Off-Label DES Raise Thrombosis Risk, Panel Warns

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GAITHERSBURG, MD. — When used off label, coronary drug-eluting stents are associated with a greater risk of stent thrombosis, death, and myocardial infarction, and this critical information needs to be communicated to physicians and patients, a Food and Drug Administration advisory panel agreed last week.

The safety of drug-eluting stents (DES) was the topic of a 2-day meeting of the FDA's Circulatory System Devices Panel, where expert panelists heard testimony and presentations on DES from FDA officials, manufacturers of the two drug-eluting stents marketed in the United States, and representatives from medical associations and researchers in the United States and Europe. The meeting was convened by the FDA to review the issue of stent thrombosis and the duration of clopidogrel treatment after DES implantation, after concerns about the safety of DES were raised by studies presented at cardiology meetings this year reporting small but significant increases in mortality and MI, possibly due to stent thrombosis in DES recipients, 18 months to 3 years after implantation.

But at least 60% of DES use is off label for conditions that include in-stent restenosis, lesions, coronary artery bypass grafts, overlapping and multiple stents per vessel; in patients with diabetes and those with multivessel disease; and in more complex patients and lesions than were included in the preapproval studies.

The two drug-eluting stents that have been on the U.S. market since 2003 and 2004 are the Cypher sirolimus-eluting coronary stent manufactured by Cordis Corporation, and the Taxus Express paclitaxel-eluting coronary stent system, respectively. The Cypher stent is approved for patients with symptomatic ischemic disease caused by "discrete de novo lesions" that are 30 mm or less in length in native coronary arteries with a reference vessel diameter of at least 2.5 mm to no more than 3.5 mm. The Taxus stent is approved for improving luminal diameter of de novo lesions no more than 28 mm in length, in native coronary arteries of at least 2.5 mm to no more than 3.75 mm in diameter.

The panel unanimously agreed that when used for the approved indications, the safety concerns of drug-eluting stents did not outweigh their benefits, when compared with bare metal stents (BMS). The data indicate that when the stents are used on label, there appears to be a numerical excess of late stent thrombosis in DES recipients, but "the magnitude of that risk is uncertain, based on the available data," said the panel's chair, Dr. William Maisel of Beth Israel Deaconess Medical Center, Boston. There was no association with an increase in deaths or MIs.

But the panel agreed that when used off label for more complex lesions and other uses, drug-eluting stents appeared to be associated with a greater risk of adverse events—stent thrombosis, death, and MI—and that antiplatelet treatment should be extended for at least 12 months after a DES is implanted. This is also true for bare metal stents.

The need for more studies was clear throughout the meeting. "I think we all agree that we need more data, better data, more patients, and larger studies," Dr. Maisel remarked. The panel also agreed there were not enough data to comment on how DES compared with BMS, coronary artery bypass surgery, and medical therapy.

The panel also supported the need for a label change describing the greater risks of off-label use of the stents, and the need to provide patients and physicians with the latest information on safety. "We want physicians and patients to understand" if these stents are used off label, the risk of MI, stent thrombosis, and death is higher than if they are used for approved indications, Dr. Maisel said.

While the panel agreed that more studies were necessary to determine the appropriate duration of antiplatelet therapy after implantation of a DES, they agreed that at least 12 months was appropriate, until more data are available.

At the end of the meeting, Dr. Daniel Schultz, director of the FDA's Center for Devices and Radiological Health, said that it was clear that the FDA needs to communicate the latest information to physicians and patients as soon as possible, after considering the panel's comments. Methods of communicating to physicians may include a dear health care professional letter and a public health advisory. ■