Polymer-Coated Stent Shows Promise in First Test

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HOLLYWOOD, FLA. — A new type of polymer-coated coronary stent was safe and effective during 6 months of follow-up in the first 37 patients to receive the stent when tested at a single center in Italy.

Perhaps the most notable finding from this initial clinical study was that, after 6 months, binary restenosis occurred in three patients (8%) and there were no cases of stent thrombosis even though all patients received dual-antiplatelet therapy for only 1 month, Dr. Corrado Tamburino reported at ISET 2008, an international symposium on endovascular therapy. In addition, the initial patients included 20% with type C coronary lesions (70% had type B lesions and 10% had type A lesions), and a third of the patients had diabetes.

In contrast, most series with drug-eluting coronary stents have placed patients on longer treatment with dual-antiplatelet therapy (aspirin plus a thienopyridine, either clopidogrel or ticlopidine), and usually some patients who receive drug-eluting coronary stents develop stent thrombosis.

The new stent, called CATANIA, does not contain or release any drug. Instead, the cobalt-chromium alloy stent is coated with a very thin, 40-nm layer of a polymer, Polyzene-F, which is believed to have novel physiologic properties including a substantially reduced capacity to trigger blood clots, intimal hyperplasia, and restenosis, said Dr. Tamburino, professor and chairman of cardiology at the University of Catania (Italy).

"Neointimal hyperplasia is prevented by preventing inflammation," commented Dr. Goetz M. Richter, a professor of radiology at the University of Heidelberg, Mannheim, Germany, who conducted several animal studies using the new, polymer-coated stent. Animal-study results also showed that the thin polymer coating is very stable following implantation.

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DR. TAMBURINO

The study enrolled 55 patients who underwent a percutaneous coronary intervention to treat myocardial ischemia. Their average age was 58 years, and 63% had unstable angina. The 55 patients underwent treatment on a total of 76 lesions using 89 stents. The average diameter of the treated arteries was 2.9 mm, and the average stent length used was 17 mm. The average number of stents placed in each patient was 1.4. Patients were placed on chronic aspirin treatment and received thienopyridine treatment for 1 month. The choice between treatment with clopidogrel or ticlopidine was based on the reimbursement rules of each patient's medical insurer.

One patient abruptly stopped aspirin treatment 1 day after hospital discharge, and another patient abruptly stopped aspirin and ticlopidine 2 weeks after stent placement.

At the time of Dr. Tamburino's report, 6-month follow-up data were available on 37 patients who were treated with 52 stents. This subgroup had no deaths, myocardial infarctions, or thrombotic events. The average late loss within treated coronary vessels was 0.5 mm, a rate comparable to what's been seen with various drug-eluting stents, he said. Neointimal hyperplasia occurred in 26%, and target lesion revascularization was needed for seven patients (19%), including the three patients with binary restenosis. Revascularization was done electively in four patients without binary restenosis based on the appearance of their treated artery after 6 months by quantitative coronary angiography. No binary restenosis occurred in coronary vessels wider than 2.5 mm, and five of the seven cases of lesion revascularization were in vessels less than 2.5 mm wide.

Further testing of the polymer-coated stent in patients is planned. The study was sponsored by CeloNova BioSciences Inc., which is developing the new stent. Dr. Tamburino has no financial relationship with CeloNova aside from receiving research support. ■

Peripheral Use

Biliary Stents *from page 1*

this 'end-run' path to market," Dr. Maisel said in an interview. "These stents are designed for palliative treatment of cancer patients, and the amount and type of data required for that approval [are] substantially less than what would be required for chronic, long-term use in the vasculature. Biliary stent approval typically doesn't even require clinical trial data. This has created a huge back door in marketing these stents for peripheral vascular use by just getting biliary indication."

But not all stents are created equal, Dr. Maisel contends. "You can't substitute one for another and assume they will all work the same." Stents in a leg, for example, are subject to very different stresses than those in a biliary canal, and no studies prove that biliary stents used in the leg maintain their long-term integrity.

Even medical associations have accepted this paucity of data, he said. The American College of Cardiology recommends stenting as a primary therapy for common iliac and external iliac stenoses and occlusions, despite the lack of an FDA-approved stent for this indication. "The problem is that the data on which this recommendation is based aren't always long-term data. It puts patients in the position of accepting treatment recommendations for which there is no FDA-approved product."

The rates of device malfunction and adverse events seen in off-label use of biliary stents should be enough to raise concerns about their use, Dr. Maisel said. His recent study concluded that the stents were much more problematic when used peripherally than when used in their approved manner (Am. J. Ther. 2008;15:12-8).

The study examined adverse events and device malfunctions reported to FDA's Manufacturer and User Facility Device Experience (MAUDE) database from 2003 to 2006. During this period, the MAUDE database recorded 1 million off-label biliary stent implants in the peripheral vasculature. During this same time, 1,036 device malfunctions and 561 clinical adverse events associated with total biliary stent use also were reported; 841 malfunctions occurred in off-label use, as did 493 adverse events.

Malfunctions were eight times more likely when the biliary stent was used in the periphery than in the biliary or gastrointestinal tract; 81% of the malfunctions occurred when the stents were used peripherally. Adverse events were 10 times more likely to occur during a peripheral use; 88% occurred when the stents were used in this way.

Most of the malfunctions (75%) were of the stent itself (premature dislodgement from the delivery system, premature deployment, physical damage during deployment, or migration). The most commonly reported adverse events were retained product and unanticipated additional percutaneous or surgical intervention (66% of reported events).Vascular injury (18%), threatened limb loss (3%), stroke (3%), bleeding (2%), and death (3%) also occurred.

The study clearly shows that the problems associated with off-label biliary stent use are rising, Dr. Maisel said. But the numbers don't necessarily mean that biliary stents aren't a safe and effective treatment for diseases of the peripheral vasculature, Dr. Maisel said. Rather, the problem is that no one really knows just how safe and effective they actually are.

Dr. Maisel's study muddies the true issue, said Dr. Christopher White, an interventional cardiologist and director of the Ochsner Heart and Vascular Institute in New Orleans. "It gives off-label use a negative connotation that it doesn't deserve," he said in an interview. "Yes, we do need more outcomes data and yes, we do need to stop this back-door approach to getting stents approved for peripheral use, but we can't condemn this use of biliary stents based on this one study. If off-label stent use was taken away, I could not treat my patients. It has evolved to become an integral part of medical practice."

Biliary stents aren't the only ones to have a broad off-label use, he added. "More than 70% of all coronary stents also are being used for an off-label indication. "Off-label use is part of our everyday practice and will continue to be. For instance, we have placed about 30 stents in the subclavian artery over the past 5 years. There has never been and never will be a named 'subclavian artery stent' approved. If off-label use was restricted, how would we treat these problems?"

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DR. WHITE

But device manufacturers aren't causing this problem, according to Dr. White, who laid at least some of the blame on the FDA and an archaic stent regulatory process. He said the FDA always has required each stent to be dedicated to a particular, named vessel, with all clinical research focused on that target. This makes sense in some applications—coronary arteries, for example—but simply doesn't translate into a workable research paradigm for a peripheral stent, he said.

The committee has attempted—unsuccessfully—to reach some consensus with FDA officials about how to relax regulatory requirements for a peripheral stent, Dr. White said. "We have tried to figure a way to make FDA happy and get a leg stent, but FDA has not been willing to do the necessary work to make this happen. Industry has to pitch in, too. They are not happy about being vilified when they try to market their stents."

Karen Riley, an FDA spokeswoman, refuted that argument. "FDA does not require vascular stents to be approved for every specific named vessel," she said in an interview. "However, we have not historically allowed broad indications such as 'leg arteries,' because we are aware that some vascular beds respond differently to identical devices. To approve devices intended for use in various vascular beds, we expect evidence of device performance that is appropriate for the specific vascular bed."

Rather than relaxing any standards, the FDA appears to be cracking down on off-label use. A March 2007 meeting with as many as 30 stent manufacturers focused on the growing number of adverse events associated with biliary stents in the peripheral vasculature, and on voluntary compliance with advertising restrictions, Ms. Riley said.

"We presented compelling evidence that these stents were increasingly being used off label and that we had seen overwhelming evidence of adverse events and promotional activities."

She said the pattern of adverse events was serious enough "to be viewed as a public health issue," and that company Web sites showed obvious evidence of promoting off-label use. "If manufacturers really want to see these stents approved for vascular use, they are going to have to go through the regulatory process," Ms. Riley said.

The dictum appears to be working. Since that meeting, the FDA has received 13 original investigational device exemption submissions for biliary stents for renal or infrarenal use; in 2006, there were only 7 such submissions. And there are currently several clinical trials underway. ■