A Little Good…

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My grandmother used to say, “If a little’ll do a little good, a lot’ll do a lotta good.” Unfortunately, it is not that simple with antiplatelet agents. Many relevant facts are well established. In identifiable subgroups of patients who present with transient ischemic attacks (TIAs) or minor strokes, the risk of a subsequent stroke is high.\(^1\)\(^-\)\(^2\) Most of this risk is incurred during the first few days after a warning event.\(^2\) Aspirin and other antiplatelet agents can lower the risk of secondary stroke by \(\approx 12\% - 22\%.\(^3\)\(^,\)\(^4\)\) In patients with acute coronary syndromes, another thrombotic disorder, dual antiplatelet therapy, offers a greater risk reduction than aspirin alone, at the expense of increased hemorrhagic risk.\(^6\) In symptomatic and asymptomatic patients, dual antiplatelet therapy with clopidogrel and aspirin is better than aspirin alone in reducing microembolic signals detected by transcranial Doppler ultrasound as evidence of plaque-related embolism.\(^7\)\(^,\)\(^8\) The extended use of aspirin plus clopidogrel confers an increased risk of moderate-to-severe hemorrhage when compared with either agent alone.\(^9\)\(^-\)\(^11\) Early trials of dual antiplatelet therapy for secondary stroke prevention have shown either no benefit or a benefit that was counterbalanced by the increased risk of significant hemorrhage.\(^9\)\(^,\)\(^10\)\(^,\)\(^12\) Dual antiplatelet therapy was a component of a successful regimen of secondary prevention in patients with symptomatic intracranial stenosis in the recent Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial.\(^13\)

The designers of the Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events (CHANCE) trial of dual antiplatelet therapy for secondary stroke prevention sought to enhance relative benefit by focusing on high-risk patients during their period of highest risk.\(^14\) They took advantage of the clustering of risk in the period immediately after a TIA by enrolling patients early (within 24 hours) after a TIA or minor stroke and by limiting treatment with dual agents to the first 3 weeks after an event, thus limiting the exposure risk for hemorrhagic complications. With this strategy, the CHANCE trial succeeded where other studies had failed. In the CHANCE trial, the dual-agent versus single-agent patients diverged in favor of the dual-agent group within the first few days of follow-up, and, after that, the rates of the accumulated strokes of the two groups remained equal. Therefore, with only 21 days of dual therapy, the dual-agent group retained its advantage at 3 months. The CHANCE trial was well designed and well executed. The main questions that remain concern the reproducibility and generalizability of this result.

The question of generalizability primarily concerns the population studied in the CHANCE trial. The CHANCE patients were enrolled in China where the rate of intracranial atherosclerosis is higher than in western populations. They were all enrolled within 24 hours of the event. The event was a TIA or minor stroke (defined as National Institutes of Health Stroke Scale score \(\leq 3\)). Patients had a moderate-to-high risk of recurrent stroke based on an ABCD\(^2\) score of \(\geq 4\). Also, those with isolated sensory or visual symptoms and isolated dizziness or vertigo were excluded, unless baseline computed tomography or magnetic resonance imaging showed an acute infarction. Those with moderate disability (modified Rankin scale score of \(>2\)) immediately before the qualifying event were excluded.

Strictly interpreted, the study applies to this population, and the question of generalizability beyond this is an important one. Because the randomized clinical trial is the gold standard for evidence-based decision making, the CHANCE trial is a major contribution, and the ongoing Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)\(^15\) and Triple Antiplatelets for Reducing Dependency After Ischemic Stroke (TARDIS)\(^16\) trials will address some of the limitation of the restricted population. The major important differences in design of POINT other than its limitation to the United States and Canada is that the patients will be randomized within a tighter 12-hour window, and patients in the dual antiplatelet group will receive dual therapy for the entire 90 days of the study. The tighter window might be expected to prevent some events in the very early high-risk period. The dual therapy for 90 days might be beneficial, but it sacrifices the possible advantage of concentration on the period of highest risk and eliminating the exposure to hemorrhagic risks thereafter. The TARDIS trial under way in the United Kingdom will test triple antiplatelet therapy with aspirin, dipyridamole, and clopidogrel versus standard therapy in patients enrolled within 48 hours of event onset.

In this issue of *Circulation*, Wong et al\(^17\) report the results of an updated meta-analysis of dual antiplatelet versus single-agent therapy for acute non-cardioembolic TIAs and small ischemic strokes. Although this study takes a step back from the CHANCE trial in methodological rigor, simply by virtue of the meta-analysis design, it represents an important contribution to the investigation of the question at hand of reproducibility and generalizability.

In 12 studies analyzed by Geeganage et al in a previous meta-analysis and now in 14 in the expanded meta-analysis,
selecting only patients enrolled within 3 days of the qualifying event, the trend in originally seven and now eight has favored dual therapy and in four monotherapy. In only 1, the CHANCE trial, has dual therapy shown significant benefit\(^2\) (1 study was not analyzable). The meta-analysis suggests that a dual antiplatelet therapy is superior to single-agent therapy for the prevention of early recurrent strokes.

As pointed out by the authors, this analysis has many limitations, including potential publication bias, methodological flaws in some studies (lack of blinding, no intention-to-treat analysis), and much variety in the study designs. This variety includes different stroke phenotypes, with some enrolling TIAs, some strokes of various sizes, and some both TIAs and strokes. It also includes variety in the antiplatelet agents studied and the duration of follow-up. Of the 14 studies included, 6 compared clopidogrel plus aspirin with aspirin alone, 1, the Prevention Regimen for Effectively Avoiding Second Strokes Trial, compared aspirin plus dipyridamole with clopidogrel alone, and 6 compared combinations of aspirin and dipyridamole. The authors eliminated the variety of time from onset-to-enrollment by including only patients enrolled within 3 days from all studies. Ultimately, the updated meta-analysis is primarily driven by the CHANCE trial, which contributed more than half of the patients.

With these limitations, our conclusions from this meta-analysis must be tentative. The meta-analysis does favor dual therapy with and without the inclusion of the patients from the CHANCE trial, and of the 6 studies that compare clopidogrel plus aspirin with either agent alone have shown trends favoring dual therapy for patients enrolled within 3 days. So far, only the CHANCE trial has taken advantage of the temporal profile of recurrent stroke risk after a TIA or minor stroke by limiting dual therapy to a short term. Perhaps this meta-analysis gives us a hint of the validity of generalizing from the CHANCE trial for which we hope, yet the question of doing a little good versus a little harm with dual antiplatelet agents remains open. To address it, we should strongly support enrollment in well-designed clinical trials, such as POINT and TARDIS, that test it directly.

Disclosures

None.

References


15. Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial. http://www.clinicaltrials.gov/ct2/show/NCT00991029?term=point&rank=1


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