



An Update on Antiplatelet Therapy for Secondary Stroke Prevention

Recent data on stroke, insights from other specialties, and developments in the antiplatelet arena may influence management of stroke patients.

By Paul Winnington, Editorial Director

Use of antiplatelet therapy for the secondary prevention of ischemic stroke is now standard of care. Given that relatively recently published results from the PROFESS trial suggest that clopidogrel and aspirin/extended-release dipyridamole (ASA/ER-DP) have similar efficacy, choice of a specific agent often depends on physician and patient preference. Practical considerations, such as once-daily dosing may make clopidogrel preferable. Twice-daily ASA/ER-DP is associated with a

risk of headache. But if cost is a significant concern, data suggest some patients can obtain sufficient benefit from aspirin alone. Evidence now suggest the higher aspirin doses may actually be associated with improved benefits.¹

Recent Developments

To determine the effects of higher aspirin doses on all-cause mortality and bleeding, Herbert D. Aronow, MD, MPH of Michigan Heart, and colleagues investigated outcomes in

patients with recent cerebrovascular or coronary ischemic events.¹ They found that aspirin doses of 162mg/day or more were associated with lower rates of all-cause mortality, although there was no influence on the composite endpoint of death, nonfatal myocardial infarction, or nonfatal stroke. Despite these findings, Dr. Aronow says, "I have been cautious to employ changes in aspirin dosing based upon my study, as it was observational rather than randomized. Randomized study of this question is underway."

Among his patients, Dr. Aronow says that for secondary prevention of noncardioembolic stroke, "I use either aspirin/dipyridamole or clopidogrel (usually with aspirin as well) depending on other patient comorbidities. As a cardiologist, most of my patients also have coronary disease, so clopidogrel ends up being the more commonly used agent for stroke secondary prevention."

One area of concern for physicians and patients may be the use of antiplatelets in the perioperative period. As Dr. Aronow points out, "There are circumstances where these agents should be discontinued, but it is very dependent upon the reason for which antiplatelet therapy was initiated, the duration of treat-

ment to date, and the risk of bleeding associated with the surgery/medical procedure."

Despite the need for individualized decisions, some general suggestions have been made.² Typically, aspirin taken for secondary prevention does not need to be withdrawn before surgery, while aspirin taken for primary prevention may be discontinued about seven days before surgery with a higher bleeding risk. Clopidogrel may be withdrawn if the procedure in question is associated with high hemorrhagic risk or moderate to high risk of cerebrovascular sequelae. There is a risk of rebound thrombosis upon withdrawal of antiplatelets, and this risk may be greater than the risk of bleeding associated with many surgeries.

Finally, the question of adjunctive lipid management continues to garner attention, with recent AHA guidelines suggesting lipid-lowering through statin therapy for patients with atherosclerotic ischemic stroke or TIA and without known CHD.³

Looming Questions

As Dr. Aronow points out, data from randomized trials is

New Antiplatelet Not Suitable for Use in Stroke... Yet

The FDA in July approved Eli Lilly's and Daiichi Sankyo's prasugrel (Effient) for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndromes who are managed with percutaneous coronary intervention (PCI). The availability of the potent antiplatelet therapy on the US market may lead some to question if and when it could be used for secondary stroke prevention—head-to-head trials compared the novel agent to clopidogrel in the PCI population—but one expert supports the FDA findings, and warns that use in stroke is not appropriate now, nor is it likely to be in the near future.

According to Victor L. Serebruany, MD, PhD, owner of HeartDrug Research, LLC and Assistant Professor of Neurology at Johns Hopkins University, prasugrel demonstrated a front-loaded early benefit over clopidogrel in clinical trial (TRITON), but that benefit diminished after about 30 days. In the trials, prasugrel treated patients received a loading dose of 60mg prasugrel followed by a maintenance dose of 10mg daily com-

pared to clopidogrel dosed at 300mg loading and 75mg daily. Prasugrel reportedly provided a relative risk reduction of 18.2 percent in a composite endpoint of cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke. But at roughly 10 months, there was a "crossover," with regard to death. Dr. Serebruany says, in which the benefits of prasugrel fell off significantly; over time, the rates of significant bleeding events and cancer rose notably in the prasugrel arm after one to four months of therapy.

As part of the recent approval of prasugrel, FDA required boxed warnings against use of the drug in the elderly (75 years old and above), patients with relatively low body weight (less than 60kg), and patients with a history of transient ischemic events (TIAs) or strokes. Dr. Serebruany says he is not aware of any trials currently ongoing or soon enrolling to study the effects of prasugrel for secondary stroke prevention, but he notes

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essential to support clinical decision-making, and there is little to no dispute about the quality of data related to use of antiplatelet therapy for secondary stroke prevention.

However, a new analysis points out that the trial designs may overlook a significant proportion of “typical patients.”⁴ The Netherlands Stroke Survey enrolled 972 patients with TIA or ischemic stroke based on enrollment criteria from seven large antiplatelet trials. But researchers found that only 25 to 67 percent of patients fit enrollment criteria. Of note, mortality rates were significantly higher among ineligible patients than among those meeting criteria: 27 to 41 percent for the former versus 16 to 20 percent for the latter.

“Patients with ischemic attack and stroke enrolled in randomized clinical trials are only partially representative of patients in clinical practice,” the authors note, calling for less strict enrollment criteria to enhance the “generalizability” of study conclusions. **PN**

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2. Chang, S. Perioperative Antiplatelet Therapy. Presented Sept. 24, 2007. National Taiwan University.

3. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Sacco RL, Schwamm LH; American Heart Association; American Stroke Association.

Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke*. 2008 May;39(5):1647-52.

4. Maasland L, van Oostenbrugge RJ, Franke CF, Scholte Op Reimer WJ, Koudstaal PJ, Dippel DW; Netherlands Stroke Survey Investigators. Patients enrolled in large randomized clinical trials of antiplatelet treatment for prevention after transient ischemic attack or ischemic stroke are not representative of patients in clinical practice: the Netherlands stroke survey. *Stroke*. 2009 Aug;40(8):2662-8.

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that with time and a great deal of further research, new dosing regimens and additional indications for prasugrel could emerge.

According to Dr. Serebruany, prasugrel is considered to be tested in Japan at a much lower daily dose of 3mg/day—less than a third the approved dose in the US. This much lower dose could theoretically prove useful for secondary stroke prevention if that dose is shown to present a lower risk of bleeding compared to the 10mg daily dose in the US. FDA has also required a warning about bleeding risk for the current indication.

Equally important is the issue of cancer, Dr. Serebruany warns. “Based on the data so far, we can't say it definitely causes cancer,” he says, “but we can't say it's not causing cancer.” Mouse studies confirm an increased incidence of cancer associated with the therapy, and in humans that risk appears to be higher in women than men. In humans, the cancers that develop are “mostly highly metastatic, solid organ cancers: colon, rectal, lung, and breast,” Dr. Serebruany says. The risk of new solid cancer is 36.8 percent higher with prasugrel compared to clopidogrel, he says.

While the link between antiplatelet therapy and can-

cer is not entirely understood, there are theoretical models to explain the phenomenon. These, as outlined in a recent publication by Dr. Serebruany, involve, “1.) direct hazard of the experimental drug on cancer occurrence and progression; 2.) indirect modulation of tumor growth; and 3.) enhanced metastatic dissemination due to instability of platelet-tumor cell aggregates, or/and inability to keep the disease locally due by much more potent long-term platelet inhibition should be considered.” (Serebruany VL. Prasugrel and cancer risks: Potential causes and implications. *Am J Med* 2009; 122: 407-8.)

Once and if the cancer issue will be resolved and optimal dosing to balance benefits and risks is identified, then the pursuit of other indications for prasugrel may proceed, Dr. Serebruany says. Until that time, prasugrel is “absolutely, clearly contraindicated for patients who develop stroke, especially hemorrhagic stroke,” he says.

Conflicts of Interest: Dr. Serebruany is listed as an inventor, and received compensation for the U.S. Patent Application P-17232 “Method for treating vascular diseases with prasugrel” assigned to Lilly. He received funding for research studies with both clopidogrel and prasugrel.