New Stent Promising Despite High Late-Loss Rate

Endeavor stent scores clinically, but angiographic results raise questions about endothelial response.

BY MITCHEL L. ZOLER
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ORLANDO, FLA. — A new type of drug-eluting coronary stent was safe and effective in its first phase III clinical trial, compared with a similar bare-metal stent in about 1,200 patients.

But the results also raised novel issues on how effective drug-eluting stents must be at stopping the growth of coronary artery endothelium in order to prevent restenosis and the need for revascularization. That's because the new stent, brand named Endeavor and coated with a sirolimus-like drug called ABT-578, was successful at capping the target-lesion revascularization rate at 4.6% after 9 months, despite allowing a surprisingly high average late loss of 0.62 mm within stented coronary arteries.

"The current paradigm is that inflating a balloon leads to a vascular response to injury that then produces intimal proliferation, restenosis, and [cardiac] events. But it didn't work that way" in this study, commented Lloyd W. Klein, M.D., at the annual meeting of the American College of Cardiology. "It makes you wonder if we have the right paradigm. Patients don't care about their intimal thickness. They care whether they need to come back to the cath lab," said Dr. Klein of Gottlieb Memorial Hospital in Melrose, Ill.

In the study, named ENDEAVOR II, 1,197 patients were enrolled at 72 centers in Europe, Asia, and Oceania. About 20% of patients had diabetes.

The study's primary end point was the composite incidence of cardiac death, nonfatal myocardial infarction, or need for target-vessel revascularization during 9 months of follow-up. The incidence of this composite end point was 8.1% in patients who received the drug-eluting stent and 15.4% in patients who received a comparable bare-metal stent (Driver), reported William Wijns, M.D., codirector of the Cardiovascular Centre at OLV Hospital in Aalst, Belgium. The study was sponsored by Medtronic Inc. which makes both the Endeavor and Driver stents.

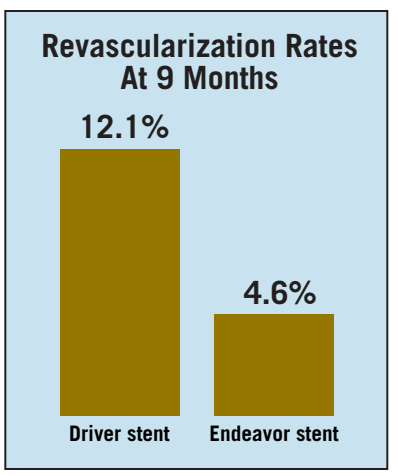
Two additional studies in progress, both funded by Medtronic, are comparing the Endeavor stent with the two competing drug-eluting stents on the U.S. market. One study matches the Endeavor and sirolimus-eluting (Cypher) stents; the other matches the Endeavor and paclitaxel-eluting (Taxus) stents. Medtronic will not seek marketing approval for the Endeavor stent in the United States until results from these studies are in.

In the current study, the ABT-578–eluting stent also looked good by other clinical end points: the 4.6% rate of target-lesion revascularization with the drug-eluting stent, compared with a 12.1% rate with the bare-metal stent; and the 0.5% rate of stent thrombosis during 9 months with the drug-eluting stent, compared with 1.2% with the bare-metal stent.

But this drug-eluting stent was less successful by the angiographic measures that were collected in 89% of the first 600 patients enrolled in the study. Although the mean late loss of 0.62 mm in the drug-eluting stents improved on the 1.03-mm rate of late loss with the bare-metal stent, it's a higher rate than has been seen in prior studies with other types of drug-eluting stents. Similarly, the in-stent binary restenosis rate of 9.5% with Endeavor in this study improved on the 32.7% rate with bare-metal stents, and was a higher restenosis rate than in earlier studies with other brands of drug-eluting stents.

In recent pivotal studies, the late-loss rate following coronary artery stenting averaged 0.17 mm with the sirolimus-eluting stent and 0.39 mm with the paclitaxel-eluting stent, said Gregg W. Stone, M.D., a cardiologist at Columbia University in New York. When compared with the 0.62-mm late loss with the ABT-578–eluting stent, these findings show "a striking difference in biologic potency" between the three drug-eluting stents.

But it's a different story for the target-lesion revascularization rates, the "purest surrogate measure of efficacy for drug-eluting stents." These rates were 4.1% with the sirolimus-eluting stent and 3.0% with the paclitaxel-eluting stent, not substantially better than the 4.6% rate with the ABT-578–eluting stent in the new study.



"We go from a marked difference in biologic response to no difference in clinical results," said Dr. Stone, although he also warned that these data were collected in three different studies, and comparisons across studies must be done cautiously.

What explains this apparent paradox? He hypothesized that the difference in late-loss rates may stem from differences in drug-elution rates. "You wouldn't expect such a difference in biologic responses based on any difference in the drugs." But 75% of the sirolimus on a Cypher stent elutes in 10 days, and it takes 30 days for all of the drug to come off. In contrast, 75% of ABT-578 is off the Endeavor stent within 2 days after a stent is placed in a coronary artery, and 100% is off within 10 days. "It's plausible that the difference in elution rates at least partially explains the difference in vascular effects between the two stents," he said.

When it comes to their clinical effect, "we know that most patients can accommodate a certain amount of stenosis before it overwhelms their coronary flow reserve," Dr. Stone said. "The target lesion revascularization rate is only 7% when late loss is 0.70 mm. A 0.62 mm late-loss rate would not be expected to cause much target-lesion revascularization."

"Late loss is significantly greater [with the Endeavor stent] than with other drug-eluting stents, but it is still low enough to produce excellent freedom from restenosis," Dr. Stone concluded.

Another factor is that the ENDEAVOR II study mostly used patients with a low relative risk for target lesion restenosis. If the stent is tested in higher-risk patients or in higher-risk lesions, such as those in narrow coronary arteries, it's possible that the higher rate of late loss will make a clinical difference, commented Laura Mauri, M.D., a cardiologist at Brigham and Women's Hospital in Boston.

Nonetheless, the Endeavor stent may have other attributes that make it an attractive option. The Driver bare-metal stent that's the platform for the ABT-578–eluting stent is widely regarded as easy to use. Plus, the Endeavor stent uses a biocompatible phosphorylcholine coating that binds the drug layer to the metal stent. The sirolimus- and paclitaxel-eluting stents use a polymer coating. The phosphorylcholine coating may explain why the rate of late thrombosis in the ENDEAVOR II study was so low, 0.5%. The polymer coats on the other drug-eluting stents may, in part, be why they have led to some problems with late thrombosis, Dr. Mauri said. But a study designed to definitively show whether these stents differ in their rate of late thrombosis would require several thousand patients. ■

Lower Costs, Higher Efficacy Seen With Drug-Eluting Stents

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WASHINGTON — With prices continuing to fall, drug-eluting coronary stents have become more cost effective than ever before.

Based on the price of drug-eluting stents, the average number of stents used per patient, and their efficacy at cutting the rate of restenosis, drug-eluting stents are now cost effective in any patient who would have a risk of restenosis of 10% or more if bare-metal stents were used for treatment, David J. Cohen, M.D., said at a meeting sponsored by the Cardiovascular Research Institute of the Washington Hospital Center.

In contrast, based on last year's averages, drug-eluting stents were cost effective whenever the restenosis rate with bare-metal stents was 12% or greater (INTERNAL MEDICINE NEWS, March 15, 2005, p. 58).

The upshot is that drug-eluting stents now make economic sense in wider coronary arteries and in vessels with shorter lesions. It is reasonable from an economic standpoint to use drug-eluting stents in most patients with coronary artery disease, said Dr. Cohen, who is associate director of interventional cardiology at Beth Israel Deaconess Medical Center in Boston.

By early 2005, the two types of drug-eluting stents sold in the United States (sirolimus-eluting and paclitaxel-eluting) cost an average of $2,300 per stent, down from an average of $2,700 last year and $3,100 in 2003. In early 2005, the difference in cost of a drug-eluting coronary stent over a comparable bare-metal stent had dropped to $1,600, down by $300 from the year before.

At Dr. Cohen's center, patients who had drug-eluting coronary stents placed in late 2004 received an average of 1.6 stents each. And the most current data from studies that compared drug-eluting stents with bare-metal stents showed that drug-eluting stents cut the need for target vessel revascularization by about 82%. One additional issue for a cost-effectiveness calculation is that patients who receive drug-eluting stents require daily treatment with clopidogrel for several months, a regimen that costs about $120 per month.

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DR. COHEN

When all of these cost-adding and cost-saving numbers are crunched together, you come up with an estimate indicating that placement of a drug-eluting stent adds no incremental cost when used in patients with an expected restenosis rate with bare-metal stents of at least 10%, he said.

Based on an analysis done by Dr. Cohen and his associates in the late 1990s, virtually all patients with diabetes have a restenosis rate of 10% or greater with bare-metal stents.

The only exceptions are patients with lesions that are less than 30 mm in length that are in coronary arteries that are at least 4.0 mm in diameter. Among patients without diabetes, a restenosis rate of less than 10% with bare-metal stents occurs in all coronary arteries that are 4.0 mm in diameter or greater, regardless of lesion length, and in vessels that are 3.5 mm in diameter or greater if the lesion length is less than 25 mm. ■

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