



Unanswered Questions — Drug-Eluting Stents and the Risk of Late Thrombosis

William H. Maisel, M.D., M.P.H.

After recognizing coronary drug-eluting stents as a “breakthrough technology” and granting them expedited review status, the Food and Drug Administration (FDA) approved two such devices

for use in 2003 (Cordis’s sirolimus-eluting Cypher stent) and 2004 (Boston Scientific’s paclitaxel-eluting Taxus stent). Cardiologists quickly embraced the new technology; by the end of 2004, drug-eluting stents were used in nearly 80% of percutaneous coronary interventions in the United States, and within 3 years, several million drug-eluting stents had been implanted worldwide. Recently, however, concerns about an increased risk of late stent thrombosis have arisen and have been exacerbated by insufficient and conflicting information in the public domain.

Initial approval of the two drug-eluting stents was based on the

results of randomized, controlled studies, each involving more than 1000 patients, that showed reduced rates of target-vessel failure, revascularization, or both at 9 months as compared with bare-metal stents. The FDA recognized the need for longer-term data on the devices, and both manufacturers agreed to complete post-approval registries of 2000 U.S. patients to “evaluate the potential for less frequent adverse events.”^{1,2} Registry reports were required at intervals beginning 3 months after approval, and manufacturers were required to follow patients enrolled in their pivotal clinical trials for 5 years.^{1,2}

Despite these efforts to collect longer-term information, concerns about late-term safety were first made public not by the FDA or the manufacturers but by academic and clinical investigators. A March 2006 presentation of the results of the Basel Stent Kosten Effektivitäts Trial — Late Thrombotic Events (BASKET-LATE) suggested that between 7 and 18 months after implantation, the rates of nonfatal myocardial infarction, death from cardiac causes, and angiographically documented stent thrombosis were higher with drug-eluting stents than with bare-metal stents. Over the ensuing 6 months, the two manufacturers of drug-eluting stents issued 19 press releases touting the virtues of these devices and none affirming a risk of late stent thrombosis.

Two additional analyses, presented in September 2006, provid-

ed conflicting results. A meta-analysis of pivotal clinical trials of drug-eluting stents reported an increased rate of death or Q-wave myocardial infarction with sirolimus-eluting stents but not with paclitaxel-eluting stents, whereas a meta-analysis of 17 randomized clinical trials concluded that total long-term mortality did not differ between patients with drug-eluting stents and those with bare-metal stents. In response, the FDA issued a statement noting that “the data we currently have do not allow us to fully characterize the mechanism, risks, and incidence of [drug-eluting-stent] thrombosis.”³ Patients and physicians were bombarded with contradictory headlines (see figure).

Shortly thereafter, the dearth of long-term safety data regarding drug-eluting stents was supplanted by voluminous — and conflicting — information, as numerous meta-analyses, subgroup analyses, regis-

try reports, and press releases contributed to the confusion. Ultimately, in December 2006, the FDA convened a meeting of the Circulatory System Devices Advisory Panel, featuring presentations by regulators, academic physicians, patients, and representatives of industry and medical professional societies.⁴ Two important factors emerged as contributors to the apparent conflicts in data: variable definitions of stent thrombosis and key differences in the characteristics of patients and coronary lesions.

Differences among clinical protocol definitions of stent thrombosis make it difficult to pool studies for analysis and to compare stents. Furthermore, most trials censored stent thromboses that occurred after target-vessel revascularization. Patients with bare-metal stents more often require reintervention, and therefore thrombosis in these patients is censored more frequently, introducing a bias against drug-

eluting stents. An Academic Research Consortium (ARC) composed of clinical investigators, industry representatives, and regulators, including the FDA, has proposed new criteria for classifying stent-thrombosis events in an attempt to establish uniformity, eliminate inappropriate censoring, and improve sensitivity (see reports based on the ARC definitions by Spaulding et al., pages 989–997, and Mauri et al., pages 1020–1029).

The other important factors affecting the performance and safety of drug-eluting stents are the variable characteristics of the patients and their coronary lesions. Approved indications for drug-eluting stents include only the treatment of discrete, previously untreated lesions in native coronary vessels, like those studied in the pivotal clinical trials. However, more than 60% of use is off-label, occurring in patients with complex conditions (such as multivessel disease or acute myocardial infarction) or with complex lesions (for example, saphenous-vein bypass grafts, bifurcating lesions, and chronic total occlusions).

On-label use of drug-eluting stents is associated with a persistent, long-term (≥ 3 -year) reduction in the need for repeated revascularization, without an evident increase in the rates of mortality or myocardial infarction. Although the cumulative incidence of stent thrombosis at 4 years does not differ significantly between patients with drug-eluting stents and those with bare-metal stents (whether the clinical protocol definition or the



ARC definition of stent thrombosis is used), the studies have been underpowered to detect even moderate, clinically significant differences in the true rate of stent thrombosis. The time distribution of thrombotic events, however, does appear to differ: more events occur very late (>1 year) after the implantation of drug-eluting stents than after the implantation of bare-metal stents.

Assessing the incidence of stent thrombosis after off-label use of drug-eluting stents is more challenging because of varying definitions, patient populations, and antiplatelet regimens. Registry data suggest that the rates of adverse events, including death, nonfatal myocardial infarction, and stent thrombosis, are higher with off-label use than with on-label use, although the same holds true for bare-metal stents. Data from the Swedish Coronary Angiography and Angioplasty Registry of more than 19,000 patients (see the report by Lagerqvist et al., pages 1009–1019) did not show a significant difference between patients with drug-eluting stents and those with bare-metal stents in the composite risk of death and myocardial infarction at 3 years of follow-up, although there is a suggestion of an increased risk of death after 6 months in those with drug-eluting stents. Stent selection, however, was not randomized among registry patients, so the observed differences may be due to confounding factors such as physician bias in stent preference. Thus, current data are inadequate for assessment of the relative benefit of off-label

use of drug-eluting stents as compared with either bare-metal stents or coronary-artery bypass surgery.

Product labeling recommends treatment with a thienopyridine

Despite the implantation of millions of drug-eluting stents, much remains uncertain about their long-term safety.

(clopidogrel or ticlopidine) for 3 months after the implantation of sirolimus-eluting stents and 6 months after the implantation of paclitaxel-eluting stents. Lifelong aspirin therapy is recommended with both. The ideal duration of dual antiplatelet therapy, however, is unknown. Premature discontinuation of such therapy appears to be associated with an increased risk of stent thrombosis, although such events do occur in patients who continue to receive dual antiplatelet therapy. Given the available data, clopidogrel treatment should continue for at least 12 months in patients with drug-eluting stents who are at low risk for bleeding.^{4,5} Alternative treatment strategies should be considered in patients who are unable to tolerate uninterrupted dual antiplatelet therapy.

Several important questions

remain unanswered. The magnitude and time course of the increased risk of stent thrombosis remain poorly defined, as do the relative long-term benefits and safety of drug-eluting stents in patients with complex conditions or coronary lesions. In addition, clinical studies are required to determine the ideal duration of antiplatelet therapy after stent implantation. Ultimately, an improved understanding of the coronary vascular response to injury after implantation of a drug-eluting stent will be required in order to develop future generations of devices that can minimize or eliminate the risk of late stent thrombosis.

The turmoil over drug-eluting stents and thrombosis represents both a success and a failure of the U.S. medical-device regulatory system. The FDA should be commended for recognizing the importance of the issue, organizing a panel meeting quickly, facilitating exchange of scientific information, and helping to educate physicians and patients. Unfortunately, despite the 5 years that have elapsed since the start of the clinical trials and the implantation of millions of drug-eluting stents, much remains uncertain about the long-term safety of the devices.

Drug-eluting stents represent an important advance in the management of coronary artery disease and have benefited many patients. In the rush to bring “breakthrough” technologies to market, unanticipated adverse events will inevitably occur. The solution is not to stop expediting the approval of novel products but

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.

Dr. Maisel is a cardiologist at Beth Israel Deaconess Medical Center and an assistant professor of medicine at Harvard Medical School — both in Boston. Dr. Maisel is also chair of the FDA Circulatory System Devices Advisory Panel.

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.

1. Cypher sirolimus-eluting coronary stent on Raptor over-the-wire delivery system or Raptor rail rapid exchange delivery system — P020026: approval order. Rockville, MD: Food and Drug Administration, 2003. (Accessed February 15, 2007, at <http://www.fda.gov/cdrh/pdf2/P020026.html>.)
2. Taxus Express 2 paclitaxel-eluting coronary stent system (monorail and over-the-wire) — P030025: approval order. Rockville, MD: Food and Drug Administration, 2004. (Accessed February 15, 2007, at <http://www.fda.gov/cdrh/pdf3/P030025.html>.)
3. FDA statement on coronary drug-eluting stents. Rockville, MD: Food and Drug Administration, September 14, 2006. (Accessed

February 15, 2007, at <http://www.fda.gov/cdrh/news/091406.html>.)

4. Food and Drug Administration. Circulatory System Devices Advisory Panel transcript for December 8, 2006, meeting. (Accessed February 15, 2007, at <http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4253t2.rtf>.)
5. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention — summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113:156-75.

Copyright © 2007 Massachusetts Medical Society.

Stent Thrombosis Redux — The FDA Perspective

Andrew Farb, M.D., and Ashley B. Boam, M.S.

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