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REVIEW

Secondary prevention of ischaemic stroke

Irene Volonghi, Alessandro Padovani, Elisabetta Del Zotto, Alessia Giossi, Paolo Costa, Andrea Morotti, Loris Poli, Alessandro Pezzini

Irene Volonghi, Alessandro Padovani, Paolo Costa, Andrea Morotti, Loris Poli, Alessandro Pezzini, Dipartimento di Scienze Cliniche e Sperimentali, Clinica Neurologica, Università degli Studi di Brescia, 25123 Brescia, Italy
Elisabetta Del Zotto, U.O. di Recupero e Rieducazione Funzionale, IRCCS Fondazione Don Gnocchi, 20149 Rovato (Brescia), Italy
Alessia Giossi, U.O. Neurologia, Istituto Clinico Sant'Anna, 25127 Brescia, Italy
Author contributions: Volonghi I and Pezzini A contributed to manuscript conception, data acquisition, revision, and wrote the paper; Padovani A contributed to manuscript conception, data acquisition and critical revision for important intellectual content; Del Zotto E, Giossi A, Costa P, Morotti A and Poli L contributed to manuscript conception and data acquisition; All the authors gave approval to final version of the manuscript.
Correspondence to: Irene Volonghi, MD, Dipartimento di Scienze Cliniche e Sperimentali, Clinica Neurologica, Università degli Studi di Brescia, P.le Spedali Civili 1, 25123 Brescia, Italy. irene.volonghi@hotmail.it
Telephone: +39-30-3384086 Fax: +39-30-3384086
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Abstract

In spite of a documented reduction in incidence in high-income countries over the last decades, stroke is still a leading cause of death and disability worldwide. With the ageing of the population stroke-related economic burden is expected to increase, because of residual disability and its complications, such as cognitive impairment, high risk of falls and fractures, depression and epilepsy. Furthermore, because of the substantial rate of early and long-term vascular recurrences after the first event, secondary prevention after cerebral ischaemia is a crucial issue. This is even more important after minor stroke and transient ischaemic attack (TIA), in order to reduce the risk of potentially more severe and disabling events. To accomplish this aim, acute long-term medical and surgical treatments as well as lifestyle modifications are strongly recommended. However, apart from the well-established indications to thrombolysis, studies in acute phase after a first stroke or TIA are scarce and evidence is lacking. More trials are available for long-term secondary prevention with different classes of drugs, including antithrombotic medications for ischaemic events of arterial and cardiac origin, especially related to atrial fibrillation (antiplatelets and anticoagulants, respectively), lipid lowering agents (mainly statins), blood pressure lowering drugs, surgical and endovascular revascularization procedures.

Key words: Stroke; Transient ischaemic attack; Secondary prevention; Antiplatelets; Anticoagulants; Medical stroke treatment; Carotid stenosis

Core tip: Aggressive and combination treatments in the acute phase after transient ischaemic attack or minor stroke have been shown to be beneficial in few studies, but results of ongoing randomized trials are required. On the other side, in long-term prevention the most important innovation is the advent of new anticoagulant agents for stroke prevention in atrial fibrillation. Recent trials showed efficacy and safety of thrombin and factor Xa inhibitors, compared to vitamin K antagonists, whose use is hampered by several limitations. These new drugs will potentially increase the number of patients treated according to guidelines, thus preventing a remarkable proportion of strokes.

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INTRODUCTION

Stroke is a leading cause of death and disability worldwide[1] and its burden on global health-care expenditure is supposed to increase, mainly because of the ageing population. Incidence of stroke is higher than that of myocardial infarction in some regions[2] and in spite of a mild reduction of incidence in developed countries in the last four decades, a rise of cerebrovascular events has been observed in low-income countries[3]. Stroke has also substantial indirect costs related to complications, such as post-stroke dementia, depression, falls, fractures and epilepsy.

Almost 90% of all cerebrovascular events depends on few medical conditions, including bad habits (*e.g.*, smoking, physical inactivity, diet, alcohol excess, stress) as well as arterial hypertension, cardiac diseases, diabetes, and high ratio of apolipoprotein B to apolipoprotein A1[4]. Lifestyle modifications as well as medical and surgical preventive strategies may, therefore, reduce the risk of stroke. Although primary prevention remains a milestone, effective secondary prevention plays also a fundamental role in this regard. About 30% of strokes occur in individuals with a previous transient ischaemic attack (TIA) or stroke[2], and more than 50% occur in subjects with previous vascular events of any kind[5]. Much progress has been made in the last decades in stroke prevention, and there is now evidence from randomized trials that several treatments are effective in preventing recurrences (Figure 1). In particular, at least 80% of recurrent events might be prevented with the use of a comprehensive approach that includes dietary modifications, physical exercise, blood-pressure lowering drugs, antiplatelet therapy, and statins[6].

The effect of all these different interventions on stroke risk can only be derived from population-based studies. In this regard, it has been shown that the risk of recurrent stroke in all patients in a United Kingdom population-based study after a first-ever TIA or non-disabling stroke in the period 1981-1986 was higher than the risk of the same population during 2002-2010[5]. These findings were corroborated by a recent review[7] of randomized controlled trials in secondary prevention after stroke and vascular events. Recurrent stroke and vascular events rates declined substantially in the last 5 decades, mostly because of improved blood pressure (BP) control and more frequent use of antiplatelet therapy.

In this review we will focus on medical treatment for secondary prevention in patients with first-ever TIA or ischaemic stroke and separate acute secondary prevention (*i.e.,* prevention in the first hours or days) from long-term secondary prevention. We will also deal with surgical procedures and endovascular techniques for prevention of recurrences in carotid stenosis as well as therapeutic strategies in stroke associated with patent foramen ovale (PFO).

EARLY SECONDARY PREVENTION

Background

The risk of recurrent stroke is higher during the first 90 d after an index event, longitudinal studies showing that approximately 1 out of 2 recurrences in the first year post-stroke occurs within the first 90 d[8-12]. The 90-d risk of recurrence after a TIA has been reported to be as high as 17%, with the greatest risk in the first week[13,14]. In this regard, prospective studies have shown that stroke risk after a TIA or minor stroke is 3.1% (95%CI: 2.0-4.1) at 2 d and 5.2% (3.9-6.5) at 7 d[7,15]. After a stroke or TIA, the risk of recurrence is still high in the first month (4%) and year (12%) but falls down to about 5% per year thereafter[15]. For this reason, secondary prevention should be started urgently in the acute phase after TIA or minor stroke. Identifying patients at higher risk of recurrence is, therefore, crucial. For such a purpose several risk scores have been created. Comparison between these scores is hampered by differences in index event, methodology and factors taken into account. To date, the ABCD2 score combined with diffusion-weighted imaging (DWI) data (ABCD2I)[16-19] appears as the best predictor of the early risk of stroke after a TIA. The recently validated ABCD3I score, including carotid stenosis in addition to abnormal DWI, showed even higher predictive power, although c-statistics were less convincing in the validation set[20].

The evidence for acute treatment after TIA and minor stroke is derived from few small randomized trials, extrapolation of results from larger trials in other settings, and on two non-randomized studies of a combination of preventive treatment started urgently[21]. The Early Use of Existing Preventive Strategies for Stroke (EXPRESS) study[22] was nested in a population-based study of all acute TIAs and strokes in the Oxfordshire and compared urgent assessment and treatment (phase 1) with appointment-based clinic assessment and primary care-initiated treatment (phase 2). Results demonstrated a reduction of the 90-d risk of stroke recurrence from 10.3% in phase 1 to 2.1% in phase 2. Similarly, in the SOS-TIA study[23], urgent intensive treatment was associated with a better prognosis and a low rate of recurrent events.

Based on the results of these studies, guidelines now recommend that patients with suspected TIA should be quickly referred to a TIA clinic or to a medical centre providing rapid evaluation and appropriate treatment. In such patients, urgent vascular imaging (ultrasound, cranial tomography angiography or magnetic resonance angiography) in addiction to standardized emergency diagnostic tests, including cranial tomography or magnetic resonance imaging, electrocardiography and laboratory tests are recommended[24,25].

However, the relative contribution of antithrombotic therapy, revascularization techniques, statins and antihypertensive drugs in stroke prevention remains uncertain.

Antithrombotic treatment

Aspirin is the only antiplatelet drug evaluated in the acute phase of stroke. Given within 48 h of onset of major ischaemic stroke it reduces 14-d morbidity and mortality, mostly by reducing the risk of early recurrent stroke[26]. However, the optimal dose of aspirin has not been stud-

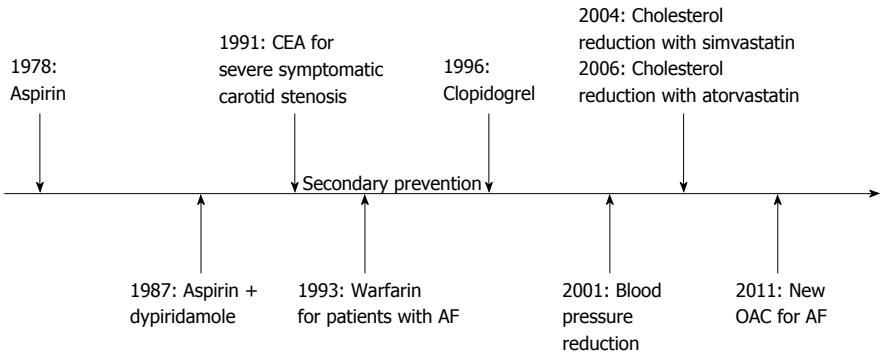

Figure 1 Medical and surgical treatments which have been proved to be effective for secondary prevention after stroke or transient ischaemic attacks in the last decades. OAC: Oral anticoagulants; CEA: Carotid endarterectomy; AF: Atrial fibrillation.

ied in head-to-head comparison. A recent meta-analysis by Chen *et al*[27], including studies in which daily doses of aspirin ranged between 160 to 325 mg, found no heterogeneity of effect on different outcomes. Similarly, optimal timing of initiation of aspirin therapy has not been studied in randomized trials. Though unproven, it seems reasonable to start aspirin therapy as soon as possible, ideally within 48 h of stroke onset. Furthermore, aspirin effect may be negligible in patients at high risk for early recurrence, such as those with stroke or TIA due to arterial thromboembolism[28]. Alternative approaches in these cases, based on the combination of multiple antiplatelet agents with different mechanisms of action, seem, therefore, reasonable. The combination of aspirin and clopidogrel is, actually, more effective than aspirin alone in preventing vascular recurrences and death in acute coronary syndromes[29]. In line with these findings, there is some evidence that a short course of more intensive antiplatelet treatment might be effective also in the acute phase after TIA and minor stroke[21]. Among 731 patients with acute ischaemic stroke or TIA (onset within 3 h) enrolled in five small trials, the addition of clopidogrel to aspirin was associated with a nonsignificant trend toward a reduction in recurrent stroke and an increase in major bleedings[30]. Although dual therapy seems not effective in lacunar strokes[31], it may be more effective than single antiplatelet therapy in preventing early recurrence in patients with acute symptomatic atherothrombosis, according to the recent Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Event trial[32] conducted on a Chinese stroke population. Because of these inconsistencies, the results of three ongoing trials investigating the safety and efficacy of dual and triple antiplatelet therapy[33-35] are required before definite recommendations can be made.

Antihypertensive agents

An increase of BP values (even in previously normotensive patients) during the acute phase of ischaemic stroke, followed by a spontaneous decline starting within 90 min of symptoms onset[36] is common finding after stroke. Although extreme arterial hypertension is clearly detrimental, as it might exacerbate oedema and favor the haemorrhagic transformation of ischemia, a moderate increase of BP values during the acute phase of stroke may improve the perfusion of the ischaemic tissue, leading to better outcomes. Conversely, an impairment of cerebral perfusion by excessive BP lowering may exacerbate the ischaemic damage, an effect that is even more evident in conditions of chronically damaged autoregulation, such as in elderly subjects, or in cases of severe carotid stenosis[37]. Unfortunately, the ideal range of BP values to be maintained early after stroke has not yet been determined. Larger trials with well-defined criteria are needed. At present, many clinicians in their daily clinical practice consider a BP greater than 220/120 mmHg an indication to active BP lowering[36]. However, this threshold might be different in cases with minor cerebral damage, such as TIA or minor strokes, where the reduction of cerebral perfusion is likely to be of less concern. In line with this view, antihypertensive therapy started immediately after the acute event did not negatively influence the outcome in the EXPRESS[22] and SOS-TIA[23] studies.

Although antihypertensive medications are effective in the long-term secondary prevention after stroke and TIA[38], the issue of early BP lowering after a cerebrovascular event is still uncertain, recent trials suggesting no benefit[39-41]. In the Controlling Hypertension and Hypotension Immediately Post-Stroke trial[39], oral nimodipine started within 48 h after ischaemic stroke onset in 350 patients was associated with a higher mortality rate and similar functional outcome. The Scandinavian Candesartan Acute Stroke Trial[41], comparing candesartan to placebo given within 30 h of ischaemic or haemorrhagic stroke, showed no difference in the composite endpoint of vascular death, myocardial infarction or stroke after 6-mo follow-up. Similarly, in the Continue or Stop Post-Stroke Antihypertensive Collaborative Study trial[40], continuation of antihypertensive therapy during hospitalization for ischaemic stroke was not associated with a reduction of 6-mo mortality or cardiovascular event rate, when compared to discontinuation of preexisting antihypertensive drugs.

Lipid lowering agents

In the acute phase after a cerebrovascular event statins might be beneficial because of their pleiotropic effects. These include a neuroprotective effect, limiting damage

and improving recovery (in particular for major strokes), as well as an antithrombotic effect, which in turns may prevent early recurrences (especially in TIAs and non disabling strokes). The benefits related to neuroprotective effects are perhaps more evident in the first 3 to 7 d after stroke and with higher doses of statins, as suggested by some observational studies and clinical data[42-44]. However, data from the fast assessment of stroke and transient ischaemic attack to prevent early recurrence pilot trial are discordant[45]. In this recent trial patients who presented with TIA or minor stroke within 24 h of symptoms onset were randomly assigned to simvastatin or placebo. No evidence of benefit of simvastatin was shown in the primary outcome of recurrent strokes within 90 d. Furthermore, a recent meta-analysis, including 8 randomized controlled trials, found insufficient evidence to establish safety and effectiveness (also in terms of secondary prevention) of statin use in the acute phase after ischaemic stroke[46]. Similarly, initiation of statin therapy within 14 d following the onset of acute coronary syndromes does not reduce significantly the risk of death, myocardial infarction or stroke up to 4 mo[47]. The major ongoing studies aimed at further assessing the benefit of early statin administration mainly focus on functional outcomes instead on the prevention of early recurrences[46].

Glycemic control

Hyperglycemia is common during acute ischaemic stroke, being present in more than 40% of patients, mostly among those with a history of diabetes[48,49], and it is associated with worse outcome. So far, only 1 randomized efficacy trial of hyperglycemia treatment in acute stroke, the Glucose-Insulin-Stroke Trial-UK[50], has been reported. Nine hundred and thirty-three patients with acute ischaemic stroke within 24 h of symptom onset, not previously treated with insulin, were randomized to unblended intravenous treatment with insulin, potassium, and glucose versus saline for 24 h. Although the results of this trial in terms of clinical outcomes were neutral, the key questions remain unanswered because of the trial design. Thus, the definitive efficacy and safety of earlier and greater reductions in serum glucose levels during acute ischaemic stroke remain to be studied. In the meantime, it is reasonable to treat hyperglycemia to maintain blood glucose levels in a range of 140 to 180 mg/dL, preventing hypoglycemia with close monitoring, according to the current American Diabetes Association guidelines for glycemic contro[51]. No data are available for the treatment of diabetes in the setting of TIA or minor strokes, but it seems reasonable to apply the same recommendation as in major strokes. Furthermore, information concerning the value of hyperglycemic control in early secondary prevention of stroke, as well as in long-term secondary prevention, is lacking.

LONG-TERM SECONDARY PREVENTION

Evidence from randomized controlled trials for long-term secondary prevention of ischaemic stroke is more robust than for acute treatment.

Antithrombotic treatment

Ischaemic stroke is a heterogeneous clinical condition and the end-result of different underlying mechanisms: atherothrombosis (30%), cardioembolism (20%), small-vessel disease (25%). Approximately 25% of cases have no detectable cause (cryptogenic). Elucidating the mechanism of stroke is crucial to select the most appropriate therapeutic strategy and prevent further events.

Cerebral ischaemia of arterial origin: Antiplatelet agents are the cornerstone for secondary prevention of ischaemic events in patients with noncardioembolic strokes. Commonly used antiplatelet agents are aspirin, dipyridamole , and clopidogrel. Aspirin is an irreversible inhibitor of cyclooxygenase-1, which in turn inhibits the formation of thromboxane A2. Dipyridamole increases cyclic AMP by inhibiting platelet phosphodiesterase E5. Clopidogrel is a thienopyridine P2Y12 adenosine diphospate receptor blocker. Ticlopidine, which has the same mechanism of action as clopidogrel, is no longer recommended because of its side effects.

Aspirin, the most commonly used antiplatelet drug, is recommended for secondary prevention after cerebral ischaemia of arterial origin at a dose of 30-325 mg daily[24,25,52]. In order to reduce bleeding complications, after the acute phase (generally 1 or 2 wk after the event) the aspirin dose may be reduced to 75-100 mg[52]. However, in a meta-analysis of trials for secondary prevention of stroke, the relative reduction in stroke risk achieved by aspirin is small, being only 13%[53]. To date, the three large trials[54-56] which investigated whether vitamin K antagonists (VKAs) are more effective than aspirin for this indication, showed no difference, irrespective of the intensity of anticoagulation. Several trials have studied other antiplatelets as an alternative or in addition to aspirin. The second European Stroke Prevention Study (ESPS2) trial[57] and the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)[56] investigated the efficacy of the combination of aspirin plus dipyridamole versus aspirin alone. Meta-analysis showed a relative risk reduction of 18% in the vascular events in favour of the combination therapy[58]. In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study, clopidogrel achieved a non-significant 7.3% reduction in relative risk of the composite outcome of stroke, myocardial infarction or vascular death, when compared to aspirin[59]. The combination of aspirin plus clopidogrel was compared with clopidogrel alone in the Aspirin and Clopidogrel compared with Clopidogrel Alone after Recent Ischaemic Stroke or TIA in High-risk Patients (MATCH) trial[60] and with aspirin monotherapy in the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) trial[61]. Both trials showed higher rates of bleeding complications in the dual antiplatelet arm which overcome any beneficial effect. A more recent study, comparing clopidogrel plus aspirin with aspirin

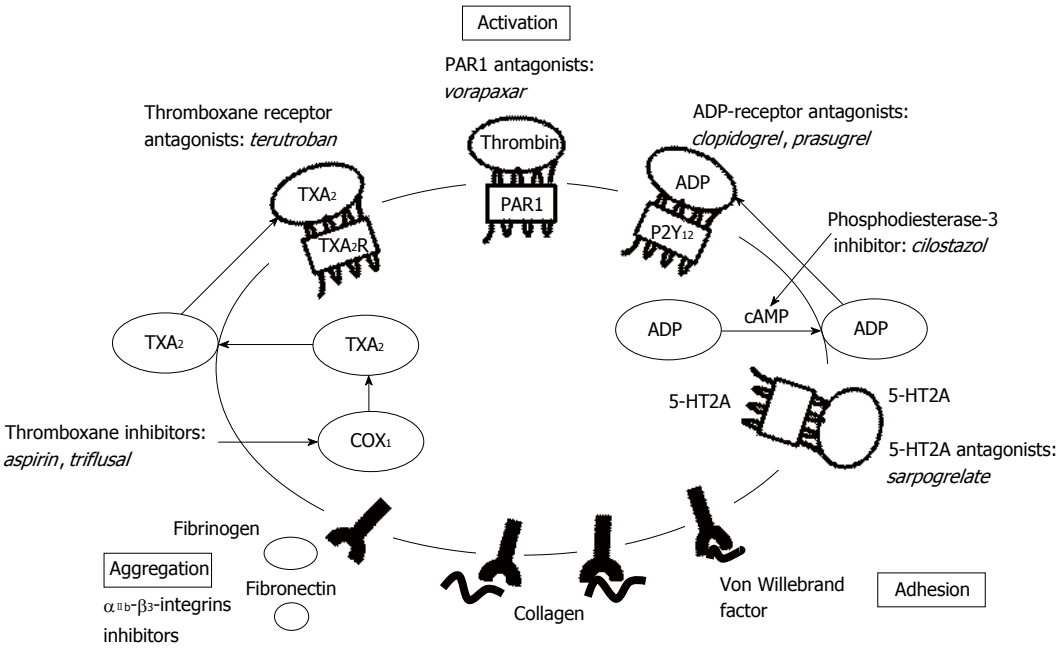

Figure 2 Old and new antiplatelet agents and their mechanism of action. PAR1: Proteinase activated receptor 1; ADP: Adenosine diphosphate; TXA_2: Thromboxane A_2; cAMP: Cyclic adenosine monophosphate; COX_1: Cyclooxygenase-1; 5-HT2A: 5-hydroxytryptamine (serotinin) receptor 2A.

alone in recent lacunar strokes confirmed these results[31]. Although in indirect comparisons the combination of aspirin plus dipyridamole was more effective than clopidogrel[62], the non-inferiority Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial did not confirm this result, showing a similar rate of recurrent stroke in both treatment groups[63]. Furthermore, the rates of discontinuation and of major systemic hemorrhages were higher in the aspirin plus dipyridamole group.

Current therapies have several limitations, including a weak inhibition of platelet function with modest clinical effect, blockade of only one platelet pathway, slow onset of action (*i.e.,* for clopidogrel), high bleeding risk, and interpatient response variability with poor inhibition of platelet activity. The concept of "antiplatelet resistance" has been proposed for those patients experiencing recurrences during correct antiplatelet therapy. It occurs when the drug biochemically fails to inhibit platelet activation, as measured by *in vitro* platelet function assays. Proposed mechanisms responsible for this phenomenon include drug-drug resistance and genetic polymorphisms of antiplatelet metabolism or drug-receptor site. However, because of the lack of a standardized assay and the poor correlation between antiplatelet resistance and recurrent clinical events, currently there is no indication to screen patients for antiplatelet resistance[64,65]. For clopidogrel, in particular, it seems prudent to avoid interactions of drugs with a well-known effect on hepatic cytochrome p450, as it has been demonstrated that these drugs might affect clopidogrel metabolism[64]. Consequently, in the last years, other antiplatelet agents with different mechanisms of action have been investigated and compared to aspirin (Figure 2). Triflusal is a thromboxane inhibitor structurally related to aspirin with a similar efficacy in preventing vascular events, but a lower risk of bleeding, in spite of more non-haemorrhagic adverse gastrointestinal events[66]. Cilostazol is a phosphodiesterase-3 inhibitor which represents a promising alternative to aspirin in Asian people with stroke. A meta-analysis including two randomized clinical trials concluded that cilostazol is more effective than aspirin in the prevention of vascular events secondary to stroke, causes more frequently minor adverse effects, but less frequently bleeding complications[67]. The Prevention of Cardiovascular Events in Ischaemic Stroke Patients with High Risk of Cerebral Haemorrhage (PICASSO) trial is an ongoing study aimed at randomizing patients with previous stroke and high bleeding risk (*i.e.*, patients with a symptomatic or asymptomatic old cerebral haemorrhage) to aspirin or cilostazol (and to probucol)[68]. Sarpogrelate, a selective inhibitor of 5-hydroxytryptamine receptors, has been investigated in comparison with aspirin and turned out to be non-inferior to the latter for prevention of stroke recurrences, with fewer bleeding events[69]. Terutroban, which is a specific antagonist of the thromboxane A2 receptor, was no more effective than aspirin for prevention of stroke in the large Prevention of Cerebrovascular and Cardiovascular Events of Ischaemic Origin with Terutroban in Patients with a History of Ischaemic Stroke or TIA (PERFORM) trial[70]. Finally, vorapaxar is a novel antiplatelet agent that selectively inhibits the cellular action of the thrombin through antagonism of proteinase activated receptor 1. In a recent trial[71] in which vorapaxar was compared to placebo in patients with vascular events, it reduced the risk of cardiovascular death or ischaemic events in patients with stable atherosclerosis who were receiving standard therapy. However, it increased major bleedings, including intracranial haemorrhages.

On the basis of these trials, international guidelines

Table 1 Antiplatelet therapy after non-cardioembolic stroke or transient ischaemic attack

	Options	Recommendation
AHA/ASA[25]	Aspirin (50-325 mg); aspirin plus dipyridamole; clopidogrel	Aspirin, aspirin plus dipyridamole or clopidogrel
ESO[24]	Aspirin; aspirin plus dipyridamole; clopidogrel; triflusal	Clopidogrel or aspirin plus dipyridamole
ACCP[52]	Aspirin (75-100 mg); clopidogrel; aspirin plus dipyridamole; cilostazol	Clopidogrel or aspirin plus dipyridamole

AHA/ASA: American Heart Association/American Stroke Association; ESO: European Stroke Organisation; ACCP: American College of Chest Physicians.

Table 2 $CHADS_2$, CHA_2DS_2VASC, and HAS-BLED risk stratification methods

$CHADS_2$	
Congestive heart failure	1
Hypertension	1
Age ⩾ 75 yr	1
Diabetes mellitus	1
Stroke, TIA, or thromboembolism	2
Maximum score	6
CHA_2DS_2VASc	
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ⩾ 75 yr	2
Diabetes mellitus	1
Stroke, TIA, or thromboembolism	2
Vascular disease (previous MI, PAD, or aortic plaque)	1
Age 65-74 yr	1
Sex category (female sex)	1
Maximum score	9
HAS-BLED	
Hypertension	1
Abnormal renal/liver function	1 point each
Stroke	1
Bleeding history or predisposition	1
Labile INR	1
Elderly (age > 65 yr)	1
Drugs (*e.g.*, concomitant antiplatelet/NSAID) or alcohol	1 point each
Maximum score	9

TIA: Transient ischaemic attack; LV: Left ventricular; MI: Myocardial infarction; PAD: Peripheral artery disease; NSAID: Nonsteroidal inflammatory drugs; INR: International normalized ratio.

still vary, but most recommend aspirin plus dipyridamole or clopidogrel as first line therapy in long-term secondary prevention of stroke. If these are not available or contraindicated, aspirin monotherapy, triflusal and cilostazol are alternatives (Table 1). However, even if both aspirin plus dipyridamole and clopidogrel alone are statistically superior compared to aspirin alone, clinical superiority is at best minimal. Furthermore, if tolerance profile is included in judgment of efficiency, then aspirin or clopidogrel monotherapy should be advised as the first-line therapy, since aspirin plus dipyridamole and aspirin plus clopidogrel carry higher rates of discontinuation and of bleeding complications, respectively. If also economic considerations are taken into account, then aspirin therapy remains the best choice[72].

Patients who present with a first or recurrent stroke are commonly already on antiplatelet therapy. To date, for patients experiencing a stroke during aspirin therapy, there is no evidence that increasing the dose of aspirin provides additional benefit. Moreover, although alternative antiplatelet agents are often considered, no single agent or combination has been studied. In such a situation it is important to take into account the compliance to therapy, as well as other vascular risk factors and possible different stroke mechanisms.

Cerebral ischaemia caused by atrial fibrillation: Roughly 20% of all TIAs and ischaemic strokes have a cardiac origin, most commonly caused by atrial fibrillation (AF). AF is associated with a five-fold increased risk of stroke, the yearly risk varying from 0.2% in patients with AF alone to more than 10% in individuals with other risk factors[73]. The major risk factors for stroke in AF patients are a history of stroke or TIA, advancing age, hypertension, systolic BP (SBP) > 160 mmHg, and diabetes. These and other risk factors have been used to create several scores for stroke risk calculation, in order to recognize patients who could benefit from anticoagulation. The most widely used model for stratification of stroke risk is $CHADS_2$ score (Table 2). However, although the score is simple and has been externally validated it does not reliably discriminate between patients with low risk, who do not need anticoagulation, and patients at intermediate risk, who do[73]. This has prompted to the development and the external validation in independent cohorts of a new score, the CHA_2DS_2VASc score (Table 2). Because of the inclusion of newly recognized risk factors for stroke, this score allows a better stroke risk stratification in patients who are considered at low or intermediate risk for stroke[74]. Beside quantification of stroke risk, another important issue is the stratification of bleeding risk associated with anticoagulation. Among the schemes created for such a stratification, the most frequently used is the HAS-BLED score (Table 2), which was originally derived from a cohort of 3456 patients with AF and a one-year follow-up[75]. HAS-BLED score, which has been validated in external cohorts, correlates with the risk of intracranial bleeding, a score of more than 3 identifying patients at high bleeding risk. In these conditions, it does not necessarily mean that anticoagulation should not be initiated but that such therapy warrants special caution, control of modifiable risk factors, and close monitoring[73]. Difficulty arises in clinical practice when patients have key risk factors for both ischaemic stroke and major bleeding (*e.g.*, age, hypertension, or previous stroke). Among these factors, previous stroke and increasing age are more strongly associated with ischaemic stroke than with intracranial bleeding[76,77].

Recommendations for patients with AF and a his-

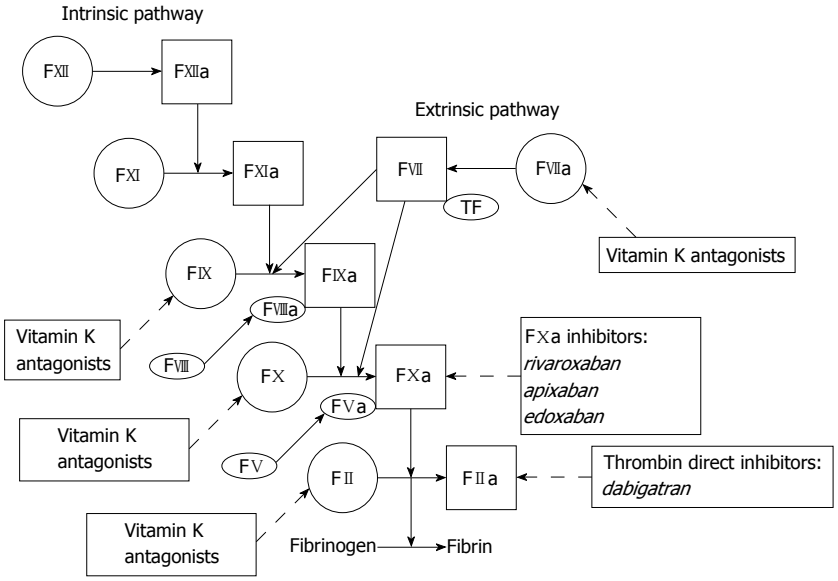

Figure 3 Vitamin K antagonist and new anticoagulant mechanism of action. F: Factor.

tory of stroke and TIA are based on the pooled effect of anticoagulation in primary and secondary prevention studies, as data on secondary prevention are limited to few studies. The first of these studies is the European AF Trial[78], in which patients were randomly allocated to VKAs, 300 mg/d-aspirin, or placebo. VKAs turned out to be the most effective treatment, despite a higher number of major haemorrhages. The findings were confirmed in patients with previous TIA or ischaemic stroke enrolled in the Stroke Prevention in AF Ⅲ trial[79], which was halted early because patients assigned to fixed low-dose VKA (INR 1.2-1.5) plus aspirin 325 mg daily had four times more ischaemic events, compared to those allocated to regular VKA dose. A further trial in patients with recent cerebral ischaemia and AF found 15% reduction of recurrences with VKA than with indobufen[80]. Adjusted-dose warfarin (target INR 2.0-3.0) turned out to be significantly more effective than the combination of aspirin plus clopidogrel in the AF Clopidogrel Trials with Irbesartan for prevention of Vascular Events (ACTIVE)[81,82]. ACTIVE W was stopped prematurely because of an excess of primary outcomes in the aspirin plus clopidogrel group than in warfarin group. ACTIVE A included patients who were not eligible for VKAs and showed a small advantage for the combination of clopidogrel and aspirin compared to aspirin alone in preventing ischaemic events, but with more bleedings.

Despite their effectiveness, VKAs have many limitations, including slow onset and offset of action, interindividual variability in their effect, narrow therapeutic index, food and drug interactions and reduced synthesis of all vitamin K-dependent proteins[83]. It has been calculated that at least a third of patients with AF who are at risk for stroke are either not started on VKAs therapy or discontinue the therapy. These limitations have prompted to the development and assessment of other agents that target the coagulation cascade at sites different from those of classic VKAs: factors Xa and direct thrombin inhibitors (Figure 3). The first of these agents, Ximelagatran, a factor Xa inhibitor, was investigated in two trials[84,85]. It resulted as effective as warfarin in prevention of stroke with fewer bleedings, but it turned out to be hepatotoxic and was then withdrew. Dabigatran, a thrombin inhibitor, was compared to dose-adjusted warfarin in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial[86] in doses of 110 and 150 mg twice daily in approximately 12000 patients, 20% of whom had a history of TIA or stroke. The lower dose of dabigatran was non-inferior to warfarin in reducing the rate of stroke or systemic embolism, while the higher dose was superior. Both doses significantly reduced major bleedings compared with warfarin in patients younger than 75 years, whereas in elderly patients the lower dose was associated with a similar rate and the higher dose with an increased rate of major bleedings[87]. The factor Xa inhibitor rivaroxaban (20 mg daily) was compared with warfarin in the Rivaroxaban-Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF (ROCKET-AF)[88]. The study population in this trial was at high risk of stroke: 55% of patients had previous stroke or TIA and 90% had either a previous stroke or TIA, or three or more risk factors for stroke (mean $CHADS_2$ score 3.5). Rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism and had a similar adverse effect profile. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF trial[89] apixaban was better than warfarin in reducing the rate of embolic events and was associated with significantly less major bleedings, less intracranial haemorrhages and lower mortality. Finally, the Apixaban *vs* Aspirin to Prevent Stroke (AVERROES) trial investigated apixaban (5 mg twice daily) versus aspirin (81-324 mg daily) in patients with AF who were unsuitable or unwilling to receive VKAs[90].

Table 3 Anticoagulation therapy after stroke or transient ischaemic attack in patients with atrial fibrillation

	Recommendation	Alternatives in patients unsuitable to anticoagulation
AHA/ASA[25]	Warfarin (INR 2.0-3.0)	Aspirin
ESO[24]	Warfarin (INR 2.0-3.0)	Aspirin plus dypiridamole
ACCP[52]	Dabigatran (150 mg twice daily)	Aspirin plus clopidogrel

AHA/ASA: American Heart Association/American Stroke Association; ESO: European Stroke Organisation; ACCP: American College of Chest Physicians; INR: International normalized ratio.

The rate of stroke or systemic embolism was significantly lower with apixaban than with aspirin, whereas the rates of major bleeding, intracranial haemorrhage, gastrointestinal bleeding, and myocardial infarction were similar in both groups. Another large phase Ⅲ trial with a new anticoagulant, edoxaban, is ongoing[91]. The proportion of patients with AF who were enrolled in all these trials and had a previous stroke or TIA varied between 14% in AVERROES and 55% in ROCKET-AF. In each trial, the absolute rate of stroke or systemic embolism was higher in patients with a previous stroke or TIA than in those without, but the relative effect of each new anticoagulant compared to warfarin in the prevention of stroke or systemic embolism was consistent among patients with or without previous cerebral ischaemic events. Similarly, the relative effect of each new agent on major bleeding did not differ[92-95]. Indirect comparisons suggest that the relative effects of each of the new oral anticoagulants compared with warfarin were consistent for stroke and systemic embolism, haemorrhagic stroke, and mortality, but not for myocardial infarction and extracranial major bleeding[96-102]. Similar results have been confirmed in a recent meta-analysis of data from 12 phase Ⅱ and phase Ⅲ randomized controlled trials comparing new oral anticoagulants with warfarin[103].

The majority of current guidelines still regard VKAs at INR 2.0-3.0 to be the standard treatment after cerebral ischaemia of cardiac origin, including AF, for patients who are suitable for such therapy, with few exceptions, on the basis of recent findings concerning new anticoagulants[24,25,52] (Table 3). Although these drugs have some advantages compared to warfarin, the unknown long-term safety profile, the absence of an antidote in the case of bleeding and their costs are important issues to consider.

Antihypertensive agents

Long term management of hypertension significantly reduces the risk of recurrent events. A meta-analysis of 7 randomized controlled trials including 15527 patients with TIA or stroke randomly allocated to treatment group within 1-14 mo after the event, showed reduction of recurrent stroke, myocardial infarction and vascular death[38]. Benefit was present irrespective of a previous diagnosis of hypertension and risk reduction was greater with larger BP lowering. However, there is uncertainty regarding the class of drugs to prefer because of the small number of trials included. Significant reductions in recurrent stroke were seen with diuretics alone and in combination with angiotensin-converting enzyme inhibitors (ACEIs) but not with β-blockers (BBs) or ACEIs used alone; nonetheless, statistical power was limited, particularly for the assessment of β-blockers, and calcium channel blockers (CCBs) and angiotensin receptor blockers (ARB) were not evaluated in any of the included trials. One of the largest trial included in the meta-analysis, the PROGRESS trial, showed a 26% reduction of the risk of stroke with the combination of perindopril and indapamide compared to placebo[104]. Patients were included regardless of baseline BP and benefits were seen even in those patients who were normotensive before admission. Since this meta-analysis, 2 additional large-scale randomized trials were published: the Morbidity and Mortality after Stroke, Eprosartan Compared to Nitrendipine for Secondary Prevention (MOSES) trial[105], and the PRoFESS trial[106]. In the MOSES, patients with an ischaemic event in the previous 2 years were randomly allocated to eprosartan (an ARB) or nitrendipine (a CCB). The risk of stroke was lower in the former group, but the benefit was only due to fewer TIAs, with no significant effect on stroke[105]. The PRoFESS failed to show a protective role of telmisartan, an ARB, in stroke prevention. Similarly, another study found no difference in a composite outcome of death from vascular causes, myocardial infarction, stroke or hospitalization for heart failure between patients with previous vascular event of any kind or diabetes randomly allocated to telmisartan or ramipril[107]. The Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events (TRANSCEND) trial[108] showed only a modest effect on prevention of vascular events in patients treated with telmisartan, thus confirming the lack of evidence of ARB effectiveness in stroke prevention.

On the basis of the available evidence, current guidelines recommend antihypertensive treatment in most patients with recent TIA or stroke, beyond the first 24 h, irrespective of a history of hypertension before admission, with some favouring the combination of an ACEI and a diuretic agent, on the basis of PROGRESS trial[25]. An absolute BP target and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of roughly 10/5 mmHg, and normal BP levels have been defined as > 120/80 mmHg[109].

However, recent studies have shown that visit-to-visit variability in BP and episodic hypertension are powerful risk factors for stroke, independently of mean BP, and that the benefits of some BP-lowering drugs are attributable partly to reduce variability in BP levels[110,111]. Although reductions in mean SBP are similar with different drug classes, CCBs and diuretics also reduce variability

in SBP, while BBs increase variability[112,113]. In particular, it has been shown that higher doses of CCBs reduce BP variability more than lower doses, and higher doses of BBs increase BP variability[114]. This means that combinations containing a low dose of BBs will have less adverse effects on variability in SBP and the associated risk of stroke, but low doses of CCBs will be less effective in reducing BP variability. Drug class effects on variability persist even in combination therapy.

Another issue to consider is the heterogeneity of stroke patients. Elderly patients seem to benefit most from a combination therapy of ACEIs and diuretics[115], as well as patients with renal impairment or diabetic nephropathy, in whom ACEIs and ARBs are recommended. The detrimental effect of such drugs on BP variability could be offset by the combination use with CCBs, as suggested in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension study[116], in whom patients with hypertension and previous vascular disease, including stroke, were randomly allocated to a combination of benazepril plus amlodipine or a combination of benazepril plus hydrochlorothiazide. The former group of patients had fewer combined cardiovascular deaths and chronic kidney disease events compared to the latter.

However, direct comparisons of drugs for secondary prevention of stroke are needed in order to recommend the most appropriate BP-lowering drug regimen. More research is required to identify ideal combinations and doses of drugs for the prevention of stroke in specific patient groups with particular reference to their effect on BP variability.

Lipid lowering agents

Although the association between serum lipid concentrations and ischaemic risk is weaker for stroke than for myocardial infarction[117], lipid levels modification is important in both primary and secondary prevention of stroke[118]. A recent observational study[44] showed a better functional outcome in stroke patients who received statin therapy before admission to hospital and who continued such a treatment during hospitalization. The prognosis was even better with higher doses of statins and when therapy was started earlier. Regarding secondary prevention, in a retrospective analysis of the Heart Protection Study (HPS) [119] restricted to subjects with a history of stroke, simvastatin did not significantly reduce the risk of stroke. In contrast, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial[120] showed a 16% reduction in stroke recurrence in patients with previous stroke or TIA, not of cardiac origin, randomized to atorvastatin 80 mg daily versus placebo, within 6 mo from index event. One concern in the SPARCL trial and in the subset of patients in HPS[119] who had a stroke before randomization was a significant increase in the risk of haemorrhagic stroke in patients allocated to statin treatment[121]. Further analysis showed that much of excess risk of haemorrhagic stroke on atorvastatin therapy was in patients with a small vessel disease stroke as qualifying event, either of haemorrhagic or ischaemic type[122]. Although in the former group there was no overall benefit, in the latter the net benefit was still in favour of treatment because of a reduction in ischaemic recurrences[122]. This suggests that statin therapy should be initiate only in patients with atherosclerotic stroke or in presence of other noncerebrovascular indications, such as coronary heart disease or diabetes[123].

Another important clinical issue relates to low-density lipoprotein (LDL) concentration. In a meta-analysis of all statin trials that looked at intense LDL lowering versus standard treatment, achievement of an LDL concentration of 100 mg/dL resulted in 16% relative reduction in risk of stroke. Subanalysis of the SPARCL trial showed a 28% reduction in stroke risk with a LDL concentration lower than 70 mg/dL in comparison with a level of 100 mg/dL[124,125]. The Treat Stroke to Target trial[126] is an ongoing study aimed at unravelling the issue regarding the optimal LDL target to reach. The working hypothesis of this trial is that the achievement of an LDL concentration of 70 mg/dL is better than 100 mg/dL in patients with previous atherosclerotic TIA or stroke. The Optimal BP and Cholesterol Targets for Preventing Recurrent Stroke in Hypertensive (ESH-CHL-SHOT) trial[127] will be started soon to address this issue. Its purpose, indeed, is to investigate both SBP and LDL cholesterol levels to achieve to optimize secondary prevention. Regarding lipid-lowering treatment in particular, the patients will be randomly allocated to one of two different LDL targets, 70 to 110 mg/dL or < 70 mg/dL, using different statins, including simvastatin, pravastatin, fluvastatin, atorvastatin or rosuvastatin.

Furthermore, there is still uncertainty regarding whether to start with high-dose or low-dose statin therapy, considering benefit and potential side effects. The SPARCL trial[120] reliably showed that high-dose atorvastain at 80 mg/d reduces the risk of stroke and other cardiovascular recurrences in patients with non cardioembolic stroke. It is however unclear, in the absence of randomized comparisons in patients with stroke, if lower doses of atorvastatin are equally or less effective than the high-dose regimen. There is evidence that atorvastatin at 80 mg/d provides significant reductions in the risk of cardiovascular events and stroke beyond that provided by a 10-mg dose in patients with coronary disease[128]. However, the high-dose regimen was complicated more frequently by higher rates of adverse events and discontinuation, both in Treating to New Targets (TNT) trial[128] and SPARCL trial[120]. Moreover, the Food and Drug Administration issued a warning regarding increased risk of myopathy in patients taking simvastatin at 80 mg/d, especially if taken in combination with CCBs, which are frequently used in patients with stroke. Although the SPARCL results support the use of high-dose atorvastatin for secondary prevention of stroke, it is unclear whether the highest currently approved doses of statins have neuroprotective effects. It is also unknown if other hydroxymethylglutaryl-coenzymeA reductase inhibitors, in different doses, could be potentially effective in pre-

vention of stroke recurrences. In this regard, two trials are ongoing to investigate the combined effect of this class of drugs[127] and that of pravastatin[129] in particular in long-term secondary prevention after stroke.

On the basis of available data the American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend statin therapy with intensive lipid-lowering effect for secondary prevention among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-level ≥ 100 mg/dL, and who are without known coronary heart disease. They suggest, as a target, a reduction of at least 50% in LDL or, alternatively, an LDL level of < 70 mg/dL[25].

Other medications used to treat dyslipidemia include niacin, fibrates, and cholesterol absorption inhibitors. These agents can be used by patients intolerant to statins, but the evidence of their efficacy for prevention of stroke recurrence is scarce. Niacin has been associated with a reduction in cerebrovascular events[130], whereas gemfibrozil reduced the rate of total strokes among men with coronary artery disease and low levels of high-density lipoprotein cholesterol (≤ 40 mg/dL) in the Veterans Affairs HDL Intervention Trial. The latter result was no more significant when adjudicated events alone were analyzed[131].

Surgical procedures

Percutaneous PFO closure: PFO is a common embryonic defect of the interatrial septum, being present in up to 25% of healthy people. In a meta-analysis PFO was found to be significantly associated with increased risk of stroke in younger patients with cryptogenic stroke, especially when atrial septal aneurysm (ASA) is also present[132]. This leads to the assumption that PFO may be the cause somehow associated to stroke occurrence, although it may also be an incidental finding[133]. The role of PFO in determining the risk of recurrence is uncertain, as well. In a substudy of the PFO in Cryptogenic Stroke Study (PICSS)[134] there were no differences in the rates of recurrent strokes in those with or without PFO, as well as no demonstrated effect on outcomes based on PFO size or presence of ASA. In contrast, the study of Mas *et al*[135] reported higher recurrence rates of stroke associated with both PFO and ASA, indicating that the presence of both these cardiac abnormalities was a predictor of an increased risk of recurrent stroke, whereas isolated PFO, whether small or large, was not. Thus, the natural history after cerebrovascular events in patients with PFO remains insufficiently defined. As a consequence, the optimal management strategy for treating patients with cryptogenic stroke who are discovered to have a PFO remains to be determined. Observational studies on medical treatment in patients with PFO with either antiplatelets or warfarin reported a risk of recurrent stroke or TIA ranging from 3% to 12% during the first year[136]. Both larger PFO size and a greater degree of right-to-left shunt increased the risk of paradoxical embolism in one study[136]. Of note, observational data for the comparative effectiveness of anticoagulants versus antiplatelet agents for secondary prevention after stroke associated to PFO show a significant benefit of warfarin, whereas the only relevant randomized study, coming from a subgroup of PICSS[134], found a non-significant trend in favor of warfarin over aspirin. On the basis of this evidence, AHA guidelines state that there are insufficient data to establish the superiority of warfarin over aspirin for secondary stroke prevention after stroke or TIA in patients with PFO[25]. However, warfarin might be more beneficial in presence of deep venous thrombosis or ASA, according to the European Stroke Organization guidelines[24]. Another therapeutic possibility is percutaneous PFO closure, which has supplanted surgical procedures. Case series and nonrandomized comparisons have long suggested that closure is a highly efficacious procedure and have led to the rapid off-label adoption of this intervention[137]. In contrast, recent randomized controlled trials failed to identify any statistically significant difference between closure and medical treatment for secondary prevention after stroke[138-140]. However, such trials have several limitations and low statistical power. In the Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or TIA due to Presumed Paradoxical Embolism through a PFO (CLOSURE) trial[138] the main limitation was the low outcome rate, compared to previous observational studies, thus pointing to a failure to select patients with PFO-related events. This may, in part, be attributable to a reluctance to randomize those patients with cryptogenic stroke who appear most likely to have had a PFO-related event (*i.e.*, patients with clinical indicators of paradoxical embolism, such as large shunt, associated ASA, Valsalva maneuver at onset of stroke, or absence of any conventional stroke risk factors). Other limitations of this trial include idiosyncratic effects, such as *in situ* thrombosis or other mechanical complications, with the use of the obsolete STARFlex device, which may have increased the outcome rates in the intervention arm, as well as the short follow-up, that may be inadequate to capture the benefit of the intervention[137]. The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial[139] confirmed the results of the CLOSURE trial in intention-to-treat analysis, in spite of important differences between the two studies with respect to the study design, the population included, and the device tested. In the RESPECT trial[139] the enrollment criteria were more stringent and the follow-up period was longer than in the CLOSURE. Moreover, the Amplatzer PFO Occluder, as compared to STARFlex used in the CLOSURE, was associated with higher effective closure rate. Finally, although different in terms of population and endpoints, the Percutaneous Closure of PFO in Cryptogenic Stroke (PC) trial[140] corroborated previous results. However, unlike the results of the CLOSURE trial, the results of the RESPECT and the PC trials have encouraged the supporters of PFO closure. The advocates of closure focus on the modest statistical power of these trials, the substantial relative effect size of the point estimates in both trials, the signifi-

cance of the per-protocol and as-treated analyses in the RESPECT, and arbitrariness of the conventional *P*-value threshold of 0.05. Although the controversy over efficacy may not be settled, it is worth noting that the safety profile of Amplatzer device appeared to be superior to that of STARFLex device tested in the CLOSURE. This supports the hypothesis that PFO closure, in certain conditions, could be superior to medical treatment and reinforces the need to carry on trials with more selected populations. Indeed, other trials are ongoing, such as the PFO Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial[141] and the GORE® HELEX® Septal Occluder/GORE® Septal Occluder for PFO Closure in Stroke Patients (REDUCE) trial[142]. However, like previous analyses, these new studies are hampered by a slow and skewed enrollment since most patients assumed to be at high risk undergo percutaneous closure. Beside, stroke pathophysiology is multifactorial, and the diagnosis of PFO-mediated paradoxical embolism is presumptive. Both a PFO and a cryptogenic stroke may coexist without causal relation in a given patient. In this case, obviously, PFO closure will not reduce the risk of recurrence. Current guidelines, which are antecedent to these recent trials, do not recommend closure because of the paucity of data[25]. However, pending other trials and based on RESPECT, it would be reasonable to discuss closure with Amplatzer device in young patients (< 50 years) with a substantial shunt and a cortical infarct, in the absence of known vascular risk factors[143].

Carotid endarterectomy and stenting for large-artery atherosclerosis

Beside medical therapy, the mainstays of treatment options for symptomatic large-artery atherosclerosis are carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS), the latter being emerged more recently as an alternative to surgical intervention to prevent recurrent strokes.

CEA plus medical therapy is more effective and safe than medical therapy alone in secondary prevention after stroke for symptomatic patients with > 70% carotid stenosis according to 3 major trials, the European Carotid Surgery Trial[144], the North American Symptomatic CEA Trial[145], and the Veterans Affairs Cooperative Study[146]. However, in all these trials medical therapy did not include aggressive atherosclerotic medical management based on statins, antihypertensive agents, antiplatelets other than aspirin, and smoking cessation, thus meaning that the benefit of surgery today may be less than in the early trials. Uncertainty exists for patients with symptomatic stenosis in the range of 50% to 69%, for whom CEA should be considered only with appropriate case selection when the risk-benefit ratio is favorable for the patient. The timing of CEA after an acute event is controversial, with experts advocating waiting anywhere from 2 to 6 wk[25]. However, early surgery (< 2 wk) turned out to be beneficial, according to pooled analysis of trials. Furthermore, early intervention (< 3 wk) may be beneficial and safe in low-risk patients with TIA and minor strokes, and in those without haemorrhagic transformation[25].

CAS is a percutaneous, less invasive procedure that has emerged as an interesting alternative to CEA for the treatment of extracranial carotid artery disease, especially thanks to the advances in endovascular technology, including embolic protection devices (EPD) and improved stent design. Complication rates are comparable to CEA. Although advantages related to the less invasive procedure, CAS durability remains unproven. The largest randomized trial in symptomatic patients, the Carotid and Vertebral Artery Transluminal Angioplasty Study 2 trial[147], showed comparable outcome between the two procedures, also in the long-term follow-up. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy trial[148] which was ended after the second interim analysis owing to the low rate of recruitment, showed similar rates of periprocedural stroke or death and ipsilateral ischaemic stroke up to 2 years between CEA and CAS. However, the fact that only 27% of patients with CAS in this study used EPD may have skewed the outcome. Because EPD reduce periprocedural stroke rates, they have been required in all stenting trials since then. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial[149] randomized both symptomatic and asymptomatic high risk patients, showing that CAS was not inferior to CEA. However, a high percentage of patients were asymptomatic (70%), thus limiting the applicability of the results to symptomatic ones. The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial[150] showed higher rates of periprocedural stroke or death at 30 d and within 4 years, as well. However, the results of this trial are influenced by the limited experience of the operators, the use of five different stents and seven different cerebral protection devices, and the fact that EPD were optional in the early phase of the study. The most important trial on this topic is the Carotid Revascularization Endarterectomy Versus Stenting Trial[151], which included patients with both symptomatic and asymptomatic carotid disease in similar proportions. It demonstrated that both procedures had similar safety and efficacy profiles for all patients, according to gender and the presence or not of previous cerebrovascular events. However, patients aged 70 years or older had better outcomes with CEA for the primary endpoint (any stroke, death or myocardial infarction (MI) within 30 d and ipsilateral stroke during long-term follow-up) and less adverse events. Younger patients had greater benefit from CAS than older subjects. The CAS group had a greater percentage of patients with stroke within the first 30 d after the procedure, but a lower rate of MI events. In trials of symptomatic patients, stenting was associated with a significantly higher risk of 30-d stroke or death, particularly in people over 70 years, compared to CEA, whereas the long-term rate of ipsilateral stroke were similar for both interventions[152]. However, stenting was associated with less MI and cranial nerve palsies.

On the basis of these studies, current AHA/ASA

guidelines recommend that patients who have experienced a TIA or stroke within the past 6 mo and have ipsilateral carotid stenosis of 70%-90% would be candidates for CEA if the perioperative morbidity and mortality risk is less than 6%. In symptomatic patients with a 50%-60% stenosis, the decision to perform CEA depends on factors such as age, comorbidities, and sex. If a patient is a good candidate for CEA, intervention within 2 wk is recommended[25]. To date, CAS is considered an alternative option for symptomatic patients with carotid stenosis of more than 70% as determined by noninvasive imaging or more than 50% as determined by catheter angiography. CAS is also an alternative in patients deemed at high risk for surgical intervention. High risk is defined by presence of severe comorbidites and challenging anatomical features (such as prior neck intervention or irradiation, postendarterectomy restenosis, surgical inaccessible lesion, contralateral carotid occlusion, contralateral vocal cord palsy, or the presence of tracheostomy)[25]. Patients are also recommended to optimize medical therapy with antiplatelets, statins and risk factor modifications.

Angioplasty and stenting for intracranial atherosclerosis

According to the Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial[153], angioplasty and stenting of intracranial stenosis did not reduce the risk of recurrent stroke compared with aggressive medical therapy, including dual antiplatelets, statins and antihypertensive agents.

CONCLUSION

Secondary prevention with antiplatelet and antihypertensives medications, statins and anticoagulants as appropriate, should be initiated urgently after TIA or minor strokes because of the high risk of early stroke recurrence. For long-term prevention, aspirin plus dipyridamole or clopidogrel must be proposed as first-line approach after cerebral ischaemia of arterial origin. For cardioembolic strokes in patients with non-valvular AF new anticoagulation agents are challenging the current standards of VKAs. Lipid and blood-pressure-lowering treatments are warranted in all cerebral ischaemia, but recommendations about optimal drug regimen, including doses and when to start therapy, as well as target levels of LDL or BP to be achieved, are still debated. Revascularization procedures, including CEA or stenting, must be taken into consideration early after the event in patients with stroke or TIA related to carotid atherosclerotic disease.

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