Stent Data Presented to FDA Panel Are Published

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Results from five new safety analyses of drug-eluting coronary stents, compared with bare-metal stents, gave added reassurance about using drug-eluting stents for their labeled indications and framed some of the concerns about off-label use of the stents.

The five reports were detailed versions of reports that were presented last December to the Circulatory System Devices Advisory Panel of the Food and Drug Administration (N. Engl. J. Med. 2007;981-1039 and 1059-60). The published form of the reports included no changed or added findings and continued to support the panel's December conclusions, said Dr. William H. Maisel, the panel's chairman and author of a perspective article that ran with the new reports.

Four of the five new papers were reanalyses of data previously collected from the studies that led to FDA approval of the sirolimus- and paclitaxel-eluting stents (Cypher and Taxus), and in aggregate the results confirmed that DESs had comparable safety to bare-metal stents (BMSs) with the advantage of a substantial reduction in the need for target lesion revascularization in the uncomplicated patients who were enrolled in these studies.

"There probably is a true increase in the rate of late stent thrombosis in the on-label group, but importantly and equally convincingly there is no evidence of increased mortality or MIs," Dr. Maisel said in an interview.

Because of these findings, "I feel comfortable with drug-eluting stents continuing to be used in that group [on-label patients], and it's the stent of choice in that group, because there is a convincingly marked reduction in the need for repeat revascularization," Dr. Maisel said.

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The meta-analyses are limited by dealing with relatively small numbers of patients. The largest of the overviews included fewer than 5,300 patients, which included both those getting BMSs and those getting DESs. "The statistical power to detect a doubling of risk was well under 50% in all of the analyses," said Dr. Steven Nissen, chairman of cardiovascular medicine at the Cleveland Clinic, in an interview done by the New England Journal of Medicine and released with the papers.

The FDA panel also recommended that all patients who receive DESs should be treated for at least 12 months with a combination of clopidogrel and aspirin. None of the new reports dealt specifically with the impact of dual antiplatelet therapy.

The fifth new article contrasted with the other four by focusing on data collected in a registry of nearly 20,000 patients, all of the patients who received a DES or BMS in Sweden during 2003 and 2004. This study and others like it are considered critical in the safety debate because they deal with "real-world" use of DESs, including thousands of patients who had off-label indications for a DES. Experts estimate that, at least until last summer, about 60% of DES use in the United States was in off-label patients.

The registry analysis showed that during 3 years of follow-up, patients who received DESs had about a 20% increased rate of deaths and of deaths or MIs, compared with patients who received BMSs; both were statistically significant differences.

Experts, including Dr. Maisel, cautioned that in this series the baseline clinical profiles of the patients who received DESs and BMSs had several important differences. The researchers from Uppsala (Sweden) University who did these analyses used a propensity-score method to try to account for this so they could focus entirely on differences between the two stent types. But while a propensity-score analysis is "the best we have" for adjusting a retrospective analysis, "it's not perfect," said Dr. Donald E. Cutlip, a cardiologist at Beth Israel Deaconess Medical Center in Boston and senior author of one of the new studies, in an interview.

Despite the limitations of the Swedish study, it prompted Dr. Nissen to recommend that DES use be limited to on-label patients until the stents are tested in other types of patients in prospective, controlled trials. "You really need at least an 8,000-patient trial. If there is a hazard and the Swedish study is right, then we might regret putting these devices in patients who have not been adequately studied for safety." said Dr. Nissen, a member of the FDA panel, in his interview with the journal.

Current data are inadequate to compare the safety and efficacy of DES, BMS, and coronary bypass surgery in off-label patients, and studies are underway to collect these data, said Dr. Maisel, also a cardiologist at Beth Israel Deaconess Medical Center in Boston. However, it is known that DESs reduce the risk of restenosis and need for revascularization, compared with BMSs, in off-label as well as on-label patients. ■

Thoracic Aortic Aneurysm Endografts: Tips of the Trade

BY KERRI WACHTER
Senior Writer

NEW YORK — While stent grafting of thoracic aortic aneurysm has become more routine, the procedure still has a number of limitations, Martin Malina, Ph.D., said at the Veith symposium on vascular medicine sponsored by the Cleveland Clinic.

Currently-available thoracic endografts are limited by issues of access, hostile neck, deployment, and durability. Dr. Malina, a consultant vascular surgeon at Malmö (Sweden) University Hospital, offered thoughts on these limitations and tips for overcoming them.

► **Access.** "We do have many quite simple tricks to get around this problem," of access said Dr. Malina.

He recommends using an ultra-stiff guidewire. And don't push the graft in. "The more you push, the more the wire buckles," he said. To avoid this, use a brachial wire to pull the graft by placing a clamp at the lower end of the wire. "This way, the more you pull, the more the wire will get straightened out."

Iliac stenosis poses an access problem. One alternative is to make an incision in the groin and to advance the sheath outside of and parallel to the external iliac artery, inserting the graft at a more favorable angle.

► **The neck.** "Very often there is no neck," said Dr. Malina. One option in these cases is to push the stent graft further around the arch, covering the left subclavian artery. Contraindications to this technique include right vertebral stenosis, aberrant right subclavian artery lusoria, and left internal mammary artery coronary bypass.

"In these cases, you still can cover the left subclavian, if you do it first," said Dr. Malina. This can be followed by transposition of the subclavian or carotid-subclavian bypass.

► **Deployment.** "It is actually very hard to assess where the stent graft will be deployed," said Dr. Malina. Whether the carotid artery will be covered is of particular concern, even after the stent has been deployed. Some projections used to view the stent may give the appearance that the carotid artery is not covered, when in fact it is or vice versa. "You have to find the ideal projection ... to really prove that you have not covered the vessel," he said.

► **Durability.** When the stent is deployed at the vertex of an elongated aortic arch, "the blood will hit the upper surface of the stent-graft and you will end up having a flapping motion," which contributes to material fatigue and possibly stent collapse, leading to occlusion or migration and high risk of death. said Dr. Malina. "Also this flapping motion may erode the arch and cause immediate rupture and hemorrhage."

Motion also should be avoided when telescoping the various components, or the stent-graft can disintegrate. Also, without sufficient overlap, the stent can migrate upward. "So wherever you place the stent-graft, you must make sure that you have enough overlap and secure the position of the stent-graft without any motion," said Dr. Malina, who disclosed that he had no conflicts of interest. ■

Stenting, Medical Management of Type B Dissections Fare the Same

NEW YORK — Stent grafts for patients with type B aortic dissections may be no better than best medical management alone in terms of mortality, according to preliminary data presented at the Veith symposium on vascular medicine sponsored by the Cleveland Clinic.

"At 1 year, a slightly higher but not statistically different rate of all-cause mortality was observed in the stent graft arm," said Dr. Christoph A. Nienaber, head of cardiology and vascular medicine at the University of Rostock (Germany).

In the Investigation of Stent Grafts in Patients with Type B Aortic Dissection (INSTEAD) trial, Dr. Nienaber and his colleagues evaluated 1-year all-cause mortality for patients with uncomplicated type B aortic dissections when treated by stent graft as an adjunct to best medical therapy or by best medical treatment alone.

The study was conducted at seven centers across Europe and involved 136 patients. Patients were included if they had a type B dissection between 2 and 52 weeks of duration, the diameter of the target vessel was no larger than 6 cm, and aortic kinking was less than 75 degrees. Patients were excluded if they had thrombocytopenia or were receiving anticoagulation therapy, had renal failure and/or a serum creatinine level greater than 2.4 mg/dL, complete thrombosis of the false lumen, ongoing infection, or cancer with a life expectancy less than 1 year.

In all, 70 patients were randomized to receive thoracic stents (Talent stent graft by Medtronic Inc.) and tailored antihypertensive therapy, while 66 patients were treated with tailored antihypertensive therapy alone.

Patients were clinically evaluated and imaged at 3, 12, and 24 months. Mortality at 1 year was 10% for the stent group and 3% for the medical management group. Of note, seven patients originally in the medical therapy group crossed over to the stent group and two patients originally in the stent group crossed over to the medical therapy group.

"Early complications within 30 days seemed to be more prevalent in the active treatment group ... whereas the later complications, beyond the first month to the end of the first year, were more prevalent and more frequent in the medical group," said Dr. Nienaber.

Standard treatment for Stanford classification type B aortic dissections has been medical management (antihypertensives). However, 1-year survival for patients treated medically is thought to be about 20%, based on various trials and registries.

Dr. Nienaber disclosed that he has no conflicts of interest.

—Kerri Wachter