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Antiplatelet therapy in ischemic stroke and transient ischemic attack: An overview of major trials and meta-analyses

Daniel G. Hackam
Robarts Research Institute

J. David Spence
Robarts Research Institute, jdspence@uwo.ca

Antiplatelet Therapy in Ischemic Stroke and Transient Ischemic Attack

An Overview of Major Trials and Meta-Analyses

Daniel G. Hackam, MD, PhD; J. David Spence, MD

Stroke is a leading cause of mortality and disability worldwide.[1] Initial manifestations of acute cerebral ischemia, such as ischemic stroke and transient ischemic attack (TIA), are often followed by recurrent vascular events, including recurrent stroke.[2] To reduce this burden, antiplatelet therapy is a key component of the management of noncardioembolic ischemic stroke and TIA.[3] This review will focus on the evidence for 4 antiplatelets: aspirin, aspirin-dipyridamole, clopidogrel, and ticagrelor (Table). These were selected because they have been the subject of definitive trials and are the most commonly discussed antiplatelets in practice guidelines.[3,4] MEDLINE was searched for randomized trials (N>500) and meta-analyses of antiplatelets in the secondary prevention of cerebrovascular disease.

Aspirin

Acetylsalicylic acid (ASA), otherwise known as aspirin, irreversibly inactivates platelet cyclooxygenase, which is responsible for prostaglandin and thromboxane synthesis.[5] In particular, aspirin irreversibly blocks production of thromboxane A2.[6] Thromboxane A2 is a potent platelet activator and proaggregant; hence by blocking thromboxane A2 synthesis, ASA is able to achieve an antiplatelet effect.

Two large randomized trials tested the effects of aspirin in the acute phase of ischemic stroke: the IST (International Stroke Trial) and the CAST (Chinese Acute Stroke Trial).[7,8] In IST, patients received 300 mg of aspirin daily, whereas in CAST, 160 mg daily was provided. A combined analysis of 40 000 patients randomized in these 2 trials was published in 2000.[9] There was a highly significant decrease of 7 recurrent ischemic strokes per 1000 patients treated and a nominally significant reduction of 4 deaths without further stroke per 1000 patients treated. Overall, there was a net decrease of 9 per 1000 treated in the risk of further stroke or death in hospital. These data indicate strong benefit for acute initiation of aspirin after ischemic stroke but have been largely superceded by trials of dual antiplatelet therapy (DAPT) in the acute setting (Clopidogrel).[10,11]

Ten trials analyzed by the Antithrombotic Trialists' Collaboration studied the longer-term effects of aspirin started in patients with a history of cerebrovascular ischemic events.[12] These trials aggregated 6170 subjects and 1308 serious vascular events for secondary prevention poststroke or TIA. Overall, aspirin reduced the risk of serious vascular events by 19% (95% CI, 7%–25%), nonfatal myocardial infarction by 36% (95% CI, 15%–52%), major coronary events by 21% (95% CI, 5%–34%), and any stroke by 17% (95% CI, 4%–28%). Probable ischemic stroke and definite ischemic stroke were both significantly reduced (by 22% and 21%, respectively). Conversely, hemorrhagic stroke (relative risk, 1.90; 95% CI, 1.06–3.44) and gastrointestinal bleeding (relative risk, 2.69; 95% CI, 1.25–5.76) were both increased. Because absolute risk reductions in serious vascular events and ischemic strokes in secondary prevention outnumber absolute risk increases in bleeding events, the net risk-benefit ratio favors aspirin therapy in this setting. Most patients with ischemic cerebrovascular disease will be started on low-dose aspirin as either monotherapy or as part of a DAPT regimen (discussed in detail below). The optimal dose of aspirin was explored in the second Antithrombotic Trialists' Collaboration overview, published in 2002.[13] Significant risk reductions in serious vascular events were seen in trials where patients received ≥75 mg/d but not in 3 trials where patients received <75 mg/d. Because higher doses are more gastrotoxic, it has been suggested that 75 to 150 mg/d is the optimal dose range for aspirin.[13]

Aspirin-Dipyridamole

Dipyridamole is a platelet aggregation inhibitor with several mechanisms of action including (1) inhibition of platelet cAMP-phosphodiesterase; (2) potentiation of adenosine inhibition of platelet function by blocking reuptake by vascular and blood cells and subsequent degradation of adenosine; and (3) potentiation of prostacyclin (PGI_2) antiaggregatory activity and enhancement of PGI_2 biosynthesis.[14]

Dipyridamole is usually given in combination with aspirin. DAPT with aspirin and dipyridamole has been studied in 6 trials in patients with ischemic stroke or TIA; in aggregate,

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From the Division of Clinical Pharmacology, Departments of Medicine, Clinical Neurological Sciences and Epidemiology/Biostatistics and Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, Western University, London, ON, Canada.

Correspondence to Daniel G. Hackam, MD, PhD, Room 100K-2, Siebens Drake Bldg, 1400 Western Rd, London, ON N6G 2V2, Canada. Email dhackam@uwo.ca

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Table. Characteristics of Key Antiplatelet Trials and Meta-Analyses in Stroke/TIA

Trial or Meta-Analysis	Patient Population	Antiplatelet Intervention	Follow-Up	Key Results
Aspirin				
IST	19 435 patients with acute ischemic stroke within 48 h of symptom onset	Aspirin 300 mg/d vs avoid aspirin	6 mo	11 fewer deaths or recurrent strokes per 1000 treated within 14 days
CAST	21 106 patients with acute ischemic stroke within 48 h of symptom onset	Aspirin 160 mg/d vs placebo	4 wk	6.8 fewer cases of death or nonfatal stroke per 1000 treated at 4 wk
IST+CAST pooled analysis	40 000 patients with acute ischemic stroke within 48 h of symptom onset	Aspirin 160–300 mg/d vs no aspirin	3 wk	9 fewer cases of stroke or death in hospital per 1000 treated
ATC-3 meta-analysis	6170 secondary prevention patients in 10 poststroke/TIA aspirin trials	Aspirin (various doses)	not stated	17% (P=0.001) reduction in serious vascular events; 36% (P=0.003) reduction in nonfatal MI; 21% (P=0.01) reduction in major coronary events; 90% (P=0.03) increase in hemorrhagic stroke; 21% (P=0.05) reduction in definite ischemic stroke; 22% (P=0.001) reduction in probable ischemic stroke; 17% (P=0.01) reduction in any stroke
ASA-dipyridamole				
ESPS-2	6602 patients with a completed ischemic stroke or TIA within the past 3 mo	Aspirin 25 mg bid; dipyridamole 200 mg BID; aspirin 25 mg BID+dipyridamole 200 mg BID; or placebo	2 y	Composite of stroke or death was reduced by 13.2% (P=0.016) with aspirin; by 15.4% (P=0.015) with dipyridamole; and by 24.4% (P<0.001) with aspirin+dipyridamole
ESPRIT	2739 patients within 6 mo of a TIA or minor ischemic stroke of presumed arterial origin	Aspirin (30–325 mg/d) and dipyridamole (200 mg BID) vs aspirin (30–325 mg/d) alone	3.5 y	Composite of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication was reduced by aspirin+dipyridamole (HR, 0.80; 95% CI, 0.66–0.98); no increase in major bleeding complications (HR, 0.67; 95% CI, 0.44–1.03)
Aspirin-dipyridamole meta-analysis	7795 patients with cerebral ischemia of presumed arterial origin in 6 antiplatelet trials	Aspirin+dipyridamole vs aspirin alone	not stated	RR=0.82 (95% CI, 0.74–0.91) for composite of vascular death, nonfatal stroke and nonfatal MI
Clopidogrel				
CAPRIE	19 185 patients with recent ischemic stroke, recent MI, or peripheral arterial disease; included n=6431 with recent ischemic stroke	Clopidogrel 75 mg/d vs aspirin 325 mg/d	1.91 y	8.7% (P=0.043) relative risk reduction for composite of ischemic stroke, MI or vascular death; 7.3% (P=0.26) relative risk reduction in stroke subgroup for this end point
MATCH	7599 patients with recent ischemic stroke or TIA and at least 1 additional vascular risk factor	Clopidogrel 75 mg/d plus aspirin 75 mg/d vs clopidogrel 75 mg/d alone	18 mo	RRR=6.4% (P=0.244) for primary outcome; ARD 1.26% (P<0.0001) for life-threatening bleeding; ARD 0.40% (P=0.029) for primary intracranial hemorrhage
SPS3	3020 patients with symptomatic lacunar stroke in the preceding 180 days	Aspirin 325 mg/d plus clopidogrel 75 mg/d vs aspirin 325 mg/d alone	3.4 y	HR=0.92 (P=0.48) for recurrent stroke; HR=1.97 (P<0.001) for major hemorrhage; HR=1.52 (P=0.004) for all-cause mortality
CHARISMA	15 603 patients with cardiovascular disease or multiple risk factors; included n=4320 with TIA or ischemic stroke	Clopidogrel 75 mg/d plus aspirin 75–162 mg/d vs aspirin 75–162 mg/d	28 mo	RR=0.93 (P=0.22) for primary composite outcome in all patients; RR=0.80 (0.62–1.03) for recurrent stroke in the TIA/stroke subgroup
PRoFESS	20 332 patients with a recent ischemic stroke (<90 days)	Aspirin 25 mg BID plus extended release dipyridamole 200 mg bid (ASA-ERDP) or clopidogrel 75 mg/d	2.5 y	HR=1.01 (95% CI, 0.92–1.11) for ASA-ERDP and recurrent stroke; HR=0.99 (95% CI, 0.92–1.07) for stroke/MI/vascular death; HR=1.15 (95% CI, 1.00–1.32) for major hemorrhage; HR=1.42 (1.11–1.83) for intracranial hemorrhage

(*Continued*)

Table. Continued

Trial or Meta-Analysis	Patient Population	Antiplatelet Intervention	Follow-Up	Key Results
CHANCE	5170 patients within 24 h after the onset of minor ischemic stroke or high-risk TIA	Clopidogrel (300 mg load then 75 mg/d) plus aspirin 75 mg/d vs aspirin 75 mg/d. DAPT given for 21 days only.	90 d	HR=0.68 (P<0.001) for stroke; HR=0.75 (P=0.01) for fatal or disabling stroke; HR=0.67 (P<0.001) for ischemic stroke; HR=0.94 (P=0.94) for severe bleeding
POINT	4881 patients within 12 h after the onset of minor ischemic stroke or high-risk TIA	Clopidogrel (600 mg load then 75 mg/d) plus aspirin 50–325 mg/d vs aspirin 50–325 mg alone	90 d	HR=0.75 (P=0.02) for major ischemic events; HR=0.72 (P=0.01) for ischemic stroke; HR=2.32 (P=0.02) for major hemorrhage; HR=2.45 (P=0.04) for nonintracranial major hemorrhage
SOCRATES	13 199 patients with nonsevere ischemic stroke or high-risk TIA within 24 h	Ticagrelor (180 mg load then 90 mg BID) vs aspirin (300 mg load then 100 mg/d)	90 d	HR=0.89 (P=0.07) for stroke/MI/death; HR=0.87 (P=0.046) for ischemic stroke; HR=0.83 (P=0.45) for major bleeding

ARD indicates absolute risk difference; ASA, acetylsalicylic acid; ATC, antithrombotic trialists' collaboration; CAPRIE, Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CAST, Chinese Acute Stroke Trial; CHANCE, Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischemia Trial; ESPS-2 European Stroke Prevention Study-2; HR, hazard ratio; IST, International Stroke Trial; MATCH, Management of Atherothrombosis With Clopidogrel in High-Risk Patients; MI, myocardial infarction; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; RR, relative risk; RRR, relative risk reduction; SOCRATES, Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes; SPS3, Secondary Prevention of Small Subcortical Strokes; and TIA, transient ischemic attack.

these trials total 7795 patients and 1158 outcomes (composite of vascular death, nonfatal stroke, and nonfatal myocardial infarction).[15] The pooled risk ratio was 0.82 (95% CI, 0.74–0.91) with no evidence for heterogeneity (I^2=0%). Most of the data (79%) come from 2 trials: the ESPS-2 (European Stroke Prevention Study 2) and the ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial).[16,17] In the ESPS-2 trial, patients in the aspirin-dipyridamole arm received modified-release dipyridamole 200 mg twice daily in a fixed-dose combination with aspirin 25 mg twice daily.[17] In ESPRIT, 83% of combination-allocated patients received modified-release dipyridamole and the dose of aspirin was allowed to vary between 30 and 325 mg/d in all patients.[16] Both trials were positive for their primary end points.

The most significant side effect of dipyridamole-containing preparations is headache, which occurs in ≈40% of patients initiating aspirin-dipyridamole.[18] This adverse effect can be minimized by slow uptitration of therapy.[19] In addition, headache drops rapidly in intensity for those patients who can push through therapy with ASA-dipyridamole.[20] In a recent large randomized trial, 5.9% of patients permanently discontinued ASA-dipyridamole because of headache.[21] However, it is likely that in real-world practice, discontinuation because of headache is more frequent; persistence is typically better in clinical trials because of the availability of counseling and close monitoring.

In summary, aspirin-dipyridamole is an acceptable antiplatelet therapy for patients with noncardioembolic ischemic stroke or TIA and probably superior to aspirin alone. Disadvantages include twice-daily dosing and headache as a common adverse drug reaction.

Clopidogrel

Clopidogrel is a thienopyridine compound whose active metabolite selectively inhibits the binding of adenosine diphosphate to its platelet $P2Y_{12}$ receptor and the subsequent adenosine diphosphate-mediated activation of the glycoprotein (GP) IIb/IIIa complex, thereby inhibiting platelet aggregation.[22] In the acute setting, a loading dose of 300 to 600 mg is administered for more rapid onset of effect.[23]

Clopidogrel was first tested in patients with cerebrovascular disease in the CAPRIE trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events), which enrolled 19 185 patients with atherosclerotic vascular disease, including 6431 with recent ischemic stroke (mean time from stroke onset to randomization, 53 days).[24] Clopidogrel 75 mg/d was compared with aspirin 325 mg/d, with a primary outcome of ischemic stroke, myocardial infarction, or vascular death. Overall, there was a relative risk reduction of 8.7% favoring clopidogrel across all patients in the trial (95% CI, 0.3%–16.5%; P=0.043). For patients with stroke, there was a similar relative risk reduction of 7.3% favoring clopidogrel, which was nonsignificant (−5.7% to 18.7%; P=0.26). In all patients, there were similar rates of intracranial hemorrhage with aspirin versus clopidogrel (0.49% versus 0.35%, respectively; P=0.23) and higher rates of gastrointestinal hemorrhage with aspirin (2.66% versus 1.99%, P=0.05).

In the MATCH trial (Management of Atherothrombosis With Clopidogrel in High-Risk Patients), the combination of clopidogrel and aspirin was compared with clopidogrel alone in 7599 patients with recent ischemic stroke or TIA and at least 1 additional vascular risk factor.[25] The primary end point was the composite of ischemic stroke, myocardial infarction, vascular death, or rehospitalization for acute ischemia (including rehospitalization for TIA, angina pectoris, or worsening peripheral arterial disease). The mean time from qualifying event to randomization was 27 days, and more than half of patients (53%) had small vessel disease as the cause of their qualifying event.

In this trial, there was no evidence of significant benefit for the combination of clopidogrel and aspirin compared with clopidogrel alone (relative risk reduction, 6.4%; 95% CI, −4.6% to 16.3%; P=0.244).[25] In addition, life-threatening bleeding was more frequent in the group assigned to DAPT versus clopidogrel alone (2.6% versus 1.3%, respectively; P<0.0001), as was major bleeding (2% versus 1%, respectively; P<0.0001).

Primary intracranial hemorrhage and gastrointestinal hemorrhage were both more frequent with DAPT.

These data are mirrored by the SPS3 trial (Secondary Prevention of Small Subcortical Strokes).[26] A total of 3020 patients with recent symptomatic lacunar infarcts were randomized to clopidogrel or placebo; both groups received aspirin 325 mg daily. The primary outcome was any recurrent stroke, including ischemic stroke and intracranial hemorrhage. After a mean follow-up of 3.4 years, there was no reduction in recurrent stroke with DAPT compared with aspirin (hazard ratio, 0.92; 95% CI, 0.72–1.16), or in recurrent ischemic stroke, recurrent lacunar stroke, or disabling or fatal stroke. Major hemorrhage was nearly doubled with DAPT (2.1% per year versus 1.1% per year; $P<0.001$), and all-cause mortality was increased in the DAPT group (2.1% per year versus 1.4% per year; $P=0.004$). The increase in all-cause mortality was unexpected and could not be explained by fatal hemorrhage, which occurred in only 13 patients in the trial.

In the CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance), 15 603 high-risk vascular patients (including 4320 patients who were enrolled with a qualifying diagnosis of documented cerebrovascular disease) were randomly assigned to receive clopidogrel plus low-dose aspirin (75–162 mg/d) or low-dose aspirin alone.[27] The primary outcome was the composite of stroke, myocardial infarction, or vascular death. In the entire trial population, the relative risk for the primary outcome with DAPT versus aspirin monotherapy was 0.93 (95% CI, 0.83–1.05). Among the 4320 patients with a qualifying diagnosis of ischemic stroke or TIA, 233 (5.4%) experienced a stroke during follow-up, of whom 103 were randomly assigned to DAPT and 130 to aspirin monotherapy (relative risk, 0.80; 95% CI, 0.62–1.03).[28] There was no evidence that DAPT changed the severity of stroke outcome events during follow-up.[28]

Clopidogrel was compared with aspirin plus extended-release dipyridamole (ASA-ERDP) in the large PRoFESS trial (Prevention Regimen for Effectively Avoiding Second Strokes).[21] Patients were enrolled at a median of 15 days from a qualifying ischemic stroke, with 40% of patients randomized within 10 days after the qualifying event. The primary outcome of recurrent stroke of any type occurred at a similar rate in both arms (8.8% in patients receiving clopidogrel and 9.0% in patients receiving ASA-ERDP; hazard ratio, 1.01 for ASA-ERDP; 95% CI, 0.92–1.11). The secondary composite outcome of stroke, myocardial infarction, or vascular death occurred in 13.1% of patients in each group (hazard ratio [HR] for ASA-ERDP, 0.99; 95% CI, 0.92–1.07). There were more major hemorrhagic events in the ASA-ERDP group (HR, 1.15; 95% CI, 1.00–1.32) and more intracranial hemorrhages (HR, 1.42; 95% CI, 1.11–1.83). In summary, although the trial did not meet the predefined criteria for noninferiority, ASA-ERDP and clopidogrel showed broadly similar efficacy at preventing vascular events across a mean follow-up of 2.5 years.

The aforementioned trials are largely longer-term studies, with selection of patients at some distance from their acute event.[21,24–26,28] Two trials have examined the efficacy of clopidogrel and aspirin DAPT in patients with acute ischemic stroke or TIA.[10,11] In the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events), combined clopidogrel (initial dose 300 mg, followed by 75 mg/d for 90 days) and low-dose aspirin (75 mg/d for the first 3 weeks) was compared with placebo plus aspirin (75 mg/d for 90 days) in 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA.[11] The primary outcome of stroke (ischemic or hemorrhagic) during 90 days of follow-up occurred in 8.2% of patients in the clopidogrel-aspirin group and 11.7% of those in the aspirin monotherapy group (HR, 0.68; 95% CI, 0.57–0.81). Fatal or disabling stroke and ischemic stroke were both reduced. Concomitantly, there was no increase in moderate or severe hemorrhage or hemorrhagic stroke. It should be noted that this trial was conducted entirely in China, and the results might not be generalizable to other regions such as North America or Europe.

However, these results are largely mirrored in the recent POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke).[10] A total of 4881 patients were enrolled within 12 hours of an acute ischemic stroke with a score of ≤3 on the National Institutes of Health Stroke Scale or a high-risk TIA with a score of ≥4 on the ABCD2 scale. Patients were randomly assigned to receive clopidogrel (with a 600 mg loading dose) plus aspirin or aspirin alone. The primary outcome of major ischemic events (the composite of ischemic stroke, myocardial infarction, or death from an ischemic vascular event) occurred in 5.0% of the DAPT group and 6.5% of the aspirin monotherapy group (HR, 0.75; 95% CI, 0.59–0.95). The secondary outcome of ischemic stroke was also reduced (HR, 0.72; 95% CI, 0.56–0.92). Major hemorrhage occurred in 0.9% of the DAPT group and 0.4% of the aspirin group (HR, 2.32; 95% CI, 1.10–4.87), an increase largely because of nonfatal nonintracranial hemorrhage (HR, 2.45; 95% CI, 1.01–5.90). The benefit of clopidogrel plus aspirin was greater in the first 7 days and in the first 30 days than in the 90 days, whereas the risk of hemorrhage with DAPT was greater during the period from 8 to 90 days than during the first 7 days. The investigators estimate that for every 1000 patients treated with DAPT for a period of 90 days, treatment would prevent 15 ischemic strokes and cause 5 major hemorrhages.

These data suggest benefit for DAPT (comprising clopidogrel and aspirin) for acute nondisabling noncardioembolic stroke and TIA, but the other trials reviewed here suggest lack of benefit in the longer term (and probable harm). The risk of recurrent stroke is highest within the first 90 days after an acute ischemic stroke or TIA, which at least partially explains the success of POINT and CHANCE.[2]

Ticagrelor

Ticagrelor is a reversible $P2Y_{12}$ receptor antagonist, which unlike clopidogrel, does not require conversion from prodrug to active drug in the liver.[29] Ticagrelor is reversible and short acting, so must be given twice daily.[30] SOCRATES (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) tested the efficacy of ticagrelor (180 mg loading dose then 90 mg twice daily) versus aspirin in 13 199 patients with an acute nonsevere ischemic stroke or high-risk TIA.[31] The primary outcome was the time to occurrence of stroke, myocardial infarction, or death within 90 days. The primary end point occurred in 6.7% of patients

treated with ticagrelor versus 7.5% treated with aspirin (HR, 0.89; 95% CI, 0.78–1.01; *P*=0.07). Ischemic stroke occurred in 5.8% in the ticagrelor arm versus 6.7% in the aspirin arm (HR, 0.87; 95% CI, 0.76–1.00; nominal *P*=0.046). There were no differences in major bleeding, intracranial hemorrhage, or fatal bleeding. There were more discontinuations because of dyspnea and minor bleeding in the ticagrelor group. Permanent discontinuation of study drug occurred in 17.5% in the ticagrelor group, versus 14.7% in the aspirin group.

In large artery disease, ticagrelor was substantially more efficacious.[32] A total of 6.7% of 1542 patients with ipsilateral stenosis in the ticagrelor group and 147 (9.6%) of 1539 patients with ipsilateral stenosis in the aspirin group had a primary event within 90 days (HR, 0.68; 95% CI, 0.53–0.88). This is likely because of the predominance of white thrombus (rich in platelet aggregates) in the mechanism of stroke/TIA in large artery atherosclerosis.

A recently published subgroup analysis from SOCRATES found that ticagrelor was effective at preventing the primary outcome in patients with a background history of aspirin use (HR, 0.76; 95% CI, 0.61–0.95; *P*=0.02).[33] This will be tested in the forthcoming THALES trial (Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death), which is randomly assigning patients with TIA or acute ischemic stroke to combined aspirin and ticagrelor versus aspirin alone. The estimated completion date of this study is December 2019.

Discussion

For acute treatment of nonembolic TIA or ischemic stroke, 2 trials have convincingly demonstrated reductions in recurrent ischemic strokes with the combination of aspirin and clopidogrel (versus aspirin monotherapy), lasting 21 or 90 days.[10,11] With a 90-day course of DAPT in POINT, prevention of ischemic stroke was only partially offset by the increase in major hemorrhage.[10] These data are likely to change practice recommendations about the treatment of acute cerebrovascular ischemia. The 2018 American Heart Association/ASA guidelines for management of acute ischemic stroke, which were published before the POINT trial, give a IIa recommendation for DAPT in acute minor stroke on the basis of the CHANCE trial.[4] This recommendation will likely be strengthened in the aftermath of POINT.

For long-term prevention of recurrent vascular events in patients with a history of ischemic stroke or TIA, several options are available. These include aspirin, aspirin-dipyridamole, and clopidogrel. DAPT combining clopidogrel and aspirin has not convincingly demonstrated prevention of recurrent events in long-term prevention trials, whereas major hemorrhage is significantly increased (MATCH, SPS3, CHARISMA).[25,26,28] Aspirin monotherapy has a strong track record in acute and chronic cerebrovascular ischemia but clearly does not prevent all recurrent events.[9,12] Aspirin-dipyridamole and clopidogrel are acceptable alternatives to aspirin for long-term prevention and were compared directly in the PRoFESS trial (with little evidence of a difference in efficacy between them).[21] The clinician should be aware that aspirin-dipyridamole has higher rates of discontinuation and noncompliance (because of headache) and monitor for these in clinical practice.

Ticagrelor was compared directly with aspirin in the SOCRATES trial, which showed a strong trend toward lower stroke rates in patients assigned to ticagrelor in the acute setting.[31] This difference was magnified in the subgroup of patients with atherosclerotic stroke.[32] The ongoing THALES trial should better define the role of ticagrelor in acute cerebrovascular disease (URL: https://www.clinicaltrials.gov. Unique identifier: NCT03354429). The combination of aspirin and ticagrelor is being compared with aspirin alone. This study is eagerly awaited and may change practice recommendations if it is positive.

There are many limitations in the body of randomized trials evaluating antiplatelet therapy for the secondary prevention of ischemic stroke and TIA. There is no evidence on aspirin-dipyridamole or clopidogrel monotherapy in acute stroke/TIA. Similarly, there are no data on ticagrelor beyond 90 days after an ischemic stroke or TIA. There are also no data to answer the question of which antiplatelet to select in a patient who has a breakthrough event (acute stroke or TIA while already on antiplatelet therapy). Strategies are needed to ensure long-term adherence to antiplatelet therapies in patients after stroke or TIA.

It is likely that many cases of major hemorrhage in patients taking antiplatelet therapy could be prevented through appropriate medical interventions. First, prompt diagnosis and treatment of *Helicobacter pylori* infection, as well as proton pump inhibition for those at high risk, is likely to prevent many cases of gastrointestinal hemorrhage. Li et al[34] have estimated that half of the major hemorrhages in patients aged 75 years or older are upper gastrointestinal, outnumbering disabling or fatal intracerebral hemorrhage by 2.5:1. Second, most intracerebral hemorrhages could be prevented by effective blood pressure control.[35] In the North American Symptomatic Carotid Endarterectomy Trial, strenuous efforts were made to achieve blood pressure control by overcoming therapeutic inertia.[36] Every time an investigator failed to intensify antihypertensive therapy in a patient whose blood pressure was above target, the investigator received a reminder that the protocol must be followed. The result of this was that hemorrhagic strokes (including subarachnoid hemorrhages and lobar infarctions, which are not because of high blood pressure) were reduced to 0.5% of stroke, at a time when ≈20% of strokes were hemorrhagic.[37]

Disclosures

Dr Spence is an officer and shareholder of Vascularis Inc, a company seeking to market software for vascular risk reclassification based on measurement of carotid plaque burden. He received honoraria from Pfizer and BMS and also receives royalties on books from Vanderbilt University Press and McGraw-Hill Medical publishers. The other author reports no conflicts.

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