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Thrombi of Different Pathologies: Implications for Diagnosis and Treatment

Carlos G. Santos-Gallego, MD[1]
Jeremías Bayón, MD[2]
Juan José Badimón, PhD[*,1]

Address
*,[1]Atherothrombosis Research Unit, The Zena and Michael A. Wiener Cardiovascular Institute, 1 Gustave Levy Place, Box 1030, Mount Sinai School of Medicine, New York, NY 10029, USA
Email: juan.badimon@mssm.edu
[2]Cardiology Department, Hospital Central de Asturias, Oviedo, Spain

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Opinion statement

Stroke is the second leading cause of cardiovascular mortality in the modern world, accounting for 80% of strokes of ischemic origin. There are two main etiologies of ischemic stroke: 70% to 80% are caused by carotid atherosclerotic plaque rupture and superimposed thrombus formation, whereas 30% are caused by systemic embolism of a cardiac thrombus (mainly in atrial fibrillation [AF] patients). Therefore, antithrombotic therapy is the cornerstone of stroke treatment. In AF patients, thrombotic risk should be assessed by means of the CHADS2 score. Patients with a score of 0 should be treated with aspirin; for those with a score of 1, oral anticoagulation (target international normalized ratio, 2–3) or aspirin is recommended. For patients with a CHADS2 score ≥2, oral anticoagulation with warfarin should be initiated (unless contraindicated). If warfarin is contraindicated, antithrombotic treatment should be prescribed (the combination of aspirin and clopidogrel seems to be superior to aspirin alone). For primary prevention in atherosclerotic patients, low-dose aspirin is useful only in women older than 45 years who are not at risk for intracranial hemorrhage and do not have gastrointestinal intolerance (a very small but significant effect). For secondary prevention in atherosclerotic patients, antithrombotic therapy should be administered. It is recommended that patients who do not require anticoagulation receive clopidogrel or a combination of aspirin and dipyridamole. Alternatively, aspirin alone or triflusal may be used. Within 4.5 h of onset of acute stroke, thrombolytic therapy (recombinant tissue plasminogen activator) must be injected urgently (unless contraindicated). Dabigatran is a new oral anticoagulant (competitive thrombin inhibitor) with a promising role in stroke prevention; at low doses, it is noninferior to warfarin for stroke prevention and is safer, whereas at high doses, it is superior to warfarin

in stroke prevention with the same incidence of bleeding. Percutaneous left atrial appendage occluders recently were approved for systemic embolism prevention. The use of warfarin after implantation is still under discussion. Dronedarone, a new antiarrhythmic agent, has been shown to decrease cardiovascular mortality and stroke in patients with AF. Carotid endarterectomy surgery is indicated in symptomatic patients with stenosis greater than 70% and in selected patients with 50% to 70% stenosis. Currently, carotid endarterectomy surgery is superior to carotid angioplasty and stenting.

Introduction

Stroke is an important cause of morbidity and mortality, and given the aging of the population, its importance probably will increase. Stroke is the leading cause of disability in the developed world (more than 800,000 people annually suffer a stroke in the United States) and the third leading cause of mortality [1]. About 80% of strokes are ischemic in nature and can be classified as cardiogenic or noncardiogenic. Cardiogenic strokes are caused by embolization of clots resulting from cardiovascular (CV) conditions such as atrial fibrillation (AF), valvular disease, and left ventricular dysfunction. Noncardiogenic strokes result from atherosclerotic plaque ruptures in intra- and extracranial lesions with superimposed thrombus formation [2•]. Therefore, antithrombotic therapy is the cornerstone of stroke treatment and prevention.

The thrombi causing stroke are classified as white or red depending on their composition, which is modulated by local blood flow characteristics. White thrombi are platelet-rich and are formed in areas of high shear stress, such as the arterial system, and thus develop on ruptured atherosclerotic plaques. In contrast, red thrombi are made of fibrin, are erythrocyte-rich, and form in low-pressure systems, such as cardiac or venous systems, as a result of activation of the coagulation cascade. Therefore, it is widely accepted that cardiac emboli are composed mainly of red thrombi. A lack of coordinated and synchronized atrial contraction due to AF, blood stasis due to slow flow in the left atrial appendage (LAA; a long structure with a narrow inlet), and smoke formation and thrombi accumulation in the LAA are the usual causes of cardiac thrombi. Akinetic/dyskinetic heart segments (secondary to myocardial infarction [MI]) are a less common cause. A third source of emboli is aortic arch atheroma (the odds ratio for stroke or peripheral embolism in patients with severe arch atheroma is >4 and for mobile atheroma, >12 [3]).

Nevertheless, recent work proved this clearcut distinction between red and white thrombi pathophysiology is a bit simplistic. In patients with stroke lasting less than 6 h, thrombi were retrieved (by means of endovascular mechanical extraction) and analyzed [4]. Seventy-five percent of the thromboemboli shared architectural features of random fibrin-platelet deposits interspersed with linear collections of nucleated cells (monocytes and neutrophils) and confined erythrocyte-rich regions. There was no relation between the source of a thrombus and its histology. The predominance of fibrin-platelets in six of seven arterial-source cerebral thromboemboli (86%) correlates with findings demonstrating that aspirin and warfarin are both effective in stroke prevention in patients with ischemic stroke of arterial origin [5,6]. Similarly, the composition of thromboemboli in patients with AF is consistent with results showing that aspirin is effective in reducing AF-related stroke, albeit not as effectively as warfarin (see later).

Can we assess the origin of the thrombus? From a therapeutic point of view, this fact is very important because vessel recanalization is more frequent and more complete in patients with cardioembolic stroke, because thrombolytic therapy (recombinant tissue plasminogen activator [rt-PA], with a high binding affinity for fibrin) will more easily lead to dissolution of thrombin-rich thrombi (ie, cardiac emboli) [7]. Based on this different composition between white and red thrombi, MRI provides some information about emboli origin [8]. Because red thrombi from the heart are rich in fibrin and eryth-

rocytes, the magnetic susceptibility effect of deoxygenated hemoglobin in red thrombi may result in hypointense signals on T2*-weighted gradient echo imaging.

Treatment

Diet and lifestyle

- Adoption of a healthy lifestyle is beneficial for all CV disease patients and plays a vital role in stroke prevention [9].
- A high body mass index (≥25) is associated with an increased risk of stroke [10].
- Physically active individuals have a lower risk of stroke or death than those who are not as active [11].
- Light alcohol consumption (<12 g/d) is associated with a reduction in both overall and ischemic stroke, whereas moderate consumption (12–24 g/d) is associated with a reduction only in ischemic stroke [12]. In contrast, heavy drinking (>60 g/d) increases the risk of both ischemic and hemorrhagic stroke.
- Cigarette smoking doubles the risk of ischemic stroke [13], and even people whose spouses/partners smoke have an increased stroke risk [14]. Therefore, smoking cessation must be highly encouraged.
- The risk of ischemic stroke is lower in people who have a high fruit and vegetable intake [15] and in those who consume fish at least once per month [16].
- Interestingly, not only do vitamin supplements not reduce the risk of stroke [17•,18], high doses of vitamin E might even increase mortality [19].

Pharmacologic treatment

Antiaggregant therapy

Acetylsalicylic acid (aspirin)

Atherothrombotic etiology/primary prevention: In a meta-analysis of more than 90,000 low-risk asymptomatic subjects, aspirin reduced coronary events and CV events, but not stroke, CV mortality, or all-cause mortality in the overall population [20]. Strikingly, there seem to be sex discordances: in women older than 45 years, aspirin reduced overall and ischemic stroke, but remarkably, it did not reduce the risk of fatal or nonfatal MI or CV death [21]. In hypertensive subjects (with no other comorbidities), aspirin did not reduce stroke or total CV events [22]. Aspirin reduces the risk of MI in patients with asymptomatic carotid artery disease [23] and reduces the risk of stroke after carotid artery surgery [24].

Atherothrombotic etiology/secondary prevention: In a meta-analysis of 11 randomized trials, aspirin decreased the risk of recurrent stroke (RRR, 13%; 95% CI, 6–19%) [25], with no relation between efficacy and

aspirin dose. In patients with symptomatic intracranial atherosclerosis in the WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) trial, aspirin was as effective as oral anticoagulation and had fewer complications [6].

Cardioembolic etiology: Aspirin reduced stroke in patients with nonvalvular AF in a meta-analysis of 11 randomized trials [26•]. However, warfarin (oral anticoagulation [OAC]; target international normalized ratio [INR], 2.0–3.0) was more effective than aspirin in reducing stroke [26•]. The CHADS2 score is the most widely used tool for assessing thrombotic risk in AF. It assigns one point for congestive heart failure, one point for hypertension, one point for age greater than 75 years, one point for diabetes, and two points for previous thromboembolism). For patients with a score of 0, aspirin is recommended. Those with a score of 1 should receive aspirin or OAC, and those with a score ≥2 should receive OAC [27].

Standard dosage	50 to 325 mg/d (preferred dosage, 75–162 mg/d).
Contraindications	Nonsteroidal anti-inflammatory drug (NSAID) allergy, viral infection in children and teenagers (associations with Reye's syndrome), third-trimester pregnancy, history of asthma or peptic ulcer, severe hepatic or renal dysfunction, bleeding disorders, and gout.
Main drug interactions	Potentiates anticoagulants, hypoglycemic agents, methotrexate, acetazolamide, valproic acid, and highly protein-bound drugs. There is increased bleeding risk with NSAIDs or chronic, heavy alcohol use. NSAIDs increase the risk of renal dysfunction.
Main side effects	Bleeding, nausea/vomiting, dyspepsia, allergic reactions (ie, urticaria, bronchospasm, angioedema).
Cost/cost-effectiveness	Number needed to treat (NNT) to prevent one stroke: 100 over 2 years versus placebo.

Clopidogrel

Atherothrombotic origin/primary prevention: Clopidogrel is not indicated. In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) study, the combination of aspirin and clopidogrel did not reduce the risk of MI, stroke, or death from CV causes compared with aspirin alone [28].

Atherothrombotic origin/secondary prevention: Clopidogrel is marginally but significantly more effective than aspirin in preventing vascular events (CAPRIE [Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events] study) [29]. It may be more effective in high-risk patients (eg, those with previous stroke, symptomatic coronary artery disease, diabetes, or peripheral artery disease) [28]. Clopidogrel monotherapy also causes less gastrointestinal (GI) bleeding than 325 mg/d aspirin but does not reduce the risk of other types of bleeding [30•].

The MATCH (Management of Atherothrombosis With Clopidogrel in High-Risk Patients With Recent Transient Ischemic Attacks or Ischemic Stroke) trial proved that compared with clopidogrel alone, simultaneous treatment with aspirin and clopidogrel did not reduce the risk of ischemic stroke, MI, vascular death, or rehospitalization [31]; however, life-threatening or major bleeding were increased with the combination. In

patients who have had an acute coronary event within 12 months, or coronary stenting, the combination of clopidogrel and aspirin reduces the risk of new vascular events [32].

Cardioembolic origin: The ACTIVE-W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) study found that the combination of aspirin and clopidogrel was less effective than warfarin (particularly in patients who were taking OAC without complications) while having a similar bleeding rate [33]. Notwithstanding, aspirin plus clopidogrel was superior to aspirin alone [34•].

Standard dosage: 75 mg/d as monotherapy.

Contraindications: Active pathologic bleeding (eg, peptic ulcer, intracranial hemorrhage), should be used with caution in patients at high risk for bleeding (eg, because of surgery, ulcers, trauma, concomitant NSAIDs); severe hepatic or renal disease. Consider discontinuing 5 days before elective surgery.

Main drug interactions: If possible, avoid concomitant CYP2C19 inhibitors (eg, omeprazole, ketoconazole, fluoxetine). Recently, there has been much interest regarding omeprazole cotreatment decreasing clopidogrel plasma levels and antithrombotic effects (at least regarding coronary stent thrombosis); for example, see Gilard et al. [35•]. However, in a retrospective analysis of PRINCIPLE-TIMI (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction) 44 and TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction) 38, there was no association between omeprazole use and the primary end point [36•]. Moreover, the only randomized clinical trial comparing clopidogrel plus omeprazole versus clopidogrel found absolutely no difference in the risk of CV events or MI (with a benefit in terms of reduced GI effects) [37••].

Main side effects: The most frequent side effects are rash and pruritus. Minor bleeding (epistaxis, purpura) also is more frequent. Major bleeding (GI, 2%; intracranial hemorrhage [ICH], 0.4%) is infrequent and more common with aspirin than clopidogrel. Severe neutropenia and thrombotic thrombocytopenic purpura are very rare (much more common with ticlopidine).

Cost/cost-effectiveness: NNT to prevent one stroke is 200 overall, but 29 for "high-risk" patients, over 2 years.

Dipyridamole

Atherothrombotic origin: Dipyridamole (DYP) reduces stroke recurrence with efficacy similar to that of aspirin [38]. In ESPRIT (Aspirin Plus Dipyridamole Versus Aspirin Alone After Cerebral Ischaemia of Arterial Origin), the combination of aspirin and extended-release dipyridamole (ASA+ER-DYP) reduced the risk of vascular death, stroke, or MI compared with aspirin. In the PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial, ASA+ER-DYP was as effective as clopidogrel in preventing stroke recurrence.

Standard dosage: 200 mg extended-release DYP plus 25 mg aspirin twice daily.

Contraindications: Allergic or hypersensitivity reactions. Because dipyridamole has a vasodilator effect, it should be used with caution in patients with a history of severe hypotension or unstable angina.

Main drug interactions	Increases the risk of GI bleeding with alcohol or NSAIDs; potentiates anticoagulants, adenosine, acetazolamide, methotrexate, and oral hypoglycemics; may increase the risk of renal dysfunction with NSAIDs. Monitor anticonvulsants.
Main side effects	The paradigmatic side effect with DYP is headache, which occurs in 24% to 70% of patients (especially women and nonsmokers). It plays a vital role because it leads to discontinuation in 10% of patients at 3 months; its incidence may be reduced by dose titration. Major bleeding complications occurred in 1.6% of patients on combination therapy. Other major side effects are GI upset and rash.
Cost/cost-effectiveness	NNT to prevent one stroke is 33 over 2 years [39].

Anticoagulants

Warfarin

Atherothrombotic etiology: OAC after noncardiac ischemic stroke is not superior to aspirin and causes more bleeding [5,40•].

Cardioembolic origin: Warfarin prevents 67% of AF-induced strokes [26•]. OAC reduces the risk of recurrent stroke in patients with nonvalvular AF [41] and most other cardiac sources of emboli. Anticoagulation should be taken long term, or for at least 3 months after cardioembolic stroke due to MI [42]. After a transient ischemic attack or minor stroke, OAC may be started immediately; however, after a major stroke with significant infarction on neuroimaging (eg, more than a third of the middle cerebral artery territory) OAC should be delayed for 4 weeks. In the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) trial, warfarin was safe and effective in older patients [43•].

For patients with AF and stable coronary disease, aspirin should not be added to OAC [44] (in the case of unstable coronary disease, this decision should be individualized). Anticoagulation may be beneficial in patients with aortic atheroma [45]. The ongoing ARCH (Aortic Arch Related Cerebral Hazard) trial is comparing OAC with clopidogrel plus aspirin for secondary prevention in patients with atherosclerotic plaques in the aortic arch.

Standard dosage	Individualized to a target INR of 2 to 3.
Contraindications	Hazardous hemorrhagic conditions or treatments; malignant hypertension; blood dyscrasias; unsupervised senile, alcoholic, uncooperative, or psychotic patients; major surgery; inadequate laboratory facilities; pregnancy (category X).
Main drug interactions	Potentiated by plasma protein-bound drugs, analgesics, antiarrhythmics, antibiotics, β-blockers, diuretics, proton pump inhibitors, psychostimulants, thyroid drugs, and uricosurics. Use caution with drugs that may cause hemorrhage (eg, NSAIDs, aspirin).
Main side effects	Hemorrhages, skin necrosis, vasculitis, purpura.

Thrombolytics

- Thrombolytic therapy with rt-PA given within 3 h after stroke onset significantly improves outcome in patients with acute ischemic stroke [46]; the NNT to achieve a favorable clinical outcome after 3 months is 7. These beneficial effects of rt-PA have since been confirmed in a large (n = 6483) open-label prospective registry, the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST), which demonstrated that this regimen is safe and effective, even in centers with little previous experience with thrombolytic stroke therapy [47].
- Several trials examined the use of rt-PA beyond the 3-hour treatment window. By contrast, ECASS (European Cooperative Acute Stroke Study) and ECASS II did not show statistically significant superiority of rt-PA for the primary end points when treatment was given within 6 h [48,49].
- However, ECASS III proved that in an appropriately selected patient population, the window of treatment for acute stroke with intravenous (IV) rt-PA may be extended to 4.5 h. The study revealed improved outcome at 90 days but also a higher rate of ICH with no difference in mortality in the rt-PA cohort [50••].
- The Third International Stroke Trial (IST III), a large open-label study, currently is enrolling patients receiving IV rt-PA up to 6 h after stroke onset to determine whether there is, in fact, a small benefit from treating patients with this extended window.
- Continuous transcranial ultrasound was associated with an increased rate of early recanalization after rt-PA in a small randomized trial [51]; this effect may be facilitated by the administration of microbubbles [52].

Standard dosage 0.9 mg/kg (maximum total dose, 90 mg) infused over 60 min, with 10% of the total dose given as an initial IV bolus over 1 min.

Contraindications Intracranial or subarachnoid hemorrhage; intracranial or intraspinal surgery; serious head trauma or previous stroke; seizure at stroke onset; active internal bleeding; intracranial neoplasm, arteriovenous malformation, or aneurysm; severe uncontrolled hypertension; bleeding diathesis.

Main drug interactions Increased risk of bleeding with heparin, warfarin, vitamin K antagonists, and drugs that alter platelet function (eg, aspirin, DYP, abciximab); angioedema risk with angiotensin-converting enzyme inhibitors (monitor); may interfere with coagulation tests.

Main side effects Cerebral edema or herniation, seizure, new ischemic stroke.

Dronedarone

- Dronedarone is a benzofuran derivative similar to amiodarone but lacking its iodine moieties, so it has no side effects on the thyroid

gland. In the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and American-Australian-African Trial With Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS), dronedarone delayed the time to first recurrence of AF compared with placebo, thus lowering the risk of first AF recurrence about 25% [53•]. Dronedarone was the first drug to decrease the risk of CV hospitalization in patients with a recent episode of AF (ATHENA trial) [54••].

- Furthermore, a subanalysis of the ATHENA trial showed an unexpected decrease in the risk of stroke compared with placebo (1.2% vs 1.8%, respectively; $P=0.027$) [55••]. Of interest, the curves indicated early and maintained benefits of dronedarone. The most important limitation of this analysis is that because dronedarone was not anticipated to reduce stroke, these outcomes were not prespecified or centrally adjudicated. The mechanism through which this reduction in stroke occurs has not yet been elucidated.

Standard dosage 400 mg twice a day.

Contraindications In the Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA), dronedarone treatment increased mortality in patients with New York Heart Association class III or IV heart failure and a left ventricular ejection fraction less than 35% [56•]. Other contraindications are second- or third-degree atrioventricular block and long QT interval.

Main side effects Worsening of creatinine levels; GI upset.

Surgical options

- Carotid endarterectomy (CEA) reduces the risk of recurrent disabling stroke or death in patients with severe (70–99%) ipsilateral internal carotid artery stenosis [57]. Patients with less severe ipsilateral carotid stenosis (50–69%), especially males with very recent hemispheric symptoms, also may benefit [57]. CEA should be performed as soon as possible (ideally within 2 weeks) after the last cerebrovascular event.
- Carotid angioplasty and/or stenting (CAS) is recommended only for selected patients, such as those with contraindications to CEA, stenosis at a surgically inaccessible site, restenosis after earlier CEA, or postradiation stenosis. Several trials have compared CEA versus CAS in nonselected patients (Tables 1, 2, and 3).

Interventional procedures

Atrial fibrillation ablation

- AF catheter ablation is used increasingly to treat patients with AF. Guidelines recommend maintaining OAC after ablation based only on embolism risk, not on ablation success. One of the potential advantages of AF ablation is the possibility of discontinuing OAC after a successful procedure. However, the safety of this strategy has

Table 1. Clinical trials of carotid endarterectomy

Study	Patients, *n*	Population	Results	Other considerations
NASCET [68]	3068	Patients with a TIA or nondisabling stroke and stenosis in the ipsilateral carotid artery within the previous 6 mo	Decrease in 2-y stroke risk, from 26% in the medical group to 9% in the CEA group, yielding an absolute risk reduction of 17% (for patients with ≥70% carotid stenosis)	Perioperative risk rate for stroke and/or death was 5.8% in the surgical arm
ECST [69]	3024	Patients with a TIA or nondisabling stroke and stenosis in the ipsilateral carotid artery within the previous 6 mo	Decrease in 3-y risk of stroke and/or death, from 26.5% in the medical group to 14.9% in the CEA group	The absolute risk reduction in the near-occlusion group was 4.2%, compared with 17.8% in those with severe stenosis but without near occlusion
ACAS [70]	1662	Patients with asymptomatic stenotic lesions eligible for CEA	Risk reduction of 5.9% in surgical patients with 60% stenosis	50% of the strokes in the CEA arm were related to the surgical procedure, whereas the others were related to contrast arteriography
ACST [71]	3120	Patients with asymptomatic stenotic lesions eligible for CEA	The 5-y risk for stroke (minor and major) in surgical patients was 6.4%, vs 11.8% for patients who deferred surgery	Absolute risk reduction of 5.4%, although a subgroup analysis showed clear benefit only for patients ≥75 y old

ACAS Asymptomatic Carotid Atherosclerosis Study; *ACST* Asymptomatic Carotid Surgery Trial; *CEA* carotid endarterectomy; *ECST* European Carotid Surgery Trial; *NASCET* North American Symptomatic Carotid Endarterectomy Trial; *TIA* transient ischemic attack.

not been demonstrated yet in large randomized studies. Only two nonrandomized studies investigated the discontinuation of OAC after successful AF ablation [58•,59•]; both concluded that compared with patients who remained on OAC after the ablation procedure, the rate of thromboembolism among those who stopped therapy was not significantly different. However, this conclusion is only hypothesis generating and needs to be confirmed by large randomized trials. Until then, the safest recommendations are as follows: 1) Warfarin is recommended for at least 2 months after AF ablation. 2) Decisions regarding the use of warfarin more than 2 months after ablation should be based on the patient's risk factors for stroke and not on the presence or type of AF. 3) Discontinuation of warfarin post ablation is not recommended in patients with a CHADS2 score greater than 2.

Assistive devices

Left atrial appendage occluders

- Because most thrombi in AF patients are formed in the LAA and from there cause systemic embolism, a strategy of LAA occlusion may seem successful. In fact, removal/closure of the LAA is recommended to reduce the risk of stroke in selected patients undergoing cardiac valve

Table 2. Prospective multicenter registries of carotid angioplasty and/or stenting with embolic protection devices in high-risk patients[a]

Study[b]	Patients, *n (% with symptoms)*	MI/stroke/death rate, %	
		30 d	1 y
BEACH [72]	480 (25.3)	5.8 (1.0/4.4/1.5)	9.1 (1.1/7.0/3.2)
SECuRITY [73]	305 (31)	8.5 (0.7/6.9/0.9)	NA
MAVerIC [74]	399	5.3	NA
ARCHeR [75]	581 (23.8)	8.3 (2.4/5.5/2.1)	9.6 (0/1.3/0)
CAPTURE [76]	3500 (13.8)	5.7 (0.9/4.8/1.8)	NA
CREATE [77]	543 (17.4)	6.2 (1.0/4.5/1.9)	NA
MO.MA [78]	157 (19.7)	5.7 (0/5.1/0.6)	NA
PRIAMUS [79]	416 (63.5)	4.6 (0/4.1/0.5)	NA
CASES-PMS [80]	1493 (21.8)	5.6	NA
CABERNET [81]	454	3.8	11.5

[a]High-risk patients were those with a surgically inaccessible lesion, previous head and/or neck radiation, spinal immobility, restenosis after carotid endarterectomy, laryngeal palsy, tracheostoma, contralateral carotid stenosis, age ≥75 years, severe comorbidity, planned coronary bypass, or a history of major surgery.
[b]These registries did not include a control group. Technical success was achieved in 97% of all patients. The incidence of 30-day myocardial infarction (MI), stroke, and/or death varied between 2.1% and 8.3%. Most registries did not differentiate between symptomatic and asymptomatic patients when analyzing results.
ARCHeR Acculink for Revascularization of Carotids in High-Risk Patients; *BEACH* Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients; *CABERNET* Carotid Artery Revascularization Using Boston Sci EPI Filterwire EX/EZ and EndoTex NexStent; *CAPTURE* Carotid Acculink/Accunet Postapproval Trial to Uncover Rare Events; *CASES-PMS* Carotid Artery Stenting With Emboli Protection Surveillance Study; *CREATE* Carotid Revascularization With ev3 Arterial Technology Evaluation; *MAVerIC* Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis; *MO.MA* Multicenter Registry to Assess the Safety and Efficacy of the MO.MA Cerebral Protection Device During Carotid Stenting; *NA* not available; *PRIAMUS* Proximal Flow Blockage Cerebral Protection During Carotid Stenting; *SECuRITY* Registry Study to Evaluate the NeuroShield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy.

surgery [60•]. Interest in this strategy has grown recently, with two percutaneous occluders under evaluation.

- The percutaneous LAA transcatheter occlusion (PLAATO) device was the first technology developed for LAA obliteration. The device is not commercially available, and there are no plans to pursue a pivotal study for it. The PLAATO device was implanted in 64 patients (no control group); during a 5-year follow-up, the annual stroke rate was 3.8%, whereas the anticipated stroke rate with CHADS2 was 6.6% [61•].
- Watchman (Atritech, Plymouth, MN) is the only LAA occluder studied in a randomized clinical trial—Embolic Protection in Patients With Atrial Fibrillation (PROTECT-AF), a multicenter, prospective, unblinded study [62••]. Because of the results of PROTECT-AF, the Watchman device is under review by the US Food and Drug Administration for prevention of systemic embolism in patients with nonvalvular AF deemed eligible for warfarin therapy. This study randomly assigned patients to receive either conventional warfarin therapy or the Watchman device (warfarin for the first 45 days, both aspirin and clopidogrel for the next 6 months, and permanent aspirin therapy thereafter). The Watchman LAA occluder was not inferior to warfarin (primary end point: ischemic and hemorrhagic

Table 3. Randomized clinical trials of carotid angioplasty and/or stenting versus carotid endarterectomy

Study (year)	Patients, *n* (CEA/CAS, *n/n*)	Patient population	Primary end point(s)		
			Description	At 30 d (CAS vs CEA), %/%	At 1 y (CAS vs CEA), %/%
Leicester (1998) [82]	23 (12/11)	Low risk, symptomatic	30-d stroke and/or death	70/0	–
CAVATAS (2001) [83]	504 (253/251)	Low risk, 96% symptomatic	30-d stroke and/or death, 1-y stroke or death	10.0/9.9	14.3/13.4
Wallstent[a] (2001) [84]	219 (112/107)	Low risk, symptomatic	1-y stroke and/or death	–	10.4/4.4
Kentucky 1 (2001) [85]	104 (51/53)	Low risk, symptomatic	30-d stroke and/or death	1.8/1.9	–
Kentucky 2 (2004) [86]	85 (42/43)	Low risk, symptomatic	30-d stroke and/or death	0/0	–
CaRESS (2003) [87]	397 (254/143)	High and low risk, 32% symptomatic	30-d stroke and/or death, 1-y stroke or death	2.1/4.3	10/13.6
SAPPHIRE (2004) [88]	334 (167/167)	High risk, symptomatic	30-d MI, stroke, and or death; 1-y stroke or death	12.2/20.1	12.2/20.1
SPACE (2006) [89]	1200 (595/605)	Low risk, symptomatic	30-d stroke and/or death	6.8/6.3	–
EVA-3S (2006) [90]	527 (262/265)	Low risk, symptomatic	30-d stroke and/or death	9.6/3.9	–
ICSS [91] (interim safety results at 120 d)	1713 (858/855)	High risk, symptomatic	120-d MI, stroke, and/or death	8.5/5.2	–
CREST [92]	2502 (1250/1252)	High risk, 53% symptomatic	30-d MI, stroke, and/or death; 4-y stroke	7.2/6.8	–

[a]Registered trademark of Boston Scientific, Natick, MA.
CaRESS Carotid Revascularization Using Endarterectomy or Stenting Systems; *CAS* carotid angioplasty and/or stenting; *CAVATAS* Carotid and Vertebral Artery Transluminal Angioplasty Study; *CEA* carotid endarterectomy; *CREST* Carotid Revascularization Endarterectomy Versus Stenting Trial; *EVA-3S* Endarterectomy Versus Stenting in Patients With Symptomatic Severe Carotid Stenosis; *ICSS* International Carotid Stenting Study; *MI* myocardial infarction; *SAPPHIRE* Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy; *SPACE* Stent-Protected Angioplasty Versus Carotid Endarterectomy.

stroke, CV and unexplained death, and systemic embolism). However, implantation of the device carries substantial procedural risk (5% of patients underwent pericardiocentesis because of pericardial effusion and 1.1% suffered acute ischemic stroke due to air or thromboemboli). The incidence of ischemic stroke and systemic embolism was not significantly higher in the device versus the control group, but the number of outcome events was small, and a real difference between the groups cannot be excluded. CV or

unexplained death and hemorrhagic stroke were significantly less common in the device than the control group.

- Because of the small sample, the primary efficacy estimate in the PROTECT-AF trial lacks precision, as reflected by the wide confidence interval (RR, 0.68; 95% CI, 0.37–1.41). Drug studies comparing alternative therapies with warfarin in patients with AF typically are five to 25 times the size of this study.

Emerging therapies

Dabigatran

- Dabigatran etexilate is an oral direct thrombin inhibitor; after conversion to its active form, dabigatran competitively inhibits thrombin activity. This conversion is carried out by a serum esterase independent of cytochrome P-450. Therefore, dabigatran should be less susceptible to dietary and drug interactions and to genetic polymorphisms that affect warfarin. Furthermore, dabigatran does not require anticoagulation monitoring.
- The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial compared two doses of dabigatran with warfarin for prevention of stroke and systemic embolism, including hemorrhagic stroke (primary end point), in 18,113 patients [63••]. Compared with warfarin, the higher dose of dabigatran (150 mg) was associated with lower rates of stroke (RR, 0.66; 95% CI, 0.53–0.82; $P<0.001$ for superiority) but similar rates of major hemorrhage. Dabigatran given at a dose of 110 mg was associated with rates of stroke (RR with dabigatran, 0.91; 95% CI, 0.74–1.11; $P<0.001$ for noninferiority) similar to those associated with warfarin, as well as lower rates of major hemorrhage. The rate of nonhemorrhagic (ie, ischemic or unspecified) stroke also was significantly lower with 150 mg of dabigatran (0.92%) than with either 110 mg of dabigatran (1.34%) or warfarin (1.20%). To prevent one nonhemorrhagic stroke, the NNT with dabigatran at a dose of 150 mg twice daily, rather than warfarin, is approximately 357. The rates of hemorrhagic stroke with the 110- and 150-mg dabigatran doses (0.12% and 0.10%) were significantly lower than that of warfarin (0.38%; NNT for preventing one hemorrhagic stroke, 370). The mortality rate was 4.13% per year in the warfarin group, compared with 3.75% per year with 110 mg of dabigatran ($P=0.13$) and 3.64% per year with 150 mg of dabigatran ($P=0.051$). Warfarin broadly inhibits coagulation (by inhibiting factors II, VII, IX, and X and proteins C and S); by selectively inhibiting only thrombin, dabigatran may have antithrombotic efficacy while preserving other hemostatic mechanisms in the coagulation system, thus potentially mitigating the risk of bleeding.

Standard dosage 110 or 150 mg twice daily.

Contraindications Patients with a creatinine clearance of less than 30 mL/ min or liver disease were excluded from RE-LY; therefore, such patients should not receive the drug.

Main drug interactions P-glycoprotein inhibitors, including verapamil, amiodarone, and especially quinidine, raise dabigatran serum concentrations considerably, but it is not known whether this fact is clinically relevant.

Main side effects *GI discomfort*. To enhance absorption of dabigatran, a low pH is required. Therefore, dabigatran capsules contain dabigatran-coated pellets with a tartaric acid core. This acidity may partly explain the increased incidence of dyspeptic symptoms with both dabigatran doses and the increased risk of GI bleeding with the 150-mg dose.

MI. In a subgroup analysis, dabigatran seemed to increase the rate of MI in the 150-mg group (RR, 1.38; 95% CI, 1.00–1.91; P=0.048), although the mechanism has not yet been ascertained.

Factor Xa inhibitors

- New OAC strategies, such as factor Xa inhibitors, have been developed and are under current review [64••]. Rivaroxaban and apixaban are two direct inhibitors of factor Xa (both within and outside the prothrombinase complex), with an oral bioavailability greater than 50%. Apixaban is being studied as a stroke prevention strategy for patients with AF in two clinical trials, ARISTOTLE (a noninferiority trial of apixaban, 5 mg twice daily, vs conventional OAC in 18,000 patients) and AVERROES (apixaban vs aspirin in 6000 patients unsuitable for conventional OAC, with a 36-month follow-up). Rivaroxaban is approved in Europe and Canada for venous thromboembolism prevention after orthopedic surgery. Rivaroxaban, 10 mg once daily, is being compared with warfarin therapy in a phase 3 trial (ROCKET-AF); the primary end point is the composite of stroke and systemic embolism and the combination of major plus clinically relevant nonmajor bleeding. Results are expected in early 2011.

Thromboxane receptor inhibitors

- Recently, it was discovered that platelets, macrophages, monocytes, endothelial cells, and vascular smooth muscle cells express TP receptors (thromboxane and prostaglandin endoperoxide PGG 2/PGH 2 receptors) [65•]. Aspirin exerts its antiaggregant properties through permanent inhibition of cyclooxygenase (COX)-1, thus blocking thromboxane A_2 (TXA_2) synthesis. However, monocytes and macrophages are the second largest source of TXA_2; they synthesize TXA_2 via their COX-2 pathway, which has a higher threshold of inhibition by aspirin than platelet COX-1. Therefore, TP inhibitors show strong antiaggregant effects. Terutroban (a selective TP receptor antagonist) also exerts specific antiatherosclerotic properties [66••]. Therefore, this seemingly attractive strategy of TP inhibition currently is being evaluated in the ongoing PERFORM trial (aspirin vs terutroban for the prevention of cerebrovascular and CV events in 19,000 patients with previous ischemic stroke).

Cilostazol

- For secondary prevention of ictus of atherothrombotic etiology, cilostazol reduced the risk of stroke by about 38% (besides having less hemorrhagic stroke) compared with aspirin in a pilot trial involving 720 Chinese patients with ischemic stroke [67•]. However, larger phase 3 trials are required to confirm this finding.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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