No Excess Deaths, MIs

Thrombosis *from page 1*

presentation of data at the European Society of Cardiology meeting in September.

The ESC presentations reported a higher risk of stent thrombosis with the DES devices than with bare metal stents.

"There's been a hysterical overreaction to recent data that was not published, but presented at the European Congress," said Dr. Leon, who is a consultant to Boston Scientific and an adviser and investor in Johnson & Johnson's Cordis division. "We do believe that there is a signal," he said, adding that thrombosis seems to surface after 1 year with the two DES devices and occurs as late as 3.5 years post implantation. But, he said, the analysis did not indicate an increase in cumulative heart attacks or deaths.

Dr. Leon presented results of the patient-level analysis of the Taxus studies at the CRF symposium, and Dr. Gregg Stone, CRF's vice chairman, presented data from the Cypher trials. The raw data were provided to CRF by the manufacturers—a courtesy that was not initially extended to European researchers such as Dr. Edoardo Camenzind of University Hospital Geneva. But Dr. Camenzind told reporters he has now received the data and is recalculating his analyses.

The CRF statistical analyses were conducted by Dr. Stuart Pocock of the London School of Hygiene and Tropical Medicine, and the clinical events were adjudicated by the Harvard Clinical Research Institute, said Dr. Leon, who was also a principal investigator in the Cypher trials.

With 4 years of follow-up, there were nine thrombosis events with the Taxus stents, compared to two with bare metal stents, all occurring after the first year. For all clinical end points, including MI and cardiac death, there was no statistically significant difference between the two groups, said Dr. Leon. However, there was a statistically significant advantage in favor of Taxus in both target lesion revascularization (TLR) and target vessel revascularization (TVR). Those rates were 20% and 25%, respectively, in patients with bare metal stents, compared with 10% and 17% in the Taxus patients.

In the Cypher studies, there were five thrombosis events with the DES, compared to none with the bare metal stent, again after 1 year, said Dr. Stone, who is also with Columbia University Medical Center, is a speaker for Boston Scientific, and was a principal investigator in the original Taxus studies. Again, there was no difference in deaths or MI, and there was a significant restenosis advantage with the Cypher. The TLR and TVR rates were 24% and 28% with bare-metal stents, compared with 8% and 12% with Cypher stents.

Overall, there was a 0.6% increase in late stent thrombosis for the Cypher and 0.5% increase for the Taxus stents.

"Patients are not being harmed with the use of drug-eluting stents, and any small increase that may occur in heart attacks or death after 1 year is offset by a reduction of those similar events before 1 year, associated with the dramatic decrease in the frequency of restenosis," said Dr. Leon.

However, he added, "We are not in any way suggesting that this signal of late stent thrombosis is not there."

Dr. Pocock said he calculated the absolute risk at one event per 500 patient-years of follow-up, a risk he characterized as "small," especially since it is not translating into an increase in major events.

Dr. Donald Cutlip, chief medical officer at the Harvard Clinical Research Institute, Boston, said the risk is "real, it's important, no one is trying to hide it, it's very transparent, and, fortunately, it seems to be pretty small."

After the two analyses were presented, Dr. Bram Zuckerman, director of the cardiovascular devices division at the Food and Drug Administration's Center for Devices and Radiological Health, told meeting attendees that the new analyses provided "more reassuring" data. But, he said, the data were limited because there were so few trials and because the trials had been carried out in low-risk patients. DES are being used in all comers, including very high-risk patients, said Dr. Zuckerman.

"The ability to expand into the real world still is quite limited," said Dr. Zuckerman, adding, "We do think there is a signal there."

The agency will hold a 2-day meeting on DES safety in early December.

The correct duration of antiplatelet therapy may be an issue also. Dr. Alaide Chieffo of the San Raffaele Scientific Institute in Milan, Italy, presented data showing that despite a dual regimen of aspirin and clopidogrel, some patients may still have stent thrombosis, as late as 6 months or more after stent placement.

She looked at more than 3,000 consecutive patients given either the Taxus or the Cypher stent during April 2002–December 2004 at four centers in Italy and Germany. With 18 months of follow-up on average, 58 patients had stent thrombosis. Forty-two occurred within 6 months, and 16 after 6 months. Noncompliance with antiplatelet therapy predicted thrombosis in the first 6 months, but after 6 months there seemed to be no impact, said Dr. Chieffo.

The bottom line, she said: "Simply, if you have to stop Plavix because of concomitant surgery or bleeding complications, there is no additional risk."

Dr. Spencer King III, professor emeritus at Emory University, Atlanta, said that Dr. Chieffo's study, combined with the evidence of later stent thrombosis events, may only add to the confusion about how long to continue antiplatelet therapy, especially since DES are used so liberally. "In the off-label use and more difficult cases, the rate of late stent thrombosis is higher," he said.

He said that perhaps more judicious use of the devices is warranted. "We should always be selective and perhaps not universally use drug-eluting stents, but rather use them where we think they are most clinically needed in reducing restenosis," said Dr. King.

"Permanent Plavix and aspirin is not a solution."

One manufacturer cautioned against lumping all the DES together. "These are not necessarily one broad class of devices," said Campbell Rogers, Cordis' chief technology officer.

Cordis is urging all the DES manufacturers to make their raw data available for analysis with a new set of standardized definitions for what constitutes stent thrombosis, said Mr. Rogers.

A joint American-European academic, industry, and regulatory group—the Academic Research Consortium—which met twice in 2006, has proposed some definitions. Dr. Cutlip presented those proposals at the CRF symposium. Applying the definitions to the pooled results of studies involving Medtronic's Endeavor stent, which is coated with a sirolimus-like drug, resulted in a higher overall rate of stent thrombosis for both bare-metal and DES. But there was no difference between bare metal and Cypher stents when the new definitions were used to reanalyze the pivotal Cypher trials.

All the researchers said that larger and longer studies were needed to tease out the potential issues with late thrombosis.

Boston Scientific announced at the symposium that it was expanding its Strategic Transcatheter Evaluation of New Therapies (STENT) registry to assess late thrombosis in about 10,000 patients. Cordis announced that it was extending follow-up from its pivotal Cypher studies out to 8 years and that it would create a new prospectively followed subset out of its existing 30,000-patient registry to assess thrombosis and the use of dual antiplatelet therapy, among other issues.

Dr. William O'Neill of the University of Miami said the registries would not provide the answers being sought. "I think the registries are okay, but they are not going to be definitive," he told reporters.

Manufacturers should instead be studying why stent thrombosis occurs, he said. Dr. O'Neill believes that it may be partly a question of how the devices are placed. "People are becoming somewhat lackadaisical with their implantation technique," he said, noting that high-pressure balloons and intravascular ultrasound are often not used. ■

Less Restenosis in New Everolimus-Eluting Stent in SPIRIT II

BY BRUCE JANCIN
Denver Bureau

BARCELONA — The Abbott Xience everolimus drug-eluting coronary stent proved significantly more effective than the Taxus paclitaxel-eluting stent in preventing neointimal hyperplasia in the randomized SPIRIT II clinical trial, Dr. Patrick W. Serruys said at a joint meeting of the European Society of Cardiology and the World Heart Federation.

"The in-stent late loss curves are completely separate. So what was envisioned originally as a noninferiority trial is, as a matter of fact, a superiority trial," said Dr. Serruys, professor of interventional cardiology at the Erasmus University Thoraxcenter, Rotterdam, the Netherlands.

In-stent late lumenal loss is widely accepted as a marker for restenosis, since both processes are driven by neointimal hyperplasia. The trouble for SPIRIT II is that the dominant topic of discussion at the European congress was the growing evidence that drug-eluting stents (DES) as a class may pose a greater long-term risk of stent thrombosis than do bare-metal stents cardiologists largely cast aside once DES became available.

SPIRIT II involved 300 patients with relatively simple de novo target coronary lesions. Only 13% were type C; the rest were the more straightforward lesion types A and B. Participants in the multinational trial were randomized 3:1 to the Xience or Taxus stent.

The Xience stent is investigational in the United States but recently gained European marketing approval. The cobalt-chromium stent carries everolimus, which is related to sirolimus and has essentially the same mechanism of action.

The primary end point in SPIRIT II was angiographic in-stent late loss in vessel diameter at 6 months follow-up. It was 0.11 mm in the Xience group, significantly better than the 0.36 mm in the Taxus group. This was reflected in the mean 16% residual stenosis at 6 months in the Xience group, compared with 21% with Taxus.

'What was envisioned originally as a noninferiority trial is, as a matter of fact, a superiority trial.'

DR. SERRUYS

Everolimus stent recipients also had a mean 73% reduction in neointimal volume measured by intravascular ultrasound, compared with those who got the paclitaxel stent: 3.8 mm^3 and 14.4 mm^3, respectively.

One late stent thrombosis occurred at 53 days despite dual antiplatelet therapy in a Xience stent recipient, and another occurred at 60 days in a patient with a Taxus stent. The overall major adverse cardiac event rate in SPIRIT II was relatively low: 2.7% with Xience and 6.5% with the Taxus stent, a nonsignificant difference.

Dr. Serruys said in a press conference that it will take several more years to learn the Xience stent's late thrombosis risk. After all, it took 3 years of follow-up in very large registries to identify a possible problem with the current sirolimus and paclitaxel stents. The challenge for DES developers, he added, will be to find the right balance between preventing neointimal hyperplasia and generating quality endothelium.

SPIRIT II was sponsored by Abbott. Now underway are the 1,380-patient SPIRIT III trial, designed to support Food and Drug Administration approval of the Xience stent, and the 1,125-patient SPIRIT IV trial, also U.S.-based. ■

Pages 10a—10b