EDITORIALS

Extending Dual Antiplatelet Therapy for TIA or Stroke

Anthony S. Kim, M.D.

Although stroke is typically understood to be a medical emergency, the same pertains when cerebral ischemia produces seemingly mild or transient symptoms. For transient ischemic attack (TIA) and minor stroke, urgent evaluation and treatment are no less important than for larger strokes, given that the risk of recurrent stroke occurs early. Nearly half the 90-day stroke risk occurs within the first 48 hours after an event.[1] The risk is modifiable with interventions such as aspirin[2] or dual antiplatelet therapy with clopidogrel–aspirin[3,4] or ticagrelor–aspirin[5] if it is initiated within 24 hours.

The trials that established the efficacy of short-term dual antiplatelet therapy (CHANCE,[3] POINT,[4] and THALES[5]) specified enrollment windows of up to 12 hours or 24 hours after symptom onset to capture the early period of highest risk and greatest potential effect. Logic dictates that at the very least, an intervention that is intended to prevent recurrent stroke must be initiated before stroke has already recurred. These trials also limited enrollment to patients with TIA or minor stroke to minimize the extent of ischemic brain tissue that would be at risk for bleeding.

Given that delayed presentations to medical care and more-than-minor strokes are common, would patients who present days later or with slightly more severe symptoms than have been studied in most trials of antiplatelet agents also benefit from dual antiplatelet therapy? Secondary analyses from the CHANCE and POINT trials seemed to say "yes" to extending the treatment time window to 72 hours after symptom onset,[6,7] and a secondary analysis from the THALES trial suggested a benefit in starting ticagrelor–aspirin therapy up to 5 days after onset.[8] Also, the THALES trial tested ticagrelor–aspirin in patients with mild-to-moderate stroke symptoms who had been excluded from the previous trials of clopidogrel–aspirin. However, time windows for enrollment beyond 24 hours have not been evaluated with a dedicated randomized trial, and a direct evaluation of clopidogrel–aspirin treatment in patients with mild, rather than minor, stroke symptoms would be welcome.

In this issue of the *Journal*, Gao and colleagues[9] report the results of the antiplatelet-therapy component of the INSPIRES (Intensive Statin and Antiplatelet Therapy for Acute High-Risk Intracranial or Extracranial Atherosclerosis) trial. Investigators at 222 hospitals in China randomly assigned 6100 patients to treatment groups no more than 72 hours after the onset of an index high-risk TIA or mild ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score of ≤5; range, 0 to 42, with higher scores indicating more severe stroke) of presumed atherosclerotic cause. Patients who were receiving thrombolysis or undergoing thrombectomy were not eligible.

Short-term dual antiplatelet therapy was accomplished with an initial loading dose of clopidogrel and clopidogrel–aspirin for 21 days, followed by clopidogrel monotherapy. This approach resulted in a risk of ischemic or hemorrhagic stroke within 90 days that was 1.9 percentage points lower than the risk with aspirin alone (7.3% vs. 9.2%; hazard ratio, 0.79; 95% confidence interval, 0.66 to 0.94; P=0.008). This finding corresponds to an approximate number needed to treat with dual antiplatelet therapy to prevent one additional stroke as compared with aspirin

of 54. Unlike findings in the CHANCE trial but as previously seen in the POINT and THALES trials, this result came at the cost of a bleeding signal. Moderate-to-severe bleeding occurred in 27 of the 3050 patients (0.9%) in the clopidogrel–aspirin group, as compared with 13 of the 3050 patients (0.4%) in the aspirin group — an absolute risk difference of 0.5 percentage points or a number needed to harm with clopidogrel–aspirin to produce one additional bleeding event as compared with aspirin of 218. Overall, for every 1000 patients with TIA or mild stroke who were treated with clopidogrel–aspirin, approximately 19 fewer strokes and 5 additional moderate-to-severe bleeding events would be expected as compared with aspirin alone, by my rough calculation.

The current trial provides evidence to support expanding the time window for dual antiplatelet therapy to 72 hours. This timing should nevertheless be interpreted as "as soon as possible, but within 72 hours" and still necessitates a loading dose of clopidogrel, since its omission would be akin to delaying treatment. The magnitude of the risk difference for recurrent stroke was lower in the current INSPIRES trial than in the CHANCE trial (which may be most directly compared with the current trial) with regard to both relative risk (21% vs. 32%) and absolute risk (1.9 vs. 3.5 percentage points).

The INSPIRES trial also provides justification for the inclusion of patients with slightly more severe stroke symptoms than have been evaluated in previous trials (up to an NIHSS score of ≤5, as had been applied in the THALES trial, as compared with the threshold of ≤3 that had been used in the CHANCE and POINT trials); however, this expanded inclusion criterion comes at the cost of a small but accruing bleeding risk that is roughly proportional to the duration of treatment.[6-8] This bleeding signal is a reminder that the appropriate duration of dual antiplatelet therapy to balance early benefit and bleeding risk seems to be approximately 21 days and that long-term use of clopidogrel–aspirin is not recommended, given that this approach has not proved beneficial and almost certainly increases bleeding risk.[10] The results of the INSPIRES trial also cannot be generalized to patients with heightened bleeding risks (such as those with a history of cerebral or systemic hemorrhage), to those with severe stroke or cardioembolic stroke (not considered to be atherosclerotic in origin), or to patients undergoing or anticipated to undergo thrombolysis or thrombectomy. In addition, there is uncertain generalization to non–Han Chinese patients, given that Han Chinese patients made up almost the entire trial population.

The incremental expansion of indications for dual antiplatelet therapy that was shown in this trial is welcome. Perhaps new, more targeted antithrombotic agents on the horizon may hold promise for delivering an even more favorable balance of benefits and risks among patients with stroke.

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

From the UCSF Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, San Francisco.

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