Updates in Hypertension and Cardiovascular Protection
Series Editors: Giuseppe Mancia · Enrico Agabiti Rosei

Antonio Coca
Editor

Hypertension and Brain Damage

ESH European Society of Hypertension

Springer

Updates in Hypertension and Cardiovascular Protection

The aim of this series is to provide informative updates on both the knowledge and the clinical management of a disease that, if uncontrolled, can very seriously damage the human body and is still among the leading causes of death worldwide. Although hypertension is associated mainly with cardiovascular, endocrine, and renal disorders, it is highly relevant to a wide range of medical specialties and fields – from family medicine to physiology, genetics, and pharmacology. The topics addressed by volumes in the series *Updates in Hypertension and Cardiovascular Protection* have been selected for their broad significance and will be of interest to all who are involved with this disease, whether residents, fellows, practitioners, or researchers.

More information about this series at http://www.springer.com/series/15049

Antonio Coca
Editor

Hypertension and Brain Damage

Springer

Editor
Antonio Coca
Hospital Clinic, University of Barcelona
Hypertension and Vascular Risk Unit
Barcelona, Spain

ISSN 2366-4606 ISSN 2366-4614 (electronic)
Updates in Hypertension and Cardiovascular Protection
ISBN 978-3-319-32072-4 ISBN 978-3-319-32074-8 (eBook)
DOI 10.1007/978-3-319-32074-8

Library of Congress Control Number: 2016940099

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Foreword

This book *Hypertension and Brain Damage* edited by Professor Antonio Coca from the University of Barcelona is the first of a series of books on hypertension and related sequelae which will be published over the next few years by Springer with the official endorsement and collaboration of the European Society of Hypertension.

Hypertension is a risk factor of major importance for a large number of cardiovascular diseases including stroke, myocardial infarction and heart failure. By favouring atherosclerosis, it promotes cognitive dysfunction and dementia, with also a top responsibility for the progression of renal damage into end stage renal disease, dialysis and renal transplantation. It affects so many people (particularly in the adulthood and elderly age) as to be by far the most common primary or contributing cause of death and illness worldwide, directly or indirectly accounting for a substantial fraction of the healthcare costs. This represents a valid reason for improving and disseminating in-depth information on hypertension. We believe that, as hypertension interacts with many other diseases and participates in the derangement of most mechanisms involved in cardiovascular regulation, these goals may benefit from the publication of volumes in which the multifold aspects of this condition are reviewed and discussed in detail. This usefully complements the contribution of textbooks where space constraints require to simultaneously provide comprehensive and analytic information, a balance not easy to achieve. We further believe that this approach, allowing to involve a relatively large number of experts for any specific area, may also suitably deal with the continuing flow of new data on the aetiological, pathophysiological, epidemiological, diagnostic and treatment aspects of hypertension that is offered by a persistently lively research, favouring their correct interpretation, translation and positioning in clinical practice.

On behalf of the European Society of Hypertension, we thank Springer for sharing with us the conviction that improving information and education on hypertension is important. Our thanks go also to Professor Antonio Coca for agreeing to start the book series with a topic of major current interest and future research

perspectives that appropriately exemplifies the importance of hypertension for public health. Finally, we wish to thank in advance the readers of this first as well as of the subsequent books of the series for their interest in this initiative. We hope that they will find this European Society of Hypertension/Springer cooperation culturally rewarding and for doctors also useful for their practice.

Milano, Italy — Giuseppe Mancia
Brescia, Italy — Enrico Agabiti-Rosei

Preface

Cardiovascular diseases, understood as those which affect cerebral, coronary, renal and large elastic arteries, and their direct and indirect consequences, are, today, the most-common reason for medical consultation, the first cause of death, and a leading cause of permanent or temporary work disability. The long-term effect of excessive blood pressure levels on the walls of the cerebral arteries results in ischaemic or haemorrhagic brain lesions that have devastating consequences on the neurons, especially due to the lack of neuronal regeneration.

Elevated blood pressure results in changes in the structure and function of the small-sized deep penetrating arteries in the white matter and middle-sized cerebral arteries. These silent lesions progress over time and, in the middle- and long-term, cause cerebrovascular complications that may be catastrophic for patients and their families: ischaemic and haemorrhagic stroke. In addition, silent cerebral lesions are also related with cognitive decline and progression to dementia in hypertensive patients. In some European countries, stroke is now the first cause of death, especially in women. The progressive aging of the European population, together with the increased incidence of vascular dementia and Alzheimer disease, is likely to provoke a social health problem of incalculable consequences in the very near future.

Hypertension is the leading cardiovascular risk factor associated with stroke and dementia; therefore, the introduction of interventional strategies that increase blood pressure control plays a key role in preventing these complications. The Working Group on Hypertension and the Brain of the European Society of Hypertension was created to improve knowledge of the physiopathology of these associations, and to make professionals involved in the management of hypertensive patients, who are aware of the excellent perspectives of preventing their complications. The publication of the first edition of *Hypertension and Brain Damage* is the result of the efforts of this Working Group, whose enthusiasm, dedication and participation made it possible. The book's 15 chapters provide information on the epidemiology, pathophysiology, associated risk factors, diagnostic imaging, clinical signs and symptoms of the conditions, the presentation forms of ischaemic and haemorrhagic complications, types of progressive cognitive decline, their detection and the possibilities of prevention and treatment. Despite the complexity of the subject, the authors of each chapter have tackled all the aspects mentioned above in-depth, with skill and professional rigour combined with practical explanations addressed to the

physicians who detect the risks and take care of these patients. This has resulted in an easy-to-read and, at the same time, enriching book that achieves its objective: putting within the reach of medical professionals current advances that, together with common sense and personal experience, may help improve the life expectancy and quality of life of our patients.

Barcelona, Spain Antonio Coca
June 2016

Acknowledgement

The European Society of Hypertension wishes to acknowledge that this book originated in an idea from the “Working Group Hypertension and the Brain” and would not have been possible without the valued contributions of its members.

Contents

1 Epidemiology of Hypertension and Brain Disease 1
Renata Cifkova and Peter Wohlfahrt

2 Comorbidities Often Associated with Brain Damage in Hypertension: Dyslipidaemia 13
Dragan Lovic, Manolis S. Kallistratos, and Athanasios J. Manolis

3 Comorbidities Often Associated with Brain Damage in Hypertension: Salt and Alcohol Intake and Smoking Habits 21
Ana Vrdoljak, Bojan Jelaković, and Dragan Lović

4 Comorbidities Often Associated with Brain Damage in Hypertension: Diabetes, Coronary Artery Disease, Chronic Kidney Disease and Obstructive Sleep Apnoea 35
Athanasios J. Manolis, Manolis S. Kallistratos, Demetrios V. Vlahakos, Asimina Mitrakou, and Leonidas E. Poulimenos

5 Pathophysiology of Brain Damage in Hypertension: Small Vessel Disease 47
Enrico Agabiti-Rosei, Damiano Rizzoni, and Pedro Cunha

6 Pathophysiology of Subclinical Brain Damage in Hypertension: Large Artery Disease 61
Stéphane Laurent, Dariusz Gasecki, Pierre Boutouyrie, and Krzysztof Narkiewicz

7 Hypertension and Ischaemic Stroke Subtypes 75
Dagmara Hering and Maciej Piskunowicz

8 Hypertension and Haemorrhagic Stroke 91
Dagmara Hering and Maciej Piskunowicz

9 Imaging Techniques for the Detection and Diagnosis of Brain Damage in Hypertension 99
Dariusz Gasecki, Edyta Szurowska, and Krzysztof Jodzio

10 Primary Stroke Prevention 129
Augusto Zaninelli, Paola Santalucia, and Simona Sacco

11 Management of High Blood Pressure in Acute Ischaemic Stroke 143
Dariusz Gasecki, Bartosz Karaszewski, and Krzysztof Narkiewicz

12 Management of High Blood Pressure in Intracerebral Haemorrhage 159
Dariusz Gasecki, Bartosz Karaszewski, and Krzysztof Narkiewicz

13 Secondary Stroke Prevention 173
Mónica Doménech, Miguel Camafort, and Antonio Coca

14 Hypertension and Subjective Cognitive Failures 183
Eila Monteagudo, Cristina Sierra, and Antonio Coca

15 Hypertension, Cognitive Decline, and Dementia 197
Cristina Sierra, Augusto Vicario, and Ona Escoda

Epidemiology of Hypertension and Brain Disease

1

Renata Cifkova and Peter Wohlfahrt

1.1 Epidemiology of Hypertension

Hypertension is the most prevalent cardiovascular disorder, affecting 20–50 % of the adult population in developed countries [1]. Systolic blood pressure (BP) increases throughout adulthood in most populations, whereas diastolic BP peaks at about 60 years of age in men and 70 years in women and falls gradually thereafter. The increase in BP with age is greater in systolic BP. Aging also results in a progressive increase in pulse pressure (difference between systolic and diastolic BP). In young and middle-aged adults, systolic and diastolic BP are higher in men than in women. However, the BP increase in adulthood is steeper in women than in men (0.6–1.2 mmHg/year in women and 0.4–0.8 mmHg/year in men from 30 years of age to the midpoint of the 70–79 years age group) [2]. Consequently, the systolic BP of women aged > 70 years is equal to or higher than that of men. Therefore, the prevalence of hypertension in the elderly is higher in women.

R. Cifkova (✉)
First Faculty of Medicine and Thomayer Hospital, Center for Cardiovascular Prevention, Charles University in Prague, Prague, Czech Republic

Department of Medicine II, Charles University Medical School I, Prague, Czech Republic

International Clinical Research Center, Brno, Czech Republic
e-mail: renata.cifkova@ftn.cz

P. Wohlfahrt
First Faculty of Medicine and Thomayer Hospital, Center for Cardiovascular Prevention, Charles University in Prague, Prague, Czech Republic

International Clinical Research Center, Brno, Czech Republic

Center of Experimental Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_1

There are huge differences in the prevalence of hypertension worldwide [1]. However, an exact comparison of reported prevalence data is difficult as studies differ substantially in methodologies (number of BP readings taken during a visit, number of visits, BP measuring devices); sometimes data are only presented from limited and incomparable age groups and regions. Therefore, some authors feel it is more appropriate and informative to present data in terms of mean BP levels. An analysis of about 230 surveys including more than 660,000 participants found consistently high mean systolic BP in Eastern Europe and Africa, whereas the lowest mean systolic BP levels were reported from South East Asia and the Western Pacific [2]. Differences in mean BP levels have also been reported within the United States, with the highest in the South and lowest in the West. This is consistent with regional differences in stroke mortality [3].

The awareness and treatment of hypertension also vary considerably between countries and regions [1]. In developed countries, approximately 50–70 % of hypertensive individuals in the general population are aware of their disease, but only 30–60 % are receiving antihypertensive drugs. A recent publication using data from the National Health and Nutrition Examination Survey 2003–2012 found an improvement in the awareness and treatment of hypertension in both sexes, which were, however, generally better in women. Results from the latest survey (2011–2012) are impressive: awareness, 79.6 % in men and 84.8 % in women; treatment, 69.6 % in men, 79.8 % in women [4]. The awareness and treatment of hypertension is lower in developing countries.

Hypertension is inadequately controlled worldwide, and predominantly uncontrolled in developing countries [1]. Better control of hypertension has repeatedly been shown in North America compared with Europe [1, 5]. An update on the epidemiology of hypertension in Canada (based on data from surveys conducted in 2012–2013) documented control of hypertension in 68.1 % of individuals [6]. Stroke mortality may be considered a surveillance measure indicating hypertension control [7]. The fact that stroke mortality in the USA and Canada continues to be substantially lower than in Europe is consistent with this idea [5, 8, 9].

1.2 Blood Pressure as a Risk Factor for Stroke

Elevated BP has been identified as a risk factor for coronary heart disease (CHD), heart failure, stroke, peripheral arterial disease, renal failure, and atrial fibrillation in both sexes in a large number of epidemiological studies. A recent systematic analysis for the Global Burden of Disease Study ranked high BP first among risk factors for the disease burden worldwide [10].

Elevated BP is the strongest modifiable risk factor for stroke, both ischemic and hemorrhagic. Approximately 85 % of strokes are ischemic, and the remaining 15 % are due to hemorrhage (about half from intracerebral hemorrhage and half from subarachnoid hemorrhage).

About 54 % of strokes worldwide are attributed to high BP (systolic BP > 115 mmHg) [11]. Data from observational studies involving one million

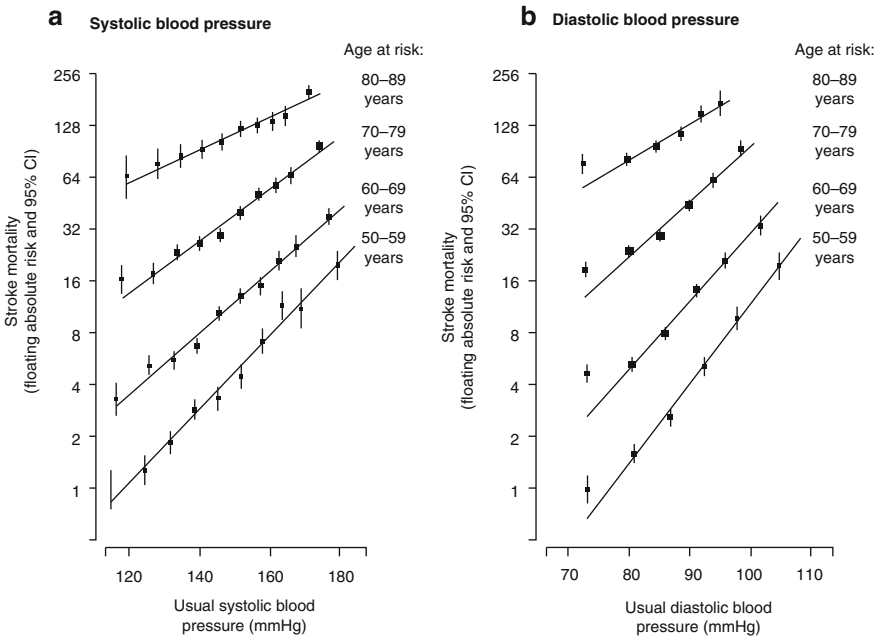

Fig. 1.1 Stroke mortality rates in decades of age plotted for the usual systolic (*left*) and diastolic (*right*) BP at the start of that decade. Data from 1,000,000 adults in 61 prospective studies (Adapted from Lewington et al. [12])

individuals have indicated that death from stroke increases progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic upward in an approximately log-linear relationship with BP (Fig. 1.1) [12]. Age attenuates this relationship and the stroke risk increases with every 10 mmHg of systolic BP by 40–50 %, 30–40 %, and 20–30 % for the < 60, 60–69, and ≥ 70 year age groups, respectively [13].

Lowering BP substantially reduces the stroke and coronary risks. A meta-analysis of randomized controlled trials comparing antihypertensive drugs with placebo showed a 30 % stroke risk reduction if BP was lowered. A meta-regression analysis suggests a risk reduction of 31 % for every 10 mmHg of systolic BP [13]. The benefit of BP reduction from clinical trials is therefore consistent with the data from observational cohort studies.

1.3 Epidemiology of Stroke

The prevalence of stroke in the general population increases with age and is particularly high for the > 80 years age group [8] (Fig. 1.2).

The incidence of stroke in the general population also increases with age. The 40-year follow-up data from the Framingham Study are shown in Table 1.1 [14].

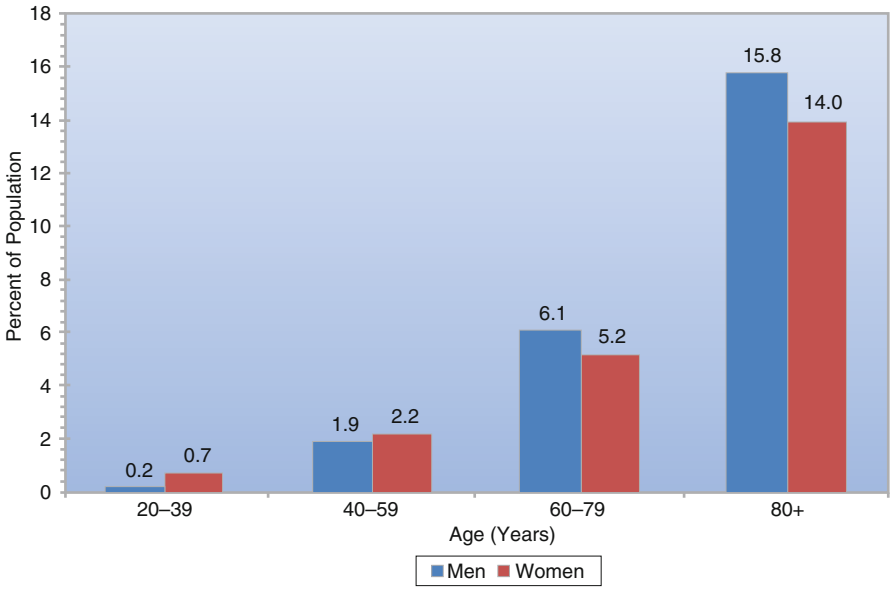

Fig. 1.2 Prevalence of stroke by age and sex. National Health and Nutrition Examination Survey 2009–2012 (Adapted from Mozaffarian et al. [8])

Table 1.1 Annual incidence of completed strokes in men and women aged 35–94 years

	Men		Women	
Age, years	*n*	Rate/1000	*n*	Rate/1000
35–44	3	0.40	4	0.44
45–54	26	1.79	18	0.99
55–64	64	3.50	62	2.60
65–74	122	8.43	129	6.12
75–84	90	16.17	137	13.46
85–94	7	…	56	24.34
Total	312	6.03[a]	406	4.53[a]

Adapted from Wolf [14]
Data are from the Framingham Study: 40-year follow-up
[a]Age adjusted, 45–84 years

The age-adjusted incidence of stroke/transient ischemic attack by race and sex in the Atherosclerosis Risk Community Study is presented in Fig. 1.3 [8].

The incidence of stroke is directly related to BP levels. The Framingham Heart Study found ischemic stroke was three times more frequent in persons with stage 2 or 3 hypertension (systolic BP ≥ 160 mmHg) and 50 % higher in stage 1 hypertension (systolic BP 140–159 mmHg) than in persons with high-normal BP and normotensives [15].

However, for a long time, diastolic BP was considered a better predictor of stroke and CHD than systolic BP. The majority of randomized controlled trials in

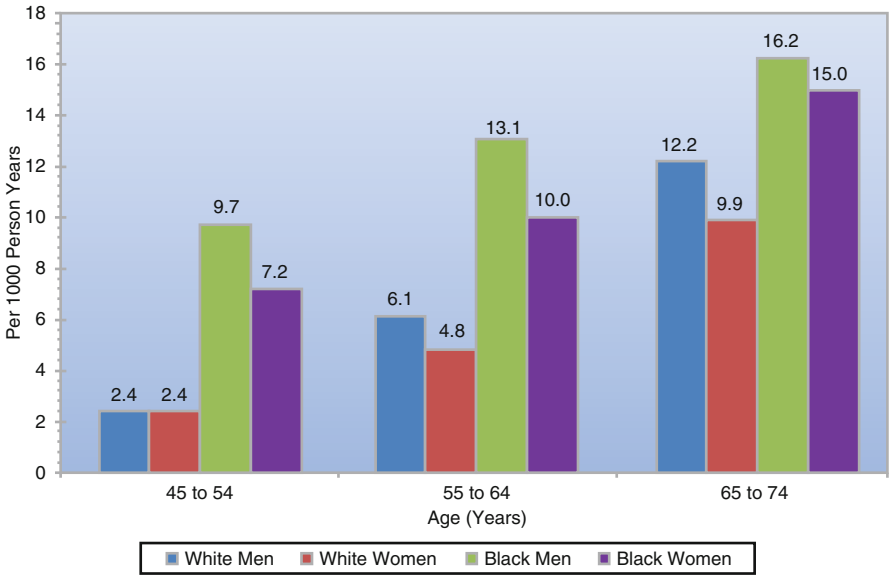

Fig. 1.3 Age-adjusted incidence of stroke/transient ischemic attack by race and sex, ages 45–74 years, Atherosclerosis Risk in Communities Study cohort, 1987–2001 (Adapted from Mozaffarian et al. [8])

hypertension used diastolic BP as an inclusion criterion until the 1990s. However, a large dataset from observational studies confirmed that both systolic and diastolic BP are associated with a continuous, graded, and independent relationship with increased stroke and CHD [12]. A 20-year follow-up of the National Health and Nutrition Examination Survey of 12,344 adults aged 25–74 years showed an increased risk of ischemic stroke and intracerebral hemorrhage in patients with borderline isolated systolic hypertension (systolic BP 140–159 mmHg and diastolic BP < 90 mmHg), similar to those with isolated systolic hypertension (systolic BP ≥ 160 mmHg and diastolic BP < 90 mmHg) and diastolic hypertension (diastolic BP ≥ 90 mmHg) (Table 1.2) [16].

Stroke is the second leading cause of death globally, with significant geographic differences. A comprehensive analysis of 119 studies (58 from high-income, and 61 from low- and middle-income countries) showed a decrease in age-standardized rates of stroke mortality worldwide in past decades; however, the age-standardized incidence of stroke decreased significantly (by 12 %) only in high-income countries [17]. Stroke is the second leading cause of death in Europe, accounting for 9 % of total mortality in men and 14 % in women [9]. Redon et al. [18] analyzed trends in stroke mortality from 1990 to 2006 in 39 countries from Europe and Central Asia. Stroke mortality decreased sharply only in countries with low adult and very low child and adult mortality. The American Heart Association/American Stroke Association concluded that the decline in stroke mortality in the USA represents a major improvement in the health of the population and has been seen for both sexes

Table 1.2 Age-adjusted and multivariate-adjusted relative risks of stroke, ischemic stroke, and intracerebral hemorrhage

Participants	Sample size	No. of strokes	Stroke rate per 100	Age-adjusted RR (95 % CI)	Multivariate-adjusted RR (95 % CI)
All strokes					
Normotension	6656	224	3.4	Reference	Reference
Diastolic hypertension	3954	397	10.0	2.2 (1.9–2.6)	1.9 (1.6–2.3)
ISH	493	86	17.4	2.8 (2.2–3.6)	2.7 (2.0–3.4)
BISH	1241	118	9.5	1.5 (1.2–1.9)	1.4 (1.1–1.8)
Ischemic stroke					
Normotension	6656	201	3.0	Reference	Reference
Diastolic hypertension	3954	354	9.0	2.2 (1.8–2.6)	1.9 (1.6–2.7)
ISH	493	82	16.6	2.9 (2.2–3.8)	2.7 (2.1–3.6)
BISH	1241	118	8.7	1.5 (1.2–1.9)	1.4 (1.1–1.8)
Intracerebral hemorrhage					
Normotension	6656	24	0.4	Reference	Reference
Diastolic hypertension	3954	49	1.2	2.8 (1.7–4.6)	2.4 (1.5–4.1)
ISH	493	9	1.8	3.2 (1.4–7.2)	3.1 (1.4–6.9)
BISH	1241	16	1.3	2.2 (1.2–4.3)	2.1 (1.1–4.1)

Adapted from Qureshi et al. [16]
Multivariate-adjusted for age, sex, race, body mass index, smoking, alcohol use, cholesterol level, education, history of myocardial infarction, and diabetes mellitus
RR indicates relative risk, *ISH* isolated systolic hypertension, *BISH* borderline isolated systolic hypertension

and all racial/ethnic and groups. The decrease in mortality is due to the reduced incidence of stroke and lower case fatality rates. This is concurrent with improved control of major cardiovascular risk factors and hypertension in particular [19].

1.4 Epidemiology of Dementia

The term dementia comprises various symptoms such as progressive memory loss and behavioral changes which, together, interfere with the independent performance of the tasks of daily living. Dementia is one of the major causes of loss of autonomy, the main reason for institutionalization in the elderly, and the sixth leading cause of death and disability in higher-income countries. The prevalence of dementia shows a strong increase with age from 5 % at the age of 65 years to 20 % at 80 years and 40 % at 90 years. Currently, an estimated 53 million people worldwide are living with dementia [20]. In the last 20 years, there has been no change in age-standardized rates of dementia, while the years lived with dementia increased by 92 % and the prevalence increased by 89 % due to aging of the population. The prevalence of dementia is expected to triple by 2050. The vast majority of new cases are expected in developing countries. For example, the number of persons with dementia in China and India will increase by 300 %, while a 100 % increase is expected in developed countries [21]. As there is

currently no effective treatment, studying and influencing the modifiable risk factors of dementia is a major health challenge in the forthcoming years.

Alzheimer disease (AD) is the main form of dementia, accounting for approximately 70 % of cases, followed by vascular dementia (VaD) (15 %). VaD has traditionally been distinguished from AD, which was considered a purely neurodegenerative form of dementia. However, several population-based cohort studies have shown that vascular risk factors are associated with the risk of both VaD and AD [22, 23]. This has led to the hypothesis that the vast majority of cases of dementia are a mix of vascular injury and neurodegenerative lesions [24]. Hypertension is one of the strongest vascular risk factors for dementia. Nonetheless, the association between hypertension and cognitive decline and dementia is complex and seems to vary with age [25].

1.4.1 Midlife Versus Late-Life Hypertension and Dementia

The strongest evidence for the association between hypertension and dementia comes from long-term follow-up observational studies with midlife measures of BP and late-life measures of cognitive performance. In a Swedish study [26], subjects who developed dementia during a follow-up of 10–15 years had higher baseline systolic and diastolic BP compared with those without later dementia. An increased risk of dementia in subjects with increased BP at baseline was also found in the Honolulu-Asia Aging Study [22] and a Finnish Study [23]. In the Kaiser Permanente study of 8,845 participants, hypertension at midlife increased the risk of dementia by 24 % (95 % confidence intervals 4–48 %) [27].

In contrast, the association between late-life measures of BP and cognition is less consistent. In the Kungsholmen project [28], increased pulse pressure increased the risk of dementia, while in the Bronx Aging Study [29] low diastolic BP was associated with a higher risk of dementia in individuals aged > 75 years. This suggests an important role of arterial stiffness and pressure pulsatility in the elderly. Other studies have shown that a decline in BP in late life is associated with poor cognition and incident dementia. The no association or inverse association between BP observed in elderly subjects or patients with manifest dementia may be explained by the observation that BP declines in the years before dementia onset, which means that BP in patients with dementia is similar to or even lower than that of individuals without dementia [26].

The age-specific association between BP and cognitive function may have several possible explanations. First, exposure to hypertension in midlife probably better reflects the total exposure to elevated BP throughout life. Second, the assessment of BP in late life may be modified by survival bias because of premature death due to hypertension-related cardiovascular diseases. Furthermore, the impact of vascular risk factors may be confounded by concomitant chronic diseases and age-related neurodegenerative diseases.

In conclusion, the link between BP and cognitive function is complex. Hypertension predisposes to cognitive decline and dementia, although BP commonly decreases when dementia develops.

1.5 Antihypertensive Therapy and Dementia

Several nonrandomized longitudinal studies have evaluated the link between antihypertensive treatment and dementia [30]. While some found no significant effect of antihypertensive therapy on the risk of dementia [31–33], most studies showed a significant benefit of antihypertensive treatment in VaD and AD. A risk reduction of 30–65 % was described in the Kungsholmen Project [34], Cache Country Study [35], the HAAS [36], and US Veterans Affairs Health System studies [37]. Interestingly, a dementia risk reduction of 19 % using antihypertensive therapy was also demonstrated in subjects without hypertension [38]. In a recent study, diuretics, angiotensin-converting enzymes (ACEis), angiotensin receptor blockers (ARBs), and beta-blockers (BBs) reduced the risk of AD in participants with normal cognition at baseline, while only diuretics decreased the risk of AD in subjects with mild cognitive impairment [39].

The results of the few randomized controlled trials have been inconsistent. In the SYST-EU (Systolic Hypertension in Europe) study, a dihydropyridine calcium channel blocker (possibly combined with an ACEi or a diuretic) decreased the risk of dementia by 50 % [40]. The extension of this trial (SYST-EUR 2) found that long-term antihypertensive therapy reduces the risk of dementia by 55 % [41]. In the PROGRESS study [42], ACEi therapy did not decrease the risk of dementia among patients without a history of stroke, while there was a trend toward a greater risk reduction in subjects treated with combination therapy (perindopril + indapamide). No benefit of antihypertensive therapy was shown in the SHEP (Systolic Hypertension in the Elderly Program) [43], SCOPE [44], or HYVET-COG [45] studies. The discrepancies between studies may be explained by the heterogeneity of the populations studied (middle-age vs. elderly), the short follow-up, small differences in BP between active and control groups and the low sensitivity of the cognitive tests used.

A network meta-analysis of published studies has shown that in hypertensive patients without prior cerebrovascular disorders, antihypertensive therapy (regardless of drug class) has a positive effect on overall cognition and all cognitive functions except language [46]. Furthermore, antihypertensive treatment decreased the risk of dementia by 9 % when randomized trials and observational studies were combined, and ARBs were more effective than other drug classes. However, the effect on dementia was not significant when only randomized studies were analyzed.

1.6 Stroke-Related Dementia

Hypertension is the strongest risk factor for stroke. Furthermore, stroke is a risk factor for post-stroke dementia, while dementia predisposes to stroke. Dementia is more frequent in individuals with a history of stroke than in those without. Soon after the first stroke, 10 % of patients develop dementia, while the rates are about three times as high after recurrent stroke [47]. It is estimated that stroke increases the risk of dementia by 2–5 times, making stroke one of the strongest risk factors for

dementia. Many randomized studies have demonstrated that BP lowering reduces the risk of stroke and stroke recurrence [48]. However, the evidence that BP lowering decreases the risk of stroke-related cognitive decline and dementia is much weaker due to the limited number of studies with a relatively short follow-up. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) in patients with a history of stroke or transient ischemic attack, an ACEi with or without a diuretic decreased the risk of post-stroke dementia by one third and halved the risk of severe cognitive decline compared with placebo [42].

References

1. Kearney PM, Whelton M, Reynolds K, Whelton PK, He J (2004) Worldwide prevalence of hypertension: a systematic review. J Hypertens 22:11–19
2. Lawes CM, Vander Hoorn S, Law MR, Elliott P, MacMahon S, Rodgers A (2006) Blood pressure and the global burden of disease 2000. Part 1: estimates of blood pressure levels. J Hypertens 24:413–422
3. Obisesan TO, Vargas CM, Gillum RF (2000) Geographic variation in stroke risk in the United States. Region, urbanization, and hypertension in the Third National Health and Nutrition Examination Survey. Stroke 31:19–25
4. Yoon SS, Gu Q, Nwankwo T, Wright JD, Hong Y, Burt V (2015) Trends in blood pressure among adults with hypertension: United States, 2003 to 2012. Hypertension 65:54–61. doi:10.1161/HYPERTENSIONAHA.114.04012, Epub 2014 Nov 16
5. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodríguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F (2003) Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 289:2363–2369
6. Padwal RS, Bienek A, McAlister FA, Campbell NR; Outcomes Research Task Force of the Canadian Hypertension Education Program (2015) Epidemiology of hypertension in Canada: an update. Can J Cardiol pii: S0828-282X(15)01306-9. doi:10.1016/j.cjca.2015.07.734. [Epub ahead of print]
7. Cooper RS (2007) Using public health indicators to measure the success of hypertension control. Hypertension 49:773–774
8. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB (2016) Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 133:e38–e360. doi:10.1161.pii: CIR.0000000000000350. [Epub ahead of print] No abstract available
9. Townsend N, Nichols M, Scarborough P, Rayner M (2015) Cardiovascular disease in Europe – epidemiological update 2015. Eur Heart J 36:2696–2705. doi:10.1093/eurheartj/ehv428
10. GBD 2013 Risk Factors Collaborators (2015) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386(10010):2287–2323
11. Lawes CM, Vander Hoorn S, Rodgers A, International Society of Hypertension (2008) Global burden of blood-pressure-related disease, 2001. Lancet 371:1513–1518
12. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360:1903–1913

13. Lawes CM, Bennett DA, Feigin VL, Rodgers A (2004) Blood pressure and stroke: an overview of published reviews. Stroke 35:1024
14. Wolf PA (1999) Cerebrovascular risk. In: Izzo JL Jr, Black HR (senior ed) Hypertension primer, 2nd edn. Lippincott, Williams & Wilkins, Baltimore, pp 203–207
15. Wolf PA, D'Agostino RB, O'Neal MA, Sytkowski P, Kase CS, Belanger AJ, Kannel WB (1992) Secular trends in stroke incidence and mortality. The Framingham Study. Stroke 23(11):1551–1555
16. Qureshi AI, Suri MF, Mohammad Y, Guterman LR, Hopkins LN (2002) Isolated and borderline isolated systolic hypertension relative to long-term risk and type of stroke: a 20-year follow-up of the national health and nutrition survey. Stroke 12:2781–2788
17. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C, Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group (2014) Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet 383(9913):245–254
18. Redon J, Olsen MH, Cooper RS, Zurriaga O, Martinez-Beneito MA, Laurent S, Cifkova R, Coca A, Mancia G (2011) Stroke mortality and trends from 1990 to 2006 in 39 countries from Europe and Central Asia: implications for control of high blood pressure. Eur Heart J 32:1424–1431. doi:10.1093/eurheartj/ehr045, Epub 2011 Apr 12
19. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, Schwamm LH, Smith EE, Towfighi A, American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; Council on Functional Genomics and Translational Biology (2014) Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke 45:315–353. doi:10.1161/01.str.0000437068.30550.cf, Epub 2013 Dec 5
20. Global Burden of Disease Study 2013 Collaborators (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England) 386:743–800
21. Ferri CP, Prince M, Brayne C et al (2005) Global prevalence of dementia: a Delphi consensus study. Lancet (London, England) 366:2112–2117
22. Launer LJ, Ross GW, Petrovitch H et al (2000) Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 21:49–55
23. Kivipelto M, Helkala EL, Laakso MP et al (2002) Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med 137:149–155
24. Viswanathan A, Rocca WA, Tzourio C (2009) Vascular risk factors and dementia: how to move forward? Neurology 72:368–374
25. Qiu C, Winblad B, Fratiglioni L (2005) The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 4:487–499
26. Skoog I, Lernfelt B, Landahl S et al (1996) 15-year longitudinal study of blood pressure and dementia. Lancet (London, England) 347:1141–1145
27. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K (2005) Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 64:277–281
28. Qiu C, Winblad B, Viitanen M, Fratiglioni L (2003) Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. Stroke J Cerebral Circ 34:594–599
29. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ (2003) Low blood pressure and the risk of dementia in very old individuals. Neurology 61:1667–1672
30. Rouch L, Cestac P, Hanon O et al (2015) Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. CNS Drugs 29:113–130

31. Yasar S, Corrada M, Brookmeyer R, Kawas C (2005) Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging. Neurobiol Aging 26:157–163
32. Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA (2001) Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol 58:1640–1646
33. Lindsay J, Laurin D, Verreault R et al (2002) Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 156:445–453
34. Qiu C, von Strauss E, Fastbom J, Winblad B, Fratiglioni L (2003) Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. Arch Neurol 60:223–228
35. Khachaturian AS, Zandi PP, Lyketsos CG et al (2006) Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. Arch Neurol 63:686–692
36. Peila R, White LR, Masaki K, Petrovitch H, Launer LJ (2006) Reducing the risk of dementia: efficacy of long-term treatment of hypertension. Stroke J Cerebral Circ 37:1165–1170
37. Li NC, Lee A, Whitmer RA et al (2010) Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ 340:b5465
38. Johnson ML, Parikh N, Kunik ME et al (2012) Antihypertensive drug use and the risk of dementia in patients with diabetes mellitus. Alzheimer's Dementia J Alzheimer's Assoc 8:437–444
39. Yasar S, Xia J, Yao W et al (2013) Antihypertensive drugs decrease risk of Alzheimer disease: Ginkgo Evaluation of Memory Study. Neurology 81:896–903
40. Forette F, Seux ML, Staessen JA et al (1998) Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet (London, England) 352:1347–1351
41. Forette F, Seux ML, Staessen JA et al (2002) The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 162:2046–2052
42. Tzourio C, Anderson C, Chapman N et al (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 163:1069–1075
43. Applegate WB, Pressel S, Wittes J et al (1994) Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med 154:2154–2160
44. Lithell H, Hansson L, Skoog I et al (2003) The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 21:875–886
45. Peters R, Beckett N, Forette F et al (2008) Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 7:683–689
46. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P (2013) Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens 31:1073–1082
47. Pendlebury ST, Rothwell PM (2009) Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 8:1006–1018
48. Law MR, Morris JK, Wald NJ (2009) Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 338:b1665. doi: 10.1136/bmj.b1665

Comorbidities Often Associated with Brain Damage in Hypertension: Dyslipidaemia

2

Dragan Lovic, Manolis S. Kallistratos, and Athanasios J. Manolis

2.1 Introduction

Lipid metabolism may be affected in several ways, leading to alteration of plasma lipoprotein function and/or levels. Dyslipidaemia is the overproduction of or deficiency in lipids and/or lipoproteins (in terms of levels and function) and is associated with a broad spectrum of disorders that both the cardiovascular (CV) system and the brain [1]. Brain function is directly and indirectly associated with lipoprotein levels and function. Lipoproteins are closely involved in the regulation of central nervous system function [2] and promote atherosclerosis, predisposing to premature cardiovascular diseases. Studies have shown that alterations in lipid metabolism may affect both brain perfusion and function, leading to the emergence of lesions that may increase morbidity and mortality. In this chapter, we focus on the effects of lipid metabolism alterations on brain function and status, emphasizing the effects of dyslipidaemias on the pathophysiology and perfusion of the brain.

2.2 Dyslipidaemia and Brain Function

The brain contains approximately 25–30 % of total human cholesterol, while 70 % of myelin is made of lipids [3]. Lipids are involved in the regulation of the central nervous system (CNS), neural plasticity and function. Experimental studies have shown that apolipoprotein (apo) E and the very low-density lipoprotein receptor (LDL receptor family members) adjust neuronal migration, which is important for

D. Lovic, FESC, FACP (✉)
Department of Cardiology, Intermedica Clinic for Internal Disease, Hypertension Center, Jovana Ristica 20/2, Nis 1800, Serbia
e-mail: draganl1@sbb.rs; lovicd@eunet.rs

M.S. Kallistratos • A.J. Manolis
Cardiology Department, Hypertension Centre, Asklepeion General Hospital, Athens, Greece

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_2

brain development, through the activation of tyrosine kinases and the transmission of extracellular signals [2]. Moreover, apo E is the most important transport protein for cholesterol in the brain. Hence, during the development of the CNS, cholesterol synthesis is increased (de novo synthesis from the brain) while it declines to very low levels in adults. The blood–brain barrier prevents cholesterol uptake from the circulation, and, in adults, cholesterol derives mainly from efficient recycling by the brain [3].

Alterations in plasma lipoprotein function and/or levels may significantly affect CNS homeostasis. HDL and apolipoprotein A-I (a major component of plasma HDL) exert a significant anti-inflammatory and antioxidant effect on endothelial cells and also affect the integrity of the blood–brain barrier [4–6]. Dyslipidaemia can potentiate pro-inflammatory and thrombogenic processes through the adhesion of molecules and recruitment of leukocytes while also inducing endothelial dysfunction [4–6]. Moreover, dyslipidaemia attenuates vascular endothelial growth factor-induced angiogenesis and impairs cerebral blood flow by decreasing the pericyte coverage of endothelial brain cells. Also compromising vessel formation and haemodynamics, dyslipidaemia also affects brain perfusion, leading to further cellular and functional deterioration [7]. Studies have linked dyslipidaemia with the presence or progress of multiple sclerosis and Alzheimer disease [8, 9].

In a retrospective longitudinal study in 492 patients with multiple sclerosis [8], patients with increased cholesterol levels presented more contrast-enhancing lesions on brain MRI. Higher HDL levels were associated with lower levels of acute inflammatory activity and lower contrast-enhancing lesion volume, while higher LDL levels were associated with a worse expanded disability status score. In addition, experimental studies in rabbits have shown that increased cholesterol levels enhance the accumulation of amyloid beta peptide in the brain, thus increasing the incidence of Alzheimer disease [10]. The mechanism responsible was an increase in the β-secretase pathway observed in patients with hypercholesterolaemia, which leads to an accumulation of Aβ 1–40 and Aβ 1–42 peptides, which increase the formation of extracellular amyloid deposits [11, 12].

Dyslipidaemia also significantly influences blood–brain barrier integrity, mainly by decreasing pericyte coverage [13] and abolishing vascular endothelial growth factor (VEGF) which is important for the preservation of the blood–brain barrier [7]. The decrease in pericyte coverage of endothelial cells observed in patients with dyslipidaemia significantly influences blood–brain barrier integrity, since pericytes also control vascular reactivity [13].

2.3 Dyslipidaemia, Atherosclerosis and Thrombosis

Lipids are closely involved in the development and progression of atherosclerosis. The process begins with the subendothelial accumulation of lipoproteins, starting a vicious cycle of lipoprotein oxidation that leads to endothelial dysfunction, activation of the inflammatory response with T cell recruitment, the secretion of cytokines and accumulation of monocytes and macrophages.

Circulating plasma lipoproteins, containing both 'free' cholesterol (nonesterified cholesterol) and cholesteryl ester, enter the subendothelial space, mainly through gaps between endothelial cells. Normally, lipoproteins are not retained in this space but re-enter the circulation. However, in patients with increased levels of lipoproteins, lipoprotein retention begins (promoted by the high concentration of lipoproteins) leading to their accumulation [14]. LDLs (low-density lipoproteins) and VLDL (very low-density lipoproteins) are the two classes of lipoproteins that mainly contribute to atherogenesis. Oxidative products secreted from the endothelium initiate lipid (especially LDL) peroxidation, while the modified/oxidized LDL is internalized from macrophages that accumulate lipoprotein-derived cholesterol in the form of intracellular cholesteryl ester droplets (foam cell formation) [15]. Macrophages are derived mainly from circulating monocytes, and the formation of foam cells marks the creation of fatty streaks, which, although not occlusive, may progress to more complex lesions over time. After the formation of fatty streaks, smooth muscle cells migrate from the media to the intima and also secrete collagen and matrix proteins [15]. Smooth cells may also accumulate lipids, becoming foam cells. At the same time, the macrophages continue to accumulate lipids, with the formation of foam cells leading to the formation of fibrous lesions. As this process continues, there is further accumulation and fusion of lipoproteins. Foam cells due to excess free cholesterol (some in crystalline form) undergo necrotic apoptosis and die, releasing lipid droplets and contributing to the formation of the lipid, or necrotic, core (atheroma) [15]. This complex lesion also involves haemorrhage, microthrombi and calcification.

Tissue factor (a potent anticoagulant) is only expressed in the adventitia, while the endothelium has anticoagulant properties. Dyslipidaemia leads to significant endothelial dysfunction (as mentioned above), while oxidized LDLs induce monocytes and endothelial cells to express high levels of tissue factor [16, 17]. Moreover, oxidized LDL increases plasminogen activator inhibitor levels [18] further increasing the prothrombotic state. Thus, rupture of the plaque exposes high levels of tissue factor, leading to thrombosis. Moreover, oxidized LDL inhibits the expression of nitric oxide synthase and subsequent vasodilation, further contributing to vessel occlusion [19].

2.4 Dyslipidaemia and Stroke

As mentioned above, dyslipidaemia not only affects brain function but also enhances the development and progression of atherosclerosis while increasing the prothrombotic state, leading to vessel occlusion and ischaemia, and predisposing to atherothrombotic and cardioembolic strokes.

After the formation of atheroma, morbidity and mortality are high due to disruptions of the surface of the lesion and subsequent haematoma/haemorrhage and thrombotic deposits, leading to vessel stenosis or occlusion. To detect atheromatous plaques at high risk of rupture/erosion leading to an acute event, the term vulnerable plaque has been introduced. The presence of thrombus, a large necrotic core, a fibrous cap covering the necrotic core, high macrophage density, few smooth muscle cells, expansive remodelling preserving the lumen, neovascularization from the

vasa vasorum, plaque haemorrhage, adventitial/perivascular inflammation and spotty calcification characterize a plaque at high risk of rupture or erosion [20].

The association between dyslipidaemia and stroke is well established, and the fact that the treatment of dyslipidaemia leads to a reduction in stroke morbidity and mortality means dyslipidaemia is one of the major modifiable risk factors. Since the treatment targets for dyslipidaemia are based on the results of clinical trials and the majority of lipid-lowering trials have used LDL-C levels as an indicator, LDL-C levels are the primary target in most dyslipidaemia management guidelines [1, 21]. It is estimated that, for every 1.0 mmol reduction in LDL-C, there is a 22 % reduction in cardiovascular morbidity and mortality [22]. Other lipoproteins have been shown to be useful in the risk assessment of the patients, including apo B, HDL-C and triglycerides, while reductions in these lipoproteins or increases in HDL-C result in improvements in CVD morbidity and mortality [1].

Although the development and progression of atheromatous plaque is probably the most recognized stroke mechanism, dyslipidaemia can induce or aggravate stroke by other mechanisms. Dyslipidaemia can disrupt cerebrovascular reflexes and worsen ischaemic perfusion defects. Impacting negatively on endothelial function, dyslipidaemia also affects complex cerebrovascular responses in the case of stroke altering cerebral blood flow while compromising the function of collateral vessels which play a critical role in sustaining tissue perfusion and survival [23]. Compromising cerebral blood flow homeostasis leading to brain hypoperfusion not only aggravates ischaemic lesions after stroke but also enhances hypoperfusion in the case of other conditions such as hypotension, leading to further ischaemic aggravation [23]. These effects of dyslipidaemia have been observed in experimental models and in vessels without atherosclerotic stenosis, signifying that, in general, the brain is exposed to hypoperfusion induced by dyslipidaemia and is more vulnerable in the case of stroke. Thus, supply or demand mismatch during functional metabolic activation can lead to chronic hypoxic ischaemia. Moreover, as mentioned above, dyslipidaemia affects blood–brain barrier permeability, which can aggravate brain oedema after stroke [24].

2.5 Reducing Cholesterol Levels and Stroke Prevention

Dyslipidaemia is a major modifiable risk factor, and therefore reducing cholesterol levels improves the prognosis in these patients. Since most cholesterol in plasma is carried in LDLs, most studies have assessed the effect of LDL lowering in primary and secondary prevention.

2.5.1 Statin Treatment and the Incidence of Stroke in Primary Prevention

Several major clinical trials have reported a significant reduction in the incidence of ischaemic stroke or transient ischaemic attacks (TIA) after statin treatment in patients at high CV risk. A meta-analysis of 7961 patients with coronary heart disease (CHD)

found that statin use was associated with a 29 % reduction in stroke incidence [25]. Data from the Cardiovascular Health Study show that patients treated with statins had a fourfold lower risk of silent cerebral infarcts compared with non-users [26]. Likewise, in the CARE (Cholesterol and Recurrent Events) study [27] and the LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) trial [28], the use of statins in patients with CHD was associated with a stroke risk reduction of 32 % and 26 %, respectively. Overall, with respect to primary stroke prevention, most trials have shown that statin treatment mainly influences the incidence of ischaemic stroke and does not affect the incidence of haemorrhagic stroke.

2.5.2 Statin Treatment in Stroke Patients and Secondary Prevention

In addition to the primary prevention of stroke, the use of statins is also beneficial in secondary prevention. In high CV risk patients, the use of statins before ischaemic stroke was associated with better post-stroke outcomes and prognosis. In a retrospective study that analysed records from 12,689 patients admitted with ischaemic stroke, the use of statins before hospitalization for ischaemic stroke was associated with improved post-stroke survival (hazard ratio, 0.85; 95 % CI, 0.79–0.93; $p = 0.001$) [29]. Patients with a higher statin dose had the most benefit. Early statin administration was associated with a further improvement in survival ($p < 0.001$). Likewise in a meta-analysis of 113,148 subjects hospitalized for ischaemic stroke, the use of statins before hospitalization was associated with a good functional outcome at 90 days (pooled odds ratio [OR], 1.41; 95 % CI, 1.29–1.56; $p < 0.001$) and with reduced fatality at 90 days (pooled OR, 0.71; 95 % CI, 0.62–0.82; $p < 0.001$) and 1 year (OR, 0.80; 95 % CI, 0.67–0.95; $p = 0.01$) [30].

In addition to retrospective studies and meta-analyses, several randomized studies have shown the efficacy of statin therapy in the secondary prevention of stroke. In the SPARCL trial of 4278 patients with TIA or stroke within 1–6 months (without known CHD and low-density lipoprotein cholesterol 100–190 mg/dL), patients were randomized to treatment with atorvastatin 80 mg per day or placebo [31]. Intensive lipid lowering with atorvastatin reduced the risk of cerebro- and cardiovascular events by 33 % (hazard ratio [HR] 0.67, 95 % CI 0.47, 0.94; $p = 0.02$) in patients with and without carotid stenosis. In patients with acute stroke, the early administration of statins improves outcomes. In the North Dublin Population Stroke Study [32], statins were prescribed and administered acutely (<72 h from the event) in 42.5 % of patients. New post-stroke statin therapy was independently associated with improved early and late survival (compared with statin-untreated patients: OR for death, 0.12; CI, 0.03–0.54 at 7 days; OR, 0.19; CI, 0.07–0.48 at 90 days; OR, 0.26; CI, 0.12–0.55 at 1 year; $p = 0.006$ for all). It seems that acute statin administration (at least in the first 3–7 days after stroke) markedly improves outcomes in those patients. The reason for this improvement lies in the pleiotropic effects of statins. Statin administration reduces inflammation and improves endothelial and laminar flow and collateral blood flow [1, 21, 22]. In addition, statins enhance endogenous

tissue-type plasminogen activator (exerting a significant antithrombotic effect) while they improve the lipid profile, which is closely related to the development and progression of atherosclerosis.

2.6 Summary and Conclusions

Lipoproteins are closely involved in the regulation of central nervous system function and also promote the development and progression of premature cardiovascular diseases, due not only to the development and progression of atheroma plaque but also to their influence on brain homeostasis. Treatment with statins and cholesterol reduction is the cornerstone of treatment in these patients, as it improves cardiovascular morbidity and mortality.

References

1. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008–2010 and 2010–2012 Committees (2011) ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 32(14):1769–1818
2. Gotthardt M, Trommsdorff M, Nevitt MF, Shelton J, Richardson JA, Stockinger W, Nimpf J, Herz J (2000) Interactions of the low density lipoprotein receptor gene family with cytosolic adaptor and scaffold proteins suggest diverse biological functions in cellular communication and signal transduction. J Biol Chem 275:25616–25624
3. Björkhem I, Meaney S (2004) Brain cholesterol: long secret life behind a barrier. Arterioscler Thromb Vasc Biol 24(5):806–815
4. Burger D, Dayer JM (2002) High-density lipoprotein-associated apolipoprotein A-I: the missing link between infection and chronic inflammation? Autoimmun Rev 1:111–117
5. Ferretti G, Bacchetti T, Principi F, Di Ludovico F, Viti B, Angeleri VA, Danni M, Provinciali L (2005) Increased levels of lipid hydroperoxides in plasma of patients with multiple sclerosis: a relationship with paraoxonase activity. Mult Scler 11:677–682
6. Jamroz-Wisniewska A, Beltowski J, Stelmasiak Z, Bartosik-Psujek H (2009) Paraoxonase 1 activity in different types of multiple sclerosis. Mult Scler 15:399–402
7. Zechariah A, ElAli A, Hagemann N, Jin F, Doeppner TR, Helfrich I, Mies G, Hermann DM (2013) Hyperlipidemia attenuates vascular endothelial growth factor-induced angiogenesis, impairs cerebral blood flow, and disturbs stroke recovery via decreased pericyte coverage of brain endothelial cells. Arterioscler Thromb Vasc Biol 33(7):1561–1567
8. Weinstock-Guttman B, Zivadinov R, Mahfooz N, Carl E, Drake A, Schneider J, Teter B, Hussein S, Mehta B, Weiskopf M, Durfee J, Bergsland N, Ramanathan M (2011) Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis. J Neuroinflammation 8:127
9. Fernández JA, Rojo L, Kuljis RO, Maccioni RB (2008) The damage signals hypothesis of Alzheimer's disease pathogenesis. J Alzheimers Dis 14(3):329–333
10. Sparks DL, Scheff SW, Hunsaker JC 3rd, Liu H, Landers T, Gross DR (1994) Induction of Alzheimer-like beta-amyloid immunoreactivity in the brains of rabbits with dietary cholesterol. Exp Neurol 126:88–94

11. Bodovitz S, Klein WL (1996) Cholesterol modulates alpha-secretase cleavage of amyloid precursor protein. J Biol Chem 271:4436–4440
12. Frears ER, Stephens DJ, Walters CE, Davies H, Austen BM (1999) The role of cholesterol in the biosynthesis of beta-amyloid. Neuroreport 10:1699–1705
13. Winkler EA, Bell RD, Zlokovic BV (2011) Central nervous system pericytes in health and disease. Nat Neurosci 14:1398–1405
14. Choy PC, Siow YL, Mymin D, O K (2004) Lipids and atherosclerosis. Biochem Cell Biol 82(1):212–224
15. Oorni K, Pentikainen MO, Ala-Korpela M, Kovanen ET (2000) Aggregation, fusion, and vesicle formation of modified low density lipoprotein particles: molecular mechanisms and effects on matrix interactions. J Lipid Res 41:1703–1714
16. Fei H, Berliner JA, Parhami F, Drake TA (1993) Regulation of endothelial tissue factor expression by minimally oxidized LDL and lipopolysaccharide. Arterioscler Thromb 13:1711–1717
17. Brand L, Banka CL, Madmann N, Terkeltaub RA, Fan ST, Curtiss LK (1994) Oxidized LDL enhances lipopolysaccharide-induced tissue factor expression in human adherent monocytes. Arterioscler Thromb 14:790–797
18. Latron Y, Chautan M, Anfosso F, Alessi MC, Nalbone G, Lafont H, Juhan-Vague I (1991) Stimulating effect of oxidized low density lipoproteins on plasminogen activator inhibitor-1 synthesis by endothelial cells. Arterioscler Thromb 11:1821–1829
19. Yang X, Cai B, Sciacca RR, Cannon PJ (1994) Inhibition of inducible nitric oxide synthase in macrophages by oxidized low-density lipoproteins. Circ Res 74:318–328
20. Bentzon JF, Otsuka F, Virmani R, Falk E (2014) Mechanisms of plaque formation and rupture. Circ Res 114(12):1852–1866
21. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (2014) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129(25 Suppl 2):S1–S45
22. Cholesterol Treatment Trialists' (CTT) Collaboration (2010) Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet 376:1670–1681
23. Ayata C, Shin HK, Dileköz E, Atochin DN, Kashiwagi S, Eikermann-Haerter K, Huang PL (2013) Hyperlipidemia disrupts cerebrovascular reflexes and worsens ischemic perfusion defect. J Cereb Blood Flow Metab 33(6):954–962
24. ElAli A, Doeppner TR, Zechariah A, Hermann DM (2011) Increased blood-brain barrier permeability and brain edema after focal cerebral ischemia induced by hyperlipidemia: role of lipid peroxidation and calpain-1/2, matrix metalloproteinase-2/9, and RhoA overactivation. Stroke 42(11):3238–3244
25. Hebert PR, Gaziano JM, Chan KS, Hennekens CH (1997) Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. JAMA 278(4):313–321
26. Bernick C, Katz R, Smith NI et al (2005) Statins and cognitive function in the elderly—the Cardiovascular Health Study. Neurology 65:1388–1394
27. Plehn JF, Davis BR, Sacks FM et al (1999) Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. The Care Investigators. Circulation 99(2):216–223
28. White HD, Simes RJ, Anderson NE et al (2000) Pravastatin therapy and the risk of stroke. N Engl J Med 343(5):317–326

29. Flint AC, Kamel H, Navi BB et al (2012) Statin use during ischemic stroke hospitalization is strongly associated with improved poststroke survival. Stroke 43(1):147–154
30. Ní Chróinín D, Asplund K, Åsberg S et al (2013) Statin therapy and outcome after ischemic stroke: systematic review and meta-analysis of observational studies and randomized trials. Stroke 44(2):448–456
31. Sillesen H, Amarenco P, Hennerici MG, et al. Stroke Prevention by Aggressive Reduction in Cholesterol Levels Investigators (2008) Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 39(12):3297–3302
32. Ní Chróinín D, Callaly EL, Duggan J et al (2011) Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: the North Dublin Population Stroke Study. Stroke 42(4):1021–1029

Comorbidities Often Associated with Brain Damage in Hypertension: Salt and Alcohol Intake and Smoking Habits

3

Ana Vrdoljak, Bojan Jelaković, and Dragan Lović

3.1 Introduction

Lifestyle modification is of particular interest for stroke prevention, as the incidence of stroke has decreased by up to 42 % in developed countries within the last 30 years compared with an increase of more than 100 % in developing countries, indicating the important role of lifestyle and diet, which are influenced not only by culture and tradition but also by education and the socioeconomic burden [1].

The association between alcohol consumption and stroke risk is J-shaped: slight-to-moderate alcohol intake (≤2 drinks per day for men and ≤1 drink per day for women, respectively) may reduce stroke risk by 30 %, while higher consumption significantly increases the risk of stroke [2].

Data from the United States suggests that smoking contributes to 12–14 % of all stroke deaths, and all risk assessment tools include smoking as a risk factor for stroke. A dose-response relationship has been observed [2]. The risk of stroke in passive smokers is almost double that found for active smoking, indicating that the smoking exposure threshold might be more important than the linear dose-effect relationship [2]. A former smoker has the same risk as a nonsmoker, showing that smoking cessation is effective in stroke prevention [3].

Hypertension is the most important modifiable risk factor for stroke, and excess salt intake plays a major role in the pathogenesis of elevated blood pressure (BP)

A. Vrdoljak • B. Jelaković, MD, PhD (✉)
Department of Nephrology, Hypertension, Dialysis and Transplantation, School of Medicine, Zagreb University Hospital Centre, University of Zagreb, Zagreb, Croatia
e-mail: vrdoljak.ana@gmail.com; jelakovicbojan@gmail.com

D. Lović
Department of Cardiology, Intermedica Clinic of Internal Disease, Hypertension Center, Nis, Serbia

VAMC, Washington, DC, USA
e-mail: draganl1@sbb.rs; lovicd@eunet.rs

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_3

[4]. There is ongoing debate about whether sodium intake has differing effects on cardiovascular (CV) outcomes and whether lowering salt intake is beneficial and for whom [5]. However, no study has reported an inverse association for stroke. A recent meta-analysis by Strazzulo et al. showed that higher salt intake was associated with greater risk of stroke and CV disease (CVD) [6]. It was estimated that a reduction in habitual dietary salt intake of 6 g a day would be associated with reductions in systolic/diastolic BP of 7/4 mmHg in people with hypertension and 4/2 mmHg in those without hypertension, predicting a mean reduction in the stroke rate of 24 % at the population level [7, 8].

About 38 % of stroke cases were estimated as preventable through adherence to a healthy lifestyle without gender differences and in different strata of hypertension status and antihypertensive drug treatments: therefore, primary stroke prevention is a priority [9, 10]. Evidence-based guidelines recommend that secondary prevention interventions should be initiated while the patient is in hospital and should be multimodal, including drugs in conjunction with the active provision of lifestyle information and education [11].

In addition to being effective, stroke prevention is approximately tenfold more cost-effective than treating acute stroke with tissue plasminogen activator (tPA) [12]. A major aim of health promotion and prevention is to maximize health during life rather than necessarily preventing the inevitable. In 1946, the new WHO constitution incorporated a definition of health proposed by the Croatian public health pioneer, Andrija Štampar, who said health was "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

Simple and cheap measures could prevent stroke and contribute to healthy aging. Here we offer some evidence about the importance of smoking cessation, salt intake reduction, and moderate alcohol consumption.

3.2 Alcohol and Brain Damage

Before any discussion about the relationship between alcohol and BP, CVD, or stroke, it is important to understand the nomenclature because various definitions and criteria have been used in different cultures, countries, and studies. Box 3.1 shows the definition of a standard drink, and Box 3.2 shows the type of drinking.

Box 3.1 What is a standard drink?

A standard drink is a notional drink that contains a specified amount of pure alcohol (ethanol). One standard drink always contains the same amount of alcohol regardless of the container size or type of alcohol beverage, but, nevertheless, the quantity of alcohol within a standard drink varies significantly from country to country and consequently within scientific reports and studies.

To overcome this problem, the term standard drink has been replaced by the term unit of alcohol. A unit of alcohol is defined as the quantity of pure alcohol per serving in grams. This measure also varies around the globe, but the mean alcohol per unit in Europe and the United States is 12 g [13]. Based on 12 g of pure alcohol per unit, one unit is 150 ml of wine, 350 ml of beer, and 44 ml of spirit [13].

Box 3.2 Type of drinking
A literature review shows that not only the amount of alcohol per unit and the quantity of beverage per unit vary from study to study but also that the definitions of the type of drinking pattern are not well standardized. Most commonly by US standards, moderate drinking means no more than one drink (assuming one alcohol unit) for women and no more than two drinks for men [14]. By analogy, heavy drinking is considered more than one drink for women and more than two drinks for men. In several references heavy drinking is the consumption of more than 60 g of alcohol in men and more than 40 g in women, while moderate drinking is 20–60 g per day in men and 10–40 g per day in women [15]. Binge drinking is defined as alcohol consumption that raises the blood alcohol level above 0.08 % on one occasion (typically during weekends) or more than five drinks on one occasion [16, 17]. Light drinking has no standard definition and presumably is less then moderate drinking.

3.2.1 Alcohol and Its Burden

Alcohol use contributes roughly 4 % of the global burden of disease, and its consumption is estimated to be the third most important modifiable risk factor for death and disability worldwide [13]. In 2010, the worldwide mean amount of pure alcohol consumed per person aged >15 years was 6.2 l/year or 13.5 g/day [14]. According to the literature, on average, we should all benefit from alcohol consumption. The relationship between alcohol use and health outcomes is complex and depends on the amount, type, and pattern of use. The Global Burden of Disease Study reports alcohol as a significant cause of chronic disease, but was mostly based on data from high-income countries, and alcohol consumption was mostly extrapolated from alcohol sales [15]. Unfortunately, good epidemiological data for patterns of alcohol use and health outcomes in middle-income and low-income countries are lacking, especially due to the traditional habit of drinking homemade beverages. In the PURE study (Prospective Urban Rural Epidemiology), 75 % of adult participants in high-income countries reported alcohol consumption compared with 12 % in low-income countries, who were younger and more prone to binge and heavy drinking [16]. Therefore, any potential reduced CV risk was masked by increased mortality and morbidity from alcohol-related injury in younger subjects and a higher risk of cancer in older adults [17].

3.2.2 The Good Side: How It Is Done

Alcohol in moderation affects the lipid profile; improves insulin sensitivity, endothelial function, and fibrinolysis; lowers abdominal obesity; reduces systemic inflammation and oxidative stress; and reduces postprandial hypercoagulability and platelet aggregation [18]. Many studies have tried to attribute these desirable functions not only to ethanol itself but also to various compounds in alcoholic beverages. Currently, polyphenols (found not only in wine but also beer, liqueurs, coffee, tea, oils, etc.) are

the most likely candidates, and this is supported by growing evidence that their consumption can lower BP and particularly affect endothelial function [19, 20]. A recently published study compared polyphenols in grape-wine extract and polyphenols in grape-juice extract. Grape-juice extract had no effect on BP or endothelial function, in contrast to the grape-wine extract. The authors hypothesized that this was due to the effects of the polyphenol on NO-mediated vasodilatation lasting for only 15 min and differences in the polyphenol compound profile of grape-wine and grape-juice extract (catechins and procyanidins vs. anthocyanins and flavanols) [21]. In contrast to the short-term benefits on the endothelium, the impact of alcohol on thrombolysis is more durable, lasting up to 6 h after only one drink [22]. The drinking pattern is highly important when it comes to the benefits of alcohol, as are individual characteristics [23, 24].

3.2.3 The Dark Side, "U", "J" and Other Shapes

Since stroke is the second leading cause of death and a major cause of disability, many observational epidemiologic studies have examined the role of alcohol intake as well as its potential as a protective factor. In the last two decades, data from observational studies suggest a J-shaped curve in the association of alcohol and not only stroke but every other CVD or outcome. However, sometimes the J looks more J when it comes to stroke. One meta-analysis showed a relative risk reduction for every type of stroke with 2.5–14.9 g of alcohol consumed. In the same analysis, the relative risk reduction for coronary heart disease outcomes were the same for all levels of alcohol intake above 2.5 g/day [25]. An association does not mean a causative effect, which can only be shown by large long-term interventional trials, which cannot be made for ethical reasons. It is evident that alcohol increases HDL cholesterol [26, 27]. Some major prospective studies and meta-analyses have failed to find a clear association between HDL cholesterol and the risk of stroke [28]. The apparently beneficial potential of alcohol to reduce platelet aggregation and lower fibrinogen concentrations and other haemostatic factors may seem useful for ischemic stroke, but for hemorrhagic stroke, this pattern may well explain the linear association between hemorrhagic stroke and alcohol consumption [29]. When combined with reports of poorer hypertension control in heavy drinkers, it may be asked whether it is wise to accentuate the protective role of alcohol in CV brain damage [30]. Alcohol-induced hypertension is another clinical entity responsible for the linear association between alcohol and hemorrhagic stroke or the sharp J-shape with respect to ischemic stroke. The effect was first proposed by Lian et al. in 1915 [31], but the exact threshold for the effect is not clear. While some argue that >3 drinks per day will lead to a 50 % increase in the prevalence of hypertension, most epidemiological studies draw a line at 6 drinks per day, associating heavy drinking and hypertension. In addition to constant methodological disparities, it seems that gender also makes a difference. Howard et al. found an apparent J-shaped association between alcohol and hypertension in women, while the association in men was clearly linear, with no benefits in relative risk for hypertension

in light or moderate drinkers [32]. However, the relative risk for hypertension did not rise in men until 5 drinks per day, while women benefited until 4 drinks per day, at least in this study.

The mechanisms of alcohol-induced hypertension may be divided into acute and chronic pathophysiological impairment. In the acute phase, alcohol diminishes baroreflexes by interacting with receptors in the brain stem, leading to increased sympathetic activity. Sympathetic activity is activated in heavy drinking through expansion of the extracellular fluid, leading to an increase in plasma renin activity and elevated vasopressin levels. Chronic hypertension is most likely due to alcohol-induced elevation of angiotensin II, endothelin-1, and impaired NO endothelial production [33].

In conclusion, it is undisputable that heavy alcohol intake increases the risk of ischemic and hemorrhagic stroke. However, most, if not all, large observational studies and meta-analyses only focus on stroke mortality, even though morbidity is much more common for these events. Data from the WHO Monica project suggest that changes in stroke mortality are largely attributable to changes in early case fatality and better (primarily radiological) diagnostics rather than to changes in stroke incidence [34].

In light of the fact that the alcohol-attributable stroke burden will continue to increase globally without effective alcohol control measures, and despite all the possible favorable effects of reducing the CV risk in light and moderate alcohol consumption, patients should not be encouraged to drink [35].

The question of how much is too much may have been answered long ago using only inner wisdom. In the Greek play *Semele or Dionysus*, written by Eubulus around 375 BC, the God of wine delivers this speech: *I mix three drinks for the temperate: One for health, which they empty first, The second for love and pleasure, The third for sleep. When these cups are emptied, the wise go home. The fourth drink is ours no longer, but belongs to violence, The fifth to uproar, The sixth to drunken revelry, The seventh to black eyes, The eighth to the police, The ninth to anger, And the tenth to madness and the hurling of furniture.*

According to the guidelines for primary stroke prevention, general measures should include advice on limiting alcohol consumption and underscoring the need to inform patients that they should limit their alcohol consumption to no more than two drinks per day for men and no more than one drink per day for nonpregnant women. The recommendations of current guidelines are shown in Box 3.3 [2].

Box 3.3 Recommendations for alcohol consumption

1. Reduction or elimination of alcohol consumption in heavy drinkers through established screening and counseling strategies as described in the 2004 US Preventive Services Task Force update is recommended *(class I; level of evidence A)*
2. For individuals who choose to drink alcohol, consumption of ≤2 drinks per day for men and ≤1 for nonpregnant women might be recommended *(class IIb; level of evidence B)*

3.3 Smoking and Brain Damage

Cigarette smoking is probably the most complex and the least understood risk factor in the CV continuum. Cigarette smoke contains more than 4,000 different chemicals, and these are modified differently in the human body [36]. Modern cigarettes are high-tech products, designed to deliver nicotine efficiently without an unpleasant taste or throat irritation, in order to maximize pleasure in the addicted consumer. According to the WHO, smoking is responsible for 10 % of all CVD outcomes, which are easily modifiable and preventable [37]. Unfortunately, the latest pharmacological studies suggest that nicotine dependence is associated with opioid-like receptors in the CNS, which explains why cigarette addiction is as hard to fight as heroin addiction [38]. More than 5.4 million deaths each year worldwide are currently attributed to smoking, and the striking projection is a rise to about eight million per year by 2030, with 80 % of these deaths being in developing countries [39].

3.3.1 Smoke-Endothelium-Stroke

Tobacco smoke is an aerosol formed from tar (dry, solid residue of combustion containing nicotine and numerous carcinogens) and gases (CO_2, CO, N_2, HNC, H_2S etc.), most of which are reactive oxygen species (ROS). Apart from a handful of candidates, the relevance of most compounds in cigarette smoke in CVD initiation, progression, and outcome has not been individually studied. It is likely that the interplay of these compounds with the individual genetic background and the environment defines the onset, location, and pace of CVD [40]. The cardinal mechanism in cigarette-induced endothelial dysfunction is a lack of nitric oxide (NO) bioavailability, while endothelial dysfunction is considered to be the earliest manifestation of atherosclerosis. Smoke-derived ROS trigger the activation of proinflammatory cytokines and adhesion molecules, the antiadhesive endothelial phenotype is lost, and endothelial-platelet and endothelial-leukocyte interaction occur. The acute effect of cigarette smoke on the endothelium is only functional, and the central role of the endothelium in maintaining haemostatic equilibrium can be restored. However, during chronic exposure, the endothelial layer suffers physical damage which leads to activation of the subendothelial layer – the first step in thrombus formation [41]. Once the atherosclerotic plaque is formed, cigarette smoke continues to change its stability and lipid content, leading to plaque instability and rupture. In addition to the formation and structure of plaque, acute smoking is associated with an increase in heart rate and BP, and this hypercatecholaminaemia is another contributor to atherothrombosis in smokers [42]. Impaired endothelial function, inflammation, plaque formation, and instability are only a small part of the deleterious biological impact of cigarette smoke. An increased propensity for platelet aggregation in smokers, together with a higher platelet count, increased fibrinogen levels, and elevated blood viscosity, constitutes the proatherothrombotic state in smokers. Clinically, cigarette smoking is associated with increased carotid intima-media thickness, arterial stiffness, and carotid plaque density, ultimately leading to

an increased risk of ischemic stroke [43]. In a recent meta-analysis, predominately echolucent plaques (prone to rupture) were associated with an increased risk of ipsilateral stroke regardless of the severity of stenosis [44]. Are our guidelines imprecise when assessing carotid stenosis only by the degree of lumen stenosis?

3.3.2 Smoking and Hypertension

Although smoking may not be associated with the development of essential hypertension, its impact on the prognosis of hypertensive patients with respect to CV outcomes has been extensively documented by many large epidemiological and prospective trials. Smoking decreases arterial compliance in both the large- and medium-sized arteries, leading to increased arterial and aortic stiffness, and while acute smoking has a powerful sympathetic excitatory effect, it is likely that chronic changes in the endothelium lead to constant BP elevation [45]. Even though various observational studies have reported a lower prevalence of hypertension among current smokers or an increased incidence of hypertension in prospective studies among ex-smokers compared to smokers, this may be attributed to significant weight gain in ex-smokers and to the fact that smokers are often younger and slimmer. Maybe, at present, it is most accurate to say that cigarette smoking exacerbates the effect of BP on the risk of CVD [46]. Finally, hypertensive smokers are more likely to develop malignant and renovascular forms of hypertension.

3.3.3 Smoking and the Brain

The blood-brain barrier (BBB), which is mainly composed of microvascular endothelial cells, is a major link between cigarette smoke and the brain. The BBB is rapidly exposed to harmful toxins and ROS (skipping first-pass metabolism) which trigger a strong proinflammatory response and is a start for silent cerebral infarction leading to vascular dementia, stroke, and brain vessel aneurysms. There is also a strong correlation between smoking and neurodegenerative disorders and neurodevelopmental damage during pregnancy [47]. Recent observations suggest that ROS are key mediators of BBB breakdown, and antioxidant supplementation has proven to be effective but only in vitro conditions [48]. Nevertheless, the recommended daily intake of vitamin C in smokers is more than twofold greater than in nonsmokers.

3.3.4 Smoking and Stroke

Smokers have an approximately twofold risk of incurring a stroke during their lifetime compared with nonsmokers [49]. Cigarette smoking has been associated with CVD since the first US surgeon general's report in 1964. During the last 50 years, CV mortality rates have been decreasing, along with rates of cigarette

consumption, at least in developed countries. Nevertheless, over the last quarter of a century, efforts on smoking prevention and cessation, and public awareness campaigns describing the associated health risks of smoking, have had only limited success. Due to the current rates of world population growth, even with a small percentage decline in tobacco consumption over time, absolute consumption continues to grow and will continue to do so. In short, over 1 billion more cigarettes were consumed worldwide in 2000 compared with 1980 [50]. The importance of smoking as a major risk factor will continue for decades due to the high prevalence of smoking in developing countries. Estimates from the INTERSTROKE study indicate that around 19 % of the burden of stroke is due to current smoking [51]. Numbers better put this into perspective: compared with nonsmokers, current smokers have at least a two- to fourfold (depending on the study) increased risk of stroke compared with lifelong nonsmokers or individuals who had quit smoking more than 10 years before. There is clear evidence of a dose-response relationship between smoking and stroke risk, but unfortunately, this connection is not often publicized and yet may provide helpful information when stimulating patients to at least cut the number of cigarettes smoked. One older meta-analysis showed that individuals who consumed <10 cigarettes/day had a relative risk of stroke of 1.37 compared with smokers consuming ≥20 cigarettes/day, who had a relative risk of 1.82 [52]. Irrespective of controlling for other lifestyle factors, subjects who reported current smoking at the time of recruitment had an approximatively twofold risk increase in the risk of stroke compared with never smokers, among both men and women [3]. In a more recent study, smoking was shown to be even more hazardous for women, and more for hemorrhagic stroke, and also to have a strong dose-response relationship [53]. This may be related to the stable smoking prevalence among women in recent decades, along with increased prevalence of women smokers in developing countries, leading the Million Women Study to coin the phrase: 'if women smoke like men, they die like men' [54].

Smoking is very addictive and it is hard to stimulate people to quit. Shock tactics may be tried, as may positive reinforcement (Box 3.4).

Box 3.4 A few facts which may positively stimulate smokers to quit

- Within 20 min blood pressure drops to the level it was before the last cigarette
- Within 8 h carbon monoxide levels in the blood return to normal
- Within 24 h the chance of a heart attack decreases
- Within 1–2 months, the smoking-related stroke risk due to hypercoagulability normalizes to that of nonsmokers
- At 1 year the risk of heart disease is cut in half
- At 5 years the stroke risk is reduced to that of a nonsmoker in most cases
- By 15 years the risk of heart disease is that of a nonsmoker

Cigarette smoking potentiates the effect of other stroke risk factors such as systolic BP and oral contraceptives (OC). The odds ratios of cerebral infarction were 1.3 times greater for women who smoked but did not use OC, and 2.1 times greater for nonsmokers who used OC, but 7.2 times greater for smokers who used OC. The synergistic effect of smoking and OC use was also observed in hemorrhagic stroke. The effect of smoking on ischemic stroke is higher in young adults who are carriers of the apolipoprotein E e4 allele [2].

Recent guidelines for the primary prevention of stroke, which is also valid for secondary prevention, identify smoking cessation as a general measure, as well as avoiding environmental tobacco smoke [2]. They also strongly encourage patients and families to stop smoking and support organizing and providing counseling, nicotine replacement, and other available programs (Box 3.5).

Box 3.5 Recommendations for smoking cessation [2]

1. Abstention from cigarette smoking by nonsmokers and smoking cessation by current smokers are recommended based on epidemiological studies showing a consistent relationship between smoking and both ischemic stroke and SAH *class I, level of Evidence B)*
2. Although data are lacking to show that avoidance of environmental tobacco smoke reduces incident stroke on the basis of data showing an increased stroke risk, and the effect of avoidance on the risk of other cardiovascular events avoidance of exposure to environmental tobacco smoke is reasonable (*class IIa level of evidence C)*
3. The use of multimodal techniques including counseling nicotine replacement and oral smoking-cessation medications can be useful as part of an overall smoking-cessation strategy. The status of tobacco use should be addressed at every patient encounter (*class I level of evidence B)*

3.4 Salt Intake

High salt intake is associated with a higher risk of ischemic and hemorrhagic stroke and intracerebral hemorrhages [6, 55, 56]. In most societies and cultures worldwide, salt (NaCl) consumption is several times above physiological needs and in most countries almost twice as high as currently recommended, making it one of the most important risk factor for the high prevalence of hypertension but also a significant cause of resistance to therapy. In addition, salt directly affects the endothelial, myocardial, and renal cells, increasing the global risk additionally and independently of BP. There is evidence of the deleterious effects of high salt intake on the left ventricular mass, arterial stiffness, and renal function. Perry et al. observed a significant correlation between salt intake and stroke mortality in European countries, and the correlation was stronger than the relationship between systolic BP and stroke mortality [57]. Similar findings were observed in Japan, where stroke mortality was more

closely associated with salt intake than with systolic BP [58]. However, the vast majority of data supported the hypothesis that the strongest effect of salt on stroke risk was mediated through the direct effect on BP. Residual causality could not be completely rejected, while subjects who reduced salt intake were usually prone to accept all other recommendations on healthy lifestyles. A reduction in dietary salt intake of a teaspoon (equal to 5–6 g salt) has been shown to reduce BP by 7/4 mmHg in hypertensive patients and by 23/9 mmHg in patients with resistant hypertension [7, 59]. The Dietary Approaches to Stop Hypertension (DASH) study found that older adults and Blacks, who have a high risk of stroke, are particularly sensitive to the BP-lowering effects of salt reduction [60]. In a meta-analysis of long-term trials which analyzed the effects of salt reduction, assignment to a reduced salt intervention group significantly lowered the risk of CVD by 20 % compared with assignment to a control group [61]. He et al. reported that, in the United Kingdom from 2003 to 2011, there was a decrease in stroke mortality of 42 %, in parallel with a fall in BP of 3/1.4 mmHg and decreased salt intake of 1.4 g/day measured by 24 h urinary sodium [62]. The UK findings are in agreement with observations from Japan and Finland [63, 64]. Even a small reduction in the population's average salt intake could result in a major improvement in CV health. Strazzulo et al. found that the pooled relative risk indicates a 23 % greater risk of stroke for an average difference in sodium intake of 86 mmol (equivalent to about 5 g of salt a day) and concluded that each year a 5 g reduction in daily salt intake at the population level could avert 1.25 million deaths from stroke [6]. Aburto et al. analyzed the long-term effects in healthy, free-living, prehypertensive individuals who were not taking antihypertensive drugs in whom salt intake was estimated on the basis of multiple 24-h urine specimens and found a linear 17 % increase in risk per 1 g increase in sodium [55]. These results confirmed the need for a reduction of salt intake in the general population. There is growing evidence that, in non-acutely ill adults, reduced salt intake has no adverse effect on blood lipids, catecholamine levels, or renal function [65].

Higher potassium intake is associated with a reduction in the stroke risk of 21 %, and every increase in potassium intake of 1 g per day resulted in a reduction in the stroke risk of 11 %, so it seems that this recommendation should be given simultaneously with the one for cutting down salt consumption [66, 67].

In addition to the huge impact on the health of the whole population, a cost-effective analysis by the National Institute for Health and Clinical Excellence (NICE) showed that the reduction in salt intake achieved in the United Kingdom has saved more than £1.5 billion/annum [68].

As reduced salt intake decreases BP, it is likely that consumption of a diet with reduced salt content (and increased potassium) will reduce the stroke risk. Although no J-curve has been observed for salt intake and stroke risk, it is prudent to recommend 5 g/day as a target for both primary and secondary stroke prevention. While most salt ingested comes from prepared food, this goal could not be achieved without collaboration from the food industry and government support as has been done in the United Kingdom, Japan, Finland, and Portugal and has recently been started in Croatia. Nevertheless, permanent education and increasing awareness about the hidden risk of high salt consumption are of the utmost importance, and should be a

priority task for the whole medical and scientific community, and must be included in everyday clinical practice. The recommendations of recent guidelines on diet and nutrition are shown in Box 3.6.

Box 3.6 Recommendations on diet and nutrition (B2)

1. Reduced intake of sodium and increased intake of potassium, as indicated in the Dietary Guidelines for Americans, are recommended to lower BP (*class I; level of evidence A*)
2. A DASH-style diet, which emphasizes the consumption of fruits, vegetables, and low-fat dairy products and is reduced in saturated fat, also lowers BP and is recommended (*class I; level of evidence A*)
3. A diet that is rich in fruits and vegetables and thereby high in potassium is beneficial and may lower the risk of stroke (*class I; level of evidence B*)
4. A Mediterranean diet supplemented with nuts may be considered in lowering the risk of stroke (*class IIa; level of evidence B*)

3.5 Summary and Conclusion

Most data confirm that smoking, heavy alcohol drinking, and increased salt consumption are strong but modifiable risk factors for stroke. Decreasing each of those lifestyle factors will decrease the stroke risk. However, in everyday practice it is very hard to accomplish this task due to low awareness, biochemical addiction to smoking, and the real risk that recommendations to drink moderately will not remain moderate and because reductions in salt intake cannot be achieved without the support of industry and government. Disability in stroke survivors is an additional limitation. Nevertheless, education, counseling, and all efforts should be made to change bad lifestyle habits, and recommendations must be implemented in clinical practice while always trying to change global, personal, and family attitudes to lifestyle and not focus only on separate measures.

References

1. Hankey GJ (2012) Nutrition and the risk of stroke. Lancet Neurol 11:66–81
2. Meschia JF et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translation Biology; Council of Hypertension (2014) Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 45:3754–3832
3. Wannamethee SG et al (1995) Smoking cessation and the risk of stroke in middle-aged men. JAMA 274:155–160
4. He FJ, MacGregor GA (2009) A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. J Hum Hypertens 23:363–384

5. O'Donnell M et al (2013) Salt intake and cardiovascular disease: why are the data inconsistent? Eur Heart J 34:1034–1040
6. Strazzullo P et al (2009) Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 339:b4567
7. He FJ, MacGregor GA (2002) Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. J Hum Hypertens 16:761–770
8. He FJ, MacGregor GA (2003) How far should salt intake be reduced? Hypertension 42:1093–1099
9. Tikk K et al (2014) Primary preventive potential for stroke by avoidance of major lifestyle risk factors the european prospective investigation into cancer and nutrition-heidelberg cohort. Stroke 45:2041–2046
10. Zhang Y et al (2012) Lifestyle factors and antihypertensive treatment on the risks of ischemic and hemorrhagic stroke. Hypertension 60:906–912
11. Lawrence M et al (2010) An exploration of lifestyle beliefs and lifestyle behavior following stroke: findings from a focus group study of patients and family members. BMC Fam Pract 11:97–108
12. Campbell N, Spence J (2008) Stroke prevention and sodium restriction. Can J Neurol Sci 35:278–279
13. WHO (2011) Global status report on alcohol and health. WHO, Geneva
14. WHO (2014) Global status report on alcohol and health. WHO, Geneva
15. Lim SS et al (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1999–2010: a systematic analyses for the Global Burden of Disease Study 2010. Lancet 380:2224–2260
16. Smyth A et al (2015) Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital and mortality: a prospective cohort study. Lancet 386(10007):1945–1954, Published online
17. Connor PJ (2015) Alcohol burden in low-income and middle-income countries. Lancet 386:1922–1924. http://dx.doi.org/10.1016/S0140-6736(15)00235-4
18. Kiechl S, Willeit J (2014) Complex association between alcohol consumption and myocardial infarction. Circulation 130:383–386
19. Rothwell JA et al (2013) Phenol-Explorer 3.0: a major update of the Phenol-Explorer Database to incorporate data on the effect of food processing on polyphenol content. Database (Oxford). 2013; published on line; doi: 10.1093/database/bat070
20. Larsson SC (2014) Coffee, tea and cocoa and the risk of stroke. Stroke 45:309–314
21. Draijer R et al (2015) Consumption of a polyphenol-rich grape-wine extract lowers ambulatory blood pressure in mildly hypertensive subjects. Nutrients 7:3138–3153
22. Lacoste L et al (2001) Acute and delayed antithrombotic effects of alcohol in humans. Am J Cardiol 87:82–85
23. Nilssen O et al (2005) Alcohol consumption and its relation to risk factors for cardiovascular disease in the north-west of Russia: the Arkhangelsk study. Int J Epidemiol 34:781–788
24. Yang HK et al (2015) Different effect of alcohol consumption on hypertension according to metabolic health status. J Hum Hypertens. doi:10.1038/jhh.2015.102
25. Mukamal KJ, Ronskey R (2011) Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 342. Published online 2011 Feb 22. doi:10.1136/bmj.d671
26. Mukamal KJ et al (2005) Drinking frequency, mediating biomarkers and the risk of myocardial infarction in women and men. Circulation 112:1406–1413
27. Volcik KA et al (2008) Relationship of alcohol consumption and type of alcoholic beverage consumed with plasma lipid levels: differences between Whites and African Americans of the ARIC study. Ann Epidemiol 18:101–107
28. Angelantonio D et al (2009) Emerging risk factor collaboration: major lipids, apolipoproteins and risk of vascular disease. JAMA 302:1993–2000
29. Mukamal KJ et al (2001) Alcohol consumption and haemostatic factor: analysis of the Framingham offspring cohort. Circulation 104(12):1367–1373

30. Hillbom M (1998) Alcohol consumption and stroke: benefits and risk. Alcohol Clin Exp Res 22:352s–358s
31. Lian C (1915) L'alcoholisme, cause d'hypertension arterielle. Bulletin de l'Academie de Medicine 74:525–528
32. Sesso HD et al (2008) Alcohol consumption and the risk for hypertension in women and men. Hypertension 51:1080–1087
33. Husain K et al (2014) Alcohol-induced hypertension: mechanism and prevention. World J Cardiol 26:245–252
34. Sarti C et al (2003) Are changes in mortality form stroke caused by changes in stroke event rates or case fatality? Results from the WHO MONICA Project. Stroke 34:1833–1840
35. Anderson P et al (2009) Reducing the harm done by alcohol: evidence for effectiveness and cost-effectiveness. Lancet 373:2246
36. Conrad A (2011) Exposure to tobacco smoke. In: Bernahrd D (ed) Cigarette Smoke Toxicity. Weinheim: Wiley-VCH Verlag & Co. KGaA; 2011:69–92
37. WHO global report: mortality attributable to tobacco, p 392 in WHO global report: mortality attributable to tobacco (2012), Geneva, World Health Organization, 2012
38. Ueno K et al (2014) Possible involvement of endogenous opioid system located downstream of α7 nicotinic acetylcholine receptor in mice with physical dependence on nicotine. J Pharmacol Sci 124:47–53
39. WHO Report on the Global Tobacco Epidemic, 2008: The MPOWER package. Geneva, World Health Organization, 2008
40. Messer B, Bernhard D (2014) Smoking and cardiovascular disease. Mechanisms of endothelial dysfunction and early atherogenesis. Atheroscler Thromb Vasc Biol 34(3):509–515
41. Messner B et al (2012) Apoptosis and necrosis: two different outcomes of cigarette smoke condensate-induced endothelial cell death. Cell Death Dis. doi:10.1038/cddis.2012.162
42. Csordas A, Bernhard D (2013) The biology behind the atherothrombotic effects of cigarette smoke. Nat Rev Cardiol 10(4):219–230
43. Jha P et al (2013) 21st century hazards of smoking and benefits of cessation in the United States. N Engl J Med 368:341–350
44. Gupta A et al (2015) Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. Stroke 46:91–97
45. Narkiewicz K et al (2015) Is smoking a causative factor of hypertension? Blood Press 14:69–71
46. Zeng G et al (2012) Does cigarette smoking exacerbate the effect of blood pressure on the risk of cardiovascular and all-cause mortality among hypertensive patients? J Hypertens 30:2307–2313
47. Naik P, Cucullo L (2015) Pathobiology of tobacco smoking and neurovascular disorders: untied strings and alternative products. Fluid Barriers CNS 12:25. doi:10.1186/s12987-015-0022-x
48. Hossain M et al (2011) In vitro assessment of tobacco smoke toxicity at the BBB: do antioxidant supplements have a protective role? BMC Neurosci 12:92
49. Thun MJ et al (2013) 50-year trends in smoking-related mortality in the United States. N Engl J Med 368:351–364
50. Shah RS, Cole JW (2010) Smoking and stroke: the more you smoke the more you stroke. Expert Rev Cardiovasc 8(7):917–932
51. O'Donnell MJ et al (2010) Risk factors for ischemic and intracerebral hemorrhagic stroke in 22 countries (the INTERSTROKE study): a case control study. Lancet 376:112–123
52. Shinton R, Beevers G (1989) Meta-analysis of relation between cigarette smoking and stroke. BMJ 298:789–794
53. Peters SS et al (2013) Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts. Stroke 44:2821–2828
54. Pirie K et al; Million women study collaborators (2013) The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in UK. Lancet 381:1297–1305
55. Aburto N et al (2013) Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ 346:f1326

56. Sarikaya H et al (2015) Stroke prevention – medical and lifestyle measures. Eur Neurol 73:150–157
57. Perry J, Beevers D (1992) Salt intake and stroke: a possible direct effect. J Hum Hypertens 6:23–25
58. Tomonari T et al (2011) Is salt intake an independent risk factor of stroke mortality? Demographic analysis by regions in Japan. J Am Soc Hypertens 5:456–462
59. Pimenta E et al (2009) Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. Hypertension 54:475–481
60. Bray GA et al; DASH Collaborative Research Group (2004) A further subgroup analysis of the effects of the DASH diet and three dietary sodium levels on blood pressure: results of the DASH-Sodium Trial. Am J Cardiol 94:222–227
61. He FJ et al (2011) Does reducing salt intake increase cardiovascular mortality? Kidney Int 80:696–698
62. He F et al (2014) Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischemic heart disease mortality. BMJ Open. doi:10.1136/bmjopen-2013-004549
63. Sasaki N (1979) The salt factor in apoplexy and hypertension: epidemiological studies in Japan. In: Yamori Y (ed) Prophylactic approach to hypertensive diseases. Raven, New York, pp 467–474
64. Karppanen H, Mervaala E (2006) Sodium intake and hypertension. Prog Cardiovasc Dis 49:59–75
65. Cook N et al (2014) Lower levels of sodium intake and reduced cardiovascular risk. Circulation 129:981–989
66. D'Elia L et al (2011) Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. J Am Coll Cardiol 57:1210–1219
67. Larsson SC et al (2011) Dietary potassium intake and risk of stroke: a dose-response meta-analysis of prospective studies. Stroke 42:2746–2750
68. National Institute for Health and Clinical Excellence (NICE). Guidance on the prevention of cardiovascular disease at the population level. http://guidance.nice.org.uk/PH25. Accessed Nov 2015

4 Comorbidities Often Associated with Brain Damage in Hypertension: Diabetes, Coronary Artery Disease, Chronic Kidney Disease and Obstructive Sleep Apnoea

Athanasios J. Manolis, Manolis S. Kallistratos, Demetrios V. Vlahakos, Asimina Mitrakou, and Leonidas E. Poulimenos

4.1 Introduction

In hypertensives, various comorbidities are often associated with brain damage. According to the Framingham Study [1, 2], the presence of different risk factors and diseases such as diabetes mellitus (DM), chronic kidney disease (CKD) and coronary artery disease (CAD) can increase the incidence of brain damage. Moreover, obstructive sleep apnoea (OSA) is also associated with an increased risk of stroke [3] and other cardiovascular diseases. This chapter will assess the associations between these diseases and conditions and brain damage and the stroke-related burden.

4.2 Diabetes

Epidemiological, clinical, biochemical and imaging studies have shown that elevated glucose levels and diabetes are associated with cognitive dysfunction, the most prevalent cause of which is Alzheimer's disease (AD). Common pathogenic

A.J. Manolis (✉) • M.S. Kallistratos • L.E. Poulimenos
Department of Cardiology, Hypertension Center, Asklepeion General Hospital, Athens, Greece
e-mail: ajmanol@otenet.gr

D.V. Vlahakos
Renal Unit, ATTIKON University Hospital, Athens, Greece

A. Mitrakou
Department of Clinical Therapeutics, Athens University Medical School, Athens, Greece

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_4

factors in these conditions include chronic hyperglycaemia, hyperinsulinaemia, insulin resistance, acute hypoglycaemic episodes, microvascular disease, fibrillar deposits, altered insulin processing, inflammation, obesity, dyslipidaemia and sedentary habits. Healthier lifestyle measures have a protective effect against the development of cognitive impairment due to Alzheimer's disease, as do some of the pharmacological agents used in the treatment of diabetes such as insulin (especially when delivered intranasally), metformin, peroxisome proliferator-activated receptor γ agonists, glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors.

Hyperglycaemia This is a recognized risk factor for cognitive impairment as shown by the ACCORD-MIND study and others [4, 5]. Hyperglycaemia leads to neural damage following advanced glycosylated end products and oxidative stress, osmotic stress damaging the blood–brain barrier and the resultant leak of toxic substances leading to further damage of nervous structures [6]. Apart from chronic hyperglycaemia, as assessed by glycated haemoglobin, glucose variability, as measured by continuous glucose monitoring, better correlates with cognitive function [7]. Postprandial glucose levels may also be a contributing factor, acting via oxidative stress.

Hypoglycaemia Although severe hypoglycaemia has been shown to be associated with dementia in the elderly [6], when hypoglycaemia is avoided by careful treatment in younger type 1 diabetics, as in the DCCT/EDIC study, no association was found between hypoglycaemia and cognitive dysfunction [8]. However, in the elderly, hypoglycaemia, when coupled with atherosclerosis, leads to organic brain damage, which is often irreversible [6].

Role of Insulin in the Brain Cognition may be affected not only by alterations in the level of glucose but also through the action of insulin. Insulin enters the central nervous system (CNS) by crossing the blood–brain barrier in a regulated and saturable fashion [9]. A large number of insulin receptors exist in brain areas related to memory, such as the hippocampus and cerebral cortex. In addition, insulin also aids the release of β-amyloid peptide extracellularly and increases the expression of the enzyme which degrades insulin. Insulin deficiency results in the accumulation of β-amyloid peptide. Both hyperinsulinaemia and hyperglycaemia were shown to increase neuritic plaque formation [10]. Disruption of insulin signalling makes neurons more vulnerable to metabolic stress, thus accelerating neuronal dysfunction. Defective insulin signalling is associated with decreased cognitive ability and the development of dementia, including AD.

Insulin Resistance and Alzheimer's Disease In humans, insulin improves cognition, independently of its effects on peripheral glucose. Acute increases in insulin after treatment improve cognition, but chronic hyperinsulinaemia can adversely affect neuronal function in vitro by increasing susceptibility to toxin and stress-induced effects [11]. Glycated proteins and inflammatory mediators could also have a pathogenic role [10].

Microvascular Disease and Cognitive Decline Hyperglycaemia in DM leads to microvascular complications that affect many organs. Studies have shown that retinopathy and nephropathy are associated with impaired cognition [12]. The retina shares many features with the brain, both developmental, anatomical (e.g. microvascular bed) and physiological (e.g. blood–tissue barrier), and therefore changes in the retina reveal cerebral pathological processes. AD is known to involve the retina (macula and optic disc), and retinal microvascular changes may be related to cognitive dysfunction and AD.

In conclusion, diabetes must be recognized as a risk for the development of AD; clinicians must ensure preventive care is given to control and delay both conditions, and cognitive impairment should be identified early to enable appropriate management.

4.3 Coronary Artery Disease

Coronary artery disease (CAD) is usually attributed to atherothrombotic disease. Several risk factors promote and intensify atherosclerosis, leading to CAD. However, vessels with atherosclerotic lesions are not confined only to the coronary network. The same phenomenon also occurs in the entire circulatory network, and therefore, patients with CAD usually present other vessels with atherosclerosis. Thus, it is not surprising that CAD and peripheral artery disease (PAD) often coexist. It is estimated that CAD coexists with PAD, in 42 % of PAD patients aged >50 years [13]. Moreover, 25–70 % of patients with carotid artery disease suffer from CAD [14, 15]. Thus, patients with CAD are considered at high risk for cardiovascular (CV) events such as stroke. CAD and stroke share a common denominator – atherosclerosis. Moreover, the same risk factors that contribute to the development of CAD (hypertension, diabetes, dyslipidaemia and smoking) are shared with stroke, leading once again to the development of atherothrombotic disease. Thus, patients with stroke are at high risk for the symptoms and complications of CAD and vice versa. Several studies have assessed the association between ischemic stroke (IS) and CAD. A prospective study that aimed to determine whether IS was an independent predictor of CAD using cardiac computed tomographic angiography found that patients with acute IS had a near fivefold greater probability of having coronary artery plaques (odds ratio [OR] 4.9, $P<0.01$) compared to those without IS [16]. Likewise, a prospective study of 1,304 patients with acute IS investigated the frequency of CAD and the association between coronary and cerebral artery atherosclerosis using multislice CT coronary angiography and cerebral angiography [17]. In this study, 70.1 % of patients with IS also had CAD. The presence of different risk factors such as diabetes, dyslipidaemia and peripheral artery disease markedly increased the risk of CAD, and patients with ≥2 risk factors had an increased risk of CAD [odds ratio (OR) 8.36; 95 % confidence interval (CI) 4.15–16.87].

Atherosclerosis is responsible not only for CAD and IS but also for dementia. Several studies have shown a strong association between CAD and dementia and cognitive impairment, thereby classifying CAD as an independent risk factor for both

conditions. In the Cardiovascular Health Study [18] and the AGES-Reykjavik Study [19], patients with CAD had a higher percentage of dementia and lower scores on cognitive function tests, respectively. In addition, patients with CAD present reduced hippocampal volume [20] and increased senile plaque formation in the brain cortex [21], while the platelet hyperactivity observed in CAD is also related to dementia [22].

Although CAD and stroke share risk factors, interventions in CAD patients can also increase the incidence of stroke. Several studies have shown that coronary artery disease bypass grafting (CABG) can increase the incidence of postoperative stroke. The incidence of cerebrovascular events (CVA) after CABG is approximately 1–2 % [23, 24]. This risk, however, increases markedly with age and the presence of other factors such as pre-existing cerebrovascular disease, severe atherosclerosis of the ascending aorta, protracted cardiopulmonary bypass time and severe perioperative hypotension. The presence of classical risk factors for stroke such as hypertension and diabetes, as well as prior stroke and prior transient ischemic attack, can increase markedly the incidence of postoperative stroke. In patients aged ≥70 years, his risk may increase by up to 4.5 % [23].

CAD increases the incidence of arrhythmias such as atrial fibrillation (AF), increasing the incidence of stroke. There is an increased risk of AF in patients with myocardial infarction or ST segment abnormalities due to CAD (relative risk [RR] 3.62), angina (RR 2.84) and ST-T wave abnormalities (RR 2.21) [25]. More than 20 % of patients with AF suffer from CAD. AF increases the risk of stroke by up to fivefold, while 20 % of all strokes are attributed to AF [26]. IS related to AF are often fatal, while those who survive have poorer functional performance [27]. Additionally, AF is responsible for silent cerebral infarctions leading to dementia [28]. The incidence of dementia is doubled in patients with AF and is more frequently encountered in AF patients aged <75 years [29].

CAD and stroke share similar risk factors and therefore often coexist. The incidence of brain damage in patients with CAD is attributed not only to the atherothrombotic disease responsible for both diseases but also to CAD procedures such as CABG and to arrhythmias such as AF that increase markedly the incidence of stroke and brain damage in general.

4.4 Chronic Kidney Disease

The overall prevalence of chronic kidney disease (CKD) (glomerular filtration rate – GFR <60 mL/min per 1.73 m^2) has increased significantly in recent years from 10 % in 1999 to more than 14 % currently and is even higher in older adults. Patients with CKD have a significant increase in cardiovascular risk, and the risk of death, particularly due to cardiovascular disease, is much higher than the risk of eventually requiring dialysis [30].

Functional/metabolic, structural and neuropsychiatric disorders are important complications of CKD, especially in patients with end-stage renal disease (ESRD). Uremic encephalopathy is a constellation of symptoms ranging from irritability and restlessness to seizures, coma and death and normally subsides within days after the initiation of adequate dialysis. It was more frequent and more severe in the past,

when patients suffered from severe, untreated uraemia for prolonged periods [30]. Rapid correction by haemodialysis may cause the so-called dialysis disequilibrium syndrome, a condition observed during or immediately after the dialysis session and characterized by headache, nausea, disorientation, restlessness, blurred vision and asterixis, probably due to cerebral oedema. At present, both uremic encephalopathy and dialysis disequilibrium syndrome are much less common because of the tendency to initiate dialysis at an earlier stage [31].

Factors which, alone or in combination, may result in severe CNS dysfunction in patients with CKD include uraemia; multiple electrolyte disorders, such as hypercalcaemia, hypocalcaemia, hyponatraemia and hypernatraemia; hypoglycaemia, hyperglycaemia, haemodynamic instability, whether hypotension or hypertension; drugs, such as erythropoietin, carbapenem and alcohol; air embolism; etc. Dialysis dementia due to aluminium intoxication is a rare cause of encephalopathy, because aluminium has been eliminated from dialysate by using reverse osmosis and deionization techniques and aluminium-containing phosphate binders have been replaced by newer preparations [32].

Patients with CKD are at an increased risk of cerebrovascular disease due to accelerated atherosclerosis, older age and a high incidence of hypertension, diabetes, malnutrition and hyperlipidaemia. Manifestations may include hypertensive encephalopathy, transient ischemic attacks, cerebral infarcts, intracerebral haemorrhage and subdural haematoma. All these conditions may be associated with seizure. Even patients with mild-to-moderate reductions in GFR suffer from a markedly higher stroke rate. This effect is much more pronounced in haemodialysis patients, especially when there is AF [33, 34].

Depression is the most common psychiatric disorder in younger patients with CKD and can usually be successfully treated with medication, with or without counselling [35, 36].

It is unclear to what degree cognitive impairment is related to the dialysis process itself rather than to the metabolic and uremic processes seen in CKD, the CV disease that is common in patients with CKD, or neurodegenerative disease. Leukoaraiosis, high signal intensity in the periventricular white matter on brain magnetic resonance imaging which is associated with vascular dementia, has been found to be more prevalent in dialysis and predialysis patients compared with controls in some studies [37, 38].

Uraemia may impact cognitive function in both children and adults. Neurologic findings in children range from seizures and severe intellectual disability (mental retardation) to subtle deficits resulting in poor school performance. Cognitive disturbance in older children may present with abnormal performance on tasks of verbal abstract ability, visual perceptual reasoning, memory and visual motor skills [39]. In adults, a decline in cognitive function likely begins with early kidney disease before progression to ESRD. In this regard, for each 10 mL/min per 1.73 m^2 decrease in GFR below 60 mL/min per 1.73 m^2, an 11 % increase in the prevalence of cognitive impairment has been shown [40]. A higher incidence of dementia among dialysis patients is likely due to the high number of older patients who start dialysis and have a high risk for dementia due to vascular disease. In fact, dementia, delirium and other organic disorders are the most common mental causes of

Table 4.1 Chronic kidney disease and the brain

Functional/metabolic disorders
Uremic encephalopathy
Dialysis disequilibrium syndrome
Dialysis dementia/aluminium intoxication
Haemodynamic instability, electrolyte disorders, drugs
Structural disorders
Leukoaraiosis, lacunae
Cerebral infarct
Intracerebral haemorrhage
Subdural haematoma
Neuropsychiatric disorders
Acute delirium
Seizure activity
Cognitive impairment
Dementia

hospitalization in elderly CKD patients [35]. The incidence of dementia may be greater in patients who are maintained on haemodialysis rather than on peritoneal dialysis [41] (Table 4.1).

4.5 Obstructive Sleep Apnoea

Obstructive sleep apnoea, also known as obstructive sleep apnoea syndrome (OSAS), is a chronic sleep state-dependent breathing disorder that is characterized by airway obstruction for >10 s during sleep. Excessive daytime sleepiness and an apnoea–hypopnea index (AHI) of ≥5 events per hour during polysomnography are the diagnostic criteria of OSAS [42]. The prevalence in the adult general population is estimated at 5–14 %. About 50 % of OSAS patients are hypertensive, and an estimated 30 % of hypertensive patients also have OSAS.

Episodes of hypoxia stimulate carotid chemoreceptors resulting in sympathetic activation and elevation of blood pressure [43, 44]. Over time, this originally periodic sympathetic activation, together with blood pressure elevation, may persist during the day. Nevertheless, sympathetic activation is not the only cause of the long-term consequences of OSAS. Among many others, alterations in nitric oxide, endothelin, oxidative stress, interleukins, leptin and insulin account for the glucose intolerance, systemic inflammation, endothelial dysfunction and abnormalities in coagulation markers observed [45, 46]. OSAS is related to the pathogenesis of hypertension, stroke and AF and other conditions that increase CV morbidity and mortality [47–49] and is therefore a significant risk factor for CV disease and may accelerate the progress of underlying CV disease to heart failure, stroke or death.

The high prevalence of OSAS in the general population, hypertensive patients and especially obese individuals and patients resistant to antihypertensive therapy,

highlights the need for effective screening, diagnosis and treatment of OSAS to decrease the CV risk [50].

The OSAS may affect the brain through several pathophysiological mechanisms: as described above, sympathetic activation and oxidative stress may explain the development of hypertension in patients with OSAS. The OSAS is more common in patients with resistant hypertension [51], and hypertension, and even more if it is resistant, is a risk factor for both ischemic and haemorrhagic stroke [52]. On the other hand, cerebrovascular abnormalities caused by hypoxia predispose patients with OSAS to stroke. For example, fluctuations in carbon dioxide levels can alter CNS arterial blood flow [53]. Microvascular alterations and carotid intima-media thickness have been linked to the OSAS burden, independently of blood pressure levels [54, 55]. AF is a well-recognized consequence of OSAS and a major risk factor for stroke [56]. In the Sleep Heart Health Study, individuals with OSAS had a fourfold increase in the adjusted risk for AF [57]. OSAS in patients with AF is an independent predictor of stroke [58].

4.5.1 OSAS as a Cause of Stroke

Studies evaluating the prevalence of OSAS in patients with stroke are characterized by inherent limitations, as they study only stroke survivors. On the other hand, since injury to the respiratory and other centres may precipitate OSAS, post-stroke sleep apnoea characteristics cannot be assumed to have been present before stroke. Sleep breathing characteristics also may change significantly in the post-stroke period [42].

In the Sleep Heart Health Study [3], 5,422 participants without a history of stroke at the baseline examination and untreated for sleep apnoea were followed for a median of 8.7 years, with 193 ischemic strokes being observed. A significant association between ischemic stroke and the AHI was observed in men. Men in the highest AHI quartile (>19) had an adjusted hazard ratio of 2.86 for stroke (95 % confidence interval, 1.1–7.4). In women, stroke was not significantly associated with AHI quartiles, but an increased risk was observed with an AHI >25.

In another study in 697 patients, OSAS was associated with stroke or any-cause death (hazard ratio, 2.24; 95 % CI, 1.30–3.86; $P = 0.004$). After adjustment for age, sex, race, smoking status, alcohol consumption, body-mass index and the presence or absence of DM, hyperlipidaemia, AF and hypertension, a significant association between OSAS and stroke or death was retained (hazard ratio, 1.97; 95 % confidence interval, 1.12–3.48; $P = 0.01$) [3].

The OSAS increases stroke severity leading to increased mortality and post-stroke mortality and morbidity and predicts the recurrence of ischemic strokes. In spite of the lack of RCTs and conflicting results between studies, data from well-designed cohort studies suggest that continuous positive airway pressure (CPAP) may reduce the risk of stroke in patients with OSAS [3, 59].

4.5.2 OSAS as a Cause of Neurocognitive and Behavioural Deficits and Its Role in Parkinson's Disease

Cognitive impairment in OSAS includes daytime sleepiness and other cognitive and behavioural deficits such as depression, impaired memory, mood disorders and cognition deficiencies [60]. Cognition deficiencies in OSAS patients have typically been found in attention and vigilance, memory and learning, executive functions and simulated driving [61, 62]. An earlier onset of cognitive impairment was noted in elderly subjects with OSAS compared with those who did not [63].

The prevalence of OSAS in Parkinson's disease (PD) has varied between studies, and the potential consequences and the interrelationship between the two disorders have not been well studied. It seems that OSAS is associated with increased non-motor symptoms in PD, particularly cognitive dysfunction. Nevertheless, a role of PD in the pathogenesis of OSAS is plausible [64].

The OSAS induces neurodegenerative changes resulting from two of its main and integral processes: intermittent hypoxia and sleep fragmentation. OSAS and intermittent hypoxia may cause structural neuron damage in the CNS and impair white matter integrity in vulnerable regions [65]. Vascular injuries and disturbances in blood flow may participate, and microglial apoptotic oxidative and inflammatory mechanisms due to intermittent hypoxia are involved. Amyloid β deposition and tau phosphorylation are enhanced [66].

The OSAS, therefore, is a modifiable risk factor for cognitive dysfunction, and treating OSAS prior to mild cognitive impairment may be an effective prevention strategy to reduce the risk of cognitive decline and AD in the middle aged and the elderly.

References

1. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA (2006) The lifetime risk of stroke: estimates from the Framingham Study. Stroke 37(2):345–350
2. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ (2004) Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol 15(5):1307–1315
3. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM (2010) Obstructive sleep apnea-hypopnea and incident stroke: the Sleep Heart Health Study. Am J Respir Crit Care Med 182(2):269–277
4. Cukierman-Yaffe T, Gerstein HC, Williamson JD, Lazar RM, Lovato L, Miller ME, Coker LH, Murray A, Sullivan MD, Marcovina SM, Launer LJ (2009) Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORDMIND) trial. Diabetes Care 32:221–226 [PMID: 19171735 doi:10.2337/dc08-1153]
5. Umegaki H, Kawamura T, Mogi N, Umemura T, Kanai A, Sano T (2008) Glucose control levels, ischaemic brain lesions, and hyperinsulinaemia were associated with cognitive dysfunction in diabetic elderly. Age Ageing 37:458–461 [PMID: 18339615 doi:10.1093/ageing/afn051]

6. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Selby JV (2009) Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 301:1565–1572 [PMID:19366776 doi:10.1001/jama.2009.460]
7. Rizzo MR, Marfella R, Barbieri M, Boccardi V, Vestini F, Lettieri B, Canonico S, Paolisso G (2010) Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. Diabetes Care 33:2169–2174 [PMID: 20573753 doi:10.2337/dc10-0389]
8. Jacobson AM, Musen G, Ryan CM, Silvers N, Cleary P, Waberski B, Burwood A, Weinger K, Bayless M, Dahms W, Harth J (2007) Long term effect of diabetes and its treatment on cognitive function. N Engl J Med 356:1842–1852
9. Neumann KF, Rojo L, Navarrete LP, Farías G, Reyes P, Maccioni RB (2008) Insulin resistance and Alzheimer's disease: molecular links & clinical implications. Curr Alzheimer Res 5:438–447
10. Unger JW, Livingston JN, Moss AM (1991) Insulin receptors in the central nervous system: localization, signalling mechanisms and functional aspects. Prog Neurobiol 36:343–362
11. Di Carlo M, Pasquale Picone P, Carrotta R, Giacomazza D, Biagio S (2011) Alzheimer's disease and type 2 diabetes: different pathologies and same features. In: Zimering M (ed) Topics in the prevention, treatment and complications of type 2 diabetes. INTECH Open Access Publisher, Croatia
12. Ding J, Strachan MW, Reynolds RM, Frier BM, Deary IJ, Fowkes FG, Lee AJ, McKnight J, Halpin P, Swa K, Price JF (2010) Diabetic retinopathy and cognitive decline in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes 59:2883–2889
13. Ness J, Aronow WS (1999) Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice. J Am Geriatr Soc 47(10):1255–1256
14. Rokey R, Rolak LA, Harati Y, Kutka N, Verani MS (1984) Coronary artery disease in patients with cerebrovascular disease: a prospective study. Ann Neurol 16:50–53, CrossRefMedline
15. Di Pasquale G, Andreoli A, Pinelli G, Grazi P, Manini G, Tognetti F, Testa C (1986) Cerebral ischemia and asymptomatic coronary artery disease: a prospective study of 83 patients. Stroke 17:1098–1101
16. Jensen JK, Medina HM, Nørgaard BL, Øvrehus KA, Jensen JM, Nielsen LH, Maurovich-Horvat P, Engel LC, Januzzi JL, Hoffmann U, Truong QA (2012) Association of ischemic stroke to coronary artery disease using computed tomography coronary angiography. Int J Cardiol 160(3):171–174
17. Yoo J, Yang JH, Choi BW, Kim YD, Nam HS, Choi HY, Cho HJ, Lee HS, Cha MJ, Choi D, Nam CM, Jang Y, Lee DH, Kim J, Heo JH (2012) The frequency and risk of preclinical coronary artery disease detected using multichannel cardiac computed tomography in patients with ischemic stroke. Cerebrovasc Dis 33(3):286–294
18. Newman A, Fitzpatrick A, Lopez O et al (2005) Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. J Am Geriatr Soc 53(7):1101–1107
19. Graban A, Bednarska-Makaruk M, Bochynska A, Lipczynska-Lojkowska W, Ryglewicz D, Wehr H (2009) Vascular and biochemical risk factors of vascular dementia after lacunar strokes (S-VaD) and after multiinfarcts in strategic areas (M-VaD). J Neurol Sci 283(1–2):116–118
20. Koschack J, Irle E (2005) Small hippocampal size in cognitively normal subjects with coronary artery disease. Neurobiol Aging 26:865–871
21. Soneira CF, Scott TM (1996) Severe cardiovascular disease and Alzheimer's disease: senile plaque formation in cortical areas. Clin Anat 9:118–127
22. Stellos K, Katsiki N, Tatsidou P, Bigalke B, Laske C (2012) Association of platelet activation with vascular cognitive impairment: implications in dementia development? Curr Vasc Pharmacol 12(1):152–154
23. Gardner TJ, Horneffer PJ, Manolio TA, Pearson TA, Gott VL, Baumgartner WA, Borkon AM, Watkins L Jr, Reitz BA (1985) Stroke following coronary artery bypass grafting: a ten-year study. Ann Thorac Surg 40(6):574–581

24. Puskas JD, Winston AD, Wright CE, Gott JP, Brown WM 3rd, Craver JM, Jones EL, Guyton RA, Weintraub WS (2000) Stroke after coronary artery operation: incidence, correlates, outcome, and cost. Ann Thorac Surg 69(4):1053–1056
25. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE (1995) The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 98(5):476–484
26. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 31(19):2369–2429
27. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB (1996) Stroke severity in atrial fibrillation. The Framingham Study. Stroke 27(10):1760–1764
28. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A (1997) Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. Stroke 28(2):316–321
29. Collins AJ, Foley RN, Herzog C et al (2011) US renal data system 2010 annual data report. Am J Kidney Dis 57(Suppl 1):A8, e1–e526
30. Seifter JL, Samuels MA (2011) Uremic encephalopathy and other brain disorders associated with renal failure. Semin Neurol 31(2):139–143
31. Zepeda-Orozco D, Quigley R (2012) Dialysis disequilibrium syndrome. Pediatr Nephrol 27(12):2205–2211
32. Alfrey AC, LeGendre GR, Kachney MD (1976) The dialysis encephalopathy syndrome: possible aluminum intoxication. N Engl J Med 294:184–188
33. Nakayama M, Metoki H, Terawaki H et al (2007) Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population - the Ohasama study. Nephrol Dial Transplant 22:1910
34. Vazquez E, Sanchez-Perales C, Lozano C et al (2003) Comparison of prognostic value of atrial fibrillation versus sinus rhythm in patients on long-term hemodialysis. Am J Cardiol 92:868
35. Kimmel PL, Thamer M, Richard CM, Ray NF (1998) Psychiatric illness in patients with end-stage renal disease. Am J Med 105(3):214
36. Cohen SD, Norris L, Acquaviva K, Peterson RA, Kimmel PL (2007) Screening, diagnosis, and treatment of depression in patients with end-stage renal disease. Clin J Am Soc Nephrol 2(6):1332
37. Kim CD, Lee HJ, Kim DJ et al (2007) High prevalence of leukoaraiosis in cerebral magnetic resonance images of patients on peritoneal dialysis. Am J Kidney Dis 50:98
38. Martinez-Vea A, Salvadó E, Bardají A et al (2006) Silent cerebral white matter lesions and their relationship with vascular risk factors in middle-aged predialysis patients with CKD. Am J Kidney Dis 47:241
39. Gerson AC, Butler R, Moxey-Mims M et al (2006) Neurocognitive outcomes in children with chronic kidney disease: Current findings and contemporary endeavors. Ment Retard Dev Disabil Res Rev 12(3):208–215
40. Kurella Tamura M, Wadley V, Yaffe K et al (2008) Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis 52(2):227
41. Wolfgram DF, Szabo A, Murray AM, Whittle J (2015) Risk of dementia in peritoneal dialysis patients compared with hemodialysis patients. Perit Dial Int 35(2):189–198
42. Somers VK, White DP, Amin R et al (2008) Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol 52(8):686–717

43. Heusser K, Tank J, Engeli S et al (2010) Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. Hypertension 55(3):619–626
44. Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK (1999) Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. Circulation 99(9):1183–1189
45. Weiss JW, Liu Y, Li X, Ji ES (2012) Nitric oxide and obstructive sleep apnea. Respir Physiol Neurobiol 184(2):192–196
46. Manolis AJ, Poulimenos LE, Kallistratos MS, Gavras I, Gavras H (2014) Sympathetic overactivity in hypertension and cardiovascular disease. Curr Vasc Pharmacol 12(1):4–15
47. Devulapally K, Pongonis R, Khayat R (2009) OSA: the new cardiovascular disease: part II: overview of cardiovascular diseases associated with obstructive sleep apnea. Heart Fail Rev 14(3):155–164
48. Gami AS, Pressman G, Caples SM et al (2004) Association of atrial fibrillation and obstructive sleep apnea. Circulation 110(4):364–367
49. Marin JM, Carrizo SJ, Vicente E, Agusti AG (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 365(9464):1046–1053
50. Gonzaga C, Bertolami A, Bertolami M, Amodeo C, Calhoun D (2015) Obstructive sleep apnea, hypertension and cardiovascular diseases. J Hum Hypertens 29(12):705–712
51. Logan AG, Perlikowski SM, Mente A et al (2001) High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 19(12):2271–2277
52. Gonçalves SC, Martinez D, Gus M et al (2007) Obstructive sleep apnea and resistant hypertension: a case-control study. Chest 132(6):1858–1862
53. Furtner M, Staudacher M, Frauscher B et al (2009) Cerebral vasoreactivity decreases overnight in severe obstructive sleep apnea syndrome: a study of cerebral hemodynamics. Sleep Med 10(8):875–881
54. Phillips SA, Olson EB, Morgan BJ, Lombard JH (2004) Chronic intermittent hypoxia impairs endothelium-dependent dilation in rat cerebral and skeletal muscle resistance arteries. Am J Physiol Heart Circ Physiol 286(1):H388–H393
55. Baguet JP, Hammer L, Lévy P et al (2005) The severity of oxygen desaturation is predictive of carotid wall thickening and plaque occurrence. Chest 128(5):3407–3412
56. Lipford MC, Flemming KD, Calvin AD et al (2015) Associations between cardioembolic stroke and obstructive sleep apnea. Sleep 38(11):1699–1705
57. Mehra R, Benjamin EJ, Shahar E et al (2006) Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. Am J Respir Crit Care Med 173(8):910–916
58. Yaranov DM, Smyrlis A, Usatii N et al (2015) Effect of obstructive sleep apnea on frequency of stroke in patients with atrial fibrillation. Am J Cardiol 115(4):461–465
59. Kim Y, Koo YS, Lee HY, Lee SY (2016) Can continuous positive airway pressure reduce the risk of stroke in obstructive sleep apnea patients? A systematic review and meta-analysis. PLoS One 11(1):e0146317
60. Martínez-García MA, Soler-Cataluña JJ, Ejarque-Martínez L et al (2009) Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. Am J Respir Crit Care Med 180(1):36–41
61. Yang Q, Wang Y, Feng J, Cao J, Chen B (2013) Intermittent hypoxia from obstructive sleep apnea may cause neuronal impairment and dysfunction in central nervous system: the potential roles played by microglia. Neuropsychiatr Dis Treat 9:1077–1086
62. Ferini-Strambi L, Baietto C, Di Gioia MR et al (2003) Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res Bull 61(1):87–92
63. Dewan NA, Nieto FJ, Somers VK (2015) Intermittent hypoxemia and OSA: implications for comorbidities. Chest 147(1):266–274

64. Kaminska M, Lafontaine AL, Kimoff RJ (2015) The interaction between obstructive sleep apnea and Parkinson's disease: possible mechanisms and implications for cognitive function. Parkinsons Dis 2015:849472
65. Chen HL, Lu CH, Lin HC et al (2015) White matter damage and systemic inflammation in obstructive sleep apnea. Sleep 38(3):361–370
66. Daulatzai MA (2012) Pathogenesis of cognitive dysfunction in patients with obstructive sleep apnea: a hypothesis with emphasis on the nucleus tractus solitarius. Sleep Disord 2012:251096

Pathophysiology of Brain Damage in Hypertension: Small Vessel Disease

5

Enrico Agabiti-Rosei, Damiano Rizzoni, and Pedro Cunha

5.1 Microvascular Structure in Hypertension

Resistance arteries (internal diameter <350 μm) and capillaries (internal diameter <7 μm) are key elements in the control of blood pressure (BP) [1]. Thus, structural changes in the microcirculation may directly and strongly affect BP values. In fact, it is now widely accepted that structural microvessel abnormalities are common alterations associated with chronic hypertension [1, 2]. A thickened arterial wall together with a reduced lumen (a process known as remodelling) may play an important role in the increase in vascular resistance and may also be an adaptive response to the increased haemodynamic load.

In the past few years, evidence has suggested that hypertensive injury of the small arteries may also participate in the pathophysiology of the complications of hypertension [3].

In humans, direct investigation of changes in the small resistance arteries obtained from subcutaneous and omental fat tissue of essential hypertensive

E. Agabiti-Rosei (✉)
Clinica Medica, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

Clinica Medica, Department of Medical and Surgical Sciences, University of Brescia, c/o 2a Medicina, Spedali Civili., Brescia 25100, Italy
e-mail: enrico.agabitirosei@unibs.it

D. Rizzoni
Clinica Medica, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

Division of Medicine, Istituto Clinico Città di Brescia, Brescia, Italy

P. Cunha
Department of Internal Medicine, Centro Hospitalar do Alto Ave. University of Minho, Guimarães, Portugal

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_5

patients has been made possible by using wire or pressure micromyographic methods [2, 4, 5].

The majority of the available data indicates that, in patients with essential hypertension, the resistance arteries show a greater media thickness, a reduced lumen and external diameter with an increased media-to-lumen ratio, without significant changes in the total amount of wall tissue, as indicated by an unchanged media cross-sectional area. Therefore, most structural changes observed in these patients are the consequence of inward eutrophic remodelling (rearrangement of the same amount of wall material around a smaller vessel lumen) [6], without net cell growth. In contrast, in patients with some forms of more severe hypertension or secondary hypertension (such as renovascular hypertension and primary aldosteronism) [7] and in diabetic patients [8], hypertrophic remodelling may be detected, with a more evident contribution by cell growth, including vascular smooth muscle cell hypertrophy (increase in volume) or hyperplasia (increase in cell numbers) [9]. However, the molecular events involved in the development of remodelling in systemic hypertension are still poorly understood, particularly the mechanisms leading to eutrophic remodelling, although changes in the extracellular matrix/integrins might be involved.

5.1.1 Small Resistance Artery Structure and Cardio-Cerebrovascular Risk

An important consequence of the presence of structural alterations in small resistance arteries and arterioles is impairment of the organ's vasodilator reserve [10]. The presence of structural alterations in the microcirculation may represent an important link between hypertension and ischemic heart disease, cerebral damage and renal failure. In fact, a relationship between structural alterations in the subcutaneous small resistance arteries and the occurrence of cardiovascular events has been demonstrated in a population of hypertensive and diabetic patients at relatively high cardiovascular risk during a follow-up of 5.6 years [11]. Structural alterations in the microcirculation may be considered an important link between hypertension and ischemic heart disease, heart failure, cerebral ischemic attacks and renal failure. Studies have shown that structural alterations in the microcirculation (as indicated by greater media-to-lumen ratios in subcutaneous small resistance arteries) are probably the most powerful predictor of cardiovascular events in a high-risk population of hypertensive patients [11]. In a multivariate Cox regression analysis, microvascular structure and pulse pressure were the only predictors of cardiovascular events, even when all traditional risk factors were included in the model [11].

The prognostic role of small resistance artery structure has recently been confirmed in cohorts of hypertensive patients with a medium cardiovascular risk [12, 13].

In addition, the characteristics of vascular remodelling seem to matter. For the same internal diameter values, subjects who suffered cardiovascular events had a greater media cross-sectional area, in comparison with those without cardiovascular

events [3]. Therefore, it seems that, for the same size of vessel, more-consistent cell growth (hypertrophic remodelling) means an even-worse prognosis. Therefore, smooth muscle cell growth seems to be a less efficient compensatory mechanism for increased BP values compared with eutrophic remodelling [3], with consequences in terms of cardiovascular events.

It has also recently been suggested that alterations in the microcirculation may be involved in the abrupt rise in BP during the early morning, which is, in turn, associated with an increased incidence of cardiovascular events [14].

More recently, Buus et al. [15] demonstrated a prognostic role of changes in the microvascular structure, as evaluated by the media-to-lumen ratio of the subcutaneous small resistance arteries during antihypertensive treatment. This demonstration of the prognostic role of changes in microvascular structure during treatment, independently of the extent of BP reduction, could substantially support the idea of considering the microvascular structure as an intermediate endpoint in the evaluation of the benefits of antihypertensive treatment [16].

5.1.2 Effect of Treatment on Small Artery Structure

Some intervention studies with specific drugs have demonstrated an improvement or even an almost-complete normalisation of the structure of subcutaneous small resistance arteries with angiotensin-converting enzyme (ACE) inhibitors (cilazapril, perindopril, lisinopril), calcium channel blockers (nifedipine, amlodipine, isradipine) and angiotensin II receptor blockers (losartan, irbesartan, candesartan, olmesartan and valsartan) [2, 17, 18]. In contrast, the β-blocker atenolol and the diuretic hydrochlorothiazide had no effects on resistance vessels, despite a BP reduction similar to that observed with ACE inhibitors [2, 17, 18]. More than 300 patients were investigated in these intervention studies, using a reliable and precise micromyographic approach [4, 7, 18]. ACE inhibitors proved to be significantly more effective than the β-blocker atenolol in terms of changes in the media-to-lumen ratio [18]. The same result was obtained when comparing dihydropyridine calcium channel blockers and atenolol or angiotensin receptor blockers and atenolol [18].

Various reasons may be suggested to explain the differing effects of different drug classes on the small artery structure. ACE inhibitors and angiotensin receptor blockers might possess growth-inhibiting and antioxidant properties that could be responsible for their beneficial effect on the microcirculation [2]. Additional reasons are the lack of vasodilatory effects of atenolol [19] and the heterogeneous effect of drug treatments on small and large vessel stiffness and distensibility. In one study, performed in hypertensive patients with non-insulin-dependent diabetes mellitus [20], brachial pulse pressure (a rough marker of arterial stiffness) was significantly higher in hypertensives than in normotensive subjects before random assignment and was significantly reduced only by the angiotensin receptor antagonist valsartan, while no change was observed with atenolol. Angiotensin receptor blockers seem to also be particularly effective in reducing vascular stiffness and collagen content in small resistance arteries [21, 22], while the stiffness of small

arteries (evaluated by the stress-strain relationship) was, in fact, enhanced in patients treated with atenolol [23]. Recently, a significant reduction in small resistance artery stiffness was observed in essential hypertensive patients treated with the selective mineralocorticoid receptor blocker eplerenone, but not in those treated with atenolol [23]. The effects of olmesartan on vascular remodelling have been studied in the Vascular Improvement with Olmesartan medoxomil Study (VIOS) [24]. This randomised, parallel-group study compared the effects of antihypertensive therapy based on olmesartan or atenolol on vascular remodelling in subcutaneous small resistance arteries in nondiabetic patients with stage I hypertension. After 1 year of treatment, olmesartan decreased the wall-to-lumen ratio. In contrast, atenolol-based treatment did not affect vascular remodelling. Similarly, the augmentation index, an index of large artery compliance, was improved by olmesartan, but not by atenolol [24].

In patients with more severe hypertension (i.e. patients with left ventricular hypertrophy or concomitant diabetes mellitus), a reduction, but not full normalisation of the media-to-lumen ratio of subcutaneous small resistance arteries, was obtained by effective antihypertensive treatment [17, 18], with the media-to-lumen ratio remaining significantly higher than that observed in normotensive controls.

5.2 Cerebral Autoregulation

The cerebral circulation is characterised by the physiological phenomenon of autoregulation of the perfusion. Cerebral autoregulation tightly controls blood flow to the brain by coupling cerebral metabolic demand to cerebral perfusion. In fact, in almost all mammalian studies, cerebral blood flow remains stable despite changes in cerebral perfusion pressure and in systemic arterial pressure [25].

The autoregulatory responses of cerebral blood vessels during changes in perfusion pressure are mediated by various mechanisms [26]. Metabolic mechanisms appear to predominate during reductions in perfusion pressure, but myogenic responses are detected under some conditions. There are major differences in the autoregulatory capacity of the cerebrum and brainstem [27], and some studies have suggested that the autoregulatory responses of cerebral vessels in vitro depend on the endothelium [26, 28]. Calcium entry inhibitors greatly impair the autoregulatory responses of cerebral vessels, which suggest that the entry of extracellular calcium is essential for cerebral autoregulation. Chronic hypertension alters cerebral autoregulation and is associated with changes in the cerebral microvascular structure; as a consequence, autoregulatory constriction is increased [26, 28]. In fact, chronic hypertension produces structural remodelling and hypertrophy of the cerebral blood vessels (see following chapter) and a shift in the relationship between cerebral blood flow and systemic BP [28]. Humoral mechanisms may have important effects on cerebral blood vessels and blood flow, namely, endothelium-dependent responses of cerebral arterioles to receptor- and non-receptor-mediated agonists are impaired during chronic hypertension. Alterations in the endothelium-dependent responses of cerebral arterioles during

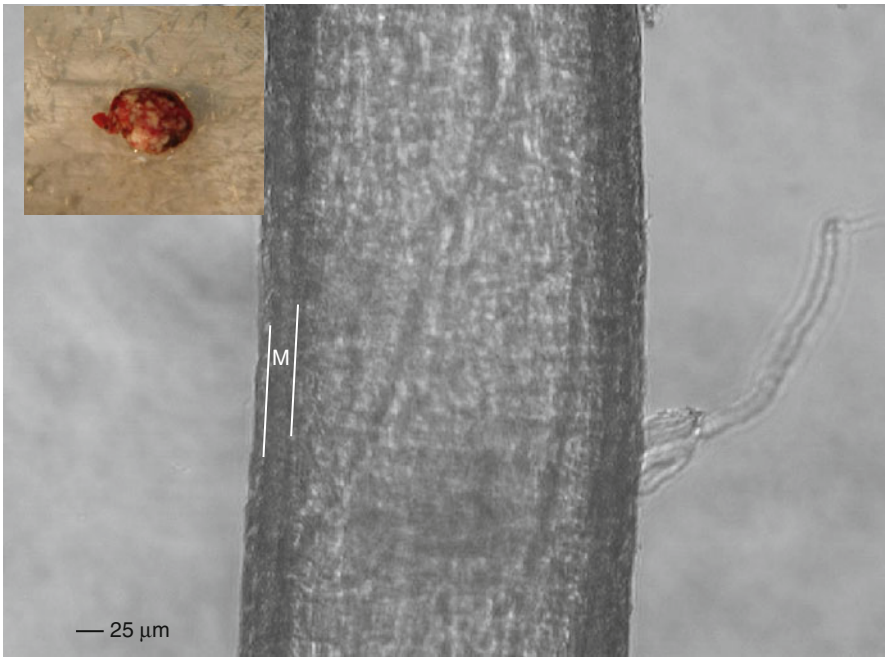

Fig. 5.1 Cerebral artery of a hypertensive patient (Z.L. 62 years) mounted on a pressure micromyograph. Media-to-lumen ratio = 0.083, internal diameter 296 µm. *Left*: photograph of the cerebral tissue from which the vessel was dissected

chronic hypertension appear to be due to release of an endothelium-derived contracting factor [28].

Due to the right shift of the pressure-flow relationship in hypertensive patients, excessive BP reduction during antihypertensive treatment might expose these patients to an abrupt decrease in regional flow and possibly to consequent cellular ischemia [29].

5.3 Cerebral Microcirculation

Studies in humans and in animal models of genetic and experimental hypertension have demonstrated the presence of an increased media-to-lumen ratio of the small resistance arteries in almost all vascular districts explored [1, 7, 17], including the cerebral vasculature [30] (Figs. 5.1 and 5.2). Eutrophic remodelling has been observed in human essential hypertension, both in the subcutaneous [7] and the cerebral small arteries [30] (Fig. 5.2). In addition, microvascular rarefaction, and especially capillary rarefaction, may be observed in hypertensive patients, in several vascular districts [17, 31], including the brain [30].

Since structural alterations in the cerebral microcirculation might be involved in clinical events observed in human essential hypertension, the possible relationships

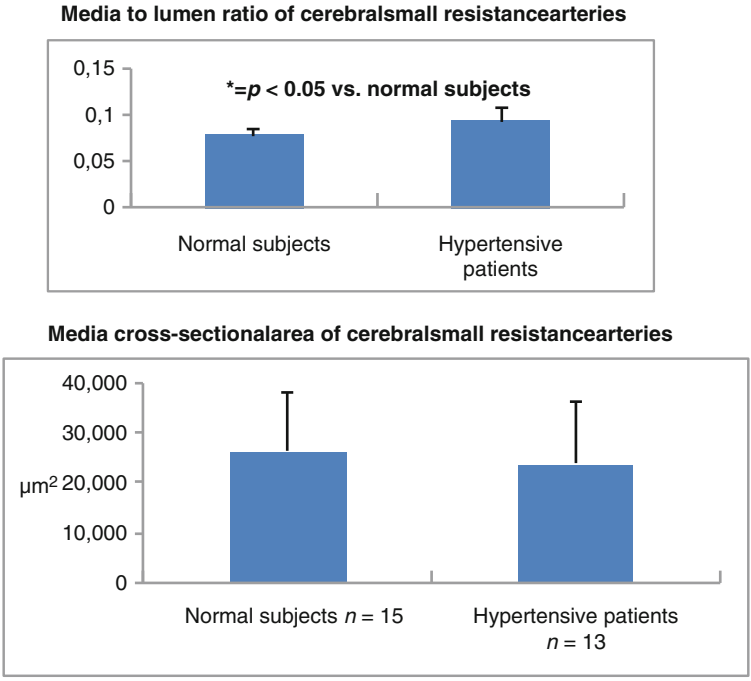

Fig. 5.2 Structural alterations in cerebral small arteries in patients with essential hypertension compared with normotensive controls: increased media-to-lumen ratio, no change in media cross-sectional area (Rizzoni et al. [30])

between the structure of small resistance arteries or microvascular density in the brain of hypertensive patients and normotensive controls and cerebral regional blood flow was studied [32]. A statistically significant negative correlation was observed between the media-to-lumen ratio of the cerebral arteries and cerebral blood flow in the cortical grey matter ($r=-0.516$, $p<0.05$), basal ganglia ($r=-0.521$, $p<0.05$), thalami ($r=-0.527$ $p<0.05$) and subcortical white matter ($r=-0.612$, $p<0.01$) (Figs. 5.3 and 5.4). Microvascular structure might play a major role in controlling cerebral blood flow, with possible clinical consequences [32]. It was previously postulated that a part of ischemic/haemorrhagic strokes could be attributed to hypertensive microvascular alterations [33–35]. In particular, it is known that cerebral small vessel diseases are responsible for 20–30 % of ischemic strokes and for a considerable proportion of cerebral haemorrhages and vascular encephalopathies [33].

Together with capillary rarefaction [36, 37], compliance and changes in distensibility ascribed to vessel wall fibrosis have been observed in the cerebral microvasculature of animal models of hypertension [38–40]. A study of the mechanical properties and elastin and collagen content of human cerebral small vessels [30] found no difference between groups in collagen content or the mechanical properties of cerebral small arteries [30]. No statistically significant evidence of increased

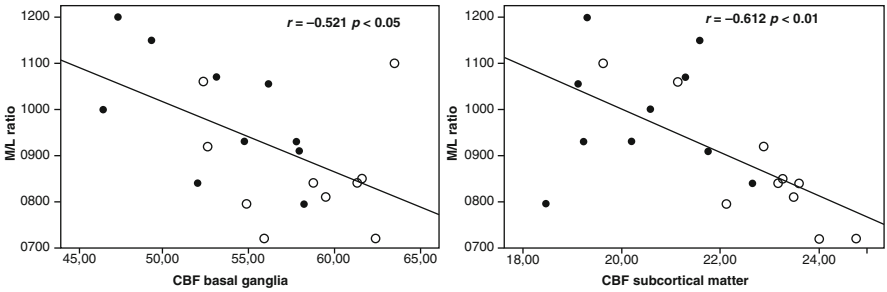

Fig. 5.3 *Left graph*: correlation between cerebral blood flow in the basal ganglia (*right*) and media-to-lumen ratio of cerebral arteries. *Right graph:* correlation between cerebral blood flow in the subcortical white matter and media-to-lumen ratio of cerebral arteries. *Empty circles*: normotensive subjects, *full circles*: hypertensive patients (De Ciuceis et al. [32])

stiffness or fibrosis was observed in the small cerebral vessels of essential hypertensive patients, although intravascular collagen content was slightly greater. However, previous data in animal models of genetic or experimental hypertension have shown reduced distensibility in the middle cerebral artery [38, 41] or in larger vessels [39], together with a paradoxically increased distensibility in smaller cerebral vessels [39, 40]. One important factor may be the age of the rat, since ageing per se is a major determinant of changes in the mechanics and composition of cerebral arterioles [42]. Little, and contested, data are available on the changes in the mechanical properties of small resistance arteries in hypertensive humans, which have mainly been evaluated in the subcutaneous vascular bed. Thybo et al. [43] found no differences in the relationship between the incremental elastic modulus and wall stress in subcutaneous small arteries obtained by gluteal biopsies from essential hypertensive patients and normotensive controls, and other studies found similar results [9, 22]. Only one study has found a paradoxical increase in distensibility in subcutaneous small arteries from essential hypertensive patients [44].

Large artery stiffening has also been shown to be related to cerebral lacunar infarctions [45] and to large white matter hyperintensities [46], which are usually an expression of cerebral microvascular disease. Elderly subjects with high intracranial pulsatility display a smaller brain volume and larger ventricles, supporting the notion that excessive cerebral arterial pulsatility harms the brain [47]. Thus, a close relationship has been established between microvascular damage in the brain and kidney and indices of age and hypertension (pulse pressure, aortic pulse wave velocity and augmentation index) [48]. A possible pathophysiological explanation for this link may be offered on the basis of differential input impedance in the brain and kidney compared with other systemic vascular beds: torrential flow and low resistance to flow in these organs expose small arterial vessels to the high-pressure fluctuations that exist in the carotid, vertebral and renal arteries. Such fluctuations, measurable as central pulse pressure, increase three- to fourfold with age. Exposure of small vessels to highly pulsatile pressure and flow explains microvascular damage and the resulting renal insufficiency and intellectual deterioration [48].

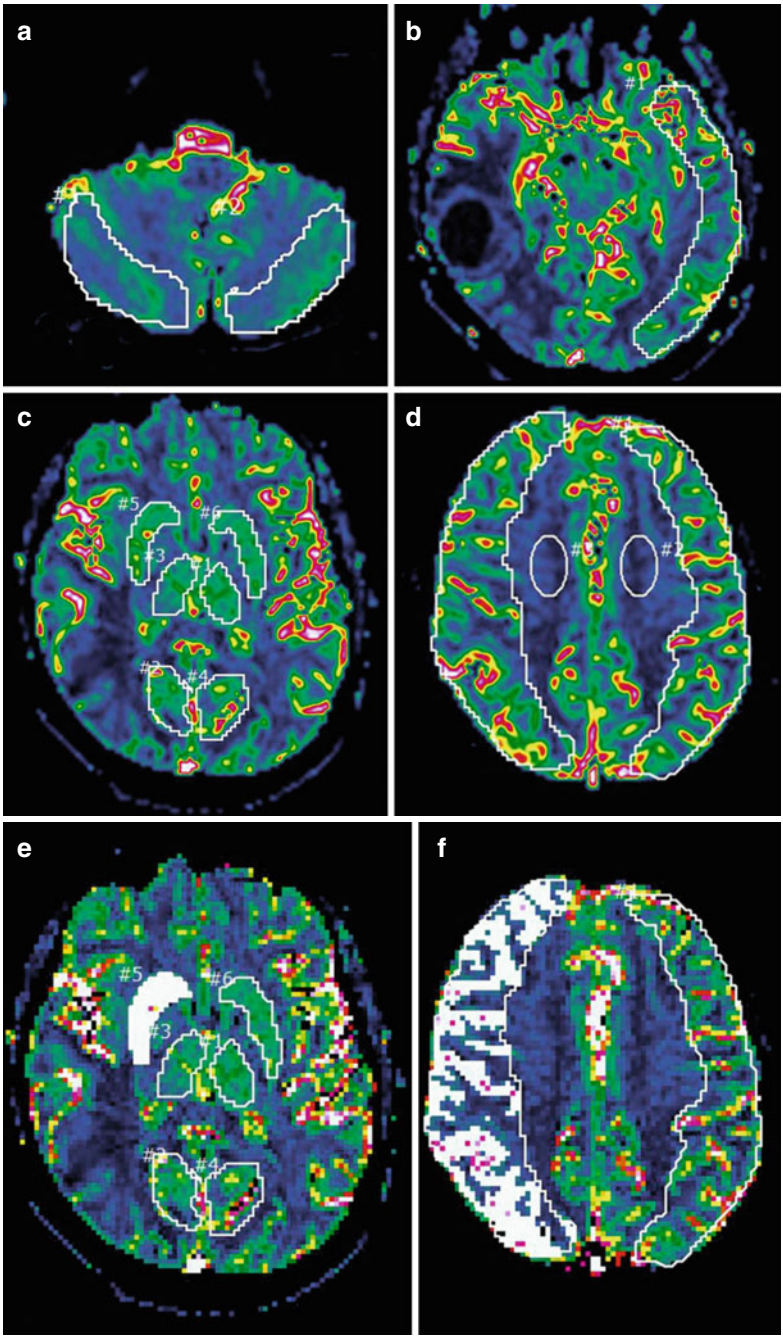

Fig. 5.4 Cerebral blood flow maps with manually traced regions of interest in the cerebellum (**a**); left temporal cortex (**b**); basal ganglia, thalami and calcarine cortex (**c**); and fronto-parietal cortex (**d**) (De Ciuceis et al. [32]). Cerebral blood flow maps with bilateral regions of interest including the basal ganglia, thalami, calcarine cortex and fronto-parietal cortex. On the right side, automatic segmentation was applied to the right basal ganglia (**e**) and fronto-parietal cortex (**f**) (De Ciuceis et al. [32])

Therefore, the logical approach to prevention and treatment requires the reduction of central pulse pressure [48]. Because the aorta and the large arteries are not directly affected by drugs, this entails a reduction in wave reflection by dilation of the conduit arteries elsewhere in the body [48]. This can be accomplished by regular exercise and by drugs such as nitrates, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [48].

Pulse pressure and pulse wave velocity, markers of arterial stiffness, have been associated with stroke, dementia and lowered levels of cognitive function. Aggressive treatment of risk factors associated with greater arterial stiffness may help preserve cognitive function with increasing age [49].

The pulsatility index has been associated with lower memory scores and worse performance on tests assessing executive function. When magnetic resonance imaging measurements (grey and white matter volumes, white matter hyperintensity volumes and prevalent subcortical infarcts) were included in cognitive models, the evidence showed that increased aortic stiffness and excessive flow pulsatility damage the microcirculation, leading to quantifiable tissue damage and reduced cognitive performance. Marked stiffening of the aorta is associated with reduced wave reflection at the interface between the carotid and aorta, the transmission of excessive flow pulsatility into the brain, microvascular structural brain damage and lower scores in various cognitive domains [50].

While aortic stiffening is the principal cause of cardiovascular disease with age in persons who escape atherosclerotic complications, it is not a specific target for therapy. The principal target is the smooth muscle in distributing arteries, whose relaxation has little effect on peripheral resistance but causes a substantial reduction in the magnitude of wave reflection. This relaxation is achieved through regular exercise and with the vasodilating drugs that are used in the current treatment of hypertension and cardiac failure [51].

Middle cerebral artery pulsatility was the strongest physiological correlate of leukoaraiosis, independent of age, and was dependent on aortic diastolic BP and pulse pressure and aortic and MCA stiffness, supporting the hypothesis that large artery stiffening results in increased arterial pulsatility with transmission to the cerebral small vessels resulting in leukoaraiosis [52].

5.4 Retinal Vessels as a Non-invasive Target to Explore the Cerebral and Systemic Microcirculation

The retinal microcirculation is, perhaps, the only microvascular district that may be directly observed and evaluated by a relatively simple funduscopic examination. The cerebral and retinal circulation share anatomic, physiological and embryological features [53], making the evaluation of microvascular structure in the retina a very good candidate for non-invasive assessment of hypertension-induced changes in the microvessels.

Recently, Harzny et al. [54] proposed a new method for the assessment of structural abnormalities in the retinal vascular district. Quantification of the

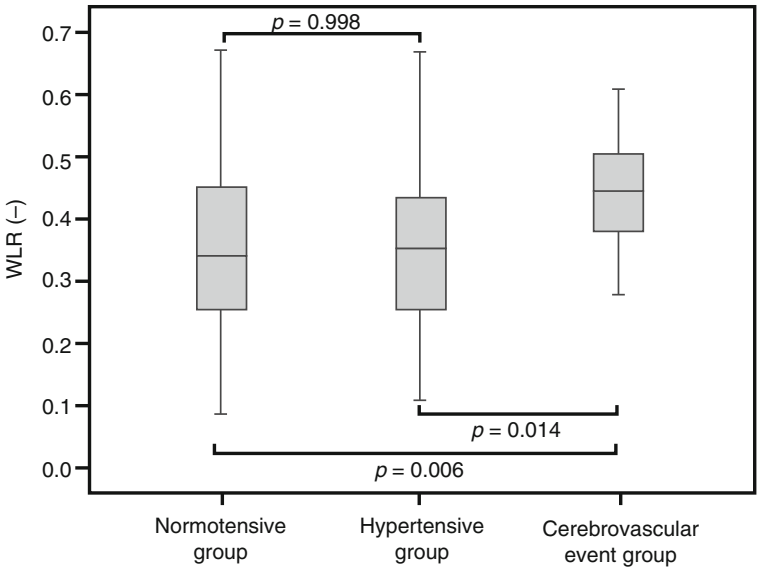

Fig. 5.5 Wall-to-lumen ratio of retinal arteries in patients with and without cerebrovascular events (From Ref. [54])

wall-to-lumen ratio of the retinal arterioles was made using scanning laser Doppler flowmetry (SLDF) [54]. This showed that the wall-to-lumen ratio of the retinal arterioles is increased in untreated hypertensive patients [55] and in treated patients with cerebrovascular events [54] (Fig. 5.5). In addition, the wall-to-lumen ratio seems to correlate with indices of microvascular damage in other vascular districts, such as albumin excretion by the kidney [56]. We recently validated this non-invasive approach by demonstrating a close correlation between the media-to-lumen ratio of the subcutaneous small arteries and the wall-to-lumen ratio of retinal arterioles evaluated non-invasively by scanning laser Doppler flowmetry [57]. Using SLDF, Ott et al. [58] have very recently shown that central pulse pressure correlated with the wall-to-lumen ratio and that the central augmentation index, normalised to a heart rate of 75 beats per minute, correlated with the wall-to-lumen ratio. Multiple regression analysis revealed an independent relationship between the wall-to-lumen ratio and central pulse pressure, but not with other classical cardiovascular risk factors.

An even more recent study using the same technique found that the wall-to-lumen ratio of the retinal arterioles was associated with clinic systolic and pulse pressure, to 24-h systolic and pulse pressure and to central systolic and pulse pressure [59].

Thus, central pulse pressure, which is indicative of changes in the large conduit arteries, is an independent determinant of vascular remodelling in the small retinal arterioles [60]. This relationship indicates coupling and crosstalk between the microvascular and macrovascular changes attributable to hypertension [60]. In fact, an increased wall-to-lumen ratio and rarefaction of the small arteries are major

factors for an increase in mean BP; the higher mean BP, in turn, may increase large artery stiffness through the loading of the stiff components of the arterial wall at high BP levels; finally, increased large artery stiffness may be a major determinant of increased pulse pressure, which, in turn, damages small arteries in different organs (heart, brain, retina, kidney) and, in general, favours the development of target organ damage [60]. Thus, the vicious circle of the crosstalk between the small and large arteries exacerbates arterial damage [60, 61].

5.5 Summary and Conclusions

Changes in the microvascular structure of the cerebral circulation, both in terms of an increased media-to-lumen ratio of the cerebral small resistance arteries or the wall-to-lumen ratio of the retinal arterioles, together with capillary rarefaction, may have important pathophysiological and clinical consequences. Cerebral small vessel disease is associated with an increased risk of death and ischemic stroke [62]. Changes in large artery stiffness (including carotid artery stiffness) may be related to microvascular alterations and contribute to cerebrovascular events, including cerebral microbleeds, even in deep locations attributable to hypertension [63]. The brain may play a crucial role in the onset of essential hypertension [48] but is also a main target of the detrimental effects of hypertension; changes in small artery structuring may be a crucial mechanism in the development of the complications of hypertension [64], especially in the brain.

References

1. Mulvany MJ, Aalkjaer C (1990) Structure and function of small arteries. Physiol Rev 70:921–971
2. Schiffrin EL (2004) Remodeling of resistance arteries in essential hypertension and effects of antihypertensive treatment. Am J Hypertens 17(12 Pt 1):1192–1200
3. Izzard AS, Rizzoni D, Agabiti-Rosei E, Heagerty AM (2005) Small artery structure and hypertension: adaptive changes and target organ damage. J Hypertens 23:247–250
4. Aalkjaer C, Haegerty AM, Petersen KK, Swales JD, Mulvany MJ (1987) Evidence for increased media thickness, increased neural amine uptake, and depressed excitation-contraction coupling in isolated resistance vessels from essential hypertensives. Circ Res 61(2):181–186
5. Aalkjaer C, Eiskjaer H, Mulvany MJ, Jespersen B, Kjaer T, Sorensen SS, Pedersen EB (1989) Abnormal structure and function of isolated subcutaneous resistance vessels from essential hypertensive patients despite antihypertensive treatment. J Hypertens 7:305–310
6. Heagerty AM, Aalkjaaer C, Bund SJ, Korsgaard N, Mulvany MJ (1993) Small artery structure in hypertension. Dual process of remodeling and growth. Hypertension 21:391–397
7. Rizzoni D, Porteri E, Castellano M, Bettoni G, Muiesan ML, Muiesan P, Giulini SM, Agabiti Rosei E (1996) Vascular hypertrophy and remodeling in secondary hypertension. Hypertension 28:785–790
8. Rizzoni D, Porteri E, Guelfi D, Muiesan ML, Valentini U, Cimino A, Girelli A, Rodella L, Bianchi R, Sleiman I, Agabiti Rosei E (2001) Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin dependent diabetes mellitus. Circulation 103:1238–1244

9. Rizzoni D, Porteri E, Guelfi D, Piccoli A, Castellano M, Pasini G, Muiesan ML, Mulvany MJ, Agabiti Rosei E (2000) Cellular hypertrophy in subcutaneous small arteries of patients with renovascular hypertension. Hypertension 35:931–935
10. Rizzoni D, Palombo C, Porteri E, Muiesan ML, Kozàkovà M, La Canna G, Nardi M, Guelfi D, Salvetti M, Morizzo C, Vittone F, Agabiti Rosei E (2003) Relationships between coronary vasodilator capacity and small artery remodeling in hypertensive patients. J Hypertens 21:625–632
11. Rizzoni D, Porteri E, Boari GEM, De Ciuceis C, Sleiman I, Muiesan ML, Castellano M, Miclini M, Agabiti-Rosei E (2003) Prognostic significance of small artery structure in hypertension. Circulation 108:2230–2235
12. De Ciuceis C, Porteri E, Rizzoni D, Rizzardi N, Paiardi S, Boari GEM, Miclini M, Zani F, Muiesan ML, Donato F, Salvetti M, Castellano M, Tiberio GA, Giulini SM, Agabiti Rosei E (2007) Structural alterations of subcutaneous small arteries may predict major cardiovascular events in hypertensive patients. Am J Hypertens 20:846–852
13. Mathiassen ON, Buus NH, Sihm I, Thybo NK, Morn B, Schroeder AP, Thygesen K, Aalkjaer C, Lederballe O, Mulvany MJ, Christensen KL (2007) Small artery structure is an independent predictor of cardiovascular events in essential hypertension. J Hypertens 25:1021–1026
14. Rizzoni D, Porteri E, Platto C, Rizzardi N, De Ciuceis C, Boari GEM, Muiesan ML, Salvetti M, Zani F, Miclini M, Paiardi S, Castellano M, Agabiti Rosei E (2007) Morning rise of blood pressure and subcutaneous small resistance artery structure. J Hypertens 25:1698–1703
15. Buus NH, Mathiassen ON, Fenger-Grøn M, Præstholm MN, Sihm I, Thybo NK, Schroeder AP, Thygesen K, Aalkjær C, Pedersen OL, Mulvany MJ, Christensen KL (2013) Small artery structure during antihypertensive therapy is an independent predictor of cardiovascular events in essential hypertension. J Hypertens 31:791–797
16. Mulvany MJ (2007) Small artery structure: time to take note? (editorial commentary). Am J Hypertens 20:853–854
17. Agabiti Rosei E, Rizzoni D (2007) Chapter 47: The effects of hypertension on the structure of human resistance arteries. In: Lip GYH, Hall JE (eds) Comprehensive hypertension. Mosby Elsevier, Philadelphia, pp 579–590
18. Agabiti-Rosei E, Heagerty AM, Rizzoni D (2009) Effects of antihypertensive treatment on small artery remodelling. J Hypertens 27(6):1107–1114
19. Mathiassen ON, Buus NH, Larsen ML, Mulvany MJ, Christensen KL (2007) Small artery structure adapts to vasodilatation rather than to blood pressure during antihypertensive treatment. J Hypertens 25:1027–1034
20. Savoia C, Touyz RM, Endemann DH, Pu Q, Ko EA, De Ciuceis C, Schiffrin EL (2006) Angiotensin receptor blocker added to previous antihypertensive agents on arteries of diabetic hypertensive patients. Hypertension 48:271–277
21. Rizzoni D, Porteri E, De Ciuceis C, Sleiman I, Rodella L, Rezzani R, Paiardi S, Bianchi R, Ruggeri G, Boari GEM, Muiesan ML, Salvetti M, Zani F, Miclini M, Agabiti Rosei E (2005) Effects of treatment with candesartan or enalapril on subcutaneous small resistance artery structure in hypertensive patients with NIDDM. Hypertension 45(Part 2):659–665
22. Park JB, Integan HD, Schiffrin EL (2000) Reduction of resistance artery stiffness by treatment with the AT(1)-receptor antagonist losartan in essential hypertension. J Renin Angiotensin Aldosterone Syst 1:40–45
23. Savoia C, Touyz RM, Amiri F, Schiffrin EL (2008) Selective mineralocorticoid receptor blocker eplerenone reduces resistance artery stiffness in hypertensive patients. Hypertension 51:432–439
24. Smith RD, Yokoyama H, Averill DB, Schiffrin EL, Ferrario CM (2008) Reversal of vascular hypertrophy in hypertensive patients through blockade of angiotensin II receptors. J Am Soc Hypertens 2:165–172
25. Dickinson J, Paton JFR (2012) Cerebrovascular hypertension. Book Guild Publishing, Sussex, pp 3–257
26. Faraci FM, Baumbach GL, Heistad DD (1989) Myogenic mechanisms in the cerebral circulation. J Hypertens Suppl 7:S61–S64

27. Baumbach GL, Heistad DD (1985) Regional, segmental, and temporal heterogeneity of cerebral vascular autoregulation. Ann Biomed Eng 13(3–4):303–310
28. Faraci FM, Baumbach GL, Heistad DD (1990) Cerebral circulation: humoral regulation and effects of chronic hypertension. J Am Soc Nephrol 1(1):53–57
29. Jordan JD, Powers WJ (2012) Cerebral autoregulation and acute ischemic stroke. Am J Hypertens 25:946–950
30. Rizzoni D, Ciuceis C, Porteri E, Paiardi S, Boari GEM, Mortini P, Cornali C, Cenzato M, Rodella LF, Borsani E, Rizzardi N, Platto C, Rezzani R, Agabiti Rosei E (2009) Altered structure of small cerebral arteries in patients with essential hypertension. J Hypertens 27(4):838–845
31. Antonios TF, Singer DR, Markandu ND, Mortimer PS, MacGregor GA (1999) Structural skin capillary rarefaction in essential hypertension. Hypertension 33:998–1001
32. De Ciuceis C, Cornali C, Porteri E, Mardighian D, Pinardi C, Fontanella MM, Rodella LF, Rezzani R, Rizzoni D, Boari GE, Agabiti Rosei E, Gasparotti R (2014) Cerebral small-resistance artery structure and cerebral blood flow in normotensive subjects and hypertensive patients. Neuroradiology 56:1103–1111
33. Ringelstein EB, Knecht S (2006) Cerebral small vessel diseases: manifestations in young women. Curr Opin Neurol 19:55–62
34. Baumgartner RW, Sidler C, Mosso M, Georgiadis D (2003) Ischemic lacunar stroke in patients with and without potential mechanism other than small-artery disease. Stroke 34:653–659
35. Dickinson CJ (2001) Why are strokes related to hypertension? Classic studies and hypotheses revisited. J Hypertens 19:1515–1521
36. Munzenmaier DH, Greene AS (2006) Chronic angiotensin II AT1 receptor blockade increases cerebral cortical microvessel density. Am J Physiol Heart Circ Physiol 290(2):H512–H516
37. Greene AS, Tonellato PJ, Lui J, Lombard JH, Cowley AW Jr (1989) Microvascular rarefaction and tissue vascular resistance in hypertension. Am J Physiol 256:H126–H131
38. Izzard AS, Horton S, Heerkens EH, Shaw L, Heagerty AM (2006) Middle cerebral artery structure and distensibility during developing and established phases of hypertension in the spontaneously hypertensive rat. J Hypertens 24:875–880
39. Hajdu MA, Baumbach GL (1994) Mechanics of large and small cerebral arteries in chronic hypertension. Am J Physiol 266(3 Pt 2):H1027–H1033
40. Baumbach GL, Hajdu MA (1993) Mechanics and composition of cerebral arterioles in renal and spontaneously hypertensive rats. Hypertension 21(6 Pt 1):816–826
41. Izzard AS, Graham D, Burnham MP, Heerkens EH, Dominiczak AF, Heagerty AM (2003) Myogenic and structural properties of cerebral arteries from the stroke-prone spontaneously hypertensive rat. Am J Physiol Heart Circ Physiol 285:H1489–H1494
42. Hajdu MA, Heistad DD, Siems JE, Baumbach GL (1990) Effects of aging on mechanics and composition of cerebral arterioles in rats. Circ Res 66:1747–1754
43. Thybo NK, Mulvany MJ, Jastrup B, Nielsen H, Aalkjaer C (1996) Some pharmacological and elastic characteristics of isolated subcutaneous small arteries from patients with essential hypertension. J Hypertens 14:993–998
44. Intengan HD, Deng LY, Li JS, Schiffrin EL (1999) Mechanics and composition of human subcutaneous resistance arteries in essential hypertension. Hypertension 33(1 Pt 2):569–574
45. Hashimoto J, Aikawa T, Imai Y (2008) Large artery stiffening as a link between cerebral lacunar infarction and renal albuminuria. Am J Hypertens 21(12):1304–1309
46. Brisset M, Boutouyrie P, Pico F, Zhu Y, Zureik M, Schilling S, Dufouil C, Mazoyer B, Laurent S, Tzourio C, Debette S (2013) Large-vessel correlates of cerebral small-vessel disease. Neurology 80:662–669
47. Wåhlin A, Ambarki K, Birgander R, Malm J, Eklund A (2014) Intracranial pulsatility is associated with regional brain volume in elderly individuals. Neurobiol Aging 35:365–372
48. O'Rourke MF, Safar ME (2005) Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 46:200–204
49. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB (2008) Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. Hypertension 51:99–104

50. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ (2011) Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. Brain 134(Pt 11):3398–3407
51. O'Rourke MF, Hashimoto J (2007) Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 50(1):1–13
52. Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM (2012) Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. Stroke 43:2631–2636
53. Wong TY, Mitchell P (2004) Hypertensive retinopathy. N Engl J Med 351:2310–2317
54. Harazny JM, Ritt M, Baleanu D, Ott C, Heckmann J, Schlaich MP, Michelson G, Schmieder RE (2007) Increased wall:lumen ratio of retinal arterioles in male patients with a history of a cerebrovascular event. Hypertension 50(4):623–829
55. Ritt M, Harazny JM, Ott C, Schlaich MP, Schneider MP, Michelson G, Schmieder RE (2008) Analysis of retinal arteriolar structure in never-treated patients with essential hypertension. J Hypertens 26(7):1427–1434
56. Ritt M, Harazny JM, Ott C, Schneider MP, Schlaich MP, Michelson G, Schmieder RE (2009) Wall-to-lumen ratio of retinal arterioles is related with urinary albumin excretion and altered vascular reactivity to infusion of the nitric oxide synthase inhibitor N-monomethyl-L-arginine. J Hypertens 27:2201–2218
57. Rizzoni D, Porteri E, Duse S, De Ciuceis C, Agabiti Rosei C, La Boria E, Semeraro F, Costagliola C, Sebastiani A, Danzi P, Tiberio GA, Giulini SM, Docchio F, Sansoni G, Sarkar A, Agabiti Rosei E (2012) Relationship between media to lumen ratio of subcutaneous small arteries and wall to lumen ratio of retinal arterioles evaluated non-invasively by scanning laser-Doppler flowmetry. J Hypertens 30:1169–1175
58. Ott C, Raff U, Harazny JM, Michelson G, Schmieder RE (2013) Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation. Hypertension 61:1340–1345
59. Salvetti M, Agabiti Rosei C, Paini A, Aggiusti C, Cancarini A, Duse S, Semeraro F, Rizzoni D, Agabiti Rosei E, Muiesan ML (2014) Relationship of wall-to-lumen ratio of retinal arterioles with clinic and 24-hour blood pressure. Hypertension 63:1110–1115
60. Laurent S, Briet M, Boutouyrie P (2009) Large and small artery cross-talk and recent morbidity-mortality trials in hypertension. Hypertension 54:388–392
61. Muiesan ML, Salvetti M, Rizzoni D, Paini A, Agabiti-Rosei C, Aggiusti C, Bertacchini F, Stassaldi D, Gavazzi A, Porteri E, De Ciuceis C, Agabiti-Rosei E (2013) Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients. Hypertension 61:130–136
62. Conijn MM, Kloppenborg RP, Algra A, Mali WP, Kappelle LJ, Vincken KL, van der Graaf Y, Geerlings MI, SMART Study Group (2011) Cerebral small vessel disease and risk of death, ischemic stroke, and cardiac complications in patients with atherosclerotic disease: the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study. Stroke 42:3105–3109
63. Ding JD, Mitchell GF, Bots ML, Sigurdsson S, Harris TB, Garcia M, Eiriksdottir G, van Buchem MA, Gudnason V, Launer LJ (2015) Carotid artery stiffness and risk of incident cerebral microbleeds in older people. The age, gene/environment susceptibility (AGES)- Reykjavik study. Arterioscler Thromb Vasc Biol 35:1889–1895
64. Heagerty AM (2007) Predicting hypertension complications from small artery structure. J Hypertens 25:939–940

Pathophysiology of Subclinical Brain Damage in Hypertension: Large Artery Disease

6

Stéphane Laurent, Dariusz Gasecki, Pierre Boutouyrie, and Krzysztof Narkiewicz

6.1 Introduction

Hypertension, beyond its well-known effect on the occurrence of clinical stroke, is also associated with the risk of subclinical brain damage seen on cerebral magnetic resonance imaging (MRI), particularly in elderly individuals. Better understanding of the haemodynamic consequences of hypertension on brain function and structure is essential in order to select the most appropriate therapeutic management and optimize prevention. In this regard, large artery damage, assessed by increased aortic stiffening and higher central pulse pressure (PP), is an interesting target. Here, we propose an integrated pathophysiological approach in order to aid understanding of how large artery damage influences pressure wave transmission, exaggerates subclinical brain damage, and leads to cerebrovascular complications.

6.2 Subclinical Brain Damage in Hypertension

Hypertension is associated with subclinical brain damage seen on cerebral MRI, particularly in elderly individuals [1–4]. The most common types of brain lesions are white matter hyperintensities (WMHs) and silent infarcts, the reported frequency of

S. Laurent, MD, PhD (✉) • P. Boutouyrie, MD, PhD
Department of Pharmacology and PARCC-INSERM U970, Hôpital Européen Georges Pompidou, Université Paris-Descartes, Assistance-Publique Hôpitaux de Paris, 56 rue Leblanc, Paris 75015, France
e-mail: stephane.laurent@egp.aphp.fr

D. Gasecki, MD, PhD
Department of Neurology of Adults, Medical University of Gdańsk, Gdansk, Poland

K. Narkiewicz, MD, PhD
Poland Hypertension Unit, Department of Hypertension and Diabetology, Medical University of Gdańsk, Gdansk, Poland

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_6

which varies between 10 and 30 % [5]. Both lesions are characterized by a high signal on T2-weighted images and silent infarcts may be differentiated by their low signal on T1-weighted images. A more recently identified type of lesion is microbleeds, which are seen in 5–25 % of community-based subjects and in about 5 % of individuals without cerebrovascular disease. Microbleeds are small homogeneous, round foci of low signal intensity on MRI gradient echo (GRE) T2* images. Like WMH and silent infarcts, microbleeds are more frequent in individuals with hypertension.

Several studies have suggested that sustained or uncontrolled hypertension is associated with a greater WMH load [3, 4, 6]. The blood pressure (BP) level also seems to play a role, with higher BP values being associated with higher grades of WMH [6, 7]. These "dose-dependent" effects of the duration and level of BP provide strong support for a causal relationship between high BP and WMH, similar to that already reported for stroke.

6.3 Predictive Value of Subclinical Brain Damage for Cognitive Impairment and Stroke

In the past 15 years, several community-based studies of a large number of subjects subjected to MRI exams have shown that these lesions are not so silent and were associated cross-sectionally with subtle cognitive or motor impairment. It was also recently discovered that they were associated with incident cognitive deterioration or dementia [8, 9], depression [10] and gait dysfunction [11, 12].

These associations are mainly due to the direct consequences of these lesions on the brain circuits and, particularly, to the disconnection of subcortical-cortical loops. Small, clinically silent brain infarctions appear to be at least as strong a risk for subsequent dementia [9] as larger, clinically evident strokes [13]. In most cases, dementia is not caused by the simple burden of vascular lesions but also by pre-existing neurodegenerative lesions, which are very common in the elderly. The occurrence of vascular lesions could simply reveal the ongoing development of Alzheimer's disease. The interaction between neurodegenerative factors and stroke in the risk of dementia was highlighted in the autopsy-based Nun Study [14], in which the presence of a small lacunar infarct was strongly associated with the diagnosis of clinical dementia (when alive) in people meeting the neuropathological criteria for Alzheimer's disease.

Several studies have described WMH or silent infarcts as a predictor of incident stroke in the general population [15, 16] and of stroke recurrence in patients with a history of transient ischaemic attack or stroke [17]. In this case, WMH may be considered as a harbinger of further clinical events. In the 3C Study, a large population-based cohort study in the elderly in which cerebral MRI was performed in 1924 participants aged ≥65 years, subjects in the highest quartile of WMH had a more than fivefold increased risk of stroke during follow-up compared to those with a WMH load under the median [18]. Interestingly, there was no increased risk of other vascular events, suggesting that WMH was a specific predictor of the risk of stroke.

6.4 Large Artery Damage in Hypertension

6.4.1 Large Artery Remodelling

In essential hypertension, large artery remodelling is characterized by an increase in intima-media thickness (IMT) (about +15 to 40 %), lumen enlargement in the proximal elastic arteries and no change in the lumen diameter of the distal muscular arteries [19–24]. Wall thickening [25] compensates for the rise in BP and tends to normalize circumferential wall stress. The increase in central systolic BP (SBP) and pressure pulsatility (PP) favours the thickening of the large artery wall, particularly the carotid wall [24]. The enlargement of the proximal elastic large arteries with elevated mean BP has been extensively described in studies using ultrasound, particularly high-resolution echotracking systems [19–23, 26–28]. Hypertension exaggerates the effects of ageing. It is generally attributed to fracture of the load-bearing elastin fibres in response to the fatiguing effect of steady and pulsatile tensile stress. However, the growth and apoptosis of vascular smooth muscle cells (VSMCs) may also be involved. The enlargement of large proximal elastic arteries, such as the thoracic aorta, with hypertension, contrasts with the lack of enlargement of distal muscular arteries, such as the iliac or femoral arteries. Thus, the tapering of the aortic tree (i.e. larger diameter upstream than downstream) is exaggerated by hypertension at a given age. This lumen mismatch creates reflection sites for the pressure wave and increases central BP.

6.4.2 Large Artery Stiffening

In patients with essential hypertension, large artery stiffness is elevated in response to the increased loading of stiff wall materials, such as collagen, by high BP levels. In addition, with age and hypertension, the repeated mechanical stress induced by local pulsatility induces biomechanical fatigue of the wall components in the load-bearing media of elastic arteries. This is associated with a loss of the orderly arrangement of smooth muscle cells (SMCs) and extracellular matrix (ECM), the degeneration of elastic fibres and a higher amount of stiff collagenous material.

In addition, chronic activation of the systemic and local renin-angiotensin system promotes VSMC proliferation, low-grade inflammation, increased collagen content and the formation of advanced glycation end products (AGEs). These mechanisms are variously associated in patients with essential hypertension, depending on the associated cardiovascular risk factors or disease. For instance, in secondary forms of hypertension, such as primary aldosteronism [29] or renovascular hypertension [30], arterial stiffness is due to the fibrotic effect of high aldosterone levels [29] together with the continuous activation of the renin-angiotensin system [30].

6.5 Large Artery Damage and Subclinical Brain Damage

The precise mechanisms underlying the development of WMH, silent infarcts and microbleeds in hypertensive patients remain unclear. However, a global pathophysiological framework implicating large artery damage as a cause, or at least as an aggravating factor, may be deduced from epidemiological and pathophysiological studies.

6.5.1 Evidence from Epidemiology

Recently, a large number of studies have reported strong relationships between large artery damage and either subclinical brain damage or cognitive impairment. Alterations in carotid wall thickening and aortic stiffening in patients with cognitive decline link vascular ageing with vascular cognitive impairment (VCI) and underline the aggravating role of hypertension.

The relationship between carotid IMT and cognitive function has been analysed in cross-sectional [31, 32] and longitudinal studies [33–35]. The study population, the definition of carotid IMT and the neuropsychological test adopted to evaluate cognition were heterogeneous. However, a significant inverse relationship between carotid IMT and cognitive function was observed in all studies. In other words, the thicker the artery, the lower the cognitive performance. This relationship was significant after controlling for age and education; some studies further adjusted for the presence of depressive symptoms [33, 34] and/or the level of CV risk factor level [33].

Carotid-femoral pulse wave velocity (cfPWV), the "gold standard" for evaluating arterial stiffness [36], was higher in all groups of cognitively impaired subjects – with or without dementia [37]. A cross-sectional inverse relationship between PWV and cognitive performance was reported [31, 38, 39]. cfPWV was also associated prospectively with cognitive decline before dementia in studies using a cognitive screening test [40, 41] and, more specifically, tests of verbal learning and delayed recall and nonverbal memory [41]. These relationships remained significant after controlling for age, gender, education and BP levels. Other studies reported a significant positive relationship between arterial stiffness and volume or localization of WMH – a known predisposing factor for vascular dementia [42] – on neuroimaging [43, 44].

6.5.1.1 Arterial Stiffness as an Intermediate End Point

Several longitudinal epidemiological studies have shown the predictive value of arterial stiffness, carotid pulse pressure and the augmentation index as intermediate end points, i.e. the greater the arterial stiffness, the greater the number of CV events. The strongest evidence has been demonstrated for aortic stiffness, measured by cfPWV. Aortic stiffness has an independent predictive value for all-cause and CV mortality, fatal and nonfatal coronary events and fatal strokes and not only in patients with uncomplicated essential hypertension [45–47]. Until now, some 19

studies – some included in a recent meta-analysis [48] – have consistently shown the independent predictive value of aortic stiffness for fatal and nonfatal CV events in various populations. Aortic stiffness can thus be considered as an intermediate end point for CV events [49].

Few studies have shown a significant relationship between aortic stiffness and the occurrence of stroke [47]. An individual participant meta-analysis [50] found no significant relationship. This is possibly related to the arterial territory studied. Carotid stiffness may also be used as a proxy for middle-sized cerebral artery stiffness and has been reported to be associated with increasing large WMH volume, independently of vascular risk factors and carotid plaque [51]. Interestingly, carotid stiffness has demonstrated an independent predictive value for stroke in an individual participant meta-analysis [52].

Arterial stiffness may also be important in recovery after stroke. A prospective study by Gasecki et al. [53] of 99 patients with acute ischaemic stroke found that aortic stiffness was an independent predictor of functional outcome. cfPWV was measured 1 week after stroke onset. The functional outcome was evaluated 90 days after stroke using the modified Rankin scale with a modified Rankin scale score of 0–1 considered an excellent outcome. In the multivariate analysis, the predictive value of cfPWV remained significant after adjustment for age, baseline neurologic deficit or NIH (National Institutes of Health) Stroke scale score on admission and a history of a previous stroke. In a subsequent study in a larger number of patients, Gasecki et al. [54] found that low aortic stiffness (cfPWV) was associated with an early (i.e. 1 week) favourable outcome, independently of other known prognostic factors.

Although the relationship between aortic stiffness and CV events in general is continuous, a threshold of 10 m/s [55] has been suggested as a conservative estimate of significant alterations in aortic function in middle-aged hypertensives and has been included in the 2013 ESH-ESC guidelines for the management of hypertension [56]. High aortic PWV may thus represent target organ damage and should be detected during the estimate of CV risk in hypertensives. Reference values for PWV [57] have been established in 1455 healthy subjects and 11,092 subjects with CV risk factors.

The independent predictive value of aortic stiffness for CV events has been demonstrated after adjustment for classical CV risk factors, including brachial pulse pressure. This indicates that aortic stiffness has a better predictive value than each of the classical risk factors. In addition, aortic stiffness retains its predictive value for CHD events after adjustment to the Framingham risk score, suggesting that it adds value to a combination of CV risk factors [45]. One reason may be that aortic stiffness integrates the damage of CV risk factors on the aortic wall over a long period of time, whereas BP, glycaemia and lipids may fluctuate over time, and their values, recorded at the time of risk assessment, may not reflect the true values damaging the arterial wall. Another explanation may be that arterial stiffness shows the patients in whom arterial risk factors have translated into real risk.

6.5.1.2 Central BP as an Intermediate End Point

In the last decade and a half, several longitudinal studies have shown that central SBP and PP have an independent predictive value for all-cause and CV mortality. Eleven studies performed in populations at various CV risk and including 5648 subjects with a mean follow-up of 3.8 years were included in a meta-analysis [58]. However, the added predictive value of central BP for CV events beyond classical CV risk factors, and particularly brachial BP, has not been consistently demonstrated. Additional studies, not included in the meta-analysis, also failed to show higher predictive values of central PP compared with brachial PP [59]. These findings contrast with the closer association between central BP and target organ damage than for brachial BP [36]. There is ongoing debate about whether the lack of a higher predictive value for central BP compared with brachial BP is related to the method used for central BP measurement or reflects a true pathophysiological issue.

6.5.2 Evidence from Pathophysiology

Large artery damage could increase the risk of white matter lesions, lacunar infarcts and microbleeds on MRI, ultimately leading to cognitive decline and, possibly, to ischaemic stroke through three main mechanisms, which are described below [1, 60].

6.5.2.1 Blood Pressure Hyperpulsatility in Cerebral Vessels

Several clinical studies [51, 61, 62] have related subclinical brain damage and cognitive decline to high local pulse pressure. In particular, three studies performed an extensive haemodynamic and MRI investigation. Mitchell et al. [61] evaluated carotid pressure and flow, cfPWV, brain MRI images and cognitive scores in 668 participants with no history of stroke, transient ischaemic attack or dementia, in the Community-Based Age, Gene/Environment Susceptibility – Reykjavik Study. Aortic characteristic impedance (the ratio of change in pressure divided by change in flow) was assessed in a random subset and the reflection coefficient at the aorta-carotid interface was computed. The carotid flow pulsatility index was significantly and negatively related to the aorta-carotid reflection coefficient. Carotid pulse pressure and cfPWV were each significantly associated with an increased risk for silent subcortical infarcts and with lower memory scores. In particular, the pulsatility index was significantly associated with lower memory scores, slower processing speed and worse performance on tests of executive function. The data indicated that marked stiffening of the aorta was associated with reduced wave reflection at the interface between the carotid and aorta, resulting in the transmission of excessive flow pulsatility into the brain, microvascular structural brain damage and lower scores in various cognitive domains. This study [61] strongly supports the hypothesis that increased aortic stiffness and excessive flow pulsatility damage the microcirculation, leading to quantifiable tissue damage and impaired cognitive performance.

Webb et al. [62] studied 100 patients recruited from the Oxford Vascular Study within 6 weeks of a transient ischaemic attack or minor stroke. They measured middle cerebral artery (MCA) flow pulsatility with transcranial ultrasound and aortic pulse wave velocity and aortic systolic, diastolic and pulse pressures with applanation tonometry (SphygmoCor) and found that MCA pulsatility and aortic PWV were significantly greater in patients with leukoaraiosis. In addition, aortic PWV was significantly associated with periventricular and deep white matter lesions, independently of aortic SBP. The multivariate analysis showed that MCA pulsatility was independently associated with aortic PWV ($P=0.016$) and aortic pulse pressure. The authors suggested that MCA pulsatility was the strongest physiological correlate of leukoaraiosis, independently of age, and was dependent on aortic pulse pressure and aortic stiffness, supporting the hypothesis that large artery stiffening results in increased arterial pulsatility with transmission to the cerebral small vessels and leads to leukoaraiosis. It should be noted, however, that hyperpulsatility could be a consequence, rather than a cause, of small cerebral vessel damage, and that cause and consequence may even be associated.

Brisset et al. [51] investigated the relationship between carotid structure and function and MRI markers of cerebral ischaemic small vessel disease in 1800 participants from the population-based, prospective 3C-Dijon Study. The presence of carotid plaque and increasing carotid lumen diameter (but not common carotid artery intima-media thickness), which are known to be significantly influenced by local BP pulsatility [24], were associated with a higher prevalence of lacunar infarcts. Carotid plaque and augmented carotid stiffness were associated with large WMH volume, independently of vascular risk factors. This shows that, in addition to and independently of carotid plaque, increasing carotid lumen diameter and carotid stiffness were associated with an increasing prevalence of lacunar infarcts and increasing WMH volume, respectively.

6.5.2.2 Propagative Models, Wave Reflection and Pulsatility of Central Blood Pressure

To understand the mechanisms linking arterial stiffness to wave reflection and augmented central pulse pressure in hypertension, the heterogeneity of elastic properties throughout the arterial tree must be taken into account. This heterogeneity creates a stiffness gradient. In normotensive subjects, the distensibility of conduit arteries decreases from the upstream elastic proximal large arteries to the downstream stiffer distal medium-sized arteries. Although all large artery segments have three layers (intima, media and adventitia), the large proximal elastic arteries and medium-sized distal muscular arteries differ in the relative amount of VSMCs and extracellular matrix (especially elastin) in their media, which plays the most influential role in elastic properties. In humans, PWV is generally accepted as the most simple, non-invasive, robust and reproducible method of determining regional arterial stiffness [36]. cfPWV (i.e. arterial stiffness) increases from 4 to 5 m/s in the ascending aorta to 5–6 m/s in the abdominal aorta and to 8–9 m/s in the iliac and femoral arteries [26, 63]. The stiffness gradient between the large elastic arteries and the medium-sized muscular arteries, together with

the geometric taper (lumen mismatch), local arterial branching and lumen narrowing of the medium size arteries (all abnormalities described above), creates an impedance mismatch, causing partial reflections of forward pressure waves travelling back to the central aorta (reflected wave). With hypertension-induced arterial stiffening, the reflected wave travels more rapidly along the arterial tree. Thus, early reflected waves arrive in early systole, superimpose on the forward wave and boost the systolic pressure further. These mechanisms explain why the structural and functional changes in large arteries in hypertension cause a premature return of reflected waves in late systole, increasing central pulse pressure and, thus, SBP.

Partial pressure wave reflections limit the transmission of pulsatile energy to the periphery and protect the microcirculation, particularly the brain vasculature. In hypertensive patients, because less proximal wave reflections are generated, as described above, the pulsatile pressure is not sufficiently dampened when it arrives at the brain and is transmitted to the cerebral microcirculation. Notably, high central PP also influences arterial remodelling, not only in the intracranial arteries but also in the extracranial arteries, increasing carotid wall thickness and leading to the development of atherosclerotic plaques [24, 64].

6.5.2.3 Pulse Wave Encephalopathy

Another possible mechanism, which was suggested 10 years ago by Bateman et al. [65], is that an excessive turnover of cerebrovascular fluid, induced by excessive pressure pulsatility, could affect the structural and functional changes of the cerebral circulation in patients with hypertension. They named this *pulse wave encephalopathy*. As indicated above, the cerebral circulation, characterized by a torrential circulation with minimal vascular resistance, is particularly susceptible to pressure pulsatility [66]. The transmission is further amplified by the incompressibility of the skull. Thus, the small cerebral arteries are particularly exposed to the high-pressure fluctuations that exist in the carotid arteries. Pulse wave encephalopathy is thought to be the mechanism underlying periventricular WMLs which, in contrast to deep subcortical WMLs, may not be of ischaemic origin. The pulsatile movements of the cerebrospinal fluid due to intracranial PP waves may damage the ependymal lining [65, 67], and these ependymal alterations have been shown to correlate significantly with the periventricular WML burden [68].

6.5.2.4 Impaired Autoregulation of Blood Flow

In hypertension, the inward remodelling of the small cerebral arteries and the associated increased myogenic tone impair vasomotor reactivity, limit the autoregulation of the cerebral blood flow and increase susceptibility to focal ischaemia when blood pressure is transiently and/or acutely low. Patients with exaggerated visit-to-visit SBP variability are at increased risk of stroke, which suggests that repeated episodes of hypoperfusion and microvascular ischaemia, which are more likely in those patients, could favour tissue damage and stroke.

In summary, all three aforementioned mechanisms – high PP in the cerebral vessels, pulse wave encephalopathy and impaired autoregulation of the cerebral blood flow – emphasize the role of aortic stiffness in central haemodynamics.

6.6 Prevention of Subclinical Brain Damage by Antihypertensive Drugs

WMH and other subclinical brain lesions are involved in the occurrence of major neurological disorders and appear to accelerate brain ageing. Trying to control their aggravation is therefore an important goal. As hypertension is the major modifiable risk factor, it seems logical to first test the hypothesis that BP-lowering treatment may modify this evolution.

This question was addressed in the PROGRESS MRI Clinical Trial [42], a sub-study of the PROGRESS Trial [69]. In this sub-study, 192 patients were enrolled (mean age 60 years), 89 patients assigned to active treatment and 103 patients to placebo. Each participant underwent a baseline MRI and a second MRI examination after a mean follow-up of 36 months. The variability between the two examinations due to technical aspects (position of the head in the scanner, sections of different sizes taken in different positions) was limited by using image analysis techniques to realign the images and for automatic segmentation after the recording of scans in an object-oriented database. These techniques rendered the images as comparable as possible, and an independent observer blind to the clinical data and order of examinations was then able to compare the scans in detail, detecting and measuring each new lesion. A neurologist analysed the initial scan results and identified 13 % of the patients as having moderate WMH and 19 % severe WMH. In the second MRI scan, SBP had decreased by a mean of 11.2 mmHg and DBP by 4.3 mmHg. The overall risk of a new WMH lesion was 43 % lower in the treatment arm than in the placebo arm, although this difference was not statistically significant ($P=0.10$) [42]. The volume of new WMH lesions in the treatment arm was only one-fifth than that of the placebo arm (0.4 cm^3 versus 2 cm^3; $P=0.047$). The greatest difference was observed in patients with severe WMH on the first MRI scan. In this group, no new lesions were observed in the treatment arm, whereas the volume of WMH increased by 7.6 cm^3 in the placebo arm ($P=0.001$) [42]. This group also displayed the most marked progression of WMH over the 4-year follow-up, thus confirming the results of several observational studies. Finally, it was recently shown in the PROGRESS Trial that patients with a high load of WMH lesions had a 7.7-fold greater risk of severe cognitive deterioration or dementia (95 % CI = 2.1–28.6) [69].

These preliminary results are encouraging because they show, for the first time, that it is possible to slow the development of WMH by lowering BP. However, given the relatively small number of patients studied, these results cannot be considered as conclusive. They require confirmation or refutation in larger groups of patients. Furthermore, all patients in the PROGRESS Study had a history of stroke, limiting the extent to which these results can be generalized.

Ideally, the next step would be a trial in patients with moderate-to-severe WMH. There is now strong evidence that this group is exposed to a rapid increase in WMH volume and also to an immediate risk of severe cognitive deterioration and dementia. As WMH have been shown to play a role in the occurrence or aggravation of cognitive decline and dementia, limiting their progression may be the cornerstone of a wider strategy to prevent dementia by controlling vascular factors.

Conclusion

Better understanding of the haemodynamic consequences of hypertension on brain damage is necessary, not only to select the most appropriate therapeutic management but also to optimize prevention, which should be started early in individuals at high risk of developing brain damage. This review has proposed an integrated pathophysiological approach in order to better understand how large artery damage influences pressure wave transmission, exaggerates subclinical brain damage and leads to cerebrovascular complications. Arterial stiffness and central blood pressure could improve our understanding of the haemodynamic consequences of hypertension on the brain considerably if they were measured non-invasively in epidemiological studies and randomized clinical trials having cognitive decline, dementia or WMLs as end points.

References

1. Tzourio C, Nilsson P, Scuteri A, Laurent S (2011) Subclinical brain damage and hypertension. European Society of Hypertension, Clinical Practice Newsletters. http://www.eshonline.org/esh-content/uploads/2015/03/ESH-Clinical-Practice-Newsletters_2011.pdf
2. Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, DeCarli C (2004) Stroke risk profile predicts white matter hyperintensity volume: the Framingham study. Stroke 35:1857–1861
3. de Leeuw FE, de Groot JC, Oudkerk M, Witteman J, Hofman A, van Gijn J, Breteler M (2002) Hypertension and cerebral white matter lesions in a prospective cohort study. Brain 125:765–772
4. Dufouil C, de KersaintGilly A, Besancon V, Levy C, Auffray E, Brunnereau L, Alperovitch A, Tzourio C (2001) Longitudinal study of blood pressure and white matter hyperintensities – the EVA MRI cohort. Neurology 56:921–926
5. Vermeer SE, Longstreth WTJ, Koudstaal PJ (2007) Silent brain infarcts: a systematic review. Lancet Neurol 6:611–619
6. van Dijk EJ, Breteler M, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, Ridder MD, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A, for the CASCADE Consortium (2004) The association between blood pressure, hypertension, and cerebral white matter lesions. The cardiovascular determinants of dementia study. Hypertension 44:625–630
7. Liao DP, Cooper L, Cai JW, Toole JF, Bryan NR, Hutchinson RG, Tyroler HA (1996) Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control: the ARIC study. Stroke 27:2262–2270
8. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, Fitzpatrick A, Fried L, Haan MN (2003) Risk factors for dementia in the cardiovascular health cognition study. Neuroepidemiology 22:13–22
9. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler M (2003) Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 348:1215–1222
10. Godin O, Dufouil C, Maillard P, Delcroix N, Mazoyer B, Crivello F, Alperovitch A, Tzourio C (2008) White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. Biol Psychiatry 63:663–669
11. Whitman GT, Tang T, Lin A, Baloh RW (2001) A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. Neurology 57:990–994
12. Soumare A, Elbaz A, Zhu Y, Maillard P, Crivello F, Tavernier B, Dufouil C, Mazoyer B, Tzourio C (2009) White matter lesions volume and motor performances in the elderly. Ann Neurol 65:706–715

13. Ivan CS, Seshadri S, Beiser A, Au R, Kase CS, KellyHayes M, Wolf PA (2004) Dementia after stroke – the Framingham study. Stroke 35:1264–1268
14. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR (1997) Brain infarction and the clinical expression of Alzheimer disease: the Nun study. JAMA 277:813–817
15. Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, Hubbard LD, Mosley TH (2002) Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 288:67–74
16. Kuller LH, Longstreth WT Jr, Arnold AM, Bernick C, Nick Bryan R, Beauchamp N, for the Cardiovascular Health Study Collaborative Research Group (2004) White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. Stroke 35:1821–1825
17. Streifler JY, Eliasziw M, Benavente OR, Alamowitch S, Fox AJ, Hachinski VC, Barnett HJ (2002) Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. Stroke 33:1651–1655
18. Buyck JF, Dufouil C, Ducimetiere P, Alperovitch A, Bousser M-G, Kurth T, Tzourio C (2009) Cerebral white matter lesions are associated with the risk of stroke but not with other vascular events. The 3C-Dijon study. Stroke 40:2327–2331
19. Laurent S, Boutouyrie P (2015) The structural factor of hypertension: large and small artery alterations. Circ Res 116:1007–1021
20. Benetos A, Laurent S, Hoeks AP, Boutouyrie PH, Safar ME (1993) Arterial alterations with ageing and high blood pressure. A noninvasive study of carotid and femoral arteries. Arterioscler Thromb 13:90–97
21. Laurent S, Girerd X, Mourad JJ, Lacolley P, Beck L, Boutouyrie P, Mignot JP, Safar M (1994) Elastic modulus of the radial artery wall is not increased in patients with essential hypertension. Arterioscler Thromb 14:1223–1231
22. Laurent S, Caviezel B, Beck L, Girerd X, Billaud E, Boutouyrie P, Hoeks A, Safar M (1994) Carotid artery distensibility and distending pressure in hypertensive humans. Hypertension 23:878–883
23. Roman MJ, Saba PS, Pini R, Spitzer M, Pickering TG, Rosen S, Alderman M, Devereux R (1992) Parallel cardiac and vascular adaptation in hypertension. Circulation 86:1909–1918
24. Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S (1999) Local steady and pulse pressure and arterial remodeling. Circulation 100:1387–1393
25. Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S, Reference Values for Arterial Measurements Collaboration (2013) Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. Eur Heart J 34:2368–2380
26. Nichols WW, O'Rourke MF (2011) Vlachopoulos C. Vascular impedance. In: Arnold H (ed) McDonald's blood flow in arteries; theoretical, experimental and clinical principles, 6th edn. London, UK, 755 p
27. Lam CS, Xanthakis V, Sullivan LM, Lieb W, Aragam J, Redfield MM, Mitchell GF, Benjamin EJ, Vasan RS (2010) Aortic root remodeling over the adult life course: longitudinal data from the Framingham Heart Study. Circulation 122:884–890
28. Milan A, Tosello F, Caserta M, Naso D, Puglisi E, Magnino C, Comoglio C, Rabbia F, Mulatero P, Veglio F (2011) Aortic size index enlargement is associated with central hemodynamics in essential hypertension. Hypertens Res 34:126–132
29. Lacolley P, Labat C, Pujol A, Delcayre C, Benetos A, Safar M (2002) Increased carotid wall elastic modulus and fibronectin in aldosterone-salt-treated rats: effects of eplerenone. Circulation 106:2848–2853
30. Zanchi A, Wiesel P, Aubert JF, Brunner HR, Hayoz D (1997) Time course changes of the mechanical properties of the carotid artery in renal hypertensive rats. Hypertension 29:1199–1203
31. Muller M, Grobbee DE, Aleman A, Bots M, van der Schouw YT (2007) Cardiovascular disease and cognitive performance in middle-aged and elderly men. Atherosclerosis 190:143–149
32. Morović S, Jurasić MJ, Martinić Popović I, Serić V, Lisak M, Demarin V (2009) Vascular characteristics of patients with dementia. J Neurol Sci 283:41–43

33. Wendell CR, Zonderman AB, Metter EJ, Najjar SS, Waldstein SR (2009) Carotid intimal medial thickness predicts cognitive decline among adults without clinical vascular disease. Stroke 40:3180–3185
34. Komulainen P, Kivipelto M, Lakka TA, Hassinen M, Helkala EL, Patja K, Nissinen A, Rauramaa R (2007) Carotid intima-media thickness and cognitive function in elderly women: a population-based study. Neuroepidemiology 28:207–213
35. Silvestrini M, Gobbi B, Pasqualetti P, Bartolini M, Baruffaldi R, Lanciotti C, Cerqua R, Altamura C, Provinciali L, Vernieri F (2009) Carotid atherosclerosis and cognitive decline in patients with Alzheimer's disease. Neurobiol Aging 30:1177–1183
36. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 27:2588–2605
37. Hanon O, Haulon S, Lenoir H, Seux ML, Rigaud AS, Safar M, Girerd X, Forette F (2005) Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. Stroke 36:2193–2197
38. Scuteri A, Brancati AM, Gianni W, Assisi A, Volpe M (2005) Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. J Hypertens 23:1211–1216
39. Elias MF, Robbins MA, Budge MM, Abhayaratna WP, Dore GA, Elias PK (2009) Arterial pulse wave velocity and cognition with advancing age. Hypertension 53:668–673
40. Scuteri A, Tesauro M, Appolloni S, Preziosi F, Brancati AM, Volpe M (2007) Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. J Hypertens 25:1035–1040
41. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB (2008) Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal study of aging. Hypertension 51:99–104
42. Dufouil C, Godin O, Chalmers J, Coskun O, MacMahon S, Tzourio-Mazoyer N, Bousser MG, Anderson C, Mazoyer B, Tzourio C, for the PROGRESS MRI Substudy Investigators (2009) Severe cerebral white matter hyperintensities predict severe cognitive decline in patients with cerebrovascular disease history. Stroke 40:2219–2221
43. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW (2008) Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension 52:1120–1126
44. Kearney-Schwartz A, Rossignol P, Bracard S, Felblinger J, Fay R, Boivin JM, Lecompte T, Lacolley P, Benetos A, Zannad F (2009) Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke 40:1229–1236
45. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S (2002) Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 39:10–15
46. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A (2001) Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 37:1236–1241
47. Laurent S, Katsahian S, Fassot C, Tropeano AI, Laloux B, Boutouyrie P (2003) Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 34:1203–1206
48. Vlachopoulos C, Aznaouridis K, Stefanadis C (2010) Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 55:1318–1327
49. Laurent S, Briet M, Boutouyrie P (2012) Arterial stiffness and central pulse pressure as surrogate markers: needed clinical trials. Hypertension 60(2):518–522
50. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T,

Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Hansen TW, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB (2014) Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 63:636–646
51. Brisset M, Boutouyrie P, Pico F, Zhu Y, Zureik M, Schilling S, Dufouil C, Mazoyer B, Laurent S, Tzourio C, Debette S (2013) Large-vessel correlates of cerebral small-vessel disease. Neurology 80:662–669
52. van Sloten TT, Sedaghat S, Laurent S, London GM, Pannier B, Ikram MA, Kavousi M, Mattace-Raso F, Franco OH, Boutouyrie P, Stehouwer CD (2015) Carotid stiffness is associated with incident stroke: a systematic review and individual participant data meta-analysis. J Am Coll Cardiol 66:2116–2125
53. Gasecki D, Rokek A, Kwarciany M, Kubach M, Boutouyrie P, Nyka V, Laurent S, Narkiewicz K (2012) Pulse wave velocity predicts functional outcome in patients after ischemic stroke. Stroke 43:543–544
54. Gasecki D, Rojek A, Kwarciany M, Kowalczyk K, Boutouyrie P, Nyka W, Laurent S, Narkiewicz K (2012) Low pulse wave velocity is associated with early neurological improvement after acute ischemic stroke. Atherosclerosis 225:348–352
55. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, Filipovsky J, Huybrechts S, Mattace-Raso FU, Protogerou AD, Schillaci G, Segers P, Vermeersch S, Weber T, on behalf of the Artery Society, the European Society of Hypertension Working Group on Vascular Structure and Function and the European Network for Noninvasive Investigation of Large Arteries (2012) Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 30:445–448
56. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, DeBacker G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31:1281–1357
57. Herbert A, Cruickshank K, Laurent S, Boutouyrie P, on behalf of The Reference Values for Arterial Measurements Collaboration (2014) Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk-factors. Eur Heart J 35:3122–3133
58. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C (2010) Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 31:1865–1871
59. Mitchell GF, Hwang SJ, Vasan RD, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ (2010) Arterial stiffness and cardiovascular events. The Framingham Heart Study. Circulation 121:505–511
60. Tzourio C, Laurent S, Debette S (2014) Is hypertension associated with an accelerated ageing of the brain? Hypertension 63:894–903
61. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ (2011) Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. Brain 134:3398–3407
62. Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM (2012) Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. Stroke 43:2631–2636
63. Latham RD, Westerhof N, Sipkema P, Rubal BJ, Reuderink P, Murgo JP (1985) Regional wave travel and reflections along the human aorta: a study with six simultaneous micromanometric pressures. Circulation 72:1257–1269

64. Zureik M, Bureau JM, Temmar M, Adamopoulos C, Courbon D, Bean K, Touboul PJ, Benetos A, Ducimetière P (2003) Echogenic carotid plaques are associated with aortic arterial stiffness in subjects with subclinical carotid atherosclerosis. Hypertension 41:519–527
65. Bateman GA, Levi CR, Schofield P, Wang Y, Lovett EC (2008) The venous manifestations of pulse wave encephalopathy: windkessel dysfunction in normal aging and senile dementia. Neuroradiology 50:491–497
66. O'Rourke MF, Safar ME (2005) Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 46:200–204
67. Henry Feugeas MC, De Marco G, Peretti II, Godon-Hardy S, Fredy D, Claeys ES (2005) Age-related cerebral white matter changes and pulse-wave encephalopathy: observations with three-dimensional MRI. Magn Reson Imaging 23:929–937
68. Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, Kamphorst W (1995) Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. Neurology 45:883–888
69. Dufouil C, Godin O, Chalmers J, Coskun O, MacMahon S, Tzourio-Mazoyer N, Bousser M-G, Anderson C, Mazoyer B, Tzourio C (2009) Severe cerebral white matter hyperintensities predict severe cognitive decline in patients with cerebrovascular disease history. Stroke 40:2219–2221

Hypertension and Ischaemic Stroke Subtypes

7

Dagmara Hering and Maciej Piskunowicz

7.1 Introduction

Stroke is a heterogeneous vascular disease with a complex and multifactorial pathogenesis which determines clinical course and outcomes. Among numerous well-recognised cardiovascular (CV) risk factors, arterial hypertension is a major causative contributor of cerebrovascular disease. Elevated blood pressure (BP) is a critical determinant of the increased risk for developing two major types of stroke, ischaemic and haemorrhage. Annually more than 12 million strokes are attributable to high BP [1]. Epidemiological studies have indicated differences in the incidence of stroke dependent on race, ethnicity, gender, age and socioeconomic status [2]. The risk of developing stroke is approximately double in African Americans when compared to Caucasians as a result of the earlier development of high BP [2]. More recently, genetic components [3], gene mutations associated with folate metabolism [4], chronic stress [5, 6], short-term use of nonsteroidal anti-inflammatory drugs in hypertensives (particularly hypertensive women with concomitant anticoagulant use) [7], job strain and long working hours [8] have been demonstrated to substantially increase the risk of stroke. Notably, more than half of primary or recurrent strokes occur in women who have a greater rate of stroke-related death. The gender-specific stroke-related risk factors in women including pregnancy, pre-eclampsia, gestational hypertension, hormonal contraception, menopause, hormone replacement therapy, metabolic syndrome, obesity, atrial fibrillation, migraine with aura and smoking may play a causative role in

D. Hering, MD, PhD (✉)
School of Medicine and Pharmacology – Royal Perth Hospital Unit,
The University of Western Australia, Level 3 MRF Building, Rear 50 Murray Street,
Perth, WA 6000 MDBP M570, Australia
e-mail: dagmara.hering@uwa.edu.au

M. Piskunowicz, MD, PhD
Department of Radiology, Medical University of Gdansk, Gdansk, Poland

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_7

this scenario [9]. The requirement for understanding the role of the different risk factors underlying stroke in females led to the release of the guidelines for the prevention of stroke in women and the need for further research aimed at addressing the existing gaps in knowledge [9].

Stroke is listed as a second leading cause of death worldwide following CV disease and remains a major public health problem. This condition is associated with poor prognosis, a high rate of recurrence, increased mortality and rising costs to the healthcare system. The stepwise increase in BP from a threshold of 115/75 mmHg has been directly linked to stroke-related death [10]. The higher risk of acute stroke is evident in the prehypertensive state and nonelderly [11]. Randomised clinical trials have provided ample evidence that a reduction in BP is the most important intervention for primary stroke prevention [12–16]. In fact the gradual reduction in stroke mortality has been largely attributable to improved control of hypertension [17]. While 77 % of all strokes are first off events, the risk of having a transient ischaemic attack (TIA) or recurrent stroke within the first year is nearly one in four [2]. Although concerns have been raised with regard to cerebral perfusion, blood flow and BP levels after stroke, evidence indicates that the use of antihypertensive drugs results in a significant reduction in recurrent stroke risk.

7.2 Classification of Acute Ischaemic Stroke Subtype

Ischaemic strokes account for 87 % of all strokes with the remaining proportion of 13 % attributable to haemorrhagic strokes. More than 150 known causes of stroke have been identified so far with numerous classification systems defining the subtypes of acute ischaemic stroke proposed over the past 40 years. While there are some strengths and limitations regarding the various categorisations, the narrow time window for therapeutic action in acute ischaemic stroke critically requires the appropriate identification of stroke subtype and underlying cause. Clinical outcomes after stroke, stroke recurrence rates and approaches for secondary prevention are strongly dependent on stroke subtype (Fig. 7.1). Recent advances in brain imaging have contributed to the precise identification of stroke subtype likely resulting in improved clinical outcomes. This indicates that consistent categorisation of patients according to stroke type and associated mechanisms is crucial in clinical trials in acute ischaemic stroke.

7.3 Harvard Cooperative Stroke Registry

The Harvard Cooperative Stroke Registry prospectively collected questionnaires including 86 items consisting of clinical, anatomical and laboratory data (i.e. when possible initial symptoms at the onset of diagnosis, past medical history, signs and findings on physical examination, cerebrospinal fluid, hospitalisation, angiography, computed tomography, etc.) from 694 patients who were hospitalised with acute stroke [18]. This study identified the stroke subtype in all patients and found that thrombosis of a large artery was the underlying cause of cerebrovascular events in 233, lacunes in 131, embolism in 215, intracranial haematoma in 70 and subarachnoid haemorrhage from aneurysm of arteriovenous malformation in 45 patients [18].

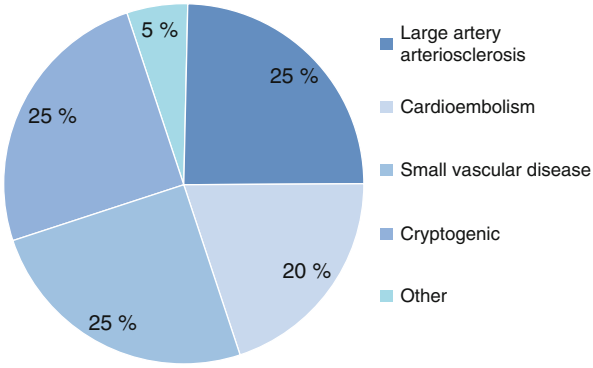

Fig. 7.1 The prevalence of ischaemic stroke subtypes including large artery arteriosclerosis (25%), cardioembolism (20%), small vascular disease (25%), cryptogenic (25%) and other (5%) causes underlying stroke [36]

Among the 694 patients, a notable number of patients ($n=358$) with a history of hypertension had lacunes or haematoma followed by thrombosis. Four hundred and one out of 694 patients who presented with high BP levels of 160/100 mmHg or more at the onset of diagnosis had a higher incidence of thrombosis, whereas patients with more severe hypertension, BP levels of 220/125 mmHg, had haematoma [18]. The majority of patients (~50%) from this registry had stroke diagnosed by clinical findings only (cerebral angiography obtained in 45%, computed tomography (CT) scan in 3% and necropsies in 4% of patients). While outcomes, stroke type, site and mechanisms were not elucidated in the Harvard Stroke Registry, it was the first prospective database published regarding any medical condition [19].

7.4 Oxford Community Stroke Project

Another commonly used stroke classification is the Oxford Community Stroke Project (OCSP) introduced by Bamford et al. (also known 'Bamford system') [20]. This system classified patients according to initial clinical symptoms and signs of focal or global loss of cerebral function with a duration of >24 h. The OCSP involved ~105,000 patients demonstrating the first event of stroke over a 4-year period, confirmed by cerebral infarction within 28 days of the onset of diagnosis with a CT scan or necropsy examination [20]. Accordingly, following confirmation of cerebral infarction and clinical pattern at the time of utmost neurological deficit induced by a stroke, patients were allocated to one of four groups which included lacunar (LACI), posterior (POCI), total anterior (TACI) and partial anterior (PACI) circulation infarcts (Fig. 7.2). This simple and rapid classification has been shown to predict functional recovery and outcomes dependent on site, underlying cause and size of cerebral infarct on CT [20]. Patients in the TACI group experienced a worsened functional outcome, a high rate of mortality with more than double the number of deaths related to complications of immobility and poor health-related quality of life [20–22]. In comparison to other groups, patients in the PACI group were at higher risk of an early recurrent stroke, whereas POCI patients were more vulnerable to develop a recurrent stroke later within the first year following acute events with a better functional prognosis. Although the size of cerebral infarcts is small in the LACI group, the impairment and disability often occur in this patient cohort.

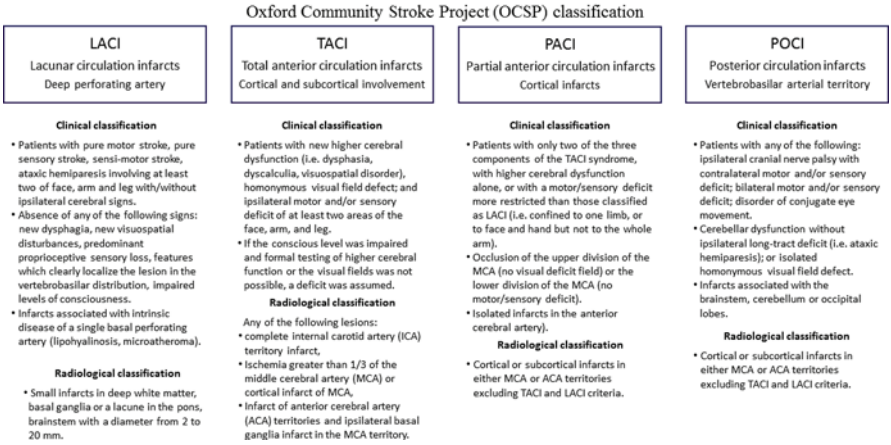

Fig. 7.2 Clinical and radiological summary of the Oxford Community Stroke Project classification

Another large observational study of a total of 8489 patients with acute ischaemic stroke has demonstrated that a number of traditional risk factors predicted stroke location when the OCSP classification was used [23]. Indeed, diabetes mellitus was associated with increased occurrence of POCI, while age, female gender, atrial fibrillation and pulmonary oedema increased the likelihood of anterior circulation ischaemic stroke [23]. Interestingly, history of hypertension, hypercholesterolaemia and smoking were unrelated to anterior or posterior circulation ischaemic stroke in this study. Although the OCSP classification has been shown to be of prognostic value in the vast majority of strokes, its accuracy and sensitivity in predicting patient outcomes are likely to be restricted to large-sized strokes and to a lesser extent on small cortical and subcortical infarcts. Patients with less functional neurological deficit, small early infarcts and negative CT imaging are more likely to be misdiagnosed. Poor accuracy for distinguishing lacunar stroke from small-volume infarcts have been recently shown in a study evaluating the association between clinical OSCP classification and diffusion-weighted magnetic resonance imaging (DWI-MRI) [24]. Clinical TACI classification was associated with correct MRI categorisation. In contrast, the OCSP clinical classification was less sensitive in differentiating between LACI and PACI syndromes as well as in patients with small-sized strokes. Given the different pathophysiology and prognosis, the distinction between lacunar infarcts and cortical infarcts is of clinical relevance in patient management and recruitment into clinical trials. CT and corresponding MRI imaging in a patient with TACI stroke showing extensive infarction of the left middle cerebral artery is demonstrated in Fig. 7.3. DWI-MRI imaging with small LACI in the subcortical white matter is depicted in Fig. 7.4.

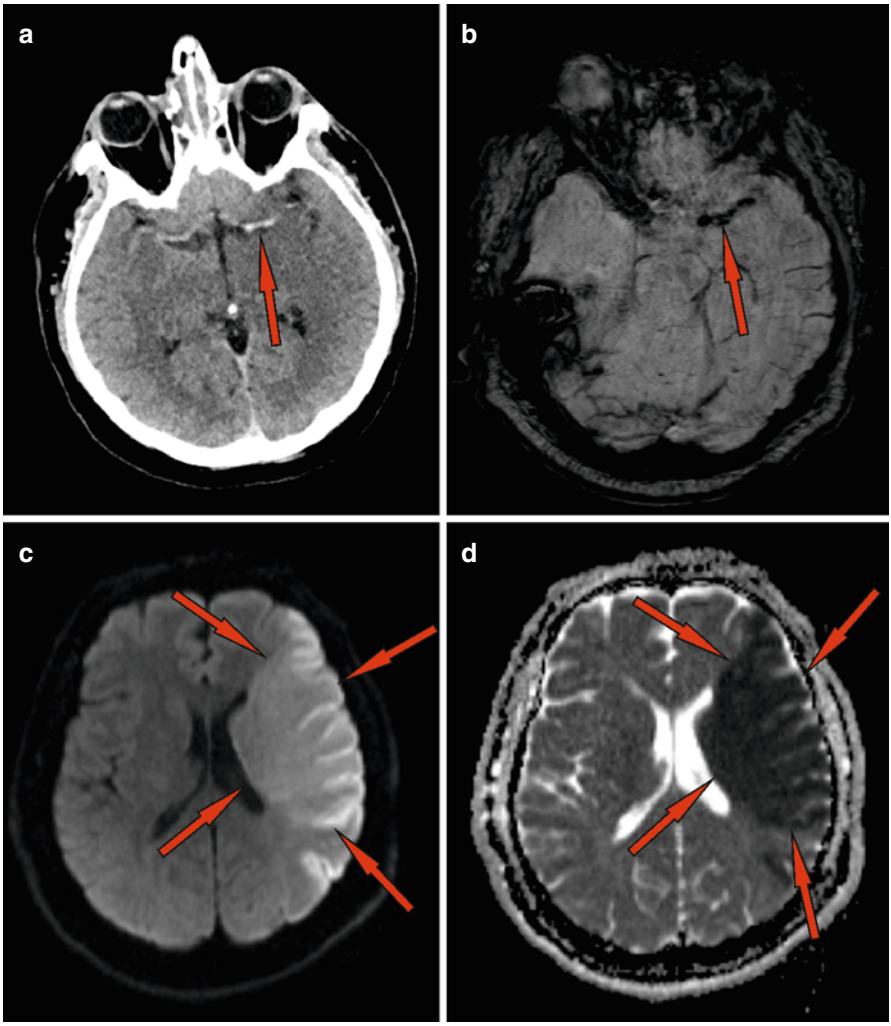

Fig. 7.3 CT and MRI imaging of a wide infarction in the left middle cerebral artery (MCA) territory (TACI stroke). CT scan (**a**) of the malignant left MCA (*red arrow*). MR SWI scan (**b**) of a clot (*red arrow*) in the left MCA with corresponding CT image. High-intensity signal in the left MCA territory (**c**) in DWI-MRI ($b = 1000$) sequence (*red arrows*) with corresponding DWI low-intensity signal in the ADC map (**d**) (*red arrows*)

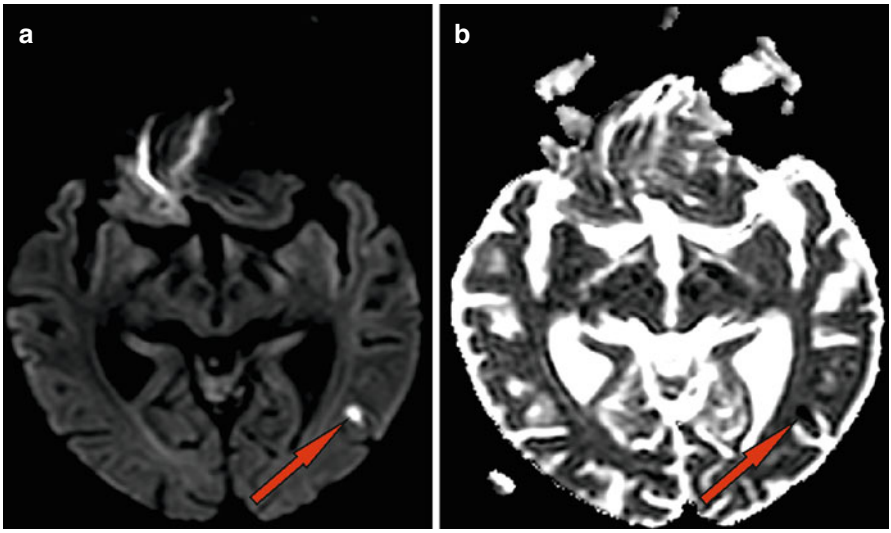

Fig. 7.4 DWI-MRI imaging of small LACI stroke in subcortical white matter close to the left inferior temporal gyrus (*red arrows*) with high-intensity signal in DWI-MRI ($b = 1000$) sequence (**a**) and corresponding DWI low-intensity signal in the MRI ADC map (**b**)

7.5 TOAST Classification

The further classification of acute ischaemic stroke introduced by Adams et al. in 1993 has been commonly used in the clinical setting and stroke management [25]. The categorisation of subtypes of ischaemic stroke based mainly on aetiology was established for the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Clinical symptoms, brain imaging (CT/MRI), cardiac imaging, duplex imaging of extracranial arteries, arteriography and laboratory findings have been considered for the development of the TOAST classification of subtypes of acute ischaemic stroke, as demonstrated in Table 7.1. The classification allowing clinicians to identify the specific stroke subtype as probable or possible based on diagnostic tools is clinically relevant in the course of diagnosis, providing rationale for the direct cause-related interventions.

7.6 SSS-TOAST, the Causative Classification System

Further modification of the TOAST classification system resulted in incorporation of comprehensive brain imaging (CT, MRI, DWI-MRI) in an attempt to identify the most probable stroke subtype, mechanisms, levels of confidence and associated criteria, thereby minimising the proportion of undetermined strokes [26]. The major advantage of the SSS-TOAST classification system is high reliability and identification of causes underlying stroke subtype. In addition to the equivalent five major

Table 7.1 TOAST classification of acute ischaemic stroke subtype and its prevalence [25]

Type	Prevalence (%)
1. Large artery atherosclerosis[a]	12.9
2. Cardioembolism[a]	36.5
3. Small vessel occlusion (lacune)[a]	18.4
4. Stroke of other determined aetiologies[a]	6
5. Stroke of undetermined aetiology	26.4–42.3
(a) Two or more causes identified	
(b) Negative evaluation	
(c) Incomplete evaluation	

[a]Possible or probable depending on results of ancillary studies

stroke subtypes as original TOAST classification, the SSS-TOAST allocates each stroke into causative category based on the levels of evidence in determining the most likely mechanism such as 'evident', 'probable' or 'possible' in the presence of multiple existing contributing factors. The causative classification system (CCS) is a web-based method that includes a questionnaire-style classification scheme for ischaemic stroke (available at http://ccs.martinos.org) and provides an automated report regarding the stroke subtype and a comprehensive description of the classification rationale [26]. In comparison to other classifications, the web-based CCS system provides a prompt analysis of clinical features with intra- and inter-examiner reliability which can be potentially utilise in clinical trials and research.

7.7 ASCO Classification

The most recent classification system provides a more complete and precise characterisation of stroke, assessing stroke aetiology, the multifactorial underlying mechanisms and coexisting clinical conditions [27]. This phenotype-based system stratifies a patient according to the A-S-C-O grades; A, atherosclerosis; S, small vessel disease; C, cardiac source; and O, other causes with each phenotype defining a potential cause accordingly to 1 (definitively a potential cause of the index stroke), 2 (casualty uncertain) and 3 (unlikely a direct cause of the index stroke despite a disease is present). A patient receives a grade 3 in the absence of any disease related to the stroke and 9 when the grade is not definable due to insufficiency in the diagnostic process. The diagnostic evidence is scored in levels (A) based on diagnostic gold standard techniques or criteria (i.e. autopsy evidence, X-ray angiography, MRI, MRI angiography, duplex echocardiography); (B) indirect evidence, less sensitive or specific diagnostic tests (i.e. only one of the diagnostics tests: duplex echocardiography or CT angiography or MRI angiography); and (C) weak evidence, no specific tests or criteria (i.e. carotid murmur only, Doppler, low-flow retinopathy) [27]. Causes linking pathophysiological categorisation to stroke type using the ASCO system have been demonstrated previously [27]. Strengths of the A-S-C-O scheme include a comprehensive examination, identification of stroke subtype and associated causative factors ultimately providing the best treatment option. The use

of detailed stroke subtyping system consistently applied among clinicians and researches is relevant in meta-analysis and clinical trials assessing the effectiveness of therapies and outcomes.

7.8 Large Artery Atherosclerotic Disease

The well-defined stroke subtype, large artery atherosclerosis (LAA), appears to be an important target for primary prevention of stroke. Intracranial atherosclerosis underlying stroke development is highly prevalent in China (ranging from 33 to 50 %), in Thailand (accounting for 47 % of all strokes) with similar findings in Japan, Singapore and Korea [28]. More recently, the Rotterdam study with 6 years of follow-up has demonstrated that intracranial carotid artery atherosclerosis accounted for 75 % of strokes, calcification of aortic arch contributed to 45 % of strokes and extracranial carotid artery atherosclerosis accounted for 25 % of acute cerebrovascular events [29]. This observation indicates that LAA is the most common vascular lesion and major risk factor for having a stroke.

Haemodynamically significant stenosis or occlusion of a major brain artery or branch cortical artery confirmed with duplex imaging or arteriography is important in the classification of stroke secondary to large artery atherosclerosis. Patients with hypertension, diabetes, metabolic syndrome, dyslipidemia and aortic or coronary plaque are at high risk of developing LAA stroke with a strong likelihood of atherosclerotic vascular disease in other peripheral arteries accompanying concomitant intracranial atherosclerosis [30–32]. TOAST system defines LAA stroke subtype in the presence of atherosclerosis and subsequent stenosis of greater than 50 % of an appropriate extracranial portion of the internal carotid artery (ICA) or intracranial large artery (i.e. intracranial portion of the ICA, middle cerebral artery stem, intracranial portion of the vertebral artery and basilar artery). The SSS-TOAST system also includes protruding atheroma with less than 50 % stenosis as an underlying cause of LAA stroke providing its association with stroke event and absence of any other evident mechanisms [26].

There is evidence to suggest that intracranial large artery disease (ICLAD) plays a leading causative role in ischaemic stroke and is particularly prevalent among Asians [33]. Previous studies have demonstrated that hypertension is a strong independent risk factor for ICLAD but not extracranial carotid disease. However, traditional risk factors including age, hyperlipidaemia, diabetes and ischaemic heart disease are associated with both atherosclerotic sites, intracranial and extracranial [34].

7.9 Cardio-Aortic Embolism

Evidence from numerous studies indicated that cardioembolic stroke comprises 14–30 % of all ischaemic strokes [35] and 20 % of all cerebral infarctions in North American and European populations [36]. Numerous cardio-aortic sources (i.e. left atrial or ventricular thrombus, AF, paroxysmal AF, sick sinus syndrome, atrial

flutter, recent myocardial infarction or previous myocardial infarction with ejection fraction <28 %, rheumatic mitral or aortic valve disease, chronic HF with EF <30 %, infective endocarditis, non-ischaemic dilated cardiomyopathy, nonbacterial thrombotic endocarditis, papillary fibroelastoma, left atrial myxoma) have been recognised as critical contributors to high primary risk of cerebral embolism [26]. The prevalence of sources with low or uncertain primary risk of stroke (i.e. patent foramen ovale, atrial septal aneurysm, complex atheroma in the ascending aorta or proximal arch, etc.) are not uncommon in the general population though their relation with cardioembolic stroke has been less apparent.

Several clinical characteristics have been indicative of cardioembolic stroke including sudden onset of neurological deficit, reduced level of consciousness, 'spectacular shrinking deficit syndrome' (rapid onset of a major hemispheric stroke syndrome followed by abrupt recovery associated with migration of an embolus), Wernicke's aphasia or global aphasia in the absence of hemiparesis [35]. The short- and long-term prognosis of patients with cardioembolic stroke differs from other stroke subtypes. The rate of recurrent stroke is predominantly high when compared to other stroke subtypes with greatest inpatient mortality at 1 month [25, 35]. The most clinically relevant high-risk conditions underlying cardioembolic stroke are atrial fibrillation, recent myocardial infarction, mechanical prosthetic valve, dilated myocardiopathy and mitral rheumatic stenosis [35]. Patients with ischaemic stroke and AF commonly have worsened neurological recovery, clinical prognosis and high risk for recurrent stroke when compared to patients with normal sinus rhythm [37]. Moreover, patients with excessive alcohol intake, hypertension, valvular heart disease, nausea, vomiting and previous ischaemic stroke confer augmented risk of early recurrent embolisation [35].

7.10 Small Artery Occlusion (Cerebral Small Vessel Disease)

Lacunar infarcts account for nearly 25 % of all ischaemic strokes. The presence of clinical features and radiological signs of typical small infarcts confirm small artery occlusion stroke type. Accordingly, patients with lacunar infarcts and subcortical or brainstem infarcts with a diameter ranging from 0.2 to 15–20 mm follow into this category [25]. In autopsy studies, Fisher recognised two types of lacunar infarcts with possibly different vascular pathologies: lipohyalinosis and microatheroma [38]. Patients with lacunar infarcts may present with a single lacune which is likely to have atherosclerotic risk factors or multiple lacunes with strong link to hypertension [39]. The strong association between lipohyalinosis and hypertension documented by Fisher has been confirmed in several studies [40]. Additionally, neurological outcome, recurrent stroke and increased mortality risk in patients with lacunar stroke and at least one asymptomatic lacunar lesion have been shown to be worse when compared to lacunar infarcts lacking these lesions [40]. The contribution of hypertension and diabetes as independent determinants of multiple lacunar infarcts is well recognised [41]. Resonance imaging studies have demonstrated that kidney dysfunction (reduced estimated glomerular filtration rate, GFR) has been

related to cerebral small vessel disease (i.e. reduced white matter volume, increased white matter lesions, small brain volume) independently of CV risk factors [42]. Although it was not statistically significant, patients with lower eGFR had more lacunar infarcts. Another MRI study showed the close association between retinopathy and cerebral small vascular disease that causes white matter lesions and lacunes in both hypertensive and normotensive patients [43]. However, not all patients with lacunar infarcts have presented with a history of elevated BP or glucose levels indicating that pathophysiology of small cerebrovascular disease is more complex than anticipated. Atherosclerotic carotid plaque or cardiac embolic source has been shown to be contributing mechanisms underlying lacunar infarcts with or without presence of hypertension and diabetes [44]. Moreover, there is evidence linking genetic predisposition, parental history of stroke, gene polymorphism and inflammatory markers to small vascular infarction [45].

The term 'hypertensive cerebral small vessel stroke' is broad and includes lacunar infarction and hypertensive primary (non-traumatic) deep intracerebral haemorrhage. Similarly to lacunar infarcts, hypertension is not always an underlying cause of primary intracerebral haemorrhage. Other contributors such as high monocyte count beyond traditional risk factors (i.e. current smoking status and hyperlipidaemia) have been related to the development of clinical lacunar infarcts in patients with acute HSVD stroke but not deep intracerebral haemorrhage [46]. The presence of lacunar infarcts and white matter lesions on MRI substantially increased the risk of vascular and nonvascular death and future ischaemic stroke in patients with symptomatic atherosclerotic disease [47]. Whether silent clinically asymptomatic infarcts have prognostic significance merits further research.

7.11 Other Determined Causes

This category includes the conditions that bore close temporal and spatial association with acute cerebral infarction including nonatherosclerotic vasculopathies (i.e. fibromuscular dysplasia, arteritis, migraine), haematological disorders (abnormalities of thrombosis and haemostasis), drug-induced stroke, moyamoya disease, meningitis, sickle-cell disease, arterial dissection, Sneddon syndrome and others [26]. Among these disorders, fibromuscular dysplasia (FMD) is a vascular disease commonly associated with secondary hypertension (i.e. renovascular hypertension). FMD most commonly affects renal arteries; however, if present in carotid or vertebral arteries, it plays a causative role in TIA, aneurysm, artery dissection, ischaemic stroke and subarachnoid haemorrhage [48].

7.12 Undetermined Causes

The CCS classification of ischaemic stroke subtype of undetermined causes includes the following stroke category: cryptogenic embolism, other cryptogenics, incomplete evaluation and unclassified categories [26]. The substantial proportion of

patients which suffered an ischaemic stroke have a defined background aetiology. However, despite a comprehensive diagnosis based on the exclusion of the other potential causes, up to 40 % of TIAs or strokes with varying proportions dependent on the patient population are of uncertain or undetermined causes, commonly known as cryptogenic TIA or stroke. The distribution of cryptogenic stroke in numerous studies in North American and European populations has averaged ~25 % (14–39 %) [36]. Ample evidence indicates that most cryptogenic strokes are of thromboembolic origin [36]. Non-lacunar strokes with a lack of identified cardioembolic source or the presences of occlusive atherosclerosis are classified into this category. Several potential causes of embolic stroke of undetermined source have been recognised that include mitral valve, aortic valve, non-atrial fibrillation, atrial structural abnormalities, left ventricular dysfunction, paroxysmal atrial fibrillation, cancer-associated emboli, arteriogenic emboli (i.e. aortic arch atherosclerotic plaques, cerebral artery non-stenotic plaque with ulceration) and paradoxical embolism (i.e. patent foramen ovale, atrial septal defect, pulmonary arteriovenous fistula) [36]. Accordingly, the well-established TOAST classification has defined a stroke of unknown origin in the presence of (1) multiple coexisting stroke risk factors which unable a physician to make a final diagnosis, (2) of atrial fibrillation accompanying ipsilateral carotid stenosis of 50 %, (3) traditional lacunar syndrome accompanying ipsilateral carotid stenosis of 50 %, or (4) an extensive investigation that the aetiology was undetermined.

Unravelling the cause of the stroke remains particularly challenging in younger patients (<50–55 years of age) in whom ~40–60 % of strokes are of cryptogenic origin [49]. Recently, data from 15 European stroke centres has demonstrated that 39.6 % of patients aged 15–49 years had undetermined aetiology of cerebrovascular events using TOAST criteria [50] with increasing prevalence of cryptogenic stroke <35 years of age [51]. Previous studies demonstrated that patients with CS stroke display a greater risk for recurrent stroke when compared to stroke caused by large artery disease, cardioembolism or small artery disease suggesting that additional occlusive artery lesions are likely to be contributing mechanisms of stroke recurrence after CS [52]. Very recently, a population-based study in the UK with 12 years of follow-up has investigated the incidence, outcome, risk factors and long-term prognosis according to the TOAST classification [53]. In this study of a total 2555 patients, 32 % of first ischaemic events were classified as cryptogenic stroke. Death or dependency at 6 months after CS was not dissimilar when compared to non-cardioembolic stroke. In contrast to other stroke types, patients with CS displayed less hypertension, diabetes, peripheral vascular disease, hypercholesterolaemia or history of smoking. Additionally, CS bore no excess risk of asymptomatic carotid disease or acute coronary events, no further risk of minor risk of echocardiographic abnormalities, paroxysmal AF prior to stroke occurrence or new AF after stroke or presumed cardioembolic events [53]. The rate of recurrent stroke in patients with cryptogenic stroke may differ between studies as a result of using dissimilar diagnosis criteria. Nevertheless, given the global burden attributable to cryptogenic stroke, a need to further research on potential causes, treatments and secondary prevention is warranted.

7.13 Future Directions

Prevention of stroke remains a challenging clinical problem. The global burden of neurological impairment attributable to stroke, the high risk of recurrence and poor prognosis indicate failure of primary and secondary preventions. Given the complexity of heterogeneous and incompletely understood pathophysiology underlying stroke, a need to continue with further clinical research to gain a better understanding of risk factors, clinical markers and outcomes associated with specific stroke subtype clearly exists. In this context, the use of consistent classification with clinical and radiological approaches providing a practical guide to stratify acute stroke by subtype, treatment and prognosis across large global trials is justified. Hopefully, currently ongoing research on stroke genetics will identify stroke subtype and predict patient response to therapies and clinical outcomes over the next decade.

References

1. Dean N, Shuaib A (2011) Hypertension: the most important preventable risk factor for cerebrovascular disease. Lancet Neurol 10:606–607
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB, American Heart Association Statistics C, Stroke Statistics S (2015) Heart disease and stroke statistics–2015 update: a report from the american heart association. Circulation 131:e29–322
3. Carty CL, Buzkova P, Fornage M, Franceschini N, Cole S, Heiss G, Hindorff LA, Howard BV, Mann S, Martin LW, Zhang Y, Matise TC, Prentice R, Reiner AP, Kooperberg C (2012) Associations between incident ischemic stroke events and stroke and cardiovascular disease-related genome-wide association studies single nucleotide polymorphisms in the population architecture using genomics and epidemiology study. Circ Cardiovasc Gene 5:210–216
4. Huo Y, Li JP, Qin XH, Huang YN, Wang XB, Gottesman RF, Tang GF, Wang BY, Chen DF, He ML, Fu J, Cai YF, Shi XL, Zhang Y, Cui YM, Sun NL, Li XY, Cheng XS, Wang JA, Yang XC, Yang TL, Xiao CS, Zhao G, Dong Q, Zhu DL, Wang X, Ge JB, Zhao LY, Hu DY, Liu LS, Hou FF, CSPPT Investigators (2015) Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in china the csppt randomized clinical trial. JAMA 313:1325–1335
5. Everson-Rose SA, Roetker NS, Lutsey PL, Kershaw KN, Longstreth WT, Sacco RL, Roux AVD, Alonso A (2014) Chronic stress, depressive symptoms, anger, hostility, and risk of stroke and transient ischemic attack in the multi-ethnic study of atherosclerosis. Stroke 45:2318–2323
6. Hering D, Lachowska K, Schlaich M (2015) Role of the sympathetic nervous system in stress-mediated cardiovascular disease. Curr Hypertens Rep 17:594
7. Chuang SY, Yu Y, Sheu WHH, Tsai YT, Liu X, Hsiung CA, Tsai HJ (2015) Association of short-term use of nonsteroidal anti-inflammatory drugs with stroke in patients with hypertension. Stroke 46:996
8. Kivimaki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, Clays E, De Bacquer D, Dragano N, Erbel R, Geuskens GA, Hamer M, Hooftman WE, Houtman IL, Jockel KH, Kittel F, Knutsson A, Koskenvuo M, Lunau T, Madsen IE, Nielsen ML, Nordin M, Oksanen T, Pejtersen JH, Pentti J, Rugulies R,

Salo P, Shipley MJ, Siegrist J, Steptoe A, Suominen SB, Theorell T, Vahtera J, Westerholm PJ, Westerlund H, O'Reilly D, Kumari M, Batty GD, Ferrie JE, Virtanen M, IPD-Work Consortium (2015) Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603 838 individuals. Lancet 386(10005):1739–1746

9. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Pina IL, Reeves MJ, Rexrode KM, Saposnik G, Singh V, Towfighi A, Vaccarino V, Walters MR, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research (2014) Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 45:1545–1588
10. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360:1903–1913
11. Lee M, Saver JL, Chang B, Chang KH, Hao Q, Ovbiagele B (2011) Presence of baseline pre-hypertension and risk of incident stroke a meta-analysis. Neurology 77:1330–1337
12. Lawes CMM, Bennett DA, Feigin VL, Rodgers A (2004) Blood pressure and stroke – an overview of published reviews. Stroke 35:776–785
13. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, The Heart Outcomes Prevention Evaluation Study Investigators (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 342:145–153
14. Turnbull F, Neal B, Algert C, Chalmers J, Woodward M, MacMahon S, MacMahon S, Baigent C, Cutler J, Fagard R, Neal B, Whelton P, Yusuf S, Algert C, Chalmers J, Chapman N, MacMahon S, Neal B, Turnbull F, Woodward M, Agodoa L, Baigent C, Black H, Boissel JP, Brenner B, Brown M, Bulpitt C, Byington R, Chalmers J, Collins R, Cutler J, Dahlof B, Davis B, Dens J, Estacio R, Fagard R, Fox K, Hansson L, Holman R, Hunsicker L, Kostis J, Kuramoto K, Lewis E, Lindholm L, Lubsen J, MacMahon S, Malacco E, Mancia G, Neal B, Pepine C, Pfeffer M, Pitt B, Poole-Wilson P, Remuzzi G, Rodgers A, Ruggenenti P, Schrier R, Sever P, Sleight P, Staessen J, Tco K, Turner R, Whelton P, Wing L, Yui Y, Yusuf S, Zanchetti A, Blood Pressure Lowering Treatment Trialists' Collaboration (2003) Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 362:1527–1535
15. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F (2013) 2013 esh/esc guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the european society of hypertension (esh) and of the european society of cardiology (esc). J Hypertens 31:1281–1357
16. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, Schwamm LH, Smith EE, Towfighi A, American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; Council on Functional Genomics and Translational Biology (2014) Factors influencing the decline in stroke mortality a statement from the american heart association/american stroke association. Stroke 45:315–353
17. Ravenni R, Jabre JF, Casiglia E, Mazza A (2011) Primary stroke prevention and hypertension treatment: which is the first-line strategy? Neurol Int 3:e12
18. Mohr JP, Caplan LR, Melski JW, Goldstein RJ, Duncan GW, Kistler JP, Pessin MS, Bleich HL (1978) The harvard cooperative stroke registry: a prospective registry. Neurology 28:754–762
19. Caplan LR (2011) Stroke classification: a personal view. Stroke 42:S3–S6
20. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C (1991) Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 337:1521–1526

21. Tei H, Uchiyama S, Ohara K, Kobayashi M, Uchiyama Y, Fukuzawa M (2000) Deteriorating ischemic stroke in 4 clinical categories classified by the Oxfordshire community stroke project. Stroke 31:2049–2054
22. Sturm JW, Donnan GA, Dewey HM, Macdonell RA, Gilligan AK, Srikanth V, Thrift AG (2004) Quality of life after stroke: the north east Melbourne stroke incidence study (nemesis). Stroke 35:2340–2345
23. Subramanian G, Silva J, Silver FL, Fang J, Kapral MK, Oczkowski W, Gould L, O'Donnell MJ, Investigators of the Registry of the Canadian Stroke Network (2009) Risk factors for posterior compared to anterior ischemic stroke: an observational study of the registry of the Canadian stroke network. Neuroepidemiology 33:12–16
24. Asdaghi N, Jeerakathil T, Hameed B, Saini M, McCombe JA, Shuaib A, Emery D, Butcher K (2011) Oxfordshire community stroke project classification poorly differentiates small cortical and subcortical infarcts. Stroke 42:2143–2148
25. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. Stroke 24:35–41
26. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, Ayata C, Towfighi A, Smith EE, Chong JY, Koroshetz WJ, Sorensen AG (2007) A computerized algorithm for etiologic classification of ischemic stroke: the causative classification of stroke system. Stroke 38:2979–2984
27. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG (2009) New approach to stroke subtyping: the a-s-c-o (phenotypic) classification of stroke. Cerebrovasc Dis 27:502–508
28. Wong LK (2006) Global burden of intracranial atherosclerosis. Int J Stroke Off J Int Stroke Soc 1:158–159
29. Bos D, Portegies ML, van der Lugt A, Bos MJ, Koudstaal PJ, Hofman A, Krestin GP, Franco OH, Vernooij MW, Ikram MA (2014) Intracranial carotid artery atherosclerosis and the risk of stroke in whites: the Rotterdam study. JAMA Neurol 71:405–411
30. Nam HS, Han SW, Lee JY, Ahn SH, Ha JW, Rim SJ, Lee BI, Heo JH (2006) Association of aortic plaque with intracranial atherosclerosis in patients with stroke. Neurology 67:1184–1188
31. Mi D, Zhang L, Wang C, Liu L, Pu Y, Zhao X, Wang Y, Wang Y (2012) Impact of metabolic syndrome on the prognosis of ischemic stroke secondary to symptomatic intracranial atherosclerosis in Chinese patients. PLoS One 7:e51421
32. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ (2012) Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 11:261–271
33. De Silva DA, Woon FP, Lee MP, Chen CP, Chang HM, Wong MC (2007) South Asian patients with ischemic stroke: intracranial large arteries are the predominant site of disease. Stroke 38:2592–2594
34. Uehara T, Tabuchi M, Mori E (2005) Risk factors for occlusive lesions of intracranial arteries in stroke-free Japanese. Eur J Neurol Off J Eur Feder Neurol Soc 12:218–222
35. Arboix A, Alio J (2010) Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Curr Cardiol Rev 6:150–161
36. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ, Cryptogenic Stroke/ESUS International Working Group (2014) Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 13:429–438
37. Khoo CW, Lip GY (2009) Clinical outcomes of acute stroke patients with atrial fibrillation. Expert Rev Cardiovasc Ther 7:371–374
38. Fisher CM (1979) Capsular infarcts: the underlying vascular lesions. Arch Neurol 36:65–73
39. Boiten J, Lodder J, Kessels F (1993) Two clinically distinct lacunar infarct entities? A hypothesis. Stroke 24:652–656
40. de Jong G, Kessels F, Lodder J (2002) Two types of lacunar infarcts: further arguments from a study on prognosis. Stroke 33:2072–2076
41. Mast H, Thompson JLP, Lee SH, Mohr JP, Sacco RL (1995) Hypertension and diabetes-mellitus as determinants of multiple lacunar infarcts. Stroke 26:30–33

42. Ikram MA, Vernooij MW, Hofman A, Niessen WJ, van der Lugt A, Breteler MMB (2008) Kidney function is related to cerebral small vessel disease. Stroke 39:55–61
43. Kwa VIH, van der Sande JJ, Stam J, Tijmes N, Vrooland JL, Grp AVM (2002) Retinal arterial changes correlate with cerebral small-vessel disease. Neurology 59:1536–1540
44. Horowitz DR, Tuhrim S, Weinberger JM, Rudolph SH (1992) Mechanisms in lacunar infarction. Stroke 23:325–327
45. Behrouz R, Malek AR, Torbey MT (2012) Small vessel cerebrovascular disease: the past, present, and future. Stroke Res Treat 2012:839151
46. Cortina MG, Campello AR, Conde JJ, Ois A, Voustianiouk A, Tellez MJ, Cuadrado E, Roquer J (2008) Monocyte count is an underlying marker of lacunar subtype of hypertensive small vessel disease. Eur J Neurol 15:671–676
47. Conijn MM, Kloppenborg RP, Algra A, Mali WP, Kappelle LJ, Vincken KL, van der Graaf Y, Geerlings MI, Group SS (2011) Cerebral small vessel disease and risk of death, ischemic stroke, and cardiac complications in patients with atherosclerotic disease: the second manifestations of arterial disease-magnetic resonance (smart-mr) study. Stroke 42:3105–3109
48. Olin JW, Gornik HL, Bacharach JM, Biller J, Fine LJ, Gray BH, Gray WA, Gupta R, Hamburg NM, Katzen BT, Lookstein RA, Lumsden AB, Newburger JW, Rundek T, Sperati CJ, Stanley JC, American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Cardiovascular Radiology and Intervention; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Functional Genomics and Translational Biology; American Heart Association Council for High Blood Pressure Research; American Heart Association Council on the Kidney in Cardiovascular Disease; American Heart Association Stroke Council (2014) Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American heart association. Circulation 129:1048–1078
49. Amarenco P (2005) Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. Cerebrovasc Dis 20(Suppl 2):68–74
50. Yesilot Barlas N, Putaala J, Waje-Andreassen U, Vassilopoulou S, Nardi K, Odier C, Hofgart G, Engelter S, Burow A, Mihalka L, Kloss M, Ferrari J, Lemmens R, Coban O, Haapaniemi E, Maaijwee N, Rutten-Jacobs L, Bersano A, Cereda C, Baron P, Borellini L, Valcarenghi C, Thomassen L, Grau AJ, Palm F, Urbanek C, Tuncay R, Durukan Tolvanen A, van Dijk EJ, de Leeuw FE, Thijs V, Greisenegger S, Vemmos K, Lichy C, Bereczki D, Csiba L, Michel P, Leys D, Spengos K, Naess H, Tatlisumak T, Bahar SZ (2013) Etiology of first-ever ischaemic stroke in European young adults: the 15 cities young stroke study. Eur J Neurolgy Off J Eur Feder Neurol Soc 20:1431–1439
51. Rolfs A, Fazekas F, Grittner U, Dichgans M, Martus P, Holzhausen M, Bottcher T, Heuschmann PU, Tatlisumak T, Tanislav C, Jungehulsing GJ, Giese AK, Putaala J, Huber R, Bodechtel U, Lichy C, Enzinger C, Schmidt R, Hennerici MG, Kaps M, Kessler C, Lackner K, Paschke E, Meyer W, Mascher H, Riess O, Kolodny E, Norrving B, Stroke in Young Fabry Patients (sifap) Investigators (2013) Acute cerebrovascular disease in the young: the stroke in young fabry patients study. Stroke 44:340–349
52. Bang OY, Lee PH, Joo SY, Lee JS, Joo IS, Huh K (2003) Frequency and mechanisms of stroke recurrence after cryptogenic stroke. Ann Neurol 54:227–234
53. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, Rothwell PM, Oxford Vascular Study (2015) Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol 14:903–913

Hypertension and Haemorrhagic Stroke

8

Dagmara Hering and Maciej Piskunowicz

8.1 Haemorrhagic Stroke

The appropriate identification of stroke-related symptoms and differentiation between ischaemic and haemorrhagic stroke subtype at onset of disease is critical in providing prompt diagnosis and immediate treatment. While the incidence of haemorrhagic stroke is 7–10 times lower when compared to ischaemic subtypes, severity and associated increased mortality are greater in haemorrhagic stroke than ischaemic stroke [1, 2]. Survival following haemorrhagic stroke is determined by the area of brain bleeding and related tissue damage. Subarachnoid haemorrhage (SAH) and intracerebral haemorrhage (IH) are the two major types of haemorrhagic stroke. SAH refers to bleeding into the subarachnoid space located between the arachnoid membrane and pia mater, an area filled with cerebrospinal fluid providing protection for the brain from injury. Intracranial haemorrhage is the pathological accumulation of blood in the functional tissue, known as brain parenchyma with further extension of bleeding into the ventricles known as intracerebral haemorrhage. While the underlying pathophysiology, treatment and prognosis depend on the type of haemorrhage, if not diagnosed and treated promptly, SAH and IH result in a loss of cognitive function and subsequent death.

D. Hering, MD, PhD (✉)
School of Medicine and Pharmacology – Royal Perth Hospital Unit,
The University of Western Australia, Level 3 MRF Building, Rear 50 Murray Street,
Perth, WA 6000 MDBP M570, Australia
e-mail: dagmara.hering@uwa.edu.au

M. Piskunowicz, MD, PhD
Department of Radiology, Medical University of Gdansk, Gdansk, Poland

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and
Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_8

8.1.1 Subarachnoid Haemorrhage

With advancements in radiological tools including computed tomography (CT) and magnetic resonance imaging (MRI), the detection of unruptured intracranial aneurysms (UIAs) and associated patient outcomes after SAH have improved. The rupture of intracranial (brain) aneurysm (saccular-type aneurysm) is considered the leading cause of SAH accounting for 85 % of cases [3] (Fig. 8.1). The remaining spontaneous causes of SAH unrelated to saccular aneurysms are non-aneurysmal perimesencephalic haemorrhage (~10 %) and rare abnormalities (~5 %) including (1) arterial dissection (mostly the vertebral artery), (2) cerebral arteriovenous malformation, (3) dural arteriovenous fistula, (4) vascular lesion around the spinal cord, (5) septic aneurysm, (6) pituitary apoplexy and (7) cocaine abuse.

Among all attributable risk factors, cigarette smoking, arterial hypertension, excessive alcohol consumption and a first-degree relative with history of the condition are critical in triggering SAH [4, 5]. A recent meta-analysis of a total of 68 studies from 21 countries has demonstrated that the prevalence of UIAs without associated co-morbidities was 3.2 % with an average age of 50 years [6]. The incidence of UIAS has been grater in patients with autosomal dominant polycystic kidney disease (6.9 %) and positive family history of intracranial aneurysm of SAH (3.4 %) with a lower prevalence in the presence of brain tumour (3.6 %), pituitary adenoma (2.0 %) or atherosclerosis (1.7 %). A higher prevalence of UIAs has been noted in women and subjects older than 50 years. The risk of rupture of UIAs (i.e. higher incidence of SAH) was determined by ethnicity (greater in Japan and Finland), size (>5 mm) and location (posterior circulation aneurysm) [7].

Another condition causing cerebral artery damage leading to acute cerebrovascular events, mostly in children, is an inherited form of anaemia known as sickle-cell disease (SCD). In this condition, the incidence of stroke subtype is determined

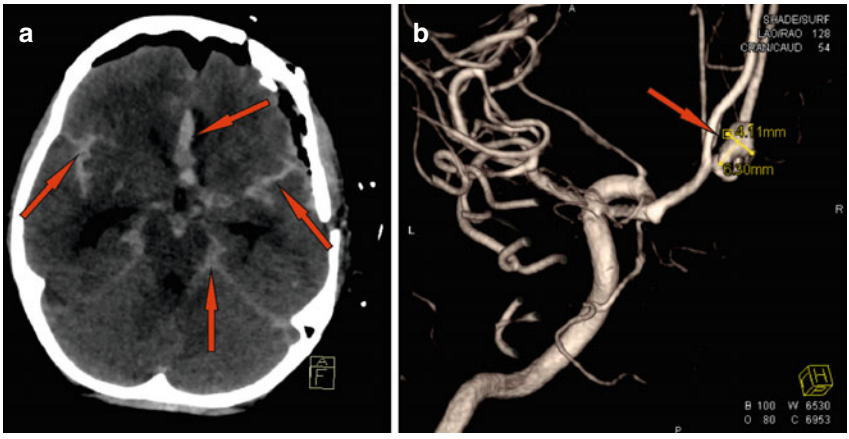

Fig. 8.1 Brain CT imaging demonstrating subarachnoid haemorrhage in the central white area (**a**) and stretching into the sulci to both sides (*red arrows*) and after neurosurgical clipping of the saccular-type aneurysm (**b**)

by age [8]. The highest peak of stroke incidence, mostly ischaemic subtype accounting for 54 % of acute events, occurs during the first decade and after the age of 30. In contrast, the increased prevalence of haemorrhagic stroke in SCD has been observed in patients aged 20–29 years and was associated with greater mortality when compared to ischaemic stroke [8]. Silent strokes are not uncommon (10–30 %) in SCD resulting in cognitive impairment. While 30 % of patients with SCD and SAH are children without an identifiable aneurysm, in adults with SCD, intracranial haemorrhage is likely to be intracerebral or SAH secondary to aneurysm [9].

8.1.2 Intracerebral Haemorrhage

Intracerebral haemorrhage (ICH) accounts for ~10–20 % of all strokes [10]. The prevalence of ICH is more than double when compared to SAH with a comparable 30-day mortality rate [11]. A systematic review and meta-analysis of 39 trials conducted over nearly three decades have demonstrated that the incidence of ICH in Asians is nearly twofold when compared to other ethnic groups [12]. This observation indicates that Asians are prone to developing not only ischaemic stroke underlying large artery arteriosclerosis but also ICH stroke type. In general, women appear to have a lower incidence of ICH than men [12]. The pathophysiology of ICH is complex involving numerous risk factors and multiple underlying mechanisms. Abundant evidence from clinical studies indicates that hypertension plays a causative role in triggering primary ICH [13] with a history of hypertension found in ~90 % of patients demonstrating ICH [14]. The risk of developing ICH is nearly fourfold higher in hypertensive subjects than normotensives and increases with blood pressure (BP) levels [15]. Markedly elevated BP on hospital admission and inadequate BP control have adversely contributed to prognosis in hypertensive ICH [14]. In fact, a substantial proportion of haemorrhages are likely to be associated with noncompliance to antihypertensive medication in addition to reflex mechanisms secondary to the increase in intracranial pressure and/or the mass effects produced by the size of the haematoma. While the clinical symptoms associated with ICH depend on size and location, the most common clinical features of intracerebral bleeding in hypertensive patients include hemiparesis/hemiplegia (78 %) followed by aphasia (60 %) with headache, vomiting (20 %) and seizures (9 %) presenting less frequently [16]. The most common sites of hypertensive haemorrhages are the basal ganglia (55 %), thalamus (26 %), cerebral hemispheres (11 %), brainstem (8 %) and cerebellum (7 %) [16]. Although the lobar haematoma is not a typical site for hypertensive bleeding, it has been noted in ~30 % of patients [17]. Across all studies, in addition to elevated blood pressure, ageing has been demonstrated as the leading unmodifiable risk factor for developing ICH with a nearly tenfold increase in octogenarians when compared to middle-aged subjects [12]. Additionally, risk factors including cigarette smoking and alcohol intake have been directly related to an increased risk of ICH in the recent INTERSTROKE study [13].

Cerebral amyloid angiopathy (CCA) is another condition contributing critically to ICH, a commonly found pathological accumulation of β-amyloid in the media and adventitia of small arteries of the leptomeninges and cerebral cortex causing

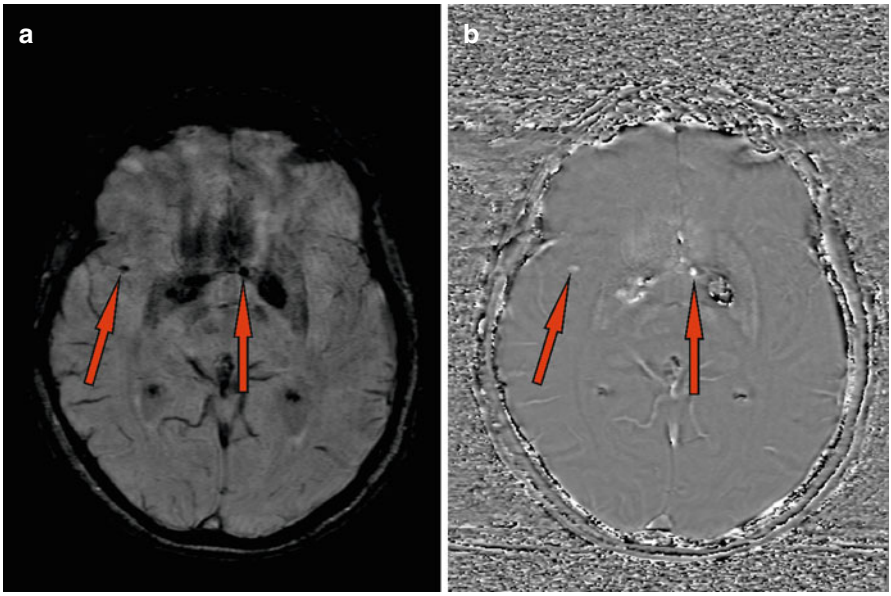

Fig. 8.2 Brain MRI of two microbleeding foci (**a**) SWI sequence (*red arrows*) with corresponding MRI SWI-Pha sequence (**b**)

cognitive dysfunction in the elderly [18]. Approximately 50 % of primary lobar ICH has been linked to CAA [19]. The remaining risk factors for ICH include intracranial vascular malformation, diabetes mellitus, anticoagulant use (i.e. warfarin, aspirin) and genetic predisposition [20].

In this context, it is noteworthy to mention that cerebral microbleeds are indicative of cerebral small vessel disease caused by leakage of blood vessels resulting in accumulation of blood in the brain tissue (Fig. 8.2). While brain microbleeds can occur in the healthy population, mostly in the elderly accounting for ~5 %, they have a higher prevalence in ischaemic stroke of ~30 % and non-traumatic ICH of ~60 % [21]. In terms of location, lobar microbleeds have been linked to CAA and deep microbleeds to hypertensive vasculopathy [22]. Moreover, brain microbleeds are commonly found in patients with hypertension without a history of cerebrovascular disease and have been independently related to ambulatory BP levels [21, 23]. Findings linking the prognostic significance of microbleeds to the risk of recurrent ICH appear to be of clinical relevance [18, 24]. Whether cerebral microbleeds should be considered a marker of hypertension-induced organ damage or a potential indicator for developing ICH merits further investigation.

8.2 Haemorrhagic Transformation of Ischaemic Stroke

Haemorrhage transformation (HT) is haemorrhage secondary to ischaemic stroke and affects ~9 % of patients with prognosis depending of the type of HT. HT has been reported as a complication following thrombolytic therapy in acute ischaemic

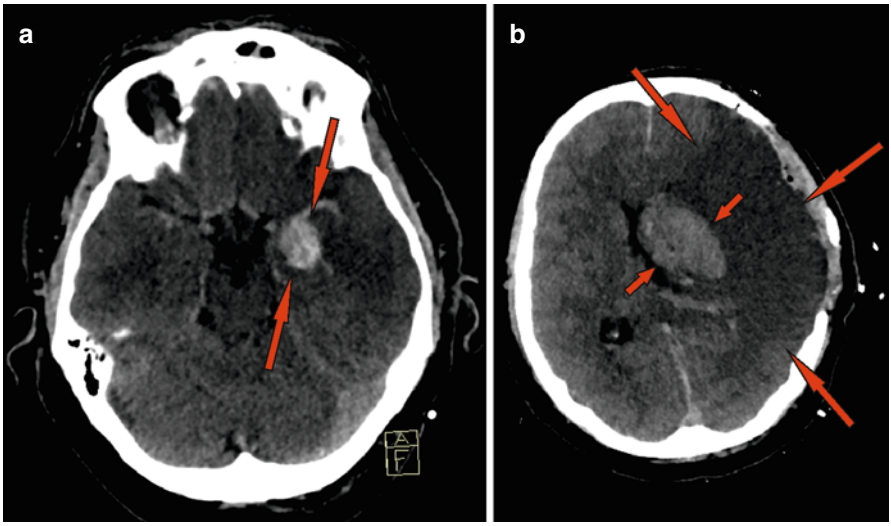

Fig. 8.3 CT scan of the haemorrhage transformation of acute ischaemic stroke following thrombolytic therapy. Imaging following 4 h thrombolytic systemic treatment (**a**) – intracranial haematoma (*red arrows*). CT imaging in the same patient 21 h after thrombolytic therapy (**b**) demonstrating intracranial haematoma (*short arrows*) and a wide area of ischaemic infarction (*long red arrows*)

stroke or natural evolution of a cerebral infarction [25] (Fig. 8.3). Based on CT imaging, HT is divided into two major types including haemorrhagic infarction (HI) and parenchymal haematoma (PH). HI is defined as a heterogeneous hyperdensity surrounding a zone of ischaemic infarction with the two following subtypes: HI-1 referring to scattered petechiae alongside the infarct zone and HI-2 reflecting more condensed petechiae throughout the infarct zone. In contrast to HI, PH is associated with the so-called mass effect with type PH-1 defined as homogenous hyperdensity haematoma of less than 30 % of the infarct area with mild mass effect and type PH-2 with haematoma >30 % of the ischaemic zone with a significant space occupying effect. HI occurs in ~5.5 % of patients and appears to have better outcomes than PH which affects ~3.2 % of patients and is associated with increased risk of death [26]. Among all HT types, only PH-2 has been shown to independently predict neurological complication and worsening prognosis [27]. While HT is not an uncommon finding in patients with acute ischaemic stroke treated with thrombolysis (i.e. tissue plasminogen activator, rtPA), this therapy results in favourable early outcomes [28].

Although the mechanisms underlying HT are not completely understood, several factors and predictors have been shown to influence the prevalence of HT. Massive cerebral infarction is one of the major risks for the development of HT with the infarction area strongly related to the incidence of HT. Atrial fibrillation, cerebral embolisms, hyperglycaemia and thrombolytic therapy have been found to predict HT, mainly PH [26].

8.3 Future Directions

As the global burden of hypertension grows, the incidence of haemorrhagic stroke is likely to rise even further. Despite newer diagnostic and therapeutic approaches in patient management, the prognosis of patients with haemorrhagic stroke remains very poor. The high mortality rate among stroke patients indicates the need for coordinated and effective multidisciplinary care to ensure accurate recognition, quality patient outcomes and secondary prevention. While multiple causative factors are implicated in this condition, it appears rational that lowering BP and improving adherence to medication can substantially reduce the risk of haemorrhagic stroke. The increasing use of anticoagulants in the cardiovascular setting merits further research aimed at prevention and minimization of risk associated with haemorrhagic drug-related complications.

References

1. Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP (2009) Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. Stroke 40:2068–2072
2. Dupont SA, Wijdicks EFM, Lanzino G, Rabinstein AA (2010) Aneurysmal subarachnoid hemorrhage: an overview for the practicing neurologist. Semin Neurol 30:545–554
3. van Gijn J, Rinkel GJ (2001) Subarachnoid haemorrhage: diagnosis, causes and management. Brain 124:249–278
4. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, Anderson CS (2005) Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke 36:2773–2780
5. Diringer MN, Bleck TP, Hemphill JC, Menon D, Shutter L, Vespa P, Bruder N, Connolly ES, Citerio G, Gress D, Haenggi D, Hoh BL, Lanzino G, Le Roux P, Rabinstein A, Schmutzhard E, Stocchetti N, Suarez JI, Treggiari M, Tseng MY, Vergouwen MDI, Wolf S, Zipfel G (2011) Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the neurocritical care society's multidisciplinary consensus conference. Neurocrit Care 15:211–240
6. Vlak MH, Algra A, Brandenburg R, Rinkel GJ (2011) Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol 10:626–636
7. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ (2007) Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke 38:1404–1410
8. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM (1998) Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 91:288–294
9. Carey J, Numaguchi Y, Nadell J (1990) Subarachnoid hemorrhage in sickle cell disease. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg 6:47–50
10. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V (2009) Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 8:355–369
11. Broderick JP, Brott T, Tomsick T, Miller R, Huster G (1993) Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage. J Neurosurg 78:188–191
12. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ (2010) Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 9:167–176

13. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S, INTERSTROKE Investigators (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the interstroke study): a case-control study. Lancet 376:112–123
14. Dandapani BK, Suzuki S, Kelley RE, Reyesiglesias Y, Duncan RC (1995) Relation between blood-pressure and outcome in intracerebral hemorrhage. Stroke 26:21–24
15. Ariesen MJ, Claus SP, Rinkel GJ, Algra A (2003) Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke 34:2060–2065
16. Zafar A, Khan FS (2008) Clinical and radiological features of intracerebral haemorrhage in hypertensive patients. JPMA J Pakistan Med Assoc 58:356–358
17. Green RM, Kelly KM, Gabrielsen T, Levine SR, Vanderzant C (1990) Multiple intracerebral hemorrhages after smoking crack cocaine. Stroke 21:957–962
18. Viswanathan A, Greenberg SM (2011) Cerebral amyloid angiopathy in the elderly. Ann Neurol 70:871–880
19. Knudsen KA, Rosand J, Karluk D, Greenberg SM (2001) Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology 56:537–539
20. Ikram MA, Wieberdink RG, Koudstaal PJ (2012) International epidemiology of intracerebral hemorrhage. Curr Atheroscler Rep 14:300–306
21. Cordonnier C, Al-Shahi Salman R, Wardlaw J (2007) Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain 130: 1988–2003
22. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM, Microbleed SG (2009) Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 8:165–174
23. Henskens LH, van Oostenbrugge RJ, Kroon AA, de Leeuw PW, Lodder J (2008) Brain microbleeds are associated with ambulatory blood pressure levels in a hypertensive population. Hypertension 51:62–68
24. Jeon SB, Kang DW, Cho AH, Lee EM, Choi CG, Kwon SU, Kim JS (2007) Initial microbleeds at mr imaging can predict recurrent intracerebral hemorrhage. J Neurol 254:508–512
25. Sussman ES, Connolly ES Jr (2013) Hemorrhagic transformation: a review of the rate of hemorrhage in the major clinical trials of acute ischemic stroke. Front Neurol 4:69
26. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, Caso V, Micheli S, Bertolani L, Venti M, Palmerini F, Biagini S, Comi G, Previdi P, Silvestrelli G (2008) Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 39:2249–2256
27. Berger C, Fiorelli M, Steiner T, Schabitz WR, Bozzao L, Bluhmki E, Hacke W, von Kummer R (2001) Hemorrhagic transformation of ischemic brain tissue – asymptomatic or symptomatic? Stroke 32:1330–1335
28. Kablau M, Kreisel SH, Sauer T, Binder J, Szabo K, Hennerici MG, Kern R (2011) Predictors and early outcome of hemorrhagic transformation after acute ischemic stroke. Cerebrovasc Dis 32:334–341

Imaging Techniques for the Detection and Diagnosis of Brain Damage in Hypertension

9

Dariusz Gasecki, Edyta Szurowska, and Krzysztof Jodzio

9.1 Introduction

Hypertension is the major causal factor of neurovascular pathology. Changes in the brain are heterogeneous and arise from both vascular and parenchymal lesions. These include large vessel and small vessel ischaemic infarctions, macrohaemorrhages and microbleeds (MBs) as well as vascular and parenchymal brain alterations leading to cerebral tissue disintegration and secondary effects on brain metabolism and function [1].

9.2 Hypertension and Large Artery Disease

Large artery disease is associated with both ischaemic and haemorrhagic stroke subtypes. The former comprises cortical and subcortical infarctions of the territorial or, less frequently, the watershed type. The latter results in bleeding into the brain parenchyma and subarachnoid space. It is estimated that large artery atherosclerosis, resulting in distal thromboembolism with or without steno-occlusion, is responsible for nearly half of all ischaemic strokes. Many cases of large vessel disease with ischaemic stroke are of the embolic type. The most common factors are atrial fibrillation, other cardiac structural or functional abnormalities and local arterial wall disease.

D. Gasecki (✉)
Department of Neurology for Adults, Medical University of Gdansk, Gdansk, Poland
e-mail: dgasecki@gumed.edu.pl

E. Szurowska
Second Department of Radiology, Medical University of Gdansk, Gdansk, Poland

K. Jodzio
Institute of Psychology, University of Gdansk, Gdansk, Poland

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_9

The main locations of large artery atherosclerosis are the arterial bifurcations and *ostia* as well as any irregularities of vessel walls. The carotid sinus, carotid siphon and carotid and vertebral ostium are the most frequent extracranial sites. The basilar artery, middle cerebral artery (MCA) and anterior inferior cerebellar artery are the most frequent intracranial sites of atherosclerosis in hypertensive patients with ischaemic stroke.

Many other vascular and non-vascular factors affect the definitive cerebral infarction pattern, which depends on the timing and location of steno-occlusion and recanalization, the size of the thrombus, the capacity of collateral flow and the metabolic state of brain tissue.

9.2.1 Patterns of Radiological Findings of Ischaemic Stroke: Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) Findings

Radiological imaging of ischaemic stroke depends mostly on the duration and anatomical extension of the restricted blood flow area (level and diameter of occluded artery). Stroke classification is based upon the duration of clinical symptoms:

- Hyperacute stage: less than 6 h
- Acute stage: 8 to 24 h
- Subacute stage: 2 days to 1 week
- Chronic stage: 8 days to 3 months

However, there are various time frames for each stage, and it is not necessary to treat them as irreplaceable. Specialists should choose and follow the one they consider most suitable.

The most frequently used imaging method in stroke diagnosis is computed tomography (CT). Pathological alternations observed in the ischaemic variants are dynamic and time dependent. CT is a reliable tool for subtype differentiation, especially in the exclusion of intracranial haemorrhage.

9.2.1.1 CT Imaging in the Hyperacute Stage (0–6 h)

Within the first minutes of ischaemia, rising lactic acid levels and the failure of cellular membrane ion pumps result in the redistribution of water from extracellular to intracellular spaces. Radiologists can measure these changes by delineating the field of cytotoxic oedema, which may reduce brain tissue radiodensity on CT scans. Ischaemic foci become hypodense compared to normal white and grey matter due to increased water uptake. The radiodensity of the ischaemic field theoretically decreases by 2 Hounsfield units (HU) every 2.5 h during stroke evolution, but these discrepancies may be imperceptible to inexperienced observers [2, 3].

In the first 6 h of ischaemic stroke, brain CT images seem to be unaffected in about 50 % of cases [3], and therefore, the negative predictive value is low (27 %) [4]. In the European Cooperative Acute Stroke Study, the sensitivity of CT during

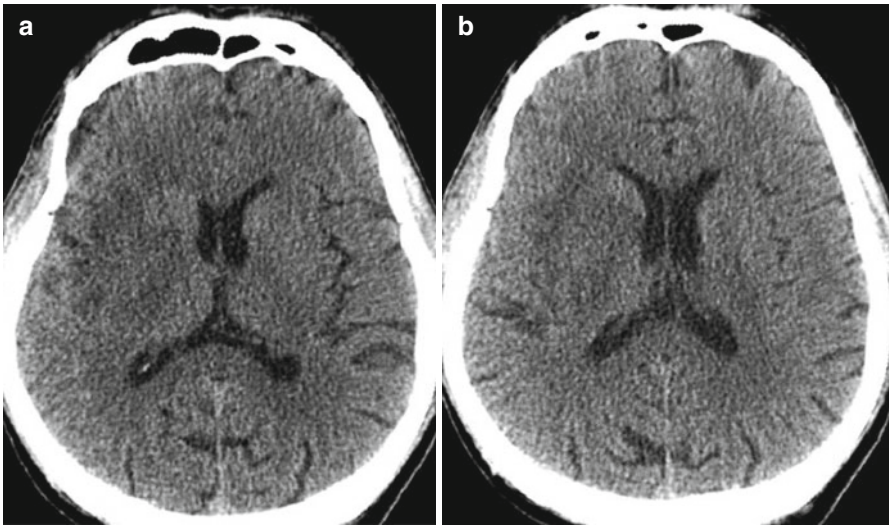

Fig. 9.1 (**a**, **b**) Unenhanced CT images show hypodensity and obscuration of the right lentiform nucleus, which appears abnormal in comparison with the left lentiform nucleus. Additionally, these scans demonstrate the loss of grey-white matter differentiation in medial margins of the right insula (insular ribbon sign)

the first 6 h of cerebral ischaemia reached 64 %, with an accuracy of 67 % [5]. Blockage of the proximal M1 segment of the MCA causes abnormal CT findings within 3 h in 75 % of cases [6]. On the other hand, in the case of lacunar infarction, there is only a 50 % chance of a confirmed diagnosis within 48 h [4]. Therefore, the lack of radiological manifestations in early CT studies does not exclude stroke [7].

Hyperacute stroke syndromes usually appear in the MCA, the most common stroke localization. The signs include loss of the insular ribbon, obscuration of the lentiform nucleus, loss of grey-white matter differentiation, sulci effacement and a hyperdense MCA sign [8]. All are considered as indirect ischaemic symptoms on CT imaging. Cytotoxic oedema of the insular cortex, which is susceptible to early and irreversible ischaemic damage, generates local hypo-attenuation, which results in the so-called insular ribbon sign (Fig. 9.1). Lack of flow to the lenticulostriate arteries causes cytotoxic oedema in the basal ganglia. The associated radiological finding is known as obscuration of the lentiform nucleus (Fig. 9.1). This phenomenon is due to occlusion of the MCA proximal M1 segment and can be seen as early as one hour post onset.

In the healthy brain, white matter is more hypodense than the cerebral cortex. Developing oedema attenuates this physiological contrast ('loss of grey-white matter differentiation'). A hyperdense MCA sign (Fig. 9.2) is an indirect marker of proximal thromboembolism within the MCA (M1 segment) and may be an early indicator of acute infarction. The high density is probably caused by impaired blood flow in the vicinity of the intraluminal clot (with an attenuation value of 60–90 HU). This sign has a high specificity (~100 %) but low sensitivity (17–50 %) [9, 10].

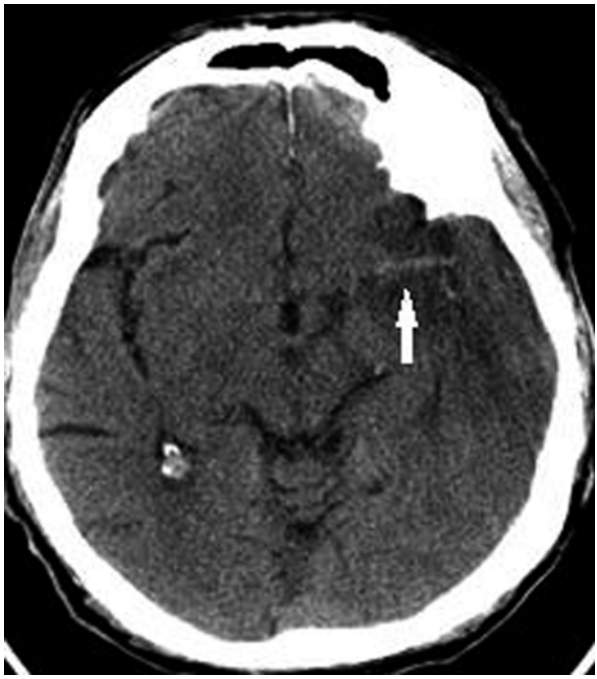

Fig. 9.2 Unenhanced CT image shows hyperattenuation in the proximal M1 segment of the left MCA (the hyperdense middle cerebral artery sign – *arrow*)

The differential diagnosis includes high haematocrit values and vessel wall calcifications, both of which ought to be apparent bilaterally.

Hyperdensity seen in the M2 or M3 MCA branches within the lateral sulcus is known as the MCA dot sign and indicates ischaemia affecting the insula and adjacent cortex. A mass effect, including swelling of the gyri, sulci contraction and effacement of the border between the cortex and white matter, is observed in brain infarctions regardless of stroke localization (Fig. 9.3). The more the brain tissue is affected, the more distinctive the changes. Other large vessels closed by emboli may also have elevated density, analogically to the hyperdense MCA sign. Classic magnetic resonance imaging (MRI) shows similar alterations in spin-echo T1, T2 and PD-weighted images with arterial blood flow restriction. Acquiring clinical patient information and modifying the CT window presets may further facilitate a correct diagnosis.

9.2.1.2 CT Angiography and MR Angiography in the Hyperacute Stage (0–6 h)

CT angiography (CTA) demonstrates disruption of vessel continuity in the presence of emboli. CTA performed after intravenous contrast agent injection is the diagnostic study of choice in assessing the large cervical and intracranial arteries (Fig. 9.4). Cerebral angiography should cover arteries superior to the aortic arch. It identifies large vessel obstruction with a sensitivity of up to 100 % (Nguyen-Huynh et al. 2008) and is a very appropriate method of predicting the extent and location of

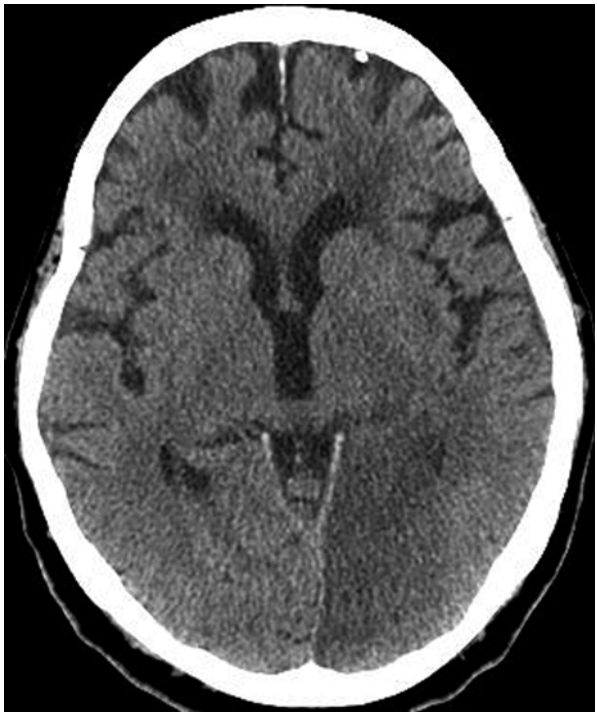

Fig. 9.3 Unenhanced CT scan shows typical radiological findings of acute infarction in the left occipital lobe: discrete hypodense area, swelling of gyri, sulci contraction and effacement of the border between the cortex and white matter

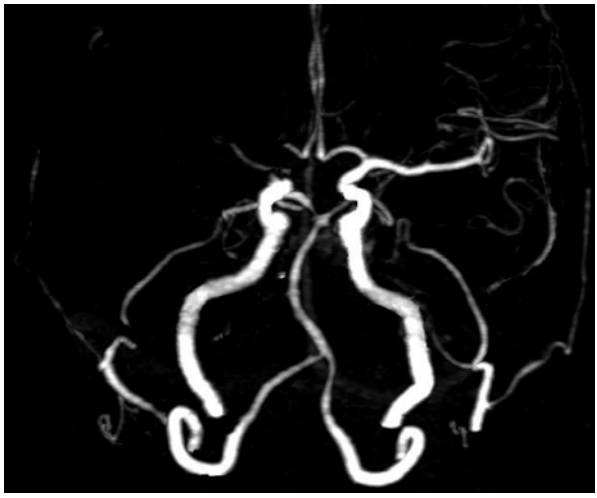

Fig. 9.4 CT angiography (maximum intensity projection (MIP) reconstruction) demonstrates the presence of an embolus in the right internal cerebral artery bifurcation and lack of flow in both proximal AI segments of ACA and M1 of the MCA. Distal AI segment of the right ACA is filled by the anterior communicating artery and contralateral ACA. Collateral vessels are not seen in the right hemisphere

ischaemic stroke and provides treatment guidance. CTA may be performed immediately after unenhanced CT, anticipating decisions on invasive thrombectomy. CTA allows better identification of vessel stenosis and vessel thrombi than non-contrast MR angiography (MRA).

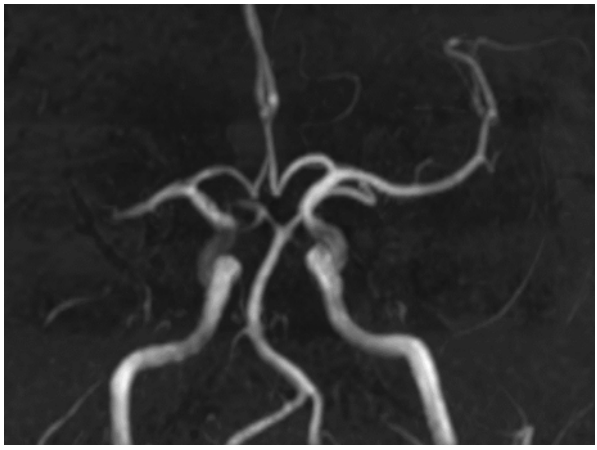

Fig. 9.5 MR angiography obtained by the TOF method shows lack of flow in the distal M1 segment of the right MCA

MRA without a contrast agent usually utilizes the time-of-flight (TOF) method (Fig. 9.5). TOF exploits differences in magnetization of stationary spins and spins flowing into the imaging slice with circulating blood. The signal from static tissues is suppressed, whereas patent vessels maintain high intensity. The data acquired is used for 2D and 3D reconstructions. A drawback of this technique is blood velocity dependency – with decreased blood flow, the signal from the vessel is so weak that it is often impossible to differentiate significant stenosis from total occlusion. Therefore, time-of-flight magnetic resonance angiography (TOF MRA) may be useful in the evaluation of proximal vessel occlusions but is not suitable for identification of more distal ones. Remonda et al. [11] stated that contrast-enhanced MRA is not bounded by this restriction and its results are comparable to digital subtraction angiography (DSA), the actual reference standard, in 86 % of cases [12]. CTA and contrast-enhanced MRA can also provide a relevant overview of collateral flow, including leptomeningeal collaterals around the ischaemic area. This information may be valuable in predicting acute stroke outcomes [13–15].

9.2.1.3 Perfusion CT and Perfusion MR in the Hyperacute Stage (0–6 h)

The term ‘cerebral perfusion’ implies a quantitative description of tissue-level blood flow to the brain by colour-coded perfusion maps. The most important parameters measured are cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT) [6]. Both perfusion CT and perfusion MR may be used. Tissue perfusion imaging enables evaluation of contrasted blood flow in the capillary bed, exposing early deficits in stroke location.

Perfusion CT adopts continuous imaging over a selected tissue slab during the administration of a high-flow contrast medium bolus. The most popular perfusion MRI technique is dynamic susceptibility contrast-enhanced magnetic resonance imaging (DSC-MRI), involving the use of a gadolinium-based contrast medium. Perfusion MR reveals gadolinium-induced tissue signal changes in T_2*-weighted

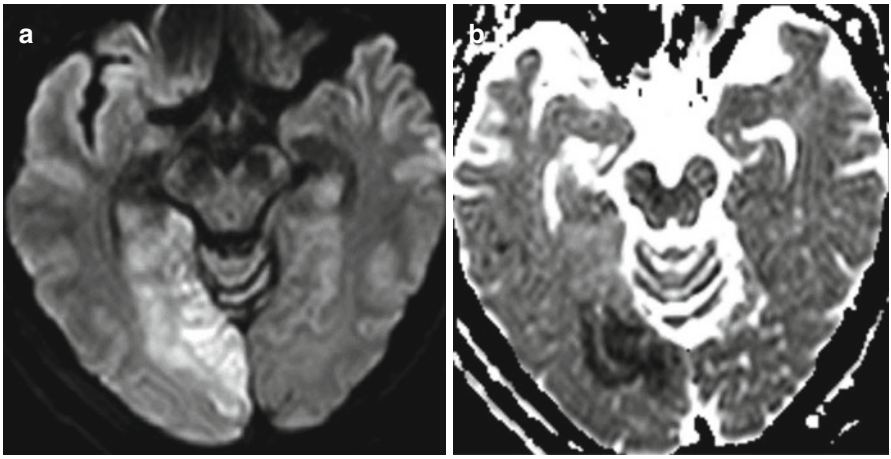

Fig. 9.6 (**a**, **b**) Hyperacute infarction in the right PCA territory. Diffusion-weighted MR image (**a**) and ADC map (**b**) show the area of restricted diffusion due to cytotoxic oedema

images that occur in the first 45–50 s after contrast administration. The main purpose of perfusion imaging is to diagnose infarction and show the proportions between the infarct core (irreversible brain tissue) and tissue at risk (surrounding brain parenchyma – potentially viable if reperfused). In the stroke area, relative decreases in CBV and CBF, as well as MTT elongation, are noted.

9.2.1.4 Diffusion-Weighted Imaging in the Hyperacute Stage (0–6 h)

Diffusion-weighted imaging (DWI) is a widely used MRI technique and has revolutionized the diagnosis of acute ischaemic stroke by identifying cytotoxic oedema within a few minutes of symptom onset [16] at a time when CT scans still appear normal. The sensitivity of ischaemia detection in MR vs. CT imaging within 6 h of onset is 81–91 % vs. 61 % [17, 18]. Infarction in the hyperacute stage is probably partially reversible. DWI may be falsely negative in very early stroke and in patients with small subcortical or vertebrobasilar infarctions.

Ischaemia leads to the shift of water from the extracellular into the intracellular compartment (cytotoxic oedema) and extracellular space reduction, restricting Brownian motion and decreasing the diffusivity of water molecules (Fig. 9.6). These changes produce a high-intensity signal on DWI and a low-intensity signal on apparent diffusion coefficient (ADC) maps, which are typical for cytotoxic oedema (Fig. 9.7). Ultrafast imaging protocols combining DWI, fluid-attenuated inversion recovery (FLAIR) and susceptibility-weighted imaging (SWI) can diagnose hyperacute/acute ischaemic stroke and exclude acute haemorrhage and stroke mimickers in the emergency room [18, 19]. Patients with ischaemic stroke who have intracranial haemorrhage excluded during the first 4½ h of the hyperacute stage qualify for intravenous thrombolytic therapy. DWI is considered the most suitable method for identifying suitable candidates.

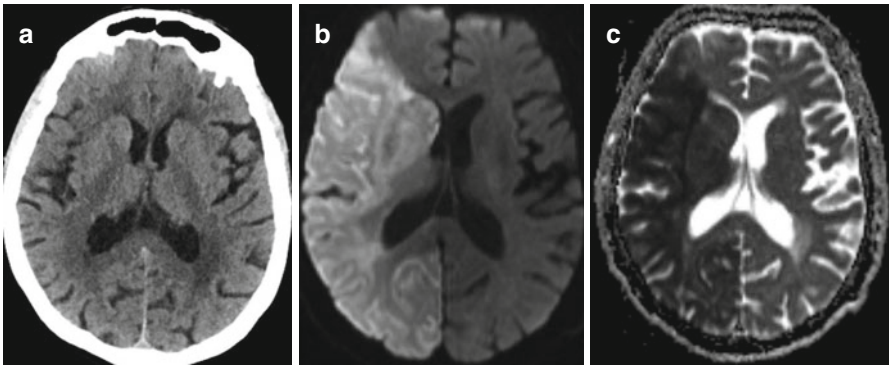

Fig. 9.7 (**a**–**c**) Large hyperacute infarction in the right MCA and PCA territories. CT scan shows no pathological changes (**a**). Diffusion-weighted MR image (**b**) shows the area of high signal intensity in the right hemisphere except for the medial part of the frontal lobe. ADC map (**c**) shows decreased ADC values in the same area. These findings are indicative of acute infarction

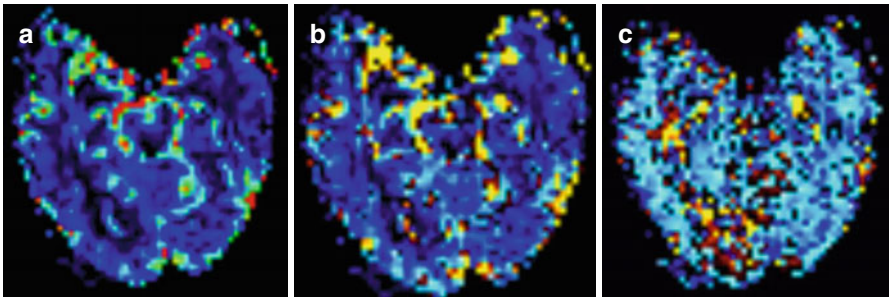

Fig. 9.8 (**a**–**c**) The same patient as in Fig. 9.6a. b. Perfusion MR images of the hyperacute stage of infarction in the right PCA territory. CBV map (**a**) and CBF map (**b**) show the decrease in perfusion in the cortex and subcortical white matter of the right occipital lobe. The MTT map (Fig. 9.9c) shows the increase in perfusion in the right occipital lobe

CT in the hyperacute stage of ischaemic stroke does not allow infarct core assessment. However, a hyperdense MCA sign documented by CT is highly predictive of fatal clinical outcomes [20]. Even so, it remains very difficult to define the infarct core and tissue at risk using current imaging techniques.

The core area of irreversibly infarcted cells is surrounded by a zone of ischaemic but salvageable tissue. The region of CT-CBV and MR-DWI abnormalities is supposed to represent the infarct core. The mismatch between CBV/DWI and MTT/CBF maps shows the area that might be salvageable by immediate reperfusion (Figs. 9.8 and 9.9). However, randomized controlled trials and meta-analyses of reperfusion therapy have demonstrated no benefits in patients selected on the basis of such criteria [21]. Both methods are highly sensitive in identifying hypoperfused tissue, but not specific enough for reliable detection of the tissue at risk.

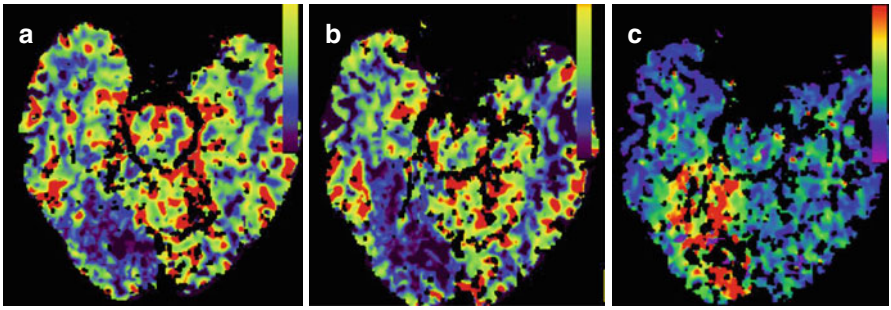

Fig. 9.9 (**a**–**c**) Perfusion CT scans of hyperacute infarction in the right PCA territory. The CBV map (**a**) and CBF map (**b**) show the decrease in perfusion in the cortex and subcortical white matter of the right occipital lobe. The MTT map (**c**) shows the increase in perfusion in the right occipital lobe. The CBV map (**a**) theoretically represents the infarct core

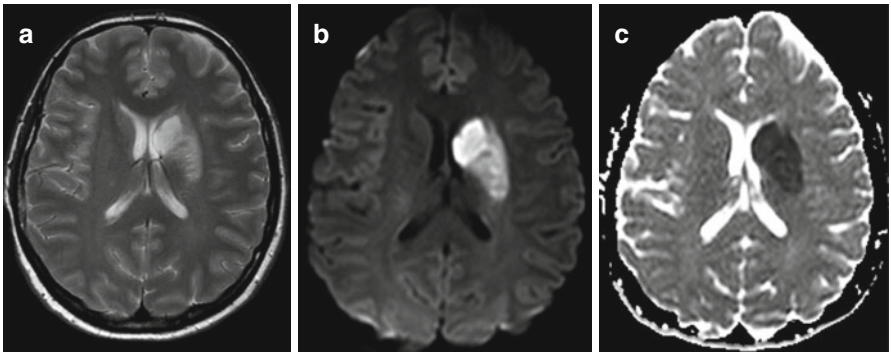

Fig. 9.10 The acute stage of deep striato-capsular infarction. The T2-weighted MR image (**a**) shows the hyperintense area in the left basal ganglia. The diffusion-weighted image (**b**) and ADC map (**c**) show the restriction in diffusion in this area defined as the infarction

Increasing attention is being paid to the significance of baseline DWI lesion volume, which is a poor outcome predictor in acute anterior territory stroke [13–15, 18, 22]. Large DWI lesion volume may be used as an exclusion criterion for thrombolytic therapy.

9.2.1.5 Imaging in the Acute Stage of Ischaemic Stroke (6–24 h)

Ischaemic stroke is a dynamic process. During the acute stage, the zone of cytotoxic oedema increases. Oxygen-free radical production and enzyme activation lead to cell membrane damage and cause neuronal and glial cell death [7]. Increased tissue water content results in hyperintensity on FLAIR sequence and T2-weighted MR images (Fig. 9.10).

The mass effect, in the form of cortex gyri thickening and sulci narrowing, advances further, becoming easier to discern in CT images as a growing hypodense area. Cytotoxic oedema in the infarct core causes an increase in the DWI signal, with a consequent drop in ADC map values. It is most prominent

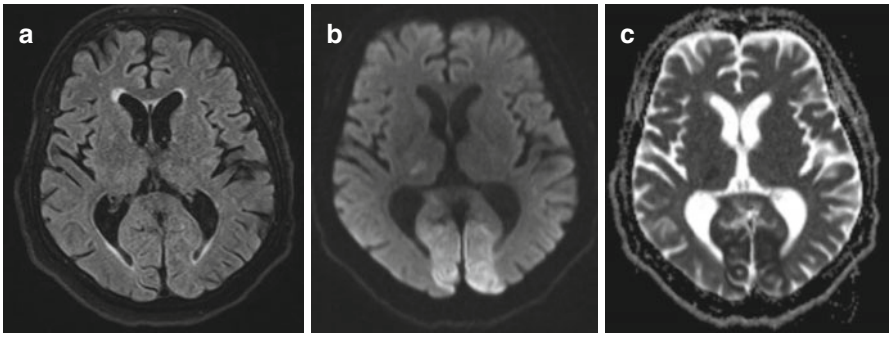

Fig. 9.11 Hyperacute stroke of the posterior circulation. The FLAIR image (**a**) shows no pathological changes. Diffusion-weighted MR image (**b**) shows areas of increased signal intensity in the right thalamus and bilateral occipital lobes. The ADC map (**c**) confirms the restriction in diffusion typical of infarction

2–3 days after the incident and lasts for 1–3 weeks, depending on individual innate repair capabilities [16].

A high FLAIR signal is apparent at the beginning of the acute phase (about 6 h from onset), while in T2-weighted images, it stays isodense for the next 2–4 h. The mismatch in DWI and FLAIR images can be used to approximate symptom onset if the patient remains asleep or in coma. In this way, it broadens the opportunities for thrombolytic intervention. When DWI findings are positive and FLAIR negative (Fig. 9.11), there is a strong likelihood that the stroke is <6 h old [23, 24]. Haemorrhagic transformation due to secondary bleeding into reperfused ischaemic tissue hardly ever occurs in the first 24 h.

9.2.1.6 Imaging in the Subacute Stage of Ischaemic Stroke (2 Days–1 Week)

The blood-brain barrier (BBB) disruption and damage to cell membranes cause an increase in vasogenic oedema, with a maximum between the second and third days [7]. In the subacute stage, all acute radiological signs are still visible: a hypodense area in CT studies (Fig. 9.12a); the mass effect; an elevated signal in PD, T2-weighted and FLAIR MRI sequences; diffusion restriction in DWI studies and ADC maps; and vessel occlusion (Fig. 9.13a–c).

The signal intensity in the ischaemic tissue remains increased on DWI maps for almost 5–7 days and may decrease thereafter. The highest reduction in ADC values is noted around the second and third days. It increases thereafter, returning to normal after 1–3 weeks. To sum up, low signal intensity on ADC maps means that the stroke is <1 week old.

Intravenous contrast agents in stroke imaging are used mainly for angiographic and perfusion CT/MR image acquisition, although they can also help to assess parenchymal enhancement – a consequence of acidosis that follows luxury perfusion. The largest effect is seen between the third day and the third week after stroke (Fig. 9.13d–f); it disappears after 3 months (so-called rule of three).

Haemorrhagic transformation takes place in 15–45 % of ischaemic stroke cases, usually between 24 and 48 h after onset. It is detected as low signal foci on T2, T2*

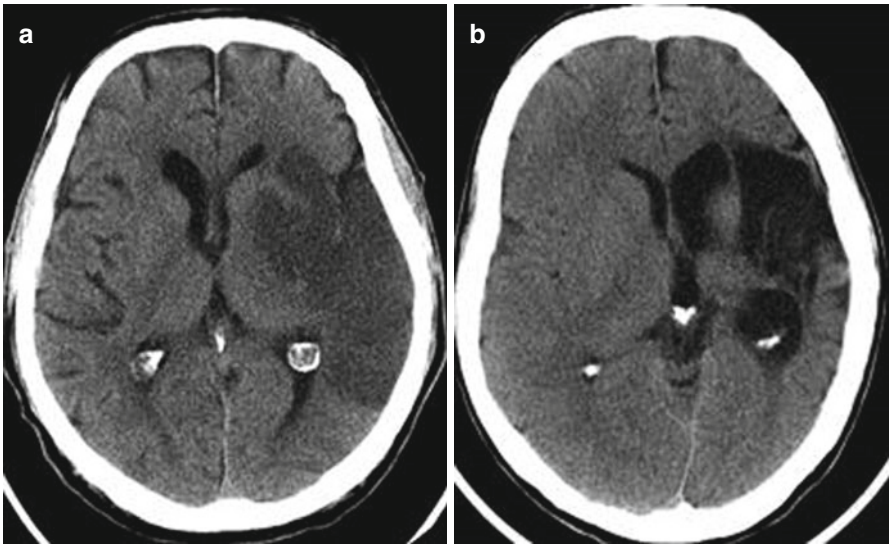

Fig. 9.12 Evolution of the lesion in ischaemic stroke in the territory of the left MCA. CT scan shows hypodense lesion in the left temporal lobe indicating the subacute stage of infarction (**a**). CT image at 3 months (**b**) shows the reduction in the size of the lesion, cavity formation, local brain atrophy and ex vacuo dilatation of the left lateral ventricle

and SW images. In T2-weighted pictures, it is surrounded by a hyperintense ischaemic zone [7]. The severity of secondary haemorrhage varies between microbleeding and a large haematoma. It is probably due to vascular injury, reperfusion or altered permeability. The hyperdense MCA sign on CT scans is associated with a higher risk of haemorrhagic transformation.

9.2.1.7 Imaging in the Chronic Stage of Ischaemic Stroke (8 Days to 3 Months)

The mass effect and vasogenic oedema begin to diminish within 7–10 days, and restoration of the BBB can be observed from the third week (Fig. 9.14) [7]. In T2-weighted and FLAIR images, a hyperintense focus including the infarct area still appears, but decreases every week and usually involves a smaller area than in the primary examination. Arteries that have not been recanalized remain hyperintense.

Typically, the DWI signal is gradually reduced, and this correlates with the normalization of the signal on the ADC maps. Signal normalization is a transitional process and is followed by an increased signal on the ADC map in the area of infarct. This is due to the pathophysiology of the stroke and the transformation from cytotoxic and vasogenic oedema to necrosis (the breakdown of the cell membranes results in a volume increase in the extracellular space and increased ADC value) [4, 16]. In the next few weeks, a glial scar (gliosis) is formed and necrotic tissue is cleaned, which causes local brain atrophy, cavity formation and ex vacuo dilatation of the adjacent ventricle [7]. Cavity areas have a typical fluid signal intensity – low in T1-weighted and FLAIR images and high in T2-weighted images, with a visible, hyperintense zone of gliosis in T2-weighted

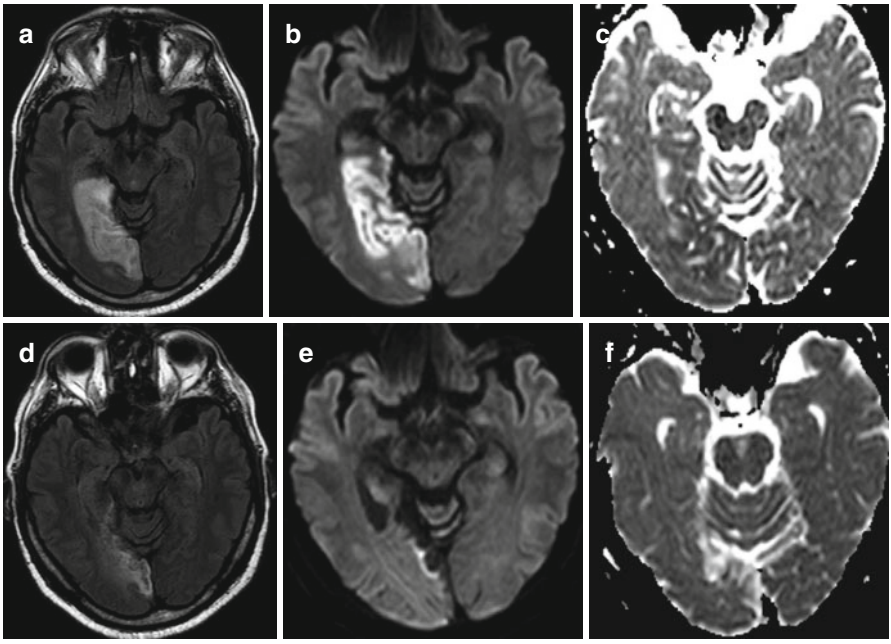

Fig. 9.13 (**a**–**f**) Evolution of the lesion in ischaemic stroke in the territory of the right PCA. The same patient as in the Figs. 9.6 and 9.8. FLAIR and diffusion-weighted MR images (**a**, **b**) on the fifth day after stroke show a hyperintense lesion in the right occipital lobe indicating the subacute stage of infarction. Normalization of the lesion signal intensity on the ADC map is shown (**c**). FLAIR image 3 months after stroke shows gliosis and cortex atrophy in the post-infarction area (**d**). The lesion is significantly smaller than 3 months earlier (in comparison with **a**). Normalization of the lesion signal intensity on diffusion-weighted image is shown (**e**). The ADC map shows free diffusion in the post-infarction area (**f**)

and FLAIR images in this area (Fig. 9.13d–f). Similar findings can be observed in CT studies (Fig. 9.12b).

In T1-weighted and FLAIR images, the brain cortex may be hyperintense due to hypoperfusion and hypoxia when it comes to formation of cortical laminar necrosis (pseudolaminar c.n.). A high signal on T1-weighted images is also a feature of the presence of methaemoglobin after secondary haemorrhagic stroke. If there is difficulty in differentiating between past bleeding and laminar necrosis, the diagnosis is based on the SWI sequence, which shows the presence of breakdown products of haemoglobin. Calcification, as well as deposition of blood products (hemosiderin), may be also seen on SWI and gradient-echo sequence (GRE) sequences [25].

9.2.2 Territorial Infarctions

Territorial infarctions happen in the range of blood supply of the large cerebral vessels. The MCA territory is the most common site of infarction, due to the direct flow from the internal carotid artery (ICA) into the MCA, which provides the easiest path

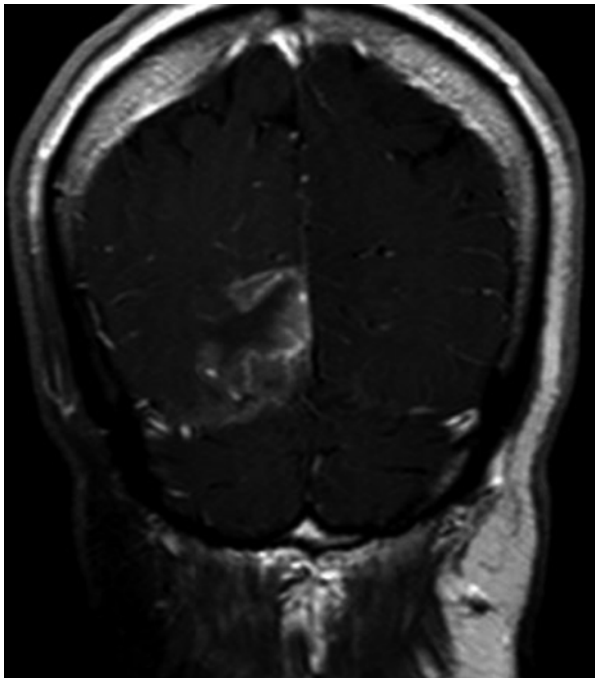

Fig. 9.14 Contrast-enhanced T1-weighted MR image shows enhancement of the infarct area due to blood-brain barrier damage

for thromboembolism. The most extensive attacks are the result of proximal part closure of M1 and the lack of efficient collateral circulation (Fig. 9.4). Closure of the distal part of M1, except the lenticulostriate branches, leads to cortico-subcortical infarcts sparing the basal ganglia and internal capsule [3]. Strokes may present a variable clinical picture depending on the efficiency of the collateral circulation and spared cortex areas. Ischaemia of the insula is found in 50 % of non-lacunar stroke cases in the MCA basin [8].

Basilar or vertebral artery occlusion is the second most common territorial infarction (Fig. 9.11) [26]. Posterior cerebral artery (PCA) infarction may sometimes lead to isolated contralateral thalamic syndrome. Basilar artery occlusion is usually associated with dramatic clinical brainstem symptoms. Cerebellar symptoms appear when a cerebellar artery, for example, the posterior inferior cerebellar artery (PICA), is closed.

Anterior cerebral artery (ACA) territory infarcts are less common due to collateral flow via the anterior communicating artery and the contralateral A1 segment of the anterior cerebral artery.

9.2.3 Subterritorial Infarctions

There are two subterritorial infarction subtypes: cortical and deep. The first is a consequence of the closure of the M2, M3 or M4 MCA branches. The upper branches of M2 occlusion usually occur due to a cardio-embolic mechanism

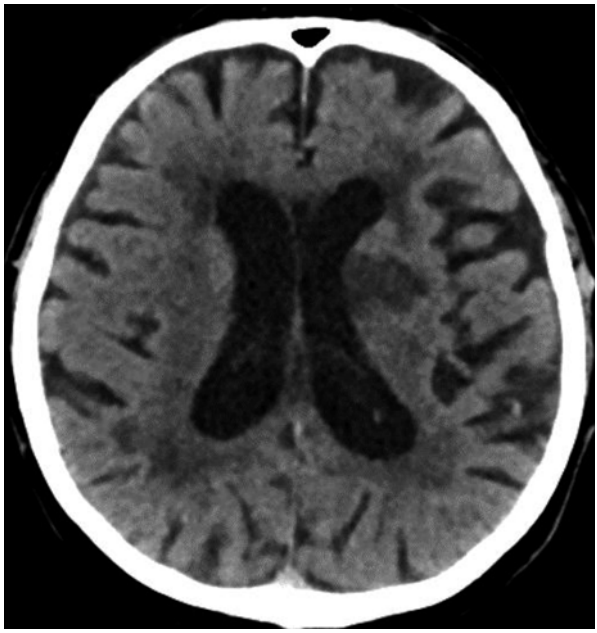

Fig. 9.15 Deep subacute striato-capsular infarction in a patient with hypertension. CT scan shows leukoaraiosis and a hypodense area in the left basal ganglia, indicating infarction

(less often thromboembolic events) and cause extensive stroke of the fronto-parietal area including the pre- and postcentral gyri [3, 4]. Ischaemia in the field of the lower branch of M2 territory is generally caused by cardiogenic embolism and includes the parietal and temporal lobes. Cortical ischaemic stroke from the M3 and M4 territory is caused by arterio-arterial or cardiogenic embolism.

Deep striato-capsular infarctions belong to the group of deep subterritorial infarctions and are the result of closure of the deep branches of the striato-capsular arteries arising from the MCA or lack of flow in many perforating branches (Figs. 9.10 and 9.15). The anatomy of these vessels is very variable, with 6–7 deep arteries forming over 20 perforating arteries. Deep striato-capsular infarctions are larger than 20 mm, and the lacunar strokes observed due to the closure of a single perforating artery are usually smaller than 15 mm.

It is difficult to differentiate between the aetiology of embolic and thrombotic stroke. However, typical imaging findings in embolisms are multiple, smaller subcortical strokes in the supra- and infratentorial compartments, multiple vascular distribution and a haemorrhagic component at presentation [7].

9.2.4 Border-Zone Infarction

Border-zone infarctions (watershed) are classified into cortical watershed infarcts and internal (subcortical) watershed infarcts. In the first type, ischaemic changes are visible in the anterior or posterior part of the cerebral cortex at the junction of the

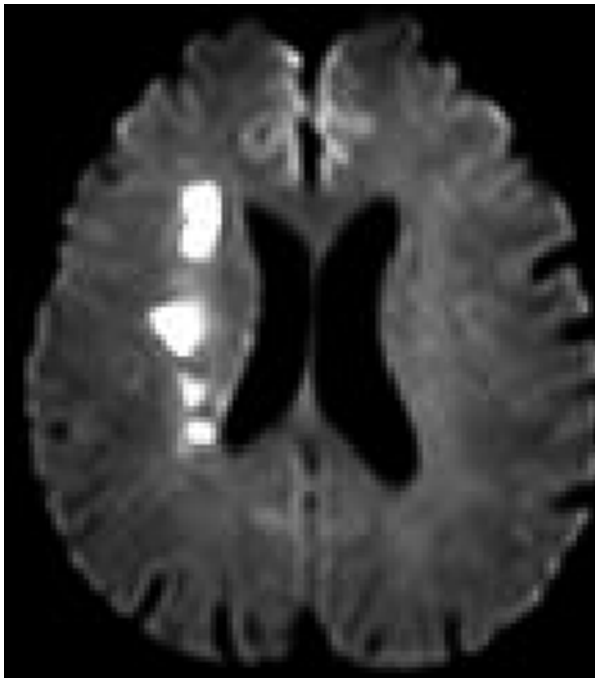

Fig. 9.16 Diffusion-weighted image shows hyperintense lesions in the right middle cerebral internal watershed territory indicating the acute stage of infarction

distal fields of two different major cerebral arteries between the MCA and ACA or the MCA and PCA [7]. In the posterior fossa, similar changes are also observed between the posteroinferior cerebellar artery and the superior cerebellar artery.

Deep internal (subcortical) watershed infarct relates to white matter above the area of the basal ganglia – at the border zones of the territories of the superficial and deep MCA branches and the deeper frontal lobe white matter on the border zones of the ACA and MCA territories. This type is caused by ischaemia, severe systemic hypotension and prolonged hypoxemia. On the basis of MR imaging, especially FLAIR and DWI sequences, internal watershed infarction can be assessed as confluent when multiple, unilateral lesions run parallel to the lateral ventricle (Fig. 9.16).

Watershed infarctions may occur bilaterally when peripheral tissue perfusion decreases secondary to generalized disruption in CBF due to haemodynamic mechanisms. It is observed most frequently in the course of cardiac arrest, extensive bleeding, anaphylactic shock or surgery under general anaesthesia. It usually occurs on one side – for example, obstruction or stenosis of the internal carotid artery or when the collateral circulation of the circle of Willis becomes inefficient, with a drop in systolic pressure. In these cases, CT angiography is appropriate to assess the carotid arteries and circle of Willis, as well as 'misery perfusion'.

In the DWI sequence and, over time, in FLAIR and T2-weighted images, the 'string of beads' symptom can be seen – minor ischaemic lesions diffused on the border zones of the ACA, MCA and PCA territories. In hyperacute and acute stages of watershed infarct, DWI is very sensitive in diagnosing both cortical and internal lesions.

9.2.5 Diffusion Tensor Imaging in Stroke

There are many studies on the use of diffusion tensor imaging (DTI) in patients with stroke. DTI is a powerful tool for the assessment of the organization of white matter fibres and brain connectivity. The orientation of white matter is due to myelin and axonal membranes. When diffusion is anisotropic, its motion can be described using DTI. Quantitative analysis of nerve fibres is made by using a fractional anisotropy (FA) parameter, which has a range of 0 to 1.0. If diffusion is only in one direction, the FA value is closer to 1.0. An FA ratio of 0 indicates isotropic diffusion (i.e. uniform in all directions). Damage and deterioration of the white matter tract result in a decreased FA value. The parallel and perpendicular diffusivity describes the movement of water molecules in one plane. Axial diffusivity (AD) is used to assess axonal injury, while perpendicular diffusivity, radial diffusivity (RD), is a marker of myelin damage, which permits its integrity to be evaluated.

Mukherjee et al. [27] found that after stroke, diffusion was significantly reduced in white matter but only slightly in grey matter. White matter damage DTI assessment after stroke may be a severity marker of neurological deficits. Mainzer's research [28] on the integrity of the hippocampus and the surrounding white matter showed a clear correlation between the loss of speech and the loss of blood supply to the temporal lobe and parts of the hippocampus following MCA stroke. They also showed that stroke patients' success in speech rehabilitation was connected with microstructure maintenance in and around the hippocampus.

The experience of other teams [29] who used DTI in stroke patients to study connectivity between brain regions suggests that patients with stroke suffer from damage to nerve fibres, not only in areas of ischaemic focus but also in the contralesional hemisphere: this could be due to degeneration of fibre pathways directly or indirectly connected to the area of primary damage stroke. A similar mechanism probably leads to corticospinal tract degeneration in patients with only hemispheric infarction. DTI has been used successfully to monitor the rehabilitation of patients after extensive stroke and to assess brain neuroplasticity and to predict functional outcomes in stroke survivors.

9.2.6 Proton Spectroscopy

Magnetic resonance spectroscopy (MRS) is not a standard method of stroke evaluation. It can be used to differentiate brain tumours with atypical ischaemia. The proton spectroscopy spectrum consists of peaks representing concentrations of the following compounds: N-acetyl-aspartate; creatine and creatine phosphate; compounds containing a group of choline, inositol, lipids, lactate, glutamine and glutamate; GABA; and glucose. The concentration of each of these compounds can be regarded as a reflection of certain biochemical processes. MRS may provide information about metabolic changes that may occur before the onset of changes seen on

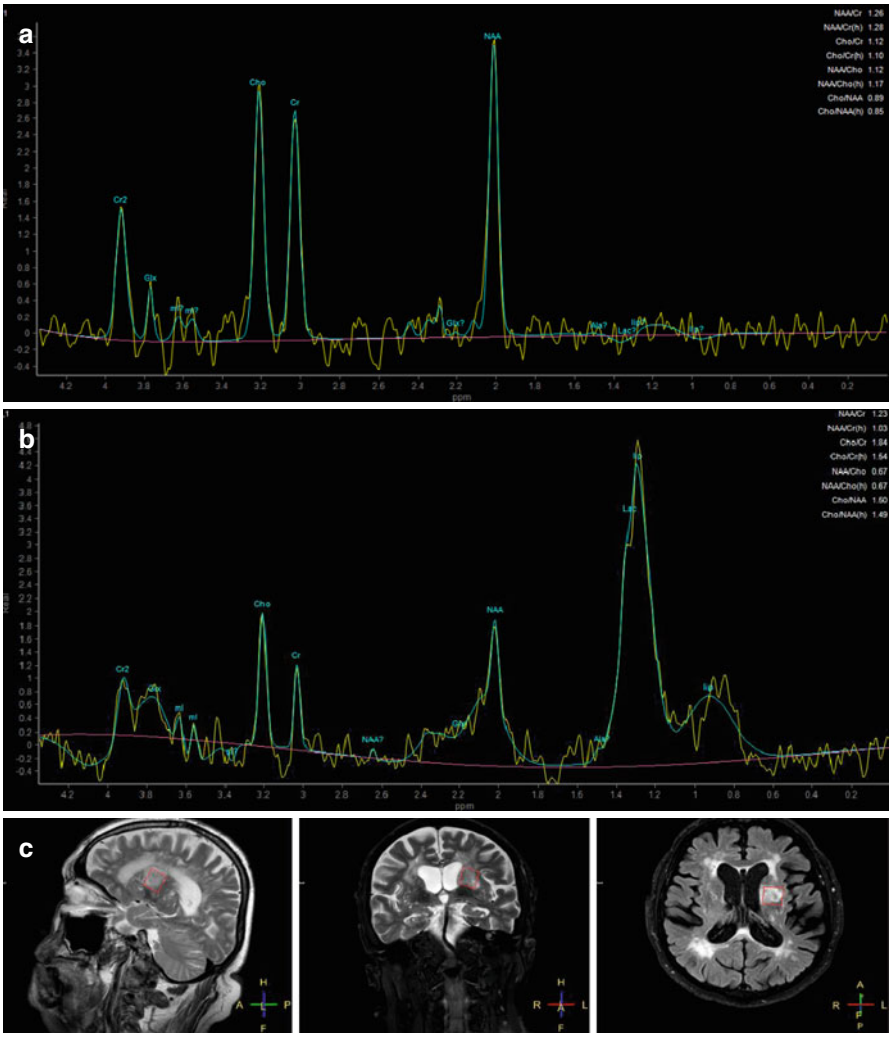

Fig. 9.17 (**a**–**c**) Single-voxel proton MR spectroscopy of the right basal ganglia without pathological changes (**a**) and MRS of the left basal ganglia 5 days after ischaemic stroke onset (**b**). In the ischaemic region, the lactate (LAC) peak is significantly higher with a larger area (1.33 ppm), while the NAA peak is lower with a smaller area (2.02 ppm) (**b**) in comparison with normal basal ganglia (**a**). The voxel placement in the left basal ganglia is seen in 3-plane MR images (**c**)

FLAIR and T2-weighted MR images. Lactate (LAC) – a product of anaerobic glycolysis – is an indicator of ischaemia in the acute phase of ischaemic stroke (Fig. 9.17). In the early stages of stroke, there is also a reduction in the level of a neuronal marker, N-acetyl-aspartate (NAA), while as cell membrane dissolution proceeds, there is an increase in a cell membrane marker – choline (Cho) [30].

9.2.7 Radioisotope Methods

Artery occlusion leads to the disruption of haemodynamic parameters, which can be demonstrated in nuclear imaging examination. Decreased blood flow or lack of blood flow in cerebral vessels is measured by two parameters: regional CBF (rCBF) and mean transit time (MTT), which allow accurate assessment of the area impaired blood perfusion of the brain tissue. Additionally, certain metabolic parameters of nervous tissue can be defined by using the oxygen isotope O-15 in inhaled gas, carbon dioxide or an aqueous spray. These include the measurement of the cerebral oxygen extraction fraction (OEF) and local oxygen consumption (cerebral metabolic rate for oxygen, CMRO). Haemodynamic parameters are most commonly assessed by single-photon emission tomography (SPECT) radiotracers containing Tc-99 m (for instance, hexa-methyl-propyleneamine-oxime, HMPAO; ethyl-cysteinate dimer, ECD) or positron emission tomography (PET), which can also measure metabolic changes. The results are displayed as colour parametric images in the selected section planes. The fusion of functional parametric images obtained in this way with morphological images of the same layer is frequently used. Studies of ischaemia dynamics, metabolic disorders in the focal hypoperfusion 'penumbra' area and interhemispheric diaschisis areas show that SPECT and PET are interesting from the point of view of early diagnosis of stroke, the topography of ischaemic changes and the dynamics of cerebral infarction. These are sensitive methods for subclinical changes or short-term transient ischaemic attack (TIA) imaging [31].

9.2.8 Summary of the Role of Imaging Techniques in Ischaemic Stroke

1. Exclusion or recognition of different causes of neurological deficit (the initial clinical diagnosis of stroke is wrong in 15–20 % of cases)
2. Clarification of doubtful cases – stroke mimickers (tumour, inflammation, traumatic change)
3. Qualification for thrombolysis/thrombectomy
4. Exclusion of complications – secondary haemorrhagic stroke (classic CT control at day 5)
5. Prediction and monitoring of the course of stroke
6. Evaluation of the aetiology of lesions according to their location

9.3 Hypertension and Small Vessel Disease

Cerebral small vessel disease is a very heterogeneous condition whose clinical picture varies from subclinical infarctions to dramatic strokes, with deficits ranging from slight to severe dysfunction. It occurs in the cerebral end arteries and arterioles and reflects age-related vascular degeneration and many other pathological processes. Pathophysiological phenotypes include white matter hyperintensities (WMH),

white matter lesions (WML), dilated Virchow-Robin spaces (dVRS) and microbleeds (MBs).

Hypertension and small vessel disease are well-documented risk factors for stroke and vascular dementia [32]. Age and ApoE4 allele status are also major determinants of both the development and extent of subcortical WML and, possibly, cognitive decline [33].

Hypertension is also the most potent risk factor for both lacunar infarctions and primary intracerebral haemorrhage (ICH) resulting from arteriolosclerosis of the penetrating arteries. While lacunar strokes develop both in the deep periventricular and subcortical areas, the specific location of ICH in hypertensives includes the deep hemispheral basal ganglia, the thalamus, pons and cerebellar white matter (so-called haemorrhages *loco typico*) and, less frequently, the subcortical brain structures. The latter location suggests the contribution of cerebral amyloid angiopathy in the pathogenesis of the primary ICH.

9.3.1 Patterns of Radiological Findings of Small Vessel Disease: CT Scan and MRI

9.3.1.1 Lacunae, Lacunar Infarct and Lacunar Stroke

The terms 'lacunae', 'lacunar infarct' and 'lacunar stroke' are often used interchangeably even though they do not have an identical meaning. Lacunae are cavities of 3 mm to 15–20 mm in size, filled with cerebrospinal fluid. They are located in the basal ganglia or white matter and are often detected in elderly people and are not directly related to neurological symptoms.

Lacunar stroke is associated with clinical symptoms, which may be caused by small subcortical or brainstem lesions. Lacunar infarct is only used when the typical ischaemic, non-haemorrhagic lesions are recognized on CT or MRI.

Lacunar infarcts are small infarcts located deeply in the brain and caused by the occlusion of a single perforating artery due to cerebral small vessel disease [34]. On CT or MR T2-weighted and FLAIR images, an acute lacunar infarct looks similar to WML. The differentiation between clinically asymptomatic WML and infarction is possible only with diffusion-weighted MR imaging. In the hyperacute and acute phases, lacunar infarct typically appears as a restriction of diffusion on DWI and ADC maps (Fig. 9.18). Its signal on ADC maps gradually normalizes, reaching hyperintensity in the chronic phase, which indicates that diffusion in the lacunar infarct is free. The majority of lacunar infarcts should cavitate completely or incompletely at the end of the chronic phase, while the size is reduced in some and a few disappear [35]. However, some lacunar infarcts take the form of a glial scar which resembles WML on MR and CT images [36]. In MRI scans, lacunae are a signal of fluid content foci (hypointense on FLAIR and T1-weighted images and hyperintense in T2-weighted images). Some larger lesions are also surrounded by a thin band of gliosis. It is difficult to depict lacunar infarcts in CT studies in the posterior fossa due to their small size (less than 2 cm) and artefacts from the petrous part of the temporal bone.

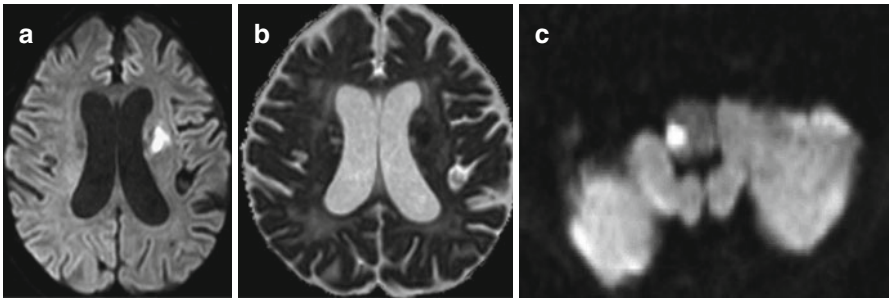

Fig. 9.18 Hyperacute lacunar infarct in the left basal ganglia and medulla oblongata in a patient with hypertension. Diffusion-weighted image (**a**) and ADC map (**b**) show the area of restricted diffusion in the left basal ganglia, indicating the infarction. In addition, the ADC map shows second-stage leukoaraiosis. Diffusion-weighted image of lacunar infarct in the medulla oblongata (**c**)

Subcortical lacunar infarcts are associated with hypertension and stroke. Basal ganglia lacunae correlate with atrial fibrillation. Some develop due to an embolic mechanism caused by occlusion of the lenticulostriate artery. Subcortical infarcts are caused by progressive ischaemia secondary to stenosis of the deep perforating arterioles. Approximately 50 % of lacunar infarcts are observed in patients with normal blood pressure (BP) and are preceded by TIA in 60 % of cases [37]. Stammering is a typical symptom in the first two days. However, depending on the location, lacunar infarct may be asymptomatic. It is common to discover silent infarcts in the lacunae phase in patients with no medical history of stroke. Lacunae are a common finding in the putamen and caudate (37 %), pons (16 %), thalamus (14 %), internal capsule (10 %) and corona radiata (10 %) [38].

9.3.2 Intracerebral Haemorrhage

Hypertension is the most significant and frequent intracerebral haemorrhage (ICH) risk factor. Poorly controlled chronic hypertension results in small vessel vasculopathy, which leads to rupture of the fragile walls of the cerebral penetrating arteries walls due to excessive BP [39]. The other risk factors are cerebral amyloid angiopathy (CAA), anticoagulant therapy and alcoholism. ICH due to hypertension is typically seen in elderly patients and usually occurs in the basal ganglia region. This haemorrhage, which is usually surrounded, may rupture into the ventricular space.

The diagnosis of ICH is made on the basis of CT rather than MR imaging, especially in acute stroke. Typical ICH findings on CT images are that acute bleeding is markedly hyperdense compared to the brain parenchyma due to high protein concentrations and usually poses little difficulties in the diagnosis. However, occasionally, acute ICH may appear as isodense or even hypodense on CT images in patients with coagulopathy or severe anaemia.

In the hyperacute and acute stage, the haemorrhage is seen as a hyperdense lesion measuring from 40 to 80 HU. In the first hours after bleeding, there may be a

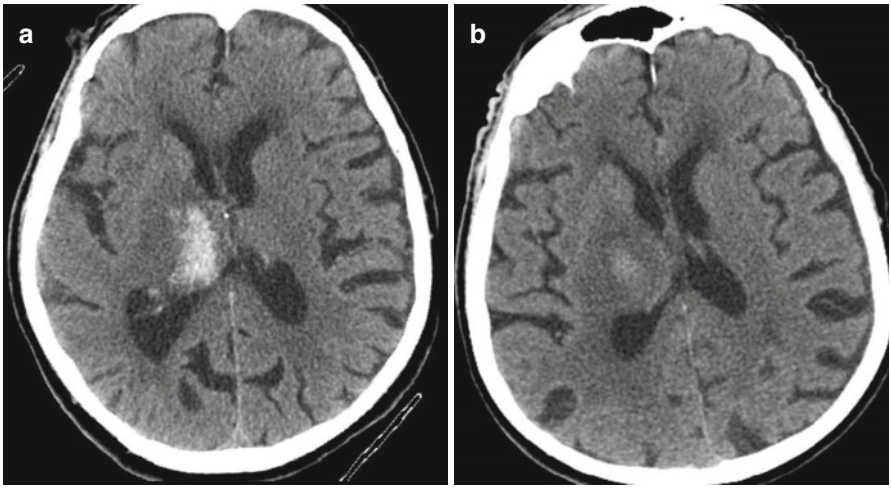

Fig. 9.19 Evolution of the intracerebral haemorrhage. (**a**) CT scan six hours after stroke onset shows a hyperdense pathological mass in the right thalamus typical of acute haemorrhage. (**b**) CT scan carried out 7 days later shows typical findings of haematoma absorption – reduced lesion size and density, especially in the periphery of the lesion

heterogeneous appearance with a fluid-fluid level, representing blood sedimentation. High attenuation of the haematoma may persist for approximately 1 week [40], and after this time, the density of the haemorrhage begins to decrease, starting from the periphery of the lesion (Fig. 9.19). Decreased density represents the absorption of necrotic and haemorrhagic tissue and cavity formation, the final stage of ICH.

The appearance of ICH on MR images depends on both the age of the blood and the pulsing sequences used [41, 42]. In general, five stages of haematoma evolution are recognized. The first depicts intracellular oxyhaemoglobin, whose signal intensity is isointense on T1-weighted images and iso- to hyperintense on T2-weighted images. After approximately 24 h, intracellular deoxyhaemoglobin appears, with a drop in the T2 signal intensity (T2 shortening), while T1 remains isointense. From the third day, intracellular methaemoglobin can be identified, characterized by high signal intensity on T1-weigthed images and low signal intensity on T2-weighted images. After a few days, extracellular methaemoglobin appears; this has high signal intensity on T1- and T2-weighted images. After approximately a month, the hemosiderin signal begins to dominate, which is very low on T2-weighted images and slightly hypointense on T1-weighted images.

Magnetic susceptibility-weighted imaging is based on the ability of a T2*-weighted MR sequence to detect very small amounts of deoxyhaemoglobin, in addition to other compounds such as those containing iron or calcium [25]. MRI and CT are equivalent in detecting acute haemorrhage (96 % concordance), but MRI can better demonstrate haemorrhagic transformation of areas of ischaemia and deposits of hemosiderin in chronic haemorrhage (microbleeds) and provides superior information on the age and location of ICH.

9.3.3 White Matter Hyperintensities

WMH and WML, also called periventricular leukomalacia or leukoaraiosis (LA), are depicted on MRI as hyperintense areas on proton density (PD), T2-weighted and FLAIR images and hypointense areas on T1-weighted images. On DWI maps, these lesions do not cause restricted diffusion, and on ADC maps, they have a high signal. No enhancement after intravenous infusion of contrast media is indicated. On CT scans, the lesions are hypodense (Fig. 9.15), but the sensitivity of CT scans in detecting WMH is lower than MRI. The most frequent etiological factor for WMH is hypertension, and therefore, coexisting microhaemorrhages, well depicted on SWI as hypointense lesions, may be seen.

Histologically, WMH have a decreased amount of oligodendroglia and myelin. The number of axons declines, there is fibre fragmentation, and many reactive astrocytes are seen. Glassy scars occur in blood vessel walls, and smooth muscle tissue is replaced by collagen. These changes lead to thickening of the vessel walls and narrowing of their lumen [39].

Diffuse white matter disease is progressive and clinically represented by cognitive decline, walking disorders and falls. At present it is classified in the group of cerebral small vessel diseases (CSVD), which are caused by chronic ischaemia due to vasculopathy of the cerebral small arteries. CSVD is a risk factor for stroke and one of the main factors in subcortical vascular dementia. However, there is a lack of correlation between radiological and histological phenotypes [43].

A Framingham population analysis showed that LA in the white matter forecast premature death, independently of earlier stroke or dementia [44]. The Rotterdam Scan Study found a correlation between LA and the severity of cognitive decline [45], especially in subcortical areas – with an increased risk of clinical depression in the elderly. Recognized factors for LA are advanced age and hypertension. High BP correlates with increasing severity of LA. Effective hypertension management can decrease the risk of bleeding and dementia, but diastolic BP levels should be kept sufficient for brain perfusion.

There are several LA evaluation scales. One is the Fazekas scale, rated from 0 to III, where 0 represents no changes or single punctate WML, I represents multiple punctate WMLs, and in grade II they begin to fuse (beginning confluence of WML – bridging). In grade III, vast WML fusion areas dominate. Grade I can occur in the physiological brain ageing process, but grades II and III indicate small vessel disease.

Blood vessel changes related to hypertension can also cause Binswanger disease, which originates in subcortical damage to the white matter. Initially, it shows clinically as cognitive decline, difficulties in decision-making or disturbances in attention, although memory impairment is relatively small. Nonetheless, the progression of dementia in Binswanger disease is rapid and not related to stroke or TIA.

9.3.4 Dilated Virchow-Robin Spaces

Virchow-Robin spaces (VRS) are perivascular spaces surrounding the small arteries and arterioles. VRS may be dilated (dVRS) and seen as punctate or linear hyperintensities on T2-weighted images, lying along penetrating arteries or as

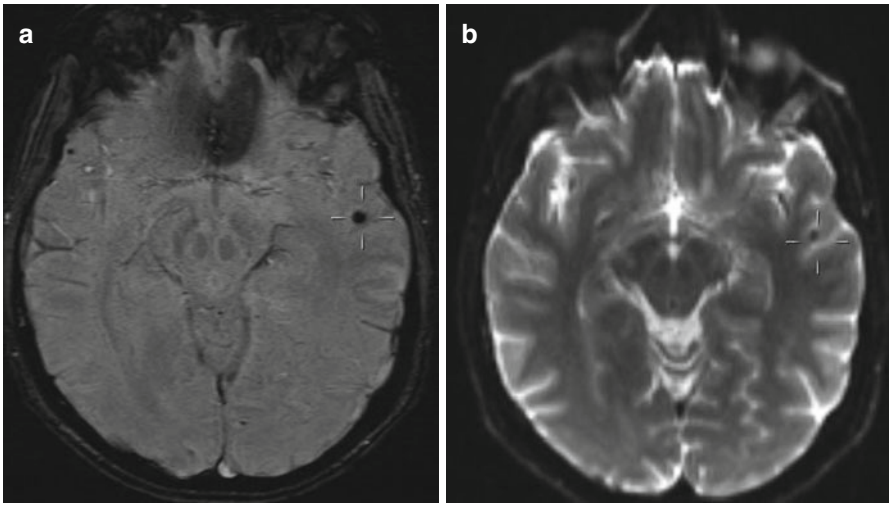

Fig. 9.20 (**a**, **b**) Microbleed in a patient with hypertension. SWI scan shows a hypointense focus of the microbleed in the left temporal lobe (**a**), which is less visible on the T2-weighted MR image (**b**)

fluid spaces in FLAIR images. dVRS are widely detected in healthy people and in stroke patients and are independently associated with age, hypertension and cerebral small vessel disease such as LA and lacunae in stroke- and dementia-free populations [46]. Age, LA and microhaemorrhage influence the severity of dVRS widening in patients with a history of intracranial haemorrhage [47]. Most commonly, dRVS are located in the lower half of the basal ganglia, substantia nigra, dentate nucleus, subinsular region, corpus callosum and cingulate gyrus. They are divided into three main types according to their location: type 1, located in the area supplied by the lenticulostriate arteries entering the basal ganglia; type 2, located in the area supplied by the perforating medullary arteries as they enter the cortical grey matter; and type 3, located in the midbrain. Wide perivascular spaces are an anatomical variation. They should always be evaluated collectively with other cerebral changes.

9.3.5 Cerebral Microbleeds

Cerebral microbleeds (MBs) are shown on MRI scan, especially in GRE-T2*-weighted or SW map imaging, as small perivascular hypointense lesions (Fig. 9.20). The name comes from neuroradiology and was used for the first time by Fazekas [48]. Cerebral microbleeds are small and homogenous foci measuring 2–5 mm and are characterized by magnetic susceptibility and the blooming effect, which means foci seen on GRE-T2*/SW-MR images are, in fact, bigger than the actual lesions. They must be differentiated from calcium and iron deposits in the cerebral basal ganglia, small cavernous haemangiomas (especially type IV), melanoma metastases, bone- and air-induced artefacts and post-traumatic diffuse axonal injury [49].

Cerebral microbleeds are classified in the group of cerebral small vessel disease, together with LA, lacunar infarcts, perivascular dVRS and so-called silent brain infarcts (SBI), which are usually small subcortical lacunar infarcts [50]. Typical locations of MBs in hypertension vasculopathy are the deep parts of the brain, such as the basal ganglia, thalamus, cerebellum and brainstem [48]. MBs are more frequent in patients with cerebral amyloid angiopathy (CAA) and neurodegenerative changes typical of Alzheimer disease (AD). The frequency of MBs in conventional MR head imaging is approximately 5 % in healthy subjects and increases distinctly with age [51]. The overall prevalence of MBs is high and increases with age from 17.8 % in persons aged 60–69 years to 38.3 % in those aged >80 years [52]. The prevalence is about 35 % in patients with ischaemic stroke and up to 60 % in those with ICH. The presence of MBs has been associated with the prevalence and severity of spontaneous intracerebral haemorrhage. The accumulation of hemosiderin deposits can be considered a biomarker of the level of progression of small vessel disease. In patients with angiopathy and AD, there is a characteristic location of MBs in the cortico-subcortical area with distinctive tendency to the involvement of posterior areas – especially the occipital and parietal lobes. The MR GRE sequence appears to be more accurate than CT for the detection of chronic MBs.

9.4 Hypertension and Alzheimer's Dementia

The relationship between hypertension and cognitive decline has been shown by epidemiological associations and by pathological and neuroimaging studies. Hypertension before the age of 60 years appears to be independently associated with late cognitive impairment [53–56]. Early BP management in midlife seems to be important in delaying or preventing cognitive decline [57], although very recent studies suggest that microstructural white matter alterations appear early in the course of hypertension and may persist despite adequate treatment of elevated BP. It is likely that prevention rather than the management of hypertension may be vital to preserving brain health in ageing [58]. By contrast, the associations between lowering BP values in very old adults without a remarkable cardiovascular history and reductions in the risk of dementia are less clear and need further study [59].

Cerebral tissue is vulnerable to abrupt BP fluctuations as well as to more chronic pathogenic mechanisms linked to hypertension. Extremely acute alterations in BP result in cerebral infarctions and haemorrhages. Parallel to these primary vascular injuries, there are degenerative deposition of amyloid in the brain parenchyma, neuritic plaque and neurofibrillary tangles, with final neuronal loss as a consequence.

Clinically, the combination of neuropathology including AD and cerebrovascular disease is common in the elderly [60] and may be sufficient to cause dementia [61]. Initially, the clinical manifestations of these disorders may be subtle and are thus often overlooked by patients and relatives. In later stages, the accumulation of the two pathogenic processes underlies the conversion from subclinical into whispering stroke or cognitive decline and, finally, into overt cerebrovascular accidents. The presence of hypertension-related vascular changes in the brain accelerates the manifestations of cognitive dysfunction.

9.4.1 Neuropsychological Aspects of Neuroimaging Findings in Hypertensive Adults

In clinical practice today, only a multidisciplinary team truly guarantees a comprehensive diagnosis of hypertension. The final diagnosis takes into consideration not only standard medical examinations and laboratory tests but also the mental status and everyday functioning of the hypertensive patient. Therefore, close integration of disciplines such as radiology, hypertension, neurology and neuropsychology is warranted.

The psychological interpretation of neuroimaging findings is helpful, particularly in the early phase of the disorder, when most symptoms are subclinical. Very mild and non-specific cerebral alterations may not easily be detected by routine medical examination and traditional methods of neuroimaging, such as computerized tomography. Neuropsychological assessment can thus be considered as an alternative method for the identification of subtle alterations in the brain and for the prediction of behavioural sequelae. In general, clinical neuropsychology explains how brain abnormalities affect behaviour. Neuroimaging findings help to clarify complex associations between hypertension and its mental (cognitive, emotional and behavioural) correlates. Neuropsychologists examine cognitive domains such as perception, attention, memory, problem-solving ability, language and visuospatial skills [62–64].

However, the neuropsychological interpretation of neuroimaging findings is a complex matter since several factors may influence neurophysiological and psychological processes in hypertensive adults, including the duration of hypertension, the type and length of antihypertensive treatment, accompanying health problems (e.g. pulmonary disease, renal or metabolic disorders, head injury, alcohol and drug use), demographic variables and personality characteristics (e.g. emotional stress, anxiety, cognitive reserve). Taken together, these factors provide an understanding of why there is no single hypertension mechanism affecting the brain. For example, in hypertensive patients, discrete regions of cerebral infarction and diffuse ischaemic changes in the periventricular and deep white matter (leukoaraiosis) may predispose to cognitive impairment. Jennings and Zanstra [65] suggested that hypertension induces a reduction in CBF that may be more marked in the frontal and subcortical regions. This opinion supports the notion expressed earlier that executive dysfunction is a prominent feature in the neuropsychological picture of hypertension, since the frontal lobes (especially the prefrontal cortex) and their connections to a complex circuitry of subcortical structures (e.g. striatal regions, thalamus) have been suggested as the anatomical substrate of executive functioning [66].

Diffuse vascular white matter changes also contribute to the pathogenesis of progressive neurodegeneration (e.g. Alzheimer's disease) by destabilizing neurons and synapses [67, 68]. Nevertheless, the time course of cognitive impairment in hypertension is a subject of much discussion [69]. Studies varied in their exclusion criteria, classification of hypertension and diagnostic validity of neuropsychological tests. Furthermore, some studies did not quantify the severity of cerebrovascular changes in subjects included nor consider this a relevant prognostic determinant. According to Waldstein et al. [63], for instance, hypertension does not typically

show a progressive decline in cognitive functioning over time. Generalized mental deterioration in hypertensive patients is also rare, since most cognitive dysfunctions are selective in nature, whereas other cognitive domains remain intact or nearly normal, i.e. language, verbal skills and general intelligence. Minimal decline has been noted in tasks requiring psychomotor speed or new learning in the elderly. In a review, Elias et al. [70] claimed that hypertension-related cognitive impairment is not a problem of old age, but a problem at all ages. However, numerous studies have provided evidence that white matter changes (LA) increase exponentially after the age of 65 years. Hypertension in the elderly may be associated with a higher prevalence of white matter abnormalities and increased shrinkage of the prefrontal cortex [71]. Thus, hypertension results in premature ageing of the brain, reflected by vascular cognitive impairment. In other words, it is possible that the hypertension-brain ageing interaction plays an important role in the development of dementia, with predominantly subcortical symptomatology, including slowing of information processing, lack of initiative, inertia, apathy, mood disturbances, forgetfulness and a defective ability to manipulate acquired knowledge [72].

References

1. Gąsecki D, Kwarciany M, Nyka W et al (2013) Hypertension, brain damage and cognitive decline. Curr Hypertens Rep 15(6):547–558
2. Vu D, Lev MH (2005) Noncontrast CT in acute stroke. Semin Ultrasound CT MRI 26:380–386
3. Gonzalez RG, Hirsch JA, Lev MH et al (2011) Acute ischemic stroke: imaging and intervention, 2nd edn. Springer, New York
4. Merino JG, Warach S (2009) Imaging of acute stroke. Nat Rev Neurol 6:560–571
5. Hacke W, Kaste M, Fieschi C et al (1998) Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 352:1245–1251
6. Muir KW, Buchan A, von Kummer R et al (2006) Imaging of acute stroke. Lancet Neurol 5:755–768
7. Kanekar SG, Zacharia T, Roller R (2012) Imaging of stroke: part 2, pathophysiology at the molecular and cellular levels and corresponding imaging changes. Am J Roentgenol 98(1): 63–74
8. Truwit CL, Barkowich AJ, Gean-Marton A et al (1990) Loss of the insular ribbon: another early CT sign of acute middle cerebral artery infarction. Radiology 176:801–806
9. Tomandl BF, Klotz E, Handschu R et al (2003) Comprehensive imaging of ischemic stroke with multisection CT. Radiographics 23:565–592
10. Provenzale JM, Jahan R, Naidich TP et al (2003) Assessment of the patient with hyperacute stroke: imaging and therapy. Radiology 229:347–359
11. Remonda L, Senn P, Barth A et al (2002) Contrast-enhanced 3D MR angiography of the carotid artery: comparison with conventional digital subtraction angiography. Am J Neuroradiol 23:213–219
12. Jauch EC, Saver JL, Adams HP Jr et al (2013) Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 44:870–947
13. Singer OC, Kurre W, Humpich MC, et al. MR Stroke Study Group Investigators (2009) Risk assessment of symptomatic intracerebral hemorrhage after thrombolysis using DWIASPECTS. Stroke 40:2743–2748

14. Nezu T, Koga M, Kimura K et al (2010) Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology 75:555–561
15. Schaefer PW, Pulli B, Copen WA et al (2015) Combining MRI with NIHSS thresholds to predict outcome in acute ischemic stroke: value for patient selection. Am J Neuroradiol 36(2):259–264
16. Schaefer PW, Grant PE, Gonzalez RG (2000) Diffusion- weighted MR imaging of the brain. Radiology 217:331–345
17. Fiebach JB, Schellinger PD, Jansen O et al (2002) CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. Stroke 33:2206–2210
18. Schellinger PD, Bryan RN, Caplan LR et al (2010) Evidence-based guideline: the role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 75(2):177–185
19. Ringelstein EB (2005) Ultrafast magnetic resonance imaging protocols in stroke. J Neurol Neurosurg Psychiatry 76(7):905
20. von Kummer R, Meyding-Lamadé U, Forsting M et al (1994) Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. Am J Neuroradiol 15(1):9–15
21. Mishra NK, Albers GW, Davis SM et al (2010) Mismatch-based delayed thrombolysis: a meta-analysis. Stroke 41(1):e25–e33
22. Yoo AJ, Verduzco LA, Schaefer PW et al (2009) MRI-based selection for intra-arterial stroke therapy: value of pretreatment diffusion-weighted imaging lesion volume in selecting patients with acute stroke who will benefit from early recanalization. Stroke 40:2046–2054
23. Allen LM, Hasso AN, Handwerker J et al (2012) Sequence-specific MR imaging findings that are useful in dating ischemic stroke. Radiographics 32(5):1285–1297
24. Xu X-Q, Zu QQ, Lu SS et al (2014) Use of FLAIR imaging to identify onset time of cerebral ischemia in a canine model. AJNR Am J Neuroradiol 35(2):311–316
25. Villringer A, Rosen BR, Belliveau JW et al (1988) Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. Magn Reson Med 6:164–174
26. Mattle HP, Arnold M, Lindsberg PJ et al (2011) Basilar artery occlusion. Lancet Neurol 10(11):1002–1014
27. Mukherjee P, Bahn MM, McKinstry RC et al (2000) Differences between gray matter and white matter water diffusion in stroke: diffusion-tensor MR imaging in 12 patients. Radiology 215(1):211–212
28. Meinzer M, Mohammadi S, Kugel H et al (2010) Integrity of the hippocampus and surrounding white matter is correlated with language training success in aphasia. Neuroimage 53(1):283–290
29. Crofts JJ, Higham DJ, Bosnell R et al (2011) Network analysis detects changes in the contralesional hemisphere following stroke. Neuroimage 54(1):161–169
30. Yan G, Dai Z, Xuan Y, Wu R (2015) Early metabolic changes following ischemia onset in rats: an in vivo diffusion-weighted imaging and 1H-magnetic resonance spectroscopy study at 7.0 T. Mol Med Rep 11(6):4109–4114
31. Heiss WD (2014) Radionuclide imaging in ischemic stroke. J Nucl Med 55(11):1831–1841
32. Dufouil C, de Kersaint-Gilly A, Besançon V et al (2001) Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. Neurology 56:921–926
33. De Leeuw F, de Groot JC, Oudkerk M et al (2002) Hypertension and cerebral white matter lesions in a prospective cohort study. Brain 125:765–772
34. Fisher CM (1982) Lacunar strokes and infarcts: a review. Stroke 32:871–876
35. Loos CM, Staals J, Wardlaw JM et al (2012) Cavitation of deep lacunar infarcts in patients with first-ever lacunar stroke: a 2-year follow-up study with MR. Stroke 43(8):2245–2247
36. Potter GM, Doubal FN, Jackson CA et al (2011) Counting cavitating lacunes underestimates the burden of lacunar infarction. Stroke 41:267–272
37. Horowitz DR, Tuhrim S, Weinberger JM et al (1992) Mechanisms in lacunar infarction. Stroke 23:325–327

38. Marks MP (2009) Cerebral ischemia and infarction. In: Atlas SW (ed) Magnetic resonance imaging of the brain and spine, vol 1, 4th edn. Williams & Wilkins, Philadelphia, pp 772–825
39. Grinberg LT, Thal DR (2010) Vascular pathology in the aged human brain. Acta Neuropathol 119(3):277–290
40. Dainer HM, Smirniotopoulos JG (2008) Neuroimaging of hemorrhage and vascular malformations. Semin Neurol 28(4):533–547
41. Latchaw RE, Alberts MJ, Lev MH, et al; American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease (2009) Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. Stroke 40:3646–3678
42. Schellinger PD, Jansen O, Fiebach JB et al (1999) A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. Stroke 30:765–768
43. Bersano A, Debette S, Zanier ER et al (2012) The genetics of small-vessel disease. Curr Med Chem 19(24):4124–4141
44. Debette S, Beiser A, DeCarli C et al (2010) Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia and mortality. The Framingham offspring study. Stroke 41:600–606
45. De Groot JC, de Leeuw FE, Oudkerk M et al (2000) Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol 47:145–151
46. Zhu YC, Tzourio C, Soumare A et al (2010) Severity of dilated Virchow-Robin spaces is associated with age, blood pressure, and MRI markers of small vessel disease: a population-based study. Stroke 41:2483–2490
47. Charidimou A, Meegahage R, Fox Z et al (2013) Enlarged perivascular spaces as a marker of underlying arteriopathy in intracerebral hemorrhage: a multicenter MRI cohort study. J Neurol Neurosurg Psychiatry 84:624–629
48. Fazekas F, Kleinert R, Roob G et al (1999) Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. Am J Neuroradiol 20:637–642
49. Greenberg SM, Vernooij MW, Cordonnier C et al (2009) Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 8:165–174
50. Gao T, Wang Y, Zhang Z (2008) Silent cerebral microbleeds on susceptibility-weighted imaging of patients with ischemic stroke and leukoaraiosis. Neurol Res 30:272–276
51. Cordonnier C, Al-Shahi Salman R, Wardlaw J (2007) Spontaneous brain micro- bleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain 130:1988–2003
52. Vernooij MW, van der Lugt A, Ikram MA et al (2008) Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology 70(14):1208–1214
53. Breteler MM, van Swieten JC, Bots ML et al (1994) Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology 44:1246–1252
54. Skoog I, Lernfelt B, Landahl S et al (1996) 15-year longitudinal study of blood pressure and dementia. Lancet 347:1141–1145
55. Kilander L, Nyman H, Boberg M et al (1998) Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension 31:780–786
56. Elias MF, Elias PK, Sullivan LM et al (2003) Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int J Obes Relat Metab Disord 27:260–268
57. Peila R (2001) Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu-Asia aging study. Stroke 32:2882–2889
58. McEvoy LK, Fennema-Notestine C, Eyler LT et al (2015) Hypertension-related alterations in white matter microstructure detectable in middle age. Hypertension 66:317–323
59. Rosano C (2015) Longitudinal systolic blood pressure characteristics and integrity of white matter tracts in a cohort of very old black and white adults. Am J Hypertens 28:326–334

60. Gorelick PB, William M (2005) Feinberg lecture: cognitive vitality and the role of stroke and cardiovascular disease risk factors. Stroke 36:875–879
61. Troncoso JC (2008) Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann Neurol 64:168–176
62. Lezak MD, Howieson DB, Loring DW (2004) Neuropsychological assessment (Fourth edition). Oxford University Press, New York
63. Waldstein SR, Manuck SB, Ryan CM et al (1991) Neuropsychological correlates of hypertension: review and methodologic consideration. Psychol Bull 110:451–468
64. Lande MB, Kupferman JC, Adams HR (2012) Neurocognitive alterations in hypertensive children and adolescents. J Clin Hypertens 14:353–359
65. Jennings JR, Zanstra Y (2009) Is the brain the essential in hypertension? Neuroimage 47:914–921
66. Miller BL, Cummings JL (eds) (2007) The human frontal lobes. Functions and disorders. The Guilford Press, New York
67. Eftekhari H, Uretsky S, Messerli FH (2007) Blood pressure, cognitive dysfunction, and dementia. J Am Soc Hypertens 1:135–144
68. Birns J, Kalra L (2009) Cognitive function and hypertension. J Hum Hypertens 23:86–96
69. Seux ML, Forette F (1999) Effects of hypertension and its treatment on mental function. Curr Hypertens Rep 3:232–237
70. Elias MF, Goodell AL, Dore GA (2012) Hypertension and cognitive functioning. A perspective in historical context. Hypertension 60:260–268
71. Cabeza R, Nyberg L, Park D (2005) Cognitive neuroscience of aging. Linking cognitive and cerebral aging. Oxford University Press, Oxford/New York
72. Albert ML (2005) Subcortical dementia: historical review and personal view. Neurocase 11:243–245

Primary Stroke Prevention

10

Augusto Zaninelli, Paola Santalucia, and Simona Sacco

10.1 The Most Important Trials in Primary Stroke Prevention

Hypertension is the major modifiable risk factor for ischaemic stroke other than cardioembolic and for haemorrhagic stroke. It has been estimated that, worldwide, 26 % of the population had high blood pressure (BP) in the year 2000 and that this proportion will increase to 29 % by 2025 [1]. Regular BP monitoring and appropriate treatment of hypertension are firmly recommended by all guidelines for primary or secondary stroke prevention based upon the strong evidence of stroke risk reduction through the correct management of BP, whether systolic blood pressure (SBP) or diastolic blood pressure (DBP). The relationship between BP and stroke risk is strong, linear, independent and etiologically predictive: thus, within the usual BP ranges, including non-hypertensive ones, the higher the BP, the greater the risk of stroke [2]. In addition, BP, particularly SBP, increases with age as does the associated stroke risk. Non-hypertensive people whose BP values are slightly elevated (i.e. prehypertension defined as SBP 120–139 mmHg or DBP 80–89 mmHg) benefit from lifestyle approaches with or without pharmacological treatments. A meta-analysis of 16 trials in 70,664 prehypertensive subjects randomized to receive pharmacological treatment compared with placebo showed a 22 % stroke risk reduction in the intervention group [3]. In hypertensive subjects, lifestyle changes combined with correct BP treatment and control resulted in a 35–40 % reduction in the stroke burden [4, 5].

A. Zaninelli (✉)
Department of General Practice, School of Medicine, University of Florence, Florence, Italy
e-mail: zaninell@interac.it

P. Santalucia
Scientific Direction, Foundation IRCCS Maggiore Hospital, Policlinico, Milan, Italy

S. Sacco
Department of Neurology, University of L'Aquila, L'Aquila, Italy

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_10

The benefit in stroke reduction of BP lowering seems not to have a clear drug class preference, although the pleiotropic effects of class-related drugs may contribute to cardiovascular risk reduction. *The cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint* (*LIFE*) *reduction in hypertension* study showed a greater benefit in subjects treated with losartan compared with atenolol in reducing the rate of fatal and non-fatal stroke, suggesting a possible role of left ventricular hypertrophy regression which, in itself, is a BP-related independent predictor of stroke [6, 7].

However, pharmacological strategies and the proportion of BP lowering remain matters of debate. Meta-analyses show that more-intensive BP control (SBP < 130 mmHg) is associated with a greater stroke risk reduction than less-intensive control (SBP 130–139 mmHg) [8]. Interestingly, the benefit from more-intensive BP control is greater for stroke than for other cardiovascular outcomes, as shown by the *ACCORD* blood pressure trial, which compared two antihypertensive regimens (SBP < 120 mmHg vs <140 mmHg) in a population with diabetes mellitus at high risk for cardiovascular events [9]. After 1 year, mean SBP in the intensive therapy group was lower than that in the standard therapy group, and the annual rates of stroke were 0.39 % and 0.53 %, respectively (95 % CI, 0.39–0.89; $p = 0.01$). Similarly, a meta-analysis of 31 trials of pharmacological interventions in subjects with diabetes mellitus showed that more-intensive BP reduction significantly reduced the risk of stroke but not myocardial infarction, with each 5 mmHg BP lowering corresponding to a stroke risk reduction of 13 % [10]. The level at which BP should be controlled in hypertensive patients without diabetes was investigated in the *Cardio-Sis* trial [11]. In this Italian randomized, open-label trial, 1,111 non-diabetic patients with treatment-resistant systolic hypertension (SBP ≥ 150 mmHg) were randomly assigned to a target SBP < 140 mmHg (usual control) or <130 mmHg (tight control). After a median follow-up of 2 years, SBP and DBP were significantly lower in the tight control than in the usual group: the reduction decreased the incidence of the pre-specified composite cardiovascular outcome, including stroke. Individual cardiovascular risk profiles, established cardiovascular disease (CVD) and intra-individual variability in BP may all account for differences in BP targets and for the effect of BP lowering on stroke risk reduction.

Isolated systolic hypertension (SBP ≥ 160 mmHg and DBP < 90 mmHg) in the elderly has been extensively investigated. The *Systolic Hypertension in Europe* (*Syst-Eur*) trial randomized 4,695 patients with isolated systolic hypertension to active treatment with a calcium channel blocker or placebo [12]. The results showed a 42 % risk reduction (95 % CI, 18–60; $p = 0.02$) in the intervention group. The *Systolic Hypertension in the Elderly Program* (*SHEP*) trial showed a 36 % stroke risk reduction (95 % CI, 18–50; $p = 0.003$) from a diuretic-based regimen [13]. In the *Hypertension in the Very Elderly* (*HYVET*) trial, 3,845 subjects aged >80 years with SBP ≥ 160 mmHg were randomized to receive indapamide or placebo, and perindopril or placebo added as needed to target a BP <150/80 mmHg. At 2 years of follow-up, there was a reduction in SBP of 15 mmHg, associated with

a 30 % stroke risk reduction, 39 % fatal stroke risk reduction and 21 % overall mortality reduction [14]. The *Systolic Blood Pressure Intervention Trial* (*SPRINT*) is a US randomized, controlled, open-label trial that compared the benefit of treatment of SBP to a target of <120 mmHg with treatment to a target of <140 mmHg in a large non-diabetic population at increased cardiovascular risk [15]. The study hypothesis was that lowering SBP to <120 mmHg, compared with a target of 140 mmHg, would result in an improvement in cardiovascular outcomes, including stroke. The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes. All major classes of antihypertensive agents were used in the trial population, although the study protocol encouraged the use of agents known to have the strongest evidence for improvements in cardiovascular outcomes. Thiazide-type diuretics were preferably prescribed as first-line agents, loop diuretics were indicated for people with advanced chronic kidney disease and beta blockers were indicated for subjects with coronary artery disease. The two treatment strategies resulted in a rapid and persistent difference in SBP reduction between the two groups, which was greater in the intensive treatment group. The intervention was halted early after a median follow-up of 3.26 years due to a 25 % lower relative risk reduction in the primary composite outcome in the intensive treatment group compared with the standard treatment group.

Intra-individual BP variability has also been investigated. The *Syst-Eur* trial [12] analysed the effect of BP variability on stroke risk and found that increased night-time SBP variability was an independent risk factor for stroke compared with daytime SBP variability. The differences between classes of antihypertensive agents with respect to their effectiveness in preventing stroke have been reported in a systematic review of randomized controlled trials [16]. The analysis showed that intra-individual variability in SBP is reduced by calcium channel blockers and non-loop diuretic drugs and increased by angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and beta blockers. The review concluded that the differing effects of antihypertensive drugs on individual BP variability may account for their differing effects in stroke prevention, regardless of their direct effect on SBP lowering. Similarly, a substudy of the *Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm* (*ASCOT-BPLA*) and of the *Medical Research Council* (*MRC*) trial concluded that the differing effects of calcium channel blockers and beta blockers on BP variability may be responsible for the greater benefit in stroke risk reduction in the former [17].

Reducing BP is pivotal in stroke risk reduction strategies. The greater the reduction in BP, the greater the benefit in stroke risk reduction. Since the first publications of the *Hypertension Detection and Follow-up Program* (*HDFP*) and the *Multiple Risk Factor Intervention Trial* (*MRFIT*) in the late 1970s and late 1980s, respectively, 20 years of subsequent research have confirmed the initial observations that the treatments of mild, moderate, severe and isolated systolic hypertension all have absolute benefits. Optimal BP targets and how far BP

lowering could be forced remain unclear. Although the relationship between BP lowering and stroke risk reduction is linear, low ranges of BP may have several adverse effects, particularly in older fragile subjects, suggesting the importance of personalized approaches. In addition, the decision on which antihypertensive drug to use should be tailored to the needs of the patient, taking into account medical and socio-demographic factors.

10.2 Hypertension Control in Primary Stroke Prevention: What Do Guidelines Suggest?

Hypertension is the leading stroke risk factor worldwide, and its treatment is one of the leading strategies to prevent ischemic and haemorrhagic stroke [18]. Numerous guidelines from scientific societies and organizations deal with the issue of managing BP for the primary prevention of cardiovascular diseases including stroke. Guidelines are periodically revised and released and in some cases do not take into the latest evidences from clinical studies.

Recommendations from selected available guidelines on BP control are shown in Table 10.1 [18–20]. Regular BP screening in the population is recommended to detect hypertension [18]. For patients with prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg), the American Heart Association/American Stroke Association (AHA/ASA) Guidelines recommend annual screening for high BP and health-promoting lifestyle modification [18]. For patients with hypertension, both lifestyle changes and drugs are useful in reducing BP values [18, 19]. Measures recommended by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) Guidelines [19] include salt restriction to 5–6 g per day; moderation of alcohol consumption to no more than 20–30 g of ethanol per day in men and 10–20 g in women; increased consumption of vegetables, fruits and low-fat dairy products; reduction of weight to body mass index (BMI) of 25 kg/m^2 and of waist circumference to <102 cm in men and <88 cm in women, unless contraindicated; regular exercise, i.e. at least 30 min of moderate dynamic exercise 5–7 days per week; and stopping smoking. According to the ESH/ESC Guidelines [19], the most appropriate strategy depends on usual BP values and on additional risk factors (Fig. 10.1), while the Eighth Joint National Committee (JNC 8) guidelines highlight the role of age and comorbid diseases (chronic kidney disease and diabetes) in treatment decisions (Table 10.1) [20]. According to the JNC8 guidelines, the threshold to initiate pharmacological treatment for subjects aged ≥60 years is 150 mmHg for systolic BP and 90 mmHg for DBP, and the goals are SBP <150 mmHg and DBP <90 mmHg. In subjects aged <60 years and those with chronic kidney disease or diabetes, the threshold for treatment initiation is lower (140 mmHg for SBP) as is the goal (<140 mmHg for SBP) (Table 10.1) [20]. Guidelines support the hypothesis that rather than the use of a specific agent, BP reduction per se is important [18, 19]. The optimal BP values that give the most advantageous effects in terms of stroke prevention are unclear, and comorbidities and age may change individual optimal thresholds. The AHA/ASA Guidelines recommend that in patients with

Table 10.1 Recommendations from available guidelines on blood pressure control for primary stroke prevention

2013 ESH/ESC Guidelines	2014 AHA/ASA	2014 JNC8
Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of cardiovascular risk, a few weeks after or simultaneously with initiation of lifestyle changes (Class I, Level of Evidence A) Lowering blood pressure with drugs is also recommended when total cardiovascular risk is high because of other diseases, diabetes, cardiovascular diseases or chronic kidney disease, even when hypertension is in the grade 1 range (Class I, Level of Evidence B) Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low-to-moderate risk, when blood pressure is within this range at several repeated visits or elevated by ambulatory blood pressure criteria, and remains within this range despite a reasonable period of time with lifestyle measures (Class IIa, Level of Evidence B) In elderly hypertensive patients drug treatment is recommended when systolic blood pressure is ≥160 mmHg (Class I, Level of Evidence A)	Regular blood pressure screening and appropriate treatment of patients with hypertension, including lifestyle modification and pharmacological therapy, are recommended (Class I, Level of Evidence A) Annual screening for high blood pressure and health-promoting lifestyle modification are recommended for patients with prehypertension (systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg) (Class I, Level of Evidence A) Patients who have hypertension should be treated with antihypertensive drugs to a target blood pressure of <140/90 mmHg (Class I, Level of Evidence A) Successful reduction of blood pressure is more important in reducing stroke risk than the choice of a specific agent, and treatment should be individualized on the basis of other patient characteristics and medication tolerance (Class I, Level of Evidence A)	In the general population aged ≥60 years, initiate pharmacological treatment to lower blood pressure at systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥90 mmHg and treat to a goal systolic blood pressure <150 mmHg and goal diastolic blood pressure <90 mmHg (Strong Recommendation – Grade A) In the general population aged ≥60 years, if pharmacological treatment for high blood pressure results in lower systolic blood pressure (e.g. <140 mmHg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted (Expert Opinion – Grade E) In the general population <60 years, initiate pharmacological treatment to lower blood pressure at systolic blood pressure ≥140 mmHg and treat to a goal systolic blood pressure <140 mmHg (Expert Opinion – Grade E) In the population aged ≥18 years with chronic kidney disease, initiate pharmacological treatment to lower blood pressure at systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and treat to goal systolic blood pressure <140 mmHg and goal diastolic blood pressure <90 mmHg (Expert Opinion – Grade E) In the population aged ≥18 years with diabetes, initiate pharmacological treatment to lower blood pressure at systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and treat to a goal systolic blood pressure <140 mmHg and goal diastolic blood pressure <90 mmHg (Expert Opinion – Grade E) In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (Moderate Recommendation – Grade B)

(continued)

Table 10.1 (continued)

2013 ESH/ESC Guidelines	2014 AHA/ASA	2014 JNC8
Antihypertensive drug treatment may also be considered in the elderly (at least when younger than 80 years) when systolic blood pressure is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated (Class IIb, Level of Evidence C) Unless the necessary evidence is obtained, it is not recommended to initiate antihypertensive drug therapy at high normal blood pressure (Class III, Level of Evidence A) Lack of evidence does not allow the recommendation to initiate antihypertensive drug therapy in young individuals with isolated elevation of brachial systolic blood pressure, but these individuals should be followed closely with lifestyle recommendations (Class III, Level of Evidence A)	Self-measured blood pressure monitoring is recommended to improve blood pressure control (Class I, Level of Evidence A)	In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker (for general black population, Moderate Recommendation – Grade B; for black patients with diabetes, Weak Recommendation – Grade C) In the population aged ≥18 years with chronic kidney disease, initial (or add-on) antihypertensive treatment should include an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to improve renal outcomes. This applies to all chronic kidney disease patients with hypertension regardless of race or diabetes status (Moderate Recommendation – Grade B) The main objective of hypertension treatment is to attain and maintain goal blood pressure. If goal blood pressure is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in previous recommendation (thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker). The clinician should continue to assess blood pressure and adjust the treatment regimen until goal blood pressure is reached. If goal blood pressure cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker together in the same patient. If goal blood pressure cannot be reached using only the drugs in the previous recommendation because of contraindications or the need to use more than 3 drugs to reach goal blood pressure, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal blood pressure cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed (Expert Opinion – Grade E)

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

Fig. 10.1 Initiation of lifestyle changes and antihypertensive drug treatment according to the 2013 European Society of Hypertension/European Society of Cardiology Guidelines. Targets of treatment are also indicated (Reproduced with permission from [19])

hypertension, antihypertensive drugs should be used with a target BP of <140/90 mmHg [18]. This is also supported by the Italian guidelines which add that in old and frail patients, treatment should be started for SBP values >160 mmHg, with a BP target between 150 and 140 mmHg [21]. Diuretics, beta blockers, calcium antagonists, ACE inhibitors and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, as supported by several guidelines [19–21]. The choice of the most appropriate is unclear as the results of clinical studies vary. Some data suggest a lower efficacy of beta blockers and ACE inhibitors in stroke prevention [22]. Beta blockers also appear to have more side effects than other drugs [23], but some of the limitations of traditional beta blockers do not appear to be shared by newer agents such as celiprolol, carvedilol and nebivolol [24–27]. Some meta-analyses have also suggested that ACE inhibitors may be somewhat inferior to other classes in preventing stroke [22, 28, 29]. The choice of the most suitable drug should take into account the fact that some classes have preferentially been used in trials in specific conditions or have shown greater effectiveness in specific types of diseases. However, no solid evidence is available that suggests that different choices should be made based on age or gender (except for caution in using angiotensin receptor blockers in women with childbearing potential due to possible teratogenic effects) [19]. In the elderly and in the presence of isolated systolic hypertension, Italian guidelines suggest the use of diuretics and calcium antagonists [21]. Suggestions from the ESH/ESC Guidelines to choose the most appropriate drug according to specific

Table 10.2 Drugs to be preferred in specific conditions according to the 2013 European Society of Hypertension/European Society of Cardiology Guidelines (Reproduced with permission from [19])

Condition	Drug
Asymptomatic organ damage	
Left ventricular hypertrophy	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical cardiovascular event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
End-stage renal disease/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Others	
Isolated systolic hypertension (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *BB* beta blocker

conditions are shown in Table 10.2. Long-acting drugs that need to be taken once daily are preferred to shorter-acting drugs that require multiple dosing [30]. In any case, physicians should pay attention to contraindications to the different drugs and to adverse events (Table 10.3). Even minor adverse events may be powerful deterrents to treatment adherence. If necessary, doses or drugs should be changed in order to combine effectiveness with tolerability. Self-measured BP monitoring is recommended to improve BP control [18].

Strategies for the choice between monotherapy and combination therapy to achieve BP reduction are shown in Fig. 10.2. In general, moving from less-intensive to more-intensive treatment is indicated when the BP target is not achieved. The American Society of Hypertension and the International Society of Hypertension suggest approximately 2–3 week intervals before increasing the dose of a drug or adding a new drug [31]. The JNC8 guidelines suggest continuing to assess BP and to adjust treatment regimens until the target BP is reached [20]. A single agent can be started when there is mild BP elevation and low-to-moderate cardiovascular risk.

Table 10.3 Compelling and possible contraindications to the use of antihypertensive drugs according to the 2013 European Society of Hypertension/European Society of Cardiology Guidelines (Reproduced with permission from [19])

Drug	Compelling	Possible
Diuretics (thiazides)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcaemia Hypokalaemia
Beta blockers	Asthma Atrioventricular block (grade 2 or 3)	Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease (except for vasodilator beta blockers)
Calcium antagonists (dihydropyridines)	–	Tachyarrhythmia Heart failure
Calcium antagonists (verapamil, diltiazem)	Atrioventricular block (grade 2 or 3, trifascicular block) Severe left ventricular dysfunction Heart failure	–
Angiotensin-converting enzyme inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	Women with childbearing potential
Angiotensin receptor blockers	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	Women with childbearing potential
Mineralocorticoid receptor antagonists	Acute or severe renal failure (estimated glomerular filtration rate <30 mL/min) Hyperkalaemia	

In patients at high risk or with markedly high baseline BP, combination treatment may be the therapeutic option ab initio [19].

Only indirect data are available from randomized trials providing data on drug combinations effective in reducing cardiovascular outcomes. The combination of an ACE inhibitor with an angiotensin receptor blocker is not recommended and should be discouraged [19–21, 31]. Suggestions from the ESH/ESC Guidelines on the combination of available drugs are shown in Table 10.4. Combinations are probably beneficial in the extent of BP reduction. Combinations that have been successfully used in trials should be preferred [19]. It is important to favour the use of combinations of two antihypertensive drugs at fixed doses in a single tablet because reducing the number of pills to be taken daily may improve adherence. Treatment advice from the ESH/ESC Guidelines is summarized in Table 10.5.

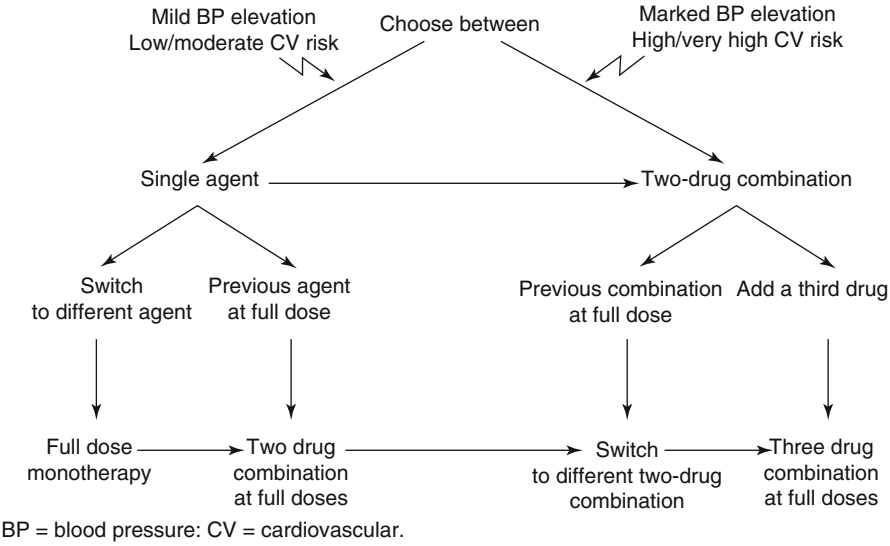

Fig. 10.2 Strategy for choosing between monotherapy and combination therapy to achieve blood pressure reduction according to the 2013 European Society of Hypertension/European Society of Cardiology Guidelines (Reproduced with permission from [19])

Attention has recently been drawn to the association between visit-to-visit variability in intra-individual BP during antihypertensive treatment and the incidence of cardiovascular events (particularly stroke) in high-risk patients [32]. BP variability may be a risk factor for stroke, but currently it is unclear whether a reduction in BP variability may have an impact on stroke prevention [32]. An analysis of the ASCOT trial has suggested that BP variability may be lower with the combination of a calcium antagonist and an ACE inhibitor than with the combination of a beta blocker and a diuretic [33], and a meta-analysis indicated that BP variability is more pronounced in patients taking beta blockers than in those receiving other drug classes [16, 34]. However, studies have not established whether BP variability is really pharmacologically driven or is a marker of treatment adherence.

Table 10.4 Possible combinations of classes of antihypertensive drugs according to the 2013 European Society of Hypertension/European Society of Cardiology Guidelines (Reproduced with permission from [19])

Drug/recommendation	Beta blockers	Thiazide diuretics	Angiotensin receptor blockers	Calcium antagonists	ACE inhibitors	Other antihypertensives
Beta blockers	–	Useful (with some limitations)	Useful (with some limitations)	Useful (with some limitations)	Useful (with some limitations)	Useful (with some limitations)
Thiazide diuretics	Useful (with some limitations)	–	Preferred	Preferred	Preferred	Possible but less well-tested combinations
Angiotensin receptor blockers	Useful (with some limitations)	Preferred	–	Preferred	Not recommended	Useful (with some limitations)
Calcium antagonists	Useful (with some limitations)	Preferred	Preferred	–	Preferred	Useful (with some limitations)
ACE inhibitors	Useful (with some limitations)	Preferred	Not recommended	Preferred	–	Useful (with some limitations)
Other antihypertensives	Useful (with some limitations)	Possible but less well-tested combinations	Useful (with some limitations)	Useful (with some limitations)	Useful (with some limitations)	–

Table 10.5 Treatment strategies and choice of drugs according to the 2013 European Society of Hypertension/European Society of Cardiology Guidelines [19]

Recommendations	Class	Level
Diuretics (thiazides, chlorthalidone and indapamide), beta blockers, calcium antagonists, ACE inhibitors and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other	I	A
Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of other diseases	IIa	C
Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure or at high cardiovascular risk	IIb	C
The combination of two antagonists of the renin-angiotensin system is not recommended and should be discouraged	III	A
Other drug combinations should be considered and are probably beneficial in proportion to the extent of blood pressure reduction. However, combinations that have been successfully used in trials may be preferable	IIa	C
Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension	IIb	B

References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J (2005) Global burden of hypertension: analysis of worldwide data. Lancet 365:217–223
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Collaboration PS (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360:1903–1913
3. Sipahi I, Swaminathan A, Natesan V, Debanne SM, Simon DI, Fang JC (2012) Effect of antihypertensive therapy on incident stroke in cohorts with pre- hypertensive blood pressure levels: a meta-analysis of randomized con- trolled trials. Stroke 43:432–440
4. Neal B, MacMahon S, Chapman N (2000) Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Lancet 356:1955–1964
5. Psaty BM, Smith NL, Siscovick DS et al (1997) Health outcomes associated with anti-hypertensive therapies used as first-line agents: a systematic review and meta-analysis. JAMA 277:739–745
6. Lindholm LH, Ibsen H, Dahlo¨f B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S, for the LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359:1004–1010.
7. Bang CN, Devereux RB, Okin PM (2014) Regression of electrocardiographic left ventricular hypertrophy or strain is associated with lower incidence of cardiovascular morbidity and mortality in hypertensive patients independent of blood pressure reduction—a LIFE review. J Electrocardiol 47:630–635
8. Lee M, Saver JL, Hong KS, Hao Q, Ovbiagele B (2012) Does achieving an intensive versus usual blood pressure level prevent stroke? Ann Neurol 71:133–140
9. The ACCORD Sutdy Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson

KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F (2010) Effects of intensive blood pressure control in type 2 diabetes mellitus. N Engl J Med 362:1575–1585
10. Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P (2011) Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. J Hypertens 29:1253–1269
11. Verdecchia P, Staessen JA, Angeli F et al (2009) Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. Lancet 374:525–533
12. Staessen JA, Fagard R, Thijs L et al (1997) Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 350:757–764
13. Cooperative Research Group (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 265:3255–3264
14. Beckett NS, Peters R, Fletcher AE et al (2008) Treatment of hypertension in patients 80 years of age or older. N Engl J Med 358:1887–1898
15. The SPRINT Research Group (2015) A randomized trial of intensive versus standard blood pressure control. N Engl J Med 373:2103–2116
16. Webb AJ, Fischer U, Mehta Z, Rothwell PM (2010) Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 375:906–915
17. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS, for the ASCOT-BPLA and MRC Trial Investigators (2010) Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol 9:469–480
18. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension (2014) Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 45:3754–3832
19. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology (2013) 2013 ESH/ESC practice guidelines for the management of arterial hypertension. J Hypertens 31:1281–1357
20. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311:507–520
21. Gensini GF, Zaninelli A (eds) (2012) Stroke Prevention and Educational Awareness Diffusion (SPREAD), 7th Release. Available at http://www.iso-spread.it/
22. Law MR, Morris JK, Wald NJ (2009) Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 338:b1665
23. Silvestri A, Galetta P, Cerquetani E, Marazzi G, Patrizi R, Fini M, Rosano GM (2003) Report of erectile dysfunction after therapy with beta blockers is related to patient knowledge of side-effects and is reversed by placebo. Eur Heart J 24:1928–1932
24. Boutouyrie P, Bussy C, Hayoz D, Hengstler J, Dartois N, Laloux B et al (2000) Local pulse pressure and regression of arterial wall hypertrophy during long-term antihypertensive treatment. Circulation 101:2601–2606

25. Dhakam Z, Yasmin MECM, Burton T, Brown MJ, Wilkinson IB (2008) A comparison of atenolol and nebivolol in isolated systolic hypertension. J Hypertens 26:351–356
26. Kampus P, Serg M, Kals J, Zagura M, Muda P, Karu K et al (2011) Differential effects of nebivolol and metoprolol on central aortic pressure and left ventricular wall thickness. Hypertension 57:1122–1128
27. Stears AJ, Woods SH, Watts MM, Burton TJ, Graggaber J, Mir FA, Brown MJ (2012) A double-blind, placebo-controlled, crossover trial comparing the effects of amiloride and hydrochlorothiazide on glucose tolerance in patients with essential hypertension. Hypertension 59:934–942
28. Blood Pressure Lowering Treatment Trialists' Collaboration (2003) Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 362:1527–1535
29. Verdecchia P, Reboldi G, Angeli F, Gattobigio R, Bentivoglio M, Thijs L et al (2005) Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. Hypertension 46:386–392
30. Mancia G, Facchetti R, Parati G, Zanchetti A (2012) Visit-to-visit blood pressure variability in the European Lacidipine Study on Atherosclerosis: methodological aspects and effects of antihypertensive treatment. J Hypertens 30:1241–1251
31. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, Flack JM, Carter BL, Materson BJ, Ram CV, Cohen DL, Cadet JC, Jean-Charles RR, Taler S, Kountz D, Townsend RR, Chalmers J, Ramirez AJ, Bakris GL, Wang J, Schutte AE, Bisognano JD, Touyz RM, Sica D, Harrap SB (2014) Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich) 16:14–22
32. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B et al (2010) Prognostic significance of visit-to-visit variability, maximum systolic blood pressure and episodic hypertension. Lancet 375:895–905
33. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B et al (2010) Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol 9:469–480
34. Webb AJ, Rothwell PM (2011) Effect of dose and combination of antihypertensives on inter-individual blood pressure variability: a systematic review. Stroke 42:2860–2865

Management of High Blood Pressure in Acute Ischaemic Stroke

11

Dariusz Gasecki, Bartosz Karaszewski, and Krzysztof Narkiewicz

11.1 Introduction

Elevated blood pressure (BP) is commonly observed in the acute phase of stroke. The prevalence of elevated BP is higher in acute ischaemic stroke (AIS) than in other acute illnesses [1], because stroke may favour the occurrence of elevated BP throughout the so-called acute hypertensive response (AHR) and because high BP is a risk factor for stroke. Elevated BP is associated with clinical outcomes and is, therefore, of clinical relevance.

It is estimated that in the first 24 h, up to 70–80 % of ischaemic stroke patients have increased BP (supine BP ≥ 140/90 mmHg) [2–4] and up to 15 % have systolic BP (SBP) > 184 mmHg [5]. BP values are highly variable during the first days after stroke, and this is mostly marked in the first hours of cerebral ischaemia. Alterations in the circadian rhythm of BP *are* a frequent finding in ischaemic stroke patients [6, 7] with abnormal nocturnal BP dipping identified in more than 75 % of patients [8].

Marked BP changes are also documented in the peri-stroke phase. Before stroke onset, BP rises in the majority of cases of AIS, with evidence that BP peaks and troughs may be a cause of stroke [9, 10]. BP elevations after AIS are greater in patients with pre-existing hypertension and with larger strokes [11, 12].

D. Gasecki (✉) • B. Karaszewski
Department of Neurology for Adults, Medical University of Gdansk, Gdansk, Poland
e-mail: dgasecki@gumed.edu.pl

K. Narkiewicz
Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_11

11.2 Pathophysiology

Both stroke-specific and non-specific external stimuli as well as other transient factors may contribute to BP changes in patients with acute stroke. BP elevation in AIS is a self-limiting phenomenon. Wallace and Levy found elevated BP in 84 % of patients in the acute phase of stroke [13]. Ten days after stroke onset, a spontaneous reduction in systolic blood pressure (SBP) (mean of 20 mmHg) and diastolic blood pressure (DBP) (mean of 10 mmHg) was seen. After this time, about one-third of patients remained hypertensive.

11.2.1 Pre-stroke Factors

Although the causes of elevated BP in acute stroke are complex and poorly understood, pre-existing chronic hypertension is probably one of the main contributors to BP elevation in the acute phase of stroke. One-half of ischaemic stroke patients have high BP prior to stroke [14, 15], with up to 50 % of stroke patients taking antihypertensive drugs before the acute event. In addition, a history of pre-existing hypertension is associated with high post-stroke SBP. Similarly, patients with diabetes mellitus are also prone to increased BP after acute stroke [13, 16, 17]. Premorbid hypertension is undiagnosed and untreated or poorly controlled in many stroke patients despite the fact that hypertensives have a 3–4 times higher risk of stroke than normotensives [18].

Another important issue is the identification of dehydration in acute stroke patients [19], as this may result in a hypertensive or hypotensive response to antihypertensive agents [20].

11.2.2 Stroke-Specific Factors: Acute Hypertensive Response in the First 24 h After Symptom Onset

The importance of stroke-specific factors in the generation of elevated BP values in the acute phase of ischaemic stroke has been supported by findings from several studies. The spontaneous reduction in BP in the first hours and days after stroke onset in most patients [1, 13, 21] strongly indicates that brain dysfunction itself may result in autonomic system dysregulation and, therefore, inadequate BP regulation.

The status of the cerebral vessels seems to be one of the critical determinants of BP evolution after stroke. Patients with occluded major cerebral arteries have higher BP values on admission. Accordingly, high BP is more likely to be observed in patients with more severe stroke and in those admitted very early after stroke onset [22]. Recent data showed that BP is highest in the first minutes after stroke onset [23]. Patients in the ultra-acute phase of ischaemic stroke only exceptionally experience an early BP reduction. However, after successful recanalization, BP decreases significantly in ischaemic stroke patients [24, 25]. By contrast, persistent vessel occlusion is associated with more durable high BP and progression of cerebral oedema and haemorrhagic transformation of an ischaemic focus.

Brain regions involved in autonomic regulation are spread through the brain. The prefrontal and insular cortices seem to play an important role in both sympathetic and parasympathetic modulations. The left ventromedial prefrontal cortex (VMPFC) was shown to be involved in parasympathetic activation, while the right VMPFC was shown to be included in sympathetic inhibition [26]. The insular cortex also seems to play an important role in the regulation of the autonomic system. Sympathetic activity was shown to be higher in insular than in non-insular infarctions, especially in patients with right hemisphere infarctions [27]. Animal studies indicate that the brainstem, especially the medulla, may also play a significant role in autonomic system regulation [28]. Dysfunction of those regions, whether direct or during the course of diaschisis, may lead to autonomic dysfunction and, eventually, elevated BP.

11.2.3 Stroke Complications After 24 h

Ischaemic stroke may lead to various acute complications which, in turn, may result in BP elevation. Many factors, including urine retention, headache, concomitant infection or stress related to serious illness or hospitalization [29], may, through different mechanisms, cause increased BP. Increased cardiac output, changes in neuroendocrine systems with activation of the sympathetic nervous system, renin-angiotensin axis and glucocorticoid system and acute abnormalities in the cardiac baroreceptor reflex may also contribute to BP rises and variations following cerebral ischaemia [30, 31]. BP at admission is thus often affected by many transient and individualized factors that may resolve within hours. Therefore, BP values during the first 12 h may not appropriately reflect the stroke patient's general condition and, more importantly, may be unreliable and misleading [32].

In the subacute phase of stroke, nearly half the patients with ischaemic stroke remain hypertensive. Permanently elevated SBP values in the acute stage of stroke may be related to evolving brain swelling in the region of ischaemia [33] and may primarily reflect progressive intracranial hypertension, although this usually does not become clinically obvious for 1–4 days [34]. Accordingly, the combination of an acute hypertensive response with bradycardia and respiratory irregularities (so-called Cushing triad) strongly suggests intracranial hypertension.

11.2.4 Low Blood Pressure

Low BP on admission (SBP < 100 mmHg) is rare (0.6% and 2.5 % in patients treated with thrombolysis [35] and in general acute stroke patients [36], respectively) and is associated with large territorial cerebral infarctions or advanced age [37].

Low initial BP may suggest underlying disease such as volume depletion, sepsis, myocardial infarction, cardiac arrhythmia, retroperitoneal haemorrhage or aortic dissection. The brain is particularly vulnerable to hypotension during acute ischaemia due to impaired cerebral autoregulation. Although the exact definition of

arterial hypotension has yet to be established, extremely low arterial BP is detrimental, as it results in decreased tissue perfusion to the ischaemic brain and to many other organs.

Patients with stroke and low BP are at increased risk of both early and late stroke complications. However, in the later stages of stroke, low SBP may be a marker of recanalization [38], and therefore, the association of low SBP with clinical outcomes may only be valid for patients with low SBP on admission [22].

11.3 Blood Pressure and Clinical Outcomes

BP levels are closely associated with clinical outcomes in patients with AIS. Various BP parameters during the acute phase of ischaemic stroke have been investigated by many studies. Observational studies show that both extremely high and extremely low BP on admission correlate with death or dependency in acute stroke patients. Accordingly, the relationship between BP at admission and stroke outcomes seems to be U or J shaped [2, 25, 37, 39–44] with the optimal SBP ranging from 121 to 200 mmHg and DBP ranging from 81 to 110 mmHg. However, some observational data have shown a more linear relationship between elevated BP during AIS and worse clinical outcomes [45, 46], although other studies only found this association in stroke patients with impaired consciousness, while no associations were found in alert patients [47]. In addition, the observed J- or U-shaped association between BP and outcomes in AIS may not be causally related.

On the other hand, in many initial studies, BP was measured relatively late after stroke, e.g. 24 h, on average, in the first International Stroke Trial (IST) [37]. However, data from the hyperacute phase of ischaemic stroke demonstrate relationship between high SBP and a high incidence of severe neurological and functional deficit [48].

Potential complications of high BP in AIS include the extension of peri-focal cerebral oedema and further acceleration of stroke complications with exaggeration of heart, renal or aortic acute or chronic failure and early recurrent cardiovascular events, including new strokes.

The area of brain ischaemia includes the core of infarction and surrounding lesions of potentially salvageable tissue called the ischaemic penumbra or “tissue at risk” [49]. Rapid restoration of cerebral perfusion to the tissue at risk can restore its temporarily lost function. Conversely, if cerebral perfusion to the penumbral areas is not restored early enough, there is new brain infarct volume which worsens the final functional outcome.

As an autoregulatory mechanism, whose physiological aim is to maintain adequate cerebral perfusion, is compromised in the penumbral areas, regional cerebral blood flow (CBF) in involved tissue becomes directly dependent on systemic BP. Thus, in the case of persistent cerebral ischaemia, BP falls may compromise the collateral blood flow and extend the total volume of brain damage. On the other hand, extremely high BP may lead to disruption of the blood-brain barrier integrity with all its consequences, such as increased permeability.

11.4 Blood Pressure and Outcomes in Thrombolized Patients

Immediately after stroke, BP reductions are observed within minutes or hours after spontaneous or induced recanalization of the parent cerebral artery (e.g. via successful thrombolysis).

An important issue is the influence of elevated BP on the outcomes in thrombolized patients. This relationship has been well documented regarding with respect to the risk of secondary haemorrhage [35, 50, 51] and long-term outcomes [52, 53]. Acute BP elevation has been shown to be related to an increased risk of haemorrhagic transformation of brain infarction in patients treated with thrombolysis [54], with a fourfold increased risk for SBP > 170 mmHg compared with 141–150 mmHg [35, 55]. This is the most common concern in patients otherwise eligible for thrombolytic treatment.

The risk of haemorrhagic transformation of cerebral infarction is increased by either high pretreatment [54] or post-treatment BP values [35]. In the recently conducted IST-3 trial, which randomized 3035 patients with ischaemic stroke to recombinant tissue-type plasminogen activator 0.9 mg/kg or open control within 6 h of symptom onset, both high BP and large BP variability during the first hours after stroke were associated with a higher rate of short-term adverse events, including death [56]. In a small observational study, BP variability was previously found to be associated with greater cerebral lesion growth in patients without early recanalization of the causative artery [57], while this did not happen in recanalized patients.

11.5 Management of Blood Pressure in Acute Ischaemic Stroke

The optimal management of hypertension in patients with ischaemic stroke is difficult. Although debated for more than 30 years, the best strategy to manage raised BP in acute stroke remains unclear and seems to depend on the underlying stroke subtype and the timing.

The immediate lowering of BP in patients with AIS should reduce early stroke oedema and the haemorrhagic complications of ischaemia. However, it might potentially decrease collateral flow in the area of tissue at risk of cerebral infarction. Finally, after the presumed penumbra no longer exists, there is no reason to maintain high BP. The main arguments for and against lowering BP in AIS are listed in Table 11.1.

Early elimination of many transient factors complicating stroke, including dehydration, infections, pain, anxiety, stress due to hospitalization and bladder dysfunction, may be associated with significant BP reductions in the first hours after stroke onset. Otherwise, BP tends to remain high in the hours and days after acute stroke.

However, interventions lowering high BP may be associated with reduction in cerebral blood flow in patients with impaired autoregulatory mechanisms. Consequently, the jeopardy to cerebral perfusion in ischaemic areas may be accentuated. Therefore, antihypertensive treatment should be used with great caution in the

Table 11.1 Reasons for and against BP reduction immediately after acute ischaemic stroke

For	Against
High BP associated with mortality	Cerebral ischaemia might be exacerbated by lowering BP due to impaired autoregulation
Lowering BP might decrease haemorrhagic transformation	The risk of converting ischaemic areas to irreversible infarction
Lowering BP might reduce cerebral oedema	BP decreases spontaneously during the first week, even without treatment
Lowering BP might be indicated for other medical reasons	The risk of worsening of perfusion distal to large-vessel stenosis
Data from recent trials suggest that lowering BP acutely is safe	Lowering BP might exacerbate or propagate intravascular thrombus

Adapted from Aiyagari [58]

first 24 h after stroke, and if implemented, only a gradual and moderate BP decrease (<20% within 24 h) may be tolerated. Rapid reduction of elevated BP in patients with significant intracranial hypertension is the most dangerous procedure.

As shown by Olivera et al., for every 10% reduction in SBP within 24 h, there is a nearly twofold increased risk of a poor outcome [21]. Particularly rapid and large BP reductions in very early acute brain ischaemia should be avoided. Therefore, BP reduction is not recommended by major guidelines on AIS until a patient is clinically stable, and BP values are not extremely high (>220/120 mmHg) or there are symptoms and signs of hypertensive emergencies (e.g. acute heart or renal failure, aortic dissection) [55, 59].

In line with many clinical observations, the balance between the beneficial and dangerous effects of BP lowering in AIS is very fine. According to recent data, a moderate BP rise maintained at SBP 140 mmHg to 159 mmHg and DBP 90 mmHg to 99 mmHg within 7 days after stroke seems to be the best prognostic marker of long-term neurological functional recovery [60]. Conversely, a large reduction in SBP is associated with poor outcomes in AIS [12]. Similarly, if thrombolized patients are given antihypertensive drugs, the prognosis is poorer than when BP is not treated [61, 62]. These observations support the concept of defective autoregulation in AIS, as discussed earlier, where the passive and linear relationship between CBF and systemic BP takes over and where BP elevation may help preserve ischaemic areas from infarction. Nevertheless, the expert-derived guidelines for the management of BP in AIS provide only an indication of the perceived harm from high BP, and the optimal BP values in AIS remain to be established.

Recent trials suggest a neutral effect of early BP lowering on the prevention of unfavourable clinical outcomes, recurrent vascular events and all-cause mortality. However, most studies assessed interventions starting within 72 h after ischaemic stroke onset, with the median time to initiation of BP lowering in 13 randomized controlled trials with 12,703 participants being no earlier than after 15 h after stroke onset [63].

The results of the Scandinavian Candesartan Acute Stroke Trial (SCAST) showed that modest BP lowering in acute stroke with candesartan had no advantage

and tended to be harmful, seen from the 6-month perspective [64]. Moreover, patients with increased SBP from day 1 to day 2 had an increased risk of early adverse events [65].

By contrast, the small Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) pilot study found that BP lowering with β-blockers or angiotensin-converting-enzyme (ACE) inhibitors in previously normotensive patients with SBP > 160 mmHg in AIS was associated with a significant reduction in 3-month mortality [66].

Since approximately one-half of patients with acute stroke are taking antihypertensive drugs, there is a question of whether this pre-stroke therapy should be continued or withdrawn. Two studies have addressed this issue. The results of the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) in patients with previously identified and treated hypertension indicate that there is no difference with regard to the prognosis between patients who continued pre-stroke antihypertensive treatment compared with those who discontinued it during the acute phase of stroke [67]. However, this study was conducted in patients with relatively mild stroke, i.e. with a small degree of neurological deficit. Similarly, the more recent large Efficacy of Nitric Oxide in Stroke (ENOS) trial of transdermal glyceryl trinitrate (GTN) found no differences in long-term functional outcomes between patients who continued pre-stroke antihypertensive therapy and those who stopped it temporarily (ENOS) for the first 7 days after AIS. Further analyses of the two trials confirmed the neutral effect of withdrawal from prior antihypertensive drugs on major end points, including death or dependency, but showed some worse outcomes with respect to disability in patients randomised to continue the treatment [68].

Finally, in the recent Cochran review of 17,011 patients enrolled in 26 randomized controlled trials assessing the clinical effectiveness of altering BP in patients with acute ischaemic or haemorrhagic stroke, BP lowering did not reduce death or dependency according to drug class, stroke type or time to treatment [68]. The timing of the intervention seemed to be of clinical importance, with significant disability reductions occurring only in patients treated during the hyperacute phase (within 6 h). The ENOS trial also found no differences between patients receiving GTN or placebo. However, the trial involved patients with stroke in the first 48 h, and the median time of drug administration was 26 h after stroke onset.

Again, recent data from a small, randomized controlled RIGHT (The Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial) study of GTN administered by paramedics before hospital administration showed that very early (<4 h of stroke onset, with median time to admission of 55 min) BP reduction with transdermal GTN may be associated with functional improvement in patients with AIS [69]. Similarly, very recent data show that although the main ENOS study was neutral, a subgroup with very early administration of GTN (within 6 h of stroke onset) showed improved functional outcomes and fewer deaths by day 90 [70]. Interestingly, the largest reduction in BP in clinical trials was demonstrated in AIS patients treated during the prehospital phase of the disease (within 4 h of stroke onset) [68].

11.6 Current Guidelines for Blood Pressure Management in Acute Ischaemic Stroke

Although it is recommended that BP be lowered in specific situations, including acute myocardial infarction, aortic dissection, acute renal failure, hypertensive encephalopathy and pulmonary oedema, current European and US guidelines recommend lowering BP without these specific indications only when BP is ≥ 220 mmHg SBP and ≥ 120 DBP (Table 11.2) [55, 59].

The problem of high BP is especially important in patients eligible for thrombolytic therapy. Existing data show that baseline pretreatment SBP is a risk factor for intracerebral parenchymal haemorrhage in acute ischaemic lesions [54, 81, 82] and elevated SBP is associated with a worse outcome (SITS-ISTR [35]). Thus, both the American guidelines and European registration of the drug stipulate that this treatment may be administered in patients whose BP is <185 mmHg SBP and <110 mmHg DBP [ESO, AHA 2013]. Specific guidelines for the treatment of hypertension are shown in Tables 11.2 and 11.3.

11.6.1 Ongoing Studies of Blood Pressure Reductions After Acute Ischaemic Stroke

ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) is an ongoing trial comparing low (0.6 mg/kg) vs standard (0.9 mg/kg) dose of intravenous recombinant tissue plasminogen activator (rtPA) and early intensive (130–140 mmHg) vs standard BP lowering (<185 mmHg before and <180 mmHg after the use of intravenous rtPA) in AIS. Could it provide more affordable and safer use of thrombolysis treatment in patients with AIS?

Primary outcome: combined end point of death and disability at 90 days
Secondary outcomes: secondary intracerebral haemorrhage, death, disability or neurological deterioration during 72 h

RIGHT 2 is an ongoing trial assessing the safety and efficacy of GTN in 850 patients in the ultra-acute (within 4 h after stroke onset) prehospital stage of AIS (http://right2-trial.org)

11.7 Choice of Antihypertensive Agents

No large comparative studies have evaluated antihypertensive agents in AIS and their BP-lowering capacity. No data are available to guide the selection of drugs to reduce BP in AIS.

In patients with AIS, calcium channel blockers, ACE inhibitors, angiotensin receptor antagonists, β-blockers and nitric oxide donors all lower BP. Initially, BP should be lowered with caution using short-term parenteral drugs. Labetalol is a

Table 11.2 Summary of major prospective clinical trials that evaluated antihypertensive treatment in the acute phase of ischaemic stroke

Trial, publication year, country	No. of patients	Mean age (years) (I; C)	Baseline SBP/ DBP, mmHg	Intervention period (days)	Outcome assessment	Comments
ACCESS [72], 2003, Germany	339	68; 68	Active: 188/99 Control: 190/99	7	Vascular events and mortality at 12 m; BI comparison at 3 mo	Total mortality, cerebral complications and cardiovascular complications reduced by 47.5% with candesartan initiated within 24 h of admission
BEST [73], 1988, United Kingdom	302	70; 69	NA	21	Neurological assessment at entry, day 8 and 1 and 6 mo	Deaths more common among patients taking β-blockers; neurological recovery and functional outcome at 6 mo did not differ
CATIS [74], 2013, China	4071	62; 62	Active: 167/97 Control: 166/97	7	Death within 14 days, major disability at 14 days or at hospital discharge (if earlier); death and major disability at 3 months	Outcome did not differ between treatment groups at day 14, hospital discharge or at 3 months
CHHIPS [66], 2009, United Kingdom (ischaemic stroke subgroup)	99	NA	NA	14	Death or dependency at 2 weeks; early neurological deterioration	Death or dependency at 2 weeks did not differ; no evidence of early neurological deterioration with active treatment
COSSACS [67], 2010, United Kingdom (ischaemic stroke subgroup)	444	NA	NA	14	Death or dependency at 2 weeks; mortality, stroke recurrence at 6 months	Continuation of antihypertensive drugs did not reduce 2-week death or dependency, cardiovascular event rate or 6-month mortality

(continued)

Table 11.2 (continued)

Trial, publication year, country	No. of patients	Mean age (years) (I; C)	Baseline SBP/ DBP, mmHg	Intervention period (days)	Outcome assessment	Comments
ENOS [75], 2015, multiple countries (ischaemic stroke subgroup)	3348	NA	Active: 158/83 Control: 162/86	7	Functional outcome at day 90	Functional outcome at day 90 did not differ in either treatment comparison
Evenson et al. [76], 2007, United Kingdom	40	73; 75	Active: 174/91 Control: 170/94	14	Stroke severity and functional status at day 14 and at day 90	Neurological and functional measures were similar between groups at follow-up
INWEST [77], 2007, Western European countries	295	72	Active: 160/89 Control: 160/31	21	Death or dependency (BI<60) at day 21, death at day 21	DBP reduction was associated with neurological worsening after intravenous administration of high-dose nimodipine
Kaste et al. [78], 1994, Finland	350	57; 58	Active: 156/92 Control: 155/93	21	Functional outcome, mobility and neurological score at 12 months	No differences in functional outcome between treatment groups; during the first 3 months, the case fatality rate was higher in nimodipine-treated patients
PRoFESS [79], 2009, multiple countries	1360	67; 67	Active: 146/84 Control 147/84	90	Functional outcome at 30 days; haemorrhagic transformation of the infarct, cerebral oedema, recurrent stroke, myocardial infarction, composite vascular events, death and serious adverse events at 7, 30 and 90 days	Combined death and dependency did not differ between the treatment groups

(continued)

SCAST [64], 2011, Northern European countries (ischaemic stroke subgroup)	1733	NA	NA	7	Death or disability at 6 mo; combination of vascular death, myocardial infarction or stroke during first 6 mo	The risk of the composite vascular end point did not differ between treatment groups; analysis of functional outcome suggested a higher risk of poor outcome in the candesartan group
VENTURE [80], 2015, South Korea	393	64; 66	Active: 162/90 Control: 163/92	7	Death or dependency at 90 days; early neurological deterioration within 7 days and 90-day major vascular events	The rate of major vascular events did not differ between groups; there was a significant increase of early neurological deterioration in the valsartan group

Modified from Lee et al. [63], Qureshi [2] and Wang et al. [71]

ACCESS indicates Acute Candesartan Cilexetil Evaluation in Stroke Survivors, *BEST* Low Dose Beta Blockade in Acute Stroke, *CATIS* China Antihypertensive Trial in Acute Ischemic Stroke, *CHHIPS* Controlling Hypertension and Hypotension Immediately Post-Stroke, *COSSACS* Continue or Stop Post-Stroke Antihypertensives Collaborative Study, *ENOS* Efficacy of Nitric Oxide in Stroke Trial, *INWEST* Intravenous Nimodipine West European Stroke Trial, *PRoFESS* The Prevention Regimen for Effectively Avoiding Second Stroke, *SCAST* The Scandinavian Candesartan Acute Stroke Trial, *VENTURE* Valsartan Efficacy on Modest Blood Pressure Reduction in Acute Ischemic Stroke, *I* intervention, *C* control, *mo* month, *BI* Barthel Index

Table 11.3 BP treatment in AIS according to SITS-MOST [83]

Patients excluded from thrombolytic therapy (initial BP reduction (SBP and/or DBP) should not exceed 20% of the initial value):
SBP ≤ 220 mmHg and DBP ≤ 120 mmHg – do not treat except when combined with:
Aortic dissection
Acute myocardial infarction
Pulmonary oedema
Hypertensive encephalopathy
Acute renal failure
SBP > 220 mmHg and/or DBP 121–140 mmHg – treat until reaching values not exceeding 220 mmHg (SBP) and 120 mmHg (DBP) (if one therapy is insufficient, another drug may be used):
IV bolus of urapidil 10–50 mg, if needed followed by continuous infusion 9–30 mg/h
Labetalol 10–20 mg IV over 1–2 min: the dose may be administered every 10 min to a maximum of 300 mg
Continuous infusion of nicardipine 5 mg/h IV: the dose may be increased every 5–15 min by 0.25 mg/h (maximum dose 15 mg/h) to reach required BP levels. Then reduce the dose to 3 mg/h
DBP > 140 mmHg
Continuous IV infusion of sodium nitroprusside 0.5 μg/kg/min: continuous BP control required
Nitroglycerine 5 mg IV, followed by continuous infusion 1–4 mg/h
Patients treated with thrombolytic therapy if BP > 185/110 mmHg:
Before rtPA therapy is introduced:
IV bolus of urapidil 10–50 mg
Labetalol 10–20 mg IV over 1–2 min
Continuous infusion of nicardipine 5 mg/h IV: the dose may be increased every 5–15 min by 0.25 mg/h (maximum dose 15 mg/h) to reach required BP levels. Then reduce the dose to 3 mg/h
BP monitoring in every patient during the therapy: every 15 min in the first 2 h, then every 30 min in the following 8 h and every 1 h in the following 16 h
If SBP > 185 mmHg and/or DBP > 110 mmHg (one of the following):
IV bolus of urapidil 10–50 mg, if needed followed by a continuous IV infusion 9–30 mg/h
Labetalol 10–20 mg IV over 1–2 min, if needed followed by:
10–20 mg IV every 10–20 min to a maximum of 300 mg
Continuous IV infusion 2–8 mg/min
If SBP > 230 mmHg and/or DBP > 121–140 mmHg (one of the following):
IV bolus of urapidil 10–50 mg, if needed followed by a continuous IV infusion 9–30 mg/h
Labetalol 10–20 mg IV over 1–2 min, if needed followed by:
10–20 mg IV every 10–20 min to a maximum of 300 mg
Continuous IV infusion 2–8 mg/min
Continuous infusion of nicardipine 5 mg/h IV: the dose may be increased every 5 min by 2.5 mg/h to a maximum dose of 15 mg/h
If the above therapy is unsuccessful and DBP is >140 mmHg, consider continuous IV infusion of sodium nitroprusside 0.5 μg/kg/min, followed by titrating doses to reach required BP levels

rtPA recombinant tissue plasminogen activator

nonselective α- and β-blocker which, due to its effect on α-receptors, acts not only by reducing cardiac output, like the majority of β-blockers, but also as a peripheral vasodilator. Nicardipine is a calcium antagonist administered parenterally. Like labetalol, it is recommended by the AHA/ASA to reduce BP as thrombolytic therapy [55]. In extreme situations, if there is no response to these drugs, nitroglycerine or sodium nitroprusside may be administered intravenously. Other parenteral medications recommended for BP lowering in AIS include clonidine, dihydralazine and metoprolol. Sublingual administration of nifedipine should be avoided due to the risk of a rapid BP reduction, steal syndrome and a high BP "rebound".

References

1. Britton M, Carlsson A, de Faire U (1986) Blood pressure course in patients with acute stroke and matched controls. Stroke 17:861–864
2. Qureshi AI (2008) Acute hypertensive response in patients with stroke pathophysiology and management. Circulation 118:176–187
3. Alqadri SL, Sreenivasan V, Qureshi AI (2013) Acute hypertensive response management in patients with acute stroke. Curr Cardiol Rep 15:426
4. Sare GM, Geeganage C, Bath PMW (2009) High blood pressure in acute ischaemic stroke – broadening therapeutic horizons. Cerebrovasc Dis 27:156–161
5. Qureshi AI, Ezzeddine MA, Nasar A et al (2007) Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med 25:32–38
6. Dawson SL, Evans SN, Manktelow BN, Fotherby MD, Robinson TG, Potter JF (1998) Diurnal blood pressure change varies with stroke subtype in the acute phase. Stroke 29:1519–1524
7. Jain S, Namboodri KK, Kumari S, Prabhakar S (2004) Loss of circadian rhythm of blood pressure following acute stroke. BMC Neurol 4. doi:10.1186/1471-2377-4-1
8. Tomii Y, Toyoda K, Suzuki R et al (2011) Effects of 24-hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. Stroke 42:3511–3517
9. Rothwell PM (2010) Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 375:938–948
10. Papadopoulos DP, Mourouzis I, Thomopoulos C, Makris T, Papademetriou V (2010) Hypertension crisis. Blood Press 19:328–336
11. Qureshi A, Ezzeddine M, Nasar A et al (2007) NIH public access. Am J Emerg Med 25:32–38
12. Geeganage CM, Bath PMW (2009) Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. Hypertension 54:775–781
13. Wallace J, Levy L (1981) Blood pressure after stroke. JAMA 246:2177–2180
14. Carlberg B, Asplund K, Hagg E (1991) Comments, opinions, and reviews factors influencing admission blood pressure levels in patients with acute stroke. Stroke 22:527–530
15. Harper G, Castleden CM, Potter JF (1994) Factors affecting changes in blood pressure after acute stroke. Stroke 25:1726–1729
16. Jørgensen HS, Nakayama H, Christensen HR, Raaschou HO, Kampmann JP, Olsen TS (2002) Blood pressure in acute stroke. The Copenhagen Stroke Study. Cerebrovasc Dis 13:204–209
17. Toyoda K, Okada Y, Fujimoto S et al (2006) Blood pressure changes during the initial week after different subtypes of ischemic stroke. Stroke 37:2637–2639
18. Pedelty L, Gorelick P (2007) Stroke risk factors: impact and management. In: Torbey M, Selim M (eds) The stroke book. Cambridge Press, New York, pp 304–318
19. McGee S, Abernethy WBI, Simel DL (1999) Is this patient hypovolemic? JAMA 281:1022–1029

20. McLaren G, Danta G (1987) Cerebral infarction due to presumed haemodynamic factors in ambulant hypertensive patients. Clin Exp Neurol 23:55–56
21. Oliveira-Filho J, Silva S, Trabuco C, Pedreira B, Sousa E, Bacellar A (2003) Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. Neurology 61:1047–1051
22. Ritter MA, Kimmeyer P, Heuschmann PU et al (2009) Blood pressure threshold violations in the first 24 hours after admission for acute stroke: frequency, timing, predictors, and impact on clinical outcome. Stroke 40:462–468
23. Fischer U, Cooney MT, Bull LM et al (2014) Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. Lancet Neurol 13:374–384
24. Mattle HP, Kappeler L, Arnold M et al (2005) Blood pressure and vessel recanalization in the first hours. Stroke 36:264–269
25. Yong M, Diener H-C, Kaste M, Mau J (2005) Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. Stroke 36:2619–2625
26. Hilz MJ, Devinsky O, Szczepanska H, Borod JC, Marthol H, Tutaj M (2006) Right ventromedial prefrontal lesions result in paradoxical cardiovascular activation with emotional stimuli. Brain 129:3343–3355
27. Meyer S, Strittmatter M, Fischer C, Georg T, Schmitz B (2004) Lateralization in autonomic dysfunction in ischemic stroke involving the insular cortex. Neuroreport 15:357–361
28. Nason MW, Mason P (2004) Modulation of sympathetic and somatomotor function by the ventromedial medulla. J Neurophysiol 92:510–522
29. Murros K, Fogelholm R, Kettunen S, Vuorela A (1993) Serum cortisol and outcome of ischemic brain infarction. J Neurol Sci 116:12–17
30. Fassbender K, Schmidt R, Mössner R, Daffertshofer MHM (1994) Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke. Stroke 25:1105–1108
31. Robinson TG, James M, Youde J, Panerai R, Potter J (1997) Cardiac baroreceptor sensitivity is impaired after acute stroke. Stroke 28:1671–1676
32. Carlberg B, Asplund K, Hägg E (1991) Factors influencing admission blood pressure levels in patients with acute stroke. Stroke 22:527–530
33. Vemmos KN, Tsivgoulis G, Spengos K et al (2003) Association between 24-h blood pressure monitoring variables and brain oedema in patients with hyperacute stroke. J Hypertens 21:2167–2173
34. Ropper AH, Shafran B (1984) Brain edema after stroke. Clinical syndrome and intracranial pressure. Arch Neurol 41:26–29
35. Ahmed N, Wahlgren N, Brainin M et al (2009) Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Stroke 40:2442–2449
36. Vemmos KN, Spengos K, Tsivgoulis G et al (2004) Factors influencing acute blood pressure values in stroke subtypes. J Hum Hypertens 18:253–259
37. Leonardi-Bee J, Bath PMW, Phillips SJ, Sandercock PAG (2002) Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 33:1315–1320
38. Mattle HP, Kappeler L, Arnold M et al (2005) Blood pressure and vessel recanalization in the first hours after ischemic stroke. Stroke 36:264–268
39. Stead LG, Gilmore RM, Decker WW, Weaver AL, Brown RD (2005) Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. Neurology 65:1179–1183
40. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS (1994) Effect of blood pressure and diabetes on stroke in progression. Lancet 344:156–159
41. Castillo J, Leira R, García MM, Serena J, Blanco M, Dávalos A (2004) Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke 35:520–526

42. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S (2005) Effects of blood pressure levels on case fatality after acute stroke. J Hypertens 23:1217–1223
43. Vemmos KN, Tsivgoulis G, Spengos K et al (2004) U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 255:257–265
44. Tikhonoff V, Zhang H, Richart T, Staessen JA (2009) Blood pressure as a prognostic factor after acute stroke. Lancet Neurol 8:938–948
45. Chamorro A, Vila N, Ascaso C, Elices E, Schonewille W, Blanc R (1998) Blood pressure and functional recovery in acute ischemic stroke. Stroke 29:1850–1853
46. Yong M, Kaste M (2008) Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. Stroke 39:366–372
47. Carlberg B, Asplund K, Hägg E (1993) The prognostic value of admission blood pressure in patients with acute stroke. Stroke 24:1372–1375
48. Sare GM, Ali M, Shuaib A, Bath PMW (2009) Relationship between hyperacute blood pressure and outcome after ischemic stroke: data from the VISTA collaboration. Stroke 40:2098–2103
49. Leiva-Salinas C, Wintermark M, Kidwell CS (2011) Neuroimaging of cerebral ischemia and infarction. Neurotherapeutics 8:19–27
50. Perini F, De Boni A, Marcon M, Bolgan I, Pellizzari M, Di Dionisio L (2010) Systolic blood pressure contributes to intracerebral haemorrhage after thrombolysis for ischemic stroke. J Neurol Sci 297:52–54
51. Butcher K, Christensen S, Parsons M et al (2010) Postthrombolysis blood pressure elevation is associated with hemorrhagic transformation. Stroke 41:72–77
52. Ahmed N, Wahlgren G (2001) High initial blood pressure after acute stroke is associated with poor functional outcome. J Intern Med 249:467–473
53. Ntaios G, Lambrou D, Michel P (2011) Blood pressure change and outcome in acute ischemic stroke: the impact of baseline values, previous hypertensive disease and previous antihypertensive treatment. J Hypertens 29:1583–1589
54. Tanne D, Kasner SE, Demchuk AM et al (2002) Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. Circulation 105: 1679–1685
55. Jauch EC, Saver JL, Adams HP et al (2013) Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 44:870–947
56. Berge E, Cohen G, Lindley RI et al (2015) Effects of blood pressure and blood pressure-lowering treatment during the first 24 hours among patients in the third international stroke trial of thrombolytic treatment for acute ischemic stroke. Stroke 46:3362–3369
57. Delgado-Mederos R, Ribo M, Rovira A et al (2008) Prognostic significance of blood pressure variability after thrombolysis in acute stroke. Neurology 71:552–558
58. Aiyagari V. Acute blood pressure management after ischemic stroke. In: Aiyagari V, Gorelick P (eds) Hypertension and Stroke. Springer, New York Dordrecht Heidelberg London, 2011.
59. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee (2008) Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 25:457–507
60. Ji N, Meng P, Liu N, et al (2015) A reasonable blood pressure level for good clinical outcome after the acute phase of ischemic stroke. J Clin Hypertens; published online Sept 23. doi:10.1111/jch.12674
61. Brott T, Lu M, Kothari R et al (1998) Hypertension and its treatment in the NINDS rt-PA Stroke Trial. Stroke 29:1504–1509
62. Lindsberg PJ, Soinne L, Roine RO et al (2003) Community-based thrombolytic therapy of acute ischemic stroke in Helsinki. Stroke 34:1443–1449
63. Lee M, Ovbiagele B, Hong K-S et al (2015) Effect of blood pressure lowering in early ischemic stroke: meta-analysis. Stroke 46:1883–1889

64. Sandset EC, Bath PMW, Boysen G et al (2011) The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet 377:741–750
65. Sandset EC, Murray GD, Bath PMW, Kjeldsen SE, Berge E (2012) Relation between change in blood pressure in acute stroke and risk of early adverse events and poor outcome. Stroke 43:2108–2114
66. Potter JF, Robinson TG, Ford GA et al (2009) Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. Lancet Neurol 8:48–56
67. Robinson TG, Potter JF, Ford GA (2010) Effects of antihypertensive treatment after acute stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurol 9:767–775
68. Bath P, Krishnan K (2014) Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev (10):CD00003
69. Ankolekar S, Fuller M, Cross I et al (2013) Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: the rapid intervention with glyceryl trinitrate in Hypertensive Stroke Trial (RIGHT, ISRCTN66434824). Stroke 44:3120–3128
70. Woodhouse L, Scutt P, Krishnan K et al (2015) Effect of hyperacute administration (within 6 hours) of transdermal glyceryl trinitrate, a nitric oxide donor, on outcome after stroke: subgroup analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) Trial. Stroke 46:3194–3201
71. Wang H, Tang Y, Rong X et al (2014) Effects of early blood pressure lowering on early and long-term outcomes after acute stroke: an updated meta-analysis. PLoS One 9, e97917
72. Schrader J, Lüders S, Kulschewski A et al (2003) The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke 34:1699–1703
73. Barer DH, Cruickshank JM, Ebrahim SB, Mitchell JR (1988) Low dose beta blockade in acute stroke ('BEST' trial): an evaluation. Br Med J 296:737–741
74. He J, Zhang Y, Xu T et al (2014) Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA 311:479–489
75. Bath PMW, Woodhouse L, Scutt P et al (2015) Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. Lancet 385:617–628
76. Eveson DJ, Robinson TG, Potter JF (2007) Lisinopril for the treatment of hypertension within the first 24 hours of acute ischemic stroke and follow-up. Am J Hypertens 20:270–277
77. Ahmed N, Näsman P, Wahlgren NG (2000) Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. Stroke 31:1250–1255
78. Kaste M, Fogelholm R, Erilä T et al (1994) A randomized, double-blind, placebo-controlled trial of nimodipine in acute ischemic hemispheric stroke. Stroke 25:1348–1353
79. Bath PMW, Martin RH, Palesch Y et al (2009) Effect of telmisartan on functional outcome, recurrence, and blood pressure in patients with acute mild ischemic stroke: a PRoFESS subgroup analysis. Stroke 40:3541–3546
80. Oh MS, Yu K-H, Hong K-S et al (2015) Modest blood pressure reduction with valsartan in acute ischemic stroke: a prospective, randomized, open-label, blinded-end-point trial. Int J Stroke 10:745–751
81. Levy DE, Brott TG, Haley EC et al (1994) Factors related to intracranial hematoma formation in patients receiving tissue-type plasminogen activator for acute ischemic stroke. Stroke 25:291–297
82. Larrue V, von Kummer RR, Müller A, Bluhmki E (2001) Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). Stroke 32:438–441
83. Wahlgren N, Ahmed N, Dávalos A et al (2007) Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 369:275–282

Management of High Blood Pressure in Intracerebral Haemorrhage

12

Dariusz Gasecki, Bartosz Karaszewski, and Krzysztof Narkiewicz

12.1 Introduction

Intracerebral haemorrhage (ICH) is a devastating disease with the highest rate of mortality among the major pathological stroke subtypes. ICH is also the major contributor to disability-adjusted life years lost among all neurologic disorders [1]. Hypertension is the most important modifiable risk factor for both primary and recurrent ICH [2].

Early blood pressure (BP) elevation is observed in the majority of patients with ICH [3]. High BP appears to play a critical role in the pathogenesis of ICH, since it has been shown to be strongly related to haematoma growth [4–6] and subsequent poor clinical outcomes [7–11]. Therefore, acute BP alteration might be of clinical relevance in this cerebrovascular disorder.

In fact, recent clinical trial evidence suggests that BP lowering immediately after ICH may be an important treatment target to prevent haematoma expansion and may be associated with better outcomes [12].

12.2 Epidemiology

ICH is a less common subtype of stroke than cerebral ischaemia, accounting for 9–33 % of all acute cerebrovascular events/strokes worldwide, but is associated with higher mortality rates and poorer functional outcomes. Haemorrhagic stroke is especially common in Asia, particularly in Japan and China, and in African

D. Gasecki (✉) • B. Karaszewski
Department of Neurology for Adults, Medical University of Gdansk, Gdansk, Poland
e-mail: dgasecki@gumed.edu.pl

K. Narkiewicz
Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_12

populations, where it constitutes up to 20–33 % of all strokes [13]. In Caucasians, ICH accounts for approximately 9–15 % of all strokes [14]. The incidence of ICH rises with age and therefore the number of ICH is expected to increase substantially in the near future. ICH is associated with high early and late mortality and morbidity. The case fatality rate is 40 % at 1 month, rising to 54 % at 12 months [15, 16]. About 50 % of survivors will be permanently disabled, with only a minority of ICH patients being independent of long-term care at 12 months [17–19].

Most patients receive no warning signs before ICH. Occasionally, some patients with vascular malformations may present with recurrent, usually localized, headaches or seizures.

Among vascular risk factors, elevated BP is well established as the major contributor to ICH, with a much stronger association with ICH than with ischaemic stroke [20, 21]. BP values are linearly associated with the risk of ICH. The higher the BP, the greater the increased risk of haemorrhagic stroke and recurrent stroke, both haemorrhagic [22] and ischaemic [20, 21].

In general, hypertensives have a 2–3 times higher relative risk of ICH than non-hypertensive subjects [23]. High BP is a much stronger predictor of ICH in younger adults than in older subjects [24]. Discontinuation of antihypertensive therapy is also associated with a significantly greater risk of ICH [25].

12.3 Pathophysiology

Pathogenetically, arterial small vessel disease (so-called arteriolosclerosis), cerebral amyloid angiopathy and haemostatic and coagulation disorders – either due to intrinsic systemic or other diseases or to medications – are the leading causes of ICH in the elderly, while vascular malformations, venous disease, acute hypertensive crises or aneurysms are more likely to explain bleeding in younger patients [26, 27]. Cerebral arteriolosclerosis affects the small perforating arteries arising from the large vasculature of the brain and is related mainly, but not exclusively, to chronic uncontrolled hypertension [28]. Hypertension-related ICH tends to be located in the deep structures of the brain (e.g. basal ganglia, thalamus, white matter, pons, cerebellum), although, in rare cases, it may affect the subcortical areas [29].

The percentage of hypertension-related ICH varies between 50 and 70 % in older studies and between 35 and 54 % in more recent studies due to the availability of modern neuroimaging tools allowing other causes of ICH to be diagnosed. However, in about 20 % of ICH cases, no underlying cause is identified with currently available diagnostic tools, and thus they may still be considered cryptogenic [26].

With the advent of modern neuroimaging tools, continued bleeding and haematoma expansion have been demonstrated in one-third of patients with ICH in the first few hours [30] and in a further 10 % in the 3–24 h after stroke onset [31–33]. In ICH associated with anticoagulants, haematoma expansion persists even longer [34]. Haematoma expansion and final lesion volume, determined mainly within the first 24 h after stroke, are the key prognosticators of clinical outcomes in patients

with ICH. However, the adverse effects of peri-haematoma edema [35, 36] and inflammation [37, 38] in the first few days post-stroke may also contribute to overall morbidity and mortality.

12.4 BP and Outcomes in ICH

Acutely elevated BP in the first 24 h – the so-called acute hypertensive response (AHR) – occurs in up to 90 % of ICH cases [39–42], whereas pre-existing hypertension (self-reported) with systolic BP (SBP) ≥ 140 mmHg or >160 mmHg is found in 73 % and 60 % of ICH patients, respectively [3]. Stress, pain, increased intracranial pressure and premorbid elevations in BP are associated with AHR in ICH patients [10, 42].

In a recent study by Fisher et al., the first recorded acute-phase SBP was much higher in patients with ICH than in those with ischaemic stroke. Moreover, the first mean SBP after ICH was much higher than premorbid levels, in contrast with findings in patients with ischaemic stroke [43]. Mean SBP also increased steeply in the days and weeks before ICH, but not before ischaemic stroke. SBP appeared to rise substantially after ICH compared with usual premorbid values, and the reported difference between the highest SBP within 3 h of onset was 50 mmHg higher, on average, than the maximum premorbid SBP. Larger acute BP increases during ICH have been reported in Black populations than in Caucasian groups [44].

Rapid BP changes, with a substantial acute BP rise, seem to be specific for the ICH subtype of stroke, while in ischaemic stroke, acute post-event SBP tends to be much closer to premorbid values [43]. A possible explanation may be that ICH causes acute elevations in intracranial pressure more often than ischaemic stroke [45], followed by a reflex increase in systemic BP (the so-called Cushing triad: hypertension, bradycardia and breathing pattern abnormalities) [46]. Raised BP tends to decline spontaneously, primarily in the first few hours after intracerebral bleeding. Consistent with the data mentioned above, in the first 24 h after stroke, BP usually falls much more after ICH than after major ischaemic stroke [43]. However, in a substantial proportion of ICH patients, BP remains increased.

High BP in the acute phase after ICH has been associated with haematoma expansion [5], neurological deterioration and death and dependency [6, 47]. Furthermore, ICH patients with pathologically raised BP have more severe oedema and a higher risk of early stroke recurrence [22, 35, 36]. Therefore, BP-lowering therapy may potentially reduce the ICH-related burden. Not only mean BP values are of clinical importance in ICH patients. In a recent large, prospective randomized trial, BP variations in the first 24 h, and for several days after ICH, have been shown to be independent predictors of a poor outcome [48]. This may reflect the transient character of many individual factors associated with the initial pressor response, with episodic hypertension most likely to be related to the pathomechanisms of ICH triggering and progression. Moreover, raised BP may be both a risk factor and a risk marker for intracerebral bleeding and subsequent intracranial hypertension [8].

Factors associated with a poor outcome after ICH (other than BP) include older age [49, 50], large haemorrhage volume [17, 51–53], reduced level of consciousness [6, 54], extravasation with continued bleeding [49], haematoma expansion [31, 55], hydrocephalus and intraventricular involvement [17, 51, 54]. Patients with ICH are at high risk of other cardiovascular events, including recurrent ICH [56]. Hypertension and older age are important risk factors for ICH recurrence [57, 58]. A deep location of the initial and recurrent haemorrhage is more common in Asians, while in Caucasians, most ICHs (both initial and recurrent) tend to be located more superficially (in the lobes of the brain) [57, 59].

12.5 BP Management After ICH

Population-based studies show that most patients present with small ICH that are readily survivable with good medical care [60]. This suggests that excellent medical care probably has a potent, direct impact on ICH morbidity and mortality. The goal of ICH treatment is to prevent and reverse acute brain injury and prevent neurological impairment and disability. The evidence shows that management in an acute stroke unit improves outcomes compared with care on a general ward, reducing mortality and dependency in patients with ICH [61]. This may partially be explained by continuous monitoring of vital functions, including BP, and early treatment of complications by stroke units.

The treatment of acute BP elevation in ICH has been controversial for decades. The theoretical concept justifying early BP lowering in ICH patients is that it attempts to limit cerebral haemorrhage growth, which occurs mainly in the first few hours after stroke onset [12, 62], and to reduce cerebral oedema and minimize the risk of early hypertensive emergencies, including stroke recurrence, in the acute phase of ICH. However, the treatment plan should consider the potential risk of ischaemic injury to peri-haematoma areas or other vascular beds and the potentially higher disability and mortality, especially when the fall in BP in the acute phase is large and rapid [63]. In fact, acute BP-lowering therapy may be associated with ischaemic strokes remote from the primary haematoma in patients with ICH, as evidenced by recent MRI studies [64]. However, there is some evidence showing that reduced metabolism [65] and preserved autoregulation, the two typical features of the peri-haematoma region [66], might prevent any injury associated with SBP lowering. As indicated in recent prospective studies of acute ICH, BP reduction decreases haematoma expansion but has no adverse effect on peri-haematoma blood flow [4, 67–70].

There is also long-standing clinical debate on the optimal BP values in ICH, which should probably depend on coexisting individual factors including age, pre-existing hypertension, intracranial pressure, presumed cause of bleeding and time from stroke onset. The initial data on the effects of BP lowering in ICH were conflicting, with positive [68, 71, 72], neutral [73] and negative [63, 74, 75] effects attributed to SBP reduction. These clinical uncertainties were reflected in the heterogeneous expert-based recommendations for optimal BP lowering in acute ICH (Table 12.1).

Table 12.1 Suggested previous guidelines recommendations for BP-lowering treatment in patients with acute ICH

	Start medication	Target
ICH		
American Heart Association [76]	Systolic BP > 200 mmHg or MAP > 150 mmHg Systolic BP > 180 mmHg or MAP > 130 mmHg and possibility of elevated ICP Systolic BP > 180 mmHg or MAP > 130 mmHg and no evidence of elevated ICP	Aggressive reduction in BP Reducing BP while maintaining CPP ≥ 60 mmHg Moderate reduction in BP, e.g. MAP < 110 mmHg or BP <160/90 mmHg
International Society of Hypertension [77]	>220/120 mmHg	Up to 20 % reduction
Stroke Foundation of New Zealand [78]	>180/100 mmHg	Systolic BP < 180 mmHg or mean BP < 130 mmHg

MAP mean arterial pressure, *ICP* intracranial pressure, *CPP* cerebral pulse pressure

There is now growing evidence supporting the safety of early intensive BP lowering after ICH. Observational studies suggest that more aggressive BP lowering may have a greater effect on reductions in haematoma growth (Table 12.2).

The Antihypertensive Treatment of Acute Cerebral Haemorrhage (ATACH) trial was a small multicentre open-label pilot trial to determine the safety of intravenous nicardipine-based BP lowering in 60 patients with chronic hypertension and SBP > 170 mmHg presenting within 12 h after supratentorial ICH. Patients were enrolled into one of three tiers of increasing BP-lowering intensity (170–200, 140–170, 110–140 mmHg). Aggressive SBP lowering (110–140 mmHg) was well tolerated and safe [79].

The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTRERACT) included over 400 predominantly Chinese patients with acute ICH diagnosed by computed tomography within 6 h of stroke onset, and with SBP in the range of 150–220 mmHg, and no definitive indication or contraindication to BP treatment. Patients were assigned to intensive therapy (target SBP of 140 mmHg) or standard AHA guideline therapy (target SBP of 180 mmHg). After 24 h, SBP decreased to 146 mmHg in the intensive therapy group and to 157 mmHg in the standard therapy group. Mean proportional haematoma growth was lower in the intensive treatment group (13.5 % vs. 36.3 %; $p = 0.04$), although there was no clinical benefit at 90 days but also no higher risk of adverse events or poorer outcomes. An optimum attenuation of haematoma growth was demonstrated at SBP of 130–140 mmHg [4]. This was particularly true for very early intensive blood pressure lowering [67].

Thus, while the ATACH study was the first to prove the feasibility and tolerability of early intensive SBP lowering, the INTERACT found an additional positive effect of this type of therapy, namely, a reduction in haematoma expansion.

The recently completed INTERACT2 study of approximately 2,800 patients with an acute ICH showed improved functional recovery without any harm after

Table 12.2 Results of studies of blood pressure reduction after intracerebral haemorrhage

Trial, publication year, country	No. of patients	Mean age (years) (I; C)	Baseline SBP/DBP, mmHg	Intervention period (days)	Outcome assessment	Comments
INTERACT [67], 2010, multiple countries	404	63; 62	Active: 180/100 Control: 181/104	7	Absolute and proportional increases in haematoma and perihaematomal oedema volumes during the first 72 h after intracerebral haemorrhage	Early intensive BP-lowering treatment attenuated haematoma growth over 72 h. No appreciable effects on perihaematomal oedema
ATACH [79, 80], 2010, USA	60	62; 59; 65 (First tier, second tier, third tier)	SBP: First tier: 209 Second tier: 212 Third tier: 201	24 h	Neurological deterioration within 24 h and serious adverse events within 72 h	No significant difference was observed in average SBP change at 2 h after treatment initiation between subjects with or without neurological deterioration within 24 h
INTERACT2 [12], 2013, multiple countries	2839	63; 64	Active: 179/101 Control: 179/101	7	Combined end point of death and dependency according to the modified Rankin scale at 90 days	Intensive BP lowering did not significantly reduce the rate of the primary outcome of death or severe disability; an ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive BP lowering
SAMURAI [11], 2013, Japan	211	65 (whole group)	SBP: 200 (whole group)	24 h	Neurological deterioration, haematoma expansion and unfavourable outcome	Increased SBP was associated with an increase in neurological deterioration, an increase in haematoma expansion and an increase in unfavourable outcome
SCAST [81], 2011, Northern European countries (haemorrhagic stroke subgroup)	274	NA	NA	7	Death or disability at 6 months: combination of vascular death, myocardial infarction or stroke during first 6 months	The risk of the composite vascular end point did not differ between treatment groups; analysis of functional outcome suggested a higher risk of poor outcome in the candesartan group

an intensive strategy of BP lowering in patients with ICH. Exclusion criteria included (1) a clear indication for, or a contraindication to, intensive BP lowering; (2) severe neurological symptoms, concurrent medical conditions, a high likelihood of death within 24 h or massive ICH; and (3) early planned surgical intervention. The aggressive BP control (target SBP <140 mmHg) in very early (<6, mean time to start therapy about 3.7) hours after ICH onset was associated with a reduction in haematoma growth, as demonstrated in the INTERACT study and, more importantly, with safety and better functional outcome, as shown in the ordinal analysis of the dichotomous modified Rankin scale (mRS), although not in the primary outcome, which was the dichotomous mRS (i.e. there was a non-significant 4 % absolute treatment effect ($p = 0.06$) on the primary outcome of death or major disability) [12].

The BP-lowering protocols were based on locally available intravenous agents, as the antihypertensive drugs were not prespecified in the trial. Only one-third of patients achieved the target SBP value within 1 h (half achieved the target by 6 h), and most (75 %) presented with mild-to-moderate (<20 mL) haematomas [82].

Nonetheless, the INTERACT2 study has generally been interpreted as a positive trial, demonstrating both radiological and clinical benefit. Moreover, the more aggressive BP lowering was associated with a better outcome, with an optimal BP target around 130–139 mmHg achieved within the first 6 h [83]. Optimal recovery from ICH was observed in hypertensive patients who achieved the greatest SBP reductions (≥20 mmHg) in the first hour and which were maintained for 7 days [84].

The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement – Intracerebral Haemorrhage (SAMURAI-ICH) evaluated the effects of BP lowering in 211 Japanese patients with ICH and SBP > 180 mmHg [85]. Patients were treated with intravenous nicardipine within 3 h of stroke onset. The aim of the study was to achieve SBP between 120 and 160 mmHg and to maintain it in this range for the first 24 h. BP reduction was related to the reduction in the risk of haematoma expansion in the acute period and neurological deterioration and functional status at 3 months.

In the SCAST trial, over 200 (14 %) patients had ICH. Unfortunately, the treatment of elevated BP with candesartan (mean time to start therapy about 18 h) did not reduce, but increased, the risk of a poor outcome. It might be speculated that, if BP lowering is time dependent in ICH, the BP-altering intervention may have been too late in this trial. Alternatively, candesartan, as an angiotensin receptor blocker, might be not the best option for lowering BP in ICH.

The Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) enrolled patients with a recent stroke (time window 48 h) taking antihypertensive drugs. The majority of participants had ischaemic stroke, although 15 % of patients recruited had an ICH. At the study end point of 2 weeks, the continued treatment group had systolic/diastolic BP that was 13/8 mmHg less than the stop treatment group. However, there were no differences in rates of death and

dependency, the primary end point, or in the rates of serious adverse events, 6-month mortality or cardiovascular events. The continuation of BP-lowering agents did not have any significant efficacy on adverse events. Nevertheless, it should be stressed that the absolute number of ICH subjects enrolled in the trial was relatively small.

Thus, although the available evidence is insufficient to provide accurate guidance on the management of BP in the acute phase of ICH, there is recent evidence supporting very early aggressive BP control during this phase. Consequently, it seems reasonable that urgent initiation of the time-sensitive procedure of BP lowering should be made in the emergency department. Specific protocols for the management of ICH should be developed for more efficient, standardized management of patients with ICH.

12.6 Current Guideline Recommendations

The current American Stroke Association [82] and European Stroke Organization [86] guidelines recommend reduction of SBP to <140 mmHg in ICH patients presenting with SBP between 150 and 220 mmHg and with no contraindication to acute BP treatment. Acute lowering of SBP to 140 mmHg is regarded safe and may be effective in improving functional outcomes and may be superior to an SBP target of <180 mmHg. For ICH patients presenting with systolic BP > 220 mmHg, it may be reasonable to consider aggressive BP reduction and frequent BP monitoring. A lower limit for safe reduction is undefined. Short-acting and easily titratable antihypertensive infusions are preferred (Table 12.3).

Table 12.3 Short and rapidly acting intravenous antihypertensive agents that may be considered for control of elevated BP in patients with ICH

Agent	Dosing	Onset/duration of action
Labetalol	5–20 mg IV bolus every 15 min, up to 2 mg/min IV infusion	2–5 min/4–6 h
Nicardipine	5–15 mg/h IV infusion	5–15 min/4–6 h
Esmolol	500 μg/kg IV bolus or 25–300 μg/kg/min IV infusion	120 s/18–30 min
Urapidil	12.5–25 mg IV bolus or 5–40 mg/h IV infusion	1–5 min/1–2 h
Enalaprilat	1.25 to 5 mg every 6 h IVP	15 min/12–24 h
Hydralazine	10–20 mg IV bolus	10 min/> 1 h
Nipride	0.1–10 μg/kg/min IV infusion	Unset immediately while giving
Nitroglycerine	5–100 mg/min as IV infusion	2–5 min/5–10 min

Modified from Aiyagari et al. [87]
IVP intravenous push

12.7 Future Directions and Ongoing Studies

Further trials are needed to identify the optimal timing and the best drug classes for lowering high BP in ICH. There are no data on drugs specific for ICH patients. In some pivotal trials, the feasibility of calcium channel blockers has been shown. However, the optimal choice of drug and intensity of treatment remain elusive. The benefits (and potential risks) of aggressive BP management may vary according to age and comorbidities.

The ATACH II study – ongoing trial for intensive lowering of elevated BP within 3.5 h with nicardipine IV – will provide information about any differential effect between populations.

Other vascular factors, such as BP variability, the presence of obstructive sleep apnoea [88], obesity, frequent alcohol use [89] and illicit drug use [90], which have been linked to elevated BP and ICH, should also be considered in both the acute and chronic care of ICH patients.

References

1. Chin JH, Vora N (2014) The global burden of neurologic diseases. Neurology 83:349–351
2. Feigin VL, Forouzanfar MH, Krishnamurthi R et al (2014) Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet 383:245–254
3. O'Donnell MJ, Xavier D, Liu L et al (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 376:112–123
4. Arima H, Anderson CS, Wang JG et al (2010) Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute intracerebral hemorrhage. Hypertension 56:852–858
5. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T (1997) Predisposing factors to enlargement of spontaneous intracerebral hematoma. Stroke 28:2370–2375
6. Fogelholm R, Avikainen S, Murros K (1997) Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. Stroke 28:1396–1400
7. Vemmos KN, Tsivgoulis G, Spengos K et al (2004) U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 255:257–265
8. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A (2004) Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke 35:1364–1367
9. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S (2005) Effects of blood pressure levels on case fatality after acute stroke. J Hypertens 23:1217–1223
10. Zhang Y, Reilly KH, Tong W et al (2008) Blood pressure and clinical outcome among patients with acute stroke in Inner Mongolia, China. J Hypertens 26:1446–1452
11. Sakamoto Y, Koga M, Yamagami H et al (2013) Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. Stroke 44:1846–1851
12. Anderson CS, Heeley E, Huang Y et al (2013) Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 368:2355–2365

13. Tsai C-F, Thomas B, Sudlow CLM (2013) Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. Neurology 81:264–272
14. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V (2009) Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 8:355–369
15. Van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ (2010) Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 9:167–176
16. Poon MTC, Fonville AF, Al-Shahi SR (2014) Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 85:660–667
17. Portenoy RK, Lipton RB, Berger AR, Lesser ML, Lantos G (1987) Intracerebral haemorrhage: a model for the prediction of outcome. J Neurol Neurosurg Psychiatry 50:976–979
18. Barber M, Roditi G, Stott DJ, Langhorne P (2004) Poor outcome in primary intracerebral haemorrhage: results of a matched comparison. Postgrad Med J 80:89–92
19. Tatu L, Moulin T, El Mohamad R, Vuillier F, Rumbach L, Czorny A (2000) Primary intracerebral hemorrhages in the Besançon stroke registry. Initial clinical and CT findings, early course and 30-day outcome in 350 patients. Eur Neurol 43:209–214
20. Eastern Stroke and Coronary Heart Disease Collaborative Research Group (1998) Blood pressure, cholesterol, and stroke in eastern Asia. Lancet 352:1801–1807
21. Lawes CMM, Rodgers A, Bennett DA et al (2003) Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens 21:707–716
22. Arakawa S, Saku Y, Ibayashi S, Nagao T, Fujishima M (1998) Blood pressure control and recurrence of hypertensive brain hemorrhage. Stroke 29:1806–1809
23. Ariesen MJ, Claus SP, Rinkel GJE, Algra A (2003) Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke 34:2060–2065
24. Rapsomaniki E, Timmis A, George J et al (2014) Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet 383:1899–1911
25. Thrift AG, McNeil JJ, Forbes A, Donnan GA (1998) Three important subgroups of hypertensive persons at greater risk of intracerebral hemorrhage. Hypertension 31:1223–1229
26. Meretoja A, Strbian D, Putaala J et al (2012) SMASH-U: a proposal for etiologic classification of intracerebral hemorrhage. Stroke 43:2592–2597
27. Yeh S-J, Tang S-C, Tsai L-K, Jeng J-S (2014) Pathogenetical subtypes of recurrent intracerebral hemorrhage: designations by SMASH-U classification system. Stroke 45:2636–2642
28. Sessa M (2008) Intracerebral hemorrhage and hypertension. Neurol Sci 29(Suppl 2):S258–S259
29. Mizukami M, Kin H, Araki G, Mihara H, Yoshida Y (1976) Surgical treatment of primary intracerebral hemorrhage- part 1: new angiographical classification. Stroke 7:30–36
30. Davis SM, Broderick J, Hennerici M et al (2006) Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology 66:1175–1181
31. Brott T, Broderick J, Kothari R et al (1997) Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 28:1–5
32. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O (1994) Hematoma enlargement in spontaneous intracerebral hemorrhage. J Neurosurg 80:51–57
33. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T (1996) Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 27:1783–1787
34. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J (2004) Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. Neurology 63:1059–1064
35. Gebel JM, Jauch EC, Brott TG et al (2002) Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. Stroke 33:2631–2635
36. Carhuapoma JR, Hanley DF, Banerjee M, Beauchamp NJ (2003) Brain edema after human cerebral hemorrhage: a magnetic resonance imaging volumetric analysis. J Neurosurg Anesthesiol 15:230–233

37. Gong C, Hoff JT, Keep RF (2000) Acute inflammatory reaction following experimental intracerebral hemorrhage in rat. Brain Res 871:57–65
38. Xue M, Del Bigio MR (2000) Intracortical hemorrhage injury in rats: relationship between blood fractions and brain cell death. Stroke 31:1721–1727
39. Wallace JD, Levy LL (1981) Blood pressure after stroke. JAMA 246:2177–2180
40. Harper G, Castleden CM, Potter JF (1994) Factors affecting changes in blood pressure after acute stroke. Stroke 25:1726–1729
41. Robinson TG, Potter JF (2004) Blood pressure in acute stroke. Age Ageing 33:6–12
42. Qureshi AI, Ezzeddine MA, Nasar A et al (2007) Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med 25:32–38
43. Fischer U, Cooney MT, Bull LM et al (2014) Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. Lancet Neurol 13:374–384
44. Zahuranec DB, Wing JJ, Edwards DF et al (2012) Poor long-term blood pressure control after intracerebral hemorrhage. Stroke 43:2580–2585
45. Qureshi AI, Mendelow AD, Hanley DF (2009) Intracerebral haemorrhage. Lancet 373:1632–1644
46. Fodstad H, Kelly PJ, Buchfelder M (2006) History of the cushing reflex. Neurosurgery 59:1132–1137; discussion 1137
47. Willmot M, Leonardi-Bee J, Bath PMW (2004) High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension 43:18–24
48. Manning L, Hirakawa Y, Arima H et al (2014) Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. Lancet Neurol 13:364–373
49. Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA (1999) Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. Stroke 30:2025–2032
50. Daverat P, Castel JP, Dartigues JF, Orgogozo JM (1991) Death and functional outcome after spontaneous intracerebral hemorrhage. A prospective study of 166 cases using multivariate analysis. Stroke 22:1–6
51. Tuhrim S, Dambrosia JM, Price TR et al (1991) Intracerebral hemorrhage: external validation and extension of a model for prediction of 30-day survival. Ann Neurol 29:658–663
52. Mayer SA, Sacco RL, Shi T, Mohr JP (1994) Neurologic deterioration in noncomatose patients with supratentorial intracerebral hemorrhage. Neurology 44:1379–1384
53. Leira R, Dávalos A, Silva Y et al (2004) Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. Neurology 63:461–467
54. Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC (1994) Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. Neurology 44:133–139
55. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R (1998) Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. Stroke 29:1160–1166
56. Arima H, Tzourio C, Butcher K et al (2006) Prior events predict cerebrovascular and coronary outcomes in the PROGRESS trial. Stroke 37:1497–1502
57. Hanger HC, Wilkinson TJ, Fayez-Iskander N, Sainsbury R (2007) The risk of recurrent stroke after intracerebral haemorrhage. J Neurol Neurosurg Psychiatry 78:836–840
58. Izumihara A, Suzuki M, Ishihara T (2005) Recurrence and extension of lobar hemorrhage related to cerebral amyloid angiopathy: multivariate analysis of clinical risk factors. Surg Neurol 64:160–164; discussion 164
59. Inagawa T (2005) Recurrent primary intracerebral hemorrhage in Izumo City, Japan. Surg Neurol 64:28–35; discussion 35–6
60. Zahuranec DB, Gonzales NR, Brown DL et al (2006) Presentation of intracerebral haemorrhage in a community. J Neurol Neurosurg Psychiatry 77:340–344

61. Langhorne P, Fearon P, Ronning OM et al (2013) Stroke unit care benefits patients with intracerebral hemorrhage: systematic review and meta-analysis. Stroke 44:3044–3049
62. Anderson CS, Huang Y, Wang JG et al (2008) Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol 7:391–399
63. Qureshi AI, Bliwise DL, Bliwise NG, Akbar MS, Uzen G, Frankel MR (1999) Rate of 24-hour blood pressure decline and mortality after spontaneous intracerebral hemorrhage: a retrospective analysis with a random effects regression model. Crit Care Med 27:480–485
64. Kidwell CS, Heiss W-D (2012) Advances in stroke: imaging. Stroke 43:302–304
65. Kim-Han JS, Kopp SJ, Dugan LL, Diringer MN (2006) Perihematomal mitochondrial dysfunction after intracerebral hemorrhage. Stroke 37:2457–2462
66. Powers WJ, Zazulia AR, Videen TO et al (2001) Autoregulation of cerebral blood flow surrounding acute (6 to 22 hours) intracerebral hemorrhage. Neurology 57:18–24
67. Anderson CS, Huang Y, Arima H et al (2010) Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). Stroke 41:307–312
68. Qureshi AI, Palesch YY, Martin R et al (2010) Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study. Arch Neurol 67:570–576
69. Koch S, Romano JG, Forteza AM, Otero CM, Rabinstein AA (2008) Rapid blood pressure reduction in acute intracerebral hemorrhage: feasibility and safety. Neurocrit Care 8:316–321
70. Xu M (2011) Effect of blood pressure lowering strategy on the enlargement of hematoma and clinical outcome in patients with acute intracerebral haemorrhage. Chinese J Cerebrovasc Dis 8:23–27
71. Meyer JS, Bauer RB (1962) Medical treatment of spontaneous intracranial hemorrhage by the use of hypotensive drugs. Neurology 12:36–47
72. Suri MFK, Suarez JI, Rodrigue TC et al (2008) Effect of treatment of elevated blood pressure on neurological deterioration in patients with acute intracerebral hemorrhage. Neurocrit Care 9:177–182
73. Itabashi R, Toyoda K, Yasaka M et al (2008) The impact of hyperacute blood pressure lowering on the early clinical outcome following intracerebral hemorrhage. J Hypertens 26:2016–2021
74. Powers WJ (1993) Acute hypertension after stroke: the scientific basis for treatment decisions. Neurology 43:461–467
75. Kuwata N, Kuroda K, Funayama M, Sato N, Kubo N, Ogawa A (1995) Dysautoregulation in patients with hypertensive intracerebral hemorrhage. A SPECT study. Neurosurg Rev 18:237–245
76. Morgenstern LB, Hemphill JC, Anderson C et al (2010) Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 41:2108–2129
77. Bath P, Chalmers J, Powers W et al (2003) International Society of Hypertension (ISH): statement on the management of blood pressure in acute stroke. J Hypertens 21:665–672
78. Stroke Foundation of New Zealand and New Zealand Guidelines Group (2010) Clinical guidelines for stroke management 2010. Stroke Foundation of New Zealand, Wellington
79. Qureshi AI (2007) Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH): rationale and design. Neurocrit Care 6:56–66
80. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Investigators (2010) Antihypertensive treatment of acute cerebral hemorrhage. Crit Care Med 38:637–648
81. Sandset EC, Bath PMW, Boysen G et al (2011) The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet 377:741–750
82. Hemphill JC, Greenberg SM, Anderson CS et al (2015) Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 46:2032–2060

83. Arima H, Heeley E, Delcourt C et al (2015) Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. Neurology 84:464–471
84. Wang X, Arima H, Heeley E et al (2015) Magnitude of blood pressure reduction and clinical outcomes in acute intracerebral hemorrhage: intensive blood pressure reduction in acute cerebral hemorrhage trial study. Hypertension 65:1026–1032
85. Sakamoto Y, Koga M, Todo K et al (2015) Relative systolic blood pressure reduction and clinical outcomes in hyperacute intracerebral hemorrhage: the SAMURAI-ICH observational study. J Hypertens 33:1069–1073
86. Steiner T, Al-Shahi Salman R, Beer R et al (2014) European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke 9:840–855
87. Grysiewicz RA, Ruland SD (2011) Hypertensive encephalopathy and acute blood pressure management after hemorrhagic stroke. In: Aiyagari V, Gorelick P (eds) Hypertension and stroke. Pathophysiology and management. Humana Press, New York
88. Pontes-Neto OM, Fernandes RMF, Sander HH et al (2010) Obstructive sleep apnea is frequent in patients with hypertensive intracerebral hemorrhage and is related to perihematoma edema. Cerebrovasc Dis 29:36–42
89. Woo D, Sauerbeck LR, Kissela BM et al (2002) Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. Stroke 33:1190–1195
90. Gee P, Tallon C, Long N, Moore G, Boet R, Jackson S (2012) Use of recreational drug 1,3 Dimethylamylamine (DMAA) [corrected] associated with cerebral hemorrhage. Ann Emerg Med 60:431–434

Secondary Stroke Prevention

13

Mónica Doménech, Miguel Camafort, and Antonio Coca

13.1 Introduction

Stroke is the third most frequent cause of death after cancer and heart disease in developed countries and the first cause of death among women in many countries. It is also one of the major causes of disability worldwide, and the burden will increase in the next 20 years, mainly due to ageing [1, 2]. High blood pressure (BP) is one of the most important risk factors for development of stroke. A continuous relationship between levels of BP and the occurrence of stroke has been well established, and this association has been seen for both systolic (SBP) and diastolic (DBP) components, without a clear threshold where risk disappears [3–5].

Evidence from hypertension treatment trials has shown that even relatively small reductions in BP, such as 5–6 mmHg in DBP or 10–12 mmHg in SBP during 3–5 years, may reduce the risk of the first stroke by more than one-third, and meta-analyses of randomised controlled trials in hypertensive patients have shown that reductions in BP are associated with a reduction in the risk of stroke of up to 40 % [6–9]. On the other hand, the persistence of higher BP levels after stroke can increase the risk of its recurrence [10]. About one-third of strokes occur in subjects with a previous cerebrovascular event, either transient ischaemic attack (TIA) or stroke, and more than 50 % occur in individuals with previous vascular events in any arterial territory [11–13].

As discussed in Chap. 11, high BP is frequent in the setting of acute ischaemic stroke, although data on its immediate management are few and discordant and the optimal time to initiate antihypertensive therapy remains uncertain [14]. In this chapter, we review the evidence on hypertension as a risk factor for recurrent strokes and the role of antihypertensive treatment in secondary stroke prevention.

M. Doménech • M. Camafort • A. Coca (✉)
Hypertension and Vascular Risk Unit, Department of Internal Medicine, Hospital Clínic (IDIBAPS), University of Barcelona, Barcelona, Spain
e-mail: acoca@clinic.ub.es

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_13

Cardiovascular prevention is much more effective when managed globally including all cardiovascular risk factors involved. However, in this chapter, we only will review current evidence and recommendations on antihypertensive treatment, because treatment of other associated cardiovascular risk factors that play a role in stroke recurrence have been addressed in other chapters of the book.

13.2 High Blood Pressure and Other Cardiovascular Risk Factors Related to the Risk of Recurrent Stroke

13.2.1 High Blood Pressure and Risk of Recurrent Stroke

All forms of hypertension are related to stroke, including isolated diastolic and systolic hypertension, which is more prevalent in elderly people, and the combination of both. All have been shown to increase the risk of stroke, although the impact may be stronger for systolic than for diastolic hypertension. As the most important modifiable risk factor for stroke, epidemiological studies have found that stroke is more common than myocardial infarction in hypertensive patients [15–18]. Large-scale observational studies have demonstrated that usual levels of BP are positively and continuously associated with the risk of stroke in a log-linear fashion, and this relationship is observed from systolic levels as low as 115 mmHg and diastolic levels as low as 70 mmHg [15, 16]. The relationship between BP and stroke risk remains virtually unchanged after adjustment for serum cholesterol levels, smoking, alcohol or a history of previous cardiovascular disease [19]. Similar associations appear to exist between BP and the risk of recurrent stroke although much of the evidence comes from smaller cohort and observational studies. Data from the United Kingdom Transient Ischaemic Attack (UK TIA) Collaborative Group showed that a 10 mmHg reduction in usual SBP was associated with a 28 % reduction in the risk of recurrent stroke [19].

Although a continuous relationship between both SBP and DBP and the occurrence of stroke has been well established, there is epidemiological evidence from the MRFIT study that the systolic component may exert a strong deleterious effect on cerebrovascular disease [20]. It is also known that increased arterial stiffness results in increased characteristic impedance of the aorta and increased pulse wave velocity, which increases systolic and pulse pressures. Large-artery stiffness is the main determinant of pulse pressure. Data from the SHEP study [21] showed an 11 % increase in stroke risk and a 16 % increase in the risk of all-cause mortality for each 10 mmHg increase in pulse pressure, and aortic stiffness assessed by carotid-femoral pulse wave velocity is an independent predictor of fatal stroke in patients with essential hypertension.

13.2.2 Other Cardiovascular Risk Factors and Risk of Recurrent Stroke

Type 2 diabetes mellitus (DM-2) is a major risk factor for CV disease, with 15–33 % of all patients with ischaemic stroke having DM-2 [22–24]. Even though the best evidence supports that diabetes is a risk factor for the first episode of stroke [25, 26],

stronger evidence supporting diabetes as a risk factor for recurrent stroke is needed. Anyway, DM-2 appears to be an independent predictor of recurrent stroke in population-based studies [27], and 9.1 % of recurrent strokes has been estimated to be attributable to diabetes [28, 29]. Furthermore, observational studies have suggested that undiagnosed diabetes could be highly prevalent in stroke cohorts [30]. Dyslipidaemia, smoking habits and alcohol intake are also major modifiable risk factors for stroke recurrence and have been already discussed in Chaps. 2 and 3.

13.3 Evidence of the Relationship Between Antihypertensive Therapy and Secondary Stroke Prevention

Treatment of high blood pressure is probably the most important intervention for secondary prevention of ischaemic stroke. More than 10 years ago, a systematic review of the relationship between BP reduction and secondary stroke prevention and other vascular events [31] analysed seven randomised, controlled trials: the Dutch TIA trial with atenolol [32], the PATS with indapamide [33], the HOPE trial with ramipril [34], the PROGRESS with perindopril, with or without indapamide [11], and three other smaller trials [35–37] with a combined sample size of 15,527 participants. All of them had a previous ischaemic or haemorrhagic stroke and were studied from 3 weeks to 14 months after the event and followed for 2–5 years. Treatment with antihypertensive drugs was associated with significant reductions in all recurrent strokes. The overall reductions in stroke and all vascular events were related to the degree of BP lowering achieved, while data on the relative benefits of specific antihypertensive regimens for secondary stroke prevention were not clear.

The PATS (Post-Stroke Antihypertensive Treatment Study) was a Chinese trial in which 5665 patients with a recent TIA or minor stroke (hemorrhagic or ischaemic) were randomised to indapamide or placebo. Patients were eligible regardless of baseline BP (mean SBP was 153 mmHg in the placebo group and 154 mmHg in the indapamide group). During an average of 24 months of follow-up, the mean SBP fell by 6.7 and 12.4 mmHg in the placebo and indapamide groups, respectively. The main outcome of recurrent stroke was observed in 44.1 % of patients assigned to placebo and 30.9 % of those assigned to indapamide (relative risk reduction [RRR], 30 %; 95 % confidence interval [CI], 14–43 %) [33].

The HOPE trial [34] investigated the effect of ramipril in patients at high risk for cardiovascular events. Since 11 % of patients included had had a prior stroke, an approach to stroke secondary prevention efficacy could be made in this subgroup: the results showed a nonsignificant 17 % reduction in the relative risk of stroke recurrence.

The PROGRESS [11] study was specifically designed to test the effects of a BP-lowering regimen, including an ACE inhibitor, in 6105 patients with stroke or TIA within the previous 5 years. Randomisation was stratified by intention to use single (perindopril) or combination (perindopril plus the diuretic indapamide) therapy in both hypertensive and normotensive patients. The combination therapy reduced BP by a mean of 12/5 mmHg and resulted in a 43 % (95 % CI: 30–54) reduction in the risk of recurrent stroke (Figs. 13.1 and 13.2). The beneficial effects

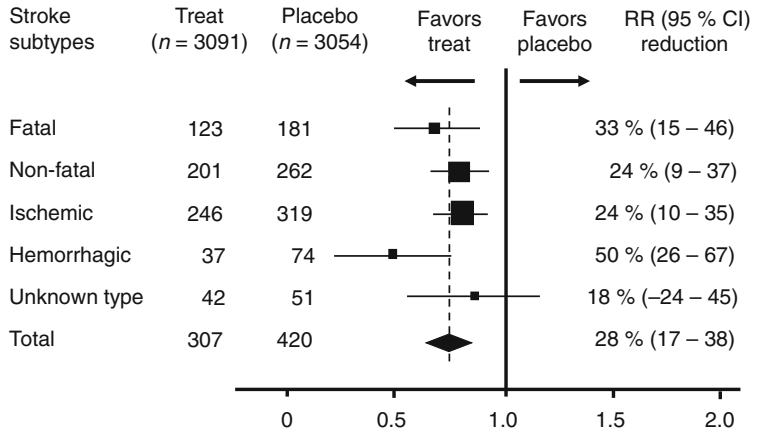

Fig. 13.1 Blood pressure lowering and secondary prevention of stroke in the PROGRESS study. All stroke types (except for unknown type) were prevented by active treatment (Adapted from Ref. [11])

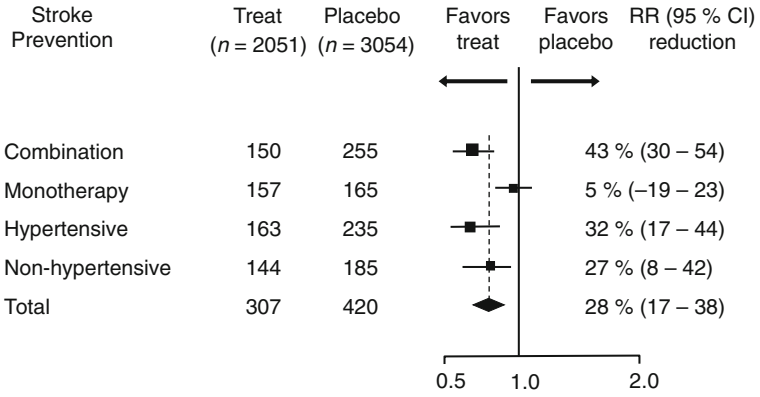

Fig. 13.2 Blood pressure lowering and secondary prevention of stroke in the PROGRESS study. Only patients treated in combination therapy showed a significant 43 % reduction in stroke recurrence (mean SBP/DBP reduction = 12.3/5.0 mmHg). Patients treated in monotherapy only had a SBP/DBP reduction of 4.9/2.8 mmHg and had no benefit (Adapted from Ref. [11])

were observed in both the hypertensive and normotensive groups. However, there was no significant benefit when the ACE inhibitor was given alone (reducing BP by an average of 5/3 mmHg). A recent new analysis found no differences between isolated systolic or diastolic hypertension [38] or between obese, overweight or normal weight individuals [39].

In the MOSES study, which tested the efficacy of the ARB eprosartan compared with the CCB nitrendipine on secondary stroke prevention, fewer cerebrovascular

and cardiovascular events were observed in eprosartan-treated patients despite a similar BP reduction [40]. A total of 1405 high-risk hypertensives with cerebral events during the last 24 months were randomised to eprosartan or nitrendipine (mean follow-up 2.5 years). The primary end point was the composite of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events. The combined primary end point was significantly lower in the eprosartan group, mainly due to a reduction in cerebrovascular events.

The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial is another large-scale randomised trial of antihypertensive medications after stroke tested the efficacy of telmisartan versus placebo in preventing the recurrence of ischaemic stroke [41]. A total of 20,332 subjects with previous ischaemic stroke were randomly assigned to telmisartan or placebo within 90 days of an ischaemic stroke. In this trial, telmisartan was not associated with a reduction in recurrent stroke (hazard ratio [HR] 0.95; 95 % CI 0.86–1.04) or major cardiovascular events (HR, 0.94; 95 % CI, 0.87–1.01) during the mean 2.5-year follow-up. However, some factors could have biased the results: the BP-lowering arm was statistically underpowered, and the difference in BP between the treatment groups was small (SBP differed by 5.4 mmHg at 1 month and 4.0 mmHg at 1 year) due to nonadherence to telmisartan and more aggressive treatment with other antihypertensive medications in the placebo group, and this may have reduced the impact of treatment on stroke recurrence.

In a combined analysis of the PRoFESS [41] and TRANSCEND [42] trials that assessed whether telmisartan would be effective in patients intolerant to ACE inhibitors with cardiovascular disease or diabetes with end-organ damage, the incidence of the composite of stroke, myocardial infarction or vascular death was 12.8 % for telmisartan versus 13.8 % for placebo (hazard ratio 0.91; 95 % CI 0.85–0.98, $p=0.013$) [43].

Another unresolved question is whether the risk of recurrent stroke is associated with higher and lower SBP levels. A post hoc observational analysis of the PRoFESS trial was made to assess the association between maintaining low-normal vs. high-normal SBP levels and the risk of recurrent stroke [44]. The primary outcome was the first recurrence of stroke of any type and the secondary outcome was a composite of stroke, myocardial infarction or death from vascular causes. SBP levels during follow-up in the very low-normal (<120 mmHg), high (140–150 mmHg) or very high (>150 mmHg) range were associated with increased risk of recurrent stroke, supporting the idea of a J-curve for BP levels in secondary stroke prevention.

The Secondary Prevention of Small Subcortical Strokes (SPS3) [45] included 3020 patients with lacunar (small-vessel disease) strokes who were randomised in an open-label study to two different target levels of SBP control: <150 mmHg vs. <130 mmHg. At baseline, mean SBP was 145 mmHg in the higher-target group and 144 mmHg in the lower-target group. At 12 months, achieved average SBP was 138 mmHg in the higher-target group versus 127 mmHg in the lower-target group. The primary outcome of recurrent stroke was observed in 152 patients assigned to higher-target group and 125 assigned to the lower-target group, but differences were not significant (HR, 0.81; 95 % CI, 0.64–1.03). Serious complications of hypotension were observed in 15 patients assigned to the higher-target group and 23 assigned to the lower-target group (0.40 % per year; HR, 1.53; 95 % CI, 0.80–2.93). In a very recent post hoc analysis of

the SPS3 trial data [46], the authors evaluated the association of mean achieved blood pressure, 6 months after randomisation and recurrent stroke, major vascular events and all-cause mortality. After a mean follow-up of 3.7 years, there was a J-shaped association between achieved blood pressure and outcomes; the lowest risk was at systolic blood pressure about 124 mmHg and about 67 mmHg for diastolic blood pressure. The lowest risk of all events occurred at a nadir between 120 and 128 mmHg systolic blood pressure and between 65 and 70 mmHg diastolic blood pressure values. Future studies should evaluate the impact of excessive blood pressure reduction, especially in older populations with preexisting vascular disease.

In fact, the only trial specifically designed to explore this issue is the European Society of Hypertension– Chinese Hypertension League Stroke in Hypertension Optimal Treatment trial (SHOT) [47], a prospective, multinational, randomised trial with a 3×2 factorial design comparing three different SBP targets (<145–135 vs. <135–125 vs. <125 mmHg) and two different LDL-C targets (2.8–1.8 mmol/l vs. <1.8 mmol/l). The trial is ongoing and will be conducted on 7500 patients aged at least 65 years (2500 in Europe and 5000 in China) with hypertension and a stroke or TIA 1–6 months before randomization. The primary outcome is time to stroke (fatal and nonfatal).

In summary, according to the American Stroke Association [48], antihypertensive treatment is recommended for the prevention of recurrent stroke. Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischaemic stroke and TIA patients although with different evidence levels:

- Initiation of BP therapy is indicated for previously untreated patients with ischaemic stroke or TIA who, after the first several days, have an established BP ≥140 mmHg systolic or ≥90 mmHg diastolic (*Class I*; *Level of Evidence B*).
- Initiation of therapy for patients with SBP <140 and DBP <90 mmHg is of uncertain benefit (*Class IIb*; *Level of Evidence C*).
- Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualised, but it is reasonable to achieve a SBP <140 mmHg and a DBP <90 mmHg (*Class IIa*; *Level of Evidence B*).

For patients with a recent lacunar stroke, it might be reasonable to target a SBP of <130 mmHg (*Class IIb*; *Level of Evidence B*).

13.4 Evidence of the Relationship Between Treatment of Other Cardiovascular Risk Factors and Secondary Stroke Prevention

Although DM-2 is an important risk factor for vascular events, no specific guidelines are available for DM-2 treatment in patients with stroke. Correct glycaemic control may reduce the impact and burden of microvascular complications and lower the risk of small-artery atherosclerotic disease. Therefore, current guidelines

on secondary prevention of cardiovascular diseases recommend a goal for glucose and HbA1c of near-normoglycaemic levels (i.e. glycated haemoglobin <7 %) for patients with diabetes and recent stroke [48, 49].

Three large, randomised controlled trials have compared aggressive glycaemic control with standard therapy in patients with DM-2 with a history of cardiovascular disease, stroke or additional vascular risk factors. All failed to demonstrate a reduction in cardiovascular events or death in patients treated with intensive glucose therapy and, although the studies were not designed to measure stroke outcomes, they showed no reduced incidence of stroke with tight glycaemic control. In the ACCORD trial 10,251 patients were randomly assigned to an intensive treatment programme targeting an HbA1c level of ≤6 % vs. a standard programme with a target HbA1c level of 7–7.9 %. The trial was halted after a mean of 3.5 years of follow-up due to an increased risk of death in patients randomised to the intensive treatment programme. There was no significant difference in the rate of nonfatal stroke or in the primary end point, which was a composite of nonfatal heart attack, nonfatal stroke, and death due to a cardiovascular cause [50].

The ADVANCE trial also found no benefit in the secondary prevention of cardiovascular events. A total of 11,140 patients with DM-2 and a history of macrovascular disease or another risk factor were randomly assigned to intensive glucose control (target HbA1c ≤6.5 %) or standard glucose control (target >7 %): 9 % of patients had a history of stroke. There was no significant reduction in the occurrence of macrovascular events alone, although there were no significant differences in mortality rate between groups [51].

Finally, the Veterans Affairs Diabetes Trial assigned 1791 patients with DM-2 to intensive blood glucose treatment or standard treatment, with no significant difference between the two groups [52]. The results of these trials indicate that glycaemic targets should not be lowered to HbA1c <6.5 % in patients with high added cardiovascular risk or those with a previous stroke or TIA. The beneficial effects of statin treatment in patients with dyslipidaemia and stroke to improve functional outcomes and stroke recurrence have been reviewed in Chap. 2.

References

1. Ivan CS, Seshadri S, Beiser A et al (2004) Dementia after stroke: the Framingham study. Stroke 35(6):1264–1268
2. Rothwell PM, Algra A, Amarenco P (2011) Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. Lancet 377:1681–1692
3. Multiple Risk Factor Intervention Trial (1990) Mortality after 10 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. Circulation 82:1616–1628
4. MacMahon S, Peto R, Cutler J et al (1990) Blood pressure, stroke, and coronary heart disease. Part 1: prolonged differences in blood pressure. Prospective observational studies corrected for the regression dilution bias. Lancet 355:765–774
5. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360:1903–1913

6. Lawes CM, Bennett DA, Feigin VL, Rodgers A (2004) Blood pressure and stroke: an overview of published reviews. Stroke 35:776–785
7. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, The Heart Outcomes Prevention Evaluation Study Investigators (2000) Effects of an angiotensin- converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 342:145–153
8. Turnbull F (2003) Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 362:1527–1535
9. Collins R, Peto R, MacMahon S et al (1990) Blood pressure, stroke, and coronary heart disease. Part 2: short-term reductions in blood pressure. Overview of randomised drug trials in their epidemiological context. Lancet 355:827–838
10. Rodgers A, MacMahon S, Gamble G, Slattery J, Sandercock P, Warlow C (1996) Blood pressure and risk of stroke in patients with cerebrovascular disease: the United Kingdom Transient Ischaemic Attack Collaborative Group. BMJ 313:147–150
11. PROGRESS Collaborative Group (2001) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 358:1033–1041
12. Rothwell PM, Coull AJ, Giles MF, et al, for the Oxford Vascular Study (2004) Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 363:1925–1933
13. Pendlebury ST, Rothwell PM (2009) Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 8:1006–1018
14. Adams HP Jr, del Zoppo G, Alberts MJ et al (2007) Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Stroke 38:1655–1711
15. Law MR, Morris JK, Wald NJ (2009) Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 338:b1665
16. Blood Pressure Lowering Treatment Trialists' Collaboration, Turnbull F, Neal B, Ninomiya T et al (2008) Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ 336:1121–1123
17. Chobanian AV, Bakris GL, Black HR et al (2003) Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 42:1206–1252
18. Kjeldsen SE, Julius S, Hedner T, Hansson L (2001) Stroke is more common than myocardial infarction in hypertension: analysis based on 11 major randomized intervention trials. Blood Press 10:190–192
19. International Society of Hypertension Writing Group (2003) International Society of Hypertension (ISH): statement on blood pressure lowering and stroke prevention. J Hypertens 21:651–663
20. Stamler J, Stamler R, Neaton JD (1993) Blood pressure, systolic and diastolic, and cardiovascular risks. Arch Intern Med 153:598–615
21. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF (1999) Isolated systolic hypertension. Prognostic information provided by pulse pressure. Hypertension 34:375–380
22. American Diabetes Association (2012) Standards of medical care in diabetes— 2012. Diabetes Care 53:S11–S63
23. Karapanayiotides T, Piechowski-Jozwiak B, van Melle G, Bogousslavsky J, Devuyst G (2004) Stroke patterns, aetiology, and prognosis in patients with diabetes mellitus. Neurology 62:1558–1562
24. Megherbi SE, Milan C, Minier D et al (2003) Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. Stroke 34:688–694

25. Manson JE, Colditz GA, Stampfer MJ et al (1991) A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med 151:1141–1147
26. Stamler J, Vaccaro O, Neaton JD, Wentworth D (1993) Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 16:434–444
27. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO (1998) Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. Neurology 50:208–216
28. Hier DB, Foulkes MA, Swiontoniowski M et al (1991) Stroke recurrence within 2 years after ischemic infarction. Stroke 22:155–161
29. Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CD (2003) Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. Stroke 34:1457–1463
30. McArthur KS, Quinn TJ, Higgins P, Langhorne P (2011) Post-acute care and secondary prevention after ischaemic stroke. BMJ 342:d2083
31. Rashid P, Leonardi-Bee J, Bath P (2003) Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. Stroke 34:2741–2748
32. The Dutch TIA Trial Study Group (1993) Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. Stroke 24:543–548
33. PATS Collaborating Group (1995) Post-stroke antihypertensive treatment study: a preliminary result. Chin Med J 108:710–717
34. HOPE Study Investigators (2000) Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 355:253–259
35. Carter AB (1970) Hypotensive therapy in stroke survivors. Lancet 1:485–489
36. Hypertension-Stroke Cooperative Study Group (1974) Effect of antihypertensive treatment on stroke recurrence. JAMA 229:409–418
37. Eriksson S, Olofsson BO, Wester PO (1995) Atenolol in secondary prevention after stroke. Cerebrovasc Dis 5:21–25
38. Arima H, Anderson C, Omae T et al (2011) Effects of blood pressure lowering on major vascular events among patients with isolated diastolic hypertension The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) Trial. Stroke 42:2339–2341
39. Czernichow S, Ninomiya T, Huxley R et al (2010) Impact of blood pressure lowering on cardiovascular outcomes in normal weight, overweight, and obese individuals. The Perindopril Protection Against Recurrent Stroke Study Trial. Hypertension 55:1193–1198
40. Schrader J, Lüders S, Kulchewski A et al (2005) Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention. Principal results of a prospective randomized controlled study (MOSES). Stroke 36:1218–1224
41. Yusuf S, Diener HC, Sacco RL et al (2008) Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 359:1225–1237
42. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators (2008) Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 372:1174–1183
43. Diener HC (2009) Preventing stroke: the PROFESS, ONTARGET, and TRANSCEND trial programs. J Hypertens 27(Suppl 5):S31–S36
44. Ovbiagele B, Diener HC, Yusuf S et al (2011) Level of systolic blood pressure within the normal range and risk of recurrent stroke. JAMA 306:2137–2144
45. White CL, Szychowski JM, Pergola PE, et al, for the Secondary Prevention of Small Subcortical Strokes Study Investigators (2015) Can blood pressure be lowered safely in older adults with lacunar stroke? The secondary prevention of small subcortical strokes study experience. J Am Geriatr Soc 63(4):722–729
46. Odden MC, McClure LA, Sawaya BP et al (2016) Achieved blood pressure and outcomes in the secondary prevention of small subcortical strokes trial. Hypertension 67:63–69

47. Zanchetti A, Liu L, Mancia G et al (2014) Blood pressure and LDL-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patient: design of the European society of hypertension-Chinese hypertension league stroke in hypertension optimal treatment randomized trial. J Hypertens 32:1888–1897
48. Kernan WN, Ovbiagele B, Black HR et al (2014) Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 45:2160–2236
49. Saposnik G, Goodman SG, Leiter LA et al (2009) Applying the evidence do patients with stroke, coronary artery disease, or both achieve similar treatment goals? Stroke 40: 1417–1424
50. ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB et al (2011) Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 364:818–828
51. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J et al (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358:2560–2572
52. Duckworth W, Abraira C, Moritz T et al (2009) Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 360:129–139

Hypertension and Subjective Cognitive Failures

14

Eila Monteagudo, Cristina Sierra, and Antonio Coca

14.1 Introduction

Cardiovascular disease (CVD) remains the leading cause of death among Europeans and people worldwide. The Global Burden of Disease Study estimated that, globally, 29.6 % of all deaths (15, 616.1 million) were caused by CVD in 2010, more than all communicable, maternal, neonatal and nutritional disorders combined, and twice the number of deaths caused by cancer [1]. The burden of CVD in Europe remains heavy, although the prevalence varies dramatically between countries. More than four million Europeans die of CVD every year, and many more are hospitalized after acute episodes or are treated for chronic cardiovascular ill health [2].

The percentage of the population affected by hypertension, one of the main risk factors for CVD, is remarkably high and, according to numerous studies, the prevalence will continue to increase as will that of coexisting diseases [3]. This increase has put hypertension under the spotlight of the health industry, which creates substantial implications for public policy and raises the need for health strategies in order to both manage and prevent hypertension and its consequences. Hypertension has three main target organs: the heart, the kidneys and the brain. All three are routinely assessed in hypertensive patients in the clinical setting in order to evaluate the deleterious effects of high blood pressure in the arteries and the structure of these organs. The evaluation of silent heart or kidney damage induced by hypertension in routine assessments was introduced some time ago, but the examination of the effects of high blood pressure on the brain remains less robust and is rarely carried out.

Despite this, progress in imaging techniques has led to an improvement in silent cerebral disease evaluation over the last decade. Therefore, investigating the degree of neurological damage has been added to the examination of heart and kidney

E. Monteagudo • C. Sierra • A. Coca (✉)
Hypertension and Vascular Risk Unit, Department of Internal Medicine, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain
e-mail: acoca@clinic.ub.es

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_14

complications, including the risk of stroke, dementia and problems in cognitive function. In fact, impaired cognitive function, along with hypertension, has become one of the leading and most devastating health problems worldwide. The incidence of cognitive decline is increasing rapidly, in tandem with the ageing population and the rise of vascular disease. Over time, this is leading to a significantly large number of people who are suffering a loss of autonomy and are becoming disabled. For this reason, there has been an increase in the diagnosis of cognitive disorders. However, this increase comprises not only severe disorders such as Alzheimer's disease and vascular dementia but also slighter changes in cognition, such as subjective cognitive failures (SCF).

In this chapter we synthesize current available evidence on SCF and its relationship with hypertension, as well as highlighting available antihypertensive treatment for SCF, focusing on the antihypertensive drugs proven to have a positive effect on the incidence of dementia.

14.2 Subjective Cognitive Failures

SCF, also known as subjective cognitive complaints, subjective cognitive impairment or subjective cognitive decline, are concerns about a person's cognitive function. They may be due to one's self-awareness or may be reported by someone close to the subject. SCF express complaints of poor cognitive function such as forgetting things a person should be familiar with or finding it difficult to remember the name of a close friend. SCF are especially common in elderly people and, normally, the first report of this memory complaint is presented to the family physician, who must decide whether it may be clinically relevant.

SCF are relevant in many disorders. A good example is that concerns about changes in cognition have been included as one of the diagnostic criteria for mild cognitive impairment [4]. In addition, some experts are starting to consider SCF as early markers or predictors of cognitive decline and even dementia, after finding independent associations between objective and subjective cognitive impairment [5]. In other words, these complaints are related to objective changes in cognition and, accordingly, might represent an early sign of cognitive dysfunction [6]. Thus, they provide a way of identifying subjects at risk of dementia.

14.3 Pathophysiology of Impairment in Cognitive Function

Several factors have been associated with SCF, although studies have shown different and even opposing relationships. Some of these associations might be expected, for example, those with cardiovascular risk factors such as hypertension, age or mood disorders, while others may be unexpected, like higher social class and having a college education, worse physical health or even gender [7], all of which have been linked with SCF. Two other interesting factors have been found to be related to cognitive dysfunction in patients with SCF: aortic stiffness and episodes of hypotension.

Age stands out as one of the most studied factors. However, despite often being associated with the elderly as a result of physiological ageing, SCF are not by any means confined to a specific age group, as found by numerous studies carried out in middle-aged rather than elderly people during recent decades [8]. Hence, age is considered a confounding factor in the presentation of cognitive decline and SCF, even though it has been shown that SCF may appear at earlier ages. Therefore, they should be referred to as a sign of a pathological process rather than regarding them exclusively as a condition that takes place during the natural course of life.

Another confounding factor in the progression of SCF is some affective disorders, particularly depression, which has led to differing opinions about whether SCF are a sign of cognitive dysfunction or simply the result of disorders in mood and affection. For instance, Montejo et al. [9] found that depression was a decisive factor in the process that leads to complaints about cognition but so was cognitive performance, while Miranda et al. [10] concluded that SCF are associated with objective memory impairment independently of depressive symptoms. On the other hand, Zlatar et al. [11] stated the SCF were more probably a consequence of depression instead of an outcome of concurrent cognitive impairment. Moreover, affective disorders have not only been considered crucial contributors to the presentation of SCF but also to their severity [12]. In any case, it is clear that depression is, practically without exception, related to SCF, which leads to the need to develop successful markers for the decline in cognition in order to decide whether a complaint is related to mood disorders or may be independently associated with objective impairment.

Aortic stiffness assessed by carotid-femoral pulse wave velocity (PWV) and episodes of hypotension have also been related to SCF. A study which investigated both factors found that a higher PWV, indicating an increase in aortic stiffness, together with a rise in arterial pulsatility led to remodelling of the microvascular system, resulting in microcirculation damage. This, together with increased vascular resistance and impairment in cerebral blood flow autoregulation, makes patients much more vulnerable to hypotension and even ischaemia, which results in cognitive decline. The resulting worse cognitive function may then be expressed by the patient as SCF, even when global cognitive function might appear normal [13].

14.4 The Role of Hypertension in Cognitive Decline

As stated, high blood pressure – the main object of this review – is one of the factors that may cause damage to several organs, of which the brain is one of the most vulnerable. Although the mechanisms are yet not fully understood, damage at both macrovascular and microvascular levels should be taken into account, as it is thought there are important interactions between the two levels [14]. Furthermore, it is likely that the vascular damage caused by hypertension represents a potential risk factor for cognitive dysfunction and that it contributes to cognitive decline through complex mechanisms which include hypertrophy and contraction of smooth muscle vascular vessels – leading to a reduced lumen and increased vascular resistance – endothelial

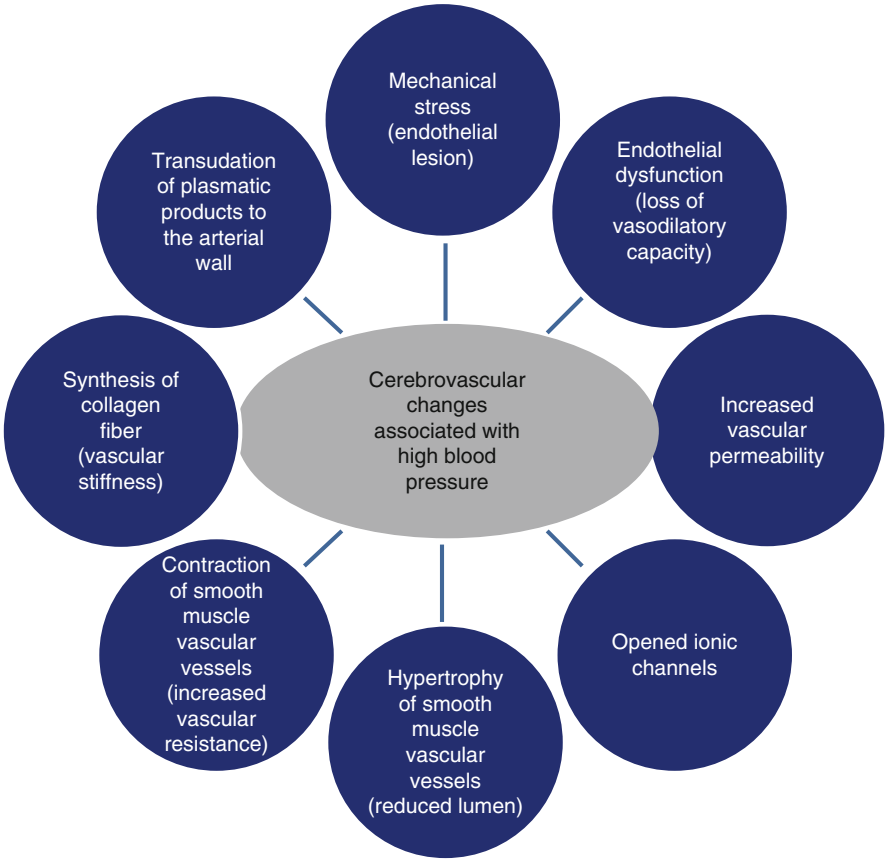

Fig. 14.1 Main cerebrovascular pathophysiological changes related to hypertension (Modified from Ref. [16])

lesions and dysfunction and increased vascular stiffness due to the synthesis of collagen fibres [15]. These mechanisms, which are shown in Fig. 14.1, may alter cerebral blood flow, metabolism and structure.

With respect to the early cerebrovascular damage that hypertension may cause, there are different pathological processes that might be implicated, and a differentiation should be made between functional and structural abnormalities. These possible processes are shown in Fig. 14.2. It seems clear that essential hypertension may be implicated in the development of cognitive impairment and that this is associated with cerebral small vessel disease (cSVD). In some cases this damage is silent and may only be detected by radiological findings, particularly magnetic resonance imaging (MRI). Moreover, over the past few years, there has been a considerable increase in reports investigating the relationship between SCF and markers of cSVD, which has led to the hypothesis that complaints are probably an indication of brain changes, even when no objective cognitive decline can be confirmed.

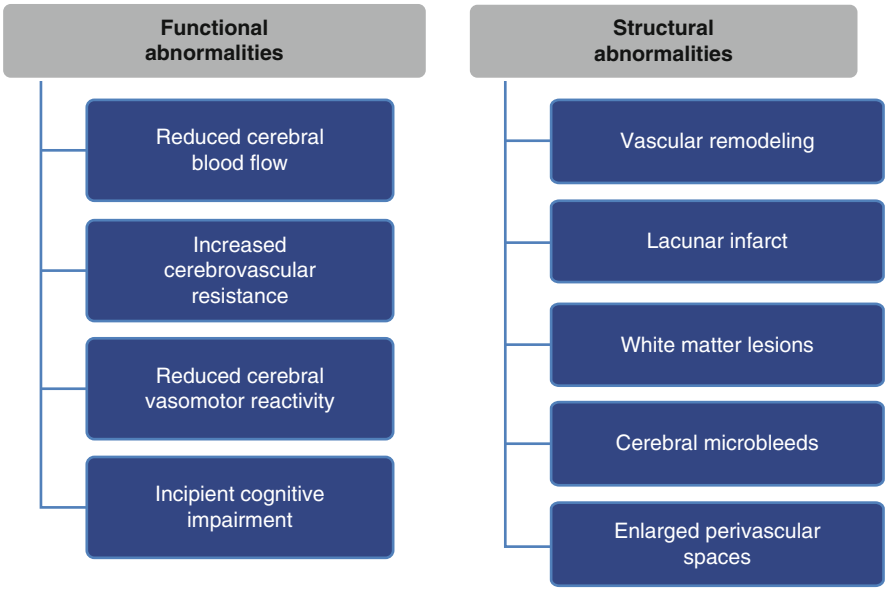

Fig. 14.2 Functional and structural changes observed at an early stage of cerebrovascular damage related to hypertension (Modified from Ref. [16])

More articles have been published on the issue of cognitive decline and hypertension in the last 5 years than in the previous thirty. As stated, the theory that SCF appear due to factors like depression has prevailed over many years as a result of the invariably strong relationship between them. However, this assumption is now being challenged by more recent research which has found an association between cSVD and both objective and subjective complaints [17].

Nevertheless, research studying the association between SCF and hypertension is still limited in some aspects. As stated, hypertension is known to be a modifiable vascular risk factor which can lead to cSVD and cognitive impairment which, in turn, can be studied by MRI. In fact, in a study by van Norden et al. [18] concluded that SCF has a detectable radiologic pathologic-anatomic substrate. Thus, MRI could become a tool to find surrogate markers of cSVD, which would be important for the study of silent brain damage.

14.5 Structural Bases of Cognitive Decline

There are four main signs of cSVD that may appear as a result of hypertension and can be detected and seen by MRI. These are white matter hyperintensities (WMH), cerebral microbleeds (CMB), lacunar infarcts (LI) and enlarged perivascular spaces (EPS). Markers of vascular changes, either structural or functional, may be related to these four signs, as shown in Fig. 14.2.

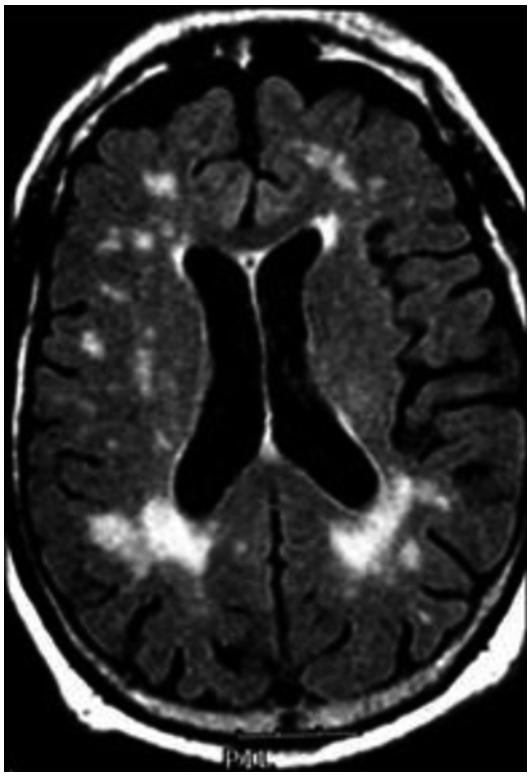

Fig. 14.3 Axial plane of a FLAIR MRI sequence. The hyperintense areas in the parenchyma correspond to white matter lesions that appear as a result of microvascular alterations and ischaemia

1. *White matter hyperintensities*: Microvascular alterations caused by hypertension may lead to hypoperfusion, hypoxia and ischaemia in the terminal distributions of the affected vessels. When these territories contain white matter, this process will alter it and cause a loss of myelin. These white matter lesions can then be seen as hyperintensities in T2-weighted MRI images (see Fig. 14.3). Kearney-Schwartz et al. [19] found that microvascular alterations such as arterial stiffening and endothelial dysfunction correlated with cognitive impairment and WMH in a population of elderly hypertensive subjects who presented memory complaints. Moreover, the study also found that the severity of WMH is inversely associated with memory function scores. Thus, studies seem to imply that hypertension is a major risk factor for WMH which, in turn, can lead to cognitive dysfunction or dementia.
2. *Cerebral microbleeds*: CMB are another sign of hypertension-related cSVD. They also participate, as vascular factors, in neurodegenerative disorders and can be seen on MRI, where they are defined as punctuate homogenous foci of low signal intensity on T2-weighted images (Fig. 14.4). It has been proposed that, depending on the location in the brain, CMB might have different etiologies. Hypertension, together with atherosclerosis, is thought to increase the risk of CMB in deep or infratentorial areas [20]. CMB have been associated with SCF

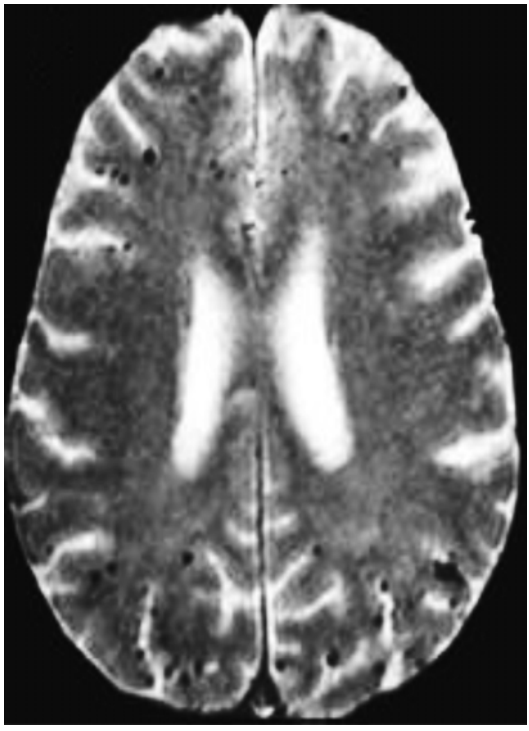

Fig. 14.4 MRI sequence (gradient-echo sequence) of small foci of hypointensities. These low signal intensity lesions correspond to cerebral microbleeds

in a study that emphasized the need to actively inquire about cognitive complaints in hypertensive patients, as they may represent a symptom of cognitive impairment caused by CMB [21]. This study highlighted the need for consideration of both neuropsychological assessment and brain imaging in these patients. Another study found that CMB are related to SCF, independently of WMH and LI, and suggested they are associated with the earliest expressions of cognitive impairment. The study made no adjustment for vascular risk factors such as hypertension, as they were accepted as an important component of the causal sequence between CMB and SCF [17].

3. *Lacunar infarcts*: These are identified as sharply demarcated hyperintense lesions in T2-weighted images, with corresponding hypointense lesions with a hyperintense rim on Fluid-attenuated inversion recovery (FLAIR). They have also been linked to cognitive functioning, although their contribution to impairment has not yet been definitively established. The number of LI has been found to be a significant predictor of executive performance, with a higher number of LI being associated with poorer execution, even in subjects who were considered to be cognitively and functionally normal [22]. New LI onset on MRI has been associated with a steeper decline in executive functioning and psychomotor speed, although no relationship was found with memory or global cognitive function [23]. Moreover, studies have investigated the effects of LI on different cognitive domains in cases in which there is a combination of vascular changes.

One study focused on both LI and WMH and the domains of memory, processing speed and motor function in the elderly and found a solid association between the two signs of cSVD in all three domains. The study concluded that both WMH and LI had negative effects on cognition, which were greater when the two brain lesions were combined rather than presenting alone [24].

4. *Enlarged perivascular spaces*: EPS (also known as Virchow-Robin spaces) are also a marker of cSVD [25] and are thought to determine cognitive impairment in small vessel disease. They appear as rounded or linear-shaped lesions with a smooth margin and an absence of mass effect and are isointense to cerebrospinal fluid on T2-weighted images but hypointense on FLAIR images without a hyperintense rim. Like LI, they frequently coexist with WMH and other brain lesions. Although there are few studies on the subject, it has been postulated that an MRI finding of EPS probably implies decreased cognitive function, even in healthy subjects [26].

In summary, WMH, CMB, LI and EPS have all been identified as lesions which appear as a result of cSVD. They represent silent damage to the brain and, although they have mostly been studied individually and each has been linked to impaired cognition, they also correlate strongly with each other. A study by Huijts et al. [27] which investigated the combined effect of these markers on different domains of cognitive function (memory, executive function, information processing speed and overall cognition) found that the accumulation of these markers of brain damage resulted in worse cognitive functioning. Additionally, all four markers of silent damage have been linked to hypertension and cognitive function, and, as stated, relationships between objective and subjective cognitive impairment have been shown [5].

14.6 Prevention of Cognitive Impairment by Antihypertensive Treatment: Current Evidence

Throughout this chapter we have presented a large amount of research and information explaining the importance of hypertension and its relationship with cognitive function and dementia. Therefore, the question is: Is it possible to stop or delay the onset of dementia or cognitive impairment or its progression if changes in cognitive function have already been detected, either objectively or subjectively, by reducing blood pressure levels?

Many studies have investigated the potential effects of blood pressure reduction on cognition. A meta-analysis by Levi et al. [28] investigated the impact that different antihypertensive drugs had on dementia and cognitive functioning and concluded that treating high blood pressure reduced the incidence of cognitive impairment and dementia. This beneficial effect was observed for overall cognition and all cognitive functions except for language, with a reduction in risk of dementia of 9 %. Their suggestion for the absence of a favourable effect on language was that the area that controls this function might remain unaffected by hypertension. However, not all studies have shown this beneficial effect, and there is, as yet, no consensus [29].

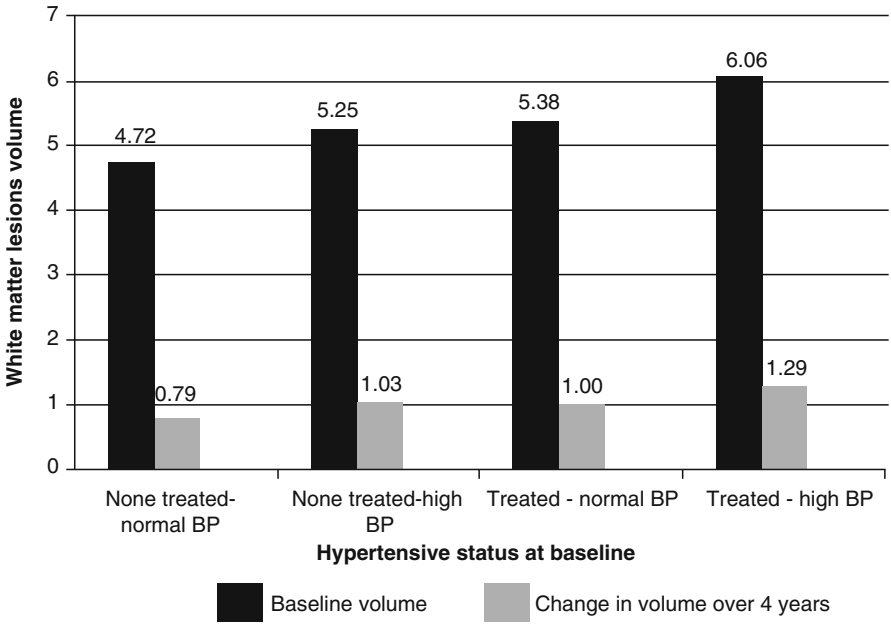

Fig. 14.5 Association between high blood pressure and antihypertensive treatment and WMH load and change in volume over 4 years (Modified from Ref. [30])

Godin et al. [30] investigated the incidence and progression of WMH in hypertensive patients. Blood pressure and the WMH total volume were measured in patients aged ≥65 years over a 4-year period, with the difference in WMH volume being measured by MRI at baseline and after 4 years. The study found that WMH were not only much more frequent in older patients and those diagnosed with hypertension, diabetes or stroke but also in patients with uncontrolled blood pressure despite sustained antihypertensive treatment. Moreover, more rapid progression of the lesions was associated with a steeper decrease in global cognitive performance throughout the 4-year follow-up. Two aspects associated with blood pressure were considered strong predictors of the progression of WMH volume, independently of confounders: blood pressure levels at baseline and changes in blood pressure during the 4-year follow-up. With respect to the effects of antihypertensive treatment on the progression of WMH, the study found a slowed progression in patients who had started effective treatment on entry to the study, especially those who had higher systolic blood pressure at baseline. Comparison of the volumes of WMH of treated patients who achieved strict blood pressure control with those who did not, despite receiving treatment, showed the former had less WMH progression. Figure 14.5 shows the interaction between high blood pressure levels and antihypertensive treatment and their relationship with WMH load at baseline and their progression over 4 years.

14.7 Are There Preferred Antihypertensive Drugs to Prevent Cognitive Impairment and Dementia?

Antihypertensive drugs that have been shown to have a beneficial effect include calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs) and their combination with thiazide or thiazide-like diuretics and angiotensin receptor blockers (ARBs) [28, 29]. Not all studies investigating specific classes of antihypertensive drugs or their combinations have reached the same conclusions, and some have even found that some drugs may have a detrimental effect on cognition. ARBs have shown an important beneficial effect and have been proposed by some authors as the most effective in preventing dementia and cognitive decline, not only when compared to placebo but also when studied in comparison with other drugs like β-blockers, ACEIs or thiazide diuretics [28]. It is reported that subjects receiving ARBs had superior cognitive performance compared to those receiving placebo. This superiority was also seen when compared with the other types of drugs, except for CCBs, suggesting that ARBs and CCBs have a greater protective effect. The mean decrease in blood pressure was similar between the different drugs, which might be interpreted as meaning that not only reductions in blood pressure are favourable for cognitive function but that there might perhaps be specific mechanisms of action that differ between the diverse classes of antihypertensive drugs and may also play a role in their effect on cognition [28].

With respect to class-specific effects, there are different interpretations of the mechanisms by which the positive effect is achieved, and some hypotheses have been proposed to explain these differences. On the one hand, ARBs might accomplish their beneficial effect by blocking AT1 receptors which, in turn, increase the action of endogenous angiotensin II via AT2 receptors, leading to a memory-enhancing effect. The blockage of AT1 receptors might also increase the synthesis of angiotensin IV which, in turn, activates AT4 receptors, which are involved in memory acquisition and recall [28]. On the other hand, the ACEI perindopril might offer protection via its lipophilicity, which allows its inhibitory action on the angiotensin-converting enzyme to occur at the cerebral level, resulting in an increase in cholinergic neurotransmission that would mitigate the decline in cognition [29]. Lipophilicity is also an outstanding characteristic shared by some CCBs that could explain their beneficial effects on cognition. Lercanidipine has a highly lipophilic profile and might have an antiatherogenic effect but may also inhibit the death of cerebral neurons, as already shown in rat models [29].

Nevertheless, the evidence that some antihypertensive drugs are better than others in reducing cognitive decline is not robust or supported by randomized clinical trials. At present, the evidence only shows that reductions in blood pressure due to antihypertensive drugs delay the incidence of dementia compared with placebo. Randomized controlled clinical trials are warranted to establish which is the best antihypertensive strategy and by which mechanisms cognitive impairment related to hypertension might be prevented or delayed.

14.8 Summary and Conclusions

Subjective cognitive failures are a reflection of a pathological process occurring in the brain, for which hypertension, together with other associated cardiovascular risk factors, may bear a large share of the blame. For this reason, the detection of early cognitive complaints in hypertensive patients is important. Patients with hypertension presenting SCF should be tested for objective cognitive dysfunction because, although further studies are required to examine the long-term predictive value of SCF in hypertensive patients, they may be an early predictor of dementia. In addition, extensive study of the brain function and structure in these patients should be performed as a part of the target organ damage evaluation to stratify the total cardiovascular risk. This evaluation should include both a neuropsychological assessment and brain MRI. With respect to the neuropsychological assessment, further research is required to develop more valid, sensitive and adequate cognitive tests capable of detecting hypertensive patients with cognitive complaints at the general practitioner's office, in order to instigate preventive measures aimed at stopping or delaying the progression of cognitive decline in patients at risk as early as possible. Randomized double-blind controlled clinical trials of antihypertensive treatments are required to determine the best blood pressure target and the best antihypertensive strategy in these patients.

References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V et al (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2095–2128
2. Nichols M, Townsend N, Scarborough P, Rayner M (2014) Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 35:2950–2959
3. Hajjar I, Kotchen JM, Kotchen TA (2006) Hypertension: trends in prevalence, incidence, and control. Annu Rev Public Health 27:465–490
4. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC et al (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:270–279
5. Begum A, Dewey M, Hassiotis A, Prince M, Wessely S, Stewart R et al (2014) Subjective cognitive complaints across the adult life span: a 14-year analysis of trends and associations using the 1993, 2000 and 2007 English Psychiatric Morbidity Surveys. Psychol Med 44: 1977–1987
6. Stewart R, Godin O, Crivello F, Maillard P, Mazoyer B, Tzourio C et al (2011) Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. Br J Psychiatry 198:199–205
7. Montenegro M, Montejo P, Claver-Martín MD, Reinoso AI, De Andrés-Montes ME, García-Marín A et al (2013) Relación de las quejas de memoria con el rendimiento de memoria, el estado de ánimo y variables sociodemográficas en adultos jóvenes. Rev Neurol 57:396–404
8. Eckerström M, Skoogh J, Rolstad S, Göthlin M, Steineck G, Johansson B et al (2013) Sahlgrenska Academy Self-reported Cognitive Impairment Questionnaire (SASCI-Q)-a research tool discriminating between subjectively cognitively impaired patients and healthy controls. Int Psychogeriatr 25:420–430

9. Montejo P, Montenegro M, Fernandez MA, Maestu F (2011) Subjective memory complaints in the elderly: prevalence and influence of temporal orientation, depression and quality of life in a population-based study in the city of Madrid. Aging Ment Health 15:85–96
10. Miranda B, Madureira S, Verdelho A, Ferro J, Pantoni L, Salvadori E et al (2008) Self-perceived memory impairment and cognitive performance in an elderly independent population with age-related white matter changes. J Neurol Neurosurg Psychiatry 79:869–873
11. Zlatar ZZ, Moore RC, Palmer BW, Thompson WK, Jeste DV (2014) Cognitive complaints correlate with depression rather than concurrent objective cognitive impairment in the successful aging evaluation baseline sample. J Geriatr Psychiatry Neurol 27:181–187
12. Buckley R, Saling MM, Ames D, Rowe CC, Lautenschlager NT, Macaulay SL et al (2013) Factors affecting subjective memory complaints in the AIBL aging study: biomarkers, memory, affect, and age. Int Psychogeriatr 25:1307–1315
13. Scuteri A, Tesauro M, Guglini L, Lauro D, Fini M, Di Daniele N et al (2013) Aortic stiffness and hypotension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss. Int J Cardiol 169:371–377
14. Triantafyllidi H, Arvaniti C, Lekakis J, Ikonomidis I, Siafakas N, Tzortzis S et al (2009) Cognitive impairment is related to increased arterial stiffness and microvascular damage in patients with never-treated essential hypertension. Am J Hypertens 22:525–530
15. Sierra C, Doménech M, Camafort M, Coca A (2012) Hypertension and mild cognitive impairment. Curr Hypertens Rep 14:548–555
16. Sierra C, Coca A (2014) Brain damage. In: Mancia G, Grassi G, Redon J (eds) Manual of hypertension of the European Society of Hypertension, 2nd edn. Informa Healthcare, London, pp 177–189
17. Van Norden AGW, van Uden IWM, de Laat KF, Gons RAR, Kessels RPC, van Dijk EJ et al (2013) Cerebral microbleeds are related to subjective cognitive failures: the RUN DMC study. Neurobiol Aging 34:2225–2230
18. Van Norden AGW, Fick WF, de Laat KF, van Uden IWM, van Oudheusden LJB, Tendolkar I et al (2008) Subjective cognitive failures and hippocampal volume in elderly with white matter lesions. Neurology 71:1152–1159
19. Kearney-Schwartz A, Rossignol P, Bracard S, Felblinger J, Fay R, Boivin JM et al (2009) Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke 40:1229–1236
20. Jia Z, Mohammed W, Qiu Y, Hong X, Shi H (2014) Hypertension increases the risk of cerebral microbleed in the territory of posterior cerebral artery: a study of the association of microbleeds categorized on a basis of vascular territories and cardiovascular risk factors. J Stroke Cerebrovasc Dis 23:e5–e11
21. Uiterwijk R, Huijts M, Staals J, Duits A, Gronenschild E, Kroon AA et al (2014) Subjective cognitive failures in patients with hypertension are related to cognitive performance and cerebral microbleeds. Hypertension 64:653–657
22. Carey CL, Kramer JH, Josephson SA, Mungas D, Reed BR, Schuff N et al (2008) Subcortical lacunes are associated with executive dysfunction in cognitively normal elderly. Stroke 39:397–402
23. Jokinen H, Gouw AA, Madureira S, Ylikoski R, van Straaten ECW, van der Flier WM et al (2011) Incident lacunes influence cognitive decline: the LADIS study. Neurology 76: 1872–1878
24. Baune BT, Roesler A, Knecht S, Berger K (2009) Single and combined effects of cerebral white matter lesions and lacunar infarctions on cognitive function in an elderly population. J Gerontol A Biol Sci Med Sci 64:118–124
25. Potter GM, Doubal FN, Jackson CA, Chappell FM, Sudlow CL, Dennis MS et al (2015) Enlarged perivascular spaces and cerebral small vessel disease. Int J Stroke 10(3):376–381
26. Maclullich AMJ, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ et al (2004) Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. J Neurol Neurosurg Psychiatry 75:1519–1523

27. Huijts M, Duits A, van Oostenbrugge RJ, Kroon AA, de Leeuw PW, Staals J et al (2013) Accumulation of MRI markers of cerebral small vessel disease is associated with decreased cognitive function. A study in first-ever lacunar stroke and hypertensive patients. Front Aging Neurosci 5:72
28. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P (2013) Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens 31:1073–1082
29. Coca A (2013) Hypertension and vascular dementia in the elderly: the potential role of antihypertensive agents. Curr Med Res Opin 29:1045–1054
30. Godin O, Tzourio C, Maillard P, Mazoyer B, Dufouil C (2011) Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: the Three-City (3C)-Dijon Magnetic Resonance Imaging Study. Circulation 123:266–273

Hypertension, Cognitive Decline, and Dementia

15

Cristina Sierra, Augusto Vicario, and Ona Escoda

15.1 Introduction

Cognitive impairment is becoming increasingly common with the aging of societies and causes an immense social, economic, and emotional burden [11]. A greater understanding of the mechanisms leading to cognitive impairment with aging is becoming a top priority for research and public health.

Dementia has many etiologies, but the most common are Alzheimer's disease (AD) and vascular dementia (VD). VD had traditionally been considered secondary to vascular disease and distinguished from AD, considered to be a purely neurodegenerative form of dementia. However, these two conditions often coexist, and there is strong evidence for a continuous spectrum of disease [38], suggesting an association between vascular risk factors and dementia, including AD. Chronic hypertension, particularly midlife high blood pressure (BP), has been associated with an increased risk for cognitive decline, VD, and AD [20, 36].

Indeed, there has been long-standing interest in a possible cause-and-effect relationship between elevated BP and cognitive outcome. The relationship has been debated over time and continues to be a focus of controversy, especially in terms of BP lowering as a means to prevent cognitive decline or dementia [50]. Despite the uncertainty surrounding a benefit of BP lowering to prevent cognitive decline or dementia, there is mounting mechanistic and epidemiologic evidence to link elevated BP to loss of cognition [50].

C. Sierra, MD, PhD (✉) • O. Escoda
Hypertension and Vascular Risk Unit, Department of Internal Medicine, Hospital Clinic (IDIBAPS), University of Barcelona, Barcelona, Spain
e-mail: csierra@clinic.ub.es

A. Vicario
Heart and Brain Unit. Department of Clinical Cardiology, Cardiovascular Institute of Buenos Aires (ICBA), Buenos Aires, Argentina

A. Coca (ed.), *Hypertension and Brain Damage*, Updates in Hypertension and Cardiovascular Protection, DOI 10.1007/978-3-319-32074-8_15

The mechanisms by which vascular risk factors increase the risk of developing cognitive impairment are not fully elucidated. Most of these factors, especially hypertension, have been shown to be associated with subcortical lesions seen on brain magnetic resonance imaging (MRI): white matter lesions (WML), lacunar infarctions, or cerebral microbleeds [34, 51].

A large number of studies have reported strong relationships between indices of vascular aging, such as arterial stiffness, and either cognitive impairment or silent cerebral small vessel disease [44]. The exposure of small vessels to highly pulsatile pressure and flow may explain microvascular damage (especially periventricular WML) and resulting intellectual deterioration [44] and the pathogenesis of AD [15].

A third of AD might be attributable to potentially modifiable risk factors (physical inactivity, smoking, midlife hypertension, midlife obesity, diabetes, and depression) [31]. Recent publications have reported that the incidence of dementia is declining, and this trend may obey to education quality improvements and better control of vascular risk factors [22].

Observational and epidemiological studies have shown that antihypertensive therapy could have protective effects on cognitive impairment and dementia [11]. However few large BP-lowering trials have incorporated cognitive assessment or a diagnosis of dementia and the results are controversial. Meta-analyses of these trials neither prove nor disprove the efficacy of antihypertensive treatment on dementia risk [11].

15.2 Clinical Aspects of Cognitive Impairment

Cognitive impairment is defined by a progressive decline of some cognitive functions that does not satisfy the diagnostic criteria of dementia. It precedes at least 50 % of dementia onsets. Cognitive impairment can be assessed by neuropsychological tests, because it is not necessarily evident in daily living. Cognitive decline can affect the memory or other domains (perception, abstract thought, judgment, planning ability, and attention). Dementia is characterized by an intellective deterioration that includes memory loss and one or more other neuropsychological alterations, such as apraxia, agnosia, and aphasia, which interfere with social and occupational living. Mental alterations include progressive memory loss, space and temporal disorientation, loss of self-sufficiency, and emotional depersonalization.

Vascular cognitive impairment (VCI) refers to the entire spectrum of vascular-related cognitive impairment, from mild to severe. Assessment of VCI requires a comprehensive cognitive battery that includes an evaluation of executive, memory, language, and spatial functions.

Cognitive impairment and dementia are one of the principal neurological disorders in the elderly. Aging is associated with a marked increase in the prevalence and incidence of degenerative and VD. The estimated prevalence is around 8 % in people aged ≥65 years and 15–20 % in those aged >80 years [36]. AD accounts for 50–60 % of cases of dementia and VD for 30 %. It is known that the prevalence of AD doubles every 4.3 years and that of VD every 5.3 years [11].

Hypertension is a major risk for cerebrovascular disease and therefore for VD. Traditionally, AD has been considered as a primary neurodegenerative disorder and not of vascular origin. However as mentioned before, emerging evidence supports the view that vascular risk factors and disorders may be involved in AD [2, 23, 46]. It appears that there is a continuous spectrum ranging from patients with pure VD to patients with pure AD and including a large majority of patients with contributions from both Alzheimer and vascular pathologies [51].

15.3 Pathological Aspects of Cerebral Microvascular Disease Related to Cognitive Impairment

The most common form of VCI is the subcortical type [34]. There are different types of small vessel disease according to their pathogenesis. The two most frequent are arteriolosclerosis and cerebral amyloid angiopathy [34]. Multiple biological systems are involved in the pathogenesis of cerebrovascular disease (Table 15.1) [42]. Arteriolosclerosis is also known as age-related and vascular risk factor-related small vessel disease. Pathologically, this kind of small vessel disease is mainly characterized by loss of smooth muscle cells from the tunica media, deposits of fibrohyaline material, narrowing of the lumen, and thickening of the vessel wall. This form of the disease is a common and systemic type that also affects the kidneys and retinas and is strongly associated with aging, diabetes, and, in particular, hypertension [34]. For this reason it is also named hypertensive small vessel disease. Other possible pathological features of this form of microangiopathy are distal manifestations of atherosclerosis (microatheroma) and the presence of elongated and dilated vessels (microaneurysms).

Hypertension and its consequent vascular brain damage compromise the functioning of the blood-brain barrier and predispose to accumulation of beta-amyloid at both the brain parenchyma and vascular level [5, 37].

Cerebral amyloid angiopathy is characterized by the progressive accumulation of congophilic, βA42 immunoreactive, amyloid protein in the walls of small-to-medium-sized arteries and arterioles predominantly located in the leptomeningeal

Table 15.1 Mechanisms of vascular aging and age-related brain changes that increase vascular vulnerability in the elderly and increase the risk of cerebrovascular disease

Vascular aging	Age-related brain changes
Oxidative stress and endothelial dysfunction	Increased brain-blood barrier permeability
Low-grade inflammation	Tortuosity of white matter arterioles
Increased arterial stiffness	Reduced brain weight, expanded ventricles, increased choroids plexus volume
Upregulation of renin-angiotensin system	Small vessel disease
Impaired endothelial progenitor cell function	Cerebral amyloid angiopathy

Adapted from Ref. [42]

space, in the cortex, and, to a lesser extent, also in the capillaries and veins. Cerebral amyloid angiopathy is a pathological hallmark of AD, in which it is almost invariably seen [19]. The beta-amyloid accumulation results from failure of beta-amyloid clearance from the brain [27]. This angiopathy is also very frequent in the general elderly population, and its frequency increases with age, occurring in up to 50 % of individuals in the ninth decade [28]. There is also an association between cerebral amyloid angiopathy and microbleeds on MRI [21], and it has also been associated with the presence of cerebral ischemic changes such as WML and microinfarcts [18].

15.4 High Blood Pressure, Cerebral Circulation, and Cognition Function

High BP influences the cerebral circulation, causing adaptive vascular changes. Chronic intraluminal pressure stimulates the growth of smooth muscle cells and enhanced media thickness in resistance arteries that results in hypertrophic remodeling. Alternatively, inward remodeling may occur, leading to eutrophic remodeling. Thus, hypertension influences the autoregulation of cerebral blood flow by shifting both the lower and upper limits of autoregulatory capacity toward higher BP, while hypertensive patients may be especially vulnerable to episodes of hypotension, which may play a role in the development of silent cerebrovascular damage such as WML [34].

Hypertension accelerates arteriosclerotic changes in the brain predisposing to atheroma formation in large diameter blood vessels and arteriosclerosis and arteriolar tortuosity of small vessels of the cerebral vasculature. These vascular changes, which include medial thickening and intimal proliferation, result in a reduced luminal diameter, increased resistance to flow, and a decline in perfusion [3, 34]. This hypoperfusion can produce discrete regions of cerebral infarction and diffuse ischemic changes in the periventricular and deep white matter causing vascular cognitive impairment and may also contribute to the pathogenesis of AD by destabilizing neurons and synapses [3].

AD and VCI are the two leading causes of cognitive impairment with the former characterized by early loss of episodic memory and the latter typically involving impairment of attention, information processing, and executive function [32].

15.5 Hypertension and Risk of Cognitive Impairment

Long-term observational studies have reported that hypertension during midlife increases risk of cognitive impairment later in life [43]. In addition, there is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment or vascular dementia through BP control [38]. By contrast, the effects of late-life BP on the brain are complex and less clear. In fact, several studies, particularly in old individuals or in patients with high cardiovascular risk, suggest that lower BP contributes to brain atrophy, cerebrovascular lesions, and

more rapid cognitive decline [36]. Although it is established that hypertension impairs cognition, one of the key issues still unsettled concerns the temporal relationships between BP elevation and cognitive decline. On the one hand, cross-sectional studies indicated that individuals with dementia have lower blood pressure, challenging the involvement of hypertension [16, 45]. On the other hand, longitudinal studies, in which patient were followed for decades, revealed that individuals that develop dementia have a history of high BP earlier in life [16].

Some studies have reported an increased incidence of dementia and AD in people with low diastolic or systolic BP, especially in people aged ≥80 years [36]. The severity of atherosclerosis increases with age, resulting in high SBP and low DBP in later life. Severe atherosclerosis in the very elderly, as well as episodic or sustained hypotension and, possibly, excessive treatment of hypertension, may induce cerebral hypoperfusion, ischemia, and hypoxia in this age group.

The mechanisms underlying hypertension-related cognitive changes are complex and not yet fully understood. As mentioned before, microvascular dysfunction and damage induced by hypertension leads to white matter disease, microinfarcts, and microhemorrhages, alterations closely correlated with the cognitive dysfunction [16].

15.6 Hypertension and Cerebral Small Vessel Disease: Which Cognitive Domains Are Affected?

As mentioned before, limited but growing literature indicates that microvascular brain damage is a potent risk factor for cognitive decline in older individuals, especially hypertensives, and for the onset of dementia. Neuropsychological evaluation and also neuroimaging are required for assessment of its clinical consequences.

Each and every middle-aged or older individual with high CV risk and/or evidence of stiffer and thicker large arteries should be screened for cognitive function and followed up for cognitive deterioration. Mild cognitive decline is a recently described syndrome that is thought to constitute a transition phase between healthy cognitive aging and dementia.

A major unsolved issue is whether there are cognitive domains specifically affected by cerebral small vessel disease and whether they differ from those more commonly detected in age-associated cognitive decline or in AD [40]. Although small vessel disease is commonly detected in patients with AD, there is a general hypothesis that cerebral small vessel disease electively and predominantly affects executive function, with slower information processing, impairment of the ability to shift from one task to another, and deficits in the ability to hold and manipulate information [40]. Executive functions are not explored by the mini mental state examination (MMSE), the most widely adopted test for clinical screening of global cognitive function, which has a low sensitivity for VCI. The National Institute of Neurological Disorders and Stroke-Canadian Stroke Network harmonization standard has proposed the use of the Montreal Cognitive Assessment (MoCA) [12]. This newly designed screening test incorporates subtests assessing executive functions and psychomotor speed [29] that are frequently impaired in VCI.

Ideally, neuropsychological evaluation should include tests exploring multiple cognitive domains: executive function and activation, language, visuospatial ability, and memory. Efforts are being made to identify whether one brief test can provide useful insight into different domains, anatomical regions, and brain networks [40].

Impairments in attention, perceptual processing, and executive function reflect more specific damage to deep subcortical white matter circuits, many of which are located in the internal watershed area of the frontal lobe [6]. Chronic hypertension has a disproportionate effect on these areas because accelerated arteriosclerotic changes in non-communicating perforating arteries may not be reversible by BP reduction once established [4]. Furthermore, episodic or sustained hypotension and, possibly, excessive treatment of hypertension may induce cerebral hypoperfusion, ischemia, and hypoxia that may, in turn, compromise neuronal function and eventually evolve to a neurodegenerative process [3].

15.7 How to Assess Cognitive Decline in Routine Clinical Practice

Unlike heart and kidney damage, silent structural and functional brain damage is usually underdiagnosed because it is not evaluated in routine clinical practice. Around 35 % of hypertensive patients have silent structural brain damage (WML, lacunar infractions, or microbleeds) without simultaneous heart or kidney damage [52]. Detection of silent vascular brain injury (VBI) is very important because the burden and its progression are closely related to hypertension treatment and BP control. Although MRI is considered the gold standard to assess silent structural damage, these silent lesions are related to cognitive status, which is not routinely assessed in clinical practice, and the early detection of cognitive dysfunction may be a costless alternative to assess brain damage induced by hypertension. The Healthy Heart Cognition Study, a cardiovascular prevention program in Villa María city (Argentina) that studied 1500 individuals, demonstrated that systolic BP increases as cognitive function decreases during the lifetime [53]. Therefore, assessing the cognitive status is an approach to the VBI, because there is growing evidence that VBI is related to the level of cognition.

The MMSE has been the most widely used tool to assess the cognitive status since 1975 and has been cited in more than 25,000 articles [54]. It is a screening tool for orientation, attention, memory, language, and visuoconstruction; i.e., it is useful to evaluate global cognition. Nevertheless, it has some weak points: It is influenced by age and educational level, it has low sensibility, and it does not explore executive function.

Executive dysfunction is the cognitive impairment characteristic of VBI that results from hypertensive damage to the small vessels [55, 57]. Arterial hypertension increases the risk of executive dysfunction fivefold [56]. High BP results in demyelination of the association fibers in the periventricular white matter and disconnects the dorsolateral prefrontal cortex from the subcortical structure (basal ganglia). The executive functions are those that allow us to plan, have abstract thoughts,

mental flexibility, processing speed, and working memory. These functions allow us to make decisions in daily activities.

In our experience, the clock drawing test (CDT) is a simple, fast, and easy to administrate test that evaluates executive function, and it is not influenced by age or educational level. Drawing a big circle on the paper, we give the patient two orders: first, draw all the numbers in the circle in order and the correct position; second, draw the hands pointing at "twenty to four." Lack of planning or spatial organization, the inability to transcode or draw the clock's hand, and impairment of setting the time or perseverations are some common mistakes observed (Fig. 15.1).

Other brief tests include the MoCA test [12] and the minimal cognitive examination [58]; however, in clinical practice, a rapid screening method such as the CDT is very useful in detecting cognitive impairment in hypertensive patients (Fig. 15.2) and may be better than the MMSE, because executive function is the cognitive domain most affected and possibly the first to be affected. The CDT detects a mean of 20 % more cognitive impairment more than the MMSE (Fig. 15.3). This trend changes in patients aged ≥80 years, possibly due to greater impairment in other cognitive domains (memory, orientation) that are evaluated by the MMSE.

Assessment of the cognitive status in hypertensive patients is essential because, in some cases, cognitive function may decline more than normal aging and crosses different thresholds. The first threshold is the cognitive one, with patients suffering from mild cognitive impairment; later the functional threshold is crossed, with patients losing autonomy and presenting the first symptoms of dementia or AD. The relationship between normal aging and dementia is dynamic and timely intervention can promote the regression, stabilization, or slowing in the progression of cognitive impairment. This was demonstrated by the FINGER study, in which a multidomain intervention (diet, exercise, cognitive training, and vascular risk monitoring) was able to improve or maintain cognitive functioning in at-risk elderly people [30].

15.8 Cognitive Impairment: Connecting Large Arteries and Cerebral Small Vessel Disease

The association between large artery stiffening and cognitive impairment has been reported by several cross-sectional studies and has been confirmed in longitudinal studies [44]. The mechanism of such association has not yet been firmly established. It is hypothesized that the relationship between arterial stiffness and cognition may be mediated by small vessel disease. A recent systematic review suggests an association between arterial stiffness and cerebral small vessel disease and arterial stiffness and decreased cognitive function [44]. However, the clinical use of arterial stiffness as a predictor of cognitive decline is yet to be established [44].

Cerebral circulation has specific characteristics making the brain continually and passively perfused at high flow throughout systole and diastole [33]. As mentioned before cerebrovascular autoregulation maintains cerebral blood flow relatively constant in the face of changes in arterial pressure within a certain range, protecting the brain from sudden changes in perfusion pressure. It has been suggested a

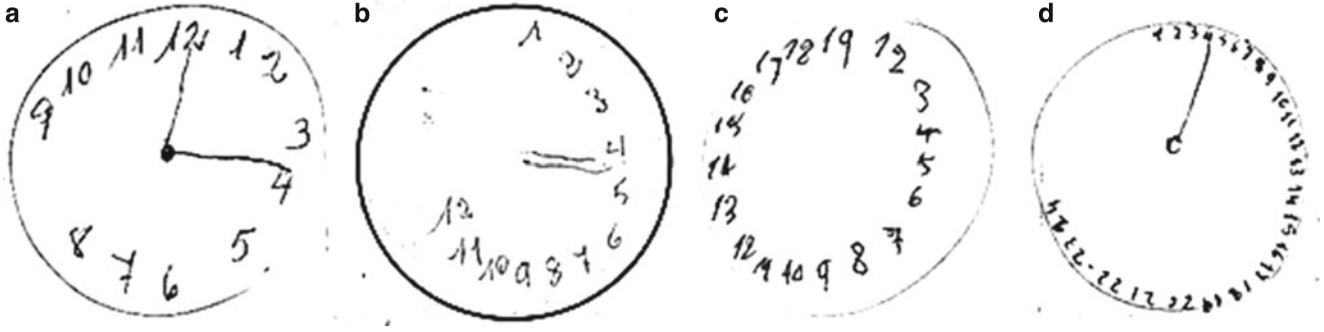

Fig. 15.1 Clock drawing test. Lack of planning (**a**, **b**); inability to transcode (**a**, **b**); impairment to draw the clock hands (**c**); perseverations (**c**, **d**)

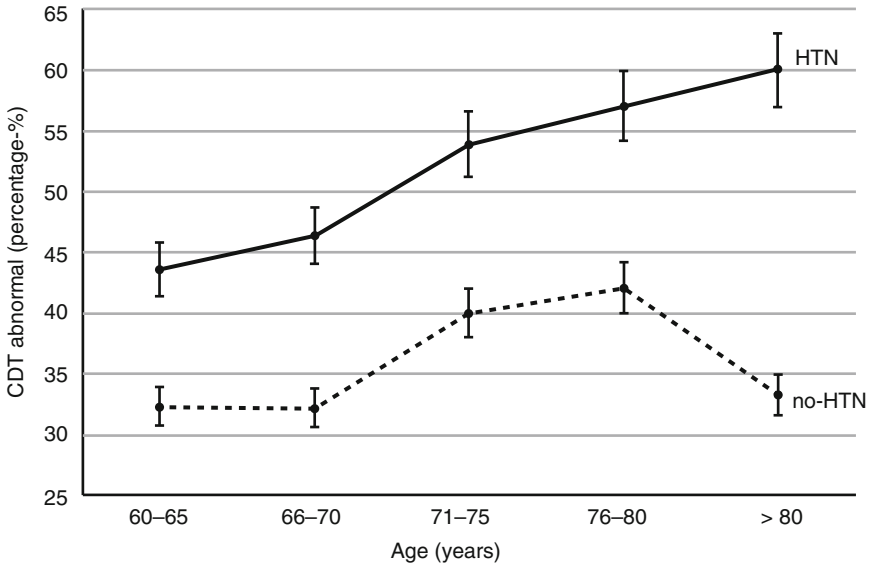

Fig. 15.2 Clock drawing test results. Prevalence (%) of abnormal clock drawing test in hypertensive and non-hypertensive patients

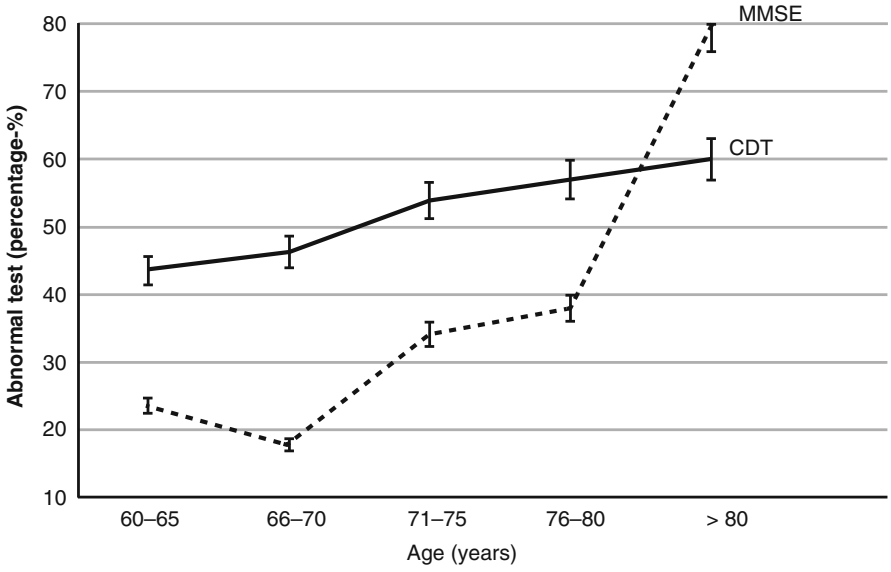

Fig. 15.3 Clock drawing test and mini mental state examination. The difference between using the MMSE and the CDT for the detection of cognitive impairment. In patients aged ≥80 years, the involvement of other cognitive domains can cause impairment in the MMSE results

pathophysiological explanation on the basis of differential input impedance in the brain, and also in the kidney, compared with other systemic vascular beds [17, 33]. The unique features of the kidney and brain are that they are continually and passively perfused at high flow throughout systole and diastole. Their vascular resistance is very low so that in comparison with other vascular beds, resistance is closer to input and characteristic impedance. Torrential flow and low resistance to flow in these organs expose small artery vessels to the high-pressure fluctuations that exist in the carotid, vertebral, and renal arteries [24].

Very recently, a randomly selected asymptomatic population ($n=591$, age = 49.2 years, 70 % women, 27 % black, and education = 18 years) underwent annual vascular and cognitive assessments. Higher pulse wave velocity (PWV), but not BP, was associated with a steeper decline in executive ($P=0.0002$), memory ($P=0.05$), and working memory ($P=0.02$) scores after adjusting for demographics, education, and baseline cognitive performance and remained significant after adjusting for hypertension. Hypertension was associated with greater decline in executive score ($P=0.0029$), and those with combined hypertension and elevated PWV (>7 m/s) had the greatest decline in executive score. Authors concluded that in healthy adults, increased arterial stiffness is superior to BP in predicting cognitive decline in all domains and in explaining the hypertension-executive function association [13]. Arterial stiffness, especially in hypertension, may be a target in the prevention of cognitive decline.

15.9 Prevention of Cognitive Impairment and Dementia by Antihypertensive Therapy

Both cross-sectional and longitudinal data from observational studies have shown some beneficial effects of antihypertensive treatment against cognitive impairment, cognitive decline, and dementia in elderly people [11]. Three large-scale placebo-controlled randomized controlled trials (RCT) have assessed the potential role of antihypertensive therapy in preventing cognitive impairment, dementia, and stroke-related cognitive decline. The SHEP study [41] found that active treatment with thiazide diuretics significantly reduced the risk of stroke and cardiovascular events (primary end points) but not of cognitive impairment and dementia (secondary end points). However, reanalysis of the data indicated that differential dropout rates between treatment and placebo groups might have obscured a potential effect of antihypertensive treatment against cognitive decline and dementia [8]. In the Syst-Eur trial, patients with isolated systolic hypertension were initially treated with nitrendipine and, if necessary, with enalapril or hydrochlorothiazide or both. This trial showed that active therapy reduced dementia incidence by 50 % over 2 years [47]. After termination of the initial trial, all participants were continued on the active therapy for another 2 years in an open study. Findings from the extended trial reinforced the initial conclusion that long-term antihypertensive therapy initiated with a long-acting dihydropyridine calcium channel blocker reduced dementia risk by 55 % (95 % CI 24–73 %) [10]. In the PROGRESS study of the prevention of recurrent

stroke, the risk of dementia and cognitive decline was evaluated as a secondary end point. This trial found no significant effect of the therapeutic regimen on the overall risk of dementia [49]. However, the regimen significantly reduced the risk of dementia with recurrent stroke by a third, the overall risk of cognitive decline by a fifth, and the risk of cognitive decline with recurrent stroke by a half [49]. The absence of a treatment effect on the overall risk of dementia might be due to the limited power to detect a more modest effect as well as premature discontinuation of active treatment by some patients. In addition, the SCOPE trial was initially designed to address whether candesartan-based antihypertensive therapy in older hypertensive patients reduced the risk of cardiovascular events, cognitive decline, and dementia. However, due to ethical concerns, this study was finally designed to compare effects between candesartan and the usual antihypertensive therapy regimens. After 4 years of observation, this trial found no significant difference in dementia incidence, cognitive decline, and changes in mean MMSE score between the two groups [26]. However in a double-blind randomized study performed in 53 patients (aged ≥60 years) with executive dysfunction, it was shown that candesartan improved performance of trial making test part B compared with lisinopril and hydrochlorothiazide [14]. A pooled analysis of the SHEP, Syst-Eur, PROGRESS, and SCOPE trials whose participants total 11,794 in the treatment group and 11,711 in the control group revealed a non-significant association between antihypertensive treatment and the risk of developing dementia (OR 0.89; 95 % CI: 0.75–1.04) [48].

The MOSES study [39] of eprosartan versus nitrendipine for secondary stroke prevention also had changes in cognitive function, measured by MMSE, as a secondary end point, and the results showed no differences between groups.

The HYVET-COG (Hypertension in the Very Elderly Trial cognitive function assessment) study [35] is based on perindopril/indapamide versus placebo-reported similar results (cognitive decline HR 0.93; 95 % CI 0.82–1.05) (incidence of dementia HR 0.86; 95 % CI 0.67–1.09). In the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) study [9], no significant difference was observed in cognitive decline between the telmisartan and the placebo groups (decrease in MMSE score of 3 points or more from the first evaluation: RR 0.95; 95 % CI 0.87–1.05). In the parallel ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular disease) trials [1], designed to investigate the effect of renin-angiotensin system blockade on major cardiovascular outcomes, no significant benefits on cognitive function were found. Recently, a nested UK primary healthcare database was examined between 1997 and 2008 and 9197 cases of dementia (5797 AD, 2186 vascular dementia, and 1214 other dementias) were found; the authors concluded that the use of angiotensin receptor blockers (ARBs) decreased the incidence of AD by 53 % [7]. In another nested database at the US Department of Health System Veterans Affairs (2002–2006), 819,491 patients were analyzed (90 % aged >65 years). They also concluded that the use of ARBs decreased the incidence of AD in 55 % and 70 % its progression [25].

There are several reviews and meta-analyses with controversial results. A scientific statement of the American Heart Association in 2011 reported that

meta-analyses neither prove nor disprove the efficacy of antihypertensive treatment on dementia risk [11]. However, most studies had evaluated cognitive function using the MMSE, which lacks sensitivity in detecting cognitive decline in non-demented subjects, and this may have biased the results toward the null effect. The MMSE does not detect the first cognitive domain affected and the most characteristic in patients with vascular disease: executive dysfunction. In addition, the follow-up in the RCT may not have been long enough to detect changes in cognitive function. Lastly, change in cognitive function and the incidence of dementia were secondary end points in most studies.

Recently, another meta-analysis [59] including observational studies and RCT disclosed benefits of antihypertensive therapy on overall cognition and risk of all-cause dementia, with angiotensin receptor blockers possibly being the most effective (adjusted effect size 0.6 ± 0.18; $p = 0.02$).

Very recently a systematic review [38] suggests that antihypertensive therapy may decrease the incidence and progression of cognitive decline and dementia, not only vascular dementia but also AD. In this systematic review, several observational studies, RCT, and meta-analyses found positive results regarding the prevention of cognitive decline and dementia; although the results are sometimes conflicting, this is probably due to methodological limitations as mentioned before. Finally, accumulating evidence suggests that antihypertensive drugs, particularly calcium channel blockers and renin-angiotensin system blockers, could reduce the risk for and progression of cognitive impairment and dementia, both by lowering BP and also by a specific neuroprotective effect [38].

In summary, despite all the limitations and methodological differences, there is moderately strong evidence to support the view that hypertension in midlife, especially if not treated effectively, negatively affects cognition and contributes to the development of dementia and even AD in late life. High BP in middle age implies a long-term cumulative effect which leads to increased severity of atherosclerosis and more vascular comorbidities in late life [36]. There is less evidence that the same negative effect on cognition is present for hypertension in later life. Indeed, due to some reports concerning the harmful cognitive effect of low BP, it seems that, in older adults, and particularly in those who are very old, an appropriate level of BP may be required to retain cognitive function by maintaining adequate cerebral perfusion. However, the optimum BP remains unknown. Observational results suggest a protective effect of antihypertensive treatment against cognitive decline and dementia. Confirmation from randomized clinical trials is limited, as it is based mainly on the Syst-Eur trial [47]. Other clinical trials did not show a clear treatment effect or showed only a beneficial effect against poststroke dementia and cognitive decline.

References

1. Anderson C, Teo K, Gao P, Arima H, Dans A, Unger T et al (2011) Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol 10(1):43–53

2. Attems J, Jellinger KA (2014) The overlap between vascular disease and Alzheimer's disease--lessons from pathology. BMC Med 12:206
3. Birns J, Kalra L (2009) Cognitive function and hypertension. J Hum Hypertens 23:86–96
4. Birns J, Markus H, Kalra L (2005) Blood pressure reduction for vascular risk: is there a price to be paid? Stroke 36:1308–1313
5. Bueche CZ, Hawkes C, Garz C, Vielhaber S, Attems J, Knight RT et al (2014) Hypertension drives parenchymal β-amyloid accumulation in the brain parenchyma. Ann Clin Transl Neurol 1:124–129
6. Cummings JL (1998) Frontal–subcortical circuits and human behavior. J Psychosom Res 44:627–628
7. Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM (2011) Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. J Alzheimers Dis 26:699–708
8. Di Bari M, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L et al (2001) Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. Am J Epidemiol 153:72–78
9. Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. for the PRoFESS Study Group (2008) Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. Lancet Neurol 7: 875–884
10. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S et al (2002) Systolic hypertension in Europe investigators. The prevention of dementia with antihypertensive treatment: new evidence from the systolic hypertension in Europe (syst-Eur) study. Arch Intern Med 162:2046–2052
11. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C et al (2011) Vascular contributions to cognitive impairment and dementia. A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 42:2672–2713
12. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE et al (2006) National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 37:2220–2241
13. Hajjar I, Goldstein FC, Martin GS, Quyyumi AA (2016) Roles of arterial stiffness and blood pressure in hypertension-associated cognitive decline in healthy adults. Hypertension 67:171–175
14. Hajjar I, Hart M, Chen YL, Mack W, Milberg W, Chui H et al (2012) Effect of antihypertensive therapy on cognitive function in early executive cognitive impairment: a double-blind randomized clinical trial. Arch Intern Med 172:442–444
15. Hughes TM, Craft S, Lopez OL (2015) Review of 'the potential role of arterial stiffness in the pathogenesis of Alzheimer's disease'. Neurodegener Dis Manag 5:121–135
16. Iadecola C (2014) Hypertension and dementia. Hypertension 64:3–5
17. Iadecola C, Davisson RL (2008) Hypertension and cerebrovascular dysfunction. Cell Metab 7:476–484
18. Imaoka K, Kobayashi S, Fujihara S, Shimode K, Nagasaki M (1999) Leukoencephalopathy with cerebral amyloid angiopathy: a semiquantitative and morphometric study. J Neurol 246:661–666
19. Jellinger KA, Attems J (2003) Incidence of cerebrovascular lesions in Alzheimer's disease: a postmortem study. Acta Neuropathol 105:14–17
20. Joas E, Bäckman K, Gustafson D, Ostling S, Waern M, Guo X et al (2012) Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. Hypertension 59:796–801
21. Koennecke HC (2006) Cerebral microbleeds on MRI: prevalence, associations, and potential clinical implications. Neurology 66:165–171
22. Larson EB, Yaffe K, Langa KM (2013) New insights into the dementia epidemic. N Engl J Med 369:2275–2277

23. Launer LJ (2002) Demonstrating the case that AD is a vascular disease: epidemiologic evidence. Ageing Res Rev 1:61–77
24. Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B et al (2003) Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 34:1203–1206
25. Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE et al (2010) Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ 340:b5465. doi:10.1136/bmj.b5465
26. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B et al (2003) The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 21:875–888
27. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC et al (2010) Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science 330(6012):1774
28. McCarron MO, Nicoll JA (2004) Cerebral amyloid angiopathy and thrombolysis-related intracerebral haemorrhage. Lancet Neurol 3:484–492
29. Nasreddine ZS, Phillips NA, Bedirian C, Charbonneau S, Whitehead V, Collin I et al (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699
30. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R et al (2015) A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 385:2255–2263
31. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 13:788–794
32. O'Brien JT, Erkinjuntti E, Reisberg B, Roman G, Sawada T, Pantoni L et al (2003) Vascular cognitive impairment. Lancet Neurol 2:89–93
33. O'Rourke MF, Safar ME (2005) Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 46:200–204
34. Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 9:689–701
35. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al. for the HYVET Investigators (2008) Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 7:683–689
36. Qiu C, Winblad B, Fratiglioni L (2005) The age dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 4:487–499
37. Rodrigue KM, Rieck JR, Kennedy KM, Devous MD Sr, Diaz-Arrastia R, Park DC (2013) Risk factors for β-amyloid deposition in healthy aging: vascular and genetic effects. JAMA Neurol 70:600–606
38. Rouch L, Cestac P, Hanon O, Cool C, Helmer C, Bouhanick B et al (2015) Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. CNS Drugs 29:113–130
39. Schrader J, Lüders S, Kulchewski A, Hammersen F, Plate K, Berger J et al (2005) Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention. Principal results of a prospective randomized controlled study (MOSES). Stroke 36:1218–1224
40. Scuteri A, Nilsson PM, Tzourio C, Redon J, Laurent S (2011) Microvascular brain damage with aging and hypertension: pathophysiological consideration and clinical implications. J Hypertens 29:1469–1477
41. SHEP Cooperative Research Group (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 24:3255–3264
42. Sierra C, Coca A, Schiffrin EL (2011) Vascular mechanisms in the pathogenesis of stroke. Curr Hypertens Rep 13:200–207

43. Sierra C, Domenech M, Camafort M, Coca A (2012) Hypertension and mild cognitive impairment. Curr Hypertens Rep 14:548–555
44. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E (2014) Arterial stiffness, the brain and cognition: a systematic review. Ageing Res Rev 15:16–27
45. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L et al (1996) 15-year longitudinal study of blood pressure and dementia. Lancet 347:1141–1145
46. Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D et al (2015) Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. Alzheimers Dement 11:710–717
47. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, et al. for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators (1997) Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 350:757–764
48. Staessen JA, Richart T, Birkenhäger WH (2007) Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. Hypertension 49:389–400
49. The PROGRESS Collaborative Group (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 163:1069–1075
50. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Task Force Members (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31:1281–1357
51. Viswanathan A, Rocca WA, Tzourio C (2009) Vascular risk factors and dementia. How to move forward? Neurology 72:368–374
52. Henskens LH, van Oostenbrugge RJ, Kroon AA, Hofman PA, Lodder J, de Leeuw PW (2009) Detection of silent cerebrovascular disease refines risk stratification of hypertensive patients. J Hypertens 27:846–853
53. Vicario A, Del Sueldo M, Fernández RA, Enders J, Zilberman J, Cerezo GH (2012) Cognition and vascular risk factors: an epidemiological study. Int J Hypertens 2012:783696. doi:10.1155/2012/783696
54. Folstein MF, Folstein SE, McHugh PR (1975) "Mini mental state" a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
55. Vicario A, Martinez CD, Baretto MD, Diaz Casale A, Nicolosi L (2005) Hypertension and cognitive decline: impact on executive function. J Clin Hypertens 7:598–604
56. Vicario A, Del Sueldo M, Zilberman J, Cerezo G (2011) Cognitive evolution in hypertensive patients: a six years follow-up. Vasc Health Risk Manag 7:1–5
57. Cerezo GH, Del Sueldo M, Zilberman J, Pawluk M, Lodolo N, De Cerchio AE et al (2015) Cognitive status in hypertensive patients. Heart and brain study in Argentine. J Hypertens 33(Suppl 1):e-57–e-58. doi:10.1097/01.hjh.0000467500.67965.ab
58. Vicario A, Cerezo GH, Taragano FE, Zilberman J (2013) Guía para la Evaluación de Trastornos Cognitivos en pacientes con enfermedad vascular. Rev Fed Arg Cardiol 42(3) on line. http://www.fac.org.ar/1/revista/13v42n3/exclusivo_online/exclusivo_01/exclusivo_online.pdf
59. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P (2013). Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens 31:1073-1082