By David Tong, MD

Aspirin Plus Clopidogrel in Stroke Patients: The Dilemma of Drug-Eluting Stents

Neurologists need to be aware of this new issue for patients who have both cardiovascular and cerebrovascular disease.

Few neurologists have kept up with the recent controversy concerning drug-eluting stents and the use of combination aspirin and Plavix for stent thrombosis prophylaxis, but this important issue is something that concerns both vascular specialists and general neurologists. The use of this combination drug regimen in cardiovascular disease patients may conflict with protocols that should be followed for the management of stroke and TIA patients. This is particularly pertinent for the large number of patients who suffer from both cardiovascular and cerebrovascular disease, which of course affects a substantial number of our patients.

For those who may not have been keeping up with this controversy, let's review.

One of the major challenges following implantation of a coronary stent is the problem of restenosis, which typically occurs in about 25 percent of patients following placement of a conventional bare metal stent. This problem was believed to have been mitigated by the introduction in 2003 of newer "drug-eluting" stents (DES), which are coated with substances that inhibit intimal hyperplasia, the primary mechanism by which restenosis occurs. The presumed success of this approach is reflected in the broad adoption of DES for most coronary artery disease patients, even though the clinical trials that were used to approve the stents only tested DES in a few specific anatomical and clinical situations. Currently, drug-eluting stents have eclipsed bare metal stents as the most commonly used type of stent among cardiologists.

What's the Issue?

There have been recent concerns over the long-term risks of stent rethrombosis from drug-eluting coronary stents. Some epidemiological data, and other indirect evidence, suggest that DES may make the patient susceptible to stent rethrombosis, a significant cause of morbidity following stent placement. Rethrombosis occurs when the stent re-occludes abruptly, leading to recurrent cardiac ischemia.

Patients with DES are believed to be at risk for late rethrombosis. Conventional uncoated stents also cause thrombosis, but this usually occurs early on (typically within six months following implantation), not later. This difference is believed to occur because DES inhibit endothelialization of the coronary vessel intima, exposing the thrombogenic metal of the stent to the bloodstream for a much longer period of time than non-DES. This in turn may result in a tendency to stent thrombosis.

Unfortunately, there are now some early preliminary data that suggest there may be a risk of late stent rethrombosis which may occur if dual antithrombotic therapy is discontinued. A small but significant increase in myocardial infarction risk among DES patients was found in data presented at the March 2006 American College of Cardiology conference and the September 2006 European Society of Cardiology annual meeting. Because of these concerns, a number of influential cardiologists have suggested that patients who have a DES implanted should receive indefinite treatment with aspirin plus clopidogrel, since this combination seems to reduce the risk of recurrent thrombosis. It is this issue that raises potential concern with vascular neurologists.

As has previously been outlined in this column, the recently-published MATCH study[1] reported that the combination of clopidogrel plus aspirin in stroke patients is harmful. In fact, it is associated with an increased risk of hemorrhagic complications, without significantly reducing the risk of ischemic stroke. In addition, more recent data from the 15,603-patient CHARISMA trial[2] and ACTIVE-W study of 6,706 atrial fibrillation patients[3] have also shown no significant reduction in the ischemic stroke rate in patients taking this combination, while the risk of hemorrhage is increased. Therefore, from the stroke perspective it is inadvisable to treat patients with the combination of aspirin plus clopidogrel over the long term.

The FDA Advisory Panel: Resolution or Confusion?

The FDA reviewed the issue of DES rethrombosis at it cardiovascular therapeutics advisory panel in Dec 2006. At this meeting, all available data from observational studies as well as clinical trials were reviewed. Importantly, four-year follow up data indicated no significant increased risk of stent thrombosis

from DES compared with bare-metal stents. Based on these data, the panel concluded that there should be no change made to the recommendations regarding the prophylactic use of aspirin and clopidogrel following DES placement. These current guidelines suggest the use of this combination for only six to nine months maximum.

It is important to note that the panel's conclusions relate primarily to the use of drug-eluting stents as applied in the clinical trials which led to DES approval. Unfortunately, DES are apparently far more widely used in cardiology, especially in higher-risk patients who were not enrolled in these trials, leading to speculation that there may be subgroups where the risk is high enough to raise concern. In a recent statement,[4] the FDA suggested that the following patient populations as deserving of concern regarding DES:

- patients with diabetes
- acute myocardial infarction or multiple vessel disease
- lesions involving arterial bifurcations, the left main coronary artery and long arterial segments

Nevertheless, because of these ongoing issues, many influential cardiologists have begun to recommend long-term, and even permanent, use of clopidogrel plus aspirin in their DES patients. This is certainly cause for concern in the large number of cardiovascular patients who also suffer from TIA or ischemic stroke. In these patients, the long-term risk of hemorrhagic complications may far outweigh the still poorly-defined risks of recurrent stent thrombosis. The FDA did not make any recommendation at this time regarding either the implantation of DES or the postoperative medical regimen, although its statement only endorsed the safety and efficacy of drug-eluting stents when used for the FDA-approved indications. The agency is in the process of convening an expert panel to review the issue and offer guidance.

What's a Neurologist to Do?

So if we have a patient with both cerebrovascular and cardiovascular risk, which of course is quite common, what's the appropriate course of action regarding preventive therapy? At this point, it should be remembered that the data supporting the possibility of DES late stent thrombosis is preliminary at best. The FDA guidelines remain unchanged, and long-term treatment is not currently recommended at this point.

Given the significant risk of both intra- and extracranial hemorrhage which has been previously reported, it seems inappropriate to go along with long-term combination aspirin/clopidogrel use, particularly in our stroke patients, who have a substantially higher risk of hemorrhage than the average coronary patient.

But stay tuned. As more data are published and the FDA convenes its expert panel this year, the standards of care may change. Hopefully, new data will emerge that will help to better clarify the overall risks and benefits of therapy, particularly in the significant number of patients who have received drug-eluting stent implantation beyond the FDA's original indications. **PN**

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2. Bhatt DL, Fox KA, Hacke W, Berger PB, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. NEJM April 20, 2006, Number 16, Volume 354:1706-1717.

3. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006 Jun 10;367(9526):1903-12.

4. FDA statement. Available online at www.fda.gov/cdrh/news/091406.html.

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