Stroke prevention

Clothilde Isabel, David Calvet, Jean-Louis Mas

Available online: Paris Descartes university, Sainte-Anne hospital, neurology department, Inserm U894, 106, rue de la Santé, 75014 Paris, France

Correspondence: Jean-Louis Mas, Paris Descartes university, Sainte-Anne hospital, neurology department, Inserm U894, 106, rue de la Santé, 75014 Paris, France. JL.MAS@ch-sainte-anne.fr

Summary

Patients who have had a stroke are at high risk for recurrent stroke, myocardial infarction, and vascular death. Prevention of these events should be initiated promptly after stroke, because many recurrent events occur early, and should be tailored to the precise cause of stroke, which may require specific treatment. Lifestyle advice including abstinence from smoking, regular exercise, Mediterranean-style diet, and reduction of salt intake and alcohol consumption are recommended for all patients with stroke. For most patients with ischemic stroke or TIA, control of risk factors, including lowering blood pressure under 140/90 mmHg and LDL cholesterol under 1 g/L, together with antiplatelet or oral anticoagulant therapy, depending on the cause of stroke, have been shown to decrease the risk of recurrent stroke and cardiovascular events. Aspirin, clopidogrel, or the combination of aspirin and dipyridamole, are all acceptable options for secondary prevention in patients with ischemic stroke or TIA of arterial origin. Dual therapy with aspirin and clopidogrel might be considered for 3 weeks after a minor ischemic stroke or TIA and for 3 months in patients with stroke due to severe intracranial stenosis. Oral anticoagulants are very effective to prevent cardioembolic stroke. Non-VKA oral anticoagulants have a favorable risk-benefit profile compared with VKAs, with significant reductions in stroke, intracranial hemorrhage, mortality, with similar major bleeding, but increased gastrointestinal bleeding. Carotid endarterectomy reduces the risk of ipsilateral stroke in patients with recent (< 6 months) non-disabling ischemic stroke or TIA in the territory and severe carotid artery stenosis. Carotid stenting is a potential alternative to surgery in patients younger than 70 years or patients with greater risk of surgery due to anatomic or medical conditions or specific circumstances such as radiation-induced stenosis or restenosis after surgery. For patients with hemorrhagic stroke due to hypertension-associated small vessel disease or cerebral amyloid angiopathy, strict control of blood pressure is essential. Restarting oral anticoagulants in patients after intracranial hemorrhage is a difficult decision that should weigh the risks of recurrent ischemic and hemorrhage stroke with and without oral anticoagulants. Several areas of uncertainty persist including the optimal target of blood pressure in patients with cerebrovascular disease, the benefit of PFO closure in patients with PFO-associated stroke, of stenting procedures in patients with atherosclerotic intracranial artery or extracranial vertebral artery stenosis, and of interventional procedures in patients with brain arteriovenous or cavernous malformations.
Despite advances in acute management of stroke, primary and secondary prevention remains the best approach to reducing the burden of stroke. Patients who have had a stroke or Transient Ischemic Attack (TIA) are at high risk for recurrent stroke, myocardial infarction, and death from vascular causes. Recurrent strokes lead to additional mortality or disability, and to greater cognitive decline. The objectives of secondary prevention are to reduce subsequent risks not only of stroke but also of other vascular events. To be effective, stroke prevention should be tailored to the cause of stroke. As stroke is a very heterogeneous condition, appropriate investigations are needed to define the precise cause of stroke, which may require specific treatment. The etiological workup needs to be performed promptly after a TIA or stroke, because the risk of stroke recurrence is highest in the early period after the acute event. This review focuses on evidence-based treatments for secondary prevention after ischemic or hemorrhagic stroke.

Risk factor control

Vascular risk factor control is the cornerstone of primary and secondary prevention of ischemic and hemorrhagic stroke. The INTERSTROKE case-control study [1], which included 26,919 participants from 32 countries (10,388 cases with ischemic stroke and 3059 with hemorrhagic stroke), quantified the importance of potentially modifiable risk factors for stroke. This study identified 10 modifiable risk factors (hypertension, smoking, diabetes mellitus, physical activity, diet, psychosocial factors, abdominal obesity, alcohol, cardiac causes, and apolipoproteins) associated with about 90% of the population attributable risk. These 10 risk factors collectively accounted for a similar population-attributable risk in different regions of the world, in men and women, and in younger and older populations. We will focus on management of modifiable risk factors for secondary stroke prevention.

Hypertension

Hypertension is considered as the most relevant and prevalent modifiable risk factor for ischemic and hemorrhagic strokes. A meta-analysis including 10 randomized controlled trials (RCTs) and 38,421 patients, showed that lowering blood pressure (BP) reduces the risk of recurrent stroke (odds ratio [OR], 0.78; 95% confidence interval [CI], 0.68–0.90) [2], regardless of BP level at baseline and type of stroke [3]. In the Perindopril protection against recurrent stroke study (PROGRESS) [3], the impact of active treatment (perindopril and indapamide) in secondary prevention was higher for intracerebral hemorrhage (ICH) (relative risk reduction 49%; 95% CI, 18%–68%) than for ischemic stroke (26%; 95% CI, 12%–38%) [4]. Optimal BP target for secondary stroke prevention is still debated. Meta-analyses of RCTs of antihypertensive therapy in primary and secondary stroke prevention have shown that a systolic BP target < 130 mmHg further reduced the risk of stroke compared with usual systolic BP target (130 to 139 mmHg), but only among patients with no established vascular disease at baseline [5,6]. In patients with established vascular disease, intensive management of hypertension may induce adverse cardiovascular and renal events [7,8]. In addition, wide pulse pressure associated with low diastolic BP should alert the clinician to lower BP slowly and to withhold up titration in the presence of orthostatic hypotension [8].

In secondary prevention after ischemic stroke, the AHA/ASA guidelines (American Heart Association/American Stroke Association) [9] support initiation of antihypertensive therapy in primary and secondary stroke prevention have shown that a systolic BP target < 130 mmHg further reduced the risk of stroke compared with usual systolic BP target (130 to 139 mmHg), but only among patients with no established vascular disease at baseline [5,6]. In patients with established vascular disease, intensive management of hypertension may induce adverse cardiovascular and renal events [7,8]. In addition, wide pulse pressure associated with low diastolic BP should alert the clinician to lower BP slowly and to withhold up titration in the presence of orthostatic hypotension [8].

In secondary prevention after ischemic stroke, the AHA/ASA guidelines (American Heart Association/American Stroke Association) [9] support initiation of antihypertensive therapy in primary and secondary stroke prevention have shown that a systolic BP target < 130 mmHg further reduced the risk of stroke compared with usual systolic BP target (130 to 139 mmHg), but only among patients with no established vascular disease at baseline [5,6]. In patients with established vascular disease, intensive management of hypertension may induce adverse cardiovascular and renal events [7,8]. In addition, wide pulse pressure associated with low diastolic BP should alert the clinician to lower BP slowly and to withhold up titration in the presence of orthostatic hypotension [8].

In secondary prevention after ischemic stroke, the AHA/ASA guidelines (American Heart Association/American Stroke Association) [9] support initiation of antihypertensive therapy in primary and secondary stroke prevention have shown that a systolic BP target < 130 mmHg further reduced the risk of stroke compared with usual systolic BP target (130 to 139 mmHg), but only among patients with no established vascular disease at baseline [5,6]. In patients with established vascular disease, intensive management of hypertension may induce adverse cardiovascular and renal events [7,8]. In addition, wide pulse pressure associated with low diastolic BP should alert the clinician to lower BP slowly and to withhold up titration in the presence of orthostatic hypotension [8].
130 mmHg. After 1 year, mean systolic blood pressure was 11 mmHg lower in the lower-target group, but the reduction in stroke rate with the lower target did not reach statistical significance (HR, 0.81; 95% CI 0.64–1.03). The rate of ICH was reduced significantly (HR, 0.37; CI 95%, 0.15–0.95). Although the reduction in stroke was not significant, the authors concluded that these results support the use of a systolic-blood-pressure target of less than 130 mmHg. Based on these results, the AHA/ASA guidelines also considered that a long-term goal of BP < 130 mmHg systolic and < 80 mmHg diastolic is reasonable for secondary prevention in patients with ICH [15].

**Dyslipidemia**

Lowering low-density lipoprotein cholesterol (LDL-C) is an important component of stroke prevention. The Cholesterol treatment trialsists’ collaboration [16] showed that the reduction of LDL-C with a statin reduced the risk of major vascular events (RR, 0.79; 95% CI, 0.77–0.81; per 1.0 mmol/L reduction), largely irrespective of age, sex, baseline LDL-C or previous vascular disease, and of vascular and all-cause mortality. In the Stroke prevention by aggressive reduction in cholesterol levels (SPARCL) study [17], specifically dedicated to secondary stroke prevention in patients who had LDL-C level ≥ 100 mg/dL, atorvastatin (80 mg) reduced the risk of recurrent stroke by 16% and the risk of major cardiovascular events by 20% compared with placebo. Concern has been raised that statin therapy could increase the risk of hemorrhagic stroke. However, a meta-analysis of 31 RCTs, which specifically addressed this issue did not find an association between statin therapy and an increased risk of ICH [18]. The AHA/ASA guidelines [9] recommend the use of statin therapy to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and a LDL-C level ≥ 100 mg/dL. The optimal LDL-C target for secondary prevention is debated. The ongoing Treat Stroke to Target (TST) study is assessing whether lowering LDL-C under 100 mg/dL may reduce recurrent stroke risk (ClinicalTrials.gov, identifier: NCT01252875).

**Diabetes mellitus**

Diabetes mellitus and disorders of glucose metabolism are associated with an increased risk for ischemic stroke. With regard to primary prevention, a meta-analysis including 9 RCTs and 59,197 patients showed that intensive glycemic control (defined as HbA1c under 6 or 6.5%, fasting plasma glucose under 6 mmol/L or high dose of treatment) did not decrease the risk of incident stroke compared with standard treatment (defined as placebo, standard care or glycemic control of reduced intensity) (RR, 0.96; 95% CI, 0.88–1.06), except for patients with Body Mass Index (BMI) > 30 (RR, 0.86; 95% CI, 0.75–0.99) [19], but doubled the risk of severe hypoglycemia [20,21]. In patients with recent ischemic stroke or TIA and insulin resistance only, pioglitazone reduced the risk of a composite outcome including stroke or myocardial infarction (hazard ratio [HR], 0.76; 95% CI, 0.62–0.93), but with some concerns about safety [22]. No major trials have specifically examined interventions of pre-diabetes mellitus or diabetes mellitus for secondary prevention in stroke patients. AHA/ASA guidelines [9] recommend the use of existing guidelines from the American Diabetes Association [23] for glycemic control (HbA1c ≤ 7%) and cardiovascular risk factor management.

**Cigarette smoking**

Cigarette smoking is a major risk factor for first stroke [24]. In the Cardiovascular Health Study, smoking was associated with an increased risk of stroke recurrence in the elderly (HR, 2.06; 95% CI, 1.39–3.56) [25]. No clinical trials have assessed the impact of smoking cessation on stroke recurrence in patients with stroke or TIA. Patient with stroke or TIA should be advised to quit smoking and to avoid environmental tobacco smoke. Counseling, nicotine products, and oral smoking cessation medications are effective in helping smokers to quit [9]. The effect of e-cigarette with or without nicotine for helping smokers to quit has not been fully investigated but appears to be modest [26]. E-cigarette is currently not recommended as a primary cessation aid, because of the lack of evidence of its efficacy [27].

**Overweight and abdominal obesity**

In a large meta-analysis, each 5 kg/m² higher BMI was associated with higher risk of stroke (adjusted HR, 1.04; 95% CI, 1.01–1.08). About three-quarters of the excess risk of stroke associated with high BMI was mediated by blood pressure, cholesterol and glucose [28]. In a recent study that assessed behavioral intervention in overweighted patients, a modest loss of weight (i.e., 10% of the initial body weight) was associated with a decrease in the incidence of cardiovascular disease (stroke, myocardial infarction, death from cardiovascular causes, or hospitalization for angina) after a median 10 years follow-up [29]. Waist-to-hip ratio has been shown to be a better predictor of cardiovascular events and mortality than waist circumference in patients with type-2 diabetes, while BMI was not associated with cardiovascular outcomes [30]. This finding is consistent with results of the Northern Manhattan Stroke study, which showed that abdominal obesity was a risk factor for ischemic stroke, independently of BMI, in all race-ethnic groups [31].

**Nutrition**

Several RCTs have assessed the impact of several diets on primary stroke prevention. A meta-analysis that included 22 studies and 190,000 patients showed that a Mediterranean-type diet was associated with a reduced risk of incident stroke (RR, 0.71; 95% CI, 0.62–0.89) [32]. The AHA/ASA guidelines [9] recommend to counsel patients with a history of stroke or TIA to follow a Mediterranean-type diet (instead a low-fat diet), with reduction of sodium intake to less than 2.4 g per day and eventually to refer them for individualized nutritional counselling.
Alcohol consumption

Heavy alcohol use and acute alcohol ingestion increase the risk of stroke. With regard to ischemic stroke, a J-shaped curve has been reported, whereby light to moderate drinkers (up to 2 drinks per day for men, and up to 1 drink per day for non-pregnant women) have less risk than abstainers. The risk of stroke due to hemorrhage increases with the amount of alcohol consumed [33]. The AHA/SA guidelines [9] recommend that patients with TIA, ischemic or hemorrhagic stroke who are heavy drinkers should eliminate or reduce their consumption of alcohol. Light to moderate consumption may be reasonable, although nondrinkers should not be counseled to start drinking.

Physical inactivity

In a longitudinal study that included 30,239 patients, physical inactivity was associated with a higher risk of primary stroke (HR, 1.14; 95% CI, 0.95–1.37) [34]. No clinical trials have assessed the impact of physical activity in secondary prevention after stroke or TIA. The AHA/ASA guidelines [9] recommend moderate-to-vigorous aerobic activity for at least 40 minutes and at least 3–4 days a week, with an adaptation to physical capacity of patients with residual disability.

Ischemic stroke and transient ischemic attack

From an etiological point of view, ischemic stroke is a very heterogeneous disorder. Three conditions account for the majority of ischemic strokes: large artery atherosclerosis (LAA), small vessel disease (SVD) (a disease of small perforating arteries of the brain that causes small deep infaracts or lacunes) and a variety of cardiac sources of embolism. Each of these categories account for about 20 to 30% of all ischemic strokes.

Large artery atherosclerosis

Risk factor control and antithrombotic therapies are the cornerstone of secondary prevention. Additional treatments are sometimes used depending on the specific cause of ischemic stroke.

Antithrombotic therapy

Antiplatelet therapy

Antiplatelet therapy is the antithrombotic treatment of choice in patients with ischemic stroke of arterial origin. This term is used to designate a somewhat heterogeneous category of patients, including patients with large artery atherosclerosis and patients with small vessel disease.

Aspirin has been the most extensively studied antiplatelet drug. In a meta-analysis of 10 trials including 6170 patients with prior stroke or TIA [35], aspirin allocation was associated with a 17% reduction in the annual rate of serious vascular events, a 21% reduction in coronary events and a 17% reduction in any stroke, despite an increase in hemorrhagic stroke and major extracranial bleeds (figure 1). A recent meta-analysis [36] suggests that the effect of aspirin in preventing early recurrent stroke and myocardial infarction after TIA or ischemic stroke may have been underestimated. Indeed, aspirin reduced the 6-week risk of recurrent stroke by about 60% and the risk of disabling or fatal ischemic stroke by about 70%, independently of the dose of aspirin, patient characteristics or etiology. A substantial part of the early benefit of aspirin was due to reduction in severity of early recurrent ischemic stroke. The effect of aspirin diminished with long-term use. By contrast, dipyridamole plus aspirin...
versus aspirin alone had no effect on risk of recurrent ischemic stroke within 12 weeks, but was effective thereafter. Clopidogrel (75 mg) was compared to aspirin (325 mg) in patients with myocardial infarction, ischemic stroke or peripheral arterial disease [37]. The relative risk reduction of major vascular events with clopidogrel was 8.7%, which corresponds to an absolute reduction of 5 per 1000 per year. In the subgroup of patients whose qualifying event was an ischemic stroke, there was only a non-significant tendency in favor of clopidogrel, but the trial was not designed to assess the superiority of clopidogrel in this particular subgroup. The bleeding risk was similar with the 2 drugs, upper gastrointestinal events were more frequent with aspirin, rashes and diarrhea with clopidogrel.

Meta-analysis of 5 RCTs including 8622 patients with prior stroke or TIA of presumed arterial origin reported that the combination of aspirin and dipyridamole was associated with an 17% relative risk reduction in stroke recurrence compared to aspirin alone [38]. The comparison of aspirin and dipyridamole to clopidogrel failed to show that either of the two treatments was superior to the other in the prevention of recurrent stroke [39].

The combination of aspirin and clopidogrel did not reduce the mid-term risk of stroke and vascular events when compared with aspirin alone [40] or with clopidogrel alone [41]. In both studies, the combination of aspirin with clopidogrel was associated with an increased risk of severe or life-threatening bleedings. However, a recent trial [42] showed that the combination of aspirin (75 mg/d) and clopidogrel (300 mg on day 1, followed by 75 mg/d) for 3 weeks in Chinese patients with recent (< 24 hours) minor stroke (NIHSS at baseline < 4) or TIA was more effective than aspirin alone to prevent early stroke recurrence: 8.2% vs. 11.7% in the aspirin group (HR, 0.68; 95% CI, 0.57–0.81). This finding is supported by a meta-analysis [43] of 8 randomized trials showing that, compared to aspirin or clopidogrel alone, short-term (< 3 months) dual antiplatelet therapy combining aspirin and clopidogrel reduces the risk of stroke recurrence (RR, 0.68; 95% CI, 0.59–0.81), without increasing the risk of hemorrhagic stroke (RR, 1.23; 95% CI, 0.50–3.04). Long-term treatment (≥ 1 year) did not reduce the risk of stroke recurrence (RR, 0.92; 95% CI, 0.83–1.03), but was associated with a higher risk of hemorrhagic stroke (RR, 1.67; 95% CI, 1.10–2.56). RCTs are underway to study dual antiplatelet therapy in the Western world [44].

A recent trial [45] failed to show any benefit of ticagrelor over aspirin in reducing the rate of ischemic stroke at 30 days (HR, 0.87; 95% CI, 0.76–1.00) in patients with non-disabling ischemic stroke or TIA.

According to AHA/ASA guidelines [9], aspirin monotherapy (50–325 mg/d), clopidogrel (75 mg/d) monotherapy, or the combination of aspirin (25 mg) and dipyridamole (200 mg) twice daily, are all acceptable options for secondary prevention in patients with ischemic stroke or TIA of arterial origin. The selection should be individualized on the basis of coexistent disorders, tolerability and cost. The combination of aspirin and clopidogrel might be considered within 24 hours after a minor ischemic stroke or TIA and continued for 21 days. The combination of aspirin and clopidogrel is not recommended for routine long-term secondary prevention, unless there is a specific indication, such as stenting or acute coronary syndrome. For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit and no alternative agent or combination has been adequately studied. In patients with recurrent cerebral ischemic events despite good compliance with antiplatelet treatment, testing platelet function may detect insufficient platelet function inhibition leading to modify the dose of the drug or to switch to another drug. However, platelet function testing is not recommended in routine clinical practice.

**Oral anticoagulants**

Several studies have compared vitamin-K antagonists (VKAs) and aspirin in secondary prevention of ischemic stroke of arterial origin. No significant difference in efficacy was detected. VKA therapy was associated with a significant increase in bleeding complications [46]. There is currently no indication of VKAs for the secondary prevention of vascular events in patients with stroke or TIA of arterial origin [9].

**Extracranial carotid disease**

Extracranial carotid stenosis caused by atherosclerosis accounts for up to 15% of all strokes and TIsAs. Large RCTs and their meta-analyses [11] have shown that the addition of carotid endarterectomy (CEA) to medical therapy is effective in reducing the risk of ipsilateral stroke in patients with recent (< 6 months) non-disabling ischemic stroke or TIA in the territory of the carotid artery stenosis. Patients with severe stenosis (70% to 99%) derived the greatest benefit (absolute risk reduction of ipsilateral stroke) from surgery compared with medical therapy (15.9%, HR 0.81, 95% CI 0.71–0.92, p < 0.001). Surgery was of marginal benefit in those with 50–69% stenosis and was harmful in patients with 30–49% stenosis.

Carotid artery stenting (CAS) has been developed as a less invasive alternative to CEA. However, CAS does not remove the atherosclerotic plaque material and may dislodge a plaque fragment during the procedure, causing embolic stroke. Meta-analysis of 16 RCTs [48] including 7572 patients with symptomatic and asymptomatic carotid artery stenosis showed that CAS is associated with a higher risk of peri-procedural stroke or death compared with CEA (OR, 1.72; 95% CI, 1.29–2.31), but with a
lower risk of periprocedural myocardial infarction (OR, 0.44; 95% CI, 0.23–0.87) and local complications (OR, 0.37; 95% CI, 0.18–0.77). After the periprocedural 30-day period, both procedures are equally effective to prevent late recurrent ipsilateral stroke up to 10 years after treatment and are associated with similar low risk of restenosis. The Carotid stenosis trialists’ collaboration [49] recently reported that increasing age has a strong effect on periprocedural risk of patients treated with CAS, which was four times greater in patients older than 70 years than in those younger than 60 years. By contrast, age had little effect on the periprocedural risk of CEA or on post-procedural risk after either procedure. Overall, CEA was clearly superior to CAS in the periprocedural risk of CEA or on post-procedural risk after younger than 60 years. By contrast, age had little effect on extracranial vertebral artery stenosis may account for 9% to 35% of posterior circulation strokes [55,56]. Possible mechanisms of the following adverse events was higher in the stenting group than in the medical group: any stroke (59 [26%] of 224 patients vs 42 [19%] of 227 patients; P = 0.0468) and major hemorrhage (29 [13%] of 224 patients vs 10 [4%] of 227 patients; P = 0.0009).

According to AHA/ASA guidelines [9], for patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable; stenting with the Wingspan stent system is not recommended as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stenting. The usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational. For patients with severe stenosis (70%–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of systolic BP < 140 mm Hg, and high-intensity statin therapy, or for patients with severe stenosis (70%–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational. For patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is not recommended given the low rate of stroke on medical management and the inherent periprocedural risk of endovascular treatment.

**Intracranial atherosclerosis**

Intracranial atherosclerosis is a common cause of stroke and is associated with a high risk of recurrent stroke [51]. The Warfarin-aspirin symptomatic intracranial disease (WASID) study [52] failed to show a benefit of warfarin (INR 2–3) over aspirin (1300 mg per day) in 569 patients with stroke or TIA attributable to 50% to 99% intracranial stenosis of the middle cerebral artery, intracranial internal carotid artery, intracranial vertebral artery, or basilar artery. The study was stopped early because of higher rates of death and major hemorrhage in the warfarin arm. During a mean follow-up of 1.8 years, the primary end point (ischemic stroke, brain hemorrhage, and nonstroke vascular death) occurred in 22% of patients in both treatment arms. The 2-year rates of stroke in the territory of the stenotic artery were 15% in the aspirin arm and 13% in the warfarin arm. Patients with ≥ 70% stenosis had higher risk of stroke in the territory of the stenotic artery (18% at 1 year) than patients with 50% to 69% stenosis (7% to 8% at 1 year). The Stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) study [53,54] showed that aggressive medical treatment (aspirin 325 mg per day and clopidogrel 75 mg per day for 90 days followed by aspirin alone, systolic blood pressure < 140 mm Hg, LDL-C < 0.7 g/L, and a lifestyle-modification program) is superior to endovascular treatment with the Wingspan stent in 451 patients with recent transient ischemic attack or stroke related to 70–99% atherosclerotic stenosis of a major intracranial artery. By 30 days, 33 (14.7%) of 224 patients in the stenting group and 13 (5.8%) of 227 patients in the medical group had died or had a stroke, leading to the stop the study prematurely. During a median follow-up of 32.4 months, 34 (15%) of 227 patients in the medical group and 52 (23%) of 224 patients in the stenting group had a primary endpoint event defined as any of the following: stroke or death within 30 days after enrolment, ischemic stroke in the territory of the qualifying artery beyond 30 days of enrolment, or stroke or death within 30 days after a revascularization procedure of the qualifying lesion (P = 0.025). The occurrence of the following adverse events was higher in the stenting group than in the medical group: any stroke (59 [26%] of 224 patients vs 42 [19%] of 227 patients; P = 0.0468) and major hemorrhage (29 [13%] of 224 patients vs 10 [4%] of 227 patients; P = 0.0009).

According to AHA/ASA guidelines [9], for patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable; stenting with the Wingspan stent system is not recommended as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stenting. The usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational. For patients with severe stenosis (70%–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of systolic BP < 140 mm Hg, and high-intensity statin therapy, or for patients with severe stenosis (70%–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational. For patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is not recommended given the low rate of stroke on medical management and the inherent periprocedural risk of endovascular treatment.

**Extracranial vertebrobasilar disease**

Extracranial vertebral artery stenosis may account for 9% to 35% of posterior circulation strokes [55,56]. Possible mechanisms of
stroke include thromboembolism and hemodynamic insufficiency. Treatment options for symptomatic extracranial vertebral artery stenosis include medical therapy, endovascular stenting, and surgical revascularization procedures (vertebral endarterectomy, vertebral artery transposition). In the VAST study [57], 115 patients with a recent transient ischemic attack or minor stroke, associated with an intracranial or extracranial vertebral artery stenosis of at least 50%, were randomly allocated to stenting plus best medical treatment or best medical treatment alone. Three patients (5%) in the stenting group had vascular death, myocardial infarction, or any stroke within 30 days after the start of treatment versus one (2%) patient in the medical treatment group. During a median follow-up of 3 years (IQR, 1.3-4.1), four (7%; 95% CI, 2%-17%) patients in the medical treatment group had a stroke in the territory of the symptomatic vertebral artery versus seven (12%; 95% CI, 6%-24%) in the stenting group. By contrast, in the Vertebral artery ischemic stenting trial (VIST trial, reported during the European Stroke Organization Congress in May 2016 [58]), 182 patients with recent ischemic stroke or TIA due to vertebral stenosis (>50%) were allocated to stenting on top of best medical care or best medical care alone (http://www.controlledtrials.com/ISRCTN95212240). Five strokes during 308 years of follow-up occurred in the stenting group versus 12 strokes during 291 years of follow-up in the medical group (HR, 0.40; 95% CI, 0.14-1.13). According to AHA/ASA guidelines [9], endovascular stenting or open surgical procedures may be considered in patients with extracranial vertebral stenosis and symptoms despite optimal medical treatment.

Aortic arch atheroma
Several studies have shown that aortic atheroma is associated with higher risk of stroke [59]. In the French study of aortic plaques in stroke including 331 patients with brain infarction [60], the relative risk of recurrent brain infarction was 3.8 (95% CI, 1.8-7.8) for patients with aortic plaque ≥4 mm thick, after adjustment for the presence of carotid stenosis, atrial fibrillation, peripheral arterial disease and other risk factors. The Aortic arch related cerebral hazard (ARCH) trial [61] failed to show a significant difference in the risk of vascular events between warfarin and dual antiplatelet therapy combining clopidogrel and aspirin in patients with ischemic stroke, TIA or peripheral embolism and plaque in the thoracic aorta >4 mm. After a median follow-up of 3.4 years, the primary endpoint (cerebral infarction, myocardial infarction, peripheral embolism, vascular death or intracranial hemorrhage) occurred in 7.6% in the dual antiplatelet group versus 11.3% in the warfarin group (P = 0.2). Surgical endarterectomy for atheroma ≥5 mm or with mobile element is associated with high mortality and intraoperative stroke rates and is not recommended [62]. AHA/ASA guidelines [9] recommend single antiplatelet therapy and statin therapy.

**Ageing and hypertension-related small vessel disease**
Small vessel disease (SVD) refers to different pathological processes [63], but this term is commonly used to designate an intrinsic disease of small perforating arteries of the brain, called arteriolosclerosis. The disease is associated with ageing and vascular risk factors, in particular hypertension. SVD is responsible for small (lacunar) infarcts (15 mm in diameter) located in the deep structures of the brain.

Secondary prevention in patients with ischemic stroke due to small vessel disease rests upon control of vascular risk factors and single antiplatelet therapy. In Secondary prevention of small subcortical stroke (SPS3) study [64], a trial specifically devoted to secondary prevention in patients with recent symptomatic small deep infarcts, the addition of clopidogrel (75 mg/d) to aspirin (325 mg/d) did not significantly reduce the risk of recurrent stroke as compared with aspirin alone (2.5% vs. 2.7% per year; HR, 0.92; 95% CI, 0.72-1.16), but did significantly increase the risk of major hemorrhage (2.1% vs. 1.1% per year; HR, 1.97; 95% CI, 1.41-2.71) and death (HR, 1.52; 95% CI, 1.14-2.04). As previously discussed (see “risk factor control’’ section), results of SPS3 [14] support the use of a systolic-blood-pressure target of less than 130 mmHg.

**Cardiogenic causes**
Hospital or population-based studies suggested that up to 20% of all ischemic strokes are due to cardioembolism [65]. Cardioembolic sources are very diverse and the risk of first or recurrent stroke varies widely from one cardiopathy to another. Accordingly, secondary prevention in patients with cardioembolic stroke depends on the underlying cardiopathy (table I). We will briefly comment on atrial fibrillation (AF) and patent foramen ovale (PFO).

**Antithrombotic therapy**

**Oral anticoagulants**
For more than 50 years, vitamin K antagonists (VKAs) have been the standard therapy for patients at high risk of cardioembolic stroke. VKA therapy is highly effective but it carries a risk of serious bleeding, in particular of intracranial hemorrhage and has several limitations that make it difficult to use in practice. Therapeutic doses have to be maintained within a very narrow range. Over-anticoagulation can lead to an increased risk of bleeding and under-anticoagulation can lead to increased risk of stroke. Maintaining patients within the narrow therapeutic range (usually INR between 2 and 3) is difficult because response to treatment is influenced by various factors including drug and food interactions. Therefore, VKA therapy requires frequent monitoring and dose adjustments. As a consequence, up to 50% of patients eligible for VKA therapy do not receive it. Furthermore, patients receiving VKAs spend only 60% of the time within the therapeutic range. Because VKAs have many drawbacks, non-vitamin K antagonists’ oral anticoagulants...
NOACs have been developed that offer advantages over VKAs, such as rapid onset and offset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions. The predictable anticoagulant effect of NOACs enables the administration of fixed doses without the need for routine coagulation monitoring, thereby simplifying treatment. Because of their short half-lives, NOACs must be taken at regular time intervals to obtain good protection against stroke. Another drawback of NOACs has been the lack of specific antidotes. Idarucizumab, an antibody fragment, was recently shown to completely reverse the anticoagulant effects of dabigatran within minutes, with no safety concerns [66]. Other antidotes such as andexanet alfa, against factor Xa inhibitors [67], and aripazine [68] are under development [69].

Antiplatelet therapy Antiplatelet therapy is used in patients with cardiopathy associated with a low risk of cardioembolic stroke (Table I). The addition of aspirin to VKAs is recommended in patients with cardiogenic embolism [9].
mechanical valves at very high embolic risk (table I) or in patients who have a strong indication for both oral anticoagulants (e.g., AF) and antiplatelet therapy (e.g., acute coronary syndrome), but this association should be as limited as possible, because it increases the risk of intracerebral hemorrhage.

Oral anticoagulant monotherapy, and not combination therapy with antiplatelet, is recommended in AF patients with stable coronary artery disease but without an acute coronary syndrome and/or coronary intervention in the previous 12 months [70]. In patients treated for acute coronary syndrome, and in those receiving a coronary stent, short-term triple combination therapy of oral anticoagulant, clopidogrel, and aspirin seems warranted [70].

Atrial fibrillation

Atrial fibrillation (AF) is a major cause of ischemic stroke accounting for approximately 20% of all ischemic strokes and 50% of cardioembolic strokes. These AF-related strokes tend to be especially severe and disabling, with high risks of early mortality and recurrence rates, if left untreated. The proportion of AF-associated strokes increases with age reaching about 45% in people over 80 years of age. In addition, a substantial proportion of patients with stroke might unknowingly have paroxysmal asymptomatic AF [65,71]. Detection of occult paroxysmal AF in patients with stroke or TIA is crucial for secondary stroke prevention.

VKAs are highly effective drugs reducing stroke by two thirds when compared with the control (placebo or no treatment). The relative risk reduction in stroke is similar in primary and secondary prevention, but the absolute risk reduction is greater for secondary stroke prevention than for primary prevention, because, in untreated patients, the risk of stroke recurrence is much higher (12%) than the risk of first-ever stroke (4.5% per year on average) [72]. There is also overwhelming evidence that VKAs are superior to aspirin, and the combination of aspirin plus clopidogrel [73,74]. In the only trial specifically devoted to secondary stroke prevention in patients with AF, the relative risk reduction in stroke recurrence (two thirds) was similar to that observed in primary prevention trials, but the absolute risk reduction was greater because the absolute risk of recurrent stroke is much higher (12%) than the risk of first-ever stroke (about 5%) [75]. Overall, as shown in one meta-analysis [76] (table II), NOACs have a favorable risk-benefit profile compared with VKAs (warfarin), with significant reductions in stroke, intracranial hemorrhage, mortality, with similar major bleeding, but increased gastrointestinal bleeding. No RCT of NOACs vs. warfarin was specifically devoted to secondary stroke prevention in patients with AF. However, in all trials, the relative efficacy and safety of NOACs compared with warfarin did not differ between patients with and those without previous stroke or TIA. Pooling the data on secondary prevention from the 4 RCTs also shows that NOACs have a favorable risk-benefit profile in secondary stroke prevention compared with warfarin, with a significant reduction in stroke and major bleedings. In both secondary and primary prevention, the reduction in stroke risk was driven by a dramatic reduction in the risk of hemorrhagic stroke. Whereas the 2014 American guidelines put VKAs and NOACs on an equal footing [9], 2016 guidelines from the European Society of Cardiology recommend to consider NOACs first for most patients with AF [70]. There is insufficient evidence to recommend one NOAC over another, although some patient characteristics may be important considerations in the choice of agent. For patients who are unable to take oral anticoagulants, the AHA/ASA guideline recommend aspirin alone or the addition of clopidogrel to aspirin [9]. By contrast, the European Society of Cardiology [70] consider that the evidence supporting

<table>
<thead>
<tr>
<th>Table II</th>
<th>Efficacy and safety of non-vitamin K antagonists oral anticoagulants (NOACs) compared to warfarin, according to a meta-analysis by Ruff and al. [76] (n = 71 683, median duration of follow-up = 1.8 to 2.8 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Pooled NOACs (events)</strong></td>
</tr>
<tr>
<td>Stroke/systemic embolism</td>
<td>911/29,312</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>665/29,292</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>130/29,292</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413/29,292</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2022/29,292</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1541/29,287</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>204/29,287</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>751/29,287</td>
</tr>
</tbody>
</table>

To cite this article: Isabel C, et al. Stroke prevention. Presse Med. (2016), http://dx.doi.org/10.1016/j.lpm.2016.10.009
antiplatelet monotherapy for stroke prevention in AF is very limited and that aspirin cannot be recommended for stroke prevention in AF patients. Percutaneous left atrial appendage occlusion (LAAO) is a potential alternative treatment in patients with AF, high risk of stroke and contraindication for long-term anticoagulation (e.g. those with a previous life-threatening bleed without a reversible cause) [70,77].

**Patent foramen ovale**

Patent foramen ovale (PFO) is a common remnant of the fetal circulation found in approximately 25% of the general population. Several case-control studies demonstrated an association between PFO and cryptogenic ischemic stroke, particularly in young patients [78,79]. However, many uncertainties persist with regard to the causative relationship between PFO and stroke and the best strategy to prevent stroke recurrence. Paradoxical embolism has been considered a main mechanism of stroke in patients with a PFO, but this mechanism remains unproven in the majority of cases [80]. Other potential mechanisms include paroxysmal AF and direct embolization of thrombi formed in the PFO tunnel or in an associated atrial septal aneurysm, but documentation of these mechanisms is lacking [81,82]. Stroke might also result from an occult disorder, itself associated with PFO. As PFO is common in the general population, it may coexist by chance alone in patients with cryptogenic stroke. The probability that a PFO detected in a typical population of cryptogenic stroke patients younger than 55 years is incidental rather than stroke-related is as high as 50% [83]. The younger the patient and the fewer the number of atherosclerotic vascular risk factors, the higher the probability that the PFO is stroke-related [84].

Therapeutic options for secondary stroke prevention in cryptogenic stroke patients with a PFO include antiplatelet therapy, oral anticoagulants, and PFO closure [85]. Antiplatelet drugs are well tolerated and lower stroke recurrence rates in the general population of patients who have had a recent stroke or TIA. Oral anticoagulation is superior to antiplatelet therapy to prevent deep venous thrombosis and thrombus formation in the heart, two potential mechanisms of PFO-associated stroke. But oral anticoagulants have many drawbacks and carry a risk of major bleeding. PFO closure can prevent paradoxical embolism, but this treatment will not be relevant if a PFO-unrelated mechanism of ischemic stroke is the cause. PFO closure is an invasive procedure with potential complications including cardiac perforation, tamponade, air embolism, device embolization (requiring surgical revision), arrhythmias, thrombus formation on the device, and complications related to vascular access or antithrombotic treatment, some of which may be responsible for periprocedural stroke [86]. In addition, device closure leaves an implant behind, with potential mid-term or long-term complications such as atrial fibrillation [87]. PFO closure does not guarantee shunt closure, as residual shunts are seen in 15-20% of patients at 6 months [88].

Currently available evidence from RCTs do not provide definitive evidence on the superiority of either PFO closure or oral anticoagulants over antiplatelet therapy in patients with PFO-associated cryptogenic stroke [85,89]. The American Academy of Neurology [90] recently recommended that:

- in the absence of another indication for anticoagulation, clinicians may routinely offer antiplatelet medications instead of anticoagulation to patients with cryptogenic stroke and PFO;
- clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting, except in rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified.

**Other conditions**

Many other conditions, such as diverse arteriopathies and coagulation disorders can be responsible for ischemic stroke. Most of them account for only a very small proportion of ischemic strokes. Some of these conditions may need specific treatments for secondary prevention [9]. Cervical artery dissection is a common cause of ischemic stroke in young adults (8% to 25% of ischemic strokes in patients < 45 years old) [91]. Whether antiplatelet therapy or anticoagulation are effective to prevent stroke recurrence is unknown, as is the optimal duration of treatment. In the only RCT [92] that compared antiplatelet with anticoagulation therapy in patients with recent symptomatic cervical artery dissection, no difference was found between treatment. The rate of recurrent stroke was very low in both groups and the trial was underpowered to detect a modest difference. According to AHA/ASA guidelines [9], antithrombotic treatment with either antiplatelet or anticoagulant therapy for at least 3 to 6 months is reasonable in patients with ischemic stroke or TIA and extracranial carotid or vertebral dissection. For patients who have recurrent cerebral ischemic events despite medical therapy, endovascular therapy may be considered. Antiphospholipid antibodies are sometimes detected in patients with an otherwise unexplained ischemic stroke or TIA. For patients who meet the criteria for the antiphospholipid syndrome, anticoagulant therapy might be considered. When the criteria are not fulfilled, antiplatelet therapy is recommended [9].

**Cryptogenic stroke**

Despite a detailed etiological work-up, no cause is identified in about 10 to 40% of ischemic strokes, defined as cryptogenic [93]. Control of vascular risk factors and aspirin is recommended for secondary prevention [9]. The new concept of embolic stroke of undetermined source (ESUS) defines a new entity of patients with cryptogenic stroke that postulates an embolic mechanism of ischemic stroke [94]. It is based on the exclusion of lacunar infarction, extracranial or intracranial atherosclerosis causing at least 50% luminal
Stroke prevention

Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) causes 10 to 15% of all strokes [96]. The cumulative risk of recurrence is estimated between 1% and 5% per year [15]. There are many causes of ICH, but 4 are by far the commonest: small vessel disease associated ageing and hypertension, cerebral amyloid angiopathy, bleeding diathesis and vascular malformations.

Small vessel diseases

In addition to small deep infarcts and white-matter lesions (see “ageing and hypertension related small vessel disease” section, chapter “Ischemic stroke and transient ischemic attack”), SVD of brain perforating arteries associated with ageing and vascular risk factors (arteriosclerosis) is a major cause ICH. These hemorrhages are frequently localized in the deep structures of the brain and associated with lacunar infarcts and white-matter lesions. Cerebral amyloid angiopathy (CAA) is a common SVD in the elderly involving leptomeningeal and cortical vessels of the cerebral lobes and cerebellum [63]. CAA led to development of lobar intracerebral macrohemorrhages, cortical microbleeds, cortical superficial siderosis, small cortical infarcts and ischemic changes of the white matter.

In terms of secondary prevention, strict blood pressure control is recommended in patients with SVD (see “hypertension” section, chapter “Risk factor control”). In PROGRESS [97], antihypertensive treatment with perindopril and indapamide lowered the risk of CAA-related ICH by 77% (95% CI, 19%-93%) and that of hypertension-related ICH by 46% (95% CI, 4%-69%).

Bleeding diathesis

The most common bleeding diathesis associated with intracranial hemorrhage is antithrombotic therapy, in particular oral anticoagulant therapy. Non-vitamin K antagonists’ oral anticoagulants are associated with a risk of ICH which is half that of VKAs [76]. The decision to restart anticoagulant therapy in patients who have had an oral anticoagulant-related ICH and the optimal timing to resume the treatment must be individualized taking into account the risk of recurrent ICH, which depend on the cause of ICH (e.g. HTA-related small vessel disease versus cerebral amyloid angiopathy), the risk of recurrent ischemic event if left untreated, the presence of avoidable precipitating factors (fall, supratherapeutic INR . . .). Practical guidelines have been provided by the AHA/ASA [9,15] and the European Society of Cardiology [70]. Ongoing RCTs are currently addressing the issue of restarting antithrombotic treatment after ICH (APACHE-AF [98] and RESTART, ISRCTN71907627, [http://www.RESTARTrial.org/]). In patients with atrial fibrillation, high risk of ischemic stroke and contraindication for long-term anticoagulation, percutaneous left atrial appendage occlusion is a potential alternative to oral anticoagulants [70].

Vascular malformations

Rupture of a cerebral aneurysm is the main cause of subarachnoid hemorrhage. Complete obliteration of the ruptured aneurysm is recommended whenever possible and should be performed as early as feasible in the majority of patients to reduce the rate of rebleeding. The choice between endovascular coiling and surgical clipping should be a multidisciplinary decision [99].

Arteriovenous malformations (AVMs) are the single most common cause of intracerebral hemorrhage in young adults. The risk of recurrent hemorrhage is high within the first year after the rupture, ranging from 6 to 33%, and seems to decrease thereafter [100]. In a recent meta-analysis [101], a prior hemorrhage (HR, 3.2; 95% CI, 2.1-4.3), deep arteriovenous malformation location (HR, 2.4; 95% CI, 1.4-3.4), exclusively deep venous drainage (HR, 2.4; 95% CI, 1.1-3.8), and an associated aneurysms (HR, 1.8; 95% CI, 1.6-2.0) were predictive factors of ICH. Various interventions are used in an attempt to eradicate brain AVMs: neurosurgical excision, stereotactic radiotherapy/“radiosurgery”, endovascular embolization, and staged combinations of these interventions. Treatment of brain AVMs remains associated with high risk and incomplete efficacy with an overall intracranial hemorrhage rate of 1.4 (95% CI, 1.3-1.5) per 100 person-years after intervention [102]. The only RCT comparing interventional therapy to medical management alone concerned patients with unruptured brain AVMs. The trial was stopped early because the primary outcome (a composite of death or symptomatic stroke) occurred less frequently in the non-interventional (10.1%) than in the interventional therapy group (30.7%) (HR, 0.27; 95% CI, 0.14-0.54) [103]. Results after 5 years of follow-up were presented at the International stroke conference 2016 and confirmed that medical therapy is associated with a significantly lower risk for stroke and death compared with any intervention.

Cerebral cavernous malformations (CCM) account for 10%-15% of all vascular malformations. The 5-year risks are 2.4% for a first ICH and 29.5% for a recurrent ICH [104]. Brainstem cavernous malformations are associated with a higher incidence of symptomatic hemorrhage (2.8% per person year versus 0.3% in nonbrainstem lesions) or recurrent hemorrhage (32.3% versus 6.3% in nonbrainstem lesions). A first symptomatic hemorrhage increases the risk of symptomatic recurrent hemorrhage, which decreases after 2 years [105]. There are uncertainties about the best treatment (microsurgical excision vs conservative...
management) of CCM. In a prospective, population-based study, 134 adults with CCM were identified of whom 25 underwent CCM excision. Patients who underwent surgical treatment were younger and more likely to present with symptomatic intracranial hemorrhage or focal neurologic deficit than adults managed conservatively. During 5 years of follow-up, CCM excision was associated with worse outcomes compared to patients managed conservatively [106].

Conclusion
Over the past 50 years, advances in our understanding of stroke pathophysiology have led to development of therapies with proven efficacy, including antihypertensive therapy, antiplatelet therapy, VKAs and NOACs, statins, carotid endarterectomy and carotid stenting. Hong et al. [107] reported that annual rates of recurrent strokes fell from 8.71% in trials launched in 1960s, through 6.10% in 1970s, 5.41% in 1980s, 4.04% in 1990s, to 4.98% in 2000s, and identified increasing antithrombotic use and lower blood pressures as major contributors to the decline in recurrent stroke. However, compliance with secondary stroke prevention strategies is not optimal in routine clinical practice. Therefore, to render more effective the implementation of results from RCTs into clinical practice, guideline dissemination must be coupled with effective implementation strategies [9].

References
Stroke prevention


C. Isabel, D. Calvet, J.-L. Mas

To cite this article: Isabel C, et al. Stroke prevention. Presse Med. (2016), http://dx.doi.org/10.1016/j.jlpm.2016.10.009


