

to ensure a better, more timely exchange of information with the public and to require larger, longer-term post-marketing studies, particularly for permanent medical-device implants.

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The opinions expressed herein are those of the author and do not necessarily represent the practices, policies, positions, or opinions of the FDA.

This article (10.1056/NEJMp068305) was published at www.nejm.org on February 12, 2007.

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Stent Thrombosis Redux — The FDA Perspective

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In the light of recent studies suggesting that drug-eluting stents may pose a risk of thrombosis that was not observed during pre-market testing, the Food and Drug Administration (FDA) convened a meeting of its Circulatory System Devices Advisory Panel on December 7 and 8, 2006, to examine the safety of these devices. The FDA will carefully consider the information and views presented at the meeting in deciding on future actions.

An understanding of the mechanisms of neointimal growth within bare-metal stents led to the development of drug-eluting stents designed to reduce restenosis rates. Both drug-eluting stents approved by the FDA (Cordis's Cypher stent, approved in 2003, and Boston Scientific's Taxus stent, approved in 2004) were shown to be effective in reducing repeated-revascularization rates, as compared with bare-metal stents. Moreover, there

appeared to be no safety disadvantage: studies showed no increase in the rates of stent thrombosis, death, or myocardial infarction up to 1 year after implantation. Drug-eluting stents were therefore enthusiastically adopted in the United States and were soon used in approximately 80% of percutaneous coronary interventions.

Given this widespread use, it should be noted that the FDA-approved indications were limited to newly diagnosed coronary lesions, less than 28 to 30 mm long, in clinically stable patients without additional serious medical conditions. As a condition of approval, and in anticipation of U.S. usage patterns, the FDA required both manufacturers to follow patients in their original clinical trials for 5 years after implantation and to conduct registry studies of consecutively enrolled new patients to collect data on "real-world" use.

Soon after approval, there were reports of subacute stent thrombosis in patients who received Cypher stents. Stent thrombosis is a serious adverse event commonly associated with sudden death or acute myocardial infarction. There are probably multiple risk factors for such events, including complex lesions and coexisting medical conditions. The risk of stent thrombosis may be increased by delayed arterial healing associated with drug-eluting stents. The FDA responded by alerting physicians to these reports in July and October 2003.¹ An update was posted on the FDA Web site in November 2003, indicating that additional data from Cypher clinical trials revealed no increased risk of subacute thrombosis. Although these data were reassuring, detecting thrombosis signals remained a high priority for the FDA.

By early 2006, the agency had formulated several impressions

Randomized Studies of Currently Approved Drug-Eluting Stents That May Result in Expansion of Indications for Use.*						
Trial	Conditions	Treatment Groups	Expected Total Enrollment	Design	Primary End Point	Date Initiated
Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX [ClinicalTrials.gov no., NCT00114972])†	Multivessel coronary disease or disease of the left main coronary artery	Multivessel Taxus stents vs. CABG	1800	Noninferiority	12-mo rate of major adverse cardiac and cerebrovascular events (death from any cause, cerebrovascular event, myocardial infarction, or repeated revascularization)	March 2005
Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM [ClinicalTrials.gov no., NCT00086450])†	Multivessel coronary disease and diabetes mellitus	Multivessel Cypher or Taxus stents vs. CABG	2400	Superiority	Composite of death from any cause, nonfatal myocardial infarction, or stroke measured through 5 yr (minimum of 3 yr of follow-up)	April 2004
Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI)‡	Myocardial infarction with acute ST-segment elevation	Taxus stent vs. identical bare-metal Express stent	3400	Superiority	Efficacy: ischemic target-vessel revascularization at 1 yr Safety: composite of death, reinfarction, stent thrombosis, or stroke at 1 yr	March 2005

* PCI denotes percutaneous coronary intervention, and CABG coronary-artery bypass grafting.

† Information is from ClinicalTrials.gov.

‡ Registration of this trial at ClinicalTrials.gov is pending.

from its review of published reports and the registry studies: the implantation of drug-eluting stents in complex lesions (e.g., bifurcations, lesions requiring overlapping stents, or lesions from acute myocardial infarction) and in patients with conditions such as renal dysfunction or diabetes led to higher rates of stent thrombosis than implantation for the approved indications; the magnitude of the increased risk was small (from <1% to approximately 5%); premature discontinuation of antiplatelet therapy was an independent risk factor for thrombosis; and thrombosis can occur years after implantation.

In September 2006, a meta-analysis of randomized trials suggested that there is a small but significant increase in the risk of

death or Q-wave myocardial infarction throughout a period of 3 years after implantation of a Cypher stent, possibly because of late stent thrombosis.² Another study showed that stent thromboses occurred at a rate of 0.6% per year between 30 days and 3 years after implantation.³ These studies received wide attention, prompting the FDA to convene an advisory panel meeting to review the data.

The panel meeting focused on safety issues and the use of dual antiplatelet therapy. The discussions covered both on-label and off-label use of drug-eluting stents, since it is estimated that more than 60% of use is off-label — for example, the stents are implanted in types of lesions that were excluded from the pivotal trials or in patients such as those

with diabetes who were not sufficiently represented in the trial populations for a specific labeled indication.

The panel agreed, and the FDA concurs, that when drug-eluting stents are used for their approved indications, the risk of thrombosis does not outweigh their advantages over bare-metal stents in reducing the rate of repeated revascularization. But the panel also concluded that, as compared with on-label use, off-label use is associated with increased risks of both early and late stent thrombosis, as well as death or myocardial infarction.

With regard to antiplatelet therapy, data from nonrandomized studies suggest that a more prolonged course of clopidogrel than that recommended in the stent

labels (currently 3 months for recipients of the Cypher stent and 6 months for recipients of the Taxus stent) is beneficial.⁴ Nevertheless, stent thrombosis may occur despite continued dual antiplatelet therapy. Recognizing that the optimal duration of such therapy remains unknown, the panel requested that the instructions for use of both stents include a reference to the current guidelines for percutaneous coronary interventions, which state that dual antiplatelet therapy should be continued for 12 months in patients who are not at high risk for bleeding.⁵

Although the absolute risk appears to be less than 2% throughout the first 3 years after implantation when stents are used for the approved indications, thrombosis with drug-eluting stents is a clinically important problem that may occur long after implantation. It is uncertain whether cases of late stent thrombosis will continue to accrue with longer-term follow-up. Not unexpectedly, the risk of thrombosis increases when drug-eluting stents are used in complex lesions and in patients with coexisting conditions, but the magnitude of this risk as compared with that posed by alternative treatments is unknown. Early discontinuation of antiplatelet therapy is associated with an increased risk of thrombosis, but the optimal duration of clopidogrel treatment remains undefined.

It is also uncertain why the increased rates of stent thrombosis seen more than 1 year after implantation even with on-label

use (0.44% with the Taxus stent vs. 0.07% with bare-metal stents, $P=0.054$; 0.6% with the Cypher stent vs. 0% with bare-metal stents, $P=0.03$) did not translate into in-

As compared with on-label use, off-label use is associated with increased risks of stent thrombosis and death or myocardial infarction.

creased rates of death or myocardial infarction in the randomized studies, despite high rates of morbidity and mortality due to stent thrombosis. It is possible that the samples in the pooled studies were simply not large enough to permit the detection of a difference between treatment groups. Alternatively, increases in the rate of death or myocardial infarction among patients who received drug-eluting stents might have been offset by a reduction in adverse events associated with in-stent restenosis and repeated revascularization.

For infrequent events such as stent thrombosis, large studies are needed to assess risk accurately. The FDA concurs with the panel's recommendation that larger and longer studies be conducted, focusing on important safety

end points (death and myocardial infarction) and on the appropriate duration of dual antiplatelet therapy. The FDA also believes that randomized, controlled trials (see table) are needed to determine the best treatment strategies for lesions in patients with common, complex conditions such as multivessel coronary disease, diabetes, and acute myocardial infarction.

Given the benefits and risks, physicians should consider certain patient characteristics in deciding whether to use a drug-eluting or a bare-metal stent. For example, patients who cannot comply with extended clopidogrel use or have planned procedures requiring early discontinuation of antiplatelet therapy may not be candidates for a drug-eluting stent. Patients should be thoroughly educated about the need for strict adherence to the recommended course of antiplatelet therapy and should discuss any changes with their cardiologist. Health care providers who are considering discontinuation of antiplatelet therapy in order to perform invasive procedures should also consult with the patient's cardiologist.

The safety and effectiveness of drug-eluting stents as compared with those of alternative treatments deserve continued study. The lessons we have learned and the answers to remaining questions will facilitate the development and review of future drug-eluting stents.

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This article (10.1056/NEJMp068304) was published at www.nejm.org on February 12, 2007.

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at <http://www.acc.org/qualityandscience/clinical/guidelines/percutaneous/update/index.pdf>.)

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A discussion between Dr. Donald Baim, chief medical and scientific officer of Boston Scientific, and Dr. Steven Nissen, chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic, on the risks and benefits of drug-eluting stents can be heard at www.nejm.org.