Review Article

Aspirin in Neurology

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Aspirin is widely used for the prevention of recurrent stroke in patients with transient ischaemic attack (TIA) of arterial origin, because it is effective and inexpensive. Clopidogrel and the combination of aspirin and extended-release dipyridamole are more effective than aspirin, but are also much more expensive. No other antithrombotic regimens provide significant advantages over aspirin, although cilostazol and the novel platelet protease-activated receptor-1 antagonist, SCH 530348, are currently being evaluated. Numerous trials have examined the efficacy of antiplatelet drugs, primarily aspirin for prevention of vascular events in patients with a prior TIA or stroke. Although many were small and inconclusive, the Antiplatelet Trialists' Collaboration (ATC) individual patient data meta-analysis reported that among more than 23000 patients (from 21 randomized controlled trials), antiplatelet therapy (usually aspirin) compared with placebo or untreated control continued for a mean of 29 months was associated with a 22% reduction in the odds of recurrent ischemic stroke, myocardial infarction (MI), or vascular death (17.8% versus 21.4%, $P = 0.001$).

1. Introduction

Stroke is one of the leading causes of morbidity and mortality worldwide [1]. It is also the second most common cause of dementia, the most frequent cause of epilepsy in the elderly, and a frequent cause of depression [2]. In a western population of 1 million inhabitants, 500 new transient ischemic attacks and 2,400 new strokes will occur every year. Approximately 25% of strokes are recurrent strokes or first strokes after a TIA. Most ischemic strokes occur in high-risk patients, that is, in patients who have vascular risk factors, or history of acute vascular event [3, 4], and are therefore susceptible to prevention.

2. Antiplatelet Agents for Primary Prevention

2.1. Primary Prevention with Antiplatelet Agents in Low-Risk Subjects. The benefits of aspirin for the primary prevention of vascular events have been evaluated in a meta-analysis of six trials (47,293 subjects under aspirin and 45,580 under placebo) with a mean age of 64 years [4], showing that

aspirin reduces the occurrence of coronary events and of any vascular events, but not stroke, vascular death, or all-cause mortality alone [5]. In 39,876 low-risk women aged 45 years or more, aspirin reduced the occurrence of all strokes (OR 0.83; 95% CI 0.70–0.97) and of ischemic strokes (OR 0.76; 95% CI 0.63–0.93) and was associated with a nonsignificant increase in hemorrhagic strokes, without reduction in the risk of fatal or nonfatal myocardial infarction, or vascular death [6]. No data are currently available regarding the use of other antiplatelet agents in primary prevention in low-risk subjects.

2.2. Primary Prevention with Antiplatelet Agents in High-Risk Subjects. A systematic review of randomized trials comparing aspirin with placebo in patients with high Blood Pressure (BP) showed that aspirin does not reduce stroke compared to placebo in primary prevention patients with elevated BP [7].

Patients with asymptomatic atherosclerotic plaques have an increased risk of myocardial infarction, stroke, and

vascular death, which is reduced by aspirin. Aspirin also reduces the risk of stroke after carotid artery surgery [8].

In the CHARISMA trial, patients were randomly assigned to receive clopidogrel (75 mg per day) or placebo on top of aspirin (75–162 mg per day); among patients with multiple risk factors, the rate of myocardial infarction, stroke, or vascular death was 6.6% with clopidogrel and 5.5% with placebo (RR 1.2; 95% CI 0.91–1.59), and vascular mortality was increased in the clopidogrel Group (3.9 versus 2.2%, $P = 0.01$) [9].

3. Antiplatelet Agents for Secondary Prevention

The objective of ischemic stroke prevention is based on 3 principles (Table 1) [10]. This review will focus only on the role of antiplatelet agents in stroke prevention.

One of the key difficulties in determining which antiplatelet regimen to prescribe based on results of randomized clinical trials is the variability among patients in terms of stroke etiology, which may be categorized based on infarct cause and/or location. Although there is no single classification system, ischemic strokes are commonly subdivided into large-vessel atherosclerotic, small-vessel occlusive (lacunar), cardioembolic, other known origin, or unknown or uncertain origin [11, 12].

Population-based studies indicate that around one-quarter of ischemic stroke patients have large-artery atherosclerosis, another one-quarter have lacunar infarcts, and about one-third have strokes of unknown origin. However, in clinical trials, the proportion of patients enrolled with the different subtypes is often different than this “real-world” occurrence, as about one-half of all enrolled patients have lacunar infarcts. The large number of patients enrolled in clinical trials secondary to lacunar stroke suggests that the results are most applicable to this patient population [13–15].

Due to these differences, the distribution of stroke subtypes in individual clinical trials may impact overall trial results. For example, because most clinical trials enroll fewer patients with large-artery atherosclerotic strokes, the overall number of adverse events may be lower, potentially masking any therapeutic benefit. The enrollment of a high number of patients with lacunar stroke in clinical trials may also inflate rates of bleeding because these patients may be more prone to bleeding.

3.1. Large-Artery Atherosclerotic Stroke. Atherothrombosis refers to the formation of thrombus superimposed on pre-existing atherosclerosis. This common pathophysiologic process results in morbid or fatal clinical ischemic events affecting the cerebral, coronary, or peripheral arterial circulation. Because the platelet is a pivotal mediator in the initiation and propagation of thrombus formation, antiplatelet drugs have emerged as key agents for prevention of recurrent ischemic events. Patients with large-artery strokes are the most likely to have a recurrent stroke, particularly within the first 3 months [13, 14].

However, there is controversy regarding choice of oral antiplatelet therapy in patients with vascular diseases. While

it has been established that aspirin prevents recurrent atherothrombotic events across a wide range of high-risk patients (relative risk reduction of approximately 25%) [16], it is less clear if other antiplatelet agents, such as clopidogrel or dipyridamole, alone or added to aspirin, are more effective.

3.2. Small-Artery Atherosclerotic Stroke. In the WASID study, patients with stroke or TIA resulting from stenosis of intracranial vessel stenosis were randomly assigned to receive 1300 mg aspirin or warfarin with a target international normalized ratio (INR) 2.0 to 3.0 [17]. Results showed no significant difference between groups in terms of ischemic stroke, brain hemorrhage, and vascular death; (HR, warfarin versus aspirin, 0.96; 95% CI, 0.68 to 1.37), but there was a nonsignificant elevation of bleeding with warfarin. Therefore for patients with a stroke or TIA due to stenosis of a major intracranial artery, aspirin is recommended in preference to warfarin.

3.3. Small-Artery Stroke. Small-artery (lacunar) strokes comprise more than 25% of brain infarcts and occur in patients with long-standing hypertension, and accelerated hypertensive arteriolar damage of the small penetrating arteries is operative in a large number of lacunar infarcts. Patients with lacunar infarcts demonstrate the best survival and functional recovery of any stroke subtype, regardless of the treatment strategy employed [18, 19].

Currently there is no information regarding specifically the optimal antiplatelet management of patients with lacunae, but the Secondary Prevention of Small Subcortical Strokes (SPS3) study was designed to test antiplatelet therapy 325 mg aspirin daily plus 75 mg clopidogrel daily, versus 325 mg aspirin daily plus placebo in patients with lacunar infarct, and its results are expected soon [20].

3.4. Cardioembolic Stroke. A meta-analysis of randomized trials with at least 3 months of follow up showed that antiplatelet agents reduce the incidence of stroke (RR 0.78; 95% CI 0.65–0.94) in patients with nonvalvular atrial fibrillation (NVAF), but warfarin (target INR 2.0–3.0) is more effective (RR 0.36; 95% CI 0.26–0.51) [21], especially in NVAF patients who have already had a systemic emboli, are older than 75 years, have high levels of blood pressure, or have a poor left ventricular function [22]. The ACTIVE W trial was stopped because the combination of aspirin and clopidogrel was less effective than warfarin and had a similar bleeding rate, especially in those who had been under oral anticoagulation before [23]. Nowadays aspirin is only recommended for patients with cardiogenic embolism who are unable to take oral anticoagulants.

3.5. Stroke of Other Known Origin

3.5.1. Arterial Dissection. The optimal strategy for prevention of stroke in patients with arterial dissection is not known. Options range from conservative observation to surgical approaches. A Cochrane review of 26 case series

reported no difference in death or disability between antiplatelet and anticoagulant therapy (23.7% versus 14.3% with anticoagulant; (OR 1.94; 95% CI, 0.76 to 4.91)) [24]. So for these patients antithrombotic treatment with aspirin for at least 3 to 6 months is recommended.

3.5.2. *Patent Foramen Ovale (PFO)*. Given current knowledge available, the impact of PFO with or without atrial septal aneurysm for the occurrence of a first stroke or a recurrent cryptogenic stroke remains controversial for patients with an ischemic stroke or TIA and a PFO, and antiplatelet therapy with aspirin is reasonable due to the overall benefit in all stroke patients and low complication rates [25].

4. Factors to Consider when Choosing an Antiplatelet Regimen for Ischemic Stroke Patients

Factors that must be considered when choosing an antiplatelet regimen include what comorbidities and other complications a patient presents with, what adverse events are associated with treatment, and whether the patient has any socioeconomic limitations. There are several comorbidities that merit special attention, including concomitant Coronary Artery Disease (CAD) or Peripheral Artery Disease (PAD), recent acute coronary syndrome (ACS) or coronary stenting, absolute contraindications to aspirin, and requirement for oral anticoagulation (atrial fibrillation). Patients with concomitant CAD or PAD represent a particularly high-risk population, as these patients have an even greater risk of recurrent ischemic events than those with stroke alone (Table 2) [26].

There is some concern that dipyridamole may reduce distal perfusion through the coronary steal phenomenon, although this has not been adequately tested with oral dipyridamole[27]. In addition, while the combination of aspirin plus dipyridamole has only been adequately tested in the cerebrovascular bed. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease plus both aspirin and clopidogrel are proven efficacious in all vascular beds and may be the better treatment option in these patients [28]. If the patient has an absolute contraindication to aspirin, including active peptic ulceration or aspirin hypersensitivity, clopidogrel is preferred. However, the benefits of such therapy in patients with ACS and those with coronary stents suggest that dual aspirin and clopidogrel therapy is necessary and should not be avoided in stroke patients with these conditions [28, 29]. In the future, physicians treating stroke patients may also want to consider triple antiplatelet therapy.

5. Variations in Antiplatelet Regimens

Several different aspects of the antiplatelet agents themselves may have had an impact on the interpretation of overall regimen efficacy. Numerous clinical trials have tested the

TABLE 1: Principles ischemic stroke prevention.

(i) Optimal management or vascular risk factors by lifestyle modifications or pharmacological therapy.
(ii) Removal of a potential cause, by surgery or endovascular intervention.
(iii) Antithrombotic therapy, that is, either oral anticoagulation or antiplatelet therapy.

TABLE 2: Factors to choose an antiplatelet regimen.

Comorbidities	Coronary artery disease (CAD)
	Peripheral artery disease (PAD),
	Recent acute coronary syndrome (ACS)
	Coronary stenting
Contraindications	Atrial fibrillation
	Active peptic ulceration
	Aspirin hypersensitivity
Adverse events associated with treatment	
Socioeconomic limitations	

efficacy of different antiplatelet regimens principal results are summarized in the Table 3.

Although the ESPS-2, ESPRIT, and PROfESS trials were all designed to test the efficacy of aspirin plus dipyridamole, different formulations of dipyridamole were used [30, 31]. Furthermore, as ESPRIT was an open, nonblinded trial, physicians were permitted to prescribe either a fixed dose or free combination of aspirin and dipyridamole [31]. A critical point of variability in the antiplatelet regimens is the various doses of aspirin used within and among the individual trials. The CAPRIE, ESPS-2, PROfESS, and MATCH trials each used a single dose of aspirin, although the dose itself varied from 50 mg/day in ESPS-2 and PROfESS to 325 mg/day in CAPRIE [32].

The combination of aspirin with dipyridamole has been compared with aspirin monotherapy stroke prevention among patients with TIA or stroke in several clinical trials [33–35]. Dipyridamole is a pyridopyrimidine derivative that vasodilates coronary microvessels and inhibits platelet activation by increasing levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate.

6. ESPS-2

The European Stroke Prevention Study 2 (ESPS-2) evaluated this antiplatelet agent for stroke prevention in patients with TIA or stroke in the preceding 3 months [33]. The study randomly assigned 6602 patients into 1 of 4 treatment groups: low-dose aspirin (25 mg twice daily) alone (*n* = 1649); extended release dipyridamole (ER-DP) (200 mg twice daily) alone (*n* = 1654); aspirin combined with ER-DP (same doses) (*n* = 1650); or placebo (*n* = 1649). Patients were followed up for 2 years to determine the effects of these drugs on the rate of stroke and death from any cause. Compared with placebo, each of the active treatments

TABLE 3: Studies in secondary prevention of ischemic stroke.

ESPS-2 The European Stroke Prevention Study 2	Follow up during 2 years of 6602 patients prior TIA or stroke.	Aspirin (25 mg twice daily) alone, Extended release dipyridamole (ER-DP) (200 mg twice daily) alone, Aspirin combined with ER-DP, Placebo.	The combination of aspirin and ER-DP was reported to be twice as effective for stroke prevention as either drug alone.
ATC Antiplatelet Trialists' Collaboration	10404 patients with preexisting symptomatic atherosclerotic disease from 25 trials.	Aspirin (75–150 mg daily) combined with dipyridamole versus aspirin alone.	Nonsignificant 6% risk reduction in serious vascular events (nonfatal stroke, MI, vascular deaths). The apparent reduction in nonfatal stroke was derived mainly from the ESPS-2 study and was not consistent with the findings for nonfatal stroke or nonfatal MI or vascular death in other studies.
ESPRIT European/Australasian Stroke Prevention in Reversible Ischemia Trial	2739 patients with minor ischemic stroke or TIA were randomized and followed for a mean of 3.5 years.	Oral anticoagulation (INR 2.0 to 3.0) Dipyridamole (400 mg daily) plus ASA (30–325 mg/day). ASA only (same dose).	The results were “positive” for the specified primary outcome constellation of stroke, myocardial infarct, vascular death, or major hemorrhage, but the reduction in ischemic stroke was not statistically significant.
ESPRIT- 2 European Stroke Prevention Study-2 randomized double-blind trial	3299 participants followed for two years with 363 stroke events.	Dipyridamole (200 mg twice daily). Low-dose aspirin (25 mg twice daily).	Reported reduction of recurrent stroke in 23% of patients with initial TIA/stroke relative to aspirin alone. Methodological fails led to skepticism on the part of some about the incremental value of extended-release dipyridamole plus aspirin over aspirin alone for secondary stroke prevention.
Subanalysis ESPRIT-2 De Schryver et al.	Randomized trials of individuals who were within 6 months after presentation of arterial vascular disease and who were treated for at least 1 month.	Starting therapy consisted of dipyridamole (in any dose) alone or added to another antiplatelet drug compared with placebo or antiplatelet drug(s) other than dipyridamole.	Dipyridamole alone or in combination with another antiplatelet agent compared with placebo reduced vascular events such as nonfatal stroke or nonfatal MI. There was no evidence that dipyridamole alone was more efficacious than aspirin.

TABLE 3: Continued.

ESPS-2 The European Stroke Prevention Study 2	Follow up during 2 years of 6602 patients prior TIA or stroke.	Aspirin (25 mg twice daily) alone, Extended release dipyridamole (ER-DP) (200 mg twice daily) alone, Aspirin combined with ER-DP, Placebo.	The combination of aspirin and ER-DP was reported to be twice as effective for stroke prevention as either drug alone.
PROFESS Prevention Regimen for Effectively avoiding Second Strokes	20,332 patients (mean age was 66 years, 64% were men) with recent (<120 days) ischemic stroke were randomized.	Dipyridamole (200 mg)/low-dose aspirin (25 mg) twice daily. Clopidogrel 75 mg once daily in a double-blind was also randomized to receive telmistaartan versus. placebo added to usual blood pressure care.	<p>The recurrent stroke rate was 3.6% per year for those assigned extended-release dipyridamole plus aspirin and 3.5% per year for those assigned clopidogrel. There were fewer major hemorrhages in those assigned clopidogrel ($P = 0.05$): about 1 fewer major hemorrhage per year for every 200 treated patients.</p> <p>No difference for recurrent stroke or for major vascular events between clopidogrel and extended-release dipyridamole plus low-dose aspirin, with a narrow confidence interval around the hazard ratio that excludes a clinically important difference. Trends favor clopidogrel regarding fewer major hemorrhages and better tolerance, but absolute differences are small.</p>
CAPRIE Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial	Long-term prevention of recurrent atherothrombotic vascular events in 19185 patients, including 6431 with prior ischemic stroke.	Clopidogrel (75 mg/d). Aspirin (325 mg/d).	Among all patients, clopidogrel reduced the risk of stroke, MI, or vascular death by 8.7%. For the subgroup of patients with prior ischemic stroke, the relative risk reduction (RRR) was similar and not statistically different from the overall result. The safety profile of clopidogrel was comparable with that of aspirin.
MATCH Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke randomized trial	7599 patients with recent TIA or ischemic stroke.	Aspirin (75 mg) added to clopidogrel (75 mg) was compared with clopidogrel alone.	The combination of aspirin and clopidogrel did not significantly lower the incidence of ischemic strokes, MI, or vascular death but was associated with an increase in the risk of major and life-threatening bleeding absolute risk increase.
CHARISMA and MATCH Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management, and Avoidance randomized and double-blind trial	15,603 patients with stable cardiovascular disease or multiple cardiovascular risk factors during 2.3 years mean followup.	The combination of clopidogrel 75 mg/day plus aspirin (dosage range 75 mg to 162 mg daily) was compared with aspirin alone.	Among the 3645 participants who had a prior ischemic stroke a mean of 3 months before study entry, the primary event constellation was reduced by 22%, but beware of accepting positive exploratory subgroup analyses from overall negative trials.

significantly reduced the incidence of stroke (aspirin versus placebo: 12.5% versus 15%; RRR, 18.1%; $P = 0.01$; ER-DP versus placebo: 12.7% versus 15%; RRR, 16.3%; $P = 0.04$; aspirin combined with ER-DP: 9.5% versus 15%; RRR, 37.0%; $P = 0.001$). No significant reduction in myocardial infarction (MI) or mortality was observed, although the risk reduction in ischemic events defined as stroke, MI, and sudden death confirmed the benefit of ER-DP added to aspirin. The 18% risk reduction observed with low dose compared with placebo was consistent with the benefit observed in earlier studies of low-dose aspirin (75 mg) in patients with stroke [36].

The ESPS-2 trial was the first study to show an independent statistically significant reduction in stroke risk in patients treated with ER-DP. Compared with placebo, the combination of aspirin and ER-DP was reported to be twice as effective for stroke prevention as either drug alone, indicating an additive benefit; the combination was also more effective than aspirin or ER-DP given alone.

When the results of ESPS-2 trial are analyzed together with additional trials included in the meta-analysis by the ATC, 10404 patients with preexisting symptomatic atherosclerotic disease from 25 trials comparing aspirin combined with dipyridamole versus aspirin alone were combined, and the addition of dipyridamole to aspirin was associated with a nonsignificant 6% risk reduction in serious vascular events (nonfatal stroke, MI, and vascular deaths) (11.8% versus 12.4%; odds ratio, 0.95; 95% CI, 0.86 to 1.05; $P = 0.32$) [37]. The apparent reduction in nonfatal stroke was derived mainly from the ESPS-2 study [33] and was not consistent with the findings for nonfatal stroke or nonfatal MI or vascular death in other studies. Possible reasons for this difference include the use of ER-DP in the ESPS-2 study versus short-acting dipyridamole in the other studies, differences in patient characteristics, or the play of chance, as no systematic biases were apparent in this trial. The extended release form of dipyridamole has been studied in the ESPS-2 clinical trial only, and replication of its effectiveness is warranted before widespread use of this antiplatelet preparation rather than aspirin or clopidogrel is advocated.

A recent meta-analysis by De Schryver et al. included randomized trials of individuals who were within 6 months after presentation of arterial vascular disease and who were treated for at least 1 month. Starting therapy consisted of dipyridamole (in any dose) alone or added to another antiplatelet drug compared with placebo or antiplatelet drugs other than dipyridamole. Dipyridamole alone or in combination with another antiplatelet agent compared with placebo reduced vascular events such as nonfatal stroke or nonfatal MI (dipyridamole versus placebo: RRR, 0.90; 95% CI, 0.83 to 0.98; aspirin combined with dipyridamole versus aspirin alone: RRR, 0.90; 95% CI, 0.80 to 1.00). There was no evidence that dipyridamole alone was more efficacious than aspirin [38].

7. ESPRIT

The long-awaited ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial) compared the

same agents on ESP-2 and experienced independent clinical trialists led it from the Netherlands [31, 33].

In an open-label design, 2739 patients with minor ischemic stroke or TIA were randomized and followed for a mean of 3.5 years. The results were “positive” for the specified primary outcome constellation of stroke, myocardial infarct, vascular death, or major hemorrhage, but the reduction in ischemic stroke was not statistically significant.

8. PROFESS

In the PROFESS (Prevention Regimen For Effectively avoiding Second Strokes), 20,332 patients (mean age was 66 years, 64% were men) with recent (<120 days) ischemic stroke were randomized to extended-release dipyridamole (200 mg)/lowdose aspirin (25 mg) twice daily versus clopidogrel 75 mg once daily in a double-blind design carried out at 695 sites in 35 countries. The trial was planned with a noninferiority design, and, in addition to the antiplatelet comparison, participants were also randomized to receive telmestartan versus placebo added to usual blood pressure care; this component is not discussed further here. About half (52%) of qualifying strokes were attributed to cerebral small-artery disease (i.e., “lacunar” strokes), median time from qualifying stroke to study entry was 15 days, and average followup was 2.3 years. The primary outcome was recurrent stroke (i.e., combined ischemic and hemorrhagic stroke) and was not different between treatment arms: the recurrent stroke rate was 3.6% per year for those assigned extended-release dipyridamole plus aspirin and 3.5% per year for those assigned clopidogrel (hazard ratio 1.01, 95% CI 0.92–1.11). There were fewer major hemorrhages in those assigned clopidogrel ($P = 0.05$): about 1 fewer major hemorrhage per year for every 200 treated patients.

In summary, the large PROFESS trial shows no difference for recurrent stroke or for major vascular events between clopidogrel and extended-release dipyridamole plus low-dose aspirin, with a narrow confidence interval around the hazard ratio that excludes a clinically important difference. Trends favor clopidogrel regarding fewer major hemorrhages and better tolerance, but absolute differences are small [39].

9. CAPRIE

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial compared clopidogrel (75 mg/d) with aspirin (325 mg/d) for the long-term prevention of recurrent atherothrombotic vascular events in 19185 patients, including 6431 with prior ischemic stroke. Among all patients, clopidogrel reduced the risk of stroke, MI, or vascular death by 8.7% (95% confidence interval [CI], 0.3 to 16.5; $P = 0.04$). For the subgroup of patients with prior ischemic stroke, the relative risk reduction (RRR) was similar and not statistically different from the overall result. The safety profile of clopidogrel was comparable with that of aspirin [28, 40].

10. MATCH

The Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) randomized trial was published. Aspirin (75 mg) added to clopidogrel (75 mg) was compared with clopidogrel alone among 7599 patients with recent TIA or ischemic stroke. The combination of aspirin and clopidogrel did not significantly lower the incidence of ischemic strokes, MI, or vascular death (15.7% versus 16.7%; RRR, 6.4%; 95% CI -4.6 to 16.3; $P = 0.24$) but was associated with an increase in the risk of major (2% versus 1%, $P = 0.001$) and life-threatening bleeding (2.6% versus 1.3%; absolute risk increase, 1.3%; 95% CI, 0.64 to 1.9; $P = 0.001$) [32].

11. CHARISMA and MATCH

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management, and Avoidance randomized and double-blind trial show that the combination of clopidogrel 75 mg/day plus aspirin (dosage range 75 mg to 162 mg daily) was compared with aspirin alone in 15,603 patients with stable cardiovascular disease or multiple cardiovascular risk factors during 2.3-year mean followup. The mean participant age was 64 years, 70% were men, and 42% had diabetes mellitus. The primary outcome constellation (stroke, myocardial infarct, or vascular death) was not different between treatment arms, but bleeding was increased with combination therapy. The stroke rate was low, averaging 1% per year, among all CHARISMA participants. Among the 3645 participants who had a prior ischemic stroke a mean of 3 months before study entry, the primary event constellation was reduced by 22% ($P = 0.03$), but beware of accepting positive exploratory subgroup analyses from overall negative trials [41].

CHARISMA results are best considered in the context of the MATCH (Management of Atherothrombosis with Clopidogrel in High-risk patients with transient ischemic attack [TIA] or stroke) randomized trial [32]. The MATCH trial was designed to assess the value of adding aspirin to clopidogrel (rather than adding clopidogrel to aspirin as in CHARISMA) for secondary stroke prevention. In the MATCH trial, clopidogrel 75 mg daily alone was compared to clopidogrel 75 mg daily plus aspirin 75 mg daily in 7,599 patients with recent ischemic stroke or transient ischemic attack (TIA). All strokes were nearly equal (347 clopidogrel, 339 clopidogrel plus aspirin). There was an excess of 32 non-CNS life-threatening hemorrhages among those assigned combination antiplatelet therapy (an absolute increase of 0.5% per year, $P < 0.05$). In short, MATCH does not demonstrate benefits of adding aspirin 75 mg/d to clopidogrel, and serious bleeding was significantly increased among those given the combination.

The relatively consistent results of MATCH and CHARISMA show that combined antiplatelet therapy with clopidogrel and aspirin offers uncertain, minimal benefits for long-term treatment of patients after TIA or ischemic stroke compared with single therapy with either drug

alone and that serious bleeding is clearly increased by the combination [32].

12. Conclusion

The analysis of several randomized, controlled clinical trials testing the efficacy and safety of aspirin monotherapy, clopidogrel monotherapy, aspirin plus dipyridamole, and aspirin plus clopidogrel in patients with a history of non-cardioembolic ischemic stroke, the optimal antiplatelet regimen, remains uncertain.

Antiplatelet therapy is a critical component of secondary prevention for patients with noncardioembolic ischemic stroke. It is important to understand the potential impact this variability may have on clinical trial outcomes and, thus, estimates of relative risk and safety of aspirin.

Aspirin is the only antiplatelet drug used in the primary prevention, mainly to reduce the risk of MI. In the secondary prevention of noncardioembolic ischemic stroke or transient ischemic stroke, ASA in combination with long-release dipyridamole and clopidogrel alone are considered the first choice therapy. The choice of the particular antiplatelet agent should be individualized according to the patient risk factor profiles and treatment tolerance.

Disclosure

Authors of this paper declare that the paper is review article and has not been published or submitted for publication elsewhere, and that there is no any affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript that may affect the reporting of the work submitted.

Conflict of Interests

The authors declare that they have no conflict of interests.

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