified single nucleotide polymorphisms associated with high levels of proinflammatory molecules such as interferon gamma and interleukin 6 [23]. Recent genome wide association studies have identified some novel loci, which have opened up a fertile field for future atherosclerosis research [24].

Clinical Manifestations of Asymptomatic Carotid Stenosis

The main concern with asymptomatic carotid stenosis is whether the plaque will convert to a symptomatic stenosis (i.e., the risk of future cerebrovascular events). Generally the risk of stroke in patients with asymptomatic stenosis is low. In studies from the pre-statin era, patients with an asymptomatic stenosis <75 % had a 1.3 % annual risk of stroke. With a stenosis ≥75 %, the annual risk of stroke was 2–2.5 %. With the advent of statins and aggressive antihypertensive therapy, these risks are generally lower. The risk of cerebrovascular events is markedly increased if the patient has concomitant intracranial atherosclerosis (3.6 % annual risk) [25]. The risk of stroke increases with the degree of stenosis and the rate of stenosis progression [26]. Cohort studies with sequential ultrasound follow-up show that the progression rates of asymptomatic stenosis are usually low [27]. The average rate of progression tends to be faster among diabetics, especially if they continue smoking [27].

Beyond the occurrence of a cerebrovascular event, asymptomatic carotid stenosis has several other clinical implications. Studies using transcranial Doppler ultrasound can detect asymptomatic intracranial microembolic signals from carotid plaques. In the Asymptomatic Carotid Emboli Study, patients with severe asymptomatic carotid stenosis received two single hour recordings with transcranial Doppler [28]. Of 482 subjects, 10.7 % demonstrated microemboli on 1 recording, and 16.7 % showed microemboli on at least one of two recordings. Antiplatelet therapy reduced the likelihood of detecting microembolic signals [28]. In a systematic review, 10 % of 1066 patients with asymptomatic carotid stenosis demonstrated at least one microembolic signal [29]. The presence of microembolism strongly predicted future cerebrovascular events with an OR of 13.4 [29]. In a natural history study of 821 patients with asymptomatic carotid stenosis, 17.8 % of subjects showed silent embolic infarcts on head CT [30]. This finding has been replicated in other series [31]. The presence of such infarcts, while asymptomatic, increased the risk of future symptomatic cerebrovascular events [30].

A number of cohorts have convincingly demonstrated cognitive impairment among patients with otherwise asymptomatic carotid stenosis. A cognitive evaluation of 1975 subjects in the Framingham Offspring study showed that an increased internal carotid IMT was significantly associated with poorer performance on verbal and nonverbal memory measures [32]. Carotid stenosis ≥25 % was associated with poorer performance on executive function [32]. In another recent study, 17 patients with severe asymptomatic carotid stenosis and 26 controls, underwent extensive neuropsychological testing and multimodal MR imaging [33]. Patients with severe stenosis had significantly lower scores on memory and complex visuospatial performance. Multimodal MR imaging demonstrated disruption of both interhemispheric and intrahemispheric functional connectivity in the default mode network and frontoparietal networks [33]. Patients with severe carotid stenosis had lower whole brain mean fractional anisotropy (FA) and diffuse decrement of FA, indicating poorer diffusivity and microstructural disruption of white matter integrity. Eleven of the 17 patients underwent carotid revascularization. Interestingly, MR imaging at 3 months demonstrated significantly improved FA and functional connectivity. There were improvements in cognitive scores also, although these did not reach statistical significance [33]. Multiple cohorts have shown otherwise asymptomatic carotid stenosis to be a strong predictor of early postoperative cognitive impairments following CABG [34, 35].

As mentioned above, there is a higher prevalence of asymptomatic carotid stenosis in patients undergoing CABG. There are conflicting reports about the contribution of carotid stenosis to the outcome of patients undergoing surgery. In a series of 455 patients undergoing CABG, asymptomatic carotid stenosis ≥50 % was an independent predictor of mortality after surgery (OR: 2.7) [34]. In this study, patients with carotid stenosis were about 5 times more likely to have cognitive abnormalities postoperatively. Carotid stenosis did not predict postoperative strokes [34]. In another series of 878 consecutive patients undergoing CABG, severe carotid stenosis did not predict either postoperative stroke or 30 day mortality [36]. In a meta-analysis of studies of cardiac surgery patients with asymptomatic stenosis, Naylor et al. demonstrated that prophylactic carotid revascularization prior to cardiac surgery will only benefit

about 1–2 % of patients with severe and bilateral asymptomatic carotid stenosis (number needed to treat 50–100); and will not benefit patients with unilateral asymptomatic stenosis [37]. Thus, the practice of concomitant or staged carotid revascularization with CABG remains controversial.

Dizziness and syncope are common reasons for referral of patients for carotid artery screening. Fainting, without associated neurological signs is a very common symptom and can occur in about 40 % of the general population during their lifetime [38]. Fainting associated with other focal neurological symptoms and signs can be a presentation of vertebrobasilar stenosis or subclavian steal. No studies have shown carotid duplex to be valuable in the diagnosis of syncope [38]. The American Academy of Neurology listed avoidance of carotid imaging for simple syncope as one of the top five recommendations in the "Choosing Wisely" initiative [39].

Patients are often referred for Doppler evaluations of the carotid artery for an asymptomatic bruit picked up incidentally on clinical examination. However, in today's era of medical management, the benefit of detection of asymptomatic carotid stenosis does not generally outweigh the risk of early intervention [40]. Therefore, the US Preventive Services Task Force recommends against routine carotid auscultation in the general population [40]. A meta-analysis of 28 prospective cohort studies with 17,913 patients followed over 67,708 patient-years, showed an increased rate of stroke (1.6 per 100 patient-years) and transient ischemic attacks (2.6 per 100 patient years) compared to patients without bruits [41]. The corresponding rates in patients without bruits were stroke (1.3 per 100 patient-years) and transient ischemic attack (0.9 per 100 patient-years). Among 686 multiethnic, asymptomatic subjects in the Northern Manhattan Study (NOMAS) cohort, the prevalence of carotid stenosis ≥60 % was only 2.2 % and the prevalence of bruits was 4.1 % [42]. For prediction of carotid stenosis, sensitivity of auscultation for a bruit was 56 %, specificity was 98 %, positive predictive value was 25 % and negative predictive value was 99 %. Thus, a high false negative rate suggests that absence of a bruit is not sufficient to exclude carotid stenosis [42]. Therefore, it may be reasonable to restrict screening for carotid stenosis by ultrasound in high risk populations (see Section on "Prevalence").

Modalities for Detection of Carotid Artery Stenosis

The investigative modalities available for detection of carotid stenosis include duplex ultrasound, CT angiography, MR angiography and conventional digital subtraction angiography. Due to its noninvasive nature and lack of radiation, duplex ultrasonography is the most feasible test for severe carotid stenosis. However, the test has moderate sensitivity and specificity, and yields many false positive results. Therefore, a positive duplex result needs confirmation by another test. The sensitivity and specificity of duplex ultrasonography and MR Angiography were compared in a meta-analysis using digital subtraction angiography as a gold standard. [43] Among 64 patient series using duplex ultrasonography, the pooled sensitivity and specificity to detect 70–99 % stenosis were 86 % and 87 % respectively. The pooled sensitivity and specificity for MRA based on 21 patient series were 95 % and 90 %. Thus MRA seems to have a better discriminatory power for severe stenosis compared to duplex ultrasonography [43].

Another meta-analysis of studies using duplex sonography found a pooled sensitivity and specificity of 90 % and 94 % respectively for the detection of severe stenosis [44]. The caveat with duplex sonography is that different laboratories use widely varying measurement properties, thereby casting doubt on the reliability of this investigation [44].

Contrast enhanced MRA tends to overestimate the degree of carotid stenosis, particularly with mild or moderate stenosis. In this regard, a time of flight MRA performs better [45]. Although contrast enhanced MRA is an excellent screening technique because of reduced imaging time and improved signal to noise ratio, it is not the ideal test to assess degree of stenosis [45]. While CT angiography provides excellent detail of the carotid lesion, it is limited by the exposure to radiation, expense and the need for iodinated contrast. A meta-analysis of 28 studies looked at the value of CT angiography for detection of severe carotid stenosis [46]. The pooled sensitivity and specificity were 85 % and 93 %; equivalent to those achieved with duplex ultrasonography [46]. Digital subtraction angiography similarly is invasive, requires radiation exposure and has a small risk of neurological events in the order of 0.1–0.5 % [47].

The key question is: Which asymptomatic patients should be referred for screening of carotid stenosis? Several attempts have been made to determine a cost-effective and beneficial approach to this question. An excellent discussion of the different studies is provided by Qureshi et al. [48]. The general consensus from the different studies is that if the prevalence of carotid stenosis is 20 % or higher in a group of patients (for instance in populations over 65 years with multiple cardiovascular risk factors such as hypertension, coronary disease, cigarette smoking or dyslipidemia), screening for carotid stenosis would be beneficial, and could reduce stroke risk in a cost-effective manner [48]. For populations with intermediate prevalence of carotid stenosis, the benefit is marginal and is lost if perioperative complications exceed 5 %. Screening in unselected populations does not reduce stroke risk and is not recommended, as instead it could be harmful [48].

Prognosis and Treatment of Asymptomatic Carotid Stenosis

In terms of management for patients with asymptomatic carotid stenosis (ACS), all patients should receive medical therapy. Carotid revascularization, typically with carotid endarterectomy (CEA), can be useful for select patients. The role of carotid artery stenting (CAS) for patients with asymptomatic disease is uncertain.

With regard to medical therapy, all patients should receive the core elements of vascular disease therapy. This includes the following:

1. Antiplatelet therapy
2. Aggressive treatment of dyslipidemia
3. Treatment of hypertension to national guideline targets
4. Smoking cessation
5. Lifestyle modification, including dietary modification and exercise

It is beyond the scope of this chapter to discuss each of these in detail but certain observations are worthwhile. For antiplatelet therapy, aspirin is typically used (81–325 mg/day). There are no data comparing alternative antiplatelet regimens (such as clopidogrel or aspirin plus extended release dipyridamole) to aspirin for patients with ACS.

The value of lipid lowering with statins in patients with ACS has been established from several sources. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, atorvastatin 80 mg/day was compared with placebo in patients with a prior stroke or transient ischemic attack (TIA) [49]. In an analysis of patients with carotid stenosis, 1007 patients had a mean stenosis of 51 % [50]. In the atorvastatin patients, LDL was lowered from 132 mg/dl at baseline to an average of 70 mg/dl during trial follow-up. In the placebo patients, LDL decreased from 133 mg/dl to 130 mg/dl. The atorvastatin-treated patients had a 33 % reduction in any stroke, 43 % reduction in coronary events, and 56 % reduction in later carotid revascularization procedures. In the Asymptomatic Carotid Surgery Trial (ACST), there was increasing use of lipid-lowering treatment during the course of the trial [51]. For patients not on lipid lowering therapy and treated in the medical arm of the study, the 10 year risk of stroke was 24.9 %. This figure was reduced to 14.5 % for patients who were treated with lipid-lowering therapy. As a result of these observations (and other studies), treatment with high potency statins is an important component of treatment of patients with ACS.

The role of CEA in asymptomatic individuals is a matter of considerable debate. The Asymptomatic Carotid Atherosclerosis Study (ACAS) [52] and the ACST are the two largest randomized clinical trials that have investigated the value of CEA relative to medical therapy.

In ACAS, patients were randomized to receive either best medical treatment alone or medical therapy plus CEA if they had stenosis greater than 60 % but were otherwise healthy. The study was stopped early after a mean period of 2.7 years follow-up. In the surgical arm, the combined event rate for ipsilateral stroke, any perioperative stroke and death at 5 years was projected to be 5.1 %, compared with 11 % in the medical arm—a relative risk reduction of 55 % and an ARR of 5.9 % (Number Needed to Treat, NNT 17). The absolute annual benefit in ACAS of 1.2 % was considered marginal by some experts in the 1990s. The benefit seen with surgery in ACAS could be a result of the exceptionally low perioperative risk of 1.5 % achieved in the trial. Whether this low perioperative stroke rate can be uniformly achieved in "real-life" situations is doubtful. For example, in a study of over 1800 asymptomatic CEA cases from Ontario, the perioperative stroke and death rate was 4.7 % [53].

Although it is frequently reported that the ASCT findings were similar to those of the ACAS, there were important differences in the two study designs. In ACAS, the primary analysis compared strokes occurring in the territory of the operated carotid artery, while the ACST included strokes in any vascular territory. In addition, conventional angiography was not mandated for either group in ACST. After 5-years' follow-up, the risk of recurrent stroke for the surgical group in ACST was 6.4 % and 11.8 % for those on medical treatment. This difference was more or less evident even after 10 years—13.4 % versus 17.9 % with net benefit of 4.5 % (NNT 22). The risk of perioperative stroke or death was 2.8 %. Importantly, this study showed a significant reduction of fatal or disabling strokes in the surgical arm (3.5 % vs. 6.1 % in medically treated group, ARR 2.6 %; $p<0.004$). Approximately half of all ipsilateral recurrent strokes that occurred were classified as fatal or disabling. There was no clear benefit of CEA in subjects age 75 years and older in ACST.

A meta-analysis of data from 5223 patients from three major trials of CEA for asymptomatic carotid stenosis was performed by Chambers and Donnan [54]. Surgery conferred a significant benefit in terms of the composite primary outcome (any perioperative or subsequent stroke, and all-cause perioperative mortality; relative risk 0.69, 95 % CI 0.57–0.83). The overall risk of perioperative stroke or death was 2.9 %. Subgroup analysis revealed men received more benefit from surgery than did women, and younger patients benefited more than older patients. Unlike the symptomatic stenosis trials, stenosis severity did not correlate with benefit from surgery. Despite these findings, some have argued against the routine use and widespread enthusiasm for CEA in asymptomatic patients. Barnett et al. highlight that the absolute annual risk

reduction of stroke in this asymptomatic group is about 1 % with a number needed to treat of 83 to prevent one stroke in 2 years [55]. Moreover, it has been estimated that approximately half the strokes in asymptomatic individuals are not related to the stenosed carotid artery but are rather lacunar strokes or caused by cardioembolic events [56].

As discussed above, the benefit of surgery in patients with carotid stenosis is critically dependent on perioperative stroke risk. A low perioperative stroke risk is especially important for asymptomatic patients, in whom the marginal benefit can be lost if the risk is not within recommended limits. Practicing clinicians must, therefore, be aware of their institutional complication rates, in order to advise patients. In a study of 12 academic centers and 1160 procedures, Goldstein et al. reported a perioperative risk of stroke or death of 2.8 % [57]. Notably, the rate was higher in symptomatic than in asymptomatic individuals. Postoperative stroke and death was also significantly higher in women, older individuals (>75 years), those with associated congestive heart failure, and those undergoing simultaneous CABG surgery. The American Academy of Neurology guidelines recommend that CEA for asymptomatic stenosis be considered only for patients 40–75 years old with at least a 5 year life expectancy [58]. In addition, the surgeon's complication rate should be reliably documented to be less than 3 %.

In the last 15 years, the recognition of the role of early and comprehensive medical management of cerebrovascular disease has led to a great but highly underappreciated reduction of stroke risk in this population of patients [59]. There is paucity of data as to the exact annual risk of stroke in patients with asymptomatic carotid stenosis on modern medical therapy. Recent studies suggest that the annual risk of stroke has dropped significantly to <1 % per year with medical therapy alone, raising serious questions about the benefit of any revascularization procedure (Table 25.2). Spence et al. have shown that transcranial Doppler can identify a subgroup of patients with asymptomatic stenosis who have microembolic signals that are at higher risk for stroke than those who do not have these microembolic signals [60]. In this study, 10 % of 319 subjects had evidence of microemboli. Patients with microemboli had a 1 year risk of stroke of 15.6 %, compared to a 1 year risk of stroke of 1 % in patients without microemboli. These investigators further demonstrate that intensive medical therapy of arterial plaques can reduce the number of patients with microembolic signals by 90 % and that revascularization procedures should be considered only in the small minority who can be demonstrated to be at high risk [61].

Table 25.2 Prognosis of medically treated carotid stenosis

Study	*N*	Follow-up duration	Annual stroke rate
Oxford Vascular	101	3 years	0.34 %
SMART	193	5 years	0.3 %
ACES	77	2 years	3.6 % with microemboli
ACES	390	2 years	0.7 % w/o microemboli

Guidelines from the ASA/AHA indicate that patients with asymptomatic stenosis should be screened for other treatable causes of stroke and that intensive treatment of stroke risk factors should be pursued (class I, level C) [62]. In addition, the use of aspirin is recommended in subjects with asymptomatic stenosis. CEA is recommended in only in highly select patients with high grade stenosis and the surgeon should have a stroke/death rate of <3 % (class IIa, level A). There should be a thorough understanding of the goals of the procedure, the patient's life expectancy and comorbidities, and patient preferences.

Carotid artery stenting (CAS) has been proposed as an alternative to CEA. In contrast to CEA, however, CAS has never been compared against optimal medical therapy. CAS has been compared relative to CEA in several studies. The most relevant with regard to ACS is the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) [63]. CREST enrolled both symptomatic and asymptomatic patients. Asymptomatic patients were enrolled if they had >60 % stenosis on angiography or >70 % stenosis on ultrasound. In the trial as a whole, the primary endpoint (periprocedural stroke, death, or MI, and ipsilateral stroke during follow-up), there was not a difference between CEA and CAS (6.8 % vs. 7.2 %, $p=0.51$). For periprocedural events (any stroke or death) in the asymptomatic group of patients ($n=1181$), complication rates were fairly low in both arms but were higher with CAS (2.5 % vs. 1.4 %, hazard ratio 1.88, $p=0.15$). When follow-up events were included, the rate of any periprocedural stroke or death plus ipsilateral stroke during 4 year follow-up was 4.5 % with CAS and 2.7 % with CEA (hazard ratio 1.86, $p=0.07$).

Two other points are worthy of mention with regard to CAS. First, in CREST, there was a significant age interaction, with patients age 70 years and above having a higher complication rate with CAS compared to CEA. [64] Second, just as with CEA, the real world performance of CAS is considerably worse than the clinical trial results. In CREST, the overall periprocedural mortality in CAS patients was 0.7 %. In a national study of 24,701 Medicare beneficiaries who underwent CAS between 2005 and 2007, the periprocedural mortality was 1.9 %, nearly three times as high as that seen in CREST. [65] These two observations should temper the enthusiasm for performing CAS in asymptomatic patients, especially those over age 70 years.

With the renewed interest in contemporary medical therapy, new clinical trials have been launched to compare intensive medical management (IMM) alone versus IMM plus revascularization. In North America, the CREST investigators have received funding for the Carotid Revascularization

and Medical Management for Asymptomatic Stenosis Trial (CREST-2) [66]. This will consist of two parallel studies, one comparing IMM alone versus IMM plus CEA. The second component of the trial will compare IMM alone versus IMM plus CAS. Two other trials are comparing IMM versus carotid revascularization in Europe (SPACE-2 and ECST-2).

While clinicians are waiting for the next generation of asymptomatic carotid trials, we espouse the following set of pragmatic recommendations:

1. All patients should aggressive treatment of vascular risk factors
2. Carotid revascularization can be considered in select patients below age 75 years
3. Men are more likely to benefit from carotid revascularization than women
4. CEA is preferred over CAS as the revascularization method in patients who are standard surgical risk (pending the results of ongoing studies)
5. The local 30 day rate of periprocedural stroke/death should be documented to be <3 % (and preferably <2 %)
6. Patients should have a careful assessment of their 5 year life expectancy
7. If available, risk stratification with methods such as TCD microemboli detection can help guide decisions between revascularization and medical therapy
8. Consideration should be given to referring patients with asymptomatic carotid stenosis to ongoing clinical trials such as CREST-2

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Subclinical Vascular Brain Injury

26

Eric E. Smith

Introduction

With increasing use of neuroimaging, clinicians are more and more frequently confronted with evidence of incidentally discovered subclinical brain injury, and its ramifications for clinical management. With more than 1.5 million brain scans performed each year for headache alone in the USA [1], a significant number of Americans are being screened unintentionally for subclinical vascular brain injury.

The cardinal manifestations of subclinical brain injury are silent central nervous system (CNS) infarcts, white matter hyperintensities (WMH) of presumed vascular origin and microbleeds. When subclinical vascular brain injury is identified the clinician must decide on the need for further work-up and the implications for vascular risk reduction. This chapter presents a practical approach to diagnosis and management of subclinical vascular brain injury.

Epidemiology

Subclinical vascular brain injury is common. It is the most frequently identified incidental brain finding [2], with a prevalence that increases markedly with advancing age. The age-specific prevalence of silent CNS infarction and microbleeds is shown in Table 26.1. WMH may be seen to a small degree beginning in the 40s and 50s, becoming ubiquitous by the 70s.

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Clinical Manifestations

By definition, subclinical vascular brain injury is considered "silent" or "covert," meaning that it is not associated with an acute stroke syndrome. However, silent CNS infarctions and WMH are associated with lower scores on neuropsychological testing and slower gait speed, indicating that they are not truly "silent" in all patients [3–5]. Furthermore, autopsy studies show that small CNS infarcts, mostly "silent," account for much of the risk of dementia during life. In fact, silent CNS infarction is the second biggest contributor to dementia risk, after Alzheimer's disease [6]. Subclinical brain injury reduces cognitive reserve, inhibiting the capacity of the brain to tolerate the ill effects of other age-related changes including pathologies such as Alzheimer's disease. Patients with silent CNS infarctions or high burden of WMH have a twofold to threefold increased risk of future dementia as well as a twofold to threefold increased risk of future symptomatic stroke [4, 5]. In contrast, the risk of future symptomatic events in patients with microbleeds is less well understood. In sum, it is clear that subclinical vascular brain injury manifesting as silent CNS infarction or WMH identifies patients that are increased future risk of vascular cognitive impairment and stroke, warranting a careful consideration of vascular risk reduction strategies.

Pathophysiology

Most subclinical vascular brain injury is caused by small vessel diseases. The exception is that a minority of silent CNS infarctions, about 15 %, are caused by emboli from proximal sources [7]. Arteriolosclerosis, due to aging and vascular risk factors such as hypertension, may cause lacunar infarction or microbleeds.

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Table 26.1 Prevalence of silent brain infarcts and microbleeds in community-based studies

Age decade	Silent brain infarcts (%)	Microbleeds (%)
40–49	1–5	2
50–59	3–8	2–3
60–69	8–15	5–18
70–79	12–20	8–31
80+	20–35	10–38

Prevalence data are from community- and population-based studies [32, 46–48]. The wide variance in microbleed estimates reflects, in part, use of different MRI sequences with varying sensitivity

Cerebral amyloid angiopathy (CAA) is another cause of microbleeds [8]. The pathophysiology of WMH is less well understood and may be multifactorial. A vascular origin for the majority of WMH is suggested by its association with vascular risk factors and the observation that cerebral small vessel diseases, such Cerebral Autosomal Dominant Arteriopathy with Subcortical Ischemic Leukoencephalopathy (CADASIL) and CAA, are marked by high volumes of WMH [9].

Diagnosis

Subclinical vascular brain injury cannot be reliably inferred from risk factors or clinical symptoms; therefore, brain imaging is required for diagnosis. MRI is more sensitive that CT. Consensus recommendations for terminology and classification of cerebral small vessel disease have recently been published (Fig. 26.1) [10]. Lacunes of presumed vascular origin are round or ovoid, subcortical fluid filled cavities between 3 and 15 mm in diameter, compatible with a previous acute small deep brain infarct or hemorrhage. WMH of presumed vascular origin are defined as white matter signal abnormalities with hyperintensity on fluid attenuated inversion recovery (FLAIR) and T2 weighted sequences, or hypodensity on CT, without evidence of cavitation (that is, without cerebrospinal-fluid-like signal). Microbleeds are defined as small (generally 2–5 mm, but sometimes up to 10 mm) areas of signal void with associated "blooming" seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects. The sensitivity for detecting microbleeds may vary by twofold to threefold depending on the scanner field strength and sequence; newer generation sequences such as susceptibility-weighted imaging (SWI) are more sensitive than older generation T2*-weighted gradient-recalled echo (GRE) [11].

In addition to the three cardinal manifestations of subclinical vascular brain injury, many other manifestations are recognized—such as perivascular space prominence, diffusion changes, brain atrophy and others [10]—that are the subject of ongoing research but currently with less certain clinical relevance.

Clinical Implications and Management

Decisions regarding management of subclinical vascular brain injury may arise in at least three different scenarios. In the first scenario, chronic subclinical vascular brain injury is found on scans of patients with acute stroke syndromes. This is a common occurrence because chronic subclinical vascular brain injury and acute stroke have shared risk factors. When subclinical vascular brain injury is identified, it may have implications for work up and management of the acute stroke. The presence of chronic silent embolic-appearing infarcts suggests a proximal embolic source. The identification of microbleeds may prompt reconsideration of the safety of thrombolysis or anticoagulant treatment for patients with ischemic stroke (see Section "Case 1" for a more detailed discussion of this issue).

In the second scenario, subclinical vascular brain injury is discovered in a patient without acute stroke but who exhibits symptoms, such as cognitive or gait impairment, which might plausibly be considered a consequence of the subclinical vascular brain injury. In this scenario, identifying and treating the cause of the subclinical brain injury may prevent symptom progression (Section "Case 2").

In the last scenario, subclinical vascular brain injury is discovered as an incidental finding in patients who undergo brain imaging for completely unrelated reasons. In this scenario, the clinician must consider the implications of subclinical vascular brain injury for global cardiovascular and stroke risk reduction (Section "Case 3").

Case Presentation 1: An Ischemic Stroke Patient with Atrial Fibrillation and Cerebral Microbleeds

Details of the Case

A 77-year-old woman presents with acute dysarthria and mild right facial droop, with NIH Stroke Scale score 2. Electrocardiogram shows new onset atrial fibrillation. Echocardiogram shows a mildly dilated left atrium with a normal ejection fraction and no wall motion abnormalities. An MRI brain shows small areas of restricted diffusion in both hemispheres, consistent with acute infarction as the cause of her new dysarthria (Fig. 26.2). MRI SWI shows fifteen lobar microbleeds, without evidence for microbleeds in deep locations. Should this patient be anticoagulated to prevent recurrent ischemic stroke due to atrial fibrillation? What is the risk of anticoagulant-induced intracerebral hemorrhage (ICH) in patients with microbleeds?

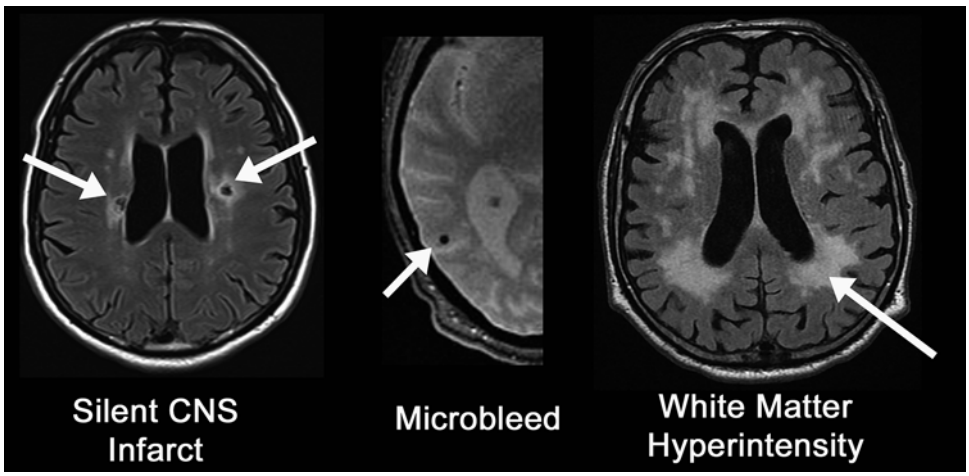

Fig. 26.1 Silent brain infarcts, microbleeds and white matter hyperintensities of presumed vascular origin. *Left panel*: axial fluid attenuated inversion recovery (FLAIR) sequence showing two lacunes of presumed vascular origin (*arrows*), *middle panel*: axial T2*-weighted gradient-recalled echo (GRE) sequence, *right panel*: axial FLAIR. *CNS* central nervous system

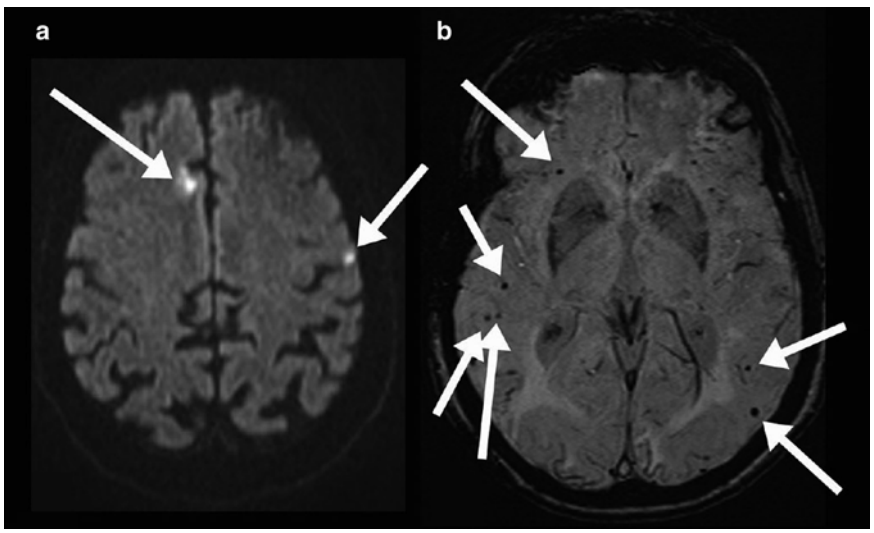

Fig. 26.2 A 77-year-old woman with acute ischemic stroke, atrial fibrillation and multiple lobar microbleeds. (**a**) Axial diffusion weighted imaging (DWI) showing two areas of hyperintensity, representing acute infarcts. (**b**) Axial susceptibility-weighted imaging (SWI) showing six microbleeds (*arrows*), all in lobar locations. In total there were 15 lobar microbleeds

Discussion

The microbleeds indicate the presence of a hemorrhage-prone vasculopathy, and the risk of subsequent ICH is probably increased. The clinical question is whether the increased risk of subsequent ICH outweighs the risk reduction that would be conferred by anticoagulation. This patient has a CHA_2DS_2-VASC (for definition see Chap. 12) score of 5 that is associated with an annual risk of recurrent ischemic stroke of ~6.7 % which would be reduced to ~2.2 % with anticoagulation [12]. Therefore, anticoagulation is indicated in the absence of other factors that would substantially increase the risk of bleeding complications.

Microbleeds appear as small, focal areas of signal loss (hypointensity) on T2* sensitive sequences such as GRE or SWI [13]. They are usually not apparent on other MRI sequences and cannot be seen on CT. In the absence of a few other specific conditions that cause microbleeds (e.g., familial cavernous malformation, infective endocarditis, and traumatic diffuse axonal injury), which should be obvious from the history, microbleeds are nearly always attributed to either arteriosclerosis, related to aging and vascular risk factors, or CAA. Radiopathological correlation studies suggest that microbleeds represent small areas of extravascular hemosiderin deposition from previous small, asymptomatic hemorrhages [14]. Microbleeds must be discriminated from several

common mimics. Blood vessels seen in cross section will appear as small round hypointense dots, because deoxygenated hemoglobin also has a susceptibility effect. Calcifications, frequently seen in the globus pallidus, may also appear as hypointensities, mimicking microbleeds. There are two published standardized rating systems to enhance specificity and reliability of microbleed identification [15, 16].

One or more chronic microbleeds are seen in up to 30–70 % of persons with acute ischemic stroke, but only 10–30 % of the general population [17]. The increased prevalence in ischemic stroke patients likely reflects shared risk factors for microbleeds and ischemic stroke, such as hypertension. The clinical concern in our patient is that the microbleeds may signify an increased risk for future ICH, and greater risk from anticoagulation. Unfortunately, the risk of warfarin-related ICH in patients with microbleeds is poorly defined. In the absence of better data from prospective studies, specific recommendations for antithrombotic strategy for atrial fibrillation in the setting of incidentally discovered lobar microbleeds cannot be provided, but general guidelines can be discussed. In general, the clinical approach should be to determine the cause of the microbleeds (hypertension, CAA, or other) with application of the Boston criteria (Table 26.2), to mitigate bleeding risk by carefully controlling hypertension, and to judge the risks and benefits of anticoagulation strategies in light of the number of microbleeds and their underlying cause. Screening with MRI to identify microbleeds before anticoagulation is not recommended, given the current lack of certainty on how they should affect management.

In the patient under discussion, the presence of multiple microbleeds in lobar brain locations, without microbleeds in deep hemispheric locations such as the basal ganglia or thalamus, suggests that CAA is the underlying cause [8]. CAA is caused by vascular amyloid deposition. Vascular beta-amyloid is toxic to vascular smooth muscle cells, leading to fibrosis, necrosis and loss of vascular wall integrity with bleeding. CAA causes about 20 % of all symptomatic ICHs. Chronic, asymptomatic microbleeds or areas of superficial siderosis (Fig. 26.3) are often seen in addition to symptomatic hemorrhagic strokes. The Boston criteria for CAA diagnosis use age, presence and number of lobar hemorrhages, microbleeds, and superficial siderosis to assign a probability of underlying CAA as the cause of ICH (Table 26.2) [18, 19]. These criteria rely on the fact that vascular beta-amyloid preferentially involves the leptomeningeal and cortical vessels, with relative sparing of vessels supplying the basal ganglia. Therefore, hemorrhages and microbleeds affecting the cortex and subcortical white matter in the elderly are potentially related to CAA (although arteriosclerosis due to conventional vascular risk factors can also cause bleeding in these locations), while hemorrhages and microbleeds in the deep hemispheric structures such as the basal ganglia are unlikely to be caused by CAA and more likely to be related to arteriosclerosis due to hypertension and other vascular risk factors (Fig. 26.4). The Boston criteria have been pathologically validated in persons with lobar ICH [19]. Although the criteria have not been pathologically validated in persons like our patient under discussion, who only had multiple lobar microbleeds without symptomatic ICH, it is likely that most elderly with

Table 26.2 Revised Boston criteria for diagnosis of cerebral amyloid angiopathy (CAA) [18]

Definite CAA	Full postmortem examination demonstrating:
	• Lobar, cortical, or corticosubcortical hemorrhage
	• Severe CAA with vasculopathy
	• Absence of other diagnostic lesions
Probable CAA with supporting pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:
	• Lobar, cortical, or corticosubcortical hemorrhage
	• Some degree of CAA in specimen
	• Absence of other diagnostic lesion
Probable CAA	Clinical data and MRI or CT demonstrating:
	• Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or Single lobar, cortical, or corticosubcortical hemorrhage and focal or disseminated superficial siderosis
	• Age ≥55 years
	• Absence of other cause of hemorrhage or other cause of superficial siderosis
Possible CAA	Clinical data and MRI or CT demonstrating:
	• Single lobar, cortical, or corticosubcortical hemorrhage or focal or disseminated superficial siderosis
	• Age ≥55 years
	• Absence of other cause of hemorrhage or other cause of superficial siderosis

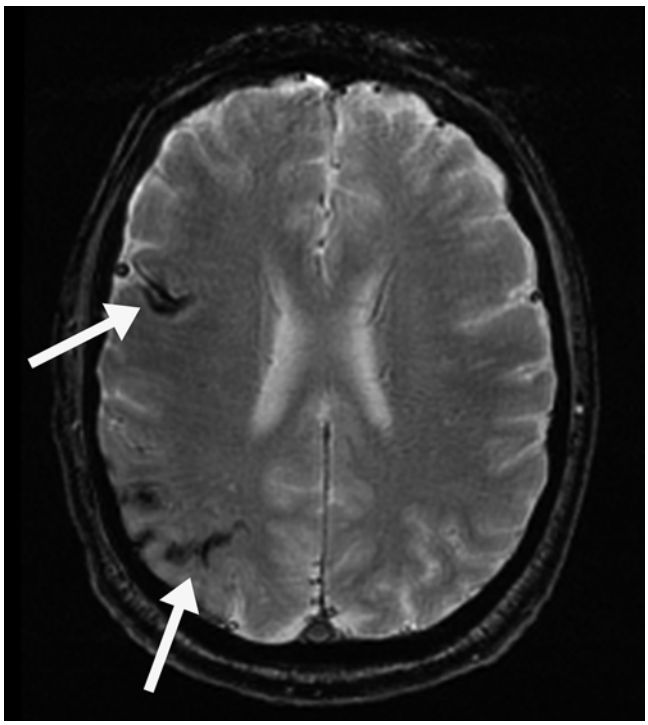

Fig. 26.3 Superficial siderosis. Axial T2*-weighted gradient-recalled echo (GRE) sequence showing regions of superficial siderosis (*arrows*). Superficial siderosis represents areas of hemisoderin deposition beneath the pia mater or in the superficial cerebral cortex, resulting from previous subpial or subarachnoid hemorrhages

multiple lobar microbleeds do in fact have CAA, based on studies showing similar genetic and risk factor profiles as pathologically proven CAA cases [20].

The finding that microbleeds are probably caused by CAA should heighten concern regarding anticoagulation, because patients with CAA have higher bleeding risk than patients with arteriosclerosis caused by conventional risk factors such as hypertension. In patients with lobar ICH and possible or probable CAA the recurrence rate is 5–10 % per year compared to only 2–3 % per year for ICH not caused by CAA. The risk for recurrent CAA-related ICH is higher in patients with larger numbers of additional asymptomatic microbleeds [21], and in post-ICH aspirin users who have more than 5 microbleeds [22]. Consequently, American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend to avoid resuming oral anticoagulation in patients with lobar ICH, but to consider resuming oral anticoagulation in patients with non-lobar ICH [23]. However, our patient with microbleeds has not had a previous symptomatic ICH; therefore her rate of new symptomatic ICH might be lower. A single cohort study of 69 patients with two or more lobar microbleeds and non-hemorrhagic symptoms of CAA (mostly transient neurological events or cognitive impairment) found that 5 % per year had incident symptomatic ICH [24]. Whether truly asymptomatic microbleeds, as in our patient, confer the same yearly risk is unknown.

In sum, our patient with lobar microbleeds has an annual expected risk reduction of ~5 % per year from anticoagulation, with an annual risk of ICH that is undefined but could be up to 5 % per year. Anticoagulation probably increases the risk of ICH, but the degree of increased risk is unknown. In this case, a strategy that minimizes bleeding risk should be considered. Conversely, if the number and pattern of microbleeds had suggested arteriosclerosis due to aging and hypertension was the probable underlying cause, then the risk for future symptomatic ICH is probably less than 2 % per year, and a strategy that emphasizes ischemic stroke risk reduction with anticoagulation could be adopted.

Strategies to minimize bleeding risk in atrial fibrillation while also reducing ischemic stroke risk include the use of novel oral anticoagulants instead of warfarin, invasive procedures to occlude or resect the left atrial appendage, rhythm control to eliminate atrial fibrillation, or use of aspirin monotherapy. All of the new oral anticoagulants have lower intracranial bleeding risk than aspirin. Apixaban might be preferred, based on a trial showing that the bleeding risk was similar to aspirin [25]. Invasive procedures such as percutaneous left atrial appendage occlusion may be considered, but there are fewer data on longer term outcomes [12]. Rhythm control is of uncertain value for prevention of thromboembolism in atrial fibrillation [12]. Aspirin is clearly less effective than anticoagulation at preventing ischemic strokes in atrial fibrillation, but probably elevates the bleeding risk only slightly. Additionally, aspirin would be less dangerous than anticoagulation if an intracerebral hemorrhage were to occur, as the mortality rate from anticoagulant-related ICH is significantly higher than ICH with antiplatelet drugs, even with the use of warfarin antidotes such as vitamin K and prothrombin complex concentrates [26]. There is no role for dual antiplatelet therapy with aspirin and clopidogrel, which is less effective than anticoagulation with the same major bleeding risks [27].

In this situation, where anticoagulation for atrial fibrillation is indicated but there are multiple asymptomatic lobar microbleeds and probable CAA, the author frequently uses apixaban because it has a similar intracranial bleeding risk as aspirin but is more effective than aspirin at reducing ischemic stroke risk. In cases where apixaban is not indicated or not available, the author would choose between warfarin and aspirin depending on clinical judgement regarding bleeding risk, and patient preferences regarding concern for recurrent ischemic stroke vs. hemorrhagic complications of therapy. For patients with non-lobar microbleeds, or a mix of microbleeds in both lobar and non-lobar locations, the author would typically use anticoagulation with a novel oral anticoagulant or warfarin.

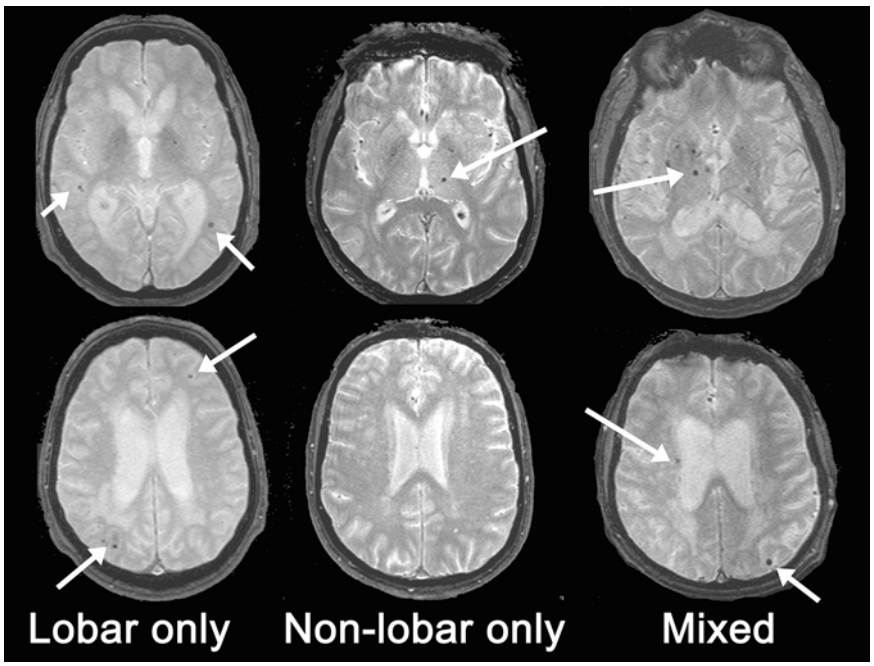

Fig. 26.4 Classification of cerebral microbleeds by Boston Criteria for diagnosis of cerebral amyloid angiopathy. Based on the number and location of microbleeds, the likelihood of underlying cerebral amyloid angiopathy can be determined using the Boston criteria [19]. Axial T2*-weighted gradient-recalled echo (GRE) sequences. *Left panels*: The presence of two or more lobar microbleeds (*arrows*), without microbleeds in non-lobar locations such as the basal ganglia, is consistent with probable cerebral amyloid angiopathy. When only one microbleed is present, the likelihood of underlying cerebral amyloid angiopathy may be classified as "possible." *Middle panels*: A microbleed in the left thalamus (*arrow*) is not consistent with cerebral amyloid angiopathy. Arteriolosclerosis due to aging and hypertension is the more likely cause. *Right panels*: Microbleeds in mixed locations including the right thalamus (not consistent with cerebral amyloid angiopathy), right corona radiate and left parietal cortex (*arrows*) is consistent either with arteriolosclerosis due to aging and hypertension, or a combination of arteriolosclerosis plus additional cerebral amyloid angiopathy. Therefore, the presence of cerebral amyloid angiopathy is uncertain

Another scenario that requires assessment of microbleed-associated bleeding risk is when thrombolysis for acute ischemic stroke is being considered. Studies of the association between cerebral microbleeds and the risk of thrombolysis-associated ICH in acute ischemic stroke show that the ICH risk is small, and unlikely to be outweighed by the benefits of thrombolysis therapy [28].

Case Presentation 2: A Patient with Cognitive Impairment, Lacunes and White Matter Hyperintensities of Presumed Vascular Origin

Details of the Case

A 59-year-old man is seen in clinic for cognitive slowing, forgetfulness and slow gait. The cognitive impairment is severe enough that he has been placed on medical leave from his job. There is a history of hypertension, with current use of an angiotensin-converting enzyme inhibitor, a thiazide diuretic, and a calcium channel blocker. Examination shows mild hyper-reflexia, a few beats of clonus at the ankles, and difficulty with tandem walk. Folstein MiniMental Status Exam (MMSE) score is 21 out of 30. Thyroid stimulating hormone, vitamin B12, and homocysteine levels are normal. Brain MRI shows extensive WMH of presumed vascular origin, as well as five lacunes in the white matter (Fig. 26.5). What is the diagnosis and management?

Discussion

The extensive WMH and multiple lacunes demonstrate the presence of subcortical ischemic disease, even though this patient does not have a history of symptomatic ischemic stroke. The clinical questions are whether the demonstrated subcortical ischemic disease is sufficient to cause cognitive impairment and how the subcortical ischemic disease should be managed.

Lacunes appear as small areas of cavitation in the internal portions of the brain, most frequently in the white matter, basal ganglia and pons [10]. Based on the pathology and risk factor profile, they are thought to represent the sequelae of previous infarction in the territory of a single penetrating artery. They are the most frequent type of silent central

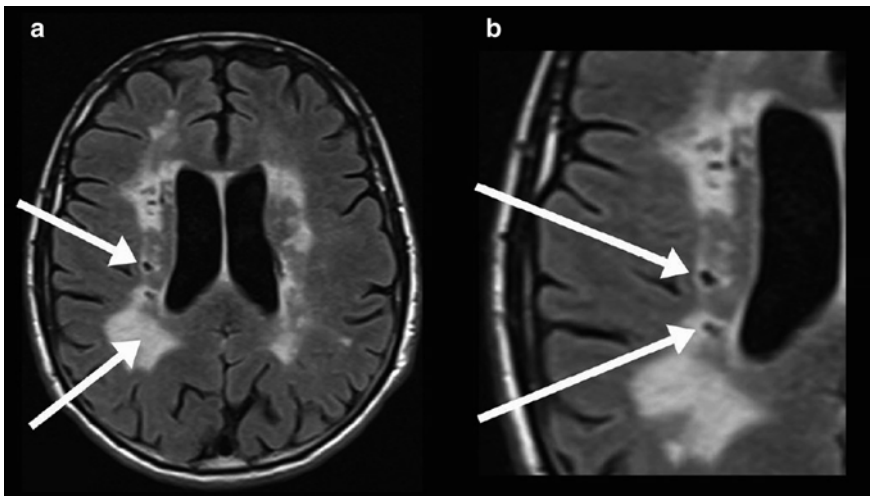

Fig. 26.5 A 59-year-old man with cognitive impairment, multiple lacunes and white matter hyperintensities of presumed vascular origin. (**a**) Axial fluid attenuated inversion recovery (FLAIR) showing extensive white matter hyperintensities of presumed vascular origin (*lower arrow*) and multiple lacunes (*arrow*, example). (**b**) Magnification of *panel A*, demonstrating multiple lacunes in the periventricular white matter (*arrows*)

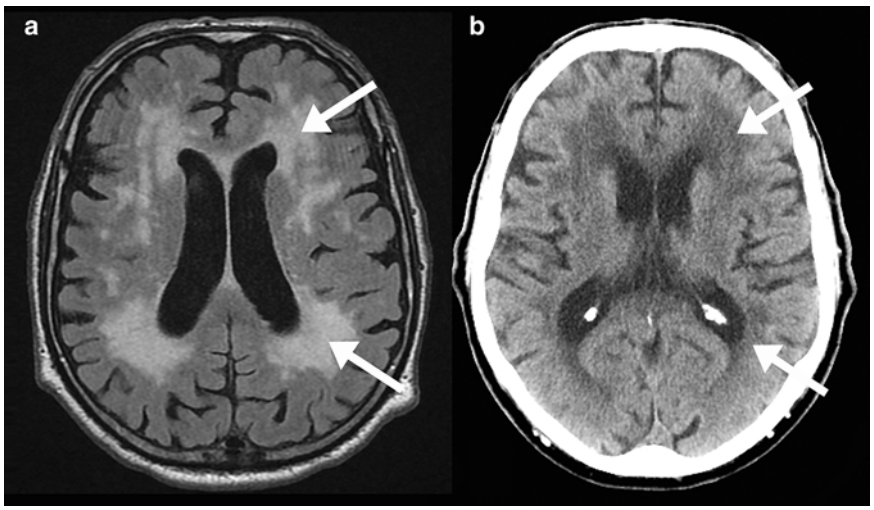

Fig. 26.6 White matter lesions of presumed vascular origin on MRI (**a**) and CT (**b**)

nervous system infarction. Radiologically, they have a central core with CSF-like signal (hypointense on T1-weighted or FLAIR images, with hyperintensity on T2-weighted images, similar to CSF). On FLAIR and T2-weighted sequences, there is frequently, but not always, a surrounding rim of milder hyperintensity that may represent peri-infarct gliosis. Small lacunes of presumed vascular origin must be distinguished from perivascular spaces; a size criterion of ≥3 mm diameter is proposed to identify lesions that are probably lacunar infarcts. Acute lacunar infarction may be silent or may be associated with an acute lacunar syndrome. When the acute lacunar syndrome patient is imaged acutely with MRI, an area of hyperintensity on diffusion-weighted imaging (DWI), corresponding to the acute infarct, is usually seen. Over months, the acute lesion evolves with a variable fate, ending up as either a small cavitated lesion (lacune), a hyperintensity without cavitation that may appear identical to focal WMH, or it may even be completely unapparent on MRI [29, 30]. The use of a high-resolution T1-weighted sequence increases the sensitivity, compared to FLAIR alone, to distinguish cavitated lacunes from nonspecific hyperintensities [30]. Patients with small vessel disease may have infarcts even smaller than lacunes, not detectable on conventional MRI, that nonetheless contribute to cognitive impairment [31]. Risk factors for silent CNS infarction include age, hypertension, diabetes and smoking [32].

WMH of presumed vascular origin, also termed leukoaraiosis, are visible as hyperintensities on MRI or hypodensities on CT (Fig. 26.6) [33]. Pathologically, WMH are associated with demyelination and arteriolosclerosis. The lesions do not

represent areas of infarction, although small areas of patchy microinfarction may be embedded within them. WMH are not specific, and may be seen in other neurological diseases such as multiple sclerosis or leukodystrophy. However, in the absence of a history of other specific neurological diseases WMH may be reasonably presumed to be of vascular origin in most older persons. Risk factors for WMH of presumed vascular origin include age, hypertension, smoking and atrial fibrillation. Although WMH are strongly associated with cerebrovascular diseases, some degree of WMH is ubiquitous with aging into the 70s and 80s.

Our patient has dementia, as documented by objective evidence of cognitive impairment (MMSE 21) that has caused a decline from a previous level of social and occupational functioning (i.e., he is now unable to work). The American Heart Association and American Stroke Association (AHA/ASA) have published diagnostic criteria for vascular cognitive impairment due to subcortical ischemic disease [34]. These criteria require the presence of either dementia or mild cognitive impairment with "a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology." Therefore, the clinical question here is whether the subcortical ischemic disease on our patient's MRI is sufficient to be clearly related to his dementia. Unfortunately, the thresholds of severity and location of subcortical ischemic disease that are sufficient to cause dementia are unproven. Accordingly, the AHA/ASA diagnostic criteria do not give a specific threshold of subcortical ischemic disease, and clinical judgment is required to operationalize the AHA/ASA criteria. Cognitive impairment is more likely in patients with more than one infarct, with infarcts in the thalamus and when very extensive WMH are present. In the case of our patient, the extensive WMH for his age and the presence of multiple (5) lacunar infarctions make it very probable, in the author's judgment, that the subcortical ischemic disease is the cause of the patient's dementia. Additionally, the patient's young age (59) makes it unlikely that a competing neurodegenerative cause of dementia, such as Alzheimer's disease, is present.

After subcortical ischemic disease is diagnosed, the next question is how to manage it to attempt to prevent or slow progression of dementia. It seems reasonable to institute the same secondary prevention measures that would be used for symptomatic stroke [35]. Prevention of WMH progression has been assessed as a secondary endpoint in six randomized controlled trials. WMH progression was reduced in a trial of a combination of an angiotensin converting enzyme inhibitor and thiazide-type diuretic in stroke patients [36], and in patients with severe small vessel disease participating in a trial of homocysteine-lowering vitamin therapy [37]. However, a trial of telmisartan did not show reduced WMH progression [38]. Treatment with statins was shown to reduce WMH progression in a clinical trial of patients with intracranial atherosclerosis [39] but not in a trial of patients with cardiovascular risk [40]. Finally, intensive glucose-lowering therapy in type 2 diabetes was associated with increased, not decreased WMH progression [41].

Recommendations for management of symptomatic vascular cognitive impairment are provided in a Scientific Statement from the AHA/ASA [34]. There is modest evidence that treatment with acetylcholinesterase inhibitors such as donepezil may provide some cognitive enhancement in vascular cognitive impairment or mixed dementia. For prevention of vascular cognitive impairment, the best evidence is for lowering blood pressure in patients with a history of stroke.

In our patient's case, an electrocardiogram was performed which failed to show atrial fibrillation, and lipid testing revealed total cholesterol 180 mg/dL with HDL 40 mg/dL. Stroke prevention with aspirin and a statin was initiated. Donepezil was started. Homocysteine-lowering vitamin therapy was not initiated because the evidence supporting this strategy is modest [37] and the patient's homocysteine level was normal; however, the author would consider testing for and treating high homocysteine levels in patients with severe cerebral small vessel disease and vascular cognitive impairment. Antihypertensive medications were adjusted to achieve strict blood pressure control to <140/90.

Case Presentation 3: An Asymptomatic Patient with an Incidentally Discovered Silent Brain Infarct

Details of the Case

A 55-year-old man undergoes an MRI scan for new onset headaches, which identifies an incidental 4 mm lacune of presumed vascular origin in the white matter of the right frontal lobe, consistent with a silent CNS infarction. He is being followed by his family doctor for borderline high blood pressures, with today's reading 135/80. Neurological examination is normal. Are more investigations required? How should this patient be managed?

Discussion

Silent cerebrovascular disease is the most common incidental finding on brain scans. Silent CNS infarcts are not rare even in 50–59-year-olds, with a prevalence of approximately 5 % (Table 26.1) [32]. Radiological characteristics and differential diagnosis of silent CNS infarcts were discussed in the previous case. The clinical questions are whether additional work-up is needed to determine the cause of the CNS

infarction, and whether the presence of the infarct should influence the vascular risk reduction strategy employed.

An AHA/ASA statement now formally defines silent CNS infarction as a form of stroke [42], implicitly suggesting that patients with silent CNS infarcts should undergo a similar work-up as that for symptomatic stroke. However, the same statement cites uncertainty regarding whether primary or secondary prevention strategies should be employed, given that patients with silent CNS infarction were not included in secondary prevention trials, and specific recommendations for work up and management of silent CNS infarction were not provided. This author suggests measurement of blood pressure, fasting blood glucose, lipid profile and electrocardiogram for all patients. Most silent CNS infarcts are subcortical lacunes, presumably caused by small vessel disease. In this circumstance, a proximal embolic source from the carotid artery or heart is unlikely and may not require extensive investigation to identify one. In contrast, if the infarct involves the cerebral cortex, is larger than 15 mm, or has other features that suggest an embolic source, then additional investigations for cardiac sources of embolism (e.g., with echocardiogram and ≥24 h of cardiac rhythm monitoring) could be considered.

It is unclear whether carotid imaging should be done in patients with silent CNS infarction. The AHA/ASA recommends carotid revascularization in the case of recent TIA or ischemic stroke within 6 months [43]. However, it is impossible to determine the timing of silent CNS infarcts on scan. Given that most silent CNS infarcts are probably greater than 6 months old, the benefit of carotid revascularization in patients with silent CNS infarction is expected to be lower than for patients with recently symptomatic carotid stroke or TIA, potentially approaching the more marginal benefit seen for endarterectomy in all asymptomatic patients. In the author's opinion, it is reasonable to obtain carotid imaging in patients with embolic-appearing silent CNS infarction, if the infarct is in the territory of the internal carotid artery, in circumstances where the patient is deemed to potentially be a good candidate for carotid revascularization.

Another unresolved question is whether silent CNS infarction should be considered equivalent to symptomatic stroke in algorithms and risk prediction tools used to determine vascular risk reduction strategies (e.g., when determining eligibility for statin therapy, or when using CHA_2DS_2-VASC to determine eligibility for anticoagulation in atrial fibrillation). Patients with silent CNS infarcts are at twofold to threefold increased risk for future symptomatic stroke [5, 44]. However, given the much higher prevalence of silent CNS infarcts compared to symptomatic stroke, one cannot assume that algorithm results or discriminative properties of risk prediction tools would be the same if silent CNS infarcts were included as equivalent to symptomatic stroke.

The clinical relevance of extensive WMH alone, in the absence of CNS infarcts, is less clear. Very high WMH burden for age, out of proportion to the degree of conventional vascular risk factors, should prompt consideration of whether CAA or a genetic cause, such as CADASIL, may be present. Good blood pressure control may reduce the risk of WMH progression (see also Section "Discussion of Case 2," previously). Because patients with extensive WMH are at twofold to threefold increased risk for subsequent ischemic stroke, starting an aspirin may be considered [5].

In the case of our patient, an electrocardiogram, fasting blood glucose, and lipid profile were obtained. More extensive cardiac investigations and carotid imaging were not done, because this small subcortical infarct was most likely caused by small vessel disease, and unlikely to be caused by embolism. Aspirin was initiated. Lipid profile showed total cholesterol 170 mg/dL, with HDL 55 mg/dL. Whether a statin should be started is unclear. New American College of Cardiology (ACC)/AHA guidelines for cholesterol-lowering therapy are based on the future risk of cardiovascular disease, rather than LDL targets [45]. If this patient's silent CNS infarct is taken as evidence of clinical atherosclerotic cardiovascular disease, then a statin is indicated. On the other hand, if the silent CNS infarct is disregarded then a statin is not indicated because his estimated 10-year cardiovascular disease from Pooled Cohort Equations is only 4.7 % [45]. In our patient's case, initiation of a statin was discussed but a plan was made instead to initiate lifestyle changes, increased physical activity and more frequent blood pressure monitoring.

Conclusions

Subclinical forms of vascular brain injury, mostly caused by cerebral small vessel disease, are more common than symptomatic stroke and are frequently identified incidentally on brain scans for other indications. Recent advances in the standardization of definitions and terminology should allow more consistent identification and reporting of subclinical brain injury. However, high quality evidence for clinical management is generally lacking. There is a need for stronger consensus on how the presence of subclinical vascular brain injury should influence common decisions regarding vascular risk reduction (see Sections "Cases 1–3"). Research needs include clinical trials of strategies to reduce progression of subclinical vascular brain injury, and development and validation of risk prediction tools that take subclinical vascular brain injury into account as another potential independent predictor of future stroke risk.

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General Concepts: Stroke Systems of Care

27

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Abbreviations

EMS	Emergency medical services
CMS	Centers for Medicare and Medicaid Services
AHA	American Heart Association
GWTG-Stroke	Get With The Guidelines-Stroke
tPA	Tissue plasminogen activator
DTN	Door to needle
ESD	Early supported discharge
IRF	Inpatient rehabilitation facility
SNF	Skilled nursing facility

The care of stroke patients is complex, involving multiple specialties across multiple epochs of care. In the pre-hospital phase, patients must be identified and directed to proper centers to optimize care. On arrival to a stroke center, coordination between services must be efficient to ensure prompt and appropriate acute treatment. Additional coordination is needed for proper evaluation and management of complications during hospitalization. Furthermore, post-acute care and rehabilitation are essential to maximize recovery and prevent further vascular events. Ideally, systems of care should exist within each realm to optimize efficiency, ensure quality, and improve patient outcomes.

Pre-hospital and Triage

The time period from stroke symptom onset to hospital arrival is critical in optimizing care and maximizing rates of thrombolysis. Prolonged onset to arrival time is the greatest single source of delay in treatment, often leading to disqualification from thrombolysis [1]. Data from the nationwide Get With The Guidelines-Stroke (GWTG-Stroke) program demonstrate onset-to-door time of ≤2 h in only 20 % of patients, and ≤3.5 h in 27 % of patients, with no improvement from 2003 to 2009 [2]. The cause of this delay is multifactorial and needs to be addressed on multiple fronts.

Patient and community awareness of stroke symptoms and the need for immediate medical attention is the first step to prompt evaluation and treatment. Time to ED arrival is decreased in more educated patients and those with witnessed symptom onset, a higher sense of urgency, and use of 911 [3, 4]. Early arrival has consistently been associated with transport by emergency medical services (EMS) [2]. Successful education programs aim to increase recognition of stroke symptoms in both high-risk patients and the broader community, and emphasize the role of EMS in receiving immediate care [5, 6]. For continued benefit, educational programs must be maintained [6].

As the first point of medical contact, EMS personnel and medical dispatchers play a critical role in expediting evaluation and treatment. Barriers to care include lack of consistency in stroke education, assessment scale use, and hospital transport. Training and skill level of personnel may vary by region and identification of stroke by first responders and dispatchers can be suboptimal. Positive predictive value of dispatchers in Los Angeles and San Diego using the medical priority dispatcher systems (MPDS) stroke protocol were only 45 % and 42.5 %, respectively [7, 8]. In addition, with a sensitivity of 41 %, over half of patients discharged with a diagnosis of stroke were not recognized [7]. Local and national training programs should emphasize a standardized scale for assessment of patients with neurologic symptoms, with many validated pre-hospital screens in use today [9–11].

Regional triage protocols are needed to ensure transport to hospitals with capabilities appropriate to the level of care required for each patient. Protocols emphasizing preferential triage to centralized stroke centers have shown improvement in stroke care internationally, with shorter onset-to-arrival

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time, door-to-needle (DTN) time, and significantly higher treatment rates seen across a variety of systems [12–14]. However, travel time is an important component, with additional transport no more than 15–20 min per American Heart Association (AHA) policy recommendations [15]. Establishing a triage protocol is understandably complex, involving consideration of hospital resources, patient status and stroke severity, time from symptom onset, transport distance, and patient preference. In addition, triage planning should include consideration of local hospitals with telemedicine capabilities that can facilitate acute evaluation, treatment decisions, and even transport to larger regional centers as necessary. Protocols need to be discussed at the local level to address unique characteristics within each region.

Within the triage protocol, pre-hospital notification of incoming stroke patients is key to minimizing delay and ensuring rapid evaluation and treatment. Prenotification allows stroke team activation and organization prior to patient arrival, and has been shown to decrease time to evaluation, imaging, and treatment, and increase IV tPA administration rates [16–20]. In addition to standardized scales, pre-hospital stroke screening protocols often consider other data points such as time of onset, blood glucose, and even pre-stroke disability [16].

Each of these components is essential to the emergent care of stroke patients, and has limited benefit in isolation. Studies combining pre-hospital notification with multidisciplinary education programs show the greatest increase in tPA administration [16]. Furthermore, novel improvements in pre-hospital care are evolving, with mobile stroke units utilizing CT scanners in the field, and telemedicine and mobile health connections to the ambulance itself [21–23]. With these and future initiatives, we are shifting the "golden hour" of stroke care from arrival-to-treatment to EMS-activation-to-treatment, to expedite emergent stroke care and hopefully improve outcomes.

Acute and Inpatient Care

tPA is the only FDA-approved treatment for acute ischemic stroke. Yet nationally, only 2–3 % of stroke patients are treated with IV tPA [24]. Stroke mortality varies regionally as well as across ethnic groups [25, 26]. However, many of these disparities improve when following evidence-based treatment recommendations [27]. Multiple systems of care aim to improve readiness and coordination through the inpatient course, including the acute evaluation, diagnosis and treatment, management of complications, and initiation of rehabilitation and discharge planning. The most expansive undertaking has been the establishment of Primary and Comprehensive Stroke Centers (PSCs and CSCs) to ensure implementation of proper infrastructure and protocols and promote consistency in diagnosis and treatment [28, 29].

Efficient, coordinated acute care is essential to optimize rates of thrombolysis. National guidelines recommend initiation of thrombolytic therapy within 60 min of hospital arrival, yet only 29.1 % of patients seen at hospitals participating in the GWTG-Stroke program in 2009 had DTN times ≤60 min [30, 31]. In addition, DTN times vary by hospital, with percentage ≤60 min between 0 and 79 % [31]. With this goal in mind, the AHA created the Target: Stroke initiative. This program provides hospitals with a "toolkit" to implement ten key strategies identified from a comprehensive literature review and selected based on ease of institution and cost-effectiveness including pre-hospital notification by EMS, rapid triage protocol and stroke team notification, single-call activation system, availability of stroke protocols and order sets, rapid acquisition and interpretation of brain imaging, rapid laboratory testing, rapid access and premixing of tPA, a team-based approach, and prompt feedback [32]. Though the majority of these are self-explanatory, the emphasis is on an organized and prepared team approach to every acute stroke patient, as well as data tracking and quality improvement, leading to efficiency of diagnosis and consistency of treatment.

Beyond existing recommendations and structured initiatives, many centers have developed independent systems of care to further increase efficiency and reduce time to thrombolysis. Utilizing "lean manufacturing" principles to increase efficiency improved DTN from 60 to 39 min and boosted the rate of thrombolysis without any change in sICH rate in one center [33]. A major emphasis of the analysis was the focus on parallel process workflow—that is, allowing multiple components of the evaluation to occur simultaneously rather than relying on the traditional method of serial processes. Similar improvements, and limiting advanced imaging (angiography and perfusion) to those cases in which diagnosis was uncertain, reduced median DTN to 20 min at another center where 31 % of ischemic stroke patients were treated with tPA [34]. An additional practice credited for reducing DTN time is locating imaging within the emergency department, or moving the patient directly to the radiology suite on arrival, though this is not feasible in all centers [35]. Effects on outcome have not yet been followed for many of these initiatives. As we continue to increase efficiency and decrease DTN time, focus needs to remain on not only rapid thrombolysis but also safe and appropriate administration of tPA.

To further improve the medical care and outcomes of stroke patients, recommendations for the establishment of Primary Stroke Centers (PSCs) were formally developed in 2000 using a similar model to that of trauma centers [28, 36]. The PSC is designed to provide rapid, quality, emergent stroke care, founded on evidence-based practices to promote consistency in the diagnosis and treatment of acute stroke. To this end, key areas of patient care and support services were identified. Patient care areas include acute stroke teams designated to provide emergent care; hospital-specific protocols

for emergency stabilization and thrombolysis; EMS standards including triage plans, proficiency in identifying stroke, and prenotification; emergency department protocols to identify roles and ensure rapid stabilization and triage; stroke units to provide stroke-specific inpatient care; and availability and expertise of neurosurgical services [28, 36]. Additions to the recommendations in 2011 noted the importance of availability and early initiation of therapy and rehabilitation services [36]. Support service recommendations include institutional commitment including designation of a stroke center director, rapid availability and interpretation of cerebral and cerebrovascular imaging, the consistent availability of laboratory services, a commitment to quality improvement including measurement of outcomes, and the development of educational programs [28, 36]. The revisions in 2011 also identify methods by which the measures can be met in the era of The Joint Commission (TJC) and other independent regulatory bodies who work to certify and maintain the standards of these stroke centers [36].

Recommendations for more advanced care at Comprehensive Stroke Centers (CSC) were developed in 2005 and 66 centers have been certified at the time this chapter was written [29]. CSC recommendations emphasize a multidisciplinary approach to provide more advanced care to complicated, seriously ill patients with ischemic and hemorrhagic stroke. These expanded recommendations include personnel with subspecialty expertise in vascular neurology and neurosurgery, availability of specialized diagnostic techniques including advanced imaging, specialized treatment options performed by experienced surgical and endovascular providers, advanced infrastructure including intensive care units to care for complex patients, and use of stroke registries to monitor outcomes [29].

Stroke centers have been shown to achieve the goals of improved care and efficiency. Many hospitals have shown increased tPA utilization following institution of primary stroke center recommendations [37, 38]. Morbidity (as measured by nursing facility care at 1 year) as well as mortality at multiple time points are decreased in stroke centers compared to general hospitals [38, 39]. This improvement in mortality is seen with or without thrombolysis [38]. In addition, fewer gaps in care are seen at CSCs, most notably at night and on weekends [40].

Though the recommendations included above provide optimal acute stroke care, there are many hospitals, particularly in rural areas, that do not have all the infrastructure needed to implement these requirements, and yet still are able to provide emergent care. These acute stroke-ready hospitals (ASRHs) are often able to stabilize the patient and establish eligibility for thrombolytic therapies before consulting with larger centers via telemedicine or transferring to a PSC or CSC, and should be incorporated into region-specific stroke systems [15].

While implementation of these recommendations may appear costly, there is evidence that the increased efficiency resulting from these process changes makes up for any additional initial costs [41]. The improved outcomes seen with increased tPA use can provide cost savings as well [42]. With reimbursements increasingly tied to outcomes, the improved care received at stroke centers is increasingly important. Though a variety of metrics have been discussed to follow quality of care at stroke centers, further work is needed to establish which outcomes to use, the appropriate risk adjustment, how to obtain them, and at what time points these should be used for assigning quality [43, 44].

Post-acute Care

For post-acute care of any condition, there are huge variances in the type and quality of care that patients receive. In fact, according to Medicare claims data, 73 % of the variance in costs throughout the continuum comes from post-acute care [45]. Because of the disability and the comorbidities associated with stroke, it requires intensive post-acute services and is the most costly for Medicare [45]. Similar to other chronic diseases, there is wide variation in the access and quality of post-acute care for stroke in the USA. Sixty-four percent of Medicare beneficiaries with stroke use some form of post-acute care (home health (HH), skilled nursing (SNF), inpatient rehabilitation facility (IRF), long-term acute care facility (LTAC)) [45]. Of those stroke patients who are discharged to an SNF or IRF, post-acute costs per episode are 3–4 times higher than for those discharged home with HH (HH $13,344, SNF $33,266, IRF $40,881). Those who are readmitted to the hospital represent 26 % of the total CMS costs for stroke patients [45]. Therefore, recent efforts have been directed towards finding ways to reduce variation, improve quality, and minimize the cost associated with post-acute care for stroke.

Quality of Care: Outcomes

Outcomes, such as 30-day readmissions and functional status after stroke, are a priority because of the shift in health care from fee-for-service-driven payments to value-based purchasing. At least one of the components of value-based purchasing is patient outcome, although the components that are currently publicly reported include patient satisfaction and clinical processes of care (discharge instructions, core measures of quality care). The value-based purchasing scores for patient satisfaction and clinical processes of care currently vary widely across hospitals based on a study from 2012 [46]. However, the current lack of outcome measurements for stroke post-discharge is a limiting factor for the assessment of outcome-based payments [47].

Understanding the impact of new integrated care models involves the measurement of outcomes for real-world clinical practice. Comparison of outcomes by hospital must be adjusted for severity (the primary driver of outcome) because a tertiary referral or CSC discharges patients with more severe strokes than hospitals that typically only keep and therefore discharge milder stroke patients. A recent AHA guideline provided recommendations that explicitly state that risk adjustment must include stroke severity to determine hospital-level variation in outcomes [44].

The risk for poor outcomes applies to the entire spectrum of stroke severity. For example, patients with a diagnosis of TIA are at a similarly high risk for poor outcomes such as all-cause rehospitalization and death as stroke patients up to 1 year after the index event [48]. Even more importantly, TIA patients may be at higher risk for stroke rehospitalization than patients initially discharged with stroke [48]. Therefore, longer term outcomes (up to 6–12 months) which are severely lacking in the evaluation of post-acute care [49] are a key component for measuring the quality of stroke systems of care.

Does the site of post-acute rehabilitation have an impact on outcome? Recent data from an analysis of four hospitals in the Kaiser health management organization (HMO) in northern California suggests that it does [50]. After following patients prospectively from acute hospital discharge to 6 months, and taking into account which facilities were utilized for post-acute care during this period, the analysis showed that patients treated at an IRF had improved self-reported function in three domains of basic mobility, basic activities of daily living, and applied cognition (instrumental ADLs) compared to patients who were treated at an SNF, home health, or outpatient therapy as part of their trajectory [50]. The assumption is that with more intensive rehabilitation available at an IRF (typically 3 h per day five times per week utilizing two different forms of therapy), this may have been the reason for the improved outcomes for these patients treated at IRFs. However, this analysis may not be generalizable to other geographic locations or settings because it was performed as part of an integrated health system. These health systems are an example of a framework that would incorporate post-acute stroke systems of care and suggests that this integration may benefit patient outcomes.

Transitional Care for Stroke: Early Supported Discharge

The post-acute care continuum for stroke includes hospital discharge planning, transitions to home from hospital of rehabilitation facility, and reintegration into the community (Fig. 27.1). Amongst each phase of the continuum, stroke patients are at particularly high risk of poor outcomes, such as readmission. In the GWTG-Stroke program, the risk of all-cause readmissions at 30 days in Medicare beneficiaries was 21 %, and 62 % at 1 year [51]. Reducing readmissions

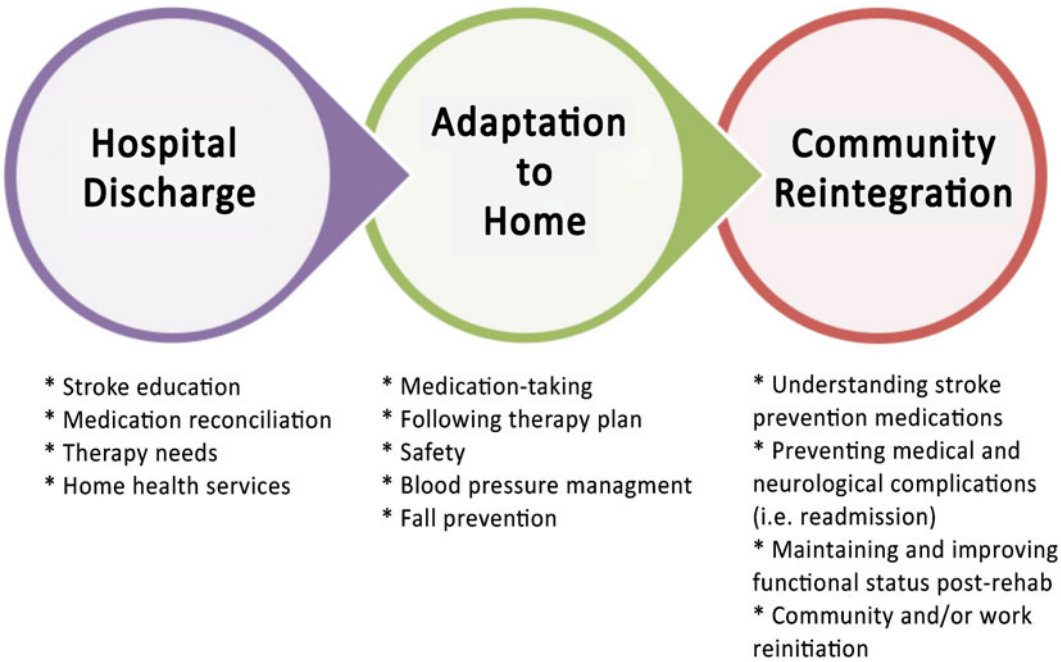

Fig. 27.1 The stroke post-acute continuum, showing the processes that could reduce the risk of poor outcomes, such as readmission and poor functional status

involves a concerted effort to coordinate the various transitions of care—most importantly, the transition from hospital to home. A systematic review of transitional care interventions for stroke showed that the best evidence for the most effective transitional care was with early supported discharge (ESD) [52]. ESD is an integration of hospital stroke care and rehabilitation performed in the home. Patients with mild to moderate stroke and who have adequate caregiver support are discharged home to continue rehabilitation services, nursing care as needed, as well as ongoing education for secondary prevention, medication management, and lifestyle change, with discharge to community services and primary care when appropriate [53]. The provided services in the home are initially of high frequency and intensity, and are then decreased as the patient becomes more functionally independent and progresses with the goals of therapy [53]. This integrated transitional care shortens extended stroke unit stays that include rehabilitation, as in Europe.

ESD was initially developed and tested in randomized controlled trials in Europe and Canada, summarized in a Cochrane Review [54], and is now part of the standard of care in the UK and Canada. In the European model, mild to moderate stroke patients (about 37 % of the stroke population) [55] are discharged home early, and are treated by a team that integrates stroke specialty care and rehabilitation in the home. In addition to efficacy, ESD reduces cost and improves function. The Canadians have projected that optimal stroke care in Canada avoids $307 million direct costs and that access to ESD generates $132.9 million of the direct cost savings [55]. In addition to the cost savings patients spend less time in hospital-based rehabilitation programs, and have better community engagement, improved patient satisfaction and self-management strategies for recovery, and reduced death and dependency at 6 months.

ESD has not been implemented in the USA, perhaps because of the traditional gaps between acute care and post-acute care. Home health services are generally not equipped or staffed to provide care for patients with significant disabilities, and therefore before ESD could be implemented in the USA, there will need to be a reengineering of home health agencies to provide more intensive services early after discharge, along with extended support from a hospital stroke specialty team and primary care with stroke expertise. Current payer models and CMS regulatory issues do not support this level of care in the home; therefore ESD would require a new payer model.

As illustrated above, the major contributions to the wide variation, high cost, and poor quality in stroke post-acute care are the fragmentation of care amongst the many possible sites where care is delivered. As patients move through these post-acute care silos, in most cases they have different providers at each location, each associated with handoffs of care, often with little or no integration or careful coordination of care and services in between. The Medicare Post-acute Care Advisory Committee (MedPAC) has thus suggested bundled payments for post-acute services as a method to incentivize providers to work together throughout the post-acute continuum to integrate services and thus improve care by reducing readmissions and improving quality [45]. Although the interdisciplinary nature of post-acute care is emphasized in the latest policy recommendations for integration of stroke systems of care, the integration of post-acute care services for stroke was not even mentioned [15]. Given the success of ESD in Canada and the UK, models of post-acute stroke care do not necessarily need to be reinvented, but focused efforts towards integration of post-acute services are clearly needed in the USA.

Conclusion

The systems described above place an emphasis on organization within each epoch of care to promote consistency and efficiency, thereby improving stroke therapy and outcomes. Although acute stroke systems have been developed and most likely contribute to increased utilization of IV tPA and thus better early outcomes, the lack of integration between systems in the post-acute continuum is evident and should be the focus of future efforts to reduce costs and improve long-term outcomes in stroke survivors.

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Stroke Centers and Related Aspects of Stroke Systems

28

Mark J. Alberts

Stroke is a common and serious medical condition, and in the acute setting must be treated as a medical emergency. For many decades healthcare systems and healthcare providers had few tools for the acute diagnosis and treatment of ischemic stroke, and limited tools for the diagnosis and treatment of hemorrhagic stroke. Then in the 1970s, with the advent of head CT imaging, acute diagnosis and treatment became feasible (at least in some limited circumstances). Even then, stroke care was often limited to a few medications such as aspirin followed by rehabilitation. In-hospital complications of stroke occurred at a high rate, and many patients had subsequent strokes and poor outcomes.

Around this time, there were advances in knowledge in several areas. These included proof that stroke units improve outcomes, that many complications of stroke could be prevented with relatively routine measures, and that hyper-acute interventions such as IV TPA could reduce the disability caused by ischemic strokes. However, even with these advances, coordinated, organized, and timely stroke care was a rare occurrence in the USA and elsewhere in the world.

Several groups, including but not limited to the Brain Attack Coalition, realized that (1) trauma centers had been a very successful concept in organizing acute care and improving outcomes, (2) stroke and trauma shared many clinical and logistical features, and (3) organizing acute stroke care in a manner that paralleled trauma systems might be a valid care paradigm. What has emerged is the concept of a stroke system of care that spans the spectrum from pre-hospital prevention to acute diagnosis and treatment, to post-stroke secondary prevention and rehabilitation, with many intermediary steps and care elements [1, 2].

This chapter reviews the organization of stroke care at a facility and regional level, and also discusses the efforts and impacts of such care as regulated or directed by national organizations such as The Joint Commission (TJC), Healthcare Facilities Accreditation Program (HFAP), and others.

An Overview of Stroke Centers

As currently envisioned, there are three main types of stroke centers: acute stroke ready (ASRH), Primary Stroke Centers (PSC), and Comprehensive Stroke Centers (CSC). Some of the key characteristics and features are summarized in Tables 28.1 and 28.2. But it is important to remember that a stroke center designation refers to a facility designation, not an isolated program. This differs substantially from other types of programs that may be recognized in isolation and not be fully integrated as part of a larger organization or facility. A stroke center designation is very similar to a trauma center designation, which encompasses the entire facility.

Some might ask why we need three different types of stroke centers in the USA. The heterogeneity of stroke centers reflects several important medical and logistical factors. The USA is a large country, with small, medium, and large population centers. While ideally all cities would have nearby high-level medical centers, in reality this is unlikely to develop due to the uneven distribution of patients and resources. However, no matter where a patient might live or be visiting, they should have some access to fundamental stroke care as well as a rapid and efficient process for accessing higher levels of stroke care if needed.

As part of this process, it is recognized that for some of the high-level and interventional care elements that some stroke patients will require, such interventions have better outcomes if they can be performed in relatively large numbers of patients but at a small number of hospitals. Thus if there are 100 patients in a city or region in need of a carotid endarterectomy (CEA) each year, is it better to have ten hospitals to each perform 10 CEAs each year, or might it be

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Table 28.1 Overview of types of stroke centers

Element/stroke center type	Acute stroke ready	Primary stroke center	Comprehensive stroke centers
Setting	Rural/small urban	Suburban, urban	Large urban
Size (beds)	<100	100–500	>500
Stroke patient volume (year)	20–70	100–600	>400
Receive patients via EMS	Yes	Yes	Yes
Transfer patients to another facility	Yes	Possibly in some cases	No
Total number in the USA-projected	Unknown-projected 1500–2000	1100–1300	150–225

Table 28.2 Specific elements of stroke centers[a]

Element	Acute stroke ready	PSC	CSC
Emergency department	Fully staffed 24/7	Fully staffed 24/7	Fully staffed 24/7
Brain imaging	CT 24/7	CT 24/7; MRI, MRA, CTA available	CT/CTA, MRI/MRA 24/7; angiography 24/7
IV TPA	24/7	24/7	24/7
Stroke unit	No	Yes	Yes
ICU/NICU	No	Optional	Yes
Neurosurgery	Within 3 h	Within 2 h	Available 24/7
Performance metrics	Yes; limited number, 3–4	Yes: 8–10	Yes; 15–20
Research programs	Optional	Optional	Required

[a]This table is not meant to be all inclusive; readers should refer to the references and specific certification requirements from the various certifying organizations for further information

better for two to three hospitals to each perform 33–50 CEAs annually?

Stroke centers are ideally envisioned to operate within a stroke system of care. This entails components that may be exterior to a stroke center hospital, and yet are integral to the stroke system; examples include emergency medical services (EMS), primary and secondary prevention, rehabilitation, and others [1, 2]. This concept also relates to when and how particular patients are transported or transferred to one or more specific facilities based on a number of geographic, medical, and logistical considerations. Typical elements or aspects of a stroke system of care can be seen in Fig. 28.1, and such systems are discussed in more detail below.

Specific Types and Levels of Stroke Centers

This section does not review detailed elements of each type of stroke center, but rather focuses on key characteristics of such centers, their certification paradigms by national agencies, their overall performance in terms of outcomes, and how they might fit into a stroke system of care. Key features can be found in Table 28.2, and detailed elements for all levels of stroke centers can be found in the literature and on the Web sites of the various certifying organizations [3–5].

It should also be noted that stroke centers, as defined in the USA, may not be equivalent to stroke centers in Europe and elsewhere. In some countries such centers may refer to aspects of care that include outpatient clinics, rehabilitation services, and other types of care. In the USA the term stroke center tends to refer to mostly acute inpatient care. Our European colleagues have recently published broad definitions for stroke units (which tend to resemble our PSCs) and stroke centers (which are similar to CSCs in the USA) [6].

Acute Stroke-Ready Hospitals

ASRHs are envisioned to be smaller facilities typically located in a rural or small city area with limited resources and capabilities. The concept is that in large states or relatively unpopulated areas of the country, where there might be a number of these small facilities, one or more will seek recognition and certification as an ASRH. This would then inform patients and assist EMS in terms of which hospital to go to should someone have a stroke. By virtue of having stroke protocols, training, expertise, and links via telestroke to another facility, patients would be more rapidly diagnosed, treated, and then transferred to a PSC or CSC. Before transfer, patients would be stabilized and receive emergency

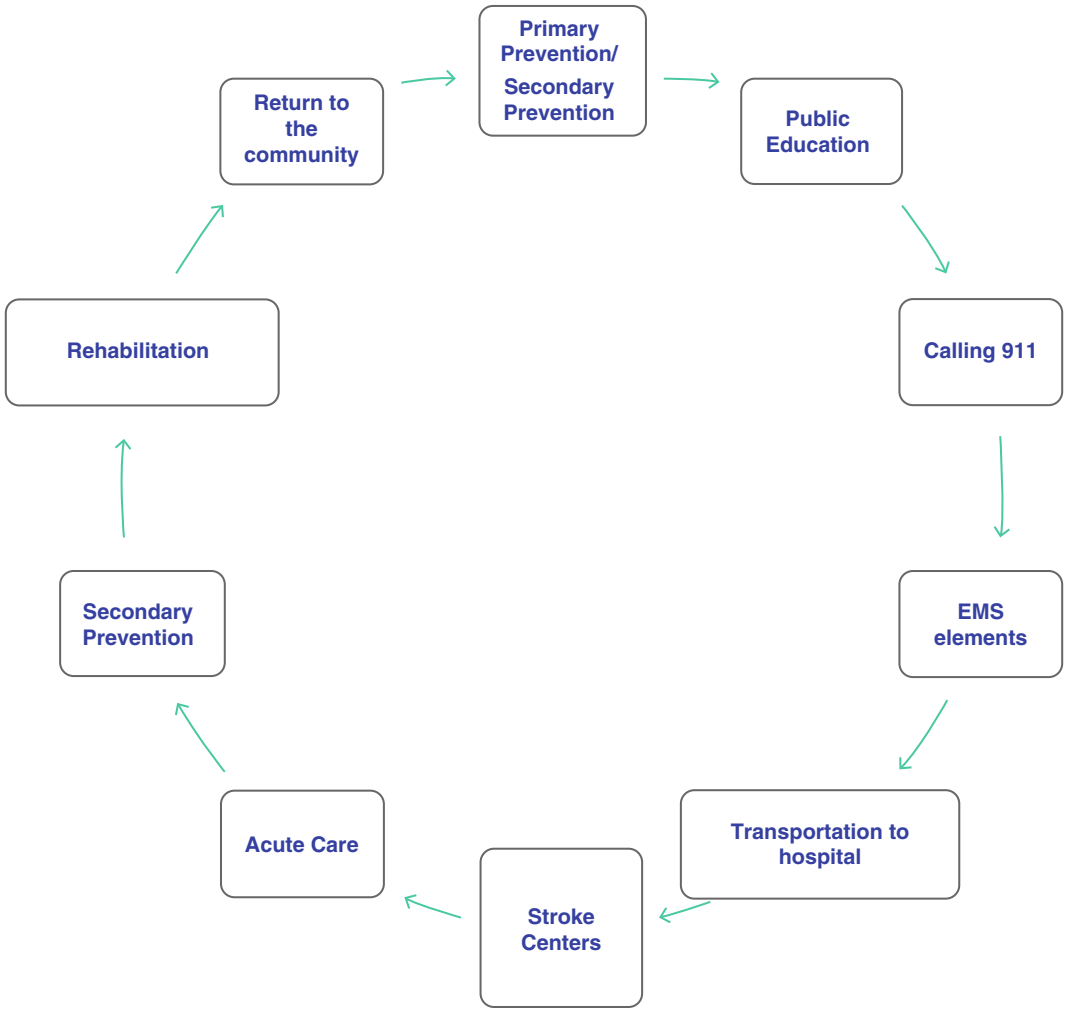

Fig. 28.1 Depiction of one concept of a stroke system of care

therapies such as IV TPA (for ischemic stroke) or perhaps reversal of anticoagulation (for a hemorrhagic stroke). It is unlikely that most patients would be admitted to an ASRH, since such facilities would not have on-site advanced imaging, personnel, stroke units, and other techniques important for a complete stroke work-up and ongoing care.

As noted above, an important aspect of an ASRH is a relationship with a nearby CSC and PSC. Although a formal or contractual agreement might be prohibited in some circumstances by antitrust issues, an informal agreement is needed to ensure that consultations and transfers can occur in a smooth and efficient manner at all times of the day. In addition to acute care issues, such a relationship should include educational efforts and perhaps research protocols in some cases [5].

Do ASRHs improve outcomes? This is hard to know at present, since this designation is relatively new and currently there are very few facilities certified as ASRHs (see below for details). While we know that some of the care elements and protocols that are required at an ASRH do improve outcomes (IV TPA for ischemic stroke), it remains to be seen if this translates to facility-level improvements in overall outcomes. It might be that the main benefits of an ASRH are to rapidly transport the patient to a PSC or CSC. But by virtue of the fact that an ASRH should lead to more rapid diagnosis and treatment, favorable outcomes might be anticipated.

Primary Stroke Centers

PSCs were the first formally designated type of stroke center. This was done because it was believed (by the BAC) that this level of care could be achieved in a relatively short period of time by a large number of hospitals, and therefore this level of care would impact the largest number of patients in the shortest period of time. At present there are approximately 1100 PSCs in the USA. PSCs can provide standard levels of care for most types of stroke patients, and can also serve as

Table 28.3 Examples of PSC care elements that improve outcomes

Element	Type of stroke	Expected outcome
DVT prophylaxis	All	Reduce DVT, PE, deaths
Dysphagia screening	All	Reduce aspiration pneumonia, sepsis, LOS
Antithrombotic therapy	Ischemic, TIA	Reduce recurrent stroke, MI, vascular death
Anticoagulation for Afib	Ischemic, TIA	Reduce recurrent strokes
Statins for LDL ≥ 100	All	Reduce stroke, MI, vascular deaths
Assessment for rehabilitation	All	Improve functional outcomes and quality of life

LOS length of stay

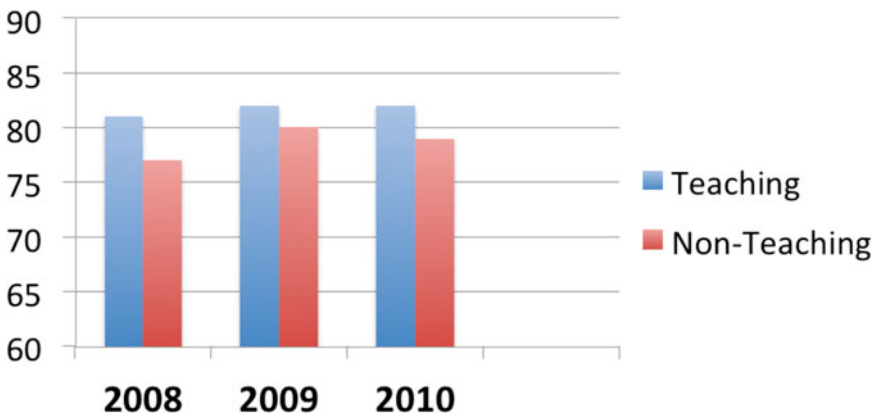

Fig. 28.2 TPA use in certified primary stroke centers, academic vs. non-academic hospitals. The *x*-axis represents year of data assessment; the *y*-axis is percentage of eligible patients treated

resource hospitals for some ASRHs. Most PSCs have an average daily census of 100–500 patients with average annual stroke admissions of 300 or more in 48 % of cases [7]. A key required element of a PSC is a stroke unit. There is robust literature and abundant data showing the positive impact that stroke units have on outcomes for many stroke patients [8–10]. The benefits of a stroke unit are apparent for patients with ischemic strokes as well as those with cerebral hemorrhages.

There continues to be a misperception that the designation of PSCs was largely driven by the need to safely administer IV TPA to more patients. Certainly the safe and effective use of IV TPA can be increased at a PSC, as well as at an ASRH or a CSC. However, when the PSC guidelines were published in 2000, it was clear that <5 % of stroke patients in the USA were being treated with IV TPA. It was equally clear that many in-hospital care elements, which could reduce peri-stroke complications and secondary stroke risk (see Table 28.3), were not being done routinely at most hospitals or for most patients. These "routine" care elements would potentially impact 100 % of the admitted patients, which the BAC believed would have a greater impact than increasing TPA utilization from 3–4 % to 5–10 % or more. But these treatment goals are certainly not mutually exclusive; both should and are being accomplished simultaneously.

We analyzed data from PSCs certified by the JC to see how such certification affected the use of IV TPA. Overall, the rate of use of IV TPA steadily increased as a facility achieved and maintained PSC certification status by 6–20 % depending on the year studied [11]. The steepest part of the increase was in the first 1–3 cycles of PSC recertification. Another trend was that, in general, academic facilities had higher overall rates of TPA utilization in eligible patients compared to nonacademic facilities (see Fig. 28.2) [11]. Other studies have also shown that admission of patients with acute ischemic stroke to a PSC was correlated with 2.5 % reduction in mortality and a 3 % increase in the use of IV TPA [12].

In a related study, we examined the rate of compliance with various quality metrics at PSCs certified by the JC compared to non-certified facilities [13]. For all of the selected measures (such as VTE prophylaxis, discharge on statins, anticoagulation for Afib), the overall compliance rates were 74 % for non-PSCs compared to 91 % for certified PSCs. Stroke education for patients and family members had one of the greatest differences (70 % vs. 89 %, non-PSC vs. PSC) [13].

PSCs implemented the collection of data using tools such as Get With The Guidelines-Stroke (GWTG-Stroke). Data on meeting the various stroke measures have been collected

Table 28.4 Compliance rates with various GWTG-Stroke measures

Measure	2003	2009
DVT prophylaxis	69.5 %	93 %
Anticoagulation for Afib	60 %	93.5 %
LDL Rx if ≥100	43 %	86 %
Smoking cessation	45 %	96 %

Data adapted from reference [14]

on close to a million patients, many of whom were at PSCs. During the initial years of GWTG-Stroke, the percentage of patients and facilities meeting various guideline elements was in the 40–80 % range, depending on which care element was examined. Over the past 5–7 years these numbers have steadily increased, so that compliance rates for most elements are now routinely in the 80–90 % range (see Table 28.4) [14]. Furthermore, hospitals that are certified as PSCs had higher compliance rates with these quality measures compared to non-certified facilities [15]. Hospitals that were JC certified or preparing for JC certification had twice the rate of error-free compliance with JC performance measures compared to other facilities [15]. Whether one analyzes PSC certification through the JC, or uses GWTG-Stroke measures, it is clear that PSCs achieve high levels of compliance with a variety of performance measures, which serve as a surrogate for quality of care [16].

Another study examined the effects of a policy change that mandated pre-hospital EMS triage to a PSC for patients with suspected acute ischemic strokes. Analysis of over 1000 patients pre- and post-intervention showed that the percentage treated with IV TPA rose from 3.8 to 10.1 %, while onset-to-needle times fell by almost 30 min (both changes were statistically significant) [17]. This study, combined with other studies showing overall higher rates of TPA use at PSCs compared to non-PSC facilities, clearly supports the utility of such facilities as well as the preferential triage of patients with acute strokes to these hospitals. A separate but related study showed that once EMS began a program to preferentially route acute stroke patients to a PSC, the number of certified PSCs increased [18].

Despite the myriad advantages of PSCs, the formation of PSCs still represents several challenges. These include the need to develop considerable infrastructure, hiring and training additional personnel, financial considerations, dealing with local and regional political and healthcare policies and specific siting issues (where should a PSCs be located within a city, state, and region) [19, 20]. Even with these challenges, forming a PSC is certainly very doable, especially since there are over 1000 PSCs certified by the JC in the USA, and perhaps several hundred certified by other organizations.

Comprehensive Stroke Centers

CSCs represent the pinnacle of stroke care. These facilities, typically located in large metropolitan areas, are capable of providing a wide variety of specialized care and interventions by highly trained subspecialists in areas such as vascular neurology, vascular neurosurgery, interventional neuroradiology, neuro-critical care, rehabilitation, and related areas. They would likely be part of an academic medical center or a large non-academic medical facility. A CSC has the personnel, facilities, infrastructure, and expertise to care for the most complex of stroke patients as well as those with strokes due to multisystem disease. CSCs are required to participate in clinical research projects, and their staffs are required to have ongoing specialized training. Outlying PSCs and ASRHs might have transfer agreements or tele-stroke arrangements with a CSC to expedite acute patient care decisions as well as patient transfers.

There are emerging data about the efficacy of CSCs. A large study from Finland found improved outcomes (mortality and functional status) for stroke patients at a CSC compared to those at a general hospital [21]. A prospective registry study found that establishment of a CSC was associated with a 43 % reduction in mortality for patients with acute ischemic stroke [22]. Recently a large Japanese study of 265 hospitals correlated mortality for patients with an ischemic or hemorrhagic stroke with CSC components. They found a significant correlation with more CSC components and reduced mortality for all stroke types [23]. A single-hospital study found improved outcomes for patients with ischemic strokes at a CSC [24]. Other ongoing studies of patient care at CSCs are likely to show improved outcomes for patients with hemorrhagic stroke. Another study showed that a CSC was able to make a diagnosis of cervical artery dissection more often than a non-CSC [25]. A multidisciplinary neurovascular team at a CSC has been shown to increase the volume of emergent CEAs while also improving outcomes [26].

When assessing the efficacy of stroke centers, it is critically important that outcomes be adjusted for initial stroke severity. Several studies have clearly demonstrated that initial stroke severity is a key predictor of stroke outcome [27, 28]. To the extent that a CSC will preferentially receive and admit those patients with the most severe strokes, outcomes at a CSC must be adjusted to account for a skewed patient population [29].

Case volumes for various procedures at a CSC are specified by the BAC as well as the JC [4, 30]. Within a certain region, if a large number of hospitals have to "share" a relatively small number of patients needing CSC-level interventions, it is possible and even likely that few of the CSCs can

or would achieve the needed threshold numbers to meet JC requirements [31, 32]. This speaks to the need for an approach to better regionalize stroke care. Besides improving patient outcomes, such an approach may lead to a more rational use of valuable but limited medical resources.

Designation of Stroke Centers

As of 2014, there are several national and international groups involved in the designation and certification of various types of stroke centers. The major organizations (in no particular order) are listed in Table 28.5. While we will not engage in a detailed review of the various certifications processes and how they differ between and among these various groups, it is accurate to say that all include some documentation of personnel, infrastructure, and care processes. Some emphasize outcomes more than processes; others focus on patient volumes more than outcomes. All are in a constant state of evolution, with frequent revisions and modifications.

In addition to the various national and international organizations, a number of states have their own processes and procedures for the recognition and designation of specific types of stroke centers. The specifications of state-based certification are highly variable; some require a fairly detailed review process (which might include a site visit) while others are a relatively simple attestation that can be accomplished by completing one to two pages of questions. Some of the state programs require re-certification every 2–3 years, while others are less rigorous in terms of when re-certification is required.

The BAC's recommendations have been clear that stroke center certification is most rigorous when it is done by an independent organization [5, 33]. Prior studies that examined the accuracy of self-certification have shown that such a process is prone to error and lack objectivity [34]. This is highly problematic if various hospitals and hospital systems are using such a designation to influence patient referrals and EMS diversion decisions. In such cases, "false advertising" could really lead to a life-and-death decision that could be based on inaccurate information.

Many stroke centers have made use of their certification status for advertising and marketing purposes. While it is important for the lay public to know which hospitals are certified and where to go in case of a stroke emergency, in some cases hospitals call themselves a stroke center without a formal definition or designation by an unbiased organization. This may do a disservice for patients, EMS personnel, and the entire medical system. With over 1000 certified PSCs, there is not the need for this type of behavior in the current healthcare environment. Some states actually prohibit hospitals from using the term "stroke center" unless a facility meets a formal definition of a stroke center as established by the state.

When certification of stroke centers began about 10 years ago, many voiced concerns about if and how a competition among hospitals might evolve. What has been seen, mostly with PCSs, is a real proliferation of such facilities with a fairly wide and diverse distribution. In many cities when one hospital became a PSC, others then followed within a few months or years. Overall this has led to a general improvement in the level of care, since in most cases they became certified by an outside organization. Thus overall the level and quality of stroke care have greatly improved in many areas.

If and how this will be duplicated with CSCs is unclear. Based on the relatively limited number of patients who will require the highly specialized interventions typical of CSC, competition for these patients within a small region might lead to reduced patient volumes at some facilities. How this impacts expertise and outcomes remains to be seen. This might be an example of how some regional or state-based coordination of care and resource planning might be needed. An analogy is that within a metropolitan area, there are a limited number of level 1 trauma centers and burn centers; the same dynamic might also be true for CSCs.

Table 28.5 Organizations involved in stroke center certification[a]

Organization[b]	Location home office	Key focus	Types of certification offered[a]
The Joint Commission	Oakbrook Terrace, IL	Certification of healthcare organizations	ASRH PSC CSC
Det Norske Veritas	Hovik, Baerum, Norway	Insurance, consulting, safety	PSC CSC
Healthcare Facilities Accreditation Program	Chicago, IL	Healthcare quality and accreditation	ASRH PSC CSC

[a]As of February, 2015; further changes expected
[b]Table does not include state-based certification agencies

Stroke Centers in a Stroke System of Care

The parts of a stroke system of care may vary depending on the specific resource and needs within a defined area. For example, such a system might look quite different in a high-density urban area versus the State of Hawaii. However, there are still some basic elements that should be fairly consistent. The basic building blocks and components of a stroke system are depicted in Fig. 28.3, with a focus on EMS and the stroke center components. Figure 28.1 provides a more complete overview of the elements of a stroke system.

A stroke system of care must include aspects of EMS identification of a stroke patient as well as proper routing [2]. EMS recognition of stroke remains suboptimal [35]. This is understandable since many stroke patients present with relatively nonspecific symptoms such as diffuse weakness, confusion, and dizziness. While EMS and dispatcher education can improve the accuracy of diagnosis, this is an ongoing challenge considering the large number of EMS personnel, their rapid turnover, and diverse background. Use of pre-hospital stroke screening tools is a key aspect of this educational approach [36, 37].

Unless EMS is able to deliver a patient with an acute stroke to a stroke center facility, many of our interventions are moot. There are many local, regional, and national factors that influence EMS routing and diversion. A recent study in California found a close relationship between EMS routing and PSC formation. It appeared that EMS routing to a PSC tended to enhance the formation of PSCs, at least within some geographic areas. In the year before EMS diversion the rate of hospital conversion to a PSC was only 3.8 %; after EMS diversion this rate increased to 16.2 % [18]. Thus many hospitals may be reluctant to have EMS bypass them due to lack of PSC designation.

EMS field triage is a vitally important aspect for any stroke system of care. Although on a national basis EMS tends to be somewhat fragmented in terms of jurisdictions and organization, regional and national programs and standards in terms of stroke care, triage, and related areas can be implemented with positive results. A study showed that a special pre-hospital assessment scale was successful in identifying patients with large artery occlusions based solely on clinical (not imaging) features [38]. Another study from Korea found that designation of a hospital as a CSC led to a substantial increase in the number of hospital transfers [39].

The use of telemedicine tools and techniques has been shown to increase the administration of IV TPA in a timely manner, but without an increase in complications such as cerebral hemorrhage [40, 41]. This is of particular importance in rural locations, where policies to encourage the establishment and use of telemedicine services could greatly expand and improve emergency patient care in the setting of an acute stroke [42].

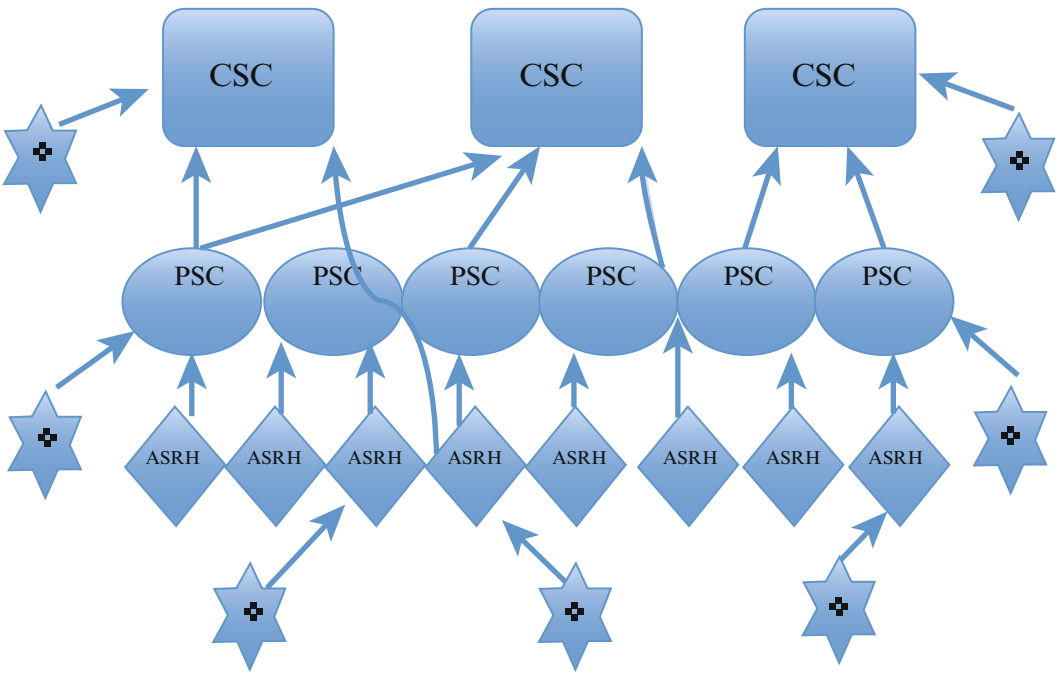

Fig. 28.3 A stroke system of care focused on EMS and hospitals/stroke centers. *CSC* comprehensive stroke center, *PSC* primary stroke center, *ASRH* acute stroke-ready hospital, *Stars with cross* represents EMS transport or helicopter transport. *Arrows* depict transportation or transfer of patients

With the relative proliferation of PSCs, what impact might this trend have on CSCs? A study in the Houston area found that patients with large ischemic strokes tended to stay at PSCs more often as the number and distribution of PSCs increased, even though CSCs were still available in the area. This might have also resulted in fewer patients participating in clinical trials [43]. However a potential benefit of this trend might be that patients could be treated closer to home and have more rapid initiation of some therapies.

Coordinating stroke care within a region can result in improved patient outcomes [44]. One study from Massachusetts General Hospital found that about 50 % of the more than 3600 patients admitted to the stroke service were transfers. In general the transfers had slightly worse stroke severities and marginally higher mortalities, but overall their outcomes were quite similar to non-transferred patients [45]. A study in California found that 25 % of patients within a region received some type of reperfusion therapy, some at a PSC, and some at a CSC [46]. Do such efforts increase the hospital-based costs for participating facilities? Although solid data are limited, recent studies suggest an overall reduction in costs for CSC facilities within such a regional network [47].

The localization of PSCs and CSCs within a city, state, and region remains a vexing issue. There are somewhat competing factors in terms of providing proper access to medical resources to all patients, although population densities are quite variable and heterogeneous within cities and states. One study found that if one could stipulate where PSCs were located, more of a state's population could be covered with a smaller number of PSCs [20]. In the current era of cost controls and limited healthcare resources, such a paradigm might be an efficient model. However, such an approach does not account for free-market influences, which might have different incentives that influence placement of PSCs and CSCs.

Conclusions

Current data clearly shows that patients cared for in stroke centers have improved outcomes compared to patients cared for at general hospitals. This is consistent with the outcomes seen at trauma centers after several decades of providing care. Although regional trauma systems work fairly well in most areas of the country, improved organization and coordination among stroke centers are needed to mirror the success of the current trauma center model. Due to an aging of the population, there is every expectation that stroke will continue to grow as a public health issue over the next several decades. Managed growth of stroke centers within well-coordinated stroke systems of care represents one path forward that can improve the outcomes for all patients with new strokes and provides opportunities to prevent subsequent strokes.

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Role of Registries and Community Models in Developed Countries

29

Mojdeh Nasiri and Mathew Reeves

Introduction

Hospital-based stroke registries or databanks, which are characterized by the systematic collection of clinical data on representative samples of acute stroke admissions, have played a prominent role in generating early descriptive data on the clinical features and epidemiology of acute stroke. In both North America and Europe these early stroke registries were predominantly based at either single referral-type hospitals or small regional hospital networks [1–4]. These studies were vital in providing information on the demographic and clinical characteristics of acute stroke events, including the stroke type (ischemic, hemorrhagic, TIA), subtype, or mechanism (e.g., lacunar, atherothrombotic, cardioembolic), presenting symptoms, severity, comorbidities and risk factors, as well as the clinical course including case fatality rates and discharge destination. These early registries helped answer questions as to what types of stroke cases were observed, in whom, and with what outcomes.

A primary concern regarding hospital-based stroke registries is the representativeness or generalizability of their data. Representativeness can be impacted by several factors [5]. First, most hospital-based registries tend to include only larger referral centers and the type of stroke events admitted at these centers are unlikely to be representative of all hospitalized stroke events. Second, not all acute stroke events in a community are hospitalized; even in developed countries the number of stroke events that do not result in a hospital admission is surprisingly variable. It has been estimated that about 15 % of stroke events are not hospitalized in the USA and Sweden [6, 7], while a recent review of over 100 population-based epidemiologic studies found that the proportion of stroke events that were not hospitalized ranged from 0 % (Brazil) to as high as 59 % (Japan) [8]. Not surprisingly non-hospitalized stroke events tend to occur in older patients who live in nursing homes and in patients with less severe stroke [7]. Third, once a stroke event is admitted, hospital-based registries can suffer from selection bias if the case identification and enrollment processes do not guarantee 100 % ascertainment, or if the registry has specific exclusion criteria (e.g., arrival >12 h after onset) [9, 10]. Biases in patient recruitment are common and may occur, for example, if older and more seriously ill cases are excluded because of difficulties in enrollment or follow-up. Overly demanding follow-up schedules may affect patient retention [5].

When stroke registries are designed to include all hospitals that treat all the acute stroke admissions in a defined geographic region, and efforts are expended to collect consistent information on all such events over a defined time period, then they may be referred to as population- or community-based stroke registries [11–18]. By capturing all stroke events in a given area over a given time period, such registries are able to provide more representative and ultimately generalizable information on acute stroke events. Critically, by defining a specific geographic area and time period these studies can rely on census data to define the size and composition of the underlying population, which in turn can be used to estimate the critical epidemiological measures of stroke incidence and stroke mortality rates (i.e., the per capita rate of stroke events and stroke-related deaths, respectively). But as valuable as community-based stroke registries are, it is important to recognize that they are still not a substitute for true population-based epidemiological studies which have the important advantage that they are able to identify factors that cause stroke [19]. Because hospital-based stroke registries only include data from acute stroke admissions, the detailed characteristics of the underlying population that gave rise to the cases remain undefined. Epidemiological studies (including cohort and case-control studies) have the advantage in that they are able to characterize

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the underlying "at-risk" population that gives rise to the new (incident) stroke events. Only by knowing the prevalence of lifestyle, behavioral, and other clinical factors in the source population can the factors that cause stroke (i.e., risk factors) be identified and their impact at the population level quantified [15–18]. Without the foundation of population-based cohort studies, which compare the incidence of stroke between those with or without a given exposure, or population-based case control studies, which compare stroke-affected individuals with unaffected individuals, we are unable to identify what the principal causal (risk) factors are for stroke, and describe their net contribution to the disease burden at the population level.

In more recent years, stroke registries have taken on a much more visible and broader role as they have been organized to provide representative information regarding the quality of care provided to acute stroke patients; quality-of-care-based stroke registries that have a national scope now exist in several countries [20–25]. The greater prominence and scope of these quality-of-care stroke registries have been driven by several factors including the recognition of the importance of providing high-quality and effective acute stroke care to all patients of tracking outcomes to determine the impact of acute stroke therapies such as thrombolysis (tPA), and the understanding that maximizing quality of care and outcomes in stroke patients can only be achieved if a systems-level approach is embraced [26, 27]. It should be recognized that the primary catalyst for much of these recent efforts has been the availability of intravenous thrombolysis (tPA), which was first made available in the USA in 1996 [28]. The availability of a novel therapy for acute stroke in conjunction with the fact that it had to be given soon after the onset of symptoms helped highlight the deficiencies in many aspects of healthcare systems for stroke patients [21, 29, 30]. This in turn led to a focus on tracking and improving the quality of a much broader range of acute stroke care processes as well as the redesign of more integrated care systems designed to deliver tPA expeditiously [28, 29]. In stimulating the development of national representative stroke registries designed to monitor and improve a broad array of quality metrics for acute stroke care, tPA has likely provided substantial collateral benefits to all acute stroke cases—even those that did not receive the actual therapy.

The expansion of these larger, nationally representative acute stroke registries has dovetailed with a broader recognition of the value and role of clinical registries in general, as articulated in an Agency for Healthcare Research and Quality (AHRQ) report on patient registries [5]. This report defines a patient registry as "an organized system that uses observational study methods to collect uniform data (clinical or other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure and that serves a predetermined scientific, clinical or policy purpose." The report further describes that such registries can serve several different purposes including measuring the quality of care, monitoring the safety and harm of specific products or services, determining the clinical effectiveness or cost-effectiveness of clinical interventions, and/or describing the natural history of disease.

The growing influence of acute stroke registries is also concordant with the recognition of the value of clinical registries in supporting the prevention and control of cardiovascular diseases, specifically by measuring healthcare delivery and supporting quality improvement for patients with cardiovascular disease and stroke [31]. There is also increasing recognition that stroke registries like other clinical registries can play an important role in providing support for essential surveillance functions to understand the population impact of stroke, although such applications tend to enhance the concerns about the representativeness of hospital-based registries when attempting to assess the true population or community-level impact of a disease [32].

Structure and Organization of Major Stroke Registries and Other Community Models in Developed Countries

Table 29.1 summarizes the structure and organizational characteristics of several of the major stroke registries from developed countries. The overall central objectives of virtually all of these registries are to measure, track, and improve the quality of care provided to acute stroke patients, and to support the development of high-quality, integrated systems of acute stroke care. Individual stroke registries may have additional specific objectives. For example, the European Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-Most) was established in 2002 when the European Medicines Evaluation Agency (EMEA) approved a license for tPA treatment of acute ischemic stroke, but wanted further data on its safety and efficacy in real-world applications. Thus the SITS-MOST registry had specific objectives to evaluate the safety (i.e., rate of symptomatic ICH and death) following thrombolysis, and efficacy (i.e., level of independence 3 months after treatment) in subjects treated with tPA within 3 h of stroke onset [25, 33].

Although all these registries have the common goal of improving the quality of stroke care, there is substantial

Table 29.1 Structure and organization of major stroke registries in developed countries [72–88]

Country Registry Time period	Funding and organizational governance	Target population (patients and hospitals), case ascertainment	Number of centers and patients	Outcomes
Sweden The National Quality Register for Stroke Care in Sweden (RIKS-Stroke) [34, 35, 39, 72] 1994–current	Funded by the National Board of Health and Welfare, and The Swedish Society and the Federation of Swedish County Councils Governance: Västerbotten County Council, Sweden	Hospitalized patients with acute stroke or other unspecified acute cerebrovascular events Hospitals: All Swedish hospitals that admit stroke patients Case ascertainment: retrospective (based on ICD codes)	In 1994 started as a voluntary registry covering half of Swedish hospitals As of 1998, all 85 hospitals in the country reported data to the registry Over 330,000 patients enrolled through 2010	Hospital discharge data 3-month follow-up data on ADL dependence and QOL collected via mailed questionnaire or telephone interview Mortality follow-up performed by linkage to national death register
United Kingdom Stroke Programme at the Royal College of Physicians (includes several audits NSSA, SINAP, and SSNAP) [22, 73–75] 1998–current	Funded by National Health Service (Healthcare Quality Improvement partnership) Governance: Royal College of Physicians, Intercollegiate Stroke Working Party (ICSWP)	Hospitalized patients with acute ischemic stroke, ICH, or TIA (excluding SAH) Hospitals: All hospitals in England, Wales, and Northern Ireland that provide services to acute stroke patients Case ascertainment: prospective.	*NSSA* (2-year cycle audits 1998–2010): data from ~200 sites and >11,000 patients *SINAP* (2011–2012): Data from >100 hospitals provided care to ~60,000 patients *SSNAP* (2013 onwards): Data from ~180 clinical teams providing acute or rehabilitation care to >63,000 stroke patients	Hospital discharge data 6-month follow-up data collection started since 2013 (SSNAP) on functional status (mRS) collected via face-to-face or telephone interview [22]
Germany German Stroke Registers Study Group (ADSR) [53, 76, 77] 1999–current	ADSR is a network of regional stroke registries across Germany Funded by the German Federal Ministry of Research since 2003 (analysis of pooled data only) Governance: Coordinating data center at University of Muenster	Hospitalized acute stroke patients Hospitals with a stroke unit that admit acute stroke patients Case ascertainment: Prospective	*Example studies from regional registries*: 6 registries (2000): ~110 hospitals and 18,000 patients annually [77] 4 cities/regions (2000): 104 hospitals, ~13,000 patients [30] Berlin Stroke Register (2007–2009): 14 stroke units, ~16,000 patients [78] Northwestern Germany stroke register (2010–2011): 158 hospitals and ~163,000 patients [79]	Hospital discharge data only
USA Paul Coverdell National Acute Stroke Registry (PCNASR) [21, 29, 80] 2001–current	Federally funded by the Centers for Disease Control and Prevention (CDC) through grants to state health departments Local Governance: State Health Departments	Hospitalized patients with acute ischemic stroke, ICH, SAH, and TIA Each state develops its own sampling scheme to select hospitals with the goal of a broadly representative state-level registry Case ascertainment: Mix of prospective and retrospective (based on ICD codes) methods	Pilot phase (2001–2004): 98 hospitals and 6867 patients in 4 states (wave I), extended to 8 states (wave II) *Implementation phase* (2005–2007): 195 hospitals and 56,969 patients in 4 states. Extended to 6 states in 2007 and to 11 states in 2012 *Currently* includes >400 hospitals, ~445,000 patients	Hospital discharge data only

(continued)

Table 29.1 (continued)

Country Registry Time period	Funding and organizational governance	Target population (patients and hospitals), case ascertainment	Number of centers and patients	Outcomes
Canada Ontario Stroke Registry (OSR), formerly the Registry of the Canadian Stroke Network (RCSN) [81–83] 2001–current	The RCSN was funded by federal support of the Canadian Stroke Network (CSN). The OSR is funded by the Ontario Ministry of Health Governance: Prior to 2011, the Canadian Stroke Network (CSN) ran the RCSN. Since Nov. 2011, the Ontario Ministry of Health has run the OSR	Hospitalized patients with acute ischemic stroke, ICH, SAH, and TIA [82] RCSN (Phase 1 and 2) included primarily stroke specialist centers across the country RCSN (Phase 3) included stroke specialist centers in Ontario The OSR includes all acute care hospitals in Ontario Case ascertainment: Prospective	RCSN Phase 1 and 2 [82] (2001–2002): 25 hospitals, from 8 provinces, 7670 patients RCSN Phase 3 [84] (2003–2008): 13 regional and district stroke hospitals in Ontario, over 11,000 patients Currently (OSR) [24]: All 150 Ontario acute care hospitals over 160,000 patients	Hospital discharge data 6-month follow-up via telephone interview was only performed in Phase 1 and 2 From Phase 3 onwards, follow-up data on mortality, and readmission obtained by linkage to provincial administrative databases
Europe (EU), including Iceland Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) [25, 33, 43] 2002–current	Funded by a variety of European and Swedish grants and sponsorship from industry Governance: The European Medicines Evaluation Agency (EMEA). Based at the Karolinska Institute (Medical University), Sweden	Hospitalized acute ischemic stroke patients 18–80 years who received thrombolysis within 3 h of onset [25] Hospitals: Specialized stroke centers Case ascertainment: Prospective	2002–2006 [33]: 285 hospitals, with data on 6483 patients from 14 countries Currently [35]: 1374 hospitals, and 105,836 patients; open to all countries worldwide participation	In-hospital and discharge data 3-month mortality follow-up is conducted using official population register or contact with the patient's primary physician 3-month functional independence data is assessed by face-to-face or telephone interview
USA Get-With-The-Guidelines (GWTG)-Stroke [27, 36, 41, 85] 2003–current	Funded by AHA (Dallas, TX) through industry contributions Governance: AHA with Coordinating data center at Duke University, NC	Hospitalized patients with acute ischemic stroke, ICH, SAH, or TIA Hospital participation is voluntary and primarily involves larger hospitals distributed throughout the USA Case ascertainment: Mix of prospective and retrospective (based on ICD codes) methods	2003 pilot project involved 99 hospitals and over 18,000 patients [85] *Currently* involves over 1600 hospitals and includes data on over 2,500,000 patients	Hospital discharge data only
Australia Australian Stroke Clinical Registry (AuSCR) [23, 37, 46, 86, 87] 2009–current	Funded by the Australian Commission on Safety and Quality in Health Care, and industry sponsors Governance: Two academic research institutes in collaboration with the National Stroke Foundation and the Stroke Society of Australia	Hospitalized patients with acute stroke (ischemic or hemorrhagic) or TIA Participating centers are a representative sample of Australian hospitals across 5 states Case ascertainment: Prospective	*Pilot study* (2009): 6 hospitals with data on 457 patients 2013 [86]: 47 hospitals, 17,130 cases	Hospital discharge data 3- to 6-month follow-up data on survival, readmission, independence, and QOL are collected through telephone interview or mailed questionnaire

Key: *ADL* activities of daily living, *AHA* American Heart Association, *ICH* intracerebral hemorrhage, *NSSA* National Sentinel Stroke Audit, *QOL* quality of life, *SAH* subarachnoid hemorrhage, *SINAP* Stroke Improvement National Audit Programme, *SSNAP* Sentinel Stroke National Audit Programme, *TIA* transient ischemic attack

variability between them in terms of their structure and organization. Only the Swedish RIKS-Stroke registry provides a complete census of all acute care hospitals in the country [34, 35]. All of the other registries include a sample of eligible hospitals (and therefore a sample of patients) but the number, type, and sampling mechanisms used to select them vary substantially. Thus the extent that these registries provide information that is generalizable to the total stroke population is somewhat questionable.

The funding sources also vary widely with most registries relying on federal and/or state/provincial level government support, with the exception being the US Get-With-The-Guidelines-Stroke (GWTG-Stroke) program, which relies heavily on pharmaceutical industry support through the American Heart Association (AHA) [36]. Other registries, such as the Australian Stroke Clinical Registry (AuSCR), have been supported by a combination of funding from nonprofit institutions, consumer donations, pharmaceutical industry, and grants [37].

All of these registries are able to report data on patient outcomes that occur during the in-hospital stay (e.g., complications, deaths) or at discharge (e.g., destination, functional status). Several registries such as the Swedish Stroke Register (RIKS-Stroke) and the Registry of the Canadian Stroke Network (RCSN) have been able to link the registry data to other data sources (including administrative, billing, vital statistics, and census data) to obtain data on longer term mortality, readmission, physician visits, and medication use [20, 24].

Some of the registries, for example RIKS-Stroke [35], AuSCR [38], SITS-MOST [25], and the UK Stroke Improvement National Audit (SINAP) [22], have been able to collect patient-reported outcome measures (PROM) following hospital discharge. This typically includes data on functional status (disability) and quality of life (QOL), and is most often collected 3 or 6 months after discharge. Follow-up data collection has been done using a variety of methods including face-to-face interviews [33], mailed questionnaires [39], or telephone interviews with either patients [23] or their caregivers [33]. Although patient-reported outcomes data are regarded as the gold standard of outcome measures, its collection represents considerable practical challenges in terms of the amount of resources (personnel time and costs) required and in obtaining individual patient consent [24].

Specific requirements of stroke registries to obtain informed consent from patients are highly variable and depend in part on the policies and preferences of local human subjects' research oversight committees. The type of data collected also has a large influence on the need for consent; some registries have been required to obtain consent from patients prior to any data collection [23, 40], whereas others have been able to collect in-hospital data after obtaining a waiver of consent [21, 41, 42]. It is reasonable to expect that individual patient consent is required when registries collect post-discharge follow-up data directly from patients or caregivers, although confirmation of this from available published reports is often lacking [43, 44]. The requirement to obtain individual patient consent for follow-up of stroke patients post-discharge is one of the major reasons that data collection in US-based registries is limited to hospital discharge data only [21, 41].

A useful lesson on the pitfalls of requiring consent from patients comes from the RCSN, which has evolved in its approach to obtaining patient consent. During the first 2 years of the RCSN (Phase 1 and 2) informed consent was required on all patients even for a basic level of data abstraction. However the results indicated that substantial selection bias was introduced due to difficulty of obtaining consent. More than 50 % of eligible subjects were not consented either because of refusal or inability to contact the patient during the in-hospital stay [40]. Patients who were consented were different from those who were not consented in important ways; for example the in-hospital mortality rate was three times higher in patients who were not consented compared to those who were. Other factors such as age, level of consciousness on admission, race, preferred language, and length of stay were also different between consented and non-consented patients [40]. Subsequently in 2003, the registry was granted special status as a "prescribed registry" and the requirement for informed consent was dropped, thus allowing it to collect data on all patients without consent. This status was extended to also include the subsequent Ontario Stroke Registry (OSR) [24, 40]. The Australian registry (AuSCR) is an example of another approach to informed consent which utilizes an "opt-out" consent protocol to minimize dropouts that can occur when written informed consent is required. The "opt-out" consent protocol provides patients with information on the purpose of the registry, explanation of the data to be collected, and details of simple, cost-free ways available to exclude their data from the registry [23]. A similar opt-out approach is used in the UK, SINAP registry, where although a waiver of consent was obtained individual patients can request that their identifiable data not be included in the registry [42].

Perhaps the most liberal approach to consent is demonstrated by the Swedish RIKS-Stroke registry, which does not require informed consent from patients because quality monitoring by the Swedish healthcare system is mandated by law and so the registry is regarded as a component of the regular healthcare system rather than a research project

[35]. This waiver of the need for consent even extends to the collection of patient data by survey or interview post-discharge. Despite many hospitals to provide patients with information about the purposes of the registry and the types of information collected, patients also are informed about an "opt-out" procedure should they wish to withdraw from participation [39].

Findings of the Major Stroke Registries and Other Community Models in Developed Countries

Contribution of Registries to Improvement in the Quality of Stroke Care

There are a large number of specific reports and peer-reviewed publications that have been generated from the quality-based stroke registries in recent years. Table 29.2 provides a few examples of the scope and objectives of reports that have been published in the last decade or so. A common approach for many of these reports has been to provide a description of the baseline quality of care and then to describe trends in performance over time. Across almost all established registries, the quality of stroke care has shown considerable improvement in terms of the overall quality of care; broad increases in the quality of care were observed following the implementation of the registries in Sweden [35], Canada [45], Australia [46], the UK [47], and the USA [48, 49].

One topic of great interest has been the implementation of thrombolysis therapy over time; specific studies have assessed its utilization [30, 50, 51], timeliness of delivery [52, 53], safety [33, 54], and efficacy [34]. The utilization of tPA therapy in ischemic stroke patients has been shown to have increased in all registries, particularly in the subgroup of ischemic stroke patients who arrive within 3 h and are eligible for treatment, where increases in treatment have been very dramatic [49, 50]. However, despite these improvements the frequency of tPA use is still less than 10 % when all ischemic stroke admissions are considered [50, 51]. Recently other registry-based studies have evaluated the safety of tPA treatment within the 3–6-h time window and have shown that safety is similar to patients treated within 3 h [53, 54].

Another topic that is commonly addressed by these registries is healthcare disparities—particularly those defined by age, sex, and race [55–57]. An analysis of age-related differences in clinical characteristics and in-hospital mortality in the GWTG-Stroke program between 2003 and 2009 found that age-related differences narrowed over time as performance improved to a great extent in older age groups [55]. Another study from the RCSN found evidence of disparities in care in the oldest old. Ischemic stroke patients aged 80 years and older were less likely to be admitted to the intensive care unit and discharged to home compared to younger patients [58].

Several registry reports have examined sex differences in the quality of care and outcomes [56, 59–61]. In a study from the Canadian registry, there were no significant sex differences in the management of stroke including use of neuroimaging, thrombolysis, antithrombotic therapy, or consultation with therapists or neurologists [53]. However, women had greater disability at 6 months and were more likely to be discharged to long-term care facilities than men [56], findings that have been replicated in several other registries [59, 62].

Registry-based analyses of racial or ethnic disparities in care are surprisingly limited. An analysis from GWTG-Stroke registry found that black patients were less likely to receive evidence-based care measures, including receiving intravenous thrombolysis, deep-vein thrombosis prophylaxis, smoking cessation, and discharge antithrombotic compared to white or Hispanic patients [57]. Similarly in a study from a state-level stroke registry in Michigan, African-American patients were found to be less likely to receive CT within 25 min of arrival, cardiac monitoring, dysphagia screening, and smoking cessation counseling; however apart from these specific differences in many other respects the quality of care for AA patients was the same as that for white patients [63].

Assessment of the Relationship Between Quality of Care and Outcomes

Of great interest is whether the improvements in quality of care demonstrated in these registries have resulted in direct improvements in patient outcomes—particularly over the longer term. Tracking patient-reported outcome measures (PROM) post-discharge has been very challenging for registries and so they are often limited to using measures generated at the time of discharge (such as in-hospital mortality, or the proportion of patients returning to home or avoiding nursing home placement). Improvements in some short-term patient outcomes have been documented by some registries including GWTG-Stroke, which found lower in-hospital case fatality, increased rates of discharge

Table 29.2 Specific objectives from example studies generated by the major stroke registries [88–94]

Registry	Example studies	Objective of the study
RIKS-Stroke (1994)	Eriksson [51]	To evaluate the rate of thrombolysis implementation for acute ischemic stroke treatment across the country between 2003 and 2008
	Glader [88]	To evaluate the persistence preventive drug use during the first 2 years after stroke
	Asplunde [34]	To describe the coverage, validity and sustainability of the longest running national stroke registry
	Appelrose [35]	To describe time trends in care, treatment, and patient outcome between 1995 and 2010
UK Stroke Programme	Report [47]	To audit the quality of care against the national stroke strategy and national guidelines. To measure the rate of changes in stroke services and quality of care compare to the previous round of the audit
	Bray [42]	To estimate the use and outcome of thrombolysis in acute ischemic stroke across all age groups
	Report [44]	To assess the process of acute stroke care through SINAP programme and to compare the results to the national standards and outlined in the national guidelines
	Campbell [89]	To evaluate the inequality in the quality of acute stroke care provided to patients admitted out of the working hours
ADSR (1999)	Heuschmann [30]	To evaluate the frequency of thrombolysis and the risk of ICH in patients with acute ischemic stroke
	Heuschmann [90]	To investigate predictors for in-hospital mortality and attributable risk of death after ischemic stroke
	Koennecke [78]	To determine factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit
	Minnerup [53]	To evaluate the impact of extended thrombolysis time on the rate of thrombolysis and door-to-needle time in the Northwestern Germany stroke registry
PCNASR (2001)	Reeves [21]	To describe the quality of acute stroke care from 4 pilot state-level registries (Michigan, Ohio, Massachusetts, and Georgia) between 2002 and 2003
	George [48]	To summarize the quality of acute stroke care during 2005–2009 using data from 7 state-level registries
	George [91]	To examine the statin use in patients with ICH in the PCNASR
	Tong [92]	To assess the risk factors associated with mortality and ICH in tPA-treated acute stroke patients
RCSN, OSR (2001)	Tu [40]	To evaluate whether consent-related bias impacts the results of the registry
	Kapral [56]	To evaluate the sex differences in stroke care and outcomes
	Fang [24]	To describe the evolution of methodology of the RCSN and OSR registries in terms of requirement for patient-level consent and use of population-based administrative data to obtain outcome information
	Shobha [84]	To assess the effect of thrombolysis on lacunar strokes compared to the other ischemic stroke subtypes
SITS-MOST (2002)	Wahlgren [33]	To assess the safety and efficacy of thrombolysis treatment in acute ischemic stroke patients (i.e., risk of ICH and mortality, independence at 3 months) in a cohort of patients treated between 2002 and 2006
	Ahmed [54]	To compare the outcome of patients who received the thrombolysis treatment after 3 h of stroke onset to those who received it within 3 h of symptom onset
	Mikulik [52]	To identify factors associated with longer door-to-needle time in patients treated with thrombolysis between 2003 and 2010
	Lorenzano [61]	To evaluate sex differences in outcomes in a cohort of ischemic stroke patients treated between 2002 and 2011
GWTG (2003)	LaBresh [85]	Pilot program to examine the impact of participation in the GWTG program for 1 year on improvement in quality of care for acute stroke patients
	Schwamm [27]	To examine the impact of participation in the GWTG program over a 5-year period on time trends of quality of care in acute stroke patients
	Fonarow [41]	To describe the characteristics, performance measures, and in-hospital outcomes of the first one million acute stroke and TIA admissions in the GWTG program between 2003 and 2009
	Saver [93]	To describe the relationship between onset to treatment times and outcomes in over 58,000 patients treated with thrombolysis
AuSCR (2009)	Cadilhac [23]	To evaluate the quality of care for stroke patients in the pilot phase of AuSCR
	Annual Report [46]	To evaluate the process of and changes in the process and quality of acute stroke care in AuSCR
	Cadilhac [94]	To investigate issues and possible solutions related to governance, ethics, quality, and analysis of the registry data
	Lannin [38]	To compare the efficiency of telephone- versus mail-based follow-up of outcome in stroke patients

to home, and decreased length of hospital stay [41]. Similarly data from RIKS-Stroke have documented an increase in the number of patients discharged to home rather than to nursing home [35], as have data from the Canadian registry [45].

Data on longer term outcomes are often limited to those that can be obtained by linking the registry to administrative or billing data to obtain information on death or readmissions [45, 64]. Data generated on longer term PROMs, particularly those relevant to functional recovery, are few and far between. The RIKS-Stroke Registry has attempted to address the impact of the registry on changes in 3-month stroke outcomes across Sweden; between 2001 and 2010, self-reported independence at 3 months increased by about 2 %; however there was a concomitant increase from 18.7 % (2001) to 20.0 % (2010) in case fatality rates after 3 months [35].

Regardless of the availability of outcome data, the interpretation of time trend data generated from registries is problematic because of the difficulty of measuring the underlying secular changes in both care processes and outcomes. The natural history of stroke has changed over recent decades with dramatic declines in mortality, recurrent stroke, and other vascular events [65, 66]. Such dramatic changes make it difficult if not impossible to determine how much, if any, of the long-term improvements in patient outcomes can be ascribed the specific activities and actions of the registries [66].

Evaluation of Stroke Systems of Care

The term stroke systems of care has been defined as the comprehensive and integrated organization of stroke care services across a definable geographic area that is designed to promote access to evidence-based care and optimize patient outcomes [67]. By addressing the full complement of healthcare services and functions relevant to stroke, including primary prevention, community education, EMS response, treatment and management of hyper acute stroke, secondary prevention of stroke, rehabilitation, and continuous QI, a true systems approach can help correct many of the deficiencies that are a result of fragmented healthcare delivery systems [26, 67].

Several reports have used registry data to help assess the impact and/or value of stroke registry data on changes at the systems level regarding the organization and quality of stroke care [20, 45, 68]. By describing access to care, current quality of care patterns, and changes over time, stroke registries provide critical information necessary for the evaluation of the effectiveness of any particular stroke system of care.

Value, Contributions, Challenges, and Opportunities of Stroke Registries

The numerous scientific publications and reports generated from the various stroke registries across the globe illustrate the value of stroke registry data. Stroke registries have played a vital role in highlighting deficiencies in both the quality of stroke care as well as with the organization of stroke care systems. Stroke registries have also been instrumental in providing data to support the development, testing, and promulgation of quality metrics [69, 70]. Through their emphasis on the systematic and ongoing collection of clinical data, stroke registries have been the primary stimulus for quality improvement and assurance efforts. Many of the studies summarized in this chapter point to the ability of stroke registries to drive improvements in the quality of care and in some cases improvements in patient outcomes. These positive effects have been seen across several different countries, each with its own unique healthcare delivery systems.

Stroke registries can also have an important symbiotic relationship with clinical guidelines. By recommending specific evidence-based treatments and care process clinical guidelines can suggest changes in the content of a registry to track compliance with such recommendations. Alternatively, registry data can highlight deficiencies in the delivery of care or in patient outcomes that in turn can help inform the need for new evidence-based treatments or care recommendations. The ability of registries to provide data on the comparative effectiveness of treatments and interventions highlighted in clinical guidelines in real-world populations is one of their most important advantages [5].

Notwithstanding the obvious value of stroke registries, we need to acknowledge that their establishment and continued operation require a substantial commitment from many groups and individuals, including governmental agencies, health advocacy organizations, hospitals, health professionals, and of course the patients themselves. Objective data on the financial costs and human resource requirements to successfully run a stroke registry are limited [20], but are clearly considerable, especially when viewed from the perspective of individual hospitals. The continued effort required by hospital staff to identify, abstract, follow up, and submit data on large numbers of stroke events on an ongoing basis is considerable. Given that in many registries such efforts are not directly supported financially by governments or other agencies, it begs the question as to whether these activities can be sustained in the long term. Table 29.3 identifies some of the challenges and opportunities that stroke registries currently

Table 29.3 Summary of current challenges and opportunities for stroke registries

Challenges	Comment
Labor intensive	Case identification and data abstraction are resource intensive
Ever-expanding wish list of variables	Frequent changes to clinical guidelines create the need to include new variables to track care
Is the primary goal quality improvement or research?	Confusion over primary goal of the registry can lead to lengthy and excessively burdensome data abstraction forms
Representativeness (generalizability)	Are the participating hospitals representative of all hospitals that care for stroke patients?
Case coverage (selection bias)	Documenting completeness of case ascertainment is challenging and time consuming. Requires ongoing assessments
Data quality	Documenting data reliability is time consuming. Requires ongoing assessments
Quality plateau	Potential to reach high-quality levels on a select few indicators may stall further efforts to improve care
Mortality and readmissions as outcomes	There is uncertainty regarding the association between quality of care and mortality and readmissions measures used in some value-based incentive programs
Need for long-term patient reported outcome measures (PROM)	Collection of PROM (for example functional status, QOL, satisfaction) requires individual patient surveys and interviews. This is resource intensive and difficult to obtain high response rates
Privacy (IRB) issues	Requirements for individual patient consent to be included in a registry and/or to provide long-term outcomes vary
Proving link between improved quality of care and better patient outcomes	Difficult to prove connection because of observational nature of all registries (no comparison data), and inability of current statistical risk adjustment methods
Accurate hospital profiling/ranking	Inability to accurately compare outcomes between hospitals is related to limitations in both statistical risk adjustment (for case mix) and small sample sizes
Value of care	Difficulty in collecting valid cost data limits the ability to document value of care (outcome per unit of spending)
Reporting requirements for pay-for-performance or other value-based incentive programs	Could diminish the role of registries if hospitals choose to collect only the data required to report to these programs
Opportunities	
Electronic data submission	Linking registries to EMR data could reduce data collection burden substantially
Sustainable collection of long-term PROM data	Further research to create a cost-efficient and sustainable system to collect valid long-term PROM data (e.g., 3 and 12 months post-discharge) is a critical need
Improved linkage to other clinical and administrative databases	Further research is needed to develop efficient mechanisms to link registry data to complementary databases including administrative and vital records data
Identify new performance measures	Mechanisms and polices to identify when quality metrics should be retired and replaced with new measures are a critical need
Quality improvement and assurance	Continued research is needed to determine how stroke registry data can best leverage hospitals and healthcare systems to produce sustained improvements in the quality of care and patient outcomes
Proving link between improved quality of care and better patient outcomes	Further research to quantify relationships between processes of care and patient outcomes is a critical need (especially for mortality and readmissions)
Accurate hospital profiling/ranking	Further research to determine the ability of stroke registries to accurately profile hospital performance is a critical need (especially when compared to existing administrative data)
Value of care	Ability to quantify costs and determine value at the individual patient level in stroke registries is a critical need
Reporting requirements for pay-for-performance or other value-based incentive programs	Research to help illustrate the added value of registry data to provide information on process and outcomes (compared to administrative data) is a critical need
Comparative effectiveness	Ongoing research to document comparative effectiveness (both benefits and harms) of interventions, especially those promoted in clinical guidelines, is a critical need
Data quality	Ability to identify more efficient approaches to document reliability and validity of registry data is a critical need

face in terms of ensuring sustainability (by increasing efficiency) and by further documenting their value (which includes addressing issues related to patient outcomes and improving hospital profiling and assessments). This list, which is by no means exhaustive, illustrates the considerable number of opportunities that exist for the continued development of stroke registries that will hopefully increase their value while ensuring that they remain a necessary but efficient mechanism to track, improve, and evaluate the quality of stroke care. Further recommendations regarding the development of clinical registries can be found in a recent AHA policy statement [31].

Conclusions

Over the last 20 years the development of stroke registries and other community-based data systems around the world has provided the data necessary to promote substantial gains in the quality of care provided to acute stroke patients. Data from these stroke registries has also been vital to our ability to inform the development and document the value of stroke systems of care. Stroke registry data from several different countries demonstrates that stroke care increasingly meets many of the attributes outlined by the seminal 2001 Institute of Medicine report *Crossing the Quality Chasm*, which states that health care should be safe, effective, patient centered, timely, efficient, and equitable [71].

Despite this unparalleled success, the future of stroke registries is far from clear as issues related to their ongoing funding, sustainability, and ultimately their value continue to arise. In the USA, the success of the stroke registries has led to efforts to include stroke care and outcomes in national level value-based incentive programs that, paradoxically, could hurt their long-term sustainability if hospitals only collect the data needed to serve the immediate goals of these programs, which are independent of the registries themselves. Continued efforts both at the research level as well as at the policy level are required to confirm that the long-term benefits of stroke registries are substantially relative to the resources required to sustain them.

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Telemedicine in Stroke Systems of Care

30

Bart Demaerschalk

Case Presentation A 75 year old man with coronary artery disease, hypertension, diabetes mellitus, and peripheral arterial disease presented to a rural emergency department (11:23) via ambulance with acute onset aphasia and right hemiparesis (11:00). After an initial triage evaluation, establishing intravenous access, drawing basic laboratory studies, and ordering a non contrast CT scan of the head, the emergency physician activated the telestroke hotline (11:35). She was immediately connected to a vascular neurologist 215 miles away. After a brief telephone discussion, the vascular neurologist connected via a hand held tablet to a robotic telepresence end point at the foot of the patient's bed to conduct a synchronous audio–video telemedicine consultation (11:50). After a focused history, a National Institutes of Health Stroke Scale (NIHSS) was conducted with the help of a telepresenter emergency department nurse (12:00). The NIHSS was 25. The neurologist viewed the CT head via a teleradiology application and recognized early ischemic changes in the left insular cortex and a probable hyper dense left middle cerebral artery sign (12:10). By 12:23 the vascular neurologist had determined the diagnosis of acute ischemic stroke, left cerebral hemisphere, and determined the patient to be eligible for intravenous thrombolysis. The neurologist and the emergency physician discussed the case and agreed that the patient harbored no radiological, laboratory, or clinical contraindications to thrombolysis. An order was placed to pharmacy and the treatment was initiated at 12:30. Arrangements were made for the patient to be transported to the nearest stroke center for consideration of additional endovascular treatment(s).

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Introduction

Acute ischemic stroke is a major public health crisis in the USA [1] and throughout the globe [2]. A concerted effort to apply evidence-based clinical practices to ischemic stroke care would improve primary and secondary stroke prevention as well as post-stroke clinical and economic outcomes. One component of this effort includes the designation and certification of acute stroke-ready hospitals, primary and comprehensive stroke centers, which have all been demonstrated to improve stroke care processes and outcomes [3]. The timely and evidence-based implementation of acute stroke evaluation and treatment are amongst the more heavily promoted aspects of a stroke center [4]. The rationale for the particular attention to expedient emergency stroke evaluation and therapy is valid, given the narrow time window and highly time-sensitive effects of rapid administration of the only Food and Drug Administration-approved medical therapy for acute ischemic stroke, recombinant tissue plasminogen activator (rtPA) [5–7].

However, geography and distance contribute to the disparity in acute stroke care, as most neurological centers are based in large, metropolitan academic medical centers. It is estimated that upwards of 40 % of the residents of the USA live in communities beyond the immediate clinical reach of a designated stroke center. This once presented a formidable barrier to the timely administration of emergency stroke treatment. Furthermore, there remains a shortage of expert stroke providers, who are best equipped to provide emergency stroke care and achieve the most favorable health-related outcomes [8–10].

In an attempt to address the rural-to-metropolitan disparity and expand the access to best ischemic stroke practices, Levine and Gorman proposed the development of telemedical outreach for acute stroke evaluation and management, which they called "telestroke." [11] Since then, the scientific evidence to support telestroke has accumulated, with excellent interrater agreement for the National Institutes of Health

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Stroke Scale (NIHSS) score between telemedicine-enabled versus bedside assessment [12–14], increased thrombolysis eligibility decision making [15–17] by telestroke as compared to telephone-only consultation, and the telestroke model has been confirmed to be cost-effective for hubs, spokes, and society in general [18–20]. In response to these observations and the perception of clinical benefit by stroke providers and patients, there has been a swift uptake and expansion of telestroke networks both in the USA [21, 22] and around the world [23]. There is less understanding about the use of telemedicine for the more complex, but equally important prehospital, subacute, and rehabilitative phases of ischemic stroke assessment, diagnosis, and treatment [24].

The Telestroke Model

The hub and spoke model is the most common way telestroke is incorporated into stroke systems of care. Stroke specialists at the hub hospital (typically a stroke center in an urban community) are on-call and available to spoke hospitals (typically a small or mid-size hospital in a rural or remote community without direct access to neurological expertise and resources). Telemedicine end points (computer, video monitor, and zoom-pan-tilt camera, mounted on a wheeled cart or platform) are positioned in the spoke environment while the hub neurologists employ desk top, lap top, mobile devices, or tablets with wired or wireless or cellular connectivity to allow high quality synchronous audio video consultation. Typically a single hub hospital will provide round the clock stroke care to a variable number of spoke hospitals in a regional network.

Evidence in Support of Telestroke

Acute Ischemic Stroke

Most telestroke studies have focused on the acute phase of stroke care ($n=155$ for acute stroke, $n=28$ for post-stroke) [16, 17, 24, 25]. Telestroke practice has evolved to the point that there are specific American Heart Association/American Stroke Association statements outlining the evidence for its use [26] and clinical practice guidelines for implementation [27, 28]. These were built upon the strength of studies that reported excellent interrater reliability of NIHSS examination between remote and bedside examiners [13, 14, 29], randomized controlled trials of telestroke versus telephone consultation for acute stroke demonstrating superiority of telemedicine for thrombolysis eligibility decision-making [15, 17], and favorable multi-perspective health economic analyses [18–20]. Telestroke is considered the new standard of care in both academic and community practices whenever or wherever an in-person stroke time cannot be immediately available [21, 22]. Additionally, it has been reported that high-quality telestroke consultations can be performed with mobile computers [30] and smartphones [11, 31, 32], demonstrating the portability of the service.

Two published randomized controlled trials compared telemedicine to telephone methods of consultation for consideration of thrombolysis eligibility in acute stroke. The first trial, published in 2008, randomized 222 patients ($n=111$ for each study arm) with acute stroke to either telephone-only or telemedicine-guided evaluation. The primary outcome was adjudication of "correct treatment" with IV thrombolysis by NINDS criteria. Typical stroke metrics were also tracked. In brief, thrombolysis decision making was adjudicated to be correct more frequently by telemedicine (98.2 %) than by telephone (82 %) consultations. Despite the telephone group having a significantly lower NIHSS on presentation at baseline (7.7) as compared to the telemedicine group (11.4) there were neither differences in 90-day mortality nor outcome, and no differences in rate of hemorrhage [17]. A second research group emulated this methodology with the intent of demonstrating feasibility of a telemedicine versus telephone consultation for acute stroke treatment trial in another region. Fifty four patients participated ($n=27$ for each arm) and no consultations were aborted but technical issues were frequent in the telemedicine arm. Adjudicated thrombolysis decision making was similar and good between the telephone (89 %) and telemedicine (85 %) groups. There were no differences in 90-day mortality or outcome, nor were there any differences in rate of hemorrhage [15]. A pooled analysis of these similarly designed trials supported the conclusions of the original trial, with a correct thrombolysis decision significantly more probable with telemedicine (96 %) versus telephone (83 %) with excellent frequency of thrombolysis administration (26 %) and no difference in mortality, outcomes or hemorrhagic complications.

There have been a substantial number of published pilot and feasibility projects that have populated the field, detailing how to effectively incorporate telemedicine into stroke systems of care. The field is advancing. Post-implementation studies and prehospital EMS studies lead the way. University of Maryland investigators, otherwise known as TeleBAT investigators, published the preliminary data on prehospital telestroke [33, 34]. Although they demonstrated reasonable interrater agreement of NIHSS between on-site and telestroke providers, their reported technology is now considered antiquated and the frame rates were unacceptably slow. The German TEMPiS study group reported on their pilot [35], called PHANTOM-S, using enhanced stroke-dedicated ambulances equipped with CT scanners, point of care laboratory, teleradiology and telemedicine capabilities. However, their early l experiences yielded an unacceptably high rate of technical failures [36]. Later studies, however, utilizing a fourth-generation (4G) mobile network for data transmission

demonstrated feasibility and excellent call-to-thrombolysis administration times for treated patients [37]. Follow-up studies are planned. The anticipated potential benefit to individual patients as well as society is substantial, but whether the cost can be justified remains to be seen.

Post-stroke and Rehabilitation

To date, 18 studies contribute primary data on the use of telemedicine technology for post-stroke evaluation, care, and rehabilitation, all small exploratory pilots. There were no randomized controlled trials, economic analyses or post-implementation studies. Of note, nearly one third of the manuscripts ($n=10$) were narrative reviews, qualitative summaries, opinion pieces [24].

The majority of the published manuscripts for post-stroke telemedicine come from the physical medicine and rehabilitation literature and summarize pilot studies of home tele rehabilitation systems for stroke patients. The studies that evaluated telemedicine for other, non-rehabilitative elements of post-stroke care are limited but show promise. For example, a pilot study conducted by Mikulik et al. compared logistics of performing a telementored transcranial Doppler (TCD) and carotid duplex (CD) examination by remote video-enabled guidance of a novice versus an in-person examination by an experienced sonographer [38]. They performed telemedical and in-person studies in each of eight subjects. There was satisfactory agreement, particularly amongst the seven patients with sonographically normal carotid and intracranial vasculature. The conclusion was that telemedical guidance of TCD and CD studies by an experienced sonographer was feasible for non-urgent studies and had satisfactory agreement with in-person studies in patients with normal vasculature.

Another aspect of post-stroke rehabilitative care for patients with aphasia is a consultation with a speech and language pathologist. A pilot study by Brennan et al. sought to determine if telemedicine is an effective means of providing this service [39]. The investigators studied 40 subjects with post-stroke aphasia who each underwent an in-person and a telemedicine observation session while performing a story-retelling procedure. The goal was to identify any differences in performance between the experimental (e.g., telemedicine) or control (e.g., in-person) settings and, if any were found, associate them with any demographics such as age, gender, or experience with technology. In fact, no significant differences were discovered in performance between the two settings, and no demographic features predicted particularly good or poor performances in any setting. The telemedicine method was also highly satisfactory to participating subjects. The authors concluded that telemedicine has potential in post-stroke aphasia evaluation but requires further study.

Tele-Health Economic Analyses

Telestroke practice is at a stage where health economic analyses have been performed and reported societal cost-effectiveness [18] and long-term cost savings from both the hospital and societal perspective [19, 20].

The first economic analysis of telestroke was designed to estimate the societal cost and consequences of "hub and spoke" telestroke system delivery of acute stroke therapy compared to usual community stroke care at 90 day and lifetime horizons. A decision-analytic model was utilized and data inputs came from the clinical experience of the investigators assuming a network of a single receiving ("hub") and eight referring ("spoke") centers. Costs and health outcome estimations were based on published studies. Briefly, it was demonstrated that telestroke for delivery of thrombolysis was more cost-effective as compared to usual care in the lifetime horizon, with an incremental cost-effectiveness ratio (ICER) of $2,449 per quality-adjusted life-year (QALY). Whereas for the 90-day horizon, the ICER was $108,363 per QALY. The authors offered that the greater cost benefit over the life span than at 90 days was likely due to the large upfront fixed costs of telemedicine equipment compared to the lifelong benefit of improved neurologic outcomes and avoidance of disability [18].

Following that study, other investigators sought to model the cost-related aspects of stroke care for hub and spoke systems of care and institutions more specifically with and without a telemedicine network in place. The researchers also employed a decision analytic model and populated the "with telestroke network" and "without telestroke network" based on their clinical experiences with referring centers. Costs and health outcome estimations were extracted from studies current as of 2011. The analysis assumed one hub and a seven-spoke network. With the telestroke network in place, the model predicted that 114 fewer stroke patients would be admitted to the hub hospital each year, whereas approximately 16 more patients would be admitted to each spoke hospital compared with a no network setting. The model predicted that 45 more patients would be treated with intravenous thrombolysis and 20 more with endovascular stroke therapy in a telestroke network per year. From the entire network perspective, an estimated average cost saving of $358,435 per year could be achieved with a telestroke network versus a network without telestroke during the first 5 years. The hub would bear positive costs of $405,121 per year, but each spoke would save $109,080 per year. With cost-sharing arrangements between the hub and spoke hospitals, this analysis proposed that each hospital could achieve equal cost savings of $44,804 per year during a 5-year time horizon. Overall, the results of this study confirm that a telestroke network may be a clinically and economically advantageous way to extend the reach of stroke specialists to

remote areas and thus to improve the overall quality of care for stroke patients [19]. The same health economic modeling exercise from a societal, rather than hospital, perspective demonstrated that compared with no network, patients treated in a telestroke network incurred $1436 lower costs and gained 0.02 QALYs over a lifetime [20]. The study revealed that a telestroke network is cost savings and more effective compared with no network from the societal perspective in most modeled scenarios [20].

Telemedicine Technology

The term "telestroke" has been defined as "live, audio-video telecommunication applied to care of acute stroke." [23] In the past, remote stroke consultation was practiced by many technological means far less sophisticated than videoconferencing including telephone [40], Multimedia Messaging Service (MMS) [41], e-mail, or some combination thereof. Although evidence-based technological standards for telestroke are lacking, most current era telestroke systems are based on high-quality videoconferencing, which an American Heart Association/American Stroke Association guideline defines as a system that "…includ[es] transmission rates and algorithms of sufficient quality to support > 20 frames per second of bidirectional synchronized audio and video at a resolution capable of being accurately displayed on monitors of ≥13 in." [26] These represent only minimum standards, however, and reflect expert consensus opinion. Additionally, telestroke networks may vary significantly in the technology platforms utilized. The technological aspects of a network are of interest as there has been expansion in the telestroke-related telecommunications market within the past decade and the cost thereof remains one of the top identified barriers to implementation of a telestroke network [22, 42]. Furthermore, in addition to hardware specifications, the desire for mobile health capability requires implementation of technical and privacy standards, as well as guaranteed quality of service frameworks for wireless data transmission.

Medical Legal and Legislative Issues

In spite of a strong and expanding evidence base supporting the use of telemedicine in general, and telestroke in particular, there are a number of legal factors that constitute a barrier to more widespread implementation.

Licensure

The hallmark of telemedicine is to disseminate medical advice and expertise to patients and local providers irrespective of cartographic and geographic boundaries. Currently, medical licensure and hospital credentialing and privileging processes run counter to that ideal, as they are predicated almost entirely on geography. In the USA, medical licensure is under the authority of an individual state. Furthermore, in most states, a physician must be licensed in the state where a patient seeks care. Thus, a telemedicine physician must undergo the rigorous licensure process in nearly each and every state and territory for the region in which he/she expects to practice. The exceptions, with a mechanism to grant a telemedical license for practitioners licensed in another state, include Alabama (ALA.CODE § 34-24-502), Louisiana (LA.REV. STAT.ANN. §1276.1), Minnesota (MINN. STAT. § 147.032(1)), Montana (MONT.ADMIN.R. 24.156.802(5)), Nevada (NRS § 630.261(e)), New Mexico (NM STAT.ANN. 1978 § 61-6-6), Ohio (OH. REV.CODE ANN. § 4731.296(C)), Oregon (OR.REV. STAT.ANN. § 677.139), Tennessee (TCA § 63-6-209(b)), Texas (22 TEX. ADMIN.CODE § 174.12), and Guam (10G.C.A. § 12202). The Federation of State Medical Boards (FSMB) proposed the Model Act in 1995 that would afford a licensed physician in any state the privilege to practice telemedicine across state lines, limiting in-person medical care to the primary state of licensure. This Act has not been formally accepted by any state to date, although the aforementioned states that grant telemedicine licensure based on a medical license in good standing elsewhere in the USA have enacted its basic tenet. A recent piece of Federal legislation (42 CFR §§ 482.12 and 482.22) helped to streamline the process of being credentialed for a telemedicine site by allowing the credentialing process of the hub site to effectively "transfer" so as to avoid duplicative administrative barriers. On April 26, 2014, FSMB published policy guidelines for the safe practice of telemedicine, which are freely available on the FSMB website.

Privacy

The right to privacy of medical records is considered fundamental and is protected by Federal law (45 CFR § 160) in the form of the Health Insurance Portability and Accountability Act (HIPAA). Compliance with HIPAA is necessary whether medical information is transmitted by hand or over the internet. Privacy and security of the telemedicine systems can be maintained by Secure Site License (SSL) conditional access, data encryption, intruder alerts, and access logging and reporting. The integration of security features into modern telemedical hardware and software ensures HIPAA compliance for telestroke consultations. Given the new ubiquity of smartphones and their high-quality videoconferencing capability, the desire to employ these inexpensive hand-held devices for telemedicine must be matched by a HIPAA-compliant means of doing so, including the use of virtual private networks (VPN) or closed wireless networks.

Many of the legal and legislative issues exist for the use of telemedicine in general, but there are some that are particularly relevant to telestroke. Some who are wary of developing a telestroke network cite the lack of legal clarity at a Federal level (or even in most states) regarding shared liability between hub and spoke sites in the instance of an unfavorable outcome. In the case of acute stroke, since it appears that the majority of stroke-related lawsuits come from thrombolysis *not* being considered or administered, implementation of a system of care that affords emergency medicine providers access to stroke specialists and has been demonstrated to increase thrombolysis use should help to mitigate this concern. Despite that being said, there remains a role for establishing clear contractual agreements between hub and spoke sites, be they supported by Federal Law or on an inter-state basis.

Summary

The advancement in the field of telestroke appears to come from the contribution of post-implementation telemedicine network studies rather than from the evidence of new randomized trials or health-care economic analyses. Moreover, the telestroke literature is rife with review articles. A possible explanation for nearly half of all manuscripts in the field being in the form of a review might be the perceived importance of promptly and broadly disseminating the data and opinions of leaders in the field. In light of the substantial up-front costs associated with implementation of a telestroke system [42, 43] it is reasonable that payers and administrators would require substantial evidence that might encourage them to make such an expenditure.

More than a decade since its published conceptualization, there is a strong and expanding literature base that supports the use of telestroke in mainstream clinical stroke practice. Telemedicine publications in acute stroke represent approximately 40 % of all published articles on telemedicine applied to the broad field of clinical neurological sciences and all of its related subspecialties [44]. The trajectory of telestroke research is mostly encouraging given the recent appearance of post-implementation studies, particularly in the prehospital EMS setting, which aim to further reduce time to stroke diagnosis and treatment. Further study is recommended to establish minimum technical standards for inhospital and prehospital telestroke use as well as to establish quality process and outcome metrics. The use of telestroke videoconferencing infrastructure for subacute stroke management, and education of trainees and the community at large about acute stroke evaluation and management also remains largely unstudied. Perhaps most importantly, there is a paucity of randomized trials and cost analyses, which might otherwise serve to solidify the practice. Overall, telemedicine is being implemented by stroke systems of care in rural and urban environments. Telestroke networks are flourishing. Uniform metrics for telestroke performance would be advantageous. In the interim, the existing clinical and economic results are favorable. It appears feasible for telemedicine to play a role in every phase of the stroke care continuum, from prehospital through to rehabilitation [45].

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