By David Tong, MD

Much Ado About Antiplatelets: What's the Role of Combination Therapy?

Three recent landmark trials cast doubt, but all hope is not lost. At least one regimen may be worth consideration.

Last month in this column, we reviewed the results of the recent ACTIVE and CHARISMA trials, which in combination with the results of the MATCH trial provide a more complete picture of the relative utility of clopidogrel in stroke patients (to review this column, please go to www.practicalneurology.com). To summarize, these trials evaluated the ability of the combination of aspirin and clopidogrel to reduce the risk of recurrent stroke in over 25,000 patients in a variety of different populations, including secondary prevention in patients with a recent stroke (MATCH), atrial fibrillation patients (ACTIVE) and those with high-risk symptomatic and asymptomatic general vascular disease patients (CHARISMA).

The major finding of these studies was that the combination did not significantly reduce the risk of recurrent vascular events. However, this regimen did increase the risk of hemorrhagic stroke, although the risk of intracerebral hemorrhage was not significantly increased. Taken together, these studies strongly suggest that the combination of aspirin plus clopidogrel should not be routinely used as chronic prophylactic therapy in individuals with stroke or at a high risk for stroke.

The Nagging Question Remains

The recent data from these studies may have closed the book for that particular course of treatment for stroke prevention, but it also brought more attention to a nagging question: What about the combination of aspirin and dipyridamole (Aggrenox)? Until recently, we had little data on which to base the answer and much controversy to consider.

As most neurologists know, this combination was shown to be effective in one large randomized trial (the European Stroke Prevention Study 2, commonly known as ESPS-2). However, controversy has clouded the impact of this study for a variety of reasons, particularly the disparity between this trial and a number of previous smaller studies, which did not identify a beneficial effect of the combination compared with aspirin alone. The lack of a confirmatory study to verify the benefit of this combination also made the vascular care community hesitant to take the data at face value.

Although a similar study (ESPS-1) did suggest efficacy, this study compared the combination treatment with a rapid release dipyridamole as opposed to the slow release in the Aggrenox formulation. In addition, this study compared the combination treatment with placebo rather than aspirin, making any comparison somewhat speculative. Moreover, one site in the study was found to have been falsifying data, which leads to concern regarding the validity of the results despite the fact that the study's findings were unchanged after excluding data from the falsifying site.

The overall conclusion was that the efficacy of the dipyridamole plus aspirin combination was questionable. This was further exacerbated by the concern that the aspirin dose used (25mg BID versus the commonly used 160mg or more for cardiac purposes) was insufficient to provide sufficient cardiac protection, adding to the doubts concerning the treatment.

New Data From ESPRIT

Because of these persistent concerns, European investigators initiated another randomized trial, the European/ Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), which was reported in *Lancet 2006; 367: 1665–73*. This was an unblinded, open-label, randomized controlled trial of aspirin (30-325mg) versus controlled-release aspirin/ dipyridamole combination either as the extended-release combination medication (Aggrenox) or as a free combination. A third arm evaluated the effectiveness of anticoagulation, but these data were not reported in this publication.

Although open label, all endpoints were adjudicated in a blinded manner. Inclusion criteria were similar to other trials of this type, including the prior ESPS-2 trial, and included patients with a minor presumable arterial stroke (modified Rankin scale score less than or equal to three) or TIA within six months of symptom onset. Patients with a presumed cardiac or carotid etiology were excluded, as were any with a known coagulation disorder or contraindication to participation in the study. Analysis was on an intention to treat basis.

The primary outcome was the composite of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication—whichever happened first. Secondary outcome events included death from all causes, death from all vascular causes, death from all vascular causes and a non-fatal stroke, all major ischemic events (nonhemorrhagic death from vascular causes, non-fatal ischemic stroke, or non-fatal

myocardial infarction), all vascular events (death from vascular causes, nonfatal stroke, or non-fatal myocardial infarction), and major bleeding complications.

Between July 1, 1997 and December 31, 2005, 2,763 patients were randomized in the trial. The mean follow-up was 3.5 years. Ninety-four percent of patients had a Rankin grade of less than or equal to≤two, indicating that these patients had fairly minor strokes. Over 95 percent of the patients received a CT or MRI, and 90 percent a carotid ultrasound.

The main finding was a statistically significant 20 percent relative risk reduction of the combination treatment compared with aspirin alone (16 percent versus 13 percent, 95 percent CI 0.66-0.98). The absolute risk reduction was one percent per year, leading to a number needed to treat of about 100. There was no significant difference between the reduction of cardiac events versus stroke. In addition, there was no significant difference in the rate of hemorrhagic complications between the two groups, and in fact the combination group had a lower incidence of major bleeding complications.

The Bottom Line

Taken together, these results strongly substantiate the hypothesis that the combination of aspirin plus dipyridamole, especially when used in the controlled-release form, is associated with a reduced risk of recurrent vascular events. The magnitude of the effect is similar to that observed in patients receiving statin therapy for cardiovascular prevention, which makes it clinically important.

However, there are some caveats to bear in mind when considering the clinical applications of this study. First, the dose of aspirin was 30mg in almost half (43 percent) of patients in both treatment arms. A higher dose of aspirin could theoretically have reduced some of the effectiveness of the DPA. In addition, the effect of treatment appears to be delayed. Most of the ischemic event reduction occurs more than two years after the start of treatment. The reason for this is uncertain, and certainly could be due to the play of chance, given the prolonged nature of the study (eight years), but is intriguing. There was also a high rate of patient dropout due to headache. About 30 percent of patients discontinued the medication for this reason, which is a higher number than we've seen in prior studies. Finally, the trial was open-label, which theoretically could open it up to bias, even though a blinded independent endpoint committee adjudicated all of the events.

Despite these points, the trial does suggest that combination dipyridamole plus aspirin is more effective than aspirin alone (or at least compared to the doses used in the study). This is important and practical information that should be known to all neurologists who treat stroke patients, especially given the relative paucity of proven effective antithrombotic therapies for this condition. The findings also allay some of the concerns that are common among cardiologists regarding the safety of low-dose aspirin. In addition, the lower bleeding rate on a combination of aspirin and dipyridamole certainly reduces concern for the safety of this particular formulation.

Aggressive Control of Cholesterol

These recent data provide a great deal of new information about the use of combination therapy for stroke patients. Hopefully, future studies will provide even more useful information on the relative merits of different preventative stroke treatments as well as their potential risks. Next month we will discuss the results of the recently reported Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, which may have significant repercussions for cholesterol treatment on stroke patients. Stay tuned. **PN**

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