Secondary Stroke Prevention With Antiplatelet Therapy With Emphasis on the Cardiac Patient

A Neurologist’s View

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The prevention of secondary vascular events is of paramount importance in patients with a history of stroke or transient ischemic attack (TIA). Most cardiologists are aware of the benefits of clopidogrel plus aspirin versus those of other antiplatelet regimens in patients with acute coronary syndrome. Using a representative post-stroke patient as an example, this article reviews data evaluating the effectiveness of antiplatelet regimens in preventing secondary vascular events in stroke and TIA patients. These results differ from those seen in clinical trials of acute coronary syndrome patients. Clinical studies provide little evidence that clopidogrel, with or without aspirin, is more efficacious in this setting than aspirin alone. Moreover, the increased risk of bleeding episodes with clopidogrel and aspirin in combination probably outweighs any small reductions in secondary event risk. In contrast, extended-release dipyridamole (ER-DP) plus aspirin reduces secondary stroke risk to a significantly greater extent (23% relative risk reduction) than aspirin alone. Currently available clinical trial data support the use of ER-DP plus aspirin, but not clopidogrel plus aspirin, to prevent secondary vascular events after stroke or TIA. (J Am Coll Cardiol 2005;46:752–5) © 2005 by the American College of Cardiology Foundation

One of the important considerations in the management of patients with symptomatic cardiovascular disease (CVD) is the prevention of secondary events. The risk of secondary events after stroke or acute myocardial infarction (AMI) is high, and reducing this risk requires careful attention to both nonpharmacological and pharmacological approaches. This article focuses solely on the use of antiplatelet medications in stroke and transient ischemic attack (TIA) patients for secondary vascular event prevention. It emphasizes the differences in the type of recurrent vascular events such patients face as compared with AMI patients. Furthermore, this report compares the efficacy and safety of various antiplatelet drug regimens in these populations.

Consider as a representative patient a 75-year-old man with a recent (within one week) ischemic stroke and a history of AMI (14 months before). In addition to continuing standard therapy for dyslipidemia (atorvastatin), the attending neurologist prescribed an aspirin plus extended-release dipyridamole (ER-DP) combination as an antiplatelet regimen. The patient’s cardiologist, citing the previous AMI and presumed existing coronary artery disease (CAD), stated that he would like the patient’s antiplatelet therapy switched to clopidogrel plus aspirin, or at least to clopidogrel alone. What is the clinical trial evidence for and against this switch in therapies?

**CLINICAL TRIALS OF ANTIPLATELET REGIMENS**

Two large clinical trials are frequently cited in support of clopidogrel as an antiplatelet agent appropriate for prevention of secondary events in all forms of CVD: the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study (1), and the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study (2).

The CAPRIE study was a large (19,185 patients at 384 clinical centers) randomized, blinded study that compared the efficacy of clopidogrel versus aspirin in preventing recurrent vascular events in patients who had suffered a recent AMI, recent stroke, or symptomatic peripheral artery disease (PAD). Patients were randomized to either aspirin (325 mg once daily) or clopidogrel (75 mg once daily) for a mean follow-up of 1.91 years. The primary end point was risk of nonfatal MI, ischemic stroke, or vascular death. The rate of the composite outcome per year was 5.32% for clopidogrel and 5.83% for aspirin, or an 8.7% relative risk reduction (RRR) (p = 0.043) favoring clopidogrel (1).

However, the comparative efficacy of clopidogrel varied sharply by index event. The greatest (and most significant) difference between clopidogrel and aspirin was observed for the PAD group (RRR for clopidogrel vs. aspirin, 23.8%; p = 0.0028). In the stroke group, the advantage for clopidogrel was much smaller (RRR 7.3%) and not statistically significant (p = 0.28). In the AMI group, aspirin had greater efficacy, although the difference once again was not
statistically significant (RRR $-3.7\%$; p = 0.56). These results suggest greater efficacy for clopidogrel as compared with aspirin after symptomatic PAD than after AMI or stroke. In fact, a statistical test of heterogeneity of treatment effect was positive in the CAPRIE trial (p = 0.042), providing statistical evidence of nonhomogeneity of the treatment effect of clopidogrel as compared with aspirin across the three treatment arms (1). Thus, the usual assumption in a clinical trial, that differences in subgroup treatment effects are caused by chance and are more likely equivalent to the overall treatment effect, is likely invalid in the CAPRIE study.

As with our representative patient, a number of patients in the CAPRIE study had a history of other vascular events before the index event. A post-hoc secondary analysis was performed to compare patients with a history of MI. When patients from the stroke and PAD groups with previous AMI were combined with the AMI groups, the event rate for clopidogrel was nonsignificantly lower than for aspirin (5.87% vs. 6.25%; RRR 7.4%; 95% confidence interval [CI] −5.2% to 18.6%). When patients from the stroke and PAD groups who had suffered a previous MI were pooled, the results also favored clopidogrel (8.35% vs. 10.74%; RRR 22.7%; 95% CI 4.9% to 37.2%). However, a far higher proportion of patients in the PAD group than in the stroke group had a previous MI (21% vs. 12%), which suggests that this analysis disproportionately reflects results from the PAD group. The results for stroke patients with a history of MI were not separately reported, preventing a direct comparison with the representative patient (1). The adverse event profiles for clopidogrel and aspirin were similar, and both agents were relatively well tolerated (1).

The CURE study randomized 12,562 patients to aspirin, plus either clopidogrel or placebo, within 24 h of the onset of acute coronary syndromes without ST-segment elevation. Nonfatal MI, stroke, or vascular death was the primary end point. Follow-up was 3 to 12 months. The clopidogrel plus aspirin combination significantly reduced composite outcome risk versus aspirin alone (9.3% vs. 11.4%; RRR 20%; 95% CI 10% to 28%; p < 0.001). There was no significant difference with regard to stroke risk; however, the number of strokes was small (75 [1.2%] vs. 87 [1.4%]) (2).

However, the clopidogrel plus aspirin combination also significantly increased the risk of major bleeding events (3.7% vs. 2.7%; RRR $-38\%$; p = 0.001) This excess of major bleeding event risk attenuates the net benefit expected from clopidogrel plus aspirin.

The recently reported Management of Atherothrombosis in High-risk Patients with Recent Transient Ischemic Attack or Ischemic Stroke (MATCH) trial randomized 7,599 patients with recent stroke or TIA and other vascular risk factors (including diabetes or a previous stroke, MI, or PAD) to treatment with clopidogrel alone or clopidogrel plus aspirin. The composite end point (ischemic stroke, MI, vascular death, or rehospitalization for ischemic event) rate over a mean 17.5-month follow-up was 15.70% for the combination therapy versus 16.73% for clopidogrel alone, a statistically nonsignificant difference (RRR 6.4%, p = 0.244). As in the CURE study, combination therapy (clopidogrel plus aspirin) was associated with a statistically significantly higher risk of life-threatening bleeding episodes than with clopidogrel alone (2.55% vs. 1.30%, respectively; relative risk 1.96, p < 0.001). There was also a statistically significant excess of other major (non–life-threatening) bleeding events for combination therapy versus clopidogrel alone (1.94% vs. 0.58%; relative risk 3.34; p < 0.001) As compared with the results of the CURE trial, however, the absolute increase in bleeding episodes associated with combination therapy was greater than the absolute reduction in vascular events. Thus, in strong contrast to the CURE trial, the results of the MATCH trial suggest net harm from the use of clopidogrel plus aspirin as compared with monotherapy in stroke and TIA patients (3).

Aspirin plus dipyridamole in combination was evaluated initially using an immediate-release dipyridamole (IR-DP) formulation (330 mg aspirin plus 75 mg dipyridamole three times daily) that showed significant benefit versus placebo in the prevention of secondary stroke (4). The ER-DP formulation with aspirin (25 mg aspirin plus 200 mg ER-DP twice daily) has superseded IR-DP for this indication. The ER-DP formulation was developed to maintain therapeutic blood concentrations with less frequent dosing than was required of the IR-DP formulation (5).

The efficacy of aspirin plus ER-DP was evaluated in the Second European Stroke Prevention Study (ESPS-2), which randomized 6,602 patients with previous stroke or TIA to treatment with aspirin alone, ER-DP alone, both aspirin and ER-DP, or placebo. Both aspirin and ER-DP monotherapy reduced the risk of stroke versus placebo (aspirin: RRR 18%; p = 0.013; ER-DP: RRR 16%, p = 0.039), as well as the risk of a composite stroke or death outcome (aspirin: RRR 13%; p = 0.016; ER-DP: RRR 15%; p = 0.015) (6).

In addition, the combination of aspirin plus ER-DP was twice as efficacious as either agent alone. Specifically, aspirin plus ER-DP reduced the relative risk of stroke by 23% compared with aspirin alone (p < 0.001), and the relative risk of stroke, MI, and sudden death by 20% compared with aspirin alone (p = 0.005). These results suggest that the combination therapy provides a clinically, as well as statis-
tically, significant degree of additive benefit when compared with aspirin monotherapy (6). Importantly, unlike the CURE and MATCH trials, there were no statistically significant differences in major or fatal bleeding events, or gastrointestinal bleeding events for the combination of aspirin plus ER-DP versus aspirin alone.

Regarding patients with a known history of CAD (such as our case patient), 36% of patients in the ESPS-2 trial fell into this category, and an additional 10% had a history of congestive heart failure. For these patients, the benefit associated with aspirin plus ER-DP for the prevention of stroke and death was as great as that observed in patients with no such history. The rate of MI was low in the ESPS-2 trial (2.5%) and was unaffected by the use of ER-DP. Aspirin use resulted in a 21% RRR of MI in the study. However, this was not statistically significant because the overall rate of MI was much lower than that of stroke in the study.

All treatments in the ESPS-2 study were relatively well tolerated. In fact, more than 97% of patients treated with ER-DP (alone or with aspirin) were compliant, as evaluated by serum assay. The most common adverse event associated with ER-DP was headache. Both all-site and gastrointestinal bleeding were significantly more frequent with aspirin (6).

**STUDY COMPARISONS**

It is possible to indirectly compare several aspects of the studies investigating clopidogrel (with or without aspirin) and aspirin plus ER-DP. Whereas the CAPRIE trial used a composite end point and enrolled patients with different index vascular events, the CURE, MATCH, and ESPS-2 trial used more limited study populations, resulting in a more focused picture of the response to pharmacological therapy in specific syndromes. Although this may help to increase the statistical strength of results, it also limits the ability to generalize them to broader groups of patients. On the other hand, the design of the CAPRIE trial assumed a broad equivalence of clopidogrel efficacy in treating different vascular events, but its results contradicted this concept, showing a pronounced heterogeneity in treatment effectiveness based on the nature of the index event. As shown compellingly by the results of the CURE and MATCH trials, it is dangerous to assume that one can generalize efficacy results from one vascular event population to another.

Similarly, the assumption of equivalent risk for recurrence of different types of vascular events in patients with recent stroke and TIA as compared with patients with recent acute coronary syndrome or MI is not supported by recent evidence. A study of secondary events after AMI and stroke has shown that the risk of recurrence of an event of the same type is three to five times greater than the risk of an event of a different type (7). In the CAPRIE study, the stroke group experienced recurrent strokes at a 6.87 times greater frequency than MI, and the AMI group experienced recurrent AMI at 4.01 times the stroke rate (1). Other recent trials comparing antiplatelet therapies for secondary stroke prevention have shown a 2.5- to 13-fold higher frequency of strokes than MIs once a patient has suffered a stroke or TIA (6,8–10). Collectively, these data strongly suggest that although similar risk factors underlie most forms of CVD, individual patients are prone to events in specific vascular beds. The most recent event seems to predict the next event, especially in stroke patients. The MATCH trial results also support these observations. To put this into perspective, our case patient had suffered both an MI and a stroke, but because the most recent event was stroke, the greatest risk for recurrence would be for another stroke.

At this point, there have been few well-controlled, well-designed trials of combination regimens such as aspirin plus clopidogrel or aspirin plus ER-DP for prevention of all vascular events. However, several studies that address various aspects of secondary prevention are planned or in progress. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial is evaluating the efficacy of aspirin plus clopidogrel, as compared with aspirin alone, in preventing vascular events in patients who either have had a recent vascular event or are at high risk for one. The latter group will provide an important first look at the efficacy and safety of clopidogrel plus aspirin for primary prevention of vascular events in high-risk patients. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is comparing aspirin plus clopidogrel with aspirin alone in prevention of recurrent lacunar or small-vessel stroke, and the Antithrombotic Therapy in Acute Recovered cerebral Ischemia (ATARI) study is comparing aspirin plus clopidogrel with aspirin alone in TIA patients. The ongoing Atrial Fibrillation Clopidogrel Trial with Irbesartan for the Prevention of Vascular Events (ACTIVE) study is evaluating the efficacy of clopidogrel in combination with the antihypertensive agent irbesartan in 14,000 patients with atrial fibrillation over a four-year period.

The Prospective Regimen For Effectively avoiding Second Strokes (PRoFESS) study will be the largest prospective secondary stroke prevention trial in history, enrolling 15,500 patients with a recent history of ischemic stroke in a 2 × 2 factorial design. The PRoFESS study will provide the first head-to-head comparison between aspirin plus ER-DP and clopidogrel. Although the original study design included a comparison between aspirin plus ER-DP and aspirin plus clopidogrel, the Data Safety Monitoring Board has eliminated aspirin from the aspirin plus clopidogrel arm in light of results from the MATCH study. Each antiplatelet regimen also will be evaluated with concurrent use of telmisartan, an angiotensin II receptor blockade antihypertensive agent. The primary end point is time to the first recurrent stroke, with a composite secondary end point (time to the first nonfatal stroke, nonfatal MI, or vascular death). Finally, the European/Australasian Stroke Preven-
tion in Reversible Ischemia Trial (ESPRIT) is another ongoing clinical trial comparing aspirin and dipyridamole with aspirin alone in TIA and stroke patients for recurrent vascular event prevention.

CONCLUSIONS

Pending the results of ongoing and planned studies, the limited number of available studies on the relative effectiveness of combination therapies based on clopidogrel and aspirin plus ER-DP makes it difficult to broadly recommend one in favor of the other. Instead, a review of the currently published data suggests the importance of focusing on the nature of the most recent vascular event and individualizing antiplatelet therapy accordingly. The evidence supporting aspirin and clopidogrel for treating acute coronary syndrome patients is strong, whereas what if any role aspirin plus ER-DP will play remains to be defined. Conversely, the evidence supporting the efficacy of aspirin plus ER-DP for secondary event prevention after stroke and TIA is strong, whereas data suggest that clopidogrel is no more efficacious than aspirin and that the combination of clopidogrel plus aspirin is probably harmful in this population.

Because between-study comparisons remain indirect, the interpretation outlined here may not be universally accepted. However, results from the four major studies evaluating these combinations suggest that there is no compelling reason to switch the representative patient from aspirin plus ER-DP to aspirin plus clopidogrel (or even to clopidogrel alone). Moreover, the MATCH study results suggest that a switch to clopidogrel plus aspirin would, if anything, be harmful rather than beneficial. Thus, the representative patient should be maintained on his current regimen of aspirin plus ER-DP.

REFERENCES