Antiplatelet Therapy after Ischemic Stroke or TIA

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Antiplatelet therapy is the mainstay for the prevention of primary stroke in patients with risk factors and for the prevention of recurrent stroke after transient ischemic attack (TIA) or ischemic stroke. An outstanding question concerns appropriate antiplatelet regimens under various clinical scenarios. The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, the results of which have now been published in the Journal, investigated antiplatelet regimens for the prevention of recurrent stroke in patients after TIA or minor stroke, with the latter being defined according to a National Institutes of Health Stroke Scale score of 3 or less (on a scale from 0 to 42, with higher scores indicating more severe stroke). The primary outcome was the prevention of subsequent ischemic stroke, myocardial infarction, or death from ischemic vascular causes. Since most subsequent ischemic events occur soon after the index TIA or stroke, treatment in the trial began within 12 hours after the index event.

It is important to emphasize which patients were not included in this trial. The POINT trial excluded patients with a cardiac source of symptoms such as atrial fibrillation, most of whom receive anticoagulation; those with severe extracranial carotid disease, who might benefit from endarterectomy or stenting; and those with severe intracranial atherosclerosis, who are typically treated with dual antiplatelet therapy for 3 months or longer (such therapy is consistent with the results of the Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis [SAMMPRIS] trial).

The POINT trial included many of the remaining patients with TIA or stroke. Although these patients are certainly at risk for subsequent ischemic events, the risk in this population is low, as shown by the need to increase the sample size midway through the trial. Patients were randomly assigned to receive either aspirin (at a dose of 50 to 325 mg daily) alone or the same dose of aspirin plus clopidogrel (at a dose of 75 mg daily, after a 600-mg loading dose), and treatment was continued for 90 days. The trial was stopped after 84% of the anticipated number of patients had been enrolled because both the efficacy and safety boundaries were crossed.

The trial results seem valid and generalizable, given that the trial was conducted in 10 countries, with only 4% of patients being lost to follow-up. The only procedural blemish is that approximately 29% of the patients discontinued the trial medication before 90 days, but the results were similar in both the intention-to-treat and as-treated analyses.

On the surface, the results might suggest no net benefit — there was a lower rate of subsequent ischemic events with clopidogrel plus aspirin than with aspirin alone, which was balanced by a higher rate of serious bleeding with the combination. These results are consistent with those of other trials of combined aspirin plus clopidogrel for stroke prevention after TIA, in which bleeding complications offset the lower rates of ischemic events.

Several points are worth noting. First, most of the prevented events were ischemic strokes — the most common and arguably most important of the outcomes after a TIA or minor stroke. Second, most of the bleeding complications were systemic, nonfatal, nonintracranial hemorrhages and not the most feared event of intracranial bleeding. Third, and most salient, is the timing of these outcomes. Most of the benefit regarding...
stroke prevention occurred in the first week of treatment with the combination, whereas most of the bleeding occurred later. In a secondary analysis, the benefit of aspirin plus clopidogrel in preventing ischemic outcomes was significant throughout the first 7 to 30 days of treatment, whereas the risk of major hemorrhage became greater only during the period from 8 to 90 days.

The results are slightly at odds with the only other trial of aspirin plus clopidogrel after minor stroke, which involved Asian patients. The Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial showed a similar lower rate of ischemic events with clopidogrel plus aspirin than with aspirin alone, but without a higher rate of bleeding with the combination. The CHANCE trial used a lower loading dose of clopidogrel, but this is an unlikely explanation for the difference, since most bleeding events in the POINT trial occurred long after the loading dose. More likely, the difference was due to a shorter duration of combined treatment (only 21 days in the CHANCE trial vs. 90 days in the POINT trial) and differences in the metabolism of clopidogrel in Asian versus non-Asian persons.

What is the take-home message for the clinician? The evidence from the SAMMPRIS, CHANCE, and POINT trials is that the combination of aspirin plus clopidogrel reduces the chance of recurrent ischemic stroke during the high-risk period in the first few weeks after a TIA or noncardioembolic ischemic stroke. However, to conform to the results of the POINT trial, if dual therapy is used, it should be confined to the first 3 weeks after a TIA or minor stroke and then transitioned to monotherapy. If patient follow-up and adherence to therapy are not reliable, then dual therapy perhaps should not be considered. Dual therapy may also not be advisable in patients with an uncertain diagnosis of TIA, who either would have been excluded from the trial or did not benefit. Finally, patients who are at increased risk for bleeding, such as those with cerebral microbleeding or a history of brain or systemic bleeding, were excluded from this trial and may not be appropriate candidates for such dual therapy. The POINT trial has provided useful data to help us further personalize our efforts in preventing recurrent stroke.

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