Stent Thrombosis Rises When Clopidogrel Stops

BASKET results suggest a trade-off between late restenosis and cardiac death with drug-eluting stents.

BY MITCHEL L. ZOLER
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ATLANTA — Patients with a drug-eluting coronary stent had a 4.9% rate of cardiac death or myocardial infarction during the first year after they stopped daily treatment with clopidogrel, more than three times the rate in patients with bare-metal stents in a study with 743 patients.

The incidence of clinical events related to late stent thrombosis was 2.4% in patients with drug-eluting stents (DES), compared with 0.8% in those with bare-metal stents (BMS), Dr. Matthias E. Pfisterer said at the annual meeting of the American College of Cardiology.

On the basis of these findings, he calculated that for every 100 patients who receive a DES instead of a BMS in a coronary artery, the consequence is an extra 3.3 late deaths and myocardial infarctions. This was balanced against a DES benefit of 5 fewer patients who needed target-vessel revascularization for every 100 treated, compared with BMS, said Dr. Pfisterer, head of the division of cardiology at University Hospital Basel (Switzerland).

"You're trading late restenosis for deaths and MI. It's a very important and worrisome trade-off," said Dr. William W. O'Neill, corporate chief of cardiology at William Beaumont Hospital, Royal Oak, Mich.

The finding "may be practice changing," commented Dr. Robert Harrington, of the department of medicine at Duke University in Durham, N.C.

The risk of late thrombosis lasted throughout a yearlong follow-up period after discontinuation of clopidogrel treatment. Events did not cluster early after the drug was stopped, but were scattered; some thromboses did not occur until the end of the follow-up period. For the time being, the best way to treat late stent thrombosis in patients who have received a DES is to continue dual antiplatelet therapy with clopidogrel and aspirin indefinitely, Dr. Pfisterer said in an interview. Another is to use the DES judiciously.

The rate of thrombosis-related events linked with DESs was higher in this study than in past reports, most likely because the study enrolled all patients who needed a coronary stent at University Hospital Basel during May 2003 to May 2004, regardless of their indication for stenting. The only exclusion was in patients with a target vessel diameter of 4.0 mm or greater, because the largest DES available then had a diameter of 3.5 mm.

As such, the cohort included a large fraction of patients with unstable coronary disease, Dr. Pfisterer said. More than two-thirds of patients had multivessel disease, and 60% had acute coronary syndrome at the time of enrollment. The patients received an average of 1.9 stents each.

The Basel Stent Kosten Effektivitäts Trial (BASKET) was designed to compare the cost-effectiveness of sirolimus-eluting stents (Cypher), paclitaxel-eluting stents (Taxus), and BMS. The study had no industry funding. The primary results of the study, which followed patients for 6 months after stent implantation, showed that the incremental cost-effectiveness ratio of DES to BMS was about 20,000 euros to avoid one major adverse cardiac event, and more than 50,000 euros per quality life year gained (Lancet 2005;366:921-9).

In DES patients, stent thrombosis was 2.4%, compared with 0.8% in those with bare-metal stents.

DR. PFISTERER

Dr. Pfisterer and his associates suggested limiting the use of DES to certain high-risk subgroups, such as elderly patients with triple-vessel disease, or patients with long lesions or lesions in small vessels.

All of the patients in the trial were taken off clopidogrel treatment after 6 months and continued to take aspirin daily, which provided an opportunity to assess the risk of late stent thrombosis after dual antiplatelet therapy was stopped. For this analysis, the 502 patients who had been initially randomized to receive either a sirolimus- or paclitaxel-eluting stent were combined into a single DES group and were compared with the 244 patients initially randomized to receive a BMS. Three patients from the DES group didn't have follow-up, reducing the group to 499.

During the year off dual therapy, 4.9% of the DES patients had cardiac death or a nonfatal MI, compared with 1.3% of BMS patients. The incidence of restenosis that required target-vessel revascularization was 6.7% in the BMS group and 4.5% in the DES group. When late thrombosis occurred in either group, it was usually clinically significant, with 88% of thrombotic events leading to death or MI.

In a multivariate analysis of risk factors for late stent thrombosis, the use of a DES was the most potent risk, raising the incidence of thrombosis 3.9-fold, compared with BMS patients. The other factors were use of a glycoprotein IIb/IIIa inhibitor during stent placement, which raised the risk 3.4-fold, and a history of MI, which raised the risk 3.0-fold, Dr. Pfisterer said. ■

Drug-Eluting Stents Top Brachytherapy for In-Stent Restenosis

BY MITCHEL L. ZOLER
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ATLANTA — Paclitaxel-eluting coronary stents were more effective for treating in-stent restenosis than was vascular brachytherapy in results from a study with almost 400 patients reported at the annual meeting of the American College of Cardiology.

The clear superiority of paclitaxel-eluting stents for this indication matched previously reported results for sirolimus-eluting stents, which were shown to be better than brachytherapy for in-stent restenosis in findings reported last November at the annual scientific sessions of the American Heart Association.

Vascular brachytherapy is currently the only treatment approved by the Food and Drug Administration for treating bare-metal stents that develop in-stent restenosis.

Both comparisons of drug-eluting stents with brachytherapy involved stenoses in bare-metal stents, but drug-eluting coronary stents also worked for treating restenosis in drug-eluting stents in a single-center series of 77 patients, which was reported in a poster at the meeting. The next challenge will be further study in finding the best way to treat restenosis in drug-eluting coronary stents.

The paclitaxel-eluting stent study was conducted at 37 centers in the United States and Canada during June 2003 to July 2004. All patients enrolled had a single, restenotic lesion in a bare-metal stent in a native coronary artery. The patients were randomized to treatment with a paclitaxel-eluting stent or vascular brachytherapy using any Food and Drug Administration-approved, β-source radiation system. The study was sponsored by Boston Scientific Corp., which markets the paclitaxel-eluting stent (Taxus) used in the study.

The primary end point was incidence of ischemia-driven target vessel revascularization 9 months after treatment. The rate of this event was 10.5% in 194 patients treated with the paclitaxel-eluting stent and 17.5% in patients treated with brachytherapy, a statistically significant difference in favor of the drug-eluting stent, reported Dr. Gregg W. Stone, professor of medicine and director of cardiovascular research and education at Columbia University in New York. Dr. Stone also is a consultant to Boston Scientific.

'The study is very definitive' for proving the superiority of paclitaxel-eluting stents over brachytherapy.

DR. WAKSMAN

The paclitaxel-eluting stent was superior to brachytherapy by several other efficacy measures assessed by angiography after 9 months. Compared with brachytherapy, stenting showed several advantages that contribute to improved long-term patency: greater initial acute gain owing to mechanical scaffolding by the stent, preservation of acute gain by limited late loss, and avoidance of the edge-effect produced by brachytherapy, said Dr. Stone.

Stenting was also at least as good as brachytherapy for both 30-day and 9-month measures of safety. The results were published simultaneously with Dr. Stone's report at the meeting (JAMA 2006;295:1253-63).

"The study is very definitive" for proving the superiority of paclitaxel-eluting stents over brachytherapy, commented Dr. Ron Waksman of the division of cardiology at the Washington (D.C.) Hospital Center, and a pioneer in the development of vascular brachytherapy.

Similar results were reported for sirolimus-eluting stents (Cypher), when compared with vascular brachytherapy for treating restenosis in bare-metal stents in a study by Dr. David R. Holmes Jr., professor of medicine at the Mayo Clinic in Rochester, Minn., and associates.

The published report of those findings appeared in the same journal issue that contained Dr. Stone's paper (JAMA 2006;295:1264-73).

An editorial that commented on both studies noted that the data from the two studies were strong enough to move brachytherapy to a second-line choice for treating in-stent restenosis, although with a few exceptions.

For the time being, brachytherapy remains the top option for treating restenosis in bifurcations; in vessels with excessive calcification, tortuosity, or angulation; or in other settings in which repeated stenting might risk procedure-related ischemic events, wrote Dr. Debabrata Mukherjee and Dr. David J. Moliterno of the University of Kentucky in Lexington (JAMA 2006;295:1307-09). The best treatment for in-stent restenosis in patients with renal dysfunction also is unclear, because those patients were excluded from both of the new studies.

Questions about how to treat in-stent restenosis will now shift to restenosis that occurs in drug-eluting stents, where brachytherapy is unlikely to have a role, wrote Dr. Mukherjee and Dr. Moliterno.

A step toward addressing this issue was made by cardiologists at the Prairie Heart Institute at Saint Johns Hospital in Springfield, Ill. They reported in a poster their experience with using a second drug-eluting stent to treat 86 lesions in 77 patients with restenosis that had occurred in a first drug-eluting stent.

Their findings suggested that using the "opposite" drug-eluting stent the second time around might be the best approach. This seems to be the first report of using drug-eluting stents to treat stenoses that form in drug-eluting stents, said Dr. Marc E. Shelton, a cardiologist at the Prairie Heart Institute. ■