Paclitaxel Stents Boost Late Thrombosis Risk

The polymer may be the culprit, leading to delayed arterial healing and greater risk of late thrombosis.

BY MITCHEL L. ZOLER
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DALLAS — Paclitaxel-eluting coronary stents posed a substantially increased risk of causing late stent thrombosis, compared with bare-metal stents, in a meta-analysis of five studies with more than 3,500 patients.

The results were less clear for sirolimus-eluting coronary stents, with no statistically significant differences in late thrombosis rates, compared with bare-metal stents, said Dr. Anthony A. Bavry, who reported on the metaanalysis at the annual scientific sessions of the American Heart Association.

The clearly increased risk linked with paclitaxel-eluting (Taxus) stents contrasted with the results of a similar meta-analysis that was reported by Dr. Bavry and his associates at the Cleveland Clinic a year ago. In that metaanalysis, the researchers failed to document a clear-cut difference in risk.

The new analysis included follow-up of as much as 3-4 years, which allowed for the collection of very late events. This was in contrast to the earlier report, which had a follow-up of only 1 year.

The researchers used the results from a total of 18 randomized, controlled comparisons between drug-eluting stents and bare-metal stents, as well as the results from two registries.

The new analysis had a follow-up of 3-4 years, allowing for the collection of very late events, whereas an earlier report had a follow-up of 1 year.

The trials included four studies that examined nonpolymeric paclitaxel-eluting stents in a total of 1,423 patients, nine studies that examined sirolimus-eluting (Cypher) stents in a total of 3,162 patients, and five studies with polymeric paclitaxel-eluting stents in 3,513 patients.

The two registries included a total of 2,171 patients.

The incidence of stent thrombosis more than 30 days after stent placement among those patients who received polymeric paclitaxel-eluting stents was 6.3/1,000 patients, compared with 1.1 events/1,000 patients in the bare-metal stent arms of these trials—a statistically significant relative risk for paclitaxel-eluting stents of 3.6, Dr. Bavry reported.

The stent thrombosis incidence for the same time period in patients who received sirolimus-eluting stents was 3.0/1,000 patients, compared with 4.5/1,000 patients in the bare-metal stent arms, a nonsignificant difference.

When thrombotic events were limited to those that occurred more than 6 months after stent placement, the rate for paclitaxel-eluting polymeric stents was 5.0 per 1,000 patients, compared with 0 among patients who received bare-metal stents, a statistically significant relative risk of 7.1. In the studies in sirolimus-eluting stents, the rate for the drug-eluting stents was 3.0 per 1,000, compared with 1.2/1,000 among the bare-metal patients, a nonsignificant difference.

Thrombotic events more than 1 year after stent placement occurred at a rate of 5.7 per 1,000 patients with the paclitaxel-eluting stent, compared with 0 in the bare-metal stent arm, a statistically significant relative risk of 5.7. The difference between groups in the sirolimus stent studies, 3.5/1,000 vs. 0 for bare-metal stents, did not reach statistical significance.

Overall, no thrombotic events were seen more than 1 year following placement of a bare-metal stent in these studies.

In contrast, however, the median time to a thrombotic event was about 16 months in patients who received a sirolimus-eluting stent and about 18 months in those who got a paclitaxel-eluting stent.

"The polymer seems to be the culprit, leading to delayed arterial healing and an increased risk of late thrombosis," added Dr. Bavry.

Because late thrombosis episodes are relatively rare, metaanalysis might be the best way to determine their incidence, he said. ■

Assortment of New Drug-Eluting Coronary Stents in the Pipeline

BY MITCHEL L. ZOLER
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DALLAS — About a year from now, in 2007, 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- to 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.

The new models will offer improved deliverability and increased competition, which might produce downward cost pressure in the coronary stent market.

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 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," Dr. Stone 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 on top of 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 clinical 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 is another sirolimus analogue, and 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 carina, 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, which uses paclitaxel, delivers the drug in a novel way. The device, which is 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. ■