Early dual antiplatelet therapy in stroke: should we take the CHANCE?

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Patients with stroke or transient ischemic attack (TIA) are at high risk of recurrence. Approximately 10-20% of patients have another stroke within the first 3 months of the index event (1,2). Recurrent strokes can be disabling for patients, sometimes resulting in fatal consequences. The role of aspirin has been established in the acute phase as well as in secondary prevention of future ischemic strokes (3). Clopidogrel, an inhibitor of adenosine diphosphate (ADP) receptor on platelet cell membranes, along with aspirin synergistically prevents platelet activation and further ischemic events. Beneficial effects of this dual antiplatelet therapy (DAPT) in acute coronary syndromes have been established, without any increased risk of bleeding, however the same cannot be said about secondary prevention of stroke (4). In the acute phase, ischemic strokes are prone to hemorrhagic transformation spontaneously and a recently published meta-analysis of five randomized controlled trials, which enrolled patients with acute ischemic stroke or TIA, reported an increase in major bleeding with the combination therapy (5).

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial was designed to assess the benefits of DAPT in the fraction of patients with TIA and mild stroke; those already at low risk for intracranial bleeding (6). To investigate the role of DAPT in preventing further strokes, Wang *et al.* (6) recruited 5,170 patients across 114 centers in China within 24 hours of symptom onset who were experiencing a minor stroke, defined as National Institutes of Health Stroke Scale score less than 3 or a TIA with high risk for stroke recurrence, defined as $ABCD^2$ score more than 4. One group of patients received a 300 mg loading dose of clopidogrel and 75 mg clopidogrel a day for 90 days in addition to 75 mg aspirin for first 21 days. The control group of patients received 75 mg aspirin for 90 days alone. Better prevention of stroke at the end of 90 days was seen in the group of patients receiving DAPT [hazard ratio =0.68; 95% confidence interval (CI): 0.57-0.81; P<0.001], without the increase of risk of bleeding (P=0.73).

With the CHANCE trial, Wang *et al.* (6) established that early initiated DAPT reduces the risk of stroke in the first 90 days. The two treatment groups diverge early on in terms of disease recurrence, however doubts were raised as to whether or not this early benefit persists over a longer time period. The recently published follow-up of the CHANCE trial addresses this issue and raises further questions.

In the current study, a large subset of patients of the parent CHANCE trial was followed for 1 year (7). Beyond the initial 90-day study period, patients and their physicians were together allowed to choose stroke prophylaxis agents. At the 1-year follow up mark, similar numbers of patients in each of the original groups were taking aspirin alone, aspirin and clopidogrel together, clopidogrel alone, or no antiplatelet agents. The primary outcome was a stroke (ischemic or hemorrhagic) during the 1-year follow-up, which was reported in 10.6% patients in the clopidogrel-aspirin group and in 14% patients in the aspirin only group (hazard ratio =0.78; 95% CI: 0.65-0.93; P=0.006). Statistically insignificant differences in moderate to severe bleeding were seen between the two groups. Findings after 1-year follow-up depict persistence of the protective effect

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of early clopidogrel despite the fact that most patients were taking aspirin alone. There was no relative risk (RR) assessment for recurrent stroke based on what agents the patients were actually taking beyond the originally stipulated study period.

Nonetheless, the CHANCE trial was unique in its requirement that patients be enrolled within 24 hours of onset of symptoms. This difference in the early use of antiplatelet agents may explain the robustness of the effect of DAPT in this trial as compared to other prior studies.

Before we understand the visible effects of the use of antiplatelet drugs in patients with acute ischemic stroke, we need to indulge in the details of how clopidogrel and aspirin work and interact at the molecular level. A damaged blood vessel exposes subendothelial collagen fibrils, which interact with circulating platelets, providing those platelets with a surface on which to stack and become activated. Activated platelets secrete thromboxane A_2 (TXA_2) and ADP, which recruit more platelets to the site. These newly recruited platelets at the site, in turn, secrete more TXA_2 and ADP. Activated platelets can also directly bind to fibrinogen, which with the help of thrombin, is converted in to fibrin to stabilize the clot. Aspirin irreversibly inhibits the cyclo-oxygenase enzyme in platelets and blocks the formation of TXA_2, resulting in inhibition of platelet aggregation. Clopidogrel irreversibly inhibits $P2Y_{12}$, an ADP chemoreceptor on platelet cell membranes, thereby inhibiting platelet aggregation. Moshfegh *et al*. demonstrated that simultaneous antagonism of TXA_2 by aspirin and of the ADP receptor by clopidogrel resulted in additional reduction of collagen and thrombin induced platelet activation, over and above that seen when the drugs are used individually (8).

As we can see, at the time that subendothelial collagen fibrils are exposed, that is early in a stroke, it is potentially advantageous to inhibit platelet function. Antiplatelet agents when used in the acute phase (less than 3 days after the index event) check the earliest steps involved in platelet aggregation. ADP, through three purinergic receptors, controls the shape change, procoagulant activity and the ability of platelets to adhere to immobilized fibrinogen (9). Similarly, TXA_2, a potent vasoconstrictor, increases the expression of glycoprotein IIb/IIIa receptors on the platelet cell membrane, to which circulating fibrinogen binds to strengthen the clot (10). Therefore it becomes important to stop these processes early on, which can only be achieved if antiplatelets are administered in the acute phase of the pathogenesis. Previously, it was established that the inhibition of platelet aggregation is concentration dependent at low doses of clopidogrel, with full activation of platelet inhibition being achieved after 2-6 hours of oral administration of 300 mg clopidogrel (11). This was supported by the work of von Beckerath *et al*. who demonstrated that a 300 mg loading dose of clopidogrel produces maximal inhibition within 6 hours, while a 600 mg loading dose attains maximal effect within 2 hours of administration (12). Therefore it appears that the primary difference between the CHANCE trial and other trials of clopidogrel for secondary prevention of stroke is the time from the index event to clopidogrel loading.

Clopidogrel is a prodrug, which requires hepatic cytochrome P450 (CYP) enzymes to form its active metabolite. Mutations in the genes coding for CYP enzymes may result in a variable response to clopidogrel (13). Of these genes, CYP2C19 carries special importance, where its allele number 17 results in enhanced platelet response to clopidogrel and allele number 2, 3 are associated with decreased activation of clopidogrel (14-16). The Chinese population is believed to have a high prevalence of genetic polymorphisms that affect clopidogrel metabolism and have been significantly associated with an increased risk of adverse clinical events in clopidogrel treated patients (5,17). Also noted is the fact that clopidogrel is often used in modern medicine in combination with atorvastatin which is known to, *in vitro*, significantly inhibit the metabolism of clopidrogrel (18). Differences in CYP2C19 and the frequency of atorvastatin use threaten the applicability of the CHANCE trial to American and European populations.

At present, there is no data to suggest that prolonged use of DAPT beyond 3 months is better. A meta-analysis by Lee *et al*., which included seven randomized controlled trials, suggested that the risk of recurrent stroke is no different in patients receiving DAPT, initiated within 1 week to 5 years of the index event, when compared with patients receiving aspirin or clopidogrel monotherapy (19). Additionally, they reported higher risk of hemorrhage when dual therapy is continued for more than a year (RR =1.46; 95% CI: 1.17-1.82). In contrast, another meta-analysis, which included 14 randomized controlled trials and where patients were treated with antiplatelet therapy within 3 days of the index event, showed significant reductions in risks of future strokes (RR =0.69; 95% CI: 0.60-0.80), without a significant increase in risks of major bleeding (RR =1.35; 95% CI: 0.70-2.59) (20). The results of the original CHANCE trial were consistent with these findings. However, it is possible that the two groups; dual antiplatelet

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versus monotherapy with aspirin, would diverge further on the Kaplan-Meir curves if clopidogrel were to be continued, along with an increased risk of major bleeding. Palacio *et al*. included 13 randomized controlled trials in a meta-analysis and demonstrated a 19% reduction (odds ratio =0.81; 95% CI: 0.74-0.89) in the occurrence of stroke with the use of DAPT comprising of clopidogrel and aspirin as compared with aspirin monotherapy (21). This benefit increased to 33% (95% CI: 3-54%) when patients with only recent brain ischemia (less than 30 days) were included in the analysis, without an increase in major bleeding. It would seem that DAPT is indicated immediately following a minor stroke, but the duration of such therapy is as yet unclear and longer use may bring an increased risk of bleeding without decreasing the stroke risk more.

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial, which is underway in many centers across the United States, is expected to answer the question of whether the addition of clopidogrel to aspirin after minor stroke or TIA is beneficial (22). We hope that the POINT trialists will do a similar long term follow up to assess for concerns of increased bleeding and to discern whether the benefits of combination therapy persist beyond the immediate post stroke period.

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Footnote

Conflicts of Interest: Dr. Sharma: None; Dr. Brandler is an investigator for the POINT Trial.

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