Up to Six Drug-Eluting Stents to Hit U.S. Market

The new models are expected to improve deliverability and increase competition, which might reduce costs.

BY MITCHEL L. ZOLER
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DALLAS — About a year from now, there may be as many as six new drug-eluting coronary stents on the U.S. market.

Although none will likely improve on the efficacy or safety of the two drug-eluting stents now available—the sirolimus-eluting (Cypher) and paclitaxel-eluting (Taxus) stents—the new models will offer improved deliverability and increased competition, which might produce downward cost pressure in the coronary stent market, Dr. Gregg Stone said at the annual scientific sessions of the American Heart Association.

"All of the studies [of the new stents] are noninferiority trials," he said. No studies are designed or powered to show that a new stent is better than the Taxus or Cypher models.

Dr. Stone reviewed the six new stents and their development status. Five feature sirolimus-like drugs, two of which use the same drug, ABT-578, which was recently renamed zotarolimus. The sixth stent uses paclitaxel.

Zotarolimus is contained in a phosphorylcholine polymer on Medtronic's Endeavor stent. The underlying stent is made from cobalt and has thin struts that make it very radioopaque, flexible, and deliverable, said Dr. Stone, director of research and education at the Center for Interventional Vascular Therapy, Columbia University, New York.

Three clinical studies, involving a total of more than 1,500 patients, have been completed with the stent. A fourth study, which is still in progress, is comparing the Endeavor with the sirolimus-eluting Cypher stent and involves another 1,500 patients.

So far, late-loss rates with the Endeavor stent have been about 0.6 mm, which is substantially higher than the 0.2 mm or less in three major Cypher studies and the 0.30–0.35-mm rate seen in three major trials with the Taxus paclitaxel-eluting stent.

Despite this, clinical measures of restenosis have shown small differences between the Endeavor stent and those now on the market. The target lesion revascularization rate, for example, was about 4%-5% in the sirolimus- and paclitaxel-eluting stent studies, and about 6% in the Endeavor studies.

One reason for this "big difference physiologically and small difference clinically" is that coronary arteries can accommodate some degree of late loss, Dr. Stone said. One recent analysis suggests that a late loss of up to 0.55 mm does not produce much clinical effect, although the incidence of adverse clinical outcomes rises linearly as the late-loss rate increases from 0.55 mm to 1 mm and exponentially as it increases above 1 mm. "The Endeavor stent sits at the cusp" with a late-loss rate of about 0.6 mm," he said.

The second coronary stent using zotarolimus is the Zomaxx device made by Abbott. It is similar to the Endeavor except that it contains a second phosphorylcholine-polymer coat over the drug layer.

The cap-coat is designed to control the elution of zotarolimus and allows for a variety of elution profiles. The formulation used in the clinical studies releases about 75% of the drug in the first 10 days after placement and about 100% in 30 days, an elution profile similar to that of sirolimus in the Cypher stent. By comparison, the Endeavor stent releases 75% of its drug in the first 2 days of placement and about 100% in 10 days.

The Zomaxx stent is based on the Trimaxx bare-metal stent, a thin-strut, radioopaque device that is very flexible and deliverable, Dr. Stone said.

There are two trials underway with the Zomaxx stent, one in Europe that will enroll about 400 patients and a second in the United States that has been designed as the pivotal trial and will enroll almost 1,700 patients.

Everolimus, another sirolimus analogue, is used on Guidant's Xience V stent, which is composed of the Multi-Link Vision coronary stent and a thin, bioabsorbable polymer. Everolimus was first used on a different stent, the Champion, but it tended to fracture and was therefore replaced. Combined angiographic outcomes data suggest that everolimus-releasing stents produce less than 0.2 mm late loss, which would make them as good as the sirolimus-eluting stent.

A European study with about 300 patients is underway, as is a pivotal U.S. study that will enroll almost 1,400 patients.

The fourth sirolimus-like agent, biolimus A9, is used on the Biomatrix stent, which is made by Biosensors and licensed to Devax. Two major trials with this stent are scheduled to start this year. A European trial is slated to enroll about 1,700 patients, and a trial in the United States will enroll more than 1,400 patients.

Devax is also testing clinically the first coronary stent to have been designed for use in a coronary bifurcation, the Axxess Plus. The system involves a reverse cone stent that is placed in the carnia, and two additional stents that can be placed in the main branch and side branch as needed. In clinical testing so far, the target lesion revascularization rate in the bifurcation has been 7.5%. "This looks like the best stent so far for bifurcations," Dr. Stone said.

The fifth new drug-eluting stent uses paclitaxel, but delivers the drug in a novel way. The device, made by Conor Medsystems, first used a steel stent with a bioabsorbable polymer that is placed in dozens of small wells drilled on the stent surface. The positioning of the wells allows for the delivery of different drugs to the endothelial surface or into the coronary lumen, and the total doses and elution rates can also be manipulated. A study with 191 patients identified two paclitaxel doses that worked best: 10 mcg and 30 mcg, both delivered over 30 days.

In more recent studies, investigators have used a cobalt and chromium stent, the Costar, that is more flexible and durable than the steel stent. In a study with 282 patients, the 10-mcg dose worked best with the Costar stent. This dose and stent are now being compared with the paclitaxel-eluting Taxus stent in a study designed to involve about 1,500 patients. ■

Stent Platforms in Development May Reduce Late Thrombosis

BY BRUCE JANCIN
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SNOWMASS, COLO. — Some of the most exciting of the drug-eluting stent platforms working through the developmental pipeline have the potential to curb the vexing problem of late stent thrombosis, Dr. Robert M. Bersin said at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

Furthest along of these is the BioMatrix stent system being developed by Biosensors International. It consists of a stainless-steel stent, a poly-L-lactide polymer as the drug-delivery vehicle, and the drug itself, a sirolimus analogue called Biolimus A9.

The technologic advantage of BioMatrix is that its drug-delivery polymer is the first to be fully bioabsorbable. That means there will be no residual polymer to flake off or promote inflammation.

"This polymer will disappear over time with no coating left behind, which is one of the issues we are currently evaluating as a potential factor in late stent thrombosis," explained Dr. Bersin, director of clinical research at the Washington Cardiovascular Research and Education Foundation, Seattle.

The sirolimus analogue is more lipophilic and elutes faster than the parent drug. It seems to be performing well, with an average in-stent late lumen loss at 6 months of only 0.26 mm, compared with 0.74 mm with a bare-metal stent (BMS). A trial to be reported later this year will give a good idea of how BioMatrix performs in terms of key clinical outcomes relative to drug-eluting stents (DESs) now on the market, he added.

A recent metaanalysis of all eight randomized prospective trials of the sirolimus-eluting Cypher stent and the paclitaxel-eluting Taxus paclitaxel stent clearly shows late stent thrombosis is a problem with both devices.

Polymer stents could eliminate the obstacles to repeat revascularization posed by permanent metal stents and could also solve the late thrombosis problem.

Thrombosis rates with the two were superimposable upon those of BMSs out to about 18 months. Then the curves diverged. At 3 years, the stent thrombosis rate was 1.1% with Cypher and 1.3% with Taxus. Each rate was an absolute 0.5% more than with BMS comparators.

"Late stent thrombosis is a big issue today with drug elution," Dr. Bersin stressed. "This is a consistent issue with drug-eluting stents, regardless of brand."

A recent analysis showed that prior brachytherapy was the strongest predictor of stent thrombosis in patients with a DES. Renal failure was second, followed by anatomically difficult features, such as bifurcation lesions, and diabetes.

Numerous manufacturers are developing fully biodegradable DESs constructed of poly-L-lactide or other polymers. Because the materials lack the mechanical strength of traditional stainless steel or cobalt-chromium, sophisticated designs have been used to increase radial strength. These stents will not only eliminate the obstacles to repeat revascularization posed by permanent metal stents, but they could also solve the late thrombosis problem.

Berlin-based Biotronik AG is conducting clinical trials of a magnesium alloy–based DES that biodegrades through controlled corrosion. The appeal is that it may provide a temporary metal scaffolding with the same strength and performance characteristics as a permanent BMS, Dr. Bersin said.

A new paradigm for restenosis prevention is being developed by OrbusNeich. Its Genous stent, rather than locally delivering cytotoxic drugs to curb an overzealous vascular intimal healing response, is designed to enhance function of endogenous modulators to promote more efficient healing.

The Genous metallic stent is coated with a fragment of antibody to CD34 in order to capture circulating endothelial progenitor cells to accelerate endothelialization. In animal studies, the BMS still had bare struts 48 hours after implantation, while the Genous stent was completely coated with a monolayer of endothelial cells. Longer term, there was less intimal hyperplasia than with the BMS, too. Clinical trials are ongoing in Europe.

"This could offer a clear advantage in terms of stent thrombosis risk, especially in patients unable to take high-level antithrombotic agents for various reasons. So it's hoped that in the end, this will be a significant player in the marketplace," the cardiologist said.

Another highly original stent platform design is a Conor DES containing nearly 600 laser-cut wells in the struts. These wells can be filled with two different drugs with a barrier layer in between—for example, an antiproliferative agent on the stent's intimal side and an antithrombotic drug on the luminal side. ■