

Combination Antiplatelet Agents in Ischemic Cerebrovascular Disease

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Abstract

Combination antiplatelet agents with multiple mechanisms of action are being used with increasing frequency for vascular disorders, including cerebrovascular disease. Limited data exist regarding the efficacy of combination antiplatelet therapy in the primary or secondary prevention of cerebral ischemia, and combination therapies are often used without adequate evidence of efficacy. However, over the last few years, several cerebrovascular and cardiovascular trials have provided some preliminary information on the effectiveness of various combination therapies in preventing cerebral ischemic disease. This article reviews recently completed cerebrovascular and cardiovascular trials that tested a combination antiplatelet regimen against aspirin alone, and that assessed cerebral ischemia as an outcome measure. Controversies pertaining to these trials and to the use of the various combination antiplatelet regimens are discussed.

Based on cardiovascular studies, clopidogrel in combination with aspirin has not been proven superior to aspirin alone for the primary prevention of cerebral ischemia. No data exists regarding the combination of clopidogrel and aspirin for the secondary prevention of cerebrovascular disease. The combination of aspirin plus extended-release dipyridamole (xrDP) appears to be superior to aspirin alone in the secondary prevention of cerebral ischemia, but may compromise cardiovascular protection in patients with coexisting coronary artery disease. Combination therapy with aspirin and clopidogrel seems to increase the risk of major hemorrhages, whereas aspirin plus xrDP does not. Ongoing trials are expected to clarify the role of various combination antiplatelet regimens.

Key Words: Antiplatelet, combination therapy, cerebral, ischemia, infarction, vascular, aspirin, clopidogrel, dipyridamole, cerebrovascular.

Introduction

SINCE THE ESTABLISHMENT OF ASPIRIN as the first antiplatelet agent proven effective for the secondary prevention of ischemic cerebrovascular disease, newer antiplatelet agents with different mechanisms of action have been developed, in the hope of providing greater antithrombotic activity and greater protection against cerebral ischemia. However, no single antiplatelet agent has yet proven to be both safer and more effective than aspirin for cerebrovascular patients (1, 2). As a result, combination therapies aimed at inhibiting platelet function by multiple mechanisms are increasingly being considered and tested. Experimental animal models have demonstrated that the combinations of aspirin plus ticlopidine (3), and aspirin plus clopidogrel (4), are more potent than aspirin alone in preventing platelet ag-

gregation. In a study on human plasma samples, the combination of aspirin and dipyridamole (DP) was found to reduce both the number and size of platelet aggregates in an additive fashion (5).

Currently available antiplatelet agents for use instead of aspirin or in combination with aspirin include the thienopyridines (ticlopidine and clopidogrel) and DP preparations (regular or extended release). Aspirin acts by irreversibly inhibiting intracellular platelet cyclooxygenase production of thromboxane A₂ (TXA₂), a potent pro-aggregant. The thienopyridines irreversibly block platelet membrane adenosine diphosphate (ADP) receptors, thereby preventing ligand-induced aggregation. DP reversibly inhibits intracellular platelet phosphodiesterase inactivation of cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP), two second messenger anti-aggregants, and prevents the uptake of adenosine by red cells and the vessel wall, leading to vasodilation (6). Whereas several recent major trials have demonstrated the relative efficacy of these agents individually against placebo or aspirin (7–9), only one modern study has compared combination antiplatelet therapy to aspirin in patients with cerebrovascular disease (10). However, antiplatelet drug combinations have also been

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tested in patients with cardiovascular disease, where cerebrovascular endpoints were included in the outcome assessment (11–13).

This article reviews and compares the data obtained from recent large, randomized cerebrovascular and cardiovascular trials that compared combination antiplatelet therapy to aspirin alone, and that assessed cerebral ischemia as a primary or secondary outcome measure. An overview of the study outcomes is provided in the accompanying table.

Review of Studies

The second European Stroke Prevention Study (ESPS-2) was the first modern trial to test combination antiplatelet treatment against aspirin in patients with cerebrovascular disease (10), and the only one to employ very-low-dose aspirin. More than 6,000 patients who had experienced a cerebral infarction (CI) or transient ischemic attack (TIA) within 3 months of enrollment were randomized to receive one of four treatments twice daily: aspirin 25 mg plus extended-release DP 200 mg (xrDP), aspirin 25 mg alone, xrDP 200 mg alone, or placebo. Outcome measures were determined at two years, and included TIA, CI, myocardial infarction (MI), vascular mortality (VM), and the composite outcome of CI/MI/VM. The combination of aspirin plus xrDP proved superior to aspirin alone for the CI and composite outcomes, but not for the TIA, MI, or VM outcomes. For the CI outcome, a 23% relative risk reduction was demonstrated for the aspirin/xrDP combination over aspirin alone, beyond the 18% relative risk reduction observed for aspirin vs. placebo. There was no increase in major hemorrhages, defined as any hemorrhage requiring trans-

fusion, in the aspirin/xrDP group compared to aspirin alone.

In the Stent Anticoagulation Restenosis Study (STARS) (11), 1,965 patients undergoing coronary artery stenting were randomized to one of three different antithrombotic regimens— aspirin 325 mg daily, aspirin plus ticlopidine 250 mg twice a day, or aspirin plus warfarin for an INR of 2–2.5. The main endpoints of this trial consisted of clinical and angiographic cardiac outcomes within 30 days of coronary stenting, and included MI and a composite outcome of MI, VM, vessel rethrombosis, and need for revascularization. In this trial, the combination of aspirin plus ticlopidine was more effective than aspirin alone or aspirin plus warfarin for the MI and composite outcomes, but resulted in more major hemorrhages, defined as any hemorrhage requiring transfusion. Unfortunately, the total number of events in each group was too small to draw firm conclusions from, and the short duration of this trial limited its overall usefulness with regard to cerebrovascular outcomes.

The Clopidogrel in Unstable angina and Recurrent Events (CURE) study selected patients who presented within one day of non-Q wave myocardial ischemia (12), and randomized over 12,500 patients to daily aspirin 75–325 mg and placebo, or to daily aspirin 75–325 mg plus clopidogrel 300 mg once followed by clopidogrel 75 mg daily. Main outcome measures at 1 year included MI, CI, and VM, individually and as a composite outcome. The combination of aspirin and clopidogrel proved to be superior to aspirin alone for the MI and composite outcomes, but not for the CI or VM outcomes. Major hemorrhages, defined as any hemorrhage requiring transfusion of two or more units of red cells, were more frequent in the aspirin/clopidogrel group. When

TABLE
Vascular Outcomes from the Various Combination Antiplatelet Trials.

	ESPS-2	STARS	CURE	CREDO
Cerebral Infarction	–23% (0.006)	NR (NS)	–14% (NS)	–25% (NS)
Myocardial Infarction	–10% (NS)	–80% (0.014)	–23% (SS)	–22% (NS)
Vascular Mortality	–3% (NS)	NR (NS)	–7% (NS)	–25% (NS)
CI / MI / VM	–22% (<0.01)	–85% (<0.001)†	–20% (<0.001)	–27% (SS)
Major Hemorrhage	NR (NS)	+306% (0.002)	+38% (0.001)	+31% (0.07)

All values pertain to combination antiplatelet therapy vs. aspirin alone. Values indicate relative risk as percentages (p-values in parentheses).

CI = cerebral infarction, MI = myocardial infarction, VM = vascular mortality.

ESPS-2 = European Stroke Prevention Study 2, STARS = Stent Anticoagulation Restenosis Study, CURE = Clopidogrel in Unstable angina and Recurrent Events, CREDO = Clopidogrel for the Reduction of Events During Observation.

NR = not reported, NS = not significant, SS = statistically significant.

†Combined outcome of MI, mortality, rethrombosis, and need for revascularization.

major hemorrhages and the composite outcome were merged as a single endpoint, the overall relative risk reduction for aspirin/clopidogrel vs. aspirin decreased from 18% to 8%. Only about 4% (n=500) of the patients enrolled in this study had a history of CI, and no data was available regarding outcome measures in this population.

In the Clopidogrel for the Reduction of Events During Observation (CREDO) study (13), 2,116 patients undergoing elective percutaneous coronary intervention (PCI) were randomized to receive either a clopidogrel 300 mg loading dose 3–24 hours prior to PCI followed by clopidogrel 75 mg daily for 1 year, or placebo prior to PCI followed by clopidogrel 75 mg daily for 4 weeks and then placebo again. All patients received 325 mg of aspirin from 3–24 hours before to 4 weeks after PCI, and then 81–325 mg each day thereafter. The main outcome measure at 1 year was the composite of MI, CI, and mortality, and these endpoints were also assessed individually. The treatment group receiving a clopidogrel load followed by daily clopidogrel for 1 year experienced a significant reduction in the combined outcome, but did not show a significant advantage regarding the individual outcomes of MI, CI, or mortality. A trend towards more major hemorrhages, defined as intracranial hemorrhage or a decrease in hemoglobin by 5 g/dL, was observed in the group continuously receiving clopidogrel (p=0.07). Fewer than 7% (n=141) of patients enrolled in this study had a history of previous CI.

Discussion

The results of the above studies suggest that the combination of aspirin plus a thienopyridine is superior to aspirin alone in preventing recurrent myocardial ischemia in patients presenting with acute coronary syndromes and in those requiring coronary artery stenting. However, in no study was aspirin plus a thienopyridine shown to be better than aspirin alone in preventing cerebral ischemic events. Conversely, in patients presenting with a cerebrovascular event, the combination of aspirin plus xrDP appeared to be twice as effective as aspirin alone in preventing recurrent cerebral ischemia, but was not shown to be superior to aspirin in preventing myocardial ischemia. All combination therapies displayed an advantage over aspirin alone in the composite outcome of CI/MI/VM, owing mostly to the dominant effect on their respective primary endpoint of MI or CI, but no combination influenced overall mortality. Finally, when compared to aspirin alone, the combination of aspirin plus a thienopyridine seemed to result in more major hemorrhagic complications, whereas aspirin plus xrDP did not.

Concordant with the results of the combination antiplatelet studies, a differential effect among single antiplatelet agents for different types of vascular disease has also been suggested in previous clinical trials and meta-analyses (9, 14). Epidemiological data has indicated that patients presenting with myocardial ischemia are more likely to experience and die from a recurrent cardiovascular event, whereas patients presenting with cerebral ischemia are more likely to experience and die from a recurrent cerebrovascular event (15, 16). Therefore, the type of clinically manifest vascular disease may not only predict the future vascular risk, but may also dictate a specific preventive antiplatelet treatment (17).

The difference in study populations among the combination antiplatelet trials, however, represents an important limitation to the direct comparison of study outcome results. Whereas ESPS-2 included patients who had experienced a cerebral ischemic event, CURE and CREDO selected patients with active or latent coronary artery disease. Therefore, with regard to ischemic cerebrovascular disease, ESPS-2 was the only study of secondary prevention, whereas CURE and CREDO were essentially primary prevention studies. Interestingly, the findings from these three combination antiplatelet studies mirror those testing the efficacy of aspirin alone, in which a benefit was shown for secondary prevention but not for the primary prevention of cerebral ischemia (18). Thus, the failure of aspirin/clopidogrel to prevent a first cerebral ischemic event may simply reflect the ineffectiveness of antiplatelet agents in general for the primary prevention of ischemic cerebrovascular disease. Alternatively, greater numbers of patients may have been needed in these studies to detect a small but relevant advantage.

Controversies

Controversy abounds regarding the most effective antiplatelet regimen available for the prevention of noncardiogenic cerebral ischemia (19). With the introduction of combination antiplatelet agents, this debate has only intensified and become more complex. Due to severe unfavorable hematologic side effects, ticlopidine alone or in combination with aspirin is now rarely used for antithrombosis in either cardiac or cerebral vascular disease (2). Consequently, with regard to combination therapy, there are currently two options frequently selected in clinical practice— aspirin plus clopidogrel or aspirin plus xrDP.

Aspirin plus xrDP

Critics of the aspirin/xrDP combination have challenged the validity of ESPS-2 in view of prior

aspirin/DP studies that failed to show a benefit over aspirin alone in the secondary prevention of cerebral ischemia (20–23). However, direct comparisons between the newer and older studies are impeded by the fact that prior studies were much smaller in size, used lower total daily doses of DP, and employed regular DP instead of the extended-release form (14, 21–23). Concern has also been voiced about determining treatment efficacy based on a single positive trial (20), yet ticlopidine and clopidogrel were also tested only once against aspirin in patients with cerebrovascular disease (8, 9), and have received general acceptance for this indication (17).

Investigational “misconduct” at one participating center raised concerns about the validity of the ESPS-2 results (24), but all data procured from the offending center was reportedly excluded from the final analysis. The use of a placebo arm at a time when aspirin had already been proven effective raised ethical concerns about the design of this trial (25), yet proponents claim that such a design validated the efficacy of low-dose aspirin, proved the efficacy of xrDP, and demonstrated the additive effects of combining antiplatelet agents (10).

Other issues raised have included the tolerability and cost effectiveness of aspirin/xrDP. In ESPS-2, 38% of patients taking aspirin/xrDP developed cephalgias, and 8% discontinued treatment for this reason (10). Despite evidence suggesting the rapid development of tolerance to this side effect, at least 3% of patients may ultimately be unable to continue taking aspirin/xrDP (26). Some practitioners have preferred using daily aspirin in combination with the less expensive immediate-release form of DP given four times a day, since generic xrDP is currently unavailable in the United States. However, this combination has not been proven superior to aspirin alone, immediate-release DP is associated with less bioavailability than the extended-release preparation (27), and patient compliance may be expected to decline with the more frequent dosing required. In one report, the combination of aspirin and xrDP was even found to be more cost effective in cerebrovascular prophylaxis than aspirin alone (28).

The very low dose of aspirin used for comparison against combination therapy in ESPS-2 has raised questions as to the validity of the results, since most antiplatelet trials have routinely employed control doses of at least 75 mg (8, 9, 11–13). Prospective randomized trials and meta-analyses, however, have shown no difference in efficacy for aspirin doses as low as 30 mg per day (29, 30). Insufficient cardioprotection by the very low aspirin dose used in the aspirin/xrDP formula for patients with concurrent cardiovascular disease has also been a major issue of contention, and has limited the

generalized application of aspirin/xrDP for patients with cerebral ischemic disease (see discussion below).

Aspirin plus Clopidogrel

Arguments against the use of aspirin plus clopidogrel have included the absence of a study primarily directed towards patients with cerebrovascular disease, the lack of an effect on cerebral ischemia in patients with cardiovascular disease, and the increased risk of severe hemorrhagic complications (31). Proponents of the use of aspirin/clopidogrel have pointed to a trend towards efficacy for cerebrovascular outcomes, and have attributed the increased rate of major hemorrhages to aspirin doses exceeding 200 mg per day, to the concomitant use of heparin or fractionated heparin products, and to the arterial punctures and surgical procedures performed (CURE data) (32). However, no difference in average aspirin dose between the two treatment arms was reported, a similar percentage of patients in each treatment arm received heparin or fractionated heparin products, and fewer patients in the aspirin/clopidogrel group received GPIIb/IIIa or fibrinolytic therapies as a result of treatment efficacy (12). In addition, fewer invasive procedures were performed in the aspirin/clopidogrel group, also because of treatment efficacy, and the number of surgically unrelated major hemorrhages from aspirin/clopidogrel was still almost twice that of aspirin alone (12).

It has also been suggested that the risk of hemorrhage from aspirin/clopidogrel may be even greater for cerebrovascular patients than for cardiac patients, given the propensity for acute cerebral infarctions to undergo hemorrhagic transformation (31). However, whether any increase in cerebral hemorrhages will be clinically relevant or asymptomatic remains purely speculative.

Cerebrovascular Disease and Cardiovascular Disease

One of the most debated topics in the management of patients with cerebrovascular disease involves the choice of antiplatelet therapy for patients with coexisting cardiovascular disease. According to major studies, as many as 35% of patients presenting with cerebral ischemia have a history of coronary artery disease (10). This issue has recently taken on greater importance with the introduction and approval of antiplatelet agents containing low doses of aspirin for the secondary prevention of cerebrovascular disease. In randomized clinical trials and meta-analyses, aspirin doses as low as 30–50 mg/day

have been shown to be effective for the secondary prevention of cerebral ischemia (10, 29, 30, 33). In contrast, aspirin doses of at least 75 mg/day are required for the primary or secondary prevention of myocardial ischemia (34, 35). For patients presenting with cerebral ischemia and a history of symptomatic coronary artery disease or an indication for the primary prevention of cardiovascular disease, no information exists regarding the optimal antithrombotic regimen. If aspirin/xrDP is to be used, the low daily dose of aspirin may compromise cardioprotection according to existing cardiac guidelines. Consideration may be given to adding extra aspirin, but the risk-benefit profile of this combination has never been tested in cerebral or cardiac vascular disease. Studies comparing low aspirin doses (<75 mg) to conventional doses in patients with coronary artery disease may be needed to resolve this issue.

For patients with acute coronary syndromes and for those undergoing percutaneous coronary interventions, daily aspirin plus clopidogrel is the indicated antiplatelet treatment (35). However, whether this regimen maintains or compromises cerebrovascular protection in patients with a history of cerebral ischemia remains uncertain. Additionally, the optimum duration of this treatment has yet to be defined (35), and the issue of whether and when to substitute another antiplatelet regimen also remains unresolved.

Adverse Drug Effects and Interactions

In addition to the commonly cited hemorrhagic and gastrointestinal complications from antiplatelet agents, several pertinent adverse effects and drug interactions from the constituent compounds of these combination therapies have been reported. Potential adverse effects from DP have included aggravation of angina in patients with severe or active coronary disease (36), exacerbation of hypotension (37), precipitation of TIAs in patients with cerebral hemodynamic insufficiency (38), and decreased potency of acetylcholinesterase inhibitors used for dementia (37). Conversely, an advantageous antihypertensive effect by DP has been suggested (39), but clinically disproved (40), and in one study the combination of DP plus aspirin was found to be significantly more cardioprotective than aspirin alone (41).

Immune-mediated thrombocytopenia represents a serious but very rare potential complication of clopidogrel use, with a total of eleven cases and one fatality reported (42). Laboratory experiments have demonstrated a reduction in platelet inhibition from the coadministration of clopidogrel and lipophilic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors such as atorvastatin (43, 44), yet

no adverse effects from this combination have been observed in clinical practice (45).

The decreased efficacy of angiotensin-converting enzyme (ACE) inhibitors and the increased efficacy of oral antihyperglycemic agents with aspirin is well known (46). Finally, aspirin resistance with decreased antiplatelet activity and thus inadequate cerebrovascular protection is an increasingly recognized consequence of aspirin use, particularly with low doses and coated preparations (47).

Conclusions

To date, no antiplatelet regimen has been proven effective in the primary prevention of ischemic cerebrovascular disease. The combination of aspirin and clopidogrel is of unproven benefit for preventing cerebral ischemia in patients with coronary artery disease (primary prevention), and may carry an increased risk of major hemorrhage. There is no data available regarding the use of this combination in the secondary prevention of cerebral ischemia. Consequently, it has been suggested that only those cerebrovascular patients with active coronary artery disease and a low risk of hemorrhage be considered for treatment using aspirin and clopidogrel (31).

The combination of aspirin and xrDP appears to be more effective than aspirin alone in preventing recurrent cerebral ischemic events (secondary prevention), and may not increase the risk of major hemorrhage. However, the combination of aspirin and xrDP is of uncertain benefit in patients with an indication for the primary or secondary prevention of coronary artery disease, and may even be detrimental, given the low dose of aspirin contained.

Future therapeutic strategies for the prevention of ischemic cerebrovascular disease may increasingly employ not only combination antithrombotic agents, but also combination treatments with antihypertensive agents, "statins," and vitamins (48).

Ongoing Trials

The MATCH study compared the combination of aspirin 75 mg plus clopidogrel 75 mg against clopidogrel 75 mg alone in 7,599 patients presenting within 3 months of a cerebral ischemic event, and possessing one other vascular risk factor. Other vascular risk factors included prior CI, MI, angina pectoris, symptomatic peripheral artery disease, or diabetes. Outcomes included a composite of CI/MI/VM, as well as the individual endpoints of CI, MI and hemorrhage, assessed at 18 months. The recently announced results (unpublished data) have indicated no benefit from

combination therapy over clopidogrel alone, and more severe hemorrhages from aspirin plus clopidogrel (49). Unfortunately, by not having an aspirin arm for comparison, it is difficult to draw conclusions regarding the relative efficacy of combination aspirin plus clopidogrel therapy versus any of the other available antiplatelet regimens, based on this study (1).

Ongoing secondary prevention trials comparing aspirin plus clopidogrel to aspirin alone include the SPS3 study of patients presenting with lacunar infarctions, the CARESS study of patients with recently symptomatic $\geq 50\%$ carotid stenosis, the FASTER study of patients with acute (< 12 hours) cerebral ischemia, and the CHARISMA study of patients with multiple vascular risk factors and various types of vascular disease. Primary outcomes in SPS3 will include recurrent infarction, magnetic resonance imaging measures of subcortical ischemic changes, and vascular impairment in intellect. The main endpoints in the CARESS study will be based on transcranial ultrasound measurements of microembolic signals in the ipsilateral middle cerebral artery, as well as platelet aggregation analyses. For FASTER, endpoints will include CI and MI/CI/VM, whereas in CHARISMA the primary outcome will simply be the composite of MI/CI/VM.

Other combination antiplatelet trials underway include the ACTIVE study of aspirin plus clopidogrel vs. warfarin or aspirin alone in patients with atrial fibrillation, and the ARCH study of aspirin plus clopidogrel vs. warfarin in patients with complex aortic atheroma. The ESPRIT study will compare the relative efficacy of aspirin, aspirin plus DP, and warfarin, in patients presenting with a cerebral ischemic event, and in what will be the largest cerebrovascular prevention trial ever conducted, and the first to compare two non-aspirin antiplatelet agents, the PROFESS study will compare aspirin plus xrDP against clopidogrel alone.

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