Late Thrombosis Haunts Drug-Eluting Stents

BY MITCHEL L. ZOLER
Philadelphia Bureau

Drug-eluting stents now dominate most applications of coronary artery stenting because they dramatically cut the rate of restenosis. But a new issue has emerged: late thrombosis.

Until more data are collected to better define the late-thrombosis risk, concern about this complication will haunt drug-eluting stents and dampen their use.

Late thrombosis occurs when a thrombus forms within a stent and abruptly closes the coronary artery a month or more after the stent was placed, a time when bare-metal stents are generally believed to have become a benign part of a patient's vasculature.

"Late thrombosis has been extremely rare with bare-metal stents," noted Mark J. Eisenberg, M.D., an interventional cardiologist at McGill University in Montreal.

That's why a report of four cases of fatal, late thrombosis in patients with drug-eluting stents in The Lancet last October caught cardiologists' attention. Even more compelling were the circumstances that tied the four cases together. In every patient, the abrupt occlusions appeared about a year after the stents were placed, and soon after the patients stopped long-term aspirin therapy (Lancet 2004;364:1519-21).

A team of physicians from the Thorax Center in Rotterdam, the Netherlands, and from the Washington Hospital Center published the clinical details of four patients who developed stent thrombosis 11-14 months after receiving a drug-eluting stent. Three patients had anterior myocardial infarctions, while the fourth manifested chest pain. Two patients had sirolimus-eluting stents (Cypher), and the other two had paclitaxel-eluting stents (Taxus). When the stents were placed, dual platelet-inhibitor therapy with aspirin and clopidogrel was used for 3-6 months, followed by aspirin-only treatment. In all four cases, the thrombosis occurred 4-14 days after aspirin was stopped (one patient was also still taking clopidogrel, which was stopped along with aspirin). In three cases, the antiplatelet drugs were stopped prior to surgery.

The risk of late thrombosis is based on the same properties that let drug-eluting stents block restenosis. As explained by Dr. Eisenberg in a comment that accompanied the four case reports, bare-metal stents become endothelialized within a few weeks of implantation, which is why their rate of late thrombosis is so low. In contrast, drug-eluting stents delay endotheliazation, which is why dual platelet inhibition is routinely used for up to 6 months.

"I've changed the way I use drug-eluting stents" because of the reports of late thrombosis, said Deepak Bhatt, M.D., an interventional cardiologist at the Cleveland Clinic.

"If I know a patient will have surgery soon, I ask myself if he or she really needs the coronary stent before surgery. I try to defer stenting when possible. If stenting must be done immediately, then I tend to use bare-metal stents. I think most of my colleagues would too," Dr. Bhatt said in an interview.

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Another approach that some cardiologists have taken is to put even greater emphasis on anti-thrombotic treatment, without cutting back on using drug-eluting stents. "The reports of subacute stent thrombosis have not prompted me nor any other interventional cardiologist who I know to change practice, other than to extend the duration of dual, oral antiplatelet therapy," said Herbert D. Aronow, M.D., director of the cardiac catheterization laboratories at the Veterans Affairs Medical Center in Philadelphia. "I typically continue aspirin and clopidogrel through surgery, if possible. When not possible, I try to continue aspirin alone. If both aspirin and clopidogrel must be stopped, I typically delay surgery until the risk of stent thrombosis is much lower, and I balance the need for surgery against the risk of stent thrombosis."

"If we find that the late thrombosis rate is two- or threefold higher [with drug-eluting stents, compared with bare-metal stents] after stopping dual antiplatelet therapy or 1 year after an implant, then we will need to reconsider … our use patterns of drug-eluting stents until we develop safer systems," Martin B. Leon, M.D., said at the American Heart Association scientific sessions last November in New Orleans. "Safety is more important in this case than antirestenosis efficacy," added Dr. Leon, associate director of the Center for Interventional Vascular Therapy at Columbia University in New York.

From the time drug-eluting stents were introduced, physicians were concerned about an increased incidence of late thrombosis. Last year, Dr. Eisenberg and his associates did a metaanalysis of data collected in 11 trials that had compared sirolimus- and paclitaxel-eluting stents with bare-metal stents in a total of 5,103 patients (Lancet 2004;364:583-91). The results showed that the pooled rate of stent thrombosis was 0.5% among the patients who received bare-metal stents and 0.7% among those who received drug-eluting stents, a nonsignificant difference. But because the rate of thrombosis is low, even this large analysis did not have the statistical power to completely rule out a twofold difference in risk between the two stent types.

Some additional analyses followed that further combed through the data from trials that had compared drug-eluting and bare-metal stents, but, by and large, these metaanalyses have used the same set of studies. For example, a metaanalysis presented by researchers from the Cleveland Clinic last November at the AHA's scientific sessions that focused on paclitaxel-eluting stents added just one additional study (TAXUS VI) to the seven studies of paclitaxel-eluting stents first reviewed by Dr. Eisenberg and his associates. The new analysis, which included a total of nearly 4,000 patients, again showed no statistically significant difference in the stent thrombosis rate between the paclitaxel and bare-metal stents.

"It's quite reassuring that we did not see even a signal of an increased risk of thrombosis," said Dr. Bhatt, a collaborator on this metaanalysis. "The real limitation is that the studies all had built-in treatment with aspirin and clopidogrel. What is unclear is whether there is any increased risk for stent thrombosis, compared with bare-metal stents in patients who are not treated with aspirin and clopidogrel. This has not been addressed."

"It would be very serious if we had to avoid surgery [to avoid stopping aspirin] forever in patients with drug-eluting stents," said David J. Cohen, M.D., associate director of interventional cardiology at Beth Israel Deaconess Medical Center in Boston.

In light of the concern about late thrombosis, Dr. Eisenberg advises physicians to take three actions:

- Reflect on the potential clinical consequences of implanting a drug-eluting stent in a specific patient, and perhaps use a bare-metal stent instead if the patient is known to later need surgery or if the patient's compliance with chronic, antiplatelet therapy is questionable.
- Use registries and postmarketing studies to better define the risk, identify clinical factors that boost a patient's risk, and determine the optimal duration of antiplatelet therapy.
- Develop new strategies to deal with potential interruptions of antiplatelet therapy, including continuing antiplatelet therapy during surgery, and delaying surgery for more than a year after a patient receives a drug-eluting stent. ■

Drug-Eluting Stents Meet Cost-Effectiveness Standards

BY MITCHEL L. ZOLER
Philadelphia Bureau

Each drug-eluting coronary stent costs a hospital an average of $2,500, about $1,800 more than the cost of a similar bare-metal stent.

Although it looks like the price of drug-eluting stents won't change substantially for at least another year, even at current prices they save costs for certain high-risk patients and are cost-effective for the majority of patients undergoing percutaneous coronary interventions, said David J. Cohen, M.D., associate director of interventional cardiology at Beth Israel Deaconess Medical Center in Boston.

Two brands of drug-eluting stents, Cypher and Taxus, currently compete in the U.S. market, and even though most experts say that there is little clinically or technically to favor one over the other, their competition is not likely to lead to a substantial price drop anytime soon.

"Both companies are selling lots of stents, so they may be happy to keep their current market shares," Dr. Cohen said in an interview. The next major shakeup in the market will not come until early next year, when Medtronic is expected to get approval to market a third, competing brand of drug-eluting stent.

Using data collected by Medicare, Dr. Cohen and his associates have calculated that an episode of restenosis following coronary artery stenting costs almost $19,000 per year. Given that the restenosis rate among Medicare beneficiaries who received bare-metal stents was about 14% during the first year following treatment, the cost of restenosis works out to about $2,550 per patient per year.

Based on current costs for drug-eluting stents, and on their ability to cut target-vessel restenosis rates by about 80%, drug-eluting stents will save money if they're used in patients with a restenosis rate of 18% or greater, and drug-eluting stents will meet accepted definitions of cost-effectiveness (costing less than $10,000 for each repeat revascularization prevented) for all patients with a bare-metal stent restenosis rate of 12% or greater. This means that drug-eluting stents are cost-effective for the majority of patients who get them, Dr. Cohen said during a talk at the American Heart Association's scientific sessions last November in New Orleans.

Dr. Cohen and his associates tested these assumptions with data collected from two recent trials. In the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) trial, which compared sirolimus-eluting stents (Cypher) with bare-metal stents, the 1-year incremental cost of the drug-eluting stent was $309 per patient. The cost per repeat revascularization avoided was $1,650, well within the ceiling for cost-effectiveness. Further analysis of these data showed that the sirolimus-eluting stent cost about $27,000 per quality-life year gained, well within the standard maximum of $50,000 per quality-life year gained based on Medicare's dialysis program.

In the TAXUS IV trial paclitaxel-eluting stents (Taxus) were compared with bare-metal stents. The cost-effectiveness rates were $760 for each repeat revascularization avoided and $5,105 for each quality-life year gained. However, the study did not routinely use follow-up angiography and instead relied on clinical assessment of patients.

Dr. Cohen has received research grants from Cordis, which markets the Cypher stent, and from Boston Scientific, which markets the Taxus stent. ■