

Antiplatelet Therapy in Cerebrovascular Disease: Implications of the Management of Artherothrombosis with Clopidogrel in High-risk Patients and The Clopidogrel for High Artherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance Studies' Results for Cardiologists

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Summary

Cardiovascular disease is prevalent among patients with stroke; thus, cardiologists frequently treat patients at high risk for stroke. Results from recent clinical trials of antiplatelet medications, given alone or in combination, may be of special interest to cardiologists. The Management of Artherothrombosis with Clopidogrel in High-risk Patients (MATCH) study demonstrated no significant difference between clopidogrel alone and clopidogrel plus aspirin in reducing risk of vascular events after stroke or transient ischemic attack. A 1.3% increased risk of major bleeding was associated with clopidogrel plus aspirin. In the Clopidogrel for High Artherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study, clopidogrel plus aspirin did not reach statistical significance versus placebo plus aspirin in reducing incidence of myocardial infarction (MI), stroke, or death from cardiovascular causes in patients with stable atherothrombotic disease; clopidogrel was associated with an increase in moderate bleeding. These results suggest that clopidogrel plus

aspirin may be inappropriate as first-line therapy for secondary stroke prevention. In patients with established cardiovascular disease at risk for MI or other vascular events, physicians must weigh the benefits and risks before choosing this therapy. Selection of an antiplatelet agent must be based on patient history, including previous MI and stroke, susceptibility to bleeding, and other high-risk factors (e.g., advanced age and diabetes). Aspirin plus extended-release dipyridamole may be more effective than clopidogrel for preventing stroke in high-risk patients. This article strives to put MATCH and CHARISMA results into context by providing an overview of antiplatelet therapy, including relevant clinical trial results, a review of current practice guidelines, and a summary of an ongoing study that will improve clinical decision making.

Key words: antiplatelet therapy, secondary stroke prevention, stroke, transient ischemic attack

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Introduction

Underlying cardiovascular disease is prevalent among patients with stroke; approximately 15 to 30% of ischemic strokes are cardioembolic in origin. Cardiac factors such as atrial fibrillation, valvular heart disease, coronary artery disease, congestive heart failure, and myocardial infarction (MI) increase stroke risk.^{1,2} Because of the array of overlapping symptoms and risk factors, cardiologists frequently care for patients who are at high risk for initial or recurrent stroke. Secondary stroke after initial stroke or transient ischemic attack (TIA) has been reported in approximately 25 to 40% of patients within 5 years of the initial event.³ Within the

first 30 days, 3%–8% of patients experience a repeat attack.³ Stroke is associated with substantial morbidity and mortality in the United States; 1 in 16 deaths annually are caused by stroke, and 15%–30% of stroke survivors are permanently disabled.⁴ In 2007, the estimated annual combined direct and indirect costs of stroke will reach nearly \$63 billion.⁴

The substantial economic costs and clinical consequences of stroke warrant aggressive treatment of risk factors, especially in high-risk populations (i.e., elderly patients, patients with preexisting vascular disease, or patients who have had an initial stroke). Antiplatelet therapy has had a substantial impact on stroke in specified populations at risk; therefore, the intent of this article is to reveal the results of several recent antiplatelet trials, with emphasis on the recent Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attack or Ischemic Stroke (MATCH) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trials and their implications for the cardiologist. The MATCH trial examined the efficacy and safety of the antiplatelet clopidogrel used alone or with aspirin for secondary stroke prevention in high-risk patients;⁵ CHARISMA evaluated the efficacy and safety of the combination compared with aspirin alone in patients with clinically evident cardiovascular disease or multiple risk factors.⁶ In an effort to put the results of these studies in context, this article also includes the following:

- Overview of antiplatelet therapy, including relevant findings from clinical trials
- Review of implications for cardiologists in light of current practice guidelines
- Summary of an ongoing study that will improve clinical decision making

Antiplatelet Therapy for Secondary Prevention of Stroke and Transient Ischemic Attack

The major antiplatelet therapies used for stroke prevention include aspirin, clopidogrel, and dipyridamole (Table 1).^{5–15} Clopidogrel and dipyridamole have been studied alone and in combination with aspirin, with variable results. To provide historical context regarding the clinical development of antiplatelet therapies for stroke prevention, this review begins with aspirin, the first and most used and studied antiplatelet drug.¹⁶

Aspirin: The antiplatelet efficacy of aspirin in preventing secondary stroke was established by three studies conducted in the late 1980s and early 1990s: the Swedish Aspirin Low-dose Trial (SALT) and the Dutch TIA and UK-TIA trials, among others, have demonstrated that aspirin—even in doses as low as 30 mg/day—reduces secondary stroke, MI, or vascular death in patients with

a history of stroke or TIA. The placebo-controlled SALT study showed that aspirin at 75 mg/day reduced the rate of recurrent stroke by 18%,⁷ whereas the Dutch TIA and UK-TIA studies showed that the efficacy of aspirin was similar across a dose range from 30 to 1,200 mg/day,^{8,9} however, higher doses were associated with increased risk for gastrointestinal and bleeding complications.^{7–9}

Two subsequent studies, the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) and the Warfarin versus Aspirin in Recurrent Stroke Prevention Study (WARSS) showed that aspirin was preferable to warfarin in preventing secondary stroke in patients with initial noncardioembolic stroke.^{10,11} The SPIRIT study was a European trial that compared warfarin with aspirin in patients with TIA or minor stroke during the previous six months.¹⁰ This study was discontinued early (only about 1,300 of the intended 3,000 patients had been recruited) because significantly higher risk for stroke, MI, vascular death, and nonfatal bleeding was noted among patients receiving warfarin. The WARSS trial was a means of determining whether lower doses of warfarin could demonstrate superior benefit to aspirin without the risk of untoward outcomes observed in the SPIRIT trial.¹¹ The results showed no significant difference in clinical efficacy for stroke prevention with warfarin versus aspirin. These studies essentially eliminated warfarin as a choice for secondary stroke prevention unless a clear cardioembolic source, such as atrial fibrillation, is present.¹⁷

In 2002, the Antiplatelet Trialists' Collaboration (APTC) conducted a meta-analysis of 197 randomized controlled trials and 90 head-to-head comparator trials of antiplatelet agents. Results showed a 23% risk reduction in combined vascular events (MI, stroke, and vascular death) with aspirin.¹⁶ In another meta-analysis, which examined only studies of aspirin use in patients with existing cerebrovascular disease, an overall reduction of 13–15% in risk of important vascular events was observed. Of importance to cardiologists, is that the effect of aspirin therapy on stroke appears to differ according to the presence or absence of vascular disease; this contrasts with outcomes when aspirin is used for prevention of MI because aspirin consistently reduces MI risk in all populations.¹⁸ Nonetheless, the U.S. Food and Drug Administration (FDA) recommends aspirin use at doses of 50 to 325 mg/day for prevention of ischemic stroke and TIA.¹⁹ The general trend among North American practitioners is to prescribe doses at the higher end of this range.^{19,20} However, a safety concern is associated with higher doses of aspirin, which may cause bleeding in some patients.

Dipyridamole: As a single agent, dipyridamole has been evaluated for prevention of stroke and other vascular events. The Antiplatelet Trialists' Collaboration

TABLE 1 Selected trial results of antiplatelet agents for secondary prevention of stroke or TIA⁵⁻¹⁵

| Trial | Patients | Follow-up | Intervention | Absolute risk, % | OR (95% CI) | Results |
|-------------------------------------|--|-----------|--|---|----------------------------------|---|
| SALT ⁷ n = 1,360 | TIA, minor ischemic stroke, or retinal artery occlusion in past 3 months | 32 months | ASA 75 mg Placebo | Composite of stroke or death ASA: 20.4 Placebo: 25 | 0.82 (0.67–0.99) | Low-dose ASA (75 mg/day) reduces the risk of stroke or death |
| DUTCH-TIA ⁸ n = 3,131 | TIA or minor stroke | 2.6 years | ASA 30 mg ASA 283 mg | Occurrence of death from vascular causes, nonfatal stroke, or MI ASA 30 mg: 14.7 ASA 283 mg: 15.2 | Hazard ratio 0.91 (0.76–1.09) | 30 mg dose of ASA is no less effective in prevention of vascular events than 283 mg dose |
| UK-TIA ⁹ n = 2,435 | Presumed TIA or minor ischemic stroke in past 3 months | 4 years | ASA 300 mg ASA 1,200 mg Placebo | Composite event of major stroke, MI, or vascular death ^a | 0.85 (0.71–1.03) | No difference in efficacy between 300 mg and 1,200 mg daily doses of ASA, but lower dose was less gastrotoxic |
| SPIRIT ¹⁰ n = 1,316 | TIA or ischemic stroke of noncardiac origin in past 6 months | 14 months | Anticoagulation (INR 3.0–4.5) ASA 30 mg | Composite of death, ischemic stroke, MI, and major bleeding Anticoagulation: 12.4 ASA: 5.4 | Hazard ratio 2.3 (1.6–3.5) | ASA superior; no benefit for high-intensity anticoagulation over ASA in noncardioembolic stroke |

TABLE 1 (Continued)

| Trial | Patients | Follow-up | Intervention | Absolute risk, % | OR (95% CI) | Results |
|------------------------------------|--|------------|---|---|--|---|
| WARSS ¹¹ n = 2,206 | Ischemic stroke of noncardiac origin in past 30 days | 2 years | Anticoagulation (INR 1.4–2.8) ASA 325 mg | Ischemic stroke or death Anticoagulation: 17.8 ASA: 16.0 Major bleeding per patient-year Anticoagulation: 2.2 ASA: 1.5 | Ischemic stroke or death: 1.13 (0.92–1.38) Major bleeding: 1.48 (0.93–2.44) | No difference between low- and moderate-intensity anticoagulation and ASA in noncardioembolic stroke ASA + DP superior |
| ESPS-2 ¹² n = 6,602 | Stroke or TIA in previous 3 months | 2 years | ASA DP ASA + DP Placebo | Stroke risk ASA: 12.9 DP: 13.2 ASA + DP: 9.9 Placebo: 15.8 | vs. placebo 0.79 (0.65–0.97) 0.81 (0.67–0.99) 0.59 (0.48–0.73) | |
| ESPRIT ¹³ n = 2,739 | Previous TIA or minor stroke | 3.5 years | ASA ASA + DP | Composite of vascular death, nonfatal stroke, nonfatal MI, or major bleeding complication ASA: 16 ASA + DP: 13 | ARR, 1.0% (0.1–1.8) | Combination of ASA + DP is preferred over ASA alone |
| CAPRIE ¹⁴ n = 19,185 | Previous MI, stroke, or PAD | 1.91 years | CP ASA | Composite of ischemic stroke, MI, or vascular death CP: 5.3 ASA: 5.8 | 0.91 (0.83–0.96) | CP superior for composite; no difference in efficacy for stroke prevention; similar safety |

TABLE 1 (Continued)

| Trial | Patients | Follow-up | Intervention | Absolute risk, % | OR (95% CI) | Results |
|-------------------------------------|--|------------------------------------|-----------------------------------|--|---|---|
| MATCH ⁵ n = 7,599 | High-risk patients with recent ischemic stroke or TIA | 18 mo | CP + ASA CP + placebo | Composite of vascular death, MI, ischemic stroke, or rehospitalization CP + ASA: 15.7 CP + placebo: 16.7 | RRR, 6.4% (-4.6-16.3) ARR, 1.0% (-0.6-2.7) | No significant difference in reducing major vascular events; risk of major and life-threatening bleeds increased by addition of ASA |
| CHARISMA ⁶ n = 15,603 | Previous stroke, MI, or PAD and primary prevention in high-risk patients | 28 mo | CP + ASA Placebo + ASA | Vascular death, MI, or stroke CP + ASA: 6.8 Placebo + ASA: 7.3 Severe bleeding CP + ASA: 1.7 Placebo + ASA: 1.3 | 0.93 (0.83-1.05) 1.25 (0.97-1.61) | CP + ASA not more beneficial than ASA in reducing risk of primary endpoint; higher risk of bleeding with CP + ASA |
| PRoFESS ¹⁵ n = 20,333 | Ischemic stroke in previous 90 days | Up to 4 y; target, 2280 strokes | ASA + ER-DP CP Telmi-sartan | Time to first recurrent stroke Composite of vascular events | TBD Study ongoing | TBD Study ongoing |

^a Absolute risk not reported for the UK-TIA study.

Abbreviations: ARR = absolute risk reduction; ASA = aspirin, CAPRIE = Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events study; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial, CP = clopidogrel; DP = dipyridamole; ER-DP = extended-release dipyridamole; ESPS-2 = Second European Stroke Prevention Study; INR = international normalized ratio; MATCH = Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attack or Ischemic Stroke trial; MI = myocardial infarction; OR = odds ratio; PAD = peripheral arterial disease; PRoFESS = Prevention Regimen for Effectively Avoiding Second Strokes study; RRR = relative risk reduction; SALT = Swedish Aspirin Low-dose Trial; SPIRIT = Stroke Prevention in Reversible Ischemia Trial; TBD = to be determined; TIA = transient ischemic attack; WARSS = Warfarin-Aspirin Recurrent Stroke Study.

(APTC) demonstrated that dipyridamole showed 16% odds reduction for stroke, MI, or vascular death versus placebo in a meta-analysis of 15 trials.¹⁶ Additionally, aspirin plus extended-release dipyridamole demonstrated 30% odds reduction for stroke, MI, or vascular death versus placebo in a meta-analysis of 46 trials. When aspirin plus extended-release dipyridamole was compared with aspirin alone, a 6% odds reduction was observed for stroke, MI, or vascular death in a meta-analysis of 25 trials. It is interesting to note that the benefit of the combination was driven by stroke outcomes alone—MI and vascular deaths were lower with aspirin alone than with combination therapy, although the difference was not significant.¹⁶

The Second European Stroke Prevention Study (ESPS-2) is one of two studies that evaluated aspirin plus extended-release dipyridamole for secondary stroke prevention.¹² In ESPS-2, 6,602 patients who had a recent ischemic stroke or TIA were enrolled in a multicenter, double-blind, placebo-controlled trial that randomly assigned them to one of four treatment groups: aspirin (25 mg, twice daily), extended-release dipyridamole (200 mg, twice daily), aspirin plus extended-release dipyridamole, or placebo.¹² Both agents given as monotherapy demonstrated an independent and statistically significant reduction in recurrent stroke (18% and 16%, respectively). However, the combination of aspirin plus extended-release dipyridamole reduced stroke recurrence by 23% compared with aspirin alone and by 37% compared with placebo. Results from ESPS-2 indicate that aspirin plus extended-release dipyridamole has significant benefit over aspirin alone for prevention of second stroke.

In ESPS-2, MI occurred at a much lower frequency than stroke, and there was no significant difference in MI incidence between groups (placebo = 45, aspirin = 39, extended-release dipyridamole = 48, aspirin plus extended-release dipyridamole = 35).¹² With regard to safety outcomes, bleeding was significantly more common in patients receiving aspirin than in those receiving placebo or extended-release dipyridamole alone; bleeding events occurred at the same frequency in the aspirin monotherapy and aspirin plus extended-release dipyridamole groups. Headache was the most important adverse event associated with extended-release dipyridamole (both in monotherapy and in combination with aspirin), and was responsible for a higher rate of treatment-related discontinuations in these groups. However, the results of ESPS-2 indicate that the benefits of aspirin plus extended-release combination therapy are achieved with no evidence of new safety or tolerability concerns compared with monotherapy with either agent.¹²

The recently completed European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), which included 2,739 patients with TIA or minor stroke of presumed arterial origin in the previous six months,

also evaluated extended-release dipyridamole plus aspirin in the prevention of secondary stroke.¹³ Patients were randomized to aspirin alone at a dose of 30 mg/day to 325 mg/day (n = 1,376; dosage was at the discretion of the treating physician) or in combination with dipyridamole 200 mg twice daily (n = 1,363). The primary composite outcome event was the first occurrence of death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complication.¹³

Mean follow-up for the study was 3.5 ± 2.0 years; median aspirin dose was 75 mg/day, and 83% of the patients who were taking the combination regimen were taking the extended-release formulation of dipyridamole. The primary outcome occurred in 173 (13%) of patients taking aspirin plus extended-release dipyridamole and 216 (16%) of patients taking aspirin monotherapy (RRR 20%, 95% CI, 0.66–0.98; absolute risk reduction 1% per year, 95% CI, 0.1–1.8). Somewhat unexpectedly, the incidence of major bleeding complications was lower in patients receiving combination therapy (n = 35) than in those receiving aspirin monotherapy (n = 53); the authors ascribe this to chance, noting that the aspirin dose was similar in both groups and that the incidence of minor bleeding was also similar (n = 171 and n = 168, respectively; risk ratio 1.03, 95% CI 0.84–1.25). As in ESPS-2, the principal adverse safety event associated with the addition of dipyridamole to aspirin was headache, leading to a higher rate of discontinuations than in patients taking aspirin monotherapy.¹³

Although 4 earlier studies using an immediate-release dipyridamole formulation did not show a benefit of combination therapy with aspirin plus dipyridamole over aspirin alone, ESPS-2 and ESPRIT provided consistent evidence of benefit with the combination.^{12,13} The ESPRIT Study Group included a meta-analysis of six comparative trials, including a total of 3,888 patients taking aspirin plus dipyridamole and 3,907 taking aspirin alone; this analysis demonstrated an overall RRR for combination therapy versus aspirin of 18% (95% CI, 0.74–0.91) for the composite outcome of vascular death, nonfatal stroke, or nonfatal MI.¹³

Ticlopidine: Ticlopidine was the first thienopyridine shown to have an advantage over aspirin in stroke prevention.²¹ However, because of the rare but serious adverse hematologic effects (neutropenia and thrombocytopenia) associated with ticlopidine, it is no longer used as a first-line agent;²² thus, it will not be further reviewed in this paper.

Clopidogrel: Clopidogrel has been evaluated as monotherapy and in combination with aspirin with regard to its efficacy in preventing secondary stroke. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, three groups (n \geq 6,300 each) with a recent history of symptomatic cardiovascular disease (stroke, MI, or peripheral arterial disease [PAD]) were randomized to clopidogrel 75 mg/day or aspirin 325 mg/day to evaluate the

composite outcome of ischemic stroke, MI, or vascular death as well as the relative safety of each drug. Clopidogrel was slightly more effective than aspirin in reducing cumulative risk of stroke, MI, or vascular death in patients with symptomatic atherosclerotic vascular disease (8.7% RRR; $p = 0.043$). However, clopidogrel did not demonstrate superiority versus aspirin in preventing recurrent stroke among patients with a history of stroke (8% RRR; $p = 0.28$), although the study was powered only to demonstrate significant differences in the overall population ($n = 19,185$). No major safety differences were observed between clopidogrel and aspirin, although the rate of serious hemorrhage was slightly higher in the aspirin group (1.55 versus 1.38%).¹⁴

The MATCH Study

The MATCH study was similar to ESPS-2 in that it compared the effectiveness of monotherapy with an antiplatelet agent (in this case, clopidogrel) with that of the same agent in combination with aspirin. On the basis of previous trial results (including CAPRIE) in patients with cardiac and cerebrovascular disease, investigators sought to determine whether the addition of aspirin to clopidogrel would further reduce the risk of recurrent ischemic attacks in high-risk patients after recent ischemic stroke or TIA. This 18-month, randomized, double-blind, placebo-controlled trial compared adjunctive aspirin (75 mg/day) to placebo in patients already taking clopidogrel (75 mg/day). Patients were included if they had a stroke or TIA within the previous 3 months and 1 or more of 5 additional high-risk factors within the previous 3 years: previous stroke, previous MI, angina, diabetes, or symptomatic PAD. Patients younger than 40 years of age, those with severe comorbid conditions or increased risk of bleeding, and those with scheduled major surgery or vascular surgery during the study period were excluded. The primary composite endpoint was the first occurrence of stroke, MI, vascular death,

or rehospitalization. As would be expected in a high-risk population, a large proportion of patients enrolled in MATCH had diabetes (68%) and hypertension (78%). About half of the recent strokes that qualified patients for the study were attributable to small-vessel occlusion (lacunar stroke).⁵

The results of MATCH showed no significant difference between clopidogrel alone and clopidogrel plus aspirin in reducing risk of vascular events after stroke or TIA. Although there was an absolute risk reduction of 1% and a relative risk reduction of 6.4% favoring clopidogrel plus aspirin, the between-group differences were not statistically significant.⁵

Outcome events in MATCH are summarized in Table 2, stratified by event type. The risk of stroke was about fourfold greater than that of MI or of other vascular death for patients in both groups, reinforcing findings from earlier studies that people with previous stroke tend to experience recurrent stroke more frequently than MI or other vascular events.² Perhaps the most significant finding from MATCH is that the absolute risks of life-threatening and major bleeding were increased with the addition of aspirin to clopidogrel (by 1.3 and 1.4%, respectively).⁵ On the basis of these findings, clopidogrel plus aspirin cannot be recommended for high-risk patients with previous stroke or TIA for the prevention of secondary stroke or other vascular events.

The CHARISMA Study

In this prospective, multicenter, randomized, double-blind, placebo-controlled study, 15,603 patients were randomized to receive clopidogrel 75 mg/day plus low-dose aspirin (75–162 mg/day) or placebo plus low-dose aspirin, with median follow-up of 28 months. All patients were 45 years of age or older and had either multiple atherothrombotic risk factors or a history of documented coronary disease, cerebrovascular disease, or symptomatic PAD. Patients were excluded

TABLE 2 Primary vascular endpoints from MATCH

| | Aspirin + clopidogrel (n = 3797) | Placebo + clopidogrel (n = 3,802) | Absolute risk reduction (95% CI) | Relative risk reduction (95% CI) | p^a |
|--|-------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|-------|
| Primary outcome ^b | 596 (16%) | 636 (17%) | 1.0% (-0.6–2.7) | 6.4% (-4.6–16.3) | 0.244 |
| MI (fatal and nonfatal) | 59 (2%) | 62 (2%) | | | |
| Ischemic stroke (fatal and nonfatal) | 299 (8%) | 319 (8%) | | | |
| Other vascular death | 69 (2%) | 74 (2%) | | | |
| Rehospitalization for acute ischemic event | 169 (4%) | 181 (5%) | | | |

^a Log-rank test.

^b Only the first event was counted. For every component of the primary endpoint, only the event regarded as the first outcome from the composite was counted.

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TABLE 3 Primary vascular endpoints from CHARISMA

| | Aspirin + clopidogrel (n = 7,802) | Aspirin + placebo (n = 7,801) | Relative risk (95% CI) | P ^a |
|----------------------------------|--------------------------------------|----------------------------------|---------------------------|----------------|
| Primary efficacy endpoint | 534 (6.8) | 573 (7.3) | 0.93 (0.83–1.05) | 0.22 |
| Death from any cause | 371 (4.8) | 374 (4.8) | 0.99 (0.86–1.14) | 0.90 |
| Death from cardiovascular causes | 238 (3.1) | 229 (2.9) | 1.04 (0.87–1.25) | 0.68 |
| MI (nonfatal) | 146 (1.9) | 155 (2.0) | 0.94 (0.75–1.18) | 0.59 |
| Ischemic stroke (nonfatal) | 132 (1.7) | 163 (2.1) | 0.81 (0.64–1.02) | 0.07 |
| Stroke (nonfatal) | 150 (1.9) | 189 (2.4) | 0.79 (0.64–0.98) | 0.03 |

^a Log-rank test.

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from participation in the study if they were taking long-term oral antithrombotic medications or nonsteroidal anti-inflammatory drugs, had established indications for clopidogrel therapy, or were scheduled to undergo revascularization. The primary efficacy endpoint was the first occurrence of MI, stroke, or death from cardiovascular causes, including hemorrhage. More than three-fourths (78%) of the patients had established cardiovascular disease, comprising the secondary prevention cohort, and 21% had multiple risk factors, comprising the primary prevention cohort; the remaining 1% did not fall into either category but were included in the analysis. Of the patients with established cardiovascular disease (n = 12,153), 4,320 (35%) had a TIA or ischemic stroke during the 5 years prior to study entry.⁶

Among all patients enrolled in CHARISMA, there was no statistically significant difference between treatment groups in the rates of occurrence of the primary efficacy endpoint (clopidogrel plus aspirin 6.8%, aspirin alone 7.3%; RR 0.93, 95% CI 0.83–1.05; p = 0.22) (Table 3). Patients with multiple risk factors but no clearly established vascular disease (primary prevention cohort) did not benefit from the addition of clopidogrel to aspirin; instead, adjunctive clopidogrel was associated with a nonsignificant 20% relative increase in the rate of primary events, as well as an excess in cardiovascular mortality (3.9 versus 2.2%, p = 0.01). In patients with established cardiovascular disease (the secondary prevention cohort), the addition of clopidogrel resulted in a marginally significant clinical benefit regarding the primary endpoint (6.9 versus 7.9% with placebo; RR 0.88; 95% CI, 0.77–0.998; p = 0.046). Results of the safety analysis showed a nonsignificant increase in the primary safety endpoint of severe bleeding with clopidogrel; the rate of moderate bleeding (that required transfusion) was 2.1% in the clopidogrel group and 1.3% in the placebo group (RR, 1.62; 95% CI, 1.27–2.08; p < 0.001).⁶ These results suggest that the benefits associated with adding aspirin to clopidogrel must be balanced against the significant increase in bleeding risk.

How do MATCH and CHARISMA Findings Contribute to Patient Treatment Strategies?

The MATCH study provided answers about aspirin and clopidogrel use in cerebrovascular patients. However, MATCH did not confirm the trend toward benefit of reduced recurrent stroke risk in cerebrovascular patients with combination aspirin and clopidogrel therapy.⁵ The marginal, nonsignificant risk reduction of 1% in MATCH was offset by the increased risk (1.3%) of life-threatening bleeds. The CHARISMA study helped to clarify the potential role of dual antiplatelet therapy in a broad population of high-risk patients, including those with established cerebrovascular disease.⁶ Clopidogrel plus aspirin did not confer statistical significance over aspirin alone in reducing the rate of MI, stroke, or death from cardiovascular causes in patients with established cardiovascular disease or multiple risk factors. Furthermore, risk of moderate bleeding was increased.

The MATCH and CHARISMA results suggest that clopidogrel plus aspirin should not be a first-line option for prevention of second stroke in cerebrovascular patients because of the lack of efficacy advantage and the increased safety concerns. This conclusion is supported by recommendations from the Seventh Annual American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombotic Therapy, which recommends aspirin plus extended-release dipyridamole or clopidogrel alone over aspirin alone for secondary stroke prevention.²³ The ACCP Conference Report stated that, based on an indirect comparison of ESPS-2 and CAPRIE, the combination of aspirin plus extended-release dipyridamole may be more effective than clopidogrel for preventing stroke, as shown in Figure 1.²³ Ongoing studies involving direct comparisons are underway to confirm this hypothesis.

Ongoing Study

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study is the largest-ever secondary stroke prevention trial.¹⁵ This trial was designed

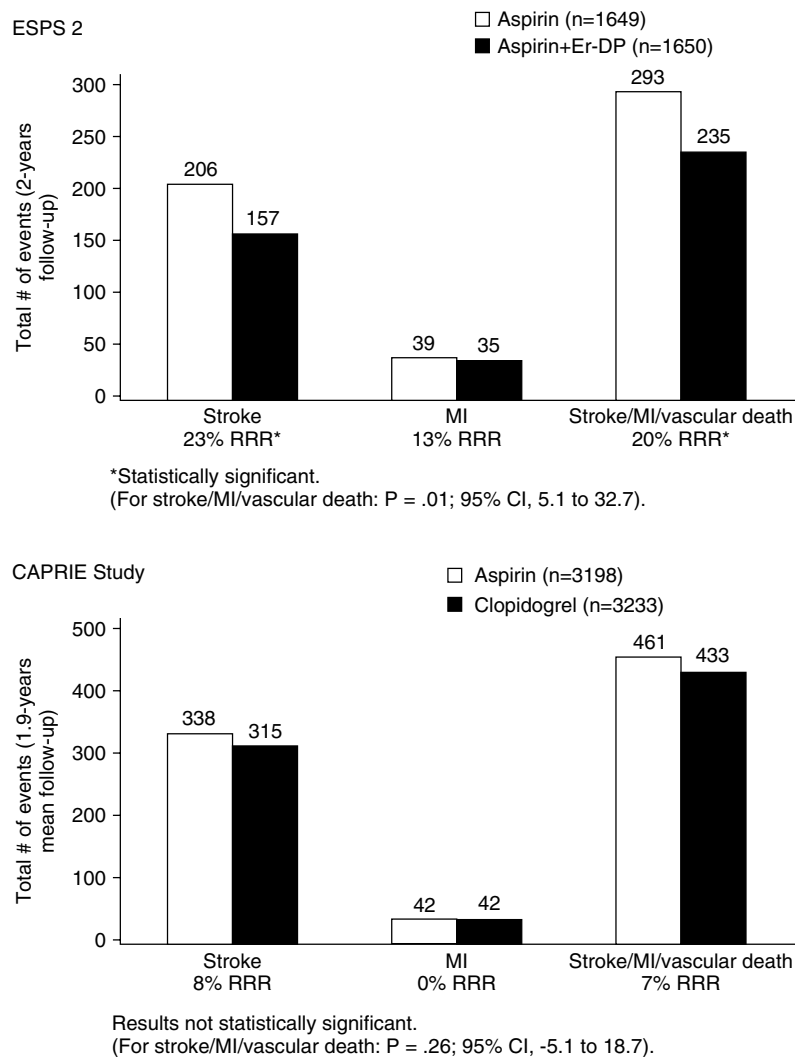


FIG. 1 Relative risks of recurrent vascular events in ESPS-2 and CAPRIE: indirect evidence that aspirin plus extended-release dipyridamole may be more effective than clopidogrel for stroke prevention. *Abbreviations:* ER-DP = extended-release dipyridamole; MI = myocardial infarction; RRR = relative risk reduction. Reprinted with permission from Albers GW et al.: *Chest* 2004;126:483S-512S.²³

as a randomized, parallel-group, international, double-blind, placebo-controlled study to directly compare the efficacy and safety of 25 mg aspirin plus 200 mg extended-release dipyridamole twice daily with clopidogrel 75 mg/day in preventing recurrent stroke. PRO-FESS employs a 2 × 2 factorial design to facilitate the simultaneous comparison of the angiotensin II receptor blocker (ARB) telmisartan 80 mg/day with placebo. Patients must be at least 55 years of age and must have experienced an ischemic stroke within 90 days of enrollment. The primary endpoint is time to first recurrent stroke over the course of the study; secondary endpoints include a composite of several vascular events. Enrollment is now complete, with a total of 20,333 patients, and results are anticipated in 2008. Notably, the trial design of PRO-FESS was modified after the MATCH results

were announced in mid-2004; an initially planned arm including the combination of clopidogrel plus aspirin was discontinued by the Data Safety Monitoring Board after these results showed no added efficacy and an increase in bleeding risk with this combination.

Translation to Clinical Practice

Results of these studies in patients with cerebrovascular disease have practical implications for cardiologists. First, appropriate use of clopidogrel and aspirin is clearly indicated in some patient populations. Even in patients with a history of stroke, clopidogrel is recommended immediately and again 3 to 6 months after a cardiac procedure such as angioplasty and stenting with drug-eluting stents, for up to 1 year, in patients with

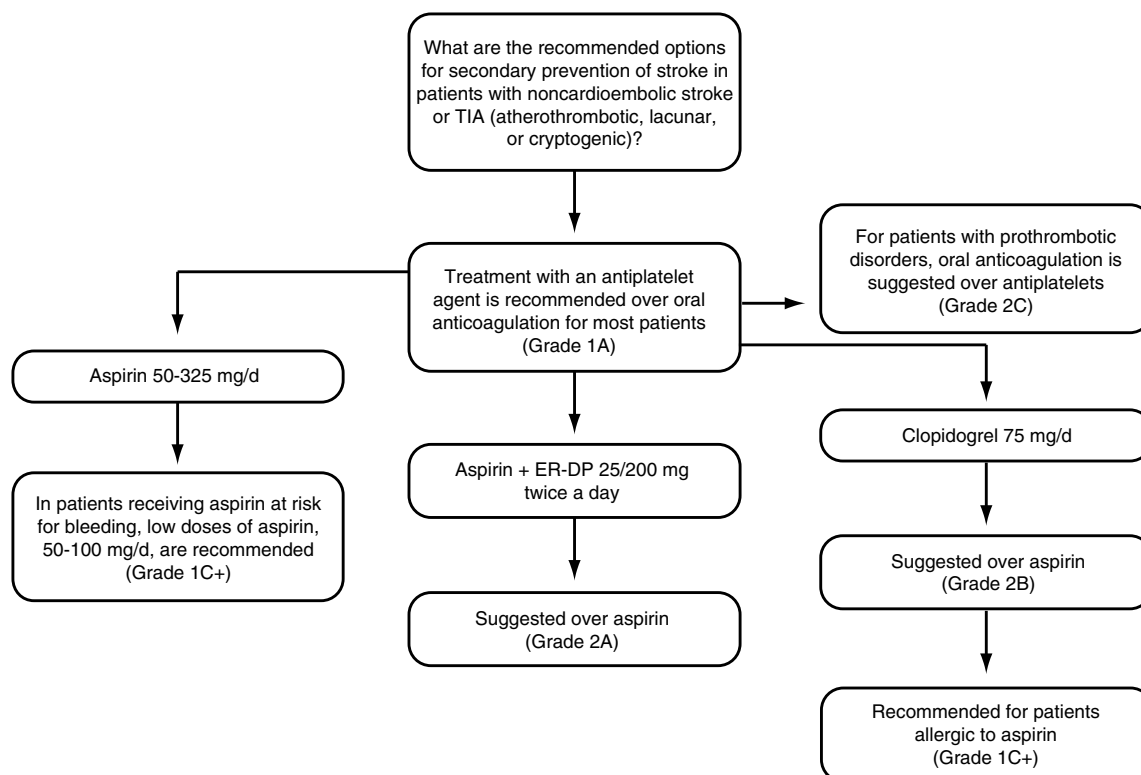


FIG. 2 The American College of Chest Physicians (ACCP) guideline-based algorithm for antiplatelet use in the secondary prevention of stroke.²³ Key to ACCP evidence-based grading levels: Grade 1 = strong recommendation; very certain that benefits do, or do not, outweigh risks, burdens, and costs; Grade 2 = weaker recommendation; less certain than Grade 1 of benefits, risks, burdens, and costs; Grade A = based on consistent results from randomized clinical trials; Grade B = based on inconsistent results from randomized clinical trials; Grade C⁺ = based on observational studies with very strong effects or secure generalizations from randomized clinical trials; Grade C = based on observational studies. 'Recommend' is used for strong recommendations (i.e., Grades 1A, 1C⁺, 1B, and 1C). 'Suggest' is used for weaker recommendations (i.e., Grades 2A, 2C⁺, 2B, and 2C). TIA = transient ischemic attack; ER-DP = extended-release dipyridamole.

a non-ST-segment elevation MI.²⁴ However, long-term indefinite therapy with clopidogrel plus aspirin may not be an optimal regimen for patients with stable atherothrombotic disease. If a patient is currently taking both clopidogrel and aspirin, physicians may want to consider discontinuing one medication to reduce risk of adverse events, depending on the patient's complete medical history (e.g., previous MI, previous stroke or TIA, bleeding). If cost is of particular concern, discontinuing clopidogrel while maintaining aspirin therapy is one possible option.

If a patient with recent stroke and history of stable coronary artery disease commences antiplatelet therapy, a dialogue between the cardiologist and the neurologist should ensue for selection of the optimal antiplatelet combination on the basis of consensus- and evidence-based guidelines and available clinical trial data (as discussed earlier). Recent guidelines from the Seventh Annual ACCP Conference on Antithrombotic and Thrombotic Therapy provide evidence-based recommendations that can guide such discussion; a graphic flow

chart summarizing these recommendations is provided as Figure 2.²³ Both aspirin plus extended-release dipyridamole and clopidogrel are recommended over aspirin for recurrent stroke prevention in patients with noncardioembolic stroke. Currently, the only combination therapy recommended by the ACCP for prevention of secondary stroke is aspirin plus extended-release dipyridamole. In light of results from the MATCH and CHARISMA trials, it is unlikely that the combination of clopidogrel plus aspirin will be recommended for stroke prevention in the next update of the ACCP guidelines.

Conclusion

Several antiplatelet agents, alone or in combination, are available for the secondary prevention of cerebrovascular disease. Results from clinical trials suggest that the selection of an agent must be based on patient history, including previous MI or stroke, susceptibility to bleeding, and other high-risk factors such as advanced age and diabetes. The MATCH and CHARISMA study results

clearly demonstrate that the risks outweigh the benefits of clopidogrel plus aspirin for preventing secondary stroke in patients with cerebrovascular disease. If the patient is also at risk for an MI or other vascular event, physicians must weigh the pros and cons of choosing this therapy. It is possible that aspirin plus extended-release dipyridamole may be more effective than clopidogrel for preventing stroke in high-risk patients. Results from the ongoing PROFESS study will provide greater clarity in the coming years.

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