Stent Thrombosis Rises When Clopidogrel Stops

BY MITCHEL L. ZOLER
Philadelphia Bureau

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," commented Dr. William W. O'Neill, corporate chief of cardiology at William Beaumont Hospital in 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 way is to use the DES judiciously. In patients with focal lesions, the advantage of a DES over a BMS is small. In the future, new types of stents that are bioabsorbable or that contain different drug coatings and formulations may provide the solution.

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–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 at the time had a diameter of 3.5 mm.

As a result, 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 initially designed to compare the cost effectiveness of sirolimus-eluting stents (Cypher), paclitaxel-eluting stents (Taxus), and BMS. The study did not have any 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).

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 did not have follow-up, which reduced the group to 499 patients.

During the year off dual therapy, 4.9% of the DES patients had cardiac death or a nonfatal MI, compared with 1.3% of patients in the BMS group. 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, three items emerged as significant predictors of risk. The use of a DES was the most potent risk, raising the incidence of thrombosis 3.9-fold, compared with patients who got a BMS. The other factors were the use of a glycoprotein IIb/IIIa inhibitor during stent placement (a marker for acute coronary syndrome at the time of stenting), which raised the risk 3.4-fold, and a history of MI, which raised the risk 3.0-fold, Dr. Pfisterer said. ■

Intensive Statin Therapy Led to Regression of Atherosclerosis

BY MITCHEL L. ZOLER
Philadelphia Bureau

ATLANTA — Intensive statin therapy that dropped serum levels of low-density lipoprotein cholesterol below 70 mg/dL in most patients led to significant regression of coronary atherosclerosis in a study with 349 patients.

The results are the first from ASTEROID (A Study To Evaluate the Effect of Rosuvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden), which uses intravascular ultrasound (IVUS) to show "unequivocal evidence of disease regression," Dr. Steven E. Nissen said at the annual meeting of the American College of Cardiology.

The results "suggest that lowering LDL cholesterol to these low levels is associated with an anatomic effect," commented Dr. Robert H. Eckel, president of the American Heart Association and professor of medicine at the University of Colorado at Denver.

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Attaining the lowest levels of LDL without adverse effects may be the optimal strategy, Dr. Steven E. Nissen said.

The results "are very exciting and break new ground," commented Dr. David O. Williams, director of interventional cardiology at Rhode Island Hospital in Providence.

But experts also cautioned that while the findings convincingly linked an aggressively lowered level of LDL cholesterol to atheroma regression, the study failed to include control patients, and it wasn't designed to examine the impact of treatment on clinical events such as death and myocardial infarctions, the accepted standards of efficacy for coronary-disease interventions. "IVUS-documented atherosclerosis regression … may not be the best measure of the treatment's effect on hard cardiovascular end points," commented Dr. Roger S. Blumenthal and Dr. Navin K. Kapur, both of the Johns Hopkins Ciccarone Preventive Cardiology Center, Baltimore, in an editorial that accompanied the on-line release of Dr. Nissen's report (JAMA 2006;295 [Epub doi:10.1001/jama.295.13.jed60019]).

The study was carried out because prior angiographic and IVUS studies had shown slowed progression of coronary atherosclerosis with statin therapy, but none had convincingly demonstrated regression, said Dr. Nissen, chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic.

He and his associates enrolled 507 patients who required angiography for a clinical indication, and had at least one coronary artery stenosis that obstructed more than 20% of the vessel. Participants also had to be statin naive, which meant they received statin therapy for no more than 3 months during the year before enrollment. Patients entered the study during November 2002–October 2003 at 53 U.S. centers.

A target coronary vessel was selected that had no more than 50% stenosis throughout a segment that was at least 40 mm in length. This segment was examined by IVUS at baseline and after 2 years of treatment. Patients were all put on a regimen of 40 mg of rosuvastatin (Crestor) daily, the highest approved dosage for this drug. The study did not specify any other drug or diet management.

Evaluable IVUS examinations at baseline and after 2 years of treatment were available for 349 patients, who were the focus of the analysis. After 2 years, serum levels of LDL cholesterol in these 349 patients had dropped from an average of 130.4 mg/dL at baseline to an average of 60.8 mg/dL, a decline of 53%. The treatment regimen also produced a "surprisingly" large boost in serum levels of HDL cholesterol, Dr. Nissen said, which rose from an average of 43.1 mg/dL at baseline to 49.0 mg/dL after 2 years, a boost of 15%. "To our knowledge, this is the highest increase in HDL ever observed in a statin trial," he said. The ratio of LDL to HDL cholesterol fell from an average of 3.2 at baseline to 1.3.

The study had two primary efficacy measures: the median change in percent atheroma volume in the coronary segment studied, which dropped by 0.79%, and the median change in total atheroma volume in the most diseased 10-mm segment examined, which fell by 5.6 mm^3. Both reductions from baseline were statistically significant (JAMA 2006;295 [Epub doi:10.1001/jama.295.13.jpc60002]).

Atheroma volume significantly declined in the subgroup of 254 patients whose serum level of LDL cholesterol was less than 70 mg/dL. The 78 patients who maintained an LDL-cholesterol level of 70-99 mg/dL, and the 17 patients whose LDL-cholesterol levels remained at 100 mg/dL or higher despite treatment had no significant fall in their atheroma volume. The relationship of atheroma regression to levels of HDL cholesterol in this study has not yet been thoroughly examined.

The researchers plotted their new finding, of an average 0.79% reduction in atheroma volume with an average achieved LDL-cholesterol level of 61 mg/dL, along with correlations between serum cholesterol and atheroma volume changes reported in four prior IVUS studies. The five data points, which all fell on a line with a high correlation coefficient, indicated that atheroma regresses when a patient's serum level of LDL cholesterol falls below 75 mg/dL. "These findings suggest [that] attaining the lowest levels of LDL cholesterol achievable without adverse effects may represent the optimal strategy," Dr. Nissen said. ■