Combination Therapy With Clopidogrel and Aspirin: Can the CURE Results Be Extrapolated to Cerebrovascular Patients?

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Several antiplatelet agents with different mechanisms of action are currently available for secondary prevention of ischemic stroke. When used as a single agent, the efficacy of antiplatelet therapy is modest. Aspirin is the best-studied and most widely used antiplatelet agent for stroke prevention; however, it provides only an approximately 15% relative risk reduction for secondary prevention of stroke or other major vascular events. Combining 2 antiplatelet agents with different mechanisms of action was demonstrated to provide a substantial increase in efficacy in the ESPS II study. In this trial, the relative risk reduction for secondary stroke prevention was 37% with use of a combination of extended-release dipyridamole and aspirin. Importantly, the risk of major bleeding attributable to the combination therapy was no greater than that seen with aspirin alone. Clopidogrel was shown to be a safe and efficacious medication for secondary prevention of vascular events in the CAPRIE study. In this trial, the benefit of clopidogrel over aspirin for the prevention of vascular events was a relative risk reduction of 8.7%. In addition, there was less major bleeding in the clopidogrel group, yielding a relative net benefit of about 10%. It has been assumed by many physicians that the combination of clopidogrel with aspirin may be substantially more effective than either agent alone. In fact, many patients with cerebrovascular disease are currently treated with this combination despite the absence of any substantial safety or efficacy data regarding the use of this combination in stroke or transient ischemic attack (TIA) patients. Recently, the results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial were published. This study assessed the safety and efficacy of the combination of clopidogrel and aspirin in patients with acute coronary syndromes without ST-segment elevation. Can the CURE results be extrapolated to cerebrovascular patients?

The CURE Trial

The CURE trial enrolled patients with unstable angina (74.9%) or suspected myocardial infarction (MI; 25.1%). The mean age was 64.2 years, and two thirds of the patients were receiving aspirin at baseline. Although the planned enrollment goal was 9000 patients, the sample size was increased to over 12,500 because the event rates were less than expected. Patients were randomized to receive clopidogrel (75 mg/d) or matched placebo for 3 to 12 months (mean treatment duration, 9 months). All patients received open-label aspirin (recommended dose, 75 to 325 mg/d).

The main efficacy assessment was based on a primary outcome measure composed of cardiovascular death, nonfatal MI (chest pain with a doubling of cardiac enzyme levels, or appropriate electrocardiographic changes) and stroke (ischemic, hemorrhagic, or uncertain when a CT scan was not performed). A primary outcome event occurred in 11.4% of the patients on aspirin alone and 9.3% of patients on the combination therapy, yielding a 20% relative risk reduction ($P<0.001$), or an absolute benefit of 2.1%.

Major bleeding, defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood, occurred in 2.7% of patients in the aspirin-alone group and 3.7% in the clopidogrel/aspirin group, yielding a 38% relative excess of major bleeding complications ($P=0.001$), with an absolute increase risk of 1.0%. In addition, minor bleeding (bleeding events that led to interruption of study medication) were twice as common in the clopidogrel/aspirin group (5.1% versus 2.4%, $P<0.001$). There was no difference in fatal bleeding complications between the 2 groups.

Although it is difficult to equate the morbidity associated with a vascular end point to that of a hemorrhagic event, it is important to consider both when assessing the net benefit of an antithrombotic therapy. In CURE, the most common primary outcome event was MI, which, like ischemic stroke, can be variable in severity and cause variable levels of disability. Of note, less disabling non–Q-wave MIs were a more common end point than Q-wave infarctions in the CURE trial.

One option to estimate the overall benefit of an antithrombotic therapy is to look at a combination end point that amalgamates major bleeding episodes and major vascular events. If this is performed for the CURE trial, a relative risk reduction of 8% favoring clopidogrel/aspirin over aspirin alone is detected (see Figure). This represents an absolute net benefit of 1.1%, with a calculated odds ratio of 1.10 (95% CI, 0.99 to 1.22). Therefore, CURE demonstrates that the clopidogrel/aspirin combination provides increased efficacy compared with aspirin alone for prevention of vascular events; however, the increased risk of major bleeding offsets a portion of the benefit.

How Do Cerebrovascular and Cardiac Patients Differ?

Before generalizing the results of a clinical trial to a different patient population, it is important to consider whether there are clinically...
Combination of the primary outcome events (myocardial infarction, stroke, or death from cerebrovascular causes) with the major bleeding events (substantially disabling bleeding, intracerebral bleeding leading to the loss of vision, or bleeding necessitating transfusion of at least 2 units of blood) in the CURE trial.

relevant differences between the 2 populations. For example, are both populations at risk for the same type of vascular events? Are there reasons to suspect that the safety profile of the agents tested may differ between the 2 populations?

There is a strong association between atherosclerosis and both cardiac and cerebral ischemic events. Despite this, the types of subsequent vascular events that occur after a stroke versus after an MI differ substantially. Numerous clinical trials have demonstrated that patients who suffer a stroke or TIA are considerably more likely to have a cerebral ischemic event, rather than an MI, as their next vascular event. Similarly, patients with acute coronary syndromes have a low risk of subsequent stroke but a high risk of future MI. For example, stroke patients enrolled in the CAPRIE trial suffered 7 times as many strokes as MIs during the study. Similarly, MI occurred approximately 5 times more commonly than stroke among the patients who were enrolled in CURE.

Bleeding complications of antithrombotic therapies also differ between cerebrovascular patients and patients with other vascular disorders. A dramatic example of this was seen in the SPIRIT trial. In this study, cerebrovascular patients were treated with oral anticoagulation therapy at an intensity (INR 3.0 to 4.5) that had previously been well tolerated in cardiac patients. This study was stopped prematurely by the safety monitoring committee because of severe bleeding complications, including 27 intracranial hemorrhages, in the anticoagulation group. Potential explanations for the higher bleeding rates observed in cerebrovascular patients include their older age, multiple concomitant medications, and underlying ischemic brain injury. Therefore, it is extremely difficult to extrapolate the bleeding risk associated with an antithrombotic therapy from cardiac to cerebrovascular patients.

Efficacy of Clopidogrel for Prevention of Stroke Versus MI

Because cerebrovascular patients are most likely to suffer subsequent strokes and cardiac patients are more likely to suffer additional MIs, it is important to consider whether the efficacy of an antithrombotic therapy differs between these populations. In the CAPRIE trial, 3 different patient populations were entered (recent ischemic stroke, recent MI, and symptomatic peripheral arterial disease). In this study, a statistically significant heterogeneity of treatment effects was seen, which suggests that the benefit of clopidogrel over aspirin differed among the populations. Of interest, the benefit of clopidogrel over aspirin for preventing the end point of MI was substantial, a highly statistically significant 19.2% relative risk reduction. In contrast, the benefit of clopidogrel over aspirin for preventing stroke appeared to be less, a non–statistically significant 5.2% relative risk reduction. These data raise the possibility that clopidogrel is more efficacious for preventing MI than stroke, therefore further limiting the ability to extrapolate data from cardiac patients to individuals with cerebrovascular disorders. The number of strokes that occurred in the CURE trial was far too small to assess the efficacy of the clopidogrel/aspirin combination versus aspirin alone for prevention of stroke. There was a trend in favor of the combination therapy; however, the difference did not approach statistical significance ($P=0.86$), as the stroke rate was $<1.5\%$ in both treatment groups.

Conclusions

Because of the substantial differences between cerebrovascular and cardiac patients, as well as uncertainties regarding the efficacy of the clopidogrel/aspirin combination for prevention of stroke, the CURE data should not be extrapolated to cerebrovascular patients. Fortunately, the ongoing MATCH study will directly assess this issue. This randomized trial compares the combination of aspirin/clopidogrel with clopidogrel alone in high-risk patients with a recent stroke/TIA. Therefore, this trial will directly assess both the efficacy and safety of the combination of clopidogrel and aspirin in a cerebrovascular patient population. The results of the MATCH study are expected in about 2 years.

In the meanwhile, which cerebrovascular patients are appropriate candidates for combination therapy with clopidogrel and aspirin? In the absence of data, this question is difficult to address. This combination may be appropriate for cerebrovascular patients who have a history of recent cardiac ischemia and appear to be at low risk for hemorrhagic complications, particularly if they suffer a recurrent stroke while on another antiplatelet therapy. In addition, we consider this combination for cerebrovascular patients with complex aortic arch atherosclerosis because these patients have a high risk of both cardiac and cerebral vascular events despite conventional therapies.

References

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