Five Reports Advance Drug-Eluting Stent Debate

BY MITCHEL L. ZOLER
Philadelphia Bureau

Results from five new safety analyses of drug-eluting coronary stents, compared with bare-metal stents, gave added reassurance about using drug-eluting stents for their labeled indications and framed some of the concerns about off-label use of the stents.

The five reports, released online by the New England Journal of Medicine on Feb. 12, were detailed versions of reports presented last December to the Circulatory System Devices Advisory Panel of the Food and Drug Administration. The published reports included no changed or added findings and continued to support the panel's December conclusions, said Dr. William H. Maisel, panel chairman and author of an accompanying perspective article (N. Engl. J. Med 2007;356:981-1039; N. Engl. J. Med. 2007;356:1059-60).

Four of the new papers were reanalyses of data from the previous studies that led to FDA approval of the sirolimus- and paclitaxel-eluting stents (Cypher and Taxus), and in aggregate the results confirmed that drug-eluting stents (DESs) had comparable safety to bare-metal stents (BMSs) with the advantage of a substantial reduction in the need for target lesion revascularization.

"There probably is a true increase in the rate of late stent thrombosis in the on-label group, but importantly and equally convincingly there is no evidence of increased mortality or myocardial infarctions," Dr. Maisel said in an interview. One possible explanation is that the reduced restenosis rate with DES leads to fewer complications from restenosis.

Because of these findings, "I feel comfortable with drug-eluting stents continuing to be used in that group [on-label patients], and it's the stent of choice in that group, because there is a convincingly marked reduction in the need for repeat revascularization," Dr. Maisel said.

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The new data are "reassuring in the sense that there were nearly equal outcomes of patients treated with drug-eluting stents and bare-metal stents. They are less reassuring in that both types of stents are associated with episodes of late thrombosis," although the rates are low, said Dr. Donald E. Cutlip, a cardiologist at Beth Israel Deaconess Medical Center in Boston and senior author of one of the new studies.

The meta-analyses are limited by relatively small numbers of patients. The largest included fewer than 5,300 patients, which included both those getting BMSs and those getting DESs. "The statistical power to detect a doubling of risk was well under 50% in all of the analyses," said Dr. Steven Nissen, chairman of cardiovascular medicine at the Cleveland Clinic, in an interview done by the New England Journal of Medicine and released with the papers.

The FDA panel recommended that all patients who receive DESs should be treated for at least 12 months with a combination of clopidogrel and aspirin. (See box.) None of the new reports dealt specifically with the impact of dual antiplatelet therapy.

The fifth article contrasted with the other four by focusing on data collected in a registry of nearly 20,000 patients, all the patients who received a DES or BMS in Sweden in 2003-2004. This study and others like it are considered critical in the safety debate because they deal with "real-world" use of DESs, including in thousands of patients who had off-label indications. Experts estimate that until last summer, about 60% of DES use in the United States was in off-label patients.

The registry analysis showed that during 3 years of follow-up, patients who received DESs had about a 20% increased rate of death and of death or myocardial infarction, compared with patients who received BMSs; both were statistically significant differences.

Experts, including Dr. Maisel, cautioned that in this series the baseline clinical profiles of the patients who received DESs and BMSs had important differences. The researchers from Uppsala (Sweden) University who did these analyses used a propensity-score method to account for this so they could focus on differences between the two stent types. But a propensity-score analysis is "not perfect," said Dr. Cutlip.

Despite the Swedish study's limitations, it prompted Dr. Nissen to recommend that DES use be limited to on-label patients until trials are conducted in other types of patients. "I'm not willing to accept on faith that we know the performance of drug-eluting stents in real-world situations," said Dr. Nissen in his interview with the journal. "You really need at least an 8,000-patient trial. If there is a hazard and the Swedish study is right, then we might regret putting these devices in patients who have not been adequately studied for safety." Dr. Nissen is on the FDA panel.

Current data are inadequate to compare the safety and efficacy of DESs, BMSs, and coronary bypass surgery in off-label patients, said Dr. Maisel, also a cardiologist at Beth Israel Deaconess Medical Center. But it is known that DESs reduce the risk of restenosis and need for revascularization, compared with BMSs, in all patients.

Cardiologists have clearly received a message from these and similar reports and are curbing their use of DESs, presumably in mostly off-label patients. One expert has reported that DESs are now used in about 72% of coronary-stent patients in the United States, down from a peak of nearly 90% last year. In Europe, DESs were being used in about 48% of such patients, down from a peak of about 56%.

A 70% rate for DES seems about right based on what's known today, said Dr. Cutlip, also chief medical officer at Harvard Clinical Research Institute, Boston. He highlighted the need to choose between a DES and a BMS on a case-by-case basis. ■

Groups Urge Extended Dual Antiplatelet Therapy in Drug-Eluting Stent Patients

The importance of keeping patients with drug-eluting stents on dual antiplatelet therapy has been vastly underestimated, according to new warnings about the risk of late thrombosis issued by the Food and Drug Administration and several professional societies.

In January, the FDA announced on its Web site that it had "made detection of DES [drug-eluting stent] thrombosis signals a priority because of the potential for serious harm to patients [even though] stent thrombosis occurs at low rates." The agency summarized recommendations issued in December by its Circulatory System Devices Advisory Panel, including that the off-label use of DESs—estimated to be about 60% of device placements—is associated with an increased risk of thrombosis, death, or myocardial infarction (www.fda.gov/cdrh//010407.html).

Shortly thereafter, the Society for Cardiovascular Angiography and Interventions (SCAI) issued a clinical alert on DESs (Cathet. Cardiovasc. Interv. 2007 Jan. 11 [Epub DOI:10.1002/ccd.21093]). It had been in the works since early October, after data suggesting an increased risk of late stent thrombosis were presented at the European Society of Cardiology, said Dr. John Hodgson, chairman of the DES writing group, in an interview.

The alert is "a wake-up call," said Dr. Hodgson, SCAI past president and chief of academic cardiology at St. Joseph's Hospital and Medical Center, Phoenix. "We've gotten a little sloppy about putting stents in and not thinking through the entire process," he said.

Physicians should first determine if any procedure—whether surgery or stenting—is required, Dr. Hodgson said. If a DES is chosen, then intravascular ultrasound should be used to "document appropriate longitudinal lesion coverage and adequate stent expansion," according to the alert.

All risks and benefits—and the importance of maintaining dual antiplatelet therapy for at least 3-6 months, and for 12 months when bleeding risk is low—should be discussed with the patient. Using a DES "can't be the default strategy," he said, noting that many patients are not appropriate candidates for the devices.

Lastly, the American Heart Association, the American College of Cardiology, SCAI, the American College of Surgeons, and the American Dental Association issued a joint science advisory on the dangers of premature discontinuation of dual antiplatelet therapy after DES placement. The advisory was published in Circulation, the Journal of the American College of Cardiology, and Catheterization and Cardiovascular Interventions.

The recommendation has been to give 75 mg daily of Plavix (clopidogrel) and 325 mg daily of aspirin for 1 month after bare-metal stent implantation, for 3 months after sirolimus-coated DES implantation, for 6 months after paclitaxel-coated DES, and up to 12 months if there is a low risk for bleeding."That's gone out the door," said lead advisory author Dr. Cindy Grines, a cardiologist at William Beaumont Hospital, Royal Oak, Mich., in an interview.

The new recommendation is dual therapy for 12 months whenever possible, according to Dr. Grines. It has become clear that many patients and physicians—primarily those who are not cardiologists—are stopping dual therapy early, and that they may not understand the consequences, she said. Reasons for halting therapy include its expense (about $120 per month) and the perceived risk of bleeding during a subsequent surgical or dental procedure, Dr. Grines said.

The AHA advisory urges physicians to discuss with patients the pros and cons of dual therapy and the need to continue it for at least 12 months. The advisory cited numerous studies showing that early stoppage led to vastly higher rates of stent thrombosis, MI, and death.

Patients at particular risk for DES-related thrombosis—those who are older or have acute coronary syndrome, diabetes, low ejection fraction, or renal failure—should consider taking dual therapy for as long as possible, according to the advisory.

If 1 year is not possible, or if patients are required to have invasive surgery within 12 months of the catheterization, alternatives to DES—including a bare-metal stent or balloon angioplasty—should be weighed.

And cardiologists need to be consulted before a patient stops antiplatelet therapy, even if they are asked to do so by another physician.

There may be benefits to dual therapy beyond 12 months, but with few solid studies, it was harder to get a consensus on extending the duration, Dr. Grines said.

Drug-eluting stents are not overused, she said, adding that this is especially true given that they've been shown to have an edge in restenosis.

"Personally, I still use drug-eluting stents in most of my patients," said Dr. Grines, noting that she makes exceptions for those who have had a recent MI, who have surgery scheduled, or who can't or aren't willing to maintain dual antiplatelet therapy for a year.

The FDA lauded the AHA document, saying it will raise awareness of the importance of dual therapy among all providers.

—Alicia Ault