Hindawi Publishing Corporation
Stroke Research and Treatment
Volume 2012, Article ID 391538, 15 pages
doi:10.1155/2012/391538

Review Article

Stroke Prevention: Managing Modifiable Risk Factors

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Received 30 July 2012; Accepted 8 October 2012

Academic Editor: Cristina Sierra-Benito

Prevention plays a crucial role in counteracting morbidity and mortality related to ischemic stroke. It has been estimated that 50% of stroke are preventable through control of modifiable risk factors and lifestyle changes. Antihypertensive treatment is recommended for both prevention of recurrent stroke and other vascular events. The use of antiplatelets and statins has been shown to reduce the risk of recurrent stroke and other vascular events. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are indicated in stroke prevention because they also promote vascular health. Effective secondary-prevention strategies for selected patients include carotid revascularization for high-grade carotid stenosis and vitamin K antagonist treatment for atrial fibrillation. The results of recent clinical trials investigating new anticoagulants (factor Xa inhibitors and direct thrombin inhibitors) clearly indicate alternative strategies in stroke prevention for patients with atrial fibrillation. This paper describes the current landscape and developments in stroke prevention with special reference to medical treatment in secondary prevention of ischemic stroke.

1. Introduction

It is estimated that 530,000 people experience each year a new ischemic stroke (IS) in the USA and on average every 40 seconds someone in the same country has a stroke [1]. In terms of mortality, stroke ranks number 4 among all causes of death after heart disease, cancer, and chronic lower respiratory disease [2]. However, it remains the first cause of adult neurological disability in developed countries [3]. About 80% of patients come back home, but about half of them needs permanent or temporary help in the home setting [4]. Data from the Framingham Heart Study showed that stroke incidence is declining over time: in particular, the age-adjusted incidence of first stroke per 1000 person-years has decreased from 7.6 for men and 6.2 for women in the period 1950–1977 to 6.2 for men and 5.1 for women in the period 1990–2004 [5]. However, a recent systematic review has shown a 42% decrease in stroke incidence in the past four decades in high-income countries and a greater than 100% increase in stroke incidence in low-to-middle income countries [6]. On the contrary, stroke severity did not vary across these periods [5].

Prevention plays a crucial role in counteracting morbidity and mortality related to IS. It has been estimated that 50% of stroke are preventable through control of modifiable risk factors and lifestyle changes. Recently, stroke prevention has been set as one of the priorities by an international community of leaders involved in this field [7], and the American Heart Association (AHA) and the American Stroke Association (ASA) have published updated guidelines for secondary prevention of stroke [8]. Among stroke risk factors, transient ischemic attacks (TIAs) confer an important short-term risk of stroke (10% within 90 days and 5% within 2 days) [9]; hypertension plays a crucial role in the risk of both ischemic stroke and intracranial hemorrhage [10]. Diabetes mellitus nearly triples while current cigarette smoking doubles this risk [11]. Atrial fibrillation, although often asymptomatic and undetected, is an important risk factor for stroke, increasing stroke risk about 5-fold throughout all ages so that its relevance could be underestimated [12, 13]. Patients with low concentrations of HDL cholesterol have been found to be at higher risk of stroke [14]. Further, depressive symptoms have been increasingly recognized as a risk factor (4-fold higher) for

stroke/TIA [15]. Primary prevention strategies that work in primary prevention of IS are treating hypertension (HTN), using statins and angiotensin-converting enzyme inhibitors (ACEIs), and anticoagulation in nonvalvular atrial fibrillation. Attention to lifestyle factors is routinely warranted in both primary and secondary IS prevention: aerobic exercise to counteract inactivity, weight loss in obesity, glucose control in diabetics, smoking cessation, and diet. Antihypertensive treatment is recommended for both prevention of recurrent stroke and other vascular events. Cholesterol lowering with statins and antiplatelets have been shown to reduce the risk of recurrent stroke and other vascular events; ACEIs or angiotensin II receptor blockers (ARBs) are indicated in stroke prevention because they promote vascular health; effective secondary-prevention strategies for selected patients include carotid revascularization for high-grade carotid stenosis and vitamin K antagonist (i.e., warfarin) treatment for atrial fibrillation. Among potentially modifiable risk factors, consensus does not exist on the role of treating, among others, hyperhomocysteinemia, coagulation disorders, and patent foramen ovale. The results of recent clinical trials investigating new anticoagulants (factor Xa inhibitors and direct thrombin inhibitors) clearly indicate alternative strategies in stroke prevention for patients with atrial fibrillation. Recently, the American College of Chest Physicians [16] and the AHA/ASA [17] have published evidence-based clinical practice guidelines for prevention of stroke in nonvalvular atrial fibrillation and antithrombotic therapy for valvular disease based on the optimal balance of thrombotic and hemorrhagic risk. The results of RCTs testing safety and efficacy of antiplatelet treatments alternative to aspirin as cilostazol, sarpogrelate, and triflusal are discussed, as well as clinical indications for combined antithrombotic medications.

This paper describes the current landscape and developments in stroke prevention with special reference to medical treatment in secondary IS prevention.

2. Hypertension Control

Arterial hypertension (HTN) is the single most important modifiable risk factor for stroke. HTN contributes to 60% of all strokes (through the following mechanisms: atheroma in carotids, vertebral arteries and aortic arch; friability of small cerebral arteries; left ventricular dysfunction and atrial fibrillation). There is a close, continuous, and approximately linear relationship between blood pressure (BP) levels and primary incidence of stroke in both hypertensive and normotensive populations. A 5-year reduction of 5-6 mm Hg diastolic blood pressure (DBP) (with mainly diuretics and beta blockers) has been associated with a 42% relative risk reduction (RRR) of first stroke [18]. Randomized trials on primary stroke prevention in middle-aged and elderly populations confirmed that treating HTN reduces the incidence of stroke. Two placebo-controlled trials (the first using chlorthalidone and atenolol, the second using nitrendipine, with the possible addition of enalapril and hydrochlorothiazide) have demonstrated 36% [19] and 42% [20] RRR for first ischemic stroke in treating systolic blood pressure (SBP) as compared to placebo. More recently, the LIFE study [21] compared losartan-based regimen versus atenolol-based regimen in 9,193 hypertensive patients with a mean followup of 4.8 years. While comparable reductions in BP were observed, losartan treatment was associated with a significant 25% risk reduction versus atenolol of fatal and nonfatal stroke. Losartan was better tolerated and seemed to confer benefits beyond reduction in BP. A recent analysis of RCTs compared first-line calcium channel blockers (CCBs) with other antihypertensive classes, in order to determine whether CCBs reduced the incidence of major adverse cardiovascular events compared to the other antihypertensive classes [22]. Eighteen RCTs, with at least 100 randomized hypertensive participants and with a followup of at least two years, with a total of 141,807 participants, were included. Although some results were not enough robust to change practice, CCBs reduced stroke as compared to beta blockers, ACEIs, and ARBs. However, diuretics were the preferred first-line treatment over CCBs to optimize the reduction of cardiovascular events and congestive heart failure. Few trials have focused on antihypertensive therapy for prevention of recurrent stroke. Two studies using ACEIs have demonstrated that, for patients with hypertension, effective control of BP reduces the risk of recurrent stroke. The Perindopril Protection against Recurrent Stroke Study (PROGRESS) [23] was started in 1996 to answer this question. In this study, about 6,000 hypertensive patients with a prior TIA or stroke in the last 5 years were randomized to receive aggressive HTN treatment (perindopril 4 mg ± indapamide 2.5 mg) versus usual care (1 drug) or placebo (1 or 2 placebo). Patients were followed up for 4 years, and the primary outcome was total strokes. Aggressive treatment was associated with a 43% RRR in stroke risk versus usual care (mean BP reduction was 12/5 and 5/3 mm Hg). The HOPE trial [24] was a RCT, with 267 participating hospitals in 19 countries. There were 9,297 patients with vascular disease or diabetes plus an additional risk factor, followed up for 4.5 years (11% of them had prior TIA or IS). Patients were randomized to receive ramipril 10 mg versus placebo. The rate of stroke and TIA were assessed. Reduction in BP was modest (3.8 SBP and 2.8 DBP). The RRR for any stroke was 32%, and the RRR of fatal stroke was 61% (17 versus 44 events) favouring ramipril. Benefits were consistent across patients' subgroups.

More recently, other trials have tested safety and efficacy of ARBs, when used alone or in combination with an ACEI, in preventing stroke recurrence in high-risk populations. In the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial [25], 20,332 ischemic stroke patients were randomized to telmisartan 80 mg or placebo. After a mean treatment of 2 years, telmisartan showed a nonsignificant lower rate of recurrent stroke versus placebo (880 versus 934; hazard ratio (HR) 0.95; 95% confidence interval (CI), 0.86–1.04). However, in a post hoc analysis, a significantly reduced number of strokes was observed in the telmisartan group compared to placebo (533 versus 608; HR 0.88; 95% CI 0.78–0.99; $P = 0.042$) [26]. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and The Telmisartan Randomized Assessment Study in aCE-iNtolerant subjects

with Cardiovascular Disease (TRANSCEND), compared telmisartan 80 mg versus ramipril 10 mg, and telmisartan 80 mg versus placebo (in patients intolerant to ACEIs), respectively. In the stroke subgroup, telmisartan 80 mg showed a trend toward reducing recurrent stroke versus ramipril 10 mg (HR 0.91; 95% CI, 0.79–1.05). In a combined analysis of PRoFESS and TRANSCEND, the incidence of the composite of stroke, myocardial infarction, or vascular death was 12.8% for telmisartan versus 13.8% for placebo (HR 0.91; 95% CI, 0.85–0.98; $P = 0.013$) [27]. The MOSES study showed for the first time superiority of an ARB (eprosartan) compared with a calcium channel antagonist (nitrendipine) in antihypertensive treatment for secondary stroke prevention [28]. In this study, 1,405 high-risk hypertensive stroke patients were randomized. BP was reduced to a comparable extent without any significant differences between the 2 groups (from 150.7/84 mm Hg and 152.0/87.2 mm Hg with eprosartan and nitrendipine therapy to 137.5/80.8 mm Hg and 136.0/80.2 mm Hg, resp.). For the same level of BP control, eprosartan was significantly more effective than nitrendipine in reducing cerebrovascular morbidity and mortality (102 strokes in the eprosartan and134 in the nitrendipine group; $P = 0.03$). Based on all these studies, the renin-angiotensin system (RAS) blockers (ACEIs and ARBs) are guideline-recognized, highly effective antihypertensive agents which offer benefits that extend beyond BP reduction alone. Experimental and clinical data suggest that reducing the activity of the RAS may have cerebroprotective effects. The Angiotensin II has hemodynamic properties (potent peripheral vasoconstrictor, stimulates aldosteron), action on endothelium (mediates endothelium dysfunction, vascular smooth cells hypertrophy), stimulates oxidative stress, including oxidation of low-density lipoprotein cholesterol (LDL-C), and inflammation (associated with expression of cellular adhesion molecules, chemotactic and proinflammatory cytokines), thus contributing to endothelial damage and arterial wall injury [29]. In a recent meta-analysis, after controlling for effects on BP control, ARBs appeared to be more effective than either ACEIs or β-blockers in stroke prevention; however, CCBs were superior to RAS blockers in stroke prevention [30]. In conclusion, epidemiological studies and clinical trials confirmed the hypothesis of managing HTN to counteract the risk of stroke. The recommendation [8] to prevent recurrent stroke is to treat HTN aggressively (Class I, Level of Evidence A); although an absolute target of BP level has not been clearly defined, benefit has been associated with an average reduction of 10/5 mm Hg, and normal BP levels have been defined as <120/80 mm 5 Class IIa, Level of Evidence B). These recommendations extend to all patients with prior IS or TIA, irrespective of history or HTN, if BP reduction is considered appropriate (Class IIa, Level of Evidence B). Studies aimed at comparing different antihypertensive drugs are insufficient and have not reached clear results, but what is clear is that the effects of antihypertensive go beyond the simple control of BP. Diuretics alone or in combination with an ACEI are indicated (Class I, Level of Evidence A). The choice of a specific drug should be individualized based on drug and patient characteristics (extracranial occlusive disease, renal impairment, cardiac disease, and diabetes) (Class IIa, Level of Evidence B).

3. Anticoagulants in Atrial Fibrillation

Patients with nonvalvular atrial fibrillation (AF) are at increased risk of stroke [12, 13]. The efficacy of warfarin over placebo has been consistently demonstrated across studies yielding an overall RRR of 68% (95% CI, 50% to 79%) and an absolute risk reduction (ARR) in annual stroke rate from 4.5% for controls to 1.4% in patients with adjusted-dose warfarin: 31 ischemic strokes will be prevented each year for 1000 patients treated [8]. Warfarin use has been also associated with a modest 1.3% annual rate of major bleeding as compared with 1% for patients on placebo or aspirin. As compared to warfarin, a weaker efficacy of aspirin has been demonstrated in a pooled analysis of three clinical trials [31]. Analysis of an additional arm of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) in patients unsuitable for vitamin K antagonists therapy [32] showed superiority of combination therapy with aspirin and clopidogrel over aspirin alone in reducing the rate of stroke (2.4% versus 3.3% per year; $P > 0.001$). However, based on the observation that the rate of major vascular events combined with major hemorrhages did not significantly differe between the two groups, aspirin remains the treatment of choice in patients with AF and a clear contraindication to vitamin K antagonists. The European Atrial Fibrillation Trial (EAFT) [33] demonstrated superiority of anticoagulation over aspirin in preventing stroke recurrence in patients with history of IS or TIA: anticoagulation was significantly more effective than aspirin (HR 0.60; 95% CI, 0.41–0.87). The incidence of major bleeding events was higher in the anticoagulation group, but low in both groups (2.8% and 0.9% per year); in absolute terms, 90 vascular events (mainly strokes) could be prevented if 1000 patients were treated with anticoagulation for one year. Aspirin demonstrated to be a valid, although less effective, alternative when anticoagulation was contraindicated, preventing 40 vascular events each year for every 1000 treated patients. More recently, a systematic review of primary prevention studies in patients with nonvalvular AF demonstrated that adjusted-dose warfarin and related oral anticoagulants reduced stroke, disabling stroke and other major vascular events by about one-third when compared with antiplatelet therapy [34]. For patients with AF who suffer an IS or TIA despite therapeutic anticoagulation, increasing the intensity of anticoagulation or adding an antiplatelet does not provide additional protection in preventing stroke while increases the risk of bleeding [31, 34]. Several new antithrombotic agents have been developed for stroke prevention in patients with nonvalvular AF. New drugs for oral anticoagulation that do not exhibit the limitations of vitamin K antagonists include direct factor Xa inhibitors and direct thrombin inhibitors. In the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III (open label, $n = 3,407$) [35] and V (double blind, $n = 3,922$) [36], safety and efficacy of the oral direct thrombin inhibitor ximelagatran (fixed dose, 36 mg twice daily) were compared

to warfarin (adjusted dose, target international normalized ratio (INR) 2.0-3.0) in patients with nonvalvular AF and at least 1 risk factor for stroke. Pooled analysis showed that the efficacy of ximelagatran was comparable (noninferior) with extremely well-controlled warfarin therapy in preventing stroke and systemic embolic events; the primary event rates were 1.65% per year and 1.62% per year in the warfarin and ximelagatran groups, respectively ($P = 0.941$). In patients with a history of stroke or TIA (about 20% of the SPORTIF population), the event rates were 3.27% per year and 2.83% per year in the warfarin and ximelagatran groups, respectively ($P = 0.625$). Intracranial hemorrhage occurred at a rate of 0.20% per year with warfarin and 0.11% per year with ximelagatran. Combined rates of minor and major bleeding were significantly lower with ximelagatran than with warfarin (32% per year versus 39% per year; $P < 0.0001$). The authors concluded that ximelagatran administered without coagulation monitoring or dose adjustment was as effective as well-controlled, adjusted-dose warfarin for prevention of stroke and systemic embolic events and was associated with significantly less total bleedings [36]. More recent trials have compared warfarin to dabigatran (RE-LY) [37], rivaroxaban (ROCKET-AF) [38], and apixaban (ARISTOTLE) [39], while in the AVERROES [40], safety and efficacy of apixaban (at a dose of 5 mg twice daily) were investigated as alternative treatment to aspirin (81 to 324 mg per day) in patients who were not suitable candidates for or were unwilling to receive vitamin K antagonist therapy. Taken together, these trials have demonstrated similar efficacy in patients with AF of these novel anticoagulants in both primary and secondary stroke prevention, with significantly lower incidences of intracranial bleeding, compared with warfarin. Of note, the AVERROES was stopped prematurely because a clear benefit in favor of apixaban was observed: apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage. Based on the results of the RE-LY study [37], and with a modest absolute reduction of stroke or systemic embolism (1.7% versus 1.1%, $P < 0.001$), the most successful alternative anticoagulant is dabigatran, given at a dose of 150 mg twice daily. A systematic review and meta-analysis of RCT has been recently performed to compare the efficacy and safety of new oral anticoagulants to those of warfarin in patients with AF [41]. The authors identified 3 studies, including 44,563 patients. Patients randomized to new oral anticoagulants had a decreased risk for all-cause stroke and systemic embolism (relative risk (RR) 0.78, 95% CI, 0.67 to 0.92), ischemic and unidentified stroke (RR 0.87, 95% CI, 0.77 to 0.99), hemorrhagic stroke (RR 0.45, 95% CI, 0.31 to 0.68), all-cause mortality (RR 0.88, 95% CI 0.82 to 0.95), and vascular mortality (RR 0.87, 95% CI, 0.77 to 0.98). Randomization to a new oral anticoagulant was associated with a lower risk for intracranial bleeding (RR 0.49, 95% CI, 0.36 to 0.66). Based on these findings, new oral anticoagulants seem to be superior to warfarin in preventing stroke and systemic embolism in patients with AF. Further, they appear to have a favorable safety profile, making them promising alternatives to warfarin. However, a recent meta-analysis of RCTs has assessed safety and efficacy outcomes in patients with AF treated with warfarin for stroke prevention compared with an alternative thromboprophylaxis strategy [42]. Eight high-quality RCTs published in the last 10 years were selected, with a total of 32,053 patients included. The pooled analysis yielded 55,789 patient-years of followup. Overall, the time spent in the therapeutic range was 55% to 68%. The annual incidence of stroke or systemic embolism in patients with AF taking warfarin was estimated to be 1.66% (95% CI, 1.41%–1.91%). Major bleeding rates varied from 1.40% to 3.40% per year across the studies. The risk of stroke per year was significantly higher in elderly patients (2.27%), female patients (2.12%), patients with a history of stroke (2.64%), and patients reporting no previous exposure to vitamin K antagonists (1.96%). The authors concluded that warfarin used as a stroke prevention agent in patients with AF was associated with a significantly lower rate of recurrent stroke or systemic embolism estimated compared to other antithrombotic treatments.

Conclusions: patients with IS or TIA with paroxysmal (intermittent) or permanent nonvalvular AF should receive anticoagulation with a vitamin K antagonist (target INR 2.5, range 2-3) (Class I, Level of Evidence A); for patients unable to take oral anticoagulants, aspirin alone is recommended (Class I, Level of Evidence A); combination therapy with aspirin plus clopidogrel carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin (Class III, Level of Evidence B) [8, 17].

Dabigatran is a useful alternative to warfarin for stroke prevention in patients with AF who do not have a prosthetic hearth valve or hemodynamically significant valve disease, severe renal failure (CrCl <15 mL/min), or advanced liver disease (impaired baseline clotting function) (Class I, Level of Evidence B) [8]. New recommendations for the clinical use of dabigatran, rivaroxaban, and apixaban as alternative treatment to warfarin have been recently released [17], also taking into account unresolved issues as lack of data directly comparing dabigatran, rivoroxaban, and apixaban to one another, the duration of followup in clinical trials, and lack of information on the increased risk of thromboembolism in noncompliant patients due to the short half-lives of these new treatments as well as to the inability to presently test their drug activity.

4. Statins in Treating Hyperlipidemia

Cholesterol levels represent an important and modifiable risk factor for coronary artery disease (CAD). However, the epidemiological association between cholesterol and stroke is controversial: direct and moderately strong, direct but fairly weak, J shaped unclear, and absent. Observational studies may be limited because cholesterol may have different effects on different stroke types; further, the incidence of stroke is lower and occurs later as compared to CAD. An association between serum cholesterol levels and both incident and recurrent stroke rate has not been clearly demonstrated. The Prospective Studies Collaboration [43] evaluated this association in pooled data of 45 prospective observational cohorts, with a total of 450,000 individuals, a mean followup

of 16 years, and a total of 13,397 strokes recorded. The analysis detected a "flat effect" of increasing cholesterol levels on stroke risk. Despite only week or no association of cholesterol levels with stroke, treatment with statins has consistently shown positive effects. The Scandinavian Simvastatin Survival Study (4S) [44] was a placebo-controlled trial which detected a 30% RRR in incidence of any stroke in patients treated with simvastatin as compared to placebo. In the Heart Protection Study (HPS) [45], 20,536 high-risk patients (CAD, occlusive arterial disease, diabetes mellitus) were enrolled in 69 UK hospitals: 13,379 (65%) with CAD, 3,280 (16%) with stroke+CAD, and 1,822 (9%) with stroke only. Patients were randomized to receive 40 mg simvastatin or placebo, and they had a followup of 5.5 years. Statin treatment was associated with a 27% RRR for all strokes, and a 25% RRR for ischemic stroke. However, no clear RRR in stroke recurrence was observed in patients with a prior stroke and no known CAD. A meta-analysis that included 16 statin trials with 34,000 patients and 860 strokes evidenced an overall 25% RRR for stroke (14% to 35%), with a nonsignificant 15% RRR (−28% to 43%) for primary, and a significant 35% RRR (18% to 49%) for secondary stroke prevention [46]. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) [47] evaluated secondary stroke prevention. The study demonstrated a 16% risk reduction of recurrent fatal or nonfatal stroke in patients randomized to 80 mg atorvastatin versus placebo.

In secondary prevention of stroke, the use of statins has shown a positive effect in both decreasing progression and/or inducing regression of carotid artery plaque and stroke recurrence. By analyzing data from all available studies on statin treatment and stroke risk, Amarenco et al. [48] demonstrated a linear relationship between low-density lipoprotein-cholesterol (LDL-C) values and RRR of stroke. Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 15.6% (95% CI, 6.7 to 23.6). This analysis also demonstrated a strong correlation between progression of carotid intima-media thickness (IMT) and LDL-C reduction. The question is why should statins prevent ischemic stroke? The possible explanations are two: (i) lipid effects (LDL-C lowering) and (ii) nonlipid effects. Among these the following have been demonstrated: (i) stabilization of atherosclerotic plaque, (ii) improvement of the endothelial function, (iii) decrease in the inflammation, (iv) decrease of platelet aggregation, (v) a direct lowering effect of blood pressure, (vi) a decrease in cardiac emboli, and (vii) miscellaneous (reduced left ventricular hypertrophy, HTN, effects on endothelial progenitor cells). Experimental data suggests that LDL-C may damage the vascular endothelium by oxidation of lipids, glycation, and oxidation of proteins. Its accumulation under the endothelium leads to activation of inflammation which triggers movements of macrophages and T cells into the intima, plaque development, and progression, as well as development of a fibrous cap over the lipid core, which ultimately leads to plaque rupture and thrombus formation. Direct evidence of the molecular mechanisms modulating the plaque composition and its instability, and of a direct effect of statins on the inflammatory processes that are supposed to be involved in the plaque rupture have been demonstrated [49].

The association of total and high-density lipoprotein cholesterol (HDL-C) with stroke risk is unclear. This association has been recently investigated in among 58,000 Finnish people aged from 25 to 74 years. During a mean follow-up period of 20.1 years, 3,914 participants developed incident stroke (3,085 were ischemic). Low levels of HDL-C and high total/HDL cholesterol ratio were associated with increased risks of ischemic stroke in both sexes. These associations attenuated after adjustment for body mass index, blood pressure, and history of diabetes [50]. Two recent meta-analyses have shown that ezetimibe coadministration with a statin provides significant additional lipid-lowering effect, allowing more patients to achieve low density lipoprotein cholesterol (LDL-C) target values [51, 52]. Although reduction of LDL-C remains the primary goal for lipid-lowering interventions, other targets (e.g., HDL-C and triglycerides) may also be important. However, there is no definitive evidence showing that raising HDL-C levels in patients on statins will result in a significant reduction in vascular events [53, 54].

Conclusions: statins are recommended to prevent the first stroke in high-risk patients to lower LDL-C level <100 mg/dL; an LDL-C < 70 mg/dL is recommended for highest risk (high risk: any of LDL > 4.1, age >45 M/55 F, positive family history, smoking, HTN, left ventricular hypertrophy; highest risk: DM or established atherosclerosis) (Class I, Level of Evidence A). A new recommendation for secondary stroke prevention: on the basis of the SPARCL trial [8], statin treatment with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events for patients with IS or TIA, evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and without known coronary artery disease (Class I, Level of Evidence B). In these patients, a target reduction of at least 50% in LDL-C or a target LDL-C level <70 mg/dL is recommended (Class IIa, Level of Evidence B). Patients with IS or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil (Class IIb, level B).

5. Diabetes Mellitus

Epidemiological studies show that diabetes is a risk factor for first ischemic stroke, while data on stroke recurrence are more sparse [8, 11]. Further, the role of tight glycemic control in reducing the risk of stroke is still uncertain [55]. Patients with diabetes have higher mortality, more severe disability, and slower recovery after a stroke, as well as higher rates of stroke recurrence at 1 month (4.9% versus 2.6%) and at 2.6 years (15.2% versus 11.4%) compared to nondiabetic stroke patients [56, 57]. In addition, the ten-year risk of ipsilateral ischemic stroke after carotid endarterectomy is higher in the presence of diabetes (HR 2.24; 95% CI 1.35–3.74; $P = 0.002$) [58]. The United Kingdom Prospective Diabetes Study (UKPDS) was a landmark study in the treatment of type 2 diabetes from the time of diagnosis [59]. This study has demonstrated that intensive treatment of type 2 diabetes versus standard treatment determined a 12% RRR

the event rate (including stroke). In the Heart Outcomes Prevention Evaluation (HOPE) [60], 3,577 people with diabetes, who had a previous cardiovascular event or at least one other cardiovascular risk factor, were randomly assigned to ramipril (10 mg/day) or placebo. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. The study was stopped 6 months early (after 4.5 years) because of a consistent benefit of ramipril compared with placebo: ramipril lowered the risk of the combined primary outcome by 25% (95% CI, 12–36, $P = 0.0004$), stroke by 33% (10–50), and, among other outcomes, total mortality by 24% (8–37). After adjustment for the changes in SBP and DBP, ramipril still lowered the risk of the combined primary outcome by 25% (12–36, $P = 0.0004$). The study demonstrated that the vasculoprotective effect of ramipril in diabetic patients was greater than that attributable to the decrease in blood pressure. A secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, which tested the effect of treatment with atorvastatin in reducing stroke in subjects with a recent stroke or TIA, investigated the effects of treatment in subjects with type 2 DM or metabolic syndrome (MetS) [61]. In this subanalysis, subjects with type 2 DM ($n = 794$) had increased risks of stroke (HR 1.62; 95% CI, 1.33–1.98; $P < 0.001$) and major cardiovascular events (HR 1.66; 95% CI, 1.39–1.97; $P < 0.001$) compared with patients with neither diabetes nor MetS ($n = 3,295$). This exploratory analysis found no difference in the effect of statins in reducing these events in subjects with or without type 2 DM. Intensive glucose therapy did not prove effective treatment in reducing the rate of cardiovascular events or death in patients with type 2 DM and prior history of cardiovascular disease, stroke, or vascular risk factors. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [62], 10,251 diabetic patients were randomly assigned to intensive glucose control (HbA1c < 6%) versus standard treatment (HbA1c 7–7.9%). The study was interrupted after 3.5 years of followup because of higher mortality in the intensive treatment group. No difference in rate of nonfatal stroke was observed between the two groups (HR 1.06; 95% CI, 0.75–1.50; $P = 0.72$). In the Action in Diabetes and Vascular Disease (ADVANCE) trial [63], 11,140 diabetic patients were randomized to intensive treatment (HbA1c ≤ 6.5%) versus standard treatment (HbA1c ≤7%). The two groups did not differ in occurrence of nonfatal stroke (HR 0.94; 95% CI, 0.84–1.06; $P = 0.32$). Also in the Veterans Affairs Diabetes Trial (VADT) trial [64], intensive glucose control did not reduce combined vascular outcomes compared to standard care (HR 1.07; 95% CI, 0.81–1.42; $P = 0.62$).

The Prospective PioglitAzone Clinical Trial in Macrovascular Events (PROactive) was designed to evaluate the efficacy of pioglitazone efficacy in preventing vascular events in patients with type 2 DM. In the subset of patients with history of stroke enrolled in the study ($n = 486$ in the pioglitazone group and $n = 498$ in the placebo group), pioglitazone was associated with a 47% RRR in recurrent fatal and nonfatal stroke (HR, 0.53; 95% CI, 0.34 to 0.85; $P = 0.008$), and 25% RRR in stroke, MI, or vascular death (HR, 0.72; 95% CI, 0.53 to 1.00; $P = 0.046$) [65]. Intensive hypertensive treatment (SBP < 120 mm Hg) in type 2 DM has not been supported by a recent analysis of the ACCORD patients. In this study, the annual rate of the primary outcome (i.e., composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) was 1.87% in the intensive BP treatment and 2.09% in the standard-therapy group (HR, 0.88; 95% CI, 0.73 to 1.06; $P = 0.20$). The annual rates of stroke were 0.32% and 0.53%, respectively (HR, 0.59; 95% CI, 0.39 to 0.89; $P = 0.01$). Serious adverse events attributed to antihypertensive treatment were significantly more frequent in the intensive-therapy group (3.3% versus 1.3%; $P < 0.001$) [62]. Conclusions: in patients with type 2 DM with history of TIA and stroke, glucose control is recommended (Class I, Level of Evidence B) [66, 67]. Levels of HbA1c < 6.5% should not be achieved in diabetic patients with history of cardiovascular disease or vascular risk factors [62–64]. Based on the current knowledge, a target BP < 130/80 mm Hg for patients with type 2 DM is recommended [66, 67]. An ongoing trial will provide further insight on pioglitazone usefulness in preventing recurrent stroke in diabetic patients.

6. Antiplatelet Therapy

Within the established efficacy in stroke prevention through pharmacological and lifestyle control of modifiable vascular risk factors, a central role is played by antiplatelets. Aspirin represents the prototype of all antiplatelets. It acts by inhibiting the cyclooxygenase pathway with subsequent reduction in platelet thromboxane A2 synthesis and partial block of the final step of platelet aggregation. In a recent meta-analysis of 16 secondary prevention trials (17,000 individuals at high average risk, 43,000 person-years, 3,306 serious vascular events) comparing long-term aspirin versus control, treatment with aspirin reduced of about a fifth the rate of total stroke (2.08% versus 2.54% per year, $P = 0.002$), with a nonsignificant increase in haemorrhagic stroke [68]. Second generation platelet inhibitors such as thienopyridines (e.g., ticlopidine or clopidogrel) work by blocking the platelet adenosine diphosphate (ADP) receptor; they may offer greater preventive efficacy, especially in specific populations of atherothrombotic disease patients. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study [69], over 19,000 patients at high risk of recurrent stroke were randomized to either treatment with clopidogrel 75 mg/day or aspirin 325 mg/day for a mean follow-up period of 1.9 years. Clopidogrel reduced the risk of major cardiovascular events (IS, MI, or vascular death) in a small but statistically significant manner compared with aspirin (RRR 8.7%; 95% CI, 0.3 to 16.5; $P = 0.043$). However, subgroup analysis revealed that the RRR was statistically significant only in PAD but not in stroke nor in myocardial infarction (MI) patients.

In the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke (MATCH) study [70], 7,599 patients were randomized to receive either clopidogrel 75 mg plus aspirin 75 mg or clopidogrel 75 mg alone. Combination therapy was not superior to clopidogrel alone in preventing

primary composite outcomes (IS, MI, vascular death, or rehospitalization for any ischemic event), with significant increase in major bleeding complications. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial [71] evaluated whether the addition of clopidogrel to aspirin better prevented recurrent stroke. In this trial, 15,603 patients with cardiovascular disease or multiple vascular risk factors for cardiovascular disease (35% had history of cerebrovascular diseases in the previous 5 years) were randomized to clopidogrel 75 mg plus low-dose aspirin (75–162 mg) or placebo plus aspirin (75–162 mg). The two groups did not differ in the rates of nonfatal IS (1.7% versus 2.1%; $P = 0.07$) and had similar rates of intracerebral hemorrhage (0.3%). Patients in the combination arm treatment had a higher rate of moderate bleeding (not of severe or fatal). The study did not demonstrate superiority of combination treatment over aspirin in the subgroup of patients with prior history of IS or TIA. Dipyridamole is a phosphodiesterase inhibitor which inhibits platelet aggregation. The European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) [72] was a randomized, nonblinded study, comparing aspirin (30–325 mg) and dipyridamole (200 mg twice daily; 83% extended-release dipyridamole) versus aspirin (30–325 mg) alone in 2,763 patients who had TIA, monocular blindness, and minor stroke (modified Rankin score ≤3) in the 6 months prior to enrollment. The mean follow-up was 3.5 years. Combined treatment conferred an absolute risk reduction of 1% for primary outcome (death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or fatal bleeding complications). Despite few study weaknesses have been detected (nonblinded, nonstandard aspirin doses, divergence of significance between the on-treatment and intention-to-treat analyses, high rate of discontinuation therapy in the combination treatment arm), this study provided additional evidence of superiority of combined therapy with aspirin plus extended-release dipyridamole compared to aspirin alone in stroke prevention in patients with noncardioembolic IS.

Further, similar rates of recurrent stroke were observed with combination dipyridamole plus aspirin compared with clopidogrel, with no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke [73]. In the PERFORM study [74], the selective thromboxane-prostaglandin receptor antagonist terutroban (30 mg per day) was compared with aspirin (100 mg per day) in prevention of IS and cardiovascular events in patients with a recent noncardioembolic IS. The primary efficacy endpoint was a composite of any IS, any MI, or other vascular death. The study was stopped prematurely for futility, because it showed similar rates of the primary endpoint with terutroban and aspirin, without safety advantages for terutroban. Recommendations for patients with history of noncardioembolic stroke or TIA are aspirin (50–325 mg/die) monotherapy (Class I, Level of Evidence A), the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I, Level of Evidence B), and clopidogrel 75 mg monotheraphy (Class IIa, Level of Evidence B), which are all acceptable options as initial therapy for prevention of recurrent stroke or other cardiovascular events. Clopidogrel is a reasonable alternative option in patients allergic to aspirin (Class IIa, Level of Evidence C). The addition of aspirin to clopidogrel increases the risk of hemorrhage, and the combination therapy is not recommended unless specific indications exist (i.e., coronary and other vascular stent or acute coronary syndrome) (Class III, Level of Evidence A). For patients who have an IS while on aspirin, alternative antiplatelets may be considered although this has not been assessed yet by RCTs (Class IIb, level of Evidence C) [8].

6.1. Double Antiplatelet Therapy or Treatment with both an Anticoagulant and Aspirin. Dual antiplatelet treatment (aspirin plus clopidogrel or, less frequently, ticlopidine) has assumed a central role in the setting of cardiovascular disease and its use is increasing in the field of cerebrovascular disease as well. Safety and efficacy of dual- (aspirin+dipyridamole and aspirin+clopidogrel) versus mono-antiplatelet therapy have been compared in a recent systematic review and meta-analysis of RCTs [75]. This analysis included 12 RCTs involving 3,766 patients with noncardioembolic acute (≤3 days) IS or TIA. In comparison with mono-antiplatelet therapy, dual antiplatelets were associated with reduced early stroke recurrence, composite vascular events (stroke, MI, and vascular death), and combined stroke, TIA, acute coronary syndrome, and all death. Dual therapy was also associated with a trend to increase major bleeding. However, a recent RCT involving 3,020 patients with recent symptomatic lacunar infarcts has shown that the addition of clopidogrel to aspirin 325 mg daily did not significantly reduce the risk of recurrent stroke as compared with aspirin alone (2.5% per year versus 2.7% per year; hazard ratio, 0.92; 95% CI, 0.72 to 1.16), while significantly increased the risk of bleeding and death (2.1% per year versus 1.1% per year ; hazard ratio, 1.97; 95% CI, 1.41 to 2.71; $P < 0.001$) [76].

Further, the combination of antiplatelet and anticoagulant therapy might be indicated for stroke prevention in a variety of conditions including AF, profound left ventricular dysfunction, and after prosthetic heart valve replacement. For this reason, the use of triple antithrombotic therapy (a dual antiplatelet regimen plus warfarin) is expected to increase along with an aging population. However, this approach carries an increased risk of bleeding complications [77].

Both the presence and degree of benefit associated with dual antiplatelet therapy are likely to depend on characteristics of the specific patient. The CHARISMA trial [71] demonstrated that dual antiplateltes (ASA plus clopidogrel) were more effective than ASA alone especially in patients with clinically evident cardiovascular disease (i.e., in secondary prevention CV death, MI, and stroke) rather than in patients with high risk profile but not established atherothrombotic disease (i.e., primary prevention). However, moderate bleeding events significantly increased (2% versus 1.3%, HR 1.6, CI 1.16 to 2.20; $P = 0.004$) [77].

Several data indicate that the increased frequency of bleeding is influenced by both duration of therapy and ASA dosage: a dose <100 mg of ASA when given in combination with a thienopyridine seems to be associated

with similar anti-ischemic efficacy but reduced bleeding event rates [78]. Further evidence is needed to define more complex antithrombotic treatment algorithm required in patients with different vascular comorbidities in whom more aggressive prevention approach is required.

6.2. Alternative Antiplatelet Treatments: Cilostazol, Sarpogrelate, and Triflusal. Cilostazol is a selective and potent selective type III phosphodiesterase (PDE 3A) inhibitor, leading to inhibition of platelet aggregation and vasodilation, with potential use in atherosclerotic conditions, including stroke [79, 80]. The Cilostazol Stroke Prevention Study (CSPS) [81, 82] was designed to evaluate safety and effectiveness of cilostazol in prevention recurrent stroke. In this double-blind, placebo-controlled trial, 1,095 patients (544 receiving cilostazol 100 mg twice daily and 548 receiving placebo) were enrolled. The recurrence rate of IS was significantly reduced by cilostazol with a 41.7% RRR (number needed to treat = 41). A subgroup analysis showed that patients with lacunar infarcts had a significant reduction in recurrence of IS, whereas no statistical significance was reached in patients with atherothrombotic or mixed-type infarctions. These results are in line with another PDE inhibitor, dipyridamole, currently used in stroke prevention, which caused withdrawal of therapy in 26% of patients in the ESPRIT trial [72].

Further potential use of cilostazol in clinical practice may derive from the benefits observed in diabetic patients. In patients with type 2 DM, cilostazol 100–200 mg/day significantly prevented IMT progression and reduced the number of silent brain infarctions which have been associated with increased risk of developing dementia [83]. Based on the results and the observed reduced efficacy of antiplatelets in diabetic patients [84, 85], cilostazol might represent an alternative to standard care at least in the subgroup of patients with lacunar stroke. This hypothesis was tested in the Cilostazol versus Aspirin for Secondary Ischemic Stroke Prevention (CASISP) trial [86], which was a pilot, multicentre, and double-blind trial, which randomly assigned 301 patients to cilostazol and 299 patients to aspirin treatment, with a follow-up period of 12 to18 months. The primary endpoint was any recurrence of stroke (IS, haemorrhagic stroke, or subarachnoid hemorrhage) during the trial period, as assessed by a follow-up MRI study. Cilostazol was associated with not-significant RRR of stroke (HR 0.62; 95% CI, 0.30–1.26; $P = 0.185$) and significantly lower rates of symptomatic and asymptomatic cerebral hemorrhages (7 versus 1, $P = 0.034$). The results suggested that cilostazol appeared to be a more effective and safer alternative to aspirin in secondary stroke prevention. Whether a reduced risk of intracranial bleedings is peculiar of PDE inhibitors, as suggested by the reduced occurrence of cerebral hemorrhage observed in patients treated with dipyridamole plus aspirin compared to aspirin alone [72], should be further investigated. Safety and effectiveness of cilostazol compared with aspirin in preventing recurrent stroke in patients with previous IS or TIA of arterial origin have been recently assessed. In this systematic review, two RCTs with 3,477 Asian participants were selected. Compared with aspirin, cilostazol was associated with a significantly lower risk of composite outcome of vascular events (6.77% versus 9.39%; RR 0.72, 95% CI, 0.57 to 0.91), haemorrhagic stroke (0.53% versus 2.01%, RR 0.26, 95% CI, 0.13 to 0.55), and minor adverse effects (8.22% versus 4.95%, RR 1.66, 95% CI, 1.51 to 1.83) [87].

Based on the available data, cilostazol seems to be more effective than aspirin in the prevention of vascular events in high-risk Asian patients. Further RCTs testing larger cohorts of vascular patients are needed in order to address the exact potential of cilostazol in the management of atherosclerosis and stroke prevention.

6.3. Sarpogrelate. The antiplatelet agent sarpogrelate is a selective inhibitor of 5-hydroxytryptamine receptors with dose-dependent inhibitory effect on platelet aggregation [88]. Similar to cilostazol, this drug has been used for years to treat patients with PAD in Japan. Based on this, its efficacy and safety in secondary stroke prevention has been tested in RCT versus aspirin in a Japanese ischemic stroke patients cohort [89]. In this study, 1,510 patients with recent infarction were enrolled which were randomly assigned to receive either sarpogrelate (100 mg $\times$ 2/day) or aspirin (81 mg/day). The study failed to demonstrate noninferiority of sarpogrelate to aspirin for prevention of stroke recurrence. However, bleeding events were significantly fewer with sarpogrelate than aspirin, although this might have been the result of the lower efficacy of sarpogrelate. A subgroup analysis of this study confirmed the superiority of aspirin in most patient subgroups, except in diabetics that could represent a specific target population of this drug, at least among Japanese stroke patients [90].

6.4. Triflusal. The efficacy of the antiplatelet agent triflusal (600 mg/d) versus aspirin (325 mg/d) for prevention of vascular events after stroke has been reported in a randomized, double-blind, and multicenter study. In this study, 2,113 patients with IS or TIA were randomly assigned to receive either triflusal ($n = 1{,}058$) or aspirin ($n = 1{,}055$). After a mean follow-up period of 30.1 months, the incidence of nonfatal stroke (HR, 1.09; 95% CI, 0.82 to 1.44), nonfatal acute myocardial infarction (HR, 0.95; 95% CI, 0.46 to 1.98,) and vascular death (HR, 1.22; 95% CI, 0.75 to 1.96) showed no differences between groups. A significantly higher incidence of major hemorrhages in the aspirin group was recorded (HR, 0.48; 95% CI, 0.28 to 0.82). The overall incidence of hemorrhage was significantly lower in the triflusal group (16.7% versus 25.2%) (OR, 0.76; 95% CI, 0.67 to 0.86; $P = 0.001$). This study failed to show significantly superior efficacy of triflusal over aspirin in the long-term prevention of vascular events after stroke, but triflusal was associated with a significantly lower rate of hemorrhagic complications [91]. Further, a metaanalysis of 4 clinical trials comparing triflusal with aspirin including a total of 2,994 patients with IS or TIA who were followed from 6 to 47 months was performed. Of relevance, the authors reported no significant differences between aspirin and triflusal in the risk of serious vascular events (OR for aspirin versus triflusal, 1.02; 95% CI, 0.83–1.26). Aspirin was associated

with a higher risk of hemorrhage, both major (OR, 2.42; 95% CI, 1.56–3.77) and minor (OR, 1.62; 95% CI, 1.31–2.01) [92]. Based on this metaanalysis, the European Stroke Organisation [93] recommends triflusal as an alternative to combined aspirin and dipyridamole, or to clopidogrel alone (Class I, Level A).

6.5. Carotid Endarterectomy (CEA) and Carotid Angioplasty with Stenting (CAS) in Secondary Stroke Prevention. The beneficial effect of CEA plus medical treatment versus medical treatment alone in prevention of stroke recurrence in symptomatic patients with high-grade carotid stenosis (>70%) has been extensively demonstrated over the last decades [94–96]. These trials also demonstrated that CEA did not decrease the risk of stroke recurrence in patients with a symptomatic stenosis <50%. Conversely, patients with a moderate (50% to 69%) symptomatic stenosis may benefit from an intervention if this is performed by an experienced surgeon with a perioperative morbidity and mortality rate of <6%. Carotid angioplasty and stenting (CAS) has emerged as an alternative treatment for stroke prevention in patients deemed at high risk for conventional endarterectomy. However, its efficacy of in stroke prevention has not been clearly established yet. In this regard, two RCTs failed to establish noninferiority of CAS compared with CEA: the EVA 3S [97] and the SPACE [98] trials were both stopped prematurely for reasons of safety and futility because of a higher 30-day stroke and death rate in the CAS group. A more recent RCT in the International Carotid Stenting Study (ICSS) [99] which enrolled 1,713 patients has shown that the periprocedural risks of CAS are significantly higher than those of CEA. In particular, the risk of stroke and death are increased in CAS patients (as in the EVA 3s and SPACE trials), with similar low rates of myocardial infarction.

Few studies demonstrated noninferiority or superiority of CAS versus CEA. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [100] was a small randomized trial suggesting that CAS was equivalent to CEA or even superior in high-risk patients. The carotid Revascularization Endarterectomy versus Stenting Trial (CREST) [101] was a large RCT evaluating the two procedures in symptomatic patients with up to a 4-year followup. The study results were broadly consistent with those of previous trials. In particular, an equivalence between CAS and CEA regarding the primary composite end point of stroke, myocardial infarction, or death was observed. However, the rate of stroke or death in this trial was still significantly higher in the CAS group than in the CEA group, both during the periprocedural period and at 4 years.

Despite the evidence supporting CEA over CAS in secondary stroke prevention, it has been observed that the conclusions achieved by the above-mentioned trials might be faded by several methodological differences: the most important issue is the choice of primary end point, followed by timing of the primary end point (ranging from 30 to 120 days after randomization); further, the rate of periprocedural stroke in patients treated by CAS differed between studies, underlining the importance of training of proceduralists; inclusion or exclusion of a patient with preexisting coronary artery disease also contributed in different rates of cardiac complications after the procedure. Further, in the CREST trial, CAS tended to have greater efficacy below 70 years and CEA above 70 years, possibly reflecting increased technical challenge of stenting in older patients, such as the atherosclerotic burden in the internal carotid artery and aortic arch and increased arterial tortuosity [102]. This has been confirmed by a recent meta-analysis, suggesting that stenting for symptomatic carotid stenosis should be avoided in older patients (age ≥70 years), but might be as safe as endarterectomy in younger patients [103].

More recently, a systematic review and meta-analysis of 13 RCTs of CEA versus CAS enrolling 7,484 (80% with symptomatic carotid artery stenosis) has shown that, compared with CEA, CAS significantly increased the risk of any stroke (relative risk (RR), 1.45; 95% CI, 1.06–1.99) and decreased the risk of MI (RR, 0.43; 95% CI, 0.26–0.71). Of relevance, when analysis was restricted to the two most recent trials with the better methodology and more contemporary technique, we found stenting to be associated with a significant increase in the risk of any stroke (RR, 1.82; 95% CI, 1.35–2.45) and mortality (RR, 2.53; 95% CI, 1.27–5.08) and a nonsignificant reduction of the risk of MI (RR, 0.39; 95% CI, 0.12–1.23). The authors observed that, for every 1,000 patients opting for stenting rather than endarterectomy, 19 more patients would have strokes and 10 fewer would have MIs [104]. Another meta-analysis of 11 RCT performed through 2009 (not including CREST) has confirmed that CEA was superior to CAS with regard to short-term outcomes but the difference was not significant for intermediate term outcomes [105]. Further, the SPACE trial also reported a higher two-year rate of restenosis in the CAS than the CEA group, with similar 2-year rates of ipsilateral stroke [106]. Another single-center prospective randomized study of CEA versus CAS with a long followup of 5 years has shown a significantly higher incidence of relevant restenosis and neurologic symptoms after CAS [107].

Until more data are available, CEA remains the preferred treatment choice for symptomatic severe carotid artery stenosis. However, given the lack of significant difference in the rate of long-term outcomes, the individualization of treatment choices is appropriate. More long-term data are needed.

6.6. Early CEA/CAS. CEA has traditionally been delayed from 4 to 8 weeks because of fear of hemorrhagic transformation of the ischemic infarct. Pooled analysis from the European Carotid Surgery Trail (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [108] has clearly shown that the benefit from CEA is maximal in symptomatic patients operated within 2 weeks of the index event. The analysis of long-term stroke prevention has shown that benefits from surgery decreased rapidly with time elapsed since the last neurological symptoms. Profit from CEA seems to depend not only on the degree of carotid stenosis, but also on delay in surgery after the presenting event, and the conclusion was that the procedure should ideally be done within 2 weeks of the patient's last symptoms. Rothwell et al. [109] also showed that early treatment (either

medical and/or surgical) of all patients presenting with a TIA or minor stroke can prevent up to 80% of early recurrent stroke. However, urgent CEA in preventing stroke recurrence proved effective in several observational single center studies. A prospective multicenter Italian study assessing safety and efficacy of early (1.5 days after the stroke) CEA after acute ischemic stroke has shown that if patients are strictly selected for early CEA after an acute stroke, early surgery patients have similar risks to elective surgery [110]. In the study of Ferrero et al. [111], cumulative rates of TIA/stroke and death after CEA were compared between patients undergoing to early (range, <48 hours) and delayed/deferred CEA (range, within 48 hours–24 weeks). The analysis demonstrated that early CEA in acute poststroke period for selected patients (not severe strokes and lesions <3 cm, no MCA occlusion) did not result in greater complication rate that performed delayed or deferred.

With growing experience in endovascular treatment, CAS has been proposed as an alternative to CEA, but data regarding the outcome of patients with acute stroke undergoing urgent endovascular surgery are still scarce. The main concern about CAS in urgent cases is that, while with CEA the plaque is completely removed, after stenting it is only remodeled and its stabilization is essential to avoid later embolic events. Safety and efficacy of early CAS after TIA (within 24–48 hours) has been demonstrated in single-center studies. Setacci et al. [112] reported the results of a small single-center study including 43 symptomatic patients who underwent to either early CAS (within 24 hours in TIA patient) or deferred CAS (between 1 and 30 days, in minor stroke patients) in selected patients (no major stroke, lesion <2.5 cm). The authors observed that early CAS is feasible and safe in selected patients with a first episode or recurrent TIA or minor stroke.

These studies suggest that safety and efficacy of emergency/urgent carotid endovascular revascularization depend on correct patient selection, and consequently on the reduction of the time loss between the index event and intervention, and on the specific skill of operators performing the procedure.

Recommendations. for patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence A). For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence B) [8]. When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery if there are no contraindications to early revascularization (Class IIa; Level of Evidence B).

CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter angiography (Class I; Level of Evidence B). Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist, such as radiation-induced stenosis, or restenosis after CEA, CAS may be considered (Class IIb; Level of Evidence B). CAS in the above setting is reasonable when performed by operators with established periprocedural morbidity and mortality rates from 4% to 6%, similar to those observed in trials of CEA and CAS (Class IIa; Level of Evidence B) [8].

7. Conclusions and Future Directions

Despite the increased knowledge on the relevance of controlling modifiable vascular risk factors, to keep them under control remains a challenge. Earlier studies observed that patients with identified risk factors for stroke do not follow physicians' suggestions regarding lifestyle changes or adherence to treatment prescribed to modify their risk [113, 114]. Several barriers can reduce the patient compliance to prescribed treatments: cultural gaps between physician and patients and socioeconomic factors, as well as the physician attitude [115]. In order to challenge this gap, few approaches have been attempted. Earlier studies have demonstrated that careful patient follow-up [116], intervention programs for coronary risk factor modification [117] and structured counseling provided by Stroke Prevention Clinics [118] were more effective than usual medical care in improving vascular risk factor control by increasing adherence to prescribed medications. More recently, a standardized electronic counseling (e-counseling) proved helpful in reducing BP in patients with HTN with greater reduction in SBP, pulse pressure, and total cholesterol as compared to general e-information [119]. Further, a structured risk factor modification program for secondary prevention of cardiovascular disease was found associated with a reduced risk of major vascular event, including nonfatal stroke [120], thus demonstrating that improving vascular risk factor control may translate into reduced cerebrovascular events. Based on this evidence, one of the objectives set by a panel of leaders in this field is to develop, implement, and evaluate a population approach for stroke prevention and public health communication strategies using traditional and novel (i.e., social media/marketing) techniques [7].

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