EDITORIALS

Dual Antiplatelet Therapy in Acute Transient Ischemic Attack and Minor Stroke

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Some patients with stroke and transient ischemic attack (TIA) of the brain are at high risk for early recurrent stroke, usually due to arterial thromboembolism.[1,2] Aspirin reduces the risk of early recurrent stroke by only 12% (95% confidence interval [CI], 3 to 20).[3] Adding clopidogrel to aspirin in patients with acute coronary syndromes reduces the risk of recurrent vascular events by 20% (95% CI, 10 to 28) but increases the risk of major bleeding by 38% (95% CI, 13 to 67).[4] For patients with acute ischemic stroke, who are prone to early spontaneous hemorrhagic transformation of infarcted brain, adding clopidogrel to aspirin may cause more major bleeding than may otherwise occur in acute coronary syndromes. Among 731 patients with acute ischemic stroke or TIA (onset within the previous 3 days) enrolled in five small trials, the addition of clopidogrel to aspirin was associated with nonsignificant trends toward a reduction in recurrent stroke (4.5% with clopidogrel and aspirin, as compared with 6.6% with aspirin alone) and an increase in major bleeding (1.1% and 0%, respectively).[5]

Wang and colleagues now report in the *Journal* the impressive results of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial.[6] Among 5170 Chinese patients with acute minor ischemic stroke or TIA (onset within the previous 24 hours) at high risk for recurrence, the addition of clopidogrel to aspirin reduced the relative risk of recurrent stroke at 90 days by 32% (8.2% vs. 11.7%; hazard ratio, 0.68; 95% CI, 0.57 to 0.81; absolute risk reduction, 3.5 percentage points). The effect was consistent among 11 predefined subgroups. There was no difference between the group that received both clopidogrel and aspirin and the group that received aspirin alone in the incidence of moderate or severe hemorrhage (0.3% in each group; P=0.73) or hemorrhagic stroke (0.3% in each group; P=0.98).

The CHANCE investigators completed a large, scientifically rigorous trial that proves the concept that dual antiplatelet therapy can be more effective than single antiplatelet therapy in preventing early recurrent stroke in patients with acute symptomatic atherothrombosis (predominantly intracranial) of the brain. Moreover, the absolute benefits of dual antiplatelet therapy can be substantial in patients at high risk for recurrent stroke[1]; treating 29 patients for 90 days with clopidogrel plus aspirin for the first 21 days, followed by clopidogrel alone from day 22 to day 90, prevented one stroke, as compared with aspirin alone. Indeed, most of the absolute benefit of clopidogrel plus aspirin is realized within the first few days after TIA and ischemic stroke, when the underlying atherosclerotic plaque is most unstable and the risk of recurrence is highest.

The safety results show that dual antiplatelet therapy can be given without excess harm in patients with acute focal brain ischemia, provided that patients have a low risk of hemorrhagic transformation — no fresh brain infarction (i.e., TIA) or a very small volume of fresh brain infarction (i.e., minor ischemic stroke). The CHANCE investigators had to screen 41,561 patients with

stroke or TIA to find 5170 appropriate patients (12.4%). Hence, the results cannot be generalized to most patients; the study excluded patients with major ischemic stroke, who are at risk for hemorrhagic transformation, and patients with TIA due to isolated sensory, visual, or vertiginous syndromes, who are at low risk for recurrence.[1] The results may also not apply to non-Chinese patients with different forms of underlying arterial disease (e.g., a higher prevalence of extracranial large-artery atherosclerosis) and different prevalences of genetic polymorphisms of liver cytochrome P-450 (CYP) isozymes, which metabolize clopidogrel to its active metabolites. The absolute benefits of clopidogrel plus aspirin observed in this trial may also not be realized in persons and populations at lower absolute risk for recurrent stroke, such as those with a low prevalence of risk factors for recurrent stroke and those with access to effective secondary stroke prevention. Finally, the results of this trial cannot be generalized beyond 90 days after ischemic stroke, when the cumulative risks of bleeding with clopidogrel plus aspirin, as compared with aspirin or clopidogrel alone, offset the benefits.[7-9]

The implication of this trial is that Chinese patients with acute TIA or minor ischemic stroke (onset within the previous 24 hours) who are at high risk for recurrence should be regarded as a medical emergency. They should be treated immediately with clopidogrel plus aspirin for 21 days, followed by clopidogrel alone, for a total of 90 days, before continuing long-term treatment with clopidogrel, aspirin, or the combination of aspirin and extended-release dipyridamole. A bolus loading dose of at least 162 mg of aspirin and 300 mg of clopidogrel is required on day 1 to rapidly inhibit platelet aggregation, given that starting with daily doses of 75 mg of aspirin and clopidogrel takes several days to produce maximal inhibition of platelet aggregation. The benefits of dual antiplatelet therapy are greatest in the first days after TIA and ischemic stroke.

I think that clinicians should continue to enroll non-Chinese patients with acute TIA and minor ischemic stroke into ongoing large clinical trials of the safety and efficacy of dual and triple antiplatelet therapy.[10,11] Moreover, I hope that researchers will evaluate new antiplatelet agents (e.g., ticagrelor and prasugrel) and new anticoagulant agents (e.g., rivaroxaban) that are effective in atherothrombotic acute coronary syndrome in patients with acute TIA and minor ischemic stroke due to arterial thromboembolism.[12,13]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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