Emerging Therapy Critiques

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CHANCE Trial
Early Short-Term Dual Antiplatelet Treatment for Stroke Prevention

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The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial tested the effect of early dual antiplatelet treatment for the prevention of secondary stroke within the first 90 days following a qualifying transient ischemic attack (TIA) or minor stroke in 5170 Chinese patients. The trial showed a significant reduction in secondary stroke in patients treated with dual antiplatelet therapy (hazard ratio, 0.68; 95% confidence interval, 0.57–0.81; P=0.001). There was no difference in the rate of moderate or severe hemorrhages (0.3% in both groups; P=0.73).1

CHANCE is critical support for early-onset and short-term intervention of antiplatelet therapy in patients with TIA and mild strokes. The trial builds on knowledge gained during the past decade, beginning with observations that the risks of stroke early after a TIA or minor stroke are substantial,2–4 with a 2-day risk of stroke following TIA of ≈5%.2,4 Greater attention has since been paid to early evaluation, identification, and treatment of modifiable risk factors and the initiation of antiplatelet treatment for noncardioembolic events within 48 hours of the initial event.5 Previous lysis and recanalization studies have shown the importance of immediate medical management following ischemic events. More recently, studies have addressed the use of antiplatelet agents in an earlier time window, seeking to address the period of highest stroke recurrence risk. The Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER) pilot trial randomized 392 patients with TIA/stroke presenting within 24 hours to aspirin plus clopidogrel or aspirin plus placebo. There was a reduction of stroke within 90 days seen with dual therapy (absolute risk reduction, 3.8%; 95% confidence interval, −9.4 to 1.9; P=0.19) and no significant difference in bleeding events between treatment arms.6 The early treatment of aspirin and extended-release dipyridamole versus aspirin alone for treatment of minor ischemic stroke within 24 hour of stroke-onset (EARLY) trial randomized 543 German patients within 24 hours of stroke or TIA to aspirin–dipyridamole for 90 days (early group) or aspirin alone for 7 days followed by aspirin–dipyridamole for days 8 to 90 (late group). The primary end point was modified Rankin Scale ≤1, with results favoring the early group (absolute difference, 4.1%; 95% confidence interval, −4.5 to 12.6; P=0.45).6

The investigators developing the CHANCE protocol sought to limit bleeding risk by reducing the period of dual therapy to the first 21 days. Other dual antiplatelet trials in stroke prevention have shown increased risk of intracerebral bleeds over time.7 While aspirin plus clopidogrel showed reduction in vascular events for acute coronary syndrome in the clopidogrel in unstable angina to prevent recurrent events (CURE) trial, there was an increased risk of major bleeding with the addition of clopidogrel.8 In addition, long-term studies of aspirin plus clopidogrel showed no significant reduction in vascular events, including strokes, but demonstrated increased risk of moderate-to-severe bleeding over clopidogrel alone (aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients [MATCH])9 and aspirin alone (clopidogrel for high atherothrombotic risk and ischemic stabilization, management and avoidance [CHARisma]).9

Although immediate initiation of dual platelet or other dual mechanism therapy is supported by CHANCE trial, the question of an optimal length of time before increasing the risk of bleeding remains. The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial is currently enrolling North American patients with inclusion/exclusion criteria similar to CHANCE trial.8 Elements in the POINT trial design that differ from CHANCE trial include the following: a stricter 12-hour window for enrollment; active treatment with dual therapy for 90 days in the aspirin–clopidogrel arm; and a different primary end point—reduction in combined major ischemic vascular events, which include ischemic stroke, myocardial infarction, and ischemic vascular death. The earlier time window and broader end point are expected to increase separation between the 2 study arms in POINT trial, but the increased length of treatment might result in more bleeding complications for the dual therapy arm. Neither CHANCE trial nor POINT trial follows the 2 study arms in POINT trial, but the increased length of treatment might result in more bleeding complications for the dual therapy arm. Neither CHANCE trial nor POINT trial follows the other dual antiplatelet trials in stroke prevention.

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of the world’s smokers live in China), and increased prevalence of obesity have been suggested as reasons for the higher ischemic and particularly hemorrhagic stroke rates, which sets the study population of the CHANCE trial apart from similar trials. The distribution of vascular occlusive disease is also different between Chinese and white populations.11 Comparing common baseline characteristics from the CHANCE cohort to the North American FASTER cohort, the Chinese cohort had higher rates of hypertension, diabetes mellitus, and hypercholesterolemia. The CHANCE trial data also demonstrated low rates of treatment for these 3 treatable risk factors.12 It is reasonable to predict that the effect of aspirin–clopidogrel therapy in North America that might come out of a trial such as POINT might not be as substantial or significant as that seen in CHANCE trial.

CHANCE trial in many ways seems to mirror the results of CURE trial in coronary disease. The benefit of dual platelet treatment seems to separate the Kaplan–Meier curves early on without further significant separation during the rest of the observation period. In other secondary stroke prevention trials, the treatment continues to separate the groups over time, suggesting sustained treatment benefit. The differences in separation pattern in other trials seem to indicate that vascular pathology leading to stroke risk is different from the athero-dominated vascular pathology in the coronary circulation. From the difference in response to treatment between China and the Western world, it is intriguing to speculate that the cerebral pathology of Chinese patients might actually resemble Western coronary pathology rather than cerebral pathology, making the results of CHANCE trial consistent with earlier dual antiplatelet trials in myocardial infarction.

Although the focus of CHANCE trial is on the immediate initiation of stroke prevention by platelet inhibition, one needs to keep in mind that immediate initiation of other prevention approaches is of equal if not higher importance. Control of blood pressure, immediate control of inflammation, stabilizing lipid metabolism, and glycemic balance have already been identified to provide sustained benefit. In the EARLY trial, a composite event rate was also tracked, and the Kaplan–Meier curves started to separate only after 1 week in favor of the early group demonstrating a sustained benefit even though the treatment differed only within the first week.5 Dipyridamole has antithrombotic activities that are complex in nature and extend beyond its amplification of endogenous antithrombotic effects to include peroxy radicals scavenging, reduction of innate inflammation, and a chronic elevation of interstitial adenosine.13 Targeting mechanisms beyond platelet inhibition will likely contribute significantly to efforts to maximize the benefits of early intervention. This sets the stage for new studies of other therapies in this time window. Combining therapies may provide even greater benefits. The ongoing triple antiplatelets for reducing dependency after ischemic stroke (TARDIS) trial is a randomizing stroke and high-risk TIA patients to aspirin–dipyridamole plus clopidogrel (triple therapy) versus aspirin–dipyridamole alone (dual therapy).14

CHANCE trial is a rallying call to focus on the early window for stroke prevention as the most useful strategy in the ongoing battle against ischemic stroke and TIA. In order for the adoption of early, short-term aspirin–clopidogrel to become widespread, we urgently need to understand the following:

1. Can data from Chinese patients with stroke be extrapolated to the Western world?
2. What is the minimum time needed for dual platelet inhibition to optimize the benefit without increasing the risk of bleeds (as seen in long-term dual PI treatment)?
3. Is the benefit sustained during the 90-day period?
4. Will risk of bleeds increase after the observation period?
5. Will immediate onset of other stroke preventive therapy have an equal or even higher preventive effect as compared with dual antiplatelet therapy?

Until we have results of trials to come, the results of CHANCE trial should be taken as further support for immediate initiation of stroke prevention. Stroke populations in Western countries seem to be different from Chinese counterparts, and extrapolation of the results of the CHANCE trial to the Western population is not warranted and needs to be tested.

Disclosures
None.

References

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