Drug-Eluting Stents Heavily Used Off Label

Off-label applications with the fastest growth were ST-segment elevation MI and in-stent restenosis.

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — More than a third of the drug-eluting stents placed in the first 9 months following marketing approval of the Cypher stent were for off-label indications, according to data from the American College of Cardiology–National Cardiovascular Data Registry.

The use of drug-eluting stents rose rapidly during this period, and growth in the off-label uses kept pace with the increase for the approved indication, Sunil V. Rao, M.D., reported at the annual scientific sessions of the American Heart Association.

Dr. Rao presented a unique picture of the clinical adoption of a major new medical technology as reflected in a large national registry experience. The American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR) is an ACC-initiated quality improvement project that to date includes more than 2 million admissions and 800,000 percutaneous coronary interventions (PCIs) at 528 participating U.S. sites.

The registry data are reassuring in that off-label use of drug-eluting stents (DESs) appeared to be safe, at least in terms of the very low associated periprocedural adverse event rate, said Dr. Rao of the Duke Clinical Research Institute, Durham, N.C. "However, long-term safety and efficacy of drug-eluting stent use in off-label situations really should be evaluated in appropriately powered, randomized controlled trials," he said.

For purposes of his study, Dr. Rao focused on PCIs involving only the Cypher stent, the first DES to reach the U.S. market between the device's April 2003 approval through the end of that year. PCIs involving placement of both a Cypher stent and one or more bare metal stents were excluded from consideration. Cypher-only procedures comprised 30% of the nearly 163,000 PCIs entered into the registry during the study period.

The official Food and Drug Administration–approved indication for the Cypher DES is for use in improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de novo coronary lesions less than 30 mm long in native arteries having a reference vessel diameter of 2.5-3.5 mm, Dr. Rao noted.

The regulatory language goes on to state that the safety and efficacy of the stent have not been established in patients with a recent myocardial infarction, where there is evidence of unresolved thrombus or poor flow, or in patients with diffuse disease or poor reflow distal to the target lesion.

Registry data showed off-label use of DESs appeared to be safe, at least in terms of the very low associated periprocedural adverse event rate seen.

Dr. Rao focused on four specific off-label applications: ST-segment elevation MI, in-stent restenosis, saphenous vein grafts, and chronic total occlusions. These four off-label uses accounted for 33% of all DES procedures during the study period. This figure is actually an underestimate of the true proportion of DES procedures that were off label, since it doesn't include other possible off-label indications, such as long lesions or bifurcations.

The fastest growth in off-label use of the DES during the 9-month study period was in cases of ST-segment elevation MI, followed by in-stent restenosis.

The incidences of in-hospital mortality and unplanned coronary artery bypass surgery in connection with off-label use of the Cypher stent were both well below 1%. Moreover, the postprocedural acute MI rate was similar to that seen with bare metal stents, Dr. Rao said.

Several audience members took issue with his call for randomized trials designed to expand the approved indications for drug-eluting stents. Some observed that companies have little incentive to conduct such trials, since business is already booming. Others argued that at this point it would be unethical to randomize patients to bare metal stents for most off-label uses and that the FDA should rely on registry data to evaluate possible expanded indications for drug-eluting stents.

Dr. Rao replied that it's highly unlikely the FDA would expand the indications on the basis of registry data, which after all are inferior to information gained from randomized trials.

"The registry data have a tremendous amount of residual confounding that cannot be accounted for regardless of the statistical analyses used. Having said that, I think registry data are invaluable when it comes to the very, very low-incidence events such as subacute thrombosis. I think registries are highly valuable for safety data. I don't think, however, we can accept efficacy data as reliable," Dr. Rao said. ■

Abciximab During Elective PCI Gave Diabetics No Benefit

BY MITCHEL L. ZOLER
Philadelphia Bureau

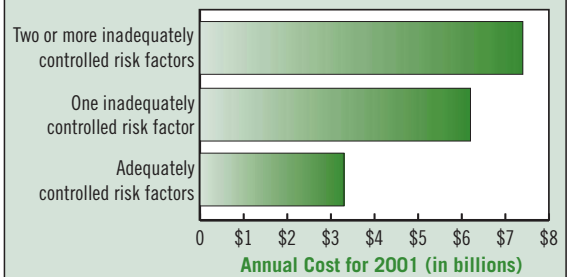
NEW ORLEANS — Treatment with abciximab failed to improve the outcomes of patients with diabetes who underwent elective percutaneous coronary interventions in a randomized study with 701 patients.

All patients in the study received a loading dose of 600 mg of the antiplatelet drug clopidogrel at least 2 hours before their percutaneous coronary intervention (PCI), which suggested that clopidogrel treatment "may obviate the need for abciximab during elective PCI in patients at low to intermediate risk," Julinda Mehilli, M.D., reported at the annual scientific sessions of the American Heart Association.

But the results from this German study, which was not sponsored by a pharmaceutical company, cannot be considered the last word on using a glycoprotein IIb/IIIa platelet inhibitor in patients with diabetes undergoing PCI, said some experts at the meeting.

DATA WATCH

Economic Impact of Inadequate Secondary Prevention in Patients With a History of MI or Stroke



Note: Based on data for 4,115 patients in the Second National Health and Nutrition Examination Survey, 1999-2000.

Source: Stroke 2004;35:2346-50

KEVIN FOLEY, RESEARCH/ANGIE RIES, DESIGN

One limitation is that the current study excluded patients with acute coronary syndrome, an acute myocardial infarction, or visible thrombus. "These patients have been the sweet spot for abciximab and other IIb/IIIa inhibitors," commented Gregg W. Stone, M.D., director of cardiovascular research and education at the Cardiovascular Research Foundation of Lenox Hill Hospital in New York.

Other shortcomings of the study included its enrollment of a relatively small number of insulin-dependent diabetics, and the fact that it was underpowered to prove that patients did just as well without abciximab as they did with the drug, said Eric R. Bates, M.D., a professor of medicine at the University of Michigan, Ann Arbor. The study was designed as a superiority trial, to prove that abciximab-treated patients fared better than those who didn't get the drug.

Dr. Bates was also skeptical that physicians who now use abciximab to treat diabetic patients undergoing elective PCI would be persuaded to change their practice based on the results of a single study.

The study was done at three German hospitals from January 2001 to October 2003. Patients were enrolled if they were on active treatment with either insulin or an oral hypoglycemic agent and were scheduled to undergo an elective PCI in a native coronary vessel. The study's primary end point was the incidence of death or myocardial infarction during the first 12 months following the procedure.

All patients received a loading dose of clopidogrel plus 500 mg aspirin. Following randomization, the patients in the abciximab group received a 0.25 mg/kg bolus followed by a 0.125 mcg/kg per minute infusion for 12 hours, along with 70 U/kg of unfractionated heparin. Patients in the placebo group received a placebo bolus and infusion, along with a 140 U/kg bolus of heparin.

Following their procedure, all patients received a 200 mg daily aspirin dosage that was continued indefinitely. Patients also received 75 mg clopidogrel b.i.d. until discharge or for a maximum of 3 days, and then continued on 75 mg clopidogrel daily for at least 6 months. Patients received other medications as indicated.

After 1 year of follow-up, the incidence of death or myocardial infarction was essentially identical between the two groups: 8.3% among the 351 patients treated with abciximab, and 8.6% among those treated with placebo, reported Dr. Mehilli of the German Heart Center in Munich.

The secondary end point of the study was the incidence of angiographic restenosis at follow-up. By this criterion, the abciximab group did better: Angiographic restenosis occurred in 28.9% of the patients in the abciximab group, compared with 37.8% of placebo patients, a statistically significant difference.

This result is already outdated, however, because the study was done largely before the advent of drug-eluting stents.

Only 10% of the patients received drug-eluting stents. In this small subgroup of patients, treatment with abciximab conferred no significant advantage over placebo.

The edge in restenosis conferred by abciximab "would have been a very important finding 2 years ago, but now it's too little too late," Dr. Stone said. "Drug-eluting stents are clearly the treatment of choice to reduce restenosis in patients with diabetes, and no drug has been shown to reduce restenosis when used on top of drug-eluting stents," he said. ■