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Case 38-2006: A 5-Year-Old Boy with Headache and Abdominal Pain
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.” 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.” Patients and physicians were bombarded with contradictory headlines (see figure).

Shortly thereafter, the dearth of long-term safety data regarding drug-eluting stents was supplant ed by voluminous — and conflicting — information, as numerous meta-analyses, subgroup analyses, registries 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. 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 (clopidogrel or ticlopidine) for 3 months after the implantation of sirolimus-eluting stents and 6 months after the implantation of paclitaxel-eluting stents. Life-long 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.

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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.

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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. 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
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. Another study showed that stent thromboses occurred at a rate of 0.6% per year between 30 days and 3 years after implantation. 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

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

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.
labels (currently 3 months for recipients of the Cypher stent and 6 months for recipients of the Taxus stent) is beneficial. 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.

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 increased rates of death or myocardial infarction.

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

Dr. Farb is a medical officer, and Ms. Boam the chief of the Interventional Cardiology Devices Branch, of the Office of Device

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 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 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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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.
A Pooled Analysis of Data Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

Patients in four randomized trials comparing sirolimus-eluting coronary-artery stents and bare-metal stents were included in a pooled analysis. At 4 years, there were no significant differences in the rates of death, myocardial infarction, or stent thrombosis between the two groups. A subgroup analysis suggested that mortality was higher among patients with diabetes receiving a sirolimus-eluting stent than among those receiving a bare-metal stent.

See P. 989; Editorial, P. 1059

Safety and Efficacy of Sirolimus- and Paclitaxel-Eluting Coronary Stents

A pooled analysis was performed comparing drug-eluting stents with bare-metal stents in terms of safety and efficacy, using data from four sirolimus-stent trials and five paclitaxel-stent trials. Between 1 and 4 years, stent thrombosis occurred more frequently with both drug-eluting stents. There were no differences between either drug-eluting stent and the bare-metal stent in rates of death or myocardial infarction.

See P. 998; Editorial, P. 1059; CME, P. 1087

Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden

In this large Swedish study of patients with coronary angioplasty, drug-eluting stents were associated with a higher rate of death than bare-metal stents. The higher death rate (and composite of death and myocardial infarction) became apparent after 6 months. The authors suggest that these findings, which might have been related to the discontinuation of clopidogrel therapy, raise uncertainty about the long-term safety of drug-eluting stents.

See P. 1009; Editorial, P. 1059

Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents

Stent thrombosis is a serious complication of treatment with coronary stents. In an analysis using data rejudicated according to criteria set by the Academic Research Consortium, the authors found no increased risk of stent thrombosis with either sirolimus-eluting stents or paclitaxel-eluting stents, as compared with bare-metal stents. However, the power to detect small differences in the risk of stent thrombosis was limited.

See P. 1020; Editorial, P. 1059

Analysis of 14 Trials Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

Sirolimus-eluting coronary-artery stents were compared with bare-metal stents in a pooled analysis of 14 randomized trials. There were no significant differences in the rates of death or myocardial infarction. The early reduction in target-lesion revascularization with the sirolimus-eluting stent was sustained. Rates of stent thrombosis with the sirolimus-eluting stent were at least as high as those with bare-metal stents.

See P. 1030; Editorial, P. 1059

Pediatric Strabismus

A healthy 3-year-old boy presents with a 6-month history of strabismus in his left eye. The visible inward deviation of the eye began intermittently but is now constant. His visual acuity is 20/20 in the right eye but only 20/100 in the left eye. The physical examination is otherwise normal. How should he be treated?

See P. 1040; CME, P. 1085

A 59-Year-Old Woman with Diabetic Renal Disease and Nonhealing Skin Ulcers

A 59-year-old woman with diabetic renal disease was admitted to the hospital because of nonhealing painful ulcers on the right leg and foot. An ulcer on the heel had developed 6 years earlier and persisted despite local treatment, with development of osteomyelitis refractory to antibiotic therapy. A few months before admission, new painful ulcers developed on the right hip and thigh. A procedure was performed.

See P. 1049; CME, P. 1086

Ethical Challenges Posed by the Solicitation of Deceased and Living Organ Donors

Given the shortage of transplantable organs, some potential recipients are going to great lengths to find organ donors on their own. This article reviews the medical, ethical, and public policy issues involved in solicitation, and it suggests possible solutions.

See P. 1062
A Pooled Analysis of Data Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

Christian Spaulding, M.D., Joost Daemen, M.D., Eric Boersma, Ph.D., Donald E. Cutlip, M.D., and Patrick W. Serruys, M.D., Ph.D.

ABSTRACT

BACKGROUND
Although randomized studies have shown a beneficial effect of drug-eluting stents in reducing the risk of repeated revascularization, these trials were underpowered to compare rates of death and myocardial infarction. The long-term safety of drug-eluting stents has been questioned recently.

METHODS
We performed a pooled analysis of 1748 patients in four randomized trials evaluating the safety of sirolimus-eluting stents as compared with bare-metal stents. Patient-level data were obtained and analyzed by independent statisticians at two academic institutions. The primary safety end point was survival at 4 years. We tested for heterogeneities in treatment effect in patient subgroups.

RESULTS
The survival rate at 4 years was 93.3% in the sirolimus-stent group, as compared with 94.6% in the bare-metal–stent group (hazard ratio for death, 1.24; 95% confidence interval [CI], 0.84 to 1.83; P=0.28). In the 428 patients with diabetes, a significant difference in the survival rate was observed in favor of the bare-metal–stent group over the sirolimus-stent group (95.6% vs. 87.8%; hazard ratio for death in the sirolimus-stent group, 2.9; 95% CI, 1.38 to 6.10; P=0.008). The lower survival rate among patients with diabetes who were treated with sirolimus-eluting stents was due to increased numbers of deaths from both cardiovascular and noncardiovascular causes. No difference in survival rate was detected among the patients without diabetes. Rates of myocardial infarction and stent thrombosis were similar in the two groups.

CONCLUSIONS
In a pooled analysis of data from four trials comparing sirolimus-eluting stents and bare-metal stents, no significant differences were found between the two treatments in rates of death, myocardial infarction, or stent thrombosis. (ClinicalTrials.gov numbers, NCT00233805, NCT00381420, NCT00232765, and NCT00235144.)
Since April 2002, randomized trials and registries have shown that drug-eluting stents, as compared with bare-metal stents, reduce the need for subsequent revascularization procedures.1–6 As a result, the use of drug-eluting stents has increased rapidly, with current rates up to 80% of all stenting procedures in some countries. However, two recent meta-analyses have suggested that rates of death and myocardial infarction may be increased in patients who have received drug-eluting stents.7,8 Impaired reendothelialization, late endothelial dysfunction, hypersensitivity reactions to the stent or its coating, and stent thrombosis have been suggested as potential causes.9–17 The consequences of even a slight increase in the rates of death and myocardial infarction would be dramatic, considering the current high rate of use of drug-eluting stents.

The early and pivotal randomized studies that led to approval of stents for marketing were individually not adequately powered to detect differences in the rates of death, myocardial infarction, or stent thrombosis. However, reliable long-term data, including information about these end points, are now available and can be pooled to conduct analyses with greater power than those in the original trials. We therefore performed a safety analysis of patient-level data collected, in four randomized trials comparing sirolimus-eluting stents and bare-metal stents, during a follow-up period of 4 years for 1748 patients.

METHODS

ORIGINAL TRIALS

Our analysis is based on pooled patient-level data from the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL), the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary-Artery Lesions (SIRIUS) trial, the European SIRIUS (E-SIRIUS) trial, and the Canadian SIRIUS (C-SIRIUS) trial, all of which were performed between August 2000 and April 2002. Each of these four trials compared a sirolimus-eluting stent (Cypher, Cordis, a Johnson & Johnson company) with a bare-metal stent of identical design (Bx Velocity, Cordis), but without polymer and drug coatings, implanted in single, previously untreated lesions in native coronary arteries, using a double-blind study design with a 1:1 randomization process.

The designs of these trials, as well as short-term angiographic and clinical outcomes, have been reported previously.1–4 In summary, RAVEL included patients in clinically stable condition with relatively low-risk lesions, whereas the three SIRIUS trials involved patients with higher-risk and more complex lesions. Patients with acute myocardial infarction were excluded in all four trials. A total of 428 patients with diabetes (treated through diet, with an oral hypoglycemic agent, or with insulin) were included.

Dual antiplatelet therapy with aspirin and clopidogrel or ticlopidine was prescribed per protocol for a minimum of 2 months in RAVEL and the E-SIRIUS and C-SIRIUS trials and for a minimum of 3 months in the SIRIUS trial. Aspirin was prescribed indefinitely; doses ranged from 81 to 325 mg daily.

The protocols called for complete angiographic follow-up at 6 months (in RAVEL) or at 8 months (in the SIRIUS, E-SIRIUS, and C-SIRIUS studies) and clinical follow-up yearly. The primary end points differed among the studies and included purely angiographic end points (in-stent late loss in RAVEL and in-stent minimal lumen diameter at 8 months in the E-SIRIUS and C-SIRIUS trials) as well as the clinical end point of target-vessel failure (a composite of death, myocardial infarction, and target-vessel revascularization) in the SIRIUS trial. Secondary end points included death, myocardial infarction, and repeated revascularization.

The study protocols were approved by the ethics committee at each participating institution and were conducted according to the principles of the Declaration of Helsinki. All patients gave written informed consent before enrollment. The studies were sponsored and monitored by Cordis.

The design of each trial specified in advance that data would be collected for up to 5 years, with adjudication of events by the independent end-points committee of the original trial. Four-year follow-up data are currently available from all four studies. All clinical follow-up information was collected at the investigating centers in a blind fashion.

CURRENT ANALYSIS

The databases of the individual studies were obtained from Cordis. Study coordination and data management were performed at two independent central research organizations (Cardialysis, Rotterdam, the Netherlands, for RAVEL, and Harvard
Clinical Research Institute, Boston, for the SIRIUS, E-SIRIUS and C-SIRIUS studies). The patient-level data were pooled and then analyzed by one independent statistician at Harvard Clinical Research Institute and another at Erasmus University Medical Center, Rotterdam. The authors were given unrestricted access to the data by Cordis and made all decisions about analysis and publication independently of the company.

STUDY END POINTS
The primary safety end point was death from any cause. Information on the circumstances of all deaths was obtained from each of the sites, and narratives were developed. These narratives were reviewed by the clinical events committees for the trials and, for the conduct of our analysis, by three of the authors.

Secondary safety end points were death from cardiovascular causes and noncardiovascular causes, death from any cause or Q-wave myocardial infarction, and death from any cause or any type of myocardial infarction. The following definitions of events were used in all four trials.

Death from cardiovascular causes was defined either as death due to acute myocardial infarction, cardiac perforation or pericardial tamponade, arrhythmia or conduction abnormality, cerebrovascular accident within 30 days or related to the procedure, or a complication of the procedure or as any death in which a cardiovascular cause could not be ruled out. Death from noncardiovascular causes was defined as any death not due to a cardiovascular cause.

Q-wave myocardial infarction was defined as the development of new, pathologic Q-waves in two or more contiguous leads as assessed by the electrocardiography core laboratory, with creatine kinase or creatine kinase MB levels elevated above the upper limit of the normal range. Non–Q-wave myocardial infarction was classified on the basis of vessel occlusion on angiography, any recurrent Q-wave myocardial infarction in an area irrigated by the stented vessel, or death from cardiac causes. Late stent thrombosis was diagnosed on the basis of any recurrent myocardial infarction with vessel occlusion on angiography. In the original trial protocols, secondary stent thrombosis — stent thrombosis in a patient who had previously undergone target-lesion revascularization — was not considered to be a stent thrombosis.

Stent thrombosis was reclassified in a blind fashion by an independent research organization (Harvard Clinical Research Institute) according to a set of definitions developed during summer 2006 by the Academic Research Consortium (ARC) of academic investigators, regulators, and industry representatives. These definitions were proposed to serve as standard criteria for stent thrombosis for the comparison of event rates across different trials and studies. According to the ARC definitions, stent thrombosis was classified as acute if it occurred within 24 hours after the index procedure, subacute if it occurred between 1 and 30 days after, late if it occurred between 31 days and 1 year after, and very late if it occurred more than 1 year after the procedure.

Furthermore, stent thrombosis was considered definite if there was angiographic confirmation of thrombus, with or without vessel occlusion, associated with clinical or electrocardiographic signs of acute ischemia or elevation of creatine kinase levels to twice the normal value within 48 hours of angiography. Stent thrombosis was classified as probable if unexplained death occurred within 30 days after the index procedure or if a myocardial infarction, occurring at any time after the index procedure, was documented in an area irrigated by the stented vessel in the absence of angiographic confirmation of stent thrombosis. Stent thrombosis was classified as possible if unexplained death occurred more than 30 days after the index procedure. During the readjudication of stent thrombosis according to the ARC definitions, events occurring after repeated target-lesion revascularization were included.

STATISTICAL ANALYSIS
The effectiveness analysis and safety evaluation were both performed in a modified intention-to-treat population, including all patients who actually underwent stent placement (whether the pro-
Table 1. Baseline Clinical and Angiographic Characteristics.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sirolimus-Stent Group</th>
<th>Bare-Metal–Stent Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
<td>62</td>
<td>0.91</td>
</tr>
<tr>
<td>IQR</td>
<td>54–70</td>
<td>54–70</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>24–92</td>
<td>32–89</td>
<td></td>
</tr>
<tr>
<td>Male sex — no./total no. (%)</td>
<td>629/878 (71.6)</td>
<td>622/870 (71.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Diabetes mellitus — no./total no. (%)</td>
<td>195/878 (22.2)</td>
<td>233/868 (26.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus — no./total no. (%)</td>
<td>51/195 (26.2)</td>
<td>62/233 (26.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Previous MI — no./total no. (%)</td>
<td>287/865 (33.2)</td>
<td>308/862 (35.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>Previous PCI — no./total no. (%)</td>
<td>201/878 (22.9)</td>
<td>184/869 (21.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Previous coronary-artery bypass graft — no./total no. (%)</td>
<td>66/878 (7.5)</td>
<td>64/870 (7.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hyperlipidemia — no./total no. (%)</td>
<td>613/866 (70.8)</td>
<td>617/859 (71.8)</td>
<td>0.63</td>
</tr>
<tr>
<td>Hypertension — no./total no. (%)</td>
<td>557/873 (63.8)</td>
<td>548/866 (63.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Current smoker — no./total no. (%)</td>
<td>183/862 (21.2)</td>
<td>210/858 (24.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Congestive heart failure — no./total no. (%)</td>
<td>36/869 (4.1)</td>
<td>49/861 (5.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>CCS angina classification III or IV — no./total no. (%)†</td>
<td>344/831 (41.4)</td>
<td>344/831 (41.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Silent ischemia — no./total no. (%)</td>
<td>152/783 (19.4)</td>
<td>155/793 (19.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Ejection fraction — %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
<td>60</td>
<td>0.55</td>
</tr>
<tr>
<td>IQR</td>
<td>50–64</td>
<td>50–65</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>25–91</td>
<td>25–89</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-vessel</td>
<td>538/876 (61.4)</td>
<td>531/868 (61.2)</td>
<td>0.92</td>
</tr>
<tr>
<td>Double-vessel</td>
<td>216/876 (24.7)</td>
<td>236/868 (27.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Triple-vessel</td>
<td>122/876 (13.9)</td>
<td>101/868 (11.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Procedure success — no./total no. (%)</td>
<td>858/877 (97.8)</td>
<td>852/868 (98.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Target vessel — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>408/878 (46.5)</td>
<td>407/870 (46.8)</td>
<td>0.98</td>
</tr>
<tr>
<td>LCx</td>
<td>210/878 (23.9)</td>
<td>207/870 (23.8)</td>
<td>0.90</td>
</tr>
<tr>
<td>RCA</td>
<td>254/878 (28.9)</td>
<td>254/870 (29.2)</td>
<td>0.96</td>
</tr>
<tr>
<td>LMCA</td>
<td>3/878 (0.3)</td>
<td>3/870 (0.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>SVG</td>
<td>0</td>
<td>1/870 (0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Severe calcification — no./total no. (%)</td>
<td>37/755 (4.9)</td>
<td>26/754 (3.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>Total occlusion — no./total no. (%)</td>
<td>25/875 (2.9)</td>
<td>20/870 (2.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Disease of branch vessel — no./total no. (%)</td>
<td>55/755 (7.3)</td>
<td>46/755 (6.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Modified ACC–AHA lesion class — no./total no. (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>61/875 (7.0)</td>
<td>61/870 (7.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>B1</td>
<td>297/875 (33.9)</td>
<td>317/870 (36.4)</td>
<td>0.28</td>
</tr>
<tr>
<td>B2</td>
<td>320/875 (36.6)</td>
<td>332/870 (38.1)</td>
<td>0.50</td>
</tr>
<tr>
<td>C</td>
<td>197/875 (22.5)</td>
<td>161/870 (18.5)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
procedure was successful or not). Patients who were randomly assigned to treatment but who did not undergo a procedure were not included in the analysis.

Summary statistics for all continuous variables are presented as medians and interquartile ranges. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between the sirolimus-stent group and the bare-metal–stent group were analyzed using the Wilcoxon–Mann–Whitney test or Fisher's exact test.

The incidence of events over time was studied with the use of the Kaplan–Meier method, whereas log-rank tests and Cox proportional-hazards regression analyses were applied to evaluate differences between the two groups. In the main analysis, hazard ratios and 95% confidence intervals (CIs) were adjusted for differences in outcome between trials. Follow-up at 1, 2, and 3 years was completed for 99.1%, 97.8%, and 96.3% of the patients, respectively. Because follow-up data for the period between 1441 and 1460 days were lacking in 675 patients, we decided to count events through 1440 days, which was interpreted as 4 years of follow-up. This 4-year follow-up was completed in 90.7% of patients (90.5% of those who received sirolimus-eluting stents and 90.9% of those who received bare-metal stents).

Exploratory analyses (not prespecified) were performed to evaluate possible heterogeneities in treatment effects on mortality according to the trial in which the patient was enrolled and the following 10 clinically relevant characteristics: age, sex, diabetes, dyslipidemia, hypertension, prior myocardial infarction, heart failure, angina classification by the Canadian Cardiovascular Society, number of diseased vessels, and left ventricular ejection fraction. Since a clinically relevant difference in treatment effect on mortality was observed in relation to diabetes status, we decided to study other end points in patients with and those without diabetes. Treatment effects were evaluated with the use of Cox regressions that included a term for the interaction between each characteristic of interest and the assigned treatment, adjusted for differences in outcome between trials. More extensive regression models incorporating predictive baseline characteristics were applied to estimate the adjusted treatment effects.

All statistical tests were two-sided, without correction for multiple testing. P values of less than 0.05 and less than 0.01 were considered to indicate statistical significance for the results of non-heterogeneity tests and tests for heterogeneity in treatment effect, respectively. All statistical analyses were performed with the use of SAS software, version 8.2 (SAS Institute).

**RESULTS**

A total of 1748 patients were included in this analysis (238 in RAVEL, 1058 in the SIRIUS study, 100 in the C-SIRIUS study, and 352 in the E-SIRIUS.
study). In total, 878 patients underwent placement of a sirolimus-eluting stent, and 870 patients underwent placement of a bare-metal stent. The clinical and angiographic characteristics of the study patients are summarized in Table 1. Complex lesions were more frequent in patients with sirolimus-eluting stents than in patients with bare-metal stents (22.5% vs. 18.5%, $P=0.04$), and diabetes was more common in the bare-metal–stent group than in the sirolimus-stent group (26.8% vs. 22.2%, $P=0.02$).

Results for all patients are shown in Table 2 and Figure 1. The 4-year cumulative survival rate was slightly, but not significantly, lower in the sirolimus-stent group than in the bare-metal–stent group (93.3% and 94.6%, respectively; hazard ratio for death in the sirolimus group, 1.24; 95% CI, 0.84 to 1.83; $P=0.28$). Narratives of all patient deaths revealed that mortality from both cardiovascular and noncardiovascular causes was slightly, but not significantly, higher in the sirolimus-stent group (Table 2 and the Supplementary Appendix, available with the full text of this article at www.nejm.org). Rates of myocardial infarction overall were similar between the two groups. Rates of Q-wave myocardial infarction were also slightly, but not significantly, higher in the sirolimus-stent group.

Table 2. Incidences of Death, Myocardial Infarction, and Stent Thrombosis after 1440 Days of Follow-up.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Sirolimus-Stent Group (N=878)</th>
<th>Bare-Metal–Stent Group (N=870)</th>
<th>Adjusted Hazard Ratio (95% CI) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>57 (6.7)</td>
<td>46 (5.4)</td>
<td>1.24 (0.84–1.83)</td>
</tr>
<tr>
<td>Cardiovascular cause</td>
<td>29 (3.5)</td>
<td>23 (2.7)</td>
<td>1.26 (0.73–2.18)</td>
</tr>
<tr>
<td>Noncardiovascular cause</td>
<td>28 (3.3)</td>
<td>23 (2.8)</td>
<td>1.22 (0.70–2.11)</td>
</tr>
<tr>
<td>MI</td>
<td>55 (6.4)</td>
<td>53 (6.2)</td>
<td>1.03 (0.71–1.51)</td>
</tr>
<tr>
<td>Q-wave</td>
<td>18 (2.1)</td>
<td>11 (1.3)</td>
<td>1.64 (0.78–3.47)</td>
</tr>
<tr>
<td>Non–Q-wave</td>
<td>37 (4.3)</td>
<td>43 (5.0)</td>
<td>0.85 (0.55–1.33)</td>
</tr>
<tr>
<td>Death or Q-wave MI</td>
<td>70 (8.2)</td>
<td>55 (6.5)</td>
<td>1.28 (0.90–1.82)</td>
</tr>
<tr>
<td>Death or any MI</td>
<td>100 (11.6)</td>
<td>90 (10.5)</td>
<td>1.11 (0.83–1.47)</td>
</tr>
</tbody>
</table>

Stent thrombosis as defined in protocols†

| Acute                         | 0                              | 0                               | —                                    |
| Subacute                      | 4 (0.5)                        | 1 (0.1)                         | 4.02 (0.45–35.98)                     | 0.21                                 |
| Late                          | 6 (0.7)                        | 4 (0.5)                         | 1.50 (0.42–5.30)                      | 0.53                                 |

Stent thrombosis as defined by the ARC‡

| Acute                         | 0                              | 0                               | —                                    |
| Subacute                      | 4 (0.5)                        | 3 (0.5)                         | 1.34 (0.30–5.93)                      | 0.70                                 |
| Late                          | 3 (0.3)                        | 11 (1.3)                        | 0.18 (0.04–0.81)                      | 0.03                                 |
| Very late                     | 23 (2.8)                       | 14 (1.7)                        | 1.65 (0.85–3.20)                      | 0.14                                 |
| Definite                      | 10 (1.2)                       | 7 (0.8)                         | 1.43 (0.54–3.76)                      | 0.47                                 |
| Definite or probable          | 13 (1.5)                       | 15 (1.8)                        | 0.87 (0.41–1.82)                      | 0.70                                 |
| Any                           | 30 (3.6)                       | 28 (3.3)                        | 1.07 (0.64–1.79)                      | 0.80                                 |

* All percentages are based on Kaplan–Meier estimates. Numbers of patients for death or Q-wave myocardial infarction (MI) and death or any MI do not total the sums for each end point alone because some patients had both end points. CI denotes confidence interval.
† Definitions of stent thrombosis according to the study protocols were as follows: acute, within 24 hours after the procedure; subacute, within 1 to 30 days after; and late, more than 30 days after.
‡ Definitions of stent thrombosis according to the Academic Research Consortium (ARC) were as follows: acute, within 24 hours after the procedure; subacute, within 1 to 30 days after; late, between 31 days and 1 year after; and very late, more than 1 year after. See text for details on stent-thrombosis adjudication per protocol and per ARC definitions.
According to the protocol definitions, there were 10 stent thromboses in the sirolimus-stent group and 5 in the bare-metal–stent group (Table 2). Five of the thromboses in the sirolimus-stent group, but none in the bare-metal–stent group, occurred after 1 year. In contrast, according to the ARC definitions, there were 30 stent thromboses in the sirolimus-stent group and 28 in the bare-metal–stent group (Fig. 2). Stent thrombosis was more frequent in the bare-metal–stent group in the first year (14, vs. 6 in the sirolimus-stent group), whereas very late stent thrombosis (occurring after the first year) was more frequent in the sirolimus-stent group (23, vs. 14 in the bare-metal–stent group).

Significant heterogeneity in the treatment effects was not found for any of the prespecified subgroups except patients with diabetes (P value for interaction = 0.008) (see the Supplementary Appendix). The 4-year cumulative survival rates among patients without diabetes did not differ significantly between the two groups. However, the survival rate for patients with diabetes was significantly lower in the sirolimus-stent group (87.8%, vs. 95.6% in the bare-metal–stent group; hazard ratio for death, 2.90; 95% CI, 1.38 to 6.10; P=0.008) (Fig. 3 and the Supplementary Appendix). A large heterogeneity in the causes of death of the patients with diabetes precluded the identification of a clear pattern of mortality (see the Supplementary Appendix). Among the patients with diabetes, there was a small excess of very late stent thrombosis as defined by the ARC (occurring more than 1 year after the procedure) in the sirolimus-stent group (11 patients, vs. 3 in the bare-metal–stent group) (see the Supplementary Appendix).

**Discussion**

In this study, we performed a pooled analysis of four randomized trials comparing sirolimus-eluting stents and bare-metal stents in 1748 patients with 4 years of follow-up. We did not find evidence of a significantly higher rate of death, myocardial...
infarction, or stent thrombosis in the patients treated with sirolimus-eluting stents. The divergence of the Kaplan–Meier survival curves over time could be interpreted as a growing trend toward a lower survival rate among patients treated with sirolimus-eluting stents as compared with those treated with bare-metal stents, although a larger number of patients, a longer follow-up period, or both would be necessary to confirm this interpretation.

In our study, we analyzed rates of stent thrombosis adjudicated according to the definitions in the original protocols and those of the ARC. We believe that this provides a more accurate picture of the incidence of stent thrombosis with either type of stent, for two reasons. First, late events such as unexplained death, which were not considered in the original protocols, were adjudicated as possible stent thrombosis. Second, all episodes of stent thrombosis, including those occurring after target-lesion revascularization, were included in the readjudicated event rates.

A significant heterogeneity of the treatment effect was found with respect to diabetes. A significantly reduced survival rate was found among patients with diabetes (but not patients without diabetes) treated with sirolimus-eluting stents. Deaths from cardiovascular and noncardiovascular causes were more frequent in the sirolimus-stent group. In the subgroup of patients with diabetes, very late stent thrombosis was adjudicated more frequently among the patients with sirolimus-eluting stents than among those with bare-metal stents. Owing to the low number of events, these findings should be interpreted with caution; it does not appear that they adequately explain the observed difference in survival among patients with diabetes in the two groups.

Previous studies have reached different conclusions regarding the benefit of drug-eluting stents in patients with diabetes. The 9-month results of a dedicated randomized trial of patients with diabetes showed that sirolimus-eluting stents were superior to bare-metal stents in reducing rates of both restenosis and repeated revascularization. Mortality at 9 months was only 1% in the sirolimus-stent group, as compared with 2% in the bare-metal–stent group. Conversely, the 2-year follow-up of 708 patients with diabetes from a large registry on the use of drug-eluting stents revealed a mortality of 13.3% among patients treated with sirolimus-eluting stents, as compared with 9.8% among patients treated with bare-metal stents. Although the difference in mortality was not significant, a hazard ratio for death of 1.55 remained after a propensity analysis. In addition, the rate of angiographically proven stent thrombosis in that study was 4.4% in the sirolimus-stent group but only 0.8% in the bare-metal–stent group. Finally, diabetes has been shown to be a consistent independent predictor of stent thrombosis in patients treated with drug-eluting stents.

Several limitations of our study should be considered. The analysis was underpowered to detect a clinically significant difference in mortality; more than 11,000 patients would have been needed for such an analysis. Patients included in the
four randomized trials were highly selected and are representative of only about 25% of patients currently treated with drug-eluting stents. Treatment with clopidogrel was required for at least 2 or 3 months, according to the original trial protocols, but no information on actual use by individual patients, even by those who had adverse events, was available. Thus, we cannot provide any specific insight into the question of whether prolonging dual antiplatelet therapy further would reduce the risk of such events. We performed multiple subgroup analyses that were not prespecified, including one for diabetes. The number of fatal events in patients with diabetes was small, so the related findings may be due to chance. Finally, lower-than-expected mortality was noted among the patients with diabetes in the bare-metal–stent group, for reasons that remain unclear.

In summary, in our pooled analysis of data from four randomized trials, we compared the effects of sirolimus-eluting stents with those of bare-metal stents on clinical events at 4 years. No significant differences in the rates of death, myocardial infarction, or stent thrombosis were found.

Dr. Spaulding reports receiving consulting and lecture fees from Cordis, Boston Scientific, and Guidant. No other potential conflict of interest relevant to this article was reported.

We thank Dr. J. Massaro (Harvard Clinical Research Institute, Boston) for the statistical analysis; H.-P. Stoll (Cordis, Waterloo, Belgium) for his assistance in the transfer of the data; and Drs. M.C. Morice, J.W. Moses, E. Schampaert, and J. Schofer for their roles as the principal investigators of the four randomized trials: RAVEL, SIRIUS, C-SIRIUS, and E-SIRIUS, respectively.

REFERENCES

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Safety and Efficacy of Sirolimus- and Paclitaxel-Eluting Coronary Stents

Gregg W. Stone, M.D., Jeffrey W. Moses, M.D., Stephen G. Ellis, M.D., Joachim Schofer, M.D., Keith D. Dawkins, M.D., Marie-Claude Morice, M.D., Antonio Colombo, M.D., Erick Schampaert, M.D., Eberhard Grube, M.D., Ajay J. Kirtane, M.D., Donald E. Cutlip, M.D., Martin Fahy, M.Sc., Stuart J. Pocock, Ph.D., Roxana Mehran, M.D., and Martin B. Leon, M.D.

ABSTRACT

Background
The safety of drug-eluting stents has been called into question by recent reports of increased stent thrombosis, myocardial infarction, and death. Such studies have been inconclusive because of their insufficient size, the use of historical controls, a limited duration of follow-up, and a lack of access to original source data.

Methods
We performed a pooled analysis of data from four double-blind trials in which 1748 patients were randomly assigned to receive either sirolimus-eluting stents or bare-metal stents and five double-blind trials in which 3513 patients were randomly assigned to receive either paclitaxel-eluting stents or bare-metal stents; we then analyzed the major clinical end points of the trials.

Results
The 4-year rates of stent thrombosis were 1.2% in the sirolimus-stent group versus 0.6% in the bare-metal–stent group (P=0.20) and 1.3% in the paclitaxel-stent group versus 0.9% in the bare-metal–stent group (P=0.30). However, after 1 year, there were five episodes of stent thrombosis in patients with sirolimus-eluting stents versus none in patients with bare-metal stents (P=0.025) and nine episodes in patients with paclitaxel-eluting stents versus two in patients with bare-metal stents (P=0.028). The 4-year rates of target-lesion revascularization were markedly reduced in both the sirolimus-stent group and the paclitaxel-stent group, as compared with the bare-metal–stent groups. The rates of death or myocardial infarction did not differ significantly between the groups with drug-eluting stents and those with bare-metal stents.

Conclusions
Stent thrombosis after 1 year was more common with both sirolimus-eluting stents and paclitaxel-eluting stents than with bare-metal stents. Both drug-eluting stents were associated with a marked reduction in target-lesion revascularization. There were no significant differences in the cumulative rates of death or myocardial infarction at 4 years.
By reducing neointimal hyperplasia after vascular injury, drug-eluting coronary-artery stents decrease late luminal loss (the difference between the minimal luminal diameter immediately after the procedure and the diameter at 6 months) and angiographic restenosis, as compared with bare-metal stents. This decrease, in turn, reduces the need for subsequent revascularization procedures. Despite these benefits, drug-eluting stents may engender adverse arterial responses, including delayed endothelialization and hypersensitivity to the polymeric coating that regulates drug dose and release kinetics. Recent reports from randomized trials and observational studies using historical controls have suggested that drug-eluting stents may be associated with increased rates of late stent thrombosis and death, as compared with bare-metal stents. These studies have been inconclusive, however, because of an insufficient number of patients, the absence of concurrent controls, a limited duration of follow-up, and a lack of access to original source data. Since more than 1 million of these permanent bioactive devices are implanted in patients annually, understanding the relative safety and efficacy of drug-eluting stents represents a major public health imperative.

To address the limitations of previous studies, we performed a pooled analysis of data from four double-blind trials in which patients were randomly assigned to receive polymer-based sirolimus-eluting stents or bare-metal stents and five double-blind trials in which patients were randomly assigned to receive polymer-based paclitaxel-eluting stents or bare-metal stents. We report on the safety and efficacy of drug-eluting stents with 4-year follow-up after device implantation.

**METHODS**

**STUDY DESCRIPTION**

The databases from four prospective, multicenter, double-blind, placebo-controlled randomized trials of sirolimus-eluting stents versus bare-metal stents were obtained from Cordis. These trials were the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary-Artery Lesions (RAVEL), the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary-Artery Lesions (SIRIUS), and the smaller European and Lat- in American (E-SIRIUS) and Canadian (C-SIRIUS) trials. Similarly, the databases from five prospective, multicenter, double-blind, placebo-controlled, randomized trials of paclitaxel-eluting stents versus bare-metal stents were obtained from Boston Scientific. These trials consisted of the studies TAXUS-I, TAXUS-II, TAXUS-IV, TAXUS-V, and TAXUS-VI. These specific trials were selected because they are the only double-blind trials that compared each of the drug-eluting stents with bare-metal controls and that also served as the basis for the approval of the drug-eluting stents in the United States and Europe. In both cases, permission was obtained for the performance of an unrestricted, patient-level pooled analysis.

Details of the design and conduct of each of the trials included in these analyses have been reported previously. In each trial, patients with a single previously untreated native coronary-artery lesion were prospectively and randomly assigned in equal proportion to receive either a drug-eluting stent or an otherwise equivalent bare-metal stent. Entry criteria, device specifications, and geographic location varied somewhat, as outlined in Table 1. At the time of this report, the patients, investigators, study personnel, and sponsors were still unaware of assignments to study groups, with follow-up continuing to 5 years. Data regarding the use of aspirin and a thienopyridine were not consistently captured during follow-up. However, data on the use of antiplatelet drugs at the time of late thrombosis associated with drug-eluting stents were obtained from the manufacturers of both drug-eluting stents. No agreements with the sponsors regarding data confidentiality exist.

**END POINTS AND DEFINITIONS**

The goals of our study were to determine the short-term and long-term safety and efficacy of drug-eluting stents as compared with bare-metal stents. Before receiving the study databases, we specified that we would examine the following end points: stent thrombosis, as defined in the study protocols (see the Supplementary Appendix, available with the full text of this article at www.nejm.org); revascularization of the target lesion or target vessel; any myocardial infarction and Q-wave and non–Q-wave myocardial infarction; death from any cause and from cardiac and noncardiac causes; composite death or myocardial infarction; composite death or Q-wave myocardial infarction; and composite death from car-
### Table 1. Characteristics of the Study Trials.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of Patients</th>
<th>Geographic Location</th>
<th>Stent Platform</th>
<th>Drug-Release Kinetics</th>
<th>Reference-Vessel Diameter (mm)</th>
<th>Lesion Length (mm)</th>
<th>Minimum Administration of Clopidogrel</th>
<th>Clinical Follow-up Attained</th>
<th>Routine Angiographic Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sirolimus-stent trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVEL&lt;sup&gt;1&lt;/sup&gt;</td>
<td>238</td>
<td>Global</td>
<td>Bx Velocity</td>
<td>Slow</td>
<td>2.5–3.5</td>
<td>&lt;18</td>
<td>2</td>
<td>At 4 yr, 225 patients (94.5%)</td>
<td>At 6 mo, 211 patients (88.7%)</td>
</tr>
<tr>
<td>SIRIUS&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1058</td>
<td>United States</td>
<td>Bx Velocity</td>
<td>Slow</td>
<td>2.5–3.5</td>
<td>15–30</td>
<td>3</td>
<td>At 4 yr, 1025 patients (96.9%)</td>
<td>At 8 mo, 703 patients (66.4%)</td>
</tr>
<tr>
<td>E-SIRIUS&lt;sup&gt;3&lt;/sup&gt;</td>
<td>352</td>
<td>Europe</td>
<td>Bx Velocity</td>
<td>Slow</td>
<td>2.5–3.0</td>
<td>15–32</td>
<td>2</td>
<td>At 4 yr, 344 patients (97.7%)</td>
<td>At 8 mo, 308 patients (87.5%)</td>
</tr>
<tr>
<td>C-SIRIUS&lt;sup&gt;4&lt;/sup&gt;</td>
<td>100</td>
<td>Canada</td>
<td>Bx Velocity</td>
<td>Slow</td>
<td>2.5–3.0</td>
<td>15–32</td>
<td>2</td>
<td>At 4 yr, 98 patients (98.0%)</td>
<td>At 8 mo, 88 patients (88.0%)</td>
</tr>
<tr>
<td><strong>Paclitaxel-stent trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXUS-I&lt;sup&gt;5&lt;/sup&gt;</td>
<td>61</td>
<td>Germany</td>
<td>NIRx</td>
<td>Slow</td>
<td>3.0–3.5</td>
<td>≤12</td>
<td>6</td>
<td>At 4 yr, 61 patients (100.0%)</td>
<td>At 6 mo, 59 patients (96.7%)</td>
</tr>
<tr>
<td>TAXUS-II&lt;sup&gt;6&lt;/sup&gt;</td>
<td>536</td>
<td>Global</td>
<td>NIRx</td>
<td>Slow and moderate</td>
<td>3.0–3.5</td>
<td>≤12</td>
<td>6</td>
<td>At 4 yr, 515 patients (96.1%)</td>
<td>At 6 mo, 520 patients (97.0%)</td>
</tr>
<tr>
<td>TAXUS-IV&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1314</td>
<td>United States</td>
<td>Express</td>
<td>Slow</td>
<td>2.5–3.75</td>
<td>10–28</td>
<td>6</td>
<td>At 4 yr, 1236 patients (94.1%)</td>
<td>At 9 mo, 559 patients (42.5%)</td>
</tr>
<tr>
<td>TAXUS-V&lt;sup&gt;8&lt;/sup&gt;</td>
<td>1156</td>
<td>United States</td>
<td>Express2</td>
<td>Slow</td>
<td>2.25–4.0</td>
<td>10–46</td>
<td>6</td>
<td>At 2 yr, 1100 patients (95.2%)</td>
<td>At 9 mo, 990 patients (85.6%)</td>
</tr>
<tr>
<td>TAXUS-VI&lt;sup&gt;9&lt;/sup&gt;</td>
<td>446</td>
<td>Europe</td>
<td>Express2</td>
<td>Moderate</td>
<td>2.5–3.75</td>
<td>18–40</td>
<td>6</td>
<td>At 3 yr, 433 patients (97.1%)</td>
<td>At 9 mo, 417 patients (93.5%)</td>
</tr>
</tbody>
</table>

<sup>*</sup> ClinicalTrials.gov numbers are as follows: RAVEL, NCT00233805; SIRIUS, NCT00232765; E-SIRIUS, NCT00235144; C-SIRIUS, NCT00381420; TAXUS-II, NCT00299026; TAXUS-IV, NCT00292474; TAXUS-V, NCT00301522; and TAXUS-VI, NCT00297804.
Safety and Efficacy of Drug-Eluting Stents

Diabetic causes or myocardial infarction. The following time periods were prespecified for analysis of event rates: the time from stent implantation until 30 days after implantation, from 30 days after implantation until the latest follow-up, from 30 days after implantation until 1 year, from 1 year after implantation until the latest follow-up, and from the time of stent implantation until the latest follow-up.

We used data from the original databases, as defined and adjudicated by the clinical events committees for each study, in our analysis. Since the individual adverse-event narratives and original source documents were not available to us, readjudication of individual events to accommodate common definitions was not possible.

**Statistical Analysis**

We compared categorical variables by the chi-square test or Fisher’s exact test. Continuous variables are described as means (±SD) and were compared by means of unpaired t-tests. At the time of this report, we had access to 5-year data from RAVEL and TAXUS-I; 4-year data from SIRIUS, E-SIRIUS, C-SIRIUS, TAXUS-II, and TAXUS-IV; 3-year data from TAXUS-VI; and 2-year data from TAXUS-V. We used Kaplan–Meier time-to-event estimates for the primary analyses, which were compared with the log-rank or exact log-rank test. Analyses were truncated at 4 years of follow-up owing to the small number of patients with data thereafter. We included data from all patients that were analyzed in each of the original study reports in our analysis, with follow-up data censored at the time of first event (for each specific event curve) or latest known follow-up. The Breslow–Day test for heterogeneity demonstrated that trials involving sirolimus-eluting stents and paclitaxel-eluting stents were sufficiently homogeneous to justify the pooled analyses performed. All P values are two-sided.

**Results**

**Patients**

A total of 1748 patients were randomly assigned to study groups and underwent percutaneous coronary intervention in the RAVEL and three SIRIUS trials comparing sirolimus-eluting stents with bare-metal stents (the sirolimus-stent trials). Another 3513 patients were randomly assigned to study groups and underwent percutaneous coronary intervention in the five TAXUS trials comparing paclitaxel-eluting stents with bare-metal stents (the paclitaxel-stent trials). The baseline demographic, procedural, and angiographic characteristics of the patients were well matched in both sets of trials (Table 2), except that in the sirolimus-stent trials, diabetes was slightly more prevalent among patients who received bare-metal stents than among those who received sirolimus-eluting stents. The lengths of lesions and total implanted stents were both greater in the paclitaxel-stent trials than in the sirolimus-stent trials (reflecting varying criteria for trial entry), although more stents per patient were used in the sirolimus-stent trials. Baseline reference measures of vessel diameter and lesion severity were similar for stenoses treated with both types of drug-eluting stents and for those treated with bare-metal stents.

**Stent Thrombosis**

From stent implantation through 4-year follow-up, the rates of stent thrombosis among patients with sirolimus-eluting stents did not differ significantly from those with bare-metal stents (1.2% and 0.6%, respectively; P=0.20) (Table 3 and Fig. 1 and 2). Similarly, there were no significant differences in the 4-year cumulative rates of stent thrombosis between patients with paclitaxel-eluting stents and those with bare-metal stents (1.3% and 0.9%, respectively; P=0.30). However, between 1 and 4 years, the rates of stent thrombosis in the sirolimus-stent group and the bare-metal–stent group were 0.6% versus none (P=0.025, consistent with one extra event per 489 patient-years); during the same period, the rates in the paclitaxel-stent group and the bare-metal–stent group were 0.7% versus 0.2% (P=0.028, consistent with one extra event per 557 patient-years). After 1 year, of the five patients who had late thrombosis associated with sirolimus-eluting stents, two patients were taking aspirin and clopidogrel, two were taking only aspirin, and one was taking no antiplatelet agent. Of the nine patients with late thrombosis associated with paclitaxel-eluting stents, three were taking only aspirin, and five were taking no antiplatelet agent; the status of one patient is unknown.

**Revascularization**

Both drug-eluting stents markedly reduced the rates of target-lesion revascularization and tar-

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**R E S U L T S**

**P A T I E N T S**

A total of 1748 patients were randomly assigned to study groups and underwent percutaneous coronary intervention in the RAVEL and three SIRIUS trials comparing sirolimus-eluting stents with bare-metal stents (the sirolimus-stent trials). Another 3513 patients were randomly assigned to study groups and underwent percutaneous coronary intervention in the five TAXUS trials comparing paclitaxel-eluting stents with bare-metal stents (the paclitaxel-stent trials). The baseline demographic, procedural, and angiographic characteristics of the patients were well matched in both sets of trials (Table 2), except that in the sirolimus-stent trials, diabetes was slightly more prevalent among patients who received bare-metal stents than among those who received sirolimus-eluting stents. The lengths of lesions and total implanted stents were both greater in the paclitaxel-stent trials than in the sirolimus-stent trials (reflecting varying criteria for trial entry), although more stents per patient were used in the sirolimus-stent trials. Baseline reference measures of vessel diameter and lesion severity were similar for stenoses treated with both types of drug-eluting stents and for those treated with bare-metal stents.
get-vessel revascularization at 4 years (Table 3). The difference in the rates of clinical restenosis peaked at approximately 1 year and then remained stable through 4 years of follow-up (Fig. 1 and 2). In the cohort of patients undergoing routine angiographic follow-up, both drug-eluting stents greatly reduced late luminal loss and binary re- 
sstenosis, as compared with bare-metal stents, both in-stent (within the stent margins) and in-seg-
ment (in-stent plus 5 mm proximal and distal mar-
gins) (see the Supplementary Appendix for de-
tails).

Deaths and Myocardial Infarction

The cumulative 4-year rate of death from any cause in the sirolimus-stent group did not differ significantly from that in the bare-metal–stent group (6.7% vs. 5.3%, P=0.23); the difference in rates between the paclitaxel-stent group and the bare-metal–stent group was also not significant (6.1% vs. 6.6%, P=0.68) (Table 3 and Fig. 1 and 2). Cumulative rates of death from any cause and from cardiac and noncardiac causes were also similar in both drug-eluting–stent groups and the bare-metal–stent group at 4 years (Table 3) and during each prespecified interval (Supplementary Appendix).

The cumulative 4-year rates of myocardial in-
farction were similar in the sirolimus-stent group and the bare-metal–stent group (6.4% vs. 6.2%, P=0.86) and in the paclitaxel-stent group and the bare-metal–stent group (7.0% vs. 6.3%, P=0.66), with no significant differences in the rates of Q-wave or non–Q-wave myocardial infarction (Table 3 and Fig. 1 and 2). The rates of myocar-
dial infarction were also similar in both drug-

Table 2. Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sirolimus-Eluting Stent</th>
<th>Bare-Metal Stent</th>
<th>P Value</th>
<th>Paclitaxel-Eluting Stent</th>
<th>Bare-Metal Stent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>61.9±11.1</td>
<td>61.9±10.7</td>
<td>0.91</td>
<td>62.4±10.8</td>
<td>62.2±10.6</td>
<td>0.49</td>
</tr>
<tr>
<td>Male sex — no./total no. (%)</td>
<td>629/878 (71.6)</td>
<td>622/870 (71.5)</td>
<td>0.96</td>
<td>1271/1755 (72.4)</td>
<td>1278/1758 (72.7)</td>
<td>0.88</td>
</tr>
<tr>
<td>Diabetes — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any type</td>
<td>195/878 (22.2)</td>
<td>233/868 (26.8)</td>
<td>0.03</td>
<td>408/1755 (23.2)</td>
<td>419/1758 (23.8)</td>
<td>0.69</td>
</tr>
<tr>
<td>Requiring insulin</td>
<td>51/878 (5.8)</td>
<td>62/868 (7.1)</td>
<td>0.28</td>
<td>127/1729 (7.3)</td>
<td>138/1730 (8.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hypertension — no./total no. (%)</td>
<td>557/873 (63.8)</td>
<td>548/866 (63.3)</td>
<td>0.84</td>
<td>1217/1755 (69.3)</td>
<td>1191/1754 (67.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyperlipidemia — no./total no. (%)</td>
<td>613/866 (70.8)</td>
<td>617/859 (71.8)</td>
<td>0.67</td>
<td>1230/1744 (70.5)</td>
<td>1237/1751 (70.6)</td>
<td>0.94</td>
</tr>
<tr>
<td>Current smoker — no./total no. (%)</td>
<td>183/862 (21.2)</td>
<td>210/858 (24.5)</td>
<td>0.12</td>
<td>413/1742 (23.7)</td>
<td>401/1749 (22.9)</td>
<td>0.60</td>
</tr>
<tr>
<td>Target coronary artery — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>408/875 (46.6)</td>
<td>407/872 (46.7)</td>
<td>1.00</td>
<td>733/1744 (42.0)</td>
<td>730/1752 (41.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>181/875 (20.7)</td>
<td>181/872 (20.8)</td>
<td>1.00</td>
<td>444/1744 (25.5)</td>
<td>419/1752 (23.9)</td>
<td>0.31</td>
</tr>
<tr>
<td>Right coronary</td>
<td>254/875 (29.0)</td>
<td>254/872 (29.1)</td>
<td>1.00</td>
<td>560/1744 (32.1)</td>
<td>592/1752 (33.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Left main coronary</td>
<td>3/875 (0.3)</td>
<td>3/872 (0.3)</td>
<td>1.00</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Saphenous-vein graft</td>
<td>0/875</td>
<td>1/872 (&lt;0.1)</td>
<td>0.50</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Reference vessel diameter — mm</td>
<td>2.72±0.45</td>
<td>2.72±0.48</td>
<td>0.98</td>
<td>2.74±0.51</td>
<td>2.74±0.51</td>
<td>0.83</td>
</tr>
<tr>
<td>Minimal luminal diameter — mm</td>
<td>0.94±0.37</td>
<td>0.93±0.36</td>
<td>0.50</td>
<td>0.91±0.35</td>
<td>0.91±0.37</td>
<td>0.58</td>
</tr>
<tr>
<td>Diameter stenosis — %</td>
<td>65.2±11.9</td>
<td>65.7±11.6</td>
<td>0.47</td>
<td>67.0±10.9</td>
<td>66.8±11.5</td>
<td>0.59</td>
</tr>
<tr>
<td>Lesion length — mm</td>
<td>13.8±5.7</td>
<td>13.9±5.9</td>
<td>0.96</td>
<td>15.1±7.9</td>
<td>15.1±8.0</td>
<td>0.88</td>
</tr>
<tr>
<td>No. of stents</td>
<td>1.42±0.69</td>
<td>1.39±0.61</td>
<td>0.38</td>
<td>1.21±0.48</td>
<td>1.19±0.46</td>
<td>0.19</td>
</tr>
<tr>
<td>Total stent length — mm</td>
<td>22.9±9.0</td>
<td>22.5±8.1</td>
<td>0.31</td>
<td>24.4±11.2</td>
<td>24.1±11.1</td>
<td>0.45</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. NA denotes not applicable.
Table 3. Clinical Outcomes at 4 Years, According to Kaplan–Meier Estimates.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sirolimus-Eluting Stent (N = 878)</th>
<th>Bare-Metal Stent (N = 870)</th>
<th>Paclitaxel-Eluting Stent (N = 1755)</th>
<th>Bare-Metal Stent (N = 1758)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. (%)</td>
<td>Hazard Ratio (95% CI)† P Value‡</td>
<td>no. (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>10 (1.2)</td>
<td>5 (0.6)</td>
<td>2.00 (0.68–5.85) 0.20</td>
<td>20 (1.1)</td>
</tr>
<tr>
<td>0 to 30 days after procedure</td>
<td>4 (0.5)</td>
<td>1 (0.1)</td>
<td>4.50 (0.14–13.62) 0.23</td>
<td>8 (0.5)</td>
</tr>
<tr>
<td>&gt;30 days to 1 yr after procedure</td>
<td>6 (0.7)</td>
<td>4 (0.5)</td>
<td>1.50 (0.42–5.30) 0.57</td>
<td>12 (0.8)</td>
</tr>
<tr>
<td>&gt;1 to 4 yr after procedure</td>
<td>5 (0.6)</td>
<td>0 (0)</td>
<td>0 (95% CI)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td>1.00 (0.03–3.22) 1.00</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>From all causes</td>
<td>57 (6.7)</td>
<td>45 (5.3)</td>
<td>1.27 (0.88–1.88) 0.23</td>
<td>86 (6.1)</td>
</tr>
<tr>
<td>0 to 30 days after procedure</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>1.00 (0.06–1.89) 1.00</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>&gt;30 days to 1 yr after procedure</td>
<td>10 (1.1)</td>
<td>6 (0.7)</td>
<td>1.66 (0.60–4.56) 0.32</td>
<td>84 (5.0)</td>
</tr>
<tr>
<td>&gt;1 to 4 yr after procedure</td>
<td>29 (3.3)</td>
<td>23 (2.7)</td>
<td>1.20 (0.73–2.28) 0.40</td>
<td>38 (2.4)</td>
</tr>
<tr>
<td>From myocardial causes</td>
<td>22 (2.7)</td>
<td>22 (2.7)</td>
<td>1.07 (0.73–2.23) 0.40</td>
<td>50 (3.1)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>57 (6.4)</td>
<td>53 (6.2)</td>
<td>1.03 (0.71–1.51) 0.86</td>
<td>111 (7.0)</td>
</tr>
<tr>
<td>Patients with any event</td>
<td>55 (6.4)</td>
<td>53 (6.2)</td>
<td>1.03 (0.71–1.51) 0.86</td>
<td>111 (7.0)</td>
</tr>
<tr>
<td>0 to 30 days after procedure</td>
<td>22 (2.5)</td>
<td>17 (2.0)</td>
<td>1.20 (0.66–2.32) 0.43</td>
<td>66 (3.8)</td>
</tr>
<tr>
<td>&gt;30 days to 1 yr after procedure</td>
<td>34 (4.1)</td>
<td>37 (4.4)</td>
<td>0.91 (0.52–1.54) 0.69</td>
<td>55 (3.1)</td>
</tr>
<tr>
<td>&gt;1 to 4 yr after procedure</td>
<td>23 (2.8)</td>
<td>18 (2.2)</td>
<td>1.28 (0.77–2.37) 0.43</td>
<td>36 (2.1)</td>
</tr>
<tr>
<td>Q-wave</td>
<td>23 (2.8)</td>
<td>18 (2.2)</td>
<td>1.28 (0.77–2.37) 0.43</td>
<td>36 (2.1)</td>
</tr>
<tr>
<td>Non-Q-wave</td>
<td>18 (4.5)</td>
<td>11 (2.6)</td>
<td>1.64 (0.97–2.74) 0.19</td>
<td>22 (1.4)</td>
</tr>
<tr>
<td>Death or myocardial infarction</td>
<td>100 (11.6)</td>
<td>89 (10.4)</td>
<td>1.12 (0.78–1.61) 0.59</td>
<td>183 (11.2)</td>
</tr>
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<td>Death or Q-wave myocardial infarction or death from cardiac causes</td>
<td>70 (8.2)</td>
<td>70 (8.2)</td>
<td>1.00 (0.77–1.32) 1.00</td>
<td>105 (7.3)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>66 (7.8)</td>
<td>70 (8.2)</td>
<td>1.07 (0.77–1.48) 0.49</td>
<td>19 (8.9)</td>
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<td>Target lesion</td>
<td>102 (12.1)</td>
<td>102 (12.1)</td>
<td>1.00 (0.78–1.28) 1.00</td>
<td>103 (7.6)</td>
</tr>
</tbody>
</table>

* Percentages are cumulative Kaplan–Meier estimates, taking into account data from patients who were lost to follow-up at different times, and may thus differ from simple binary estimates. Only the first event was counted within any interval. CI denotes confidence interval.

The estimate was calculated from a Cox proportional-hazards model.

P values were calculated by a two-sided log-rank test or exact log-rank test.

§ One patient had two episodes of stent thrombosis, one before 1 year and one after 1 year.
eluting–stent groups and bare-metal–stent group at all prespecified time periods, except that there were significantly fewer myocardial infarctions in the paclitaxel-stent group than in the bare-metal–stent group between 30 days after implantation and 1 year (0.8% vs. 1.8%, P = 0.01).

There were no differences in the 4-year composite rates of death or myocardial infarction, death or Q-wave myocardial infarction, or myocardial infarction or death from cardiac causes between either drug-eluting stent and its control (Table 3) or at any interval time period (Supplementary Appendix), except that between 30 days after implantation and 1 year, the composite rate of myocardial infarction or death from cardiac causes was lower in the paclitaxel-stent group than in the bare-metal–stent group (1.4% vs. 2.5%, P = 0.03). This reduction in rate was driven by a lower rate of non–Q-wave myocardial infarction in the paclitaxel-stent group than in the bare-metal–stent group (0.4% vs. 1.6%, P<0.001).

**DISCUSSION**

We performed a patient-level pooled meta-analysis of four randomized, double-blind trials of sirolimus-eluting stents versus bare-metal stents and five randomized, double-blind trials of paclitaxel-eluting stents versus bare-metal stents in single, previously untreated coronary lesions through...
4 years of follow-up. The principal findings were that although the overall rates of stent thrombosis were not significantly increased with drug-eluting stents, both sirolimus-eluting stents and paclitaxel-eluting stents were associated with a small but significant increase in the incidence of late stent thrombosis between 1 and 4 years after implantation. In addition, both drug-eluting stents were associated with marked reductions in ischemic target-lesion revascularization and target-vessel revascularization, an advantage that was maintained through 4 years of follow-up. The rates of death or myocardial infarction were not significantly different between the groups with drug-eluting stents and the control groups, either at 4 years of follow-up or between 1 and 4 years.

The number of episodes of stent thrombosis within the first year were identical among patients with sirolimus-eluting stents and those with bare-metal stents (5 patients with episodes in each group) and among patients with paclitaxel-eluting stents and those with bare-metal stents (12 patients in each group). Between 1 and 4 years, however, there were modest increases in stent thrombosis in both groups with drug-eluting stents, as compared with the control groups (14 patients with episodes in the groups with drug-eluting stents vs. 2 patients in the bare-metal–stent groups — a finding that is consistent with
approximately one extra stent thrombosis per 500 patient-years of treatment with drug-eluting stents). Although our study does not identify the potential causes of late stent thrombosis, possible causes include delayed or incomplete endothelialization, late polymer reactions, strut fractures, positive remodeling with stent malapposition with or without aneurysm formation, and new plaque rupture either adjacent to or within the stented site, among others.\textsuperscript{10-13,18,19}

Our study also demonstrates a marked and persistent reduction in target-lesion revascularization and target-vessel revascularization with both drug-eluting stents, as compared with bare-metal stents. The maximal difference between drug-eluting stents and bare-metal stents in clinical restenosis occurred by 1 year, with the hazard curves remaining parallel between 1 and 4 years. In this regard, the durability of clinical efficacy for drug-eluting stents during late follow-up stands in contradistinction to the “catch-up” phenomenon of late restenosis noted after coronary brachytherapy.\textsuperscript{20,21} Although the performance of routine angiographic follow-up may have increased the absolute difference in the rates of clinical restenosis between drug-eluting stents and bare-metal stents, the relative benefit is unlikely to have been affected.\textsuperscript{22}

No significant differences in the cumulative 4-year rates of death or myocardial infarction were observed between patients receiving either drug-eluting stents or bare-metal stents. It is possible that reductions in the rates of death or myocardial infarction that otherwise might result from prevention of restenosis by drug-eluting stents may be offset by adverse events resulting from late stent thrombosis. In-stent restenosis presents as acute myocardial infarction in 3.5 to 19.4% of patients\textsuperscript{23-26} and as such is not always a benign process. However, the majority of episodes of stent thrombosis present as death or myocardial infarction.\textsuperscript{27,28} Thus, a large reduction in a phenomenon with moderate clinical risk (restenosis) may be offset by a small increase in a phenomenon with high clinical risk (stent thrombosis).

It is important to note that stent thromboses occurring subsequent to any target-lesion revascularization were excluded from the counts of episodes of stent thrombosis in most of the trials (see the definitions of stent thrombosis in the Supplementary Appendix).\textsuperscript{29} The purpose of this exclusion was to ensure that only episodes of stent thrombosis related to the original stent were included. However, the procedures to treat restenosis (balloon angioplasty, brachytherapy, or additional stenting) may result in “secondary” episodes of stent thrombosis. Such secondary stent thromboses would be expected to be more common with bare-metal stents, since revascularization procedures are much more common with these stents. Indeed, in an unpublished analysis, when such secondary episodes were considered, no overall or late differences in the patient-level rates of stent thrombosis between drug-eluting stents and bare-metal stents were present.\textsuperscript{29} Since data regarding death and myocardial infarction were not censored after target-lesion revascularization, greater rates of restenosis and secondary thrombosis with bare-metal stents than with drug-eluting stents probably contributed to the similar observed overall rates of death and myocardial infarction between the stent types in our analysis. Given the difficulties in defining stent thrombosis in the absence of angiographic confirmation or results on autopsy, greater emphasis should be placed on the occurrence of death and myocardial infarction, in our opinion, rather than on stent thrombosis, as indicative of the overall safety profile of a coronary intervention. Moreover, given the observation that the directional effect of drug-eluting stents on subsequent stent thrombosis, revascularization, death, and myocardial infarction may vary, we believe that composite measures combining safety and efficacy end points should be avoided in future trials of antirestenotic devices.

Our findings differ from those of some other investigators, who have suggested, on the basis of trial-level meta-analyses, that overall rates of stent thrombosis and death are higher with drug-eluting stents than with bare-metal stents.\textsuperscript{16,17} These discrepancies may be partially explained by the fact that we had access to the complete patient-level data from the trials we examined and did not have to rely on an estimation of event rates from limited published results, abstracts, and online summaries. We also confined our analysis to a precisely defined subgroup of clinical trials involving drug-eluting stents, whereas some previous analyses have also included later studies that were not double-blind.\textsuperscript{16}

Several limitations of our analysis deserve comment. First, given the relatively infrequent occurrence of death, myocardial infarction, and stent thrombosis, larger studies with longer-term fol-
low-up are required to detect small differences in event rates. Moreover, we made no adjustments for the multiple end points examined. The interval data analyses in particular should be considered hypothesis-generating. Second, our analysis is most applicable for patients with single, previously untreated coronary lesions, as reflected in the labels for sirolimus-eluting stents (lesions as long as 30 mm in vessels of 2.5 to 3.5 mm in diameter) and paclitaxel-eluting stents (lesions as long as 28 mm in vessels of 2.5 to 3.75 mm in diameter) that were approved by the Food and Drug Administration. The rates of stent thrombosis and the relative risk–benefit ratio of drug-eluting stents versus bare-metal stents may vary in the “real world,” in which stents are implanted in more complex scenarios (i.e., “off-label” use).²⁷,²⁸

Third, the nine studies we analyzed used different clinical sites, adjudication committees, and core laboratories, with possible differences in definitions and processes. Fourth, the paclitaxel-stent trials included both the commercial slow rate–release formulation and the noncommercialized moderate rate–release formulation. However, the results were directionally similar with both devices, and no major differences have been described between the two versions of this stent.⁶

Fifth, in five of the trials, the protocol-specified definitions of stent thrombosis after 30 days required angiographic confirmation and may therefore underestimate the true event rate. Sixth, pooling of the data from sirolimus-stent trials and paclitaxel-stent trials was avoided, since the mechanisms underlying the safety and efficacy of these two types of stents may differ. Given the different entry criteria for types of lesions in the two groups of trials, as well as the different bare-metal stents used as controls, comparisons across the two pooled meta-analyses may not be valid. Finally, detailed data regarding the use of antiplatelet medication throughout the follow-up period were not available, precluding firm recommendations regarding the optimal duration of thienopyridine administration.

In conclusion, our study examined the relative safety and efficacy of drug-eluting stents, as compared with bare-metal stents, in a pooled, patient-level analysis of double-blind, randomized trial data. The use of both sirolimus-eluting stents and paclitaxel-eluting stents was associated with a small but significant increase in the incidence of late stent thrombosis between 1 and 4 years after implantation, as compared with that of bare-metal stents. We also reconfirmed the marked benefit of both types of drug-eluting stents in reducing the need for subsequent revascularization procedures, with persistence of this benefit through 4 years of follow-up. We found no significant differences between drug-eluting stents and bare-metal stents in the rates of death or myocardial infarction.

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**References**

6. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the ef-
SAFETY AND EFFICACY OF DRUG-ELUTING STENTS


Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden

Bo Lagerqvist, M.D., Ph.D., Stefan K. James, M.D., Ph.D.,
Ulf Stenestrand, M.D., Ph.D., Johan Lindbäck, M.Sc., Tage Nilsson, M.D., Ph.D.,
and Lars Wallentin, M.D., Ph.D., for the SCAAR Study Group*

ABSTRACT

BACKGROUND

Recent reports have indicated that there may be an increased risk of late stent thrombosis with the use of drug-eluting stents, as compared with bare-metal stents.

METHODS

We evaluated 6033 patients treated with drug-eluting stents and 13,738 patients treated with bare-metal stents in 2003 and 2004, using data from the Swedish Coronary Angiography and Angioplasty Registry. The outcome analysis covering a period of up to 3 years was based on 1424 deaths and 2463 myocardial infarctions and was adjusted for differences in baseline characteristics.

RESULTS

The two study groups did not differ significantly in the composite of death and myocardial infarction during 3 years of follow-up. At 6 months, there was a trend toward a lower unadjusted event rate in patients with drug-eluting stents than in those with bare-metal stents, with 13.4 fewer such events per 1000 patients. However, after 6 months, patients with drug-eluting stents had a significantly higher event rate, with 12.7 more events per 1000 patients per year (adjusted relative risk, 1.20; 95% confidence interval [CI], 1.05 to 1.37). At 3 years, mortality was significantly higher in patients with drug-eluting stents (adjusted relative risk, 1.18; 95% CI, 1.04 to 1.35), and from 6 months to 3 years, the adjusted relative risk for death in this group was 1.32 (95% CI, 1.11 to 1.57).

CONCLUSIONS

Drug-eluting stents were associated with an increased rate of death, as compared with bare-metal stents. This trend appeared after 6 months, when the risk of death was 0.5 percentage point higher and a composite of death or myocardial infarction was 0.5 to 1.0 percentage point higher per year. The long-term safety of drug-eluting stents needs to be ascertained in large, randomized trials.
Prospective, randomized clinical trials have shown that in-stent restenosis is reduced by the use of drug-eluting stents, as compared with bare-metal stents. On the basis of prospective trials involving approximately 4500 patients, the U.S. Food and Drug Administration approved the use of drug-eluting stents for patients with previously untreated coronary lesions of less than 30 mm in length and a reference-vessel diameter of 2.50 to 3.75 mm. In these trials, the use of drug-eluting stents appeared to be safe, with no significant increase in cardiovascular events, as compared with bare-metal stents. However, the use of drug-eluting stents has rapidly been expanded to all types of patients, including those with more complicated coronary lesions and in acute settings.

Recently, pathoanatomical studies and meta-analyses of randomized trials and registries have raised concern about incomplete neointimal coverage with a subsequent increase in late stent thromboses in patients with drug-eluting stents. One randomized trial indicated that the implantation of drug-eluting stents was associated with an early reduction in death and myocardial infarction — an improvement that was lost during the subsequent 6 to 18 months by a late increase in the same events. Since there have been no prospective, randomized clinical trials involving long-term follow-up of the “off-label” use of drug-eluting stents, we determined that the evaluation of large clinical registries might provide useful information concerning the long-term efficacy and safety of drug-eluting stents. Therefore, we evaluated the long-term outcome in all patients who underwent stent implantation in Sweden in 2003 and 2004, as recorded in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), and conducted a follow-up analysis of death and myocardial infarction, using other national registries.

Methods

Study Population

Our study included all patients in Sweden who had received coronary stents from January 1, 2003, to December 31, 2004, for whom complete follow-up data were available from other national registries. The analyses were based on the type of stent implanted at the first recorded procedure, in which patients who received at least one drug-eluting stent were assigned to the drug-eluting-stent group, regardless of whether they had received another type of stent at any time; otherwise, patients were assigned to the bare-metal–stent group. In a sensitivity analysis, we separately evaluated the cohort of patients who had received only one stent (the one-stent subgroup) at the initial percutaneous coronary intervention (PCI).

SCAAR Data

SCAAR holds data on consecutive patients from all 26 centers that perform coronary angiography and PCI in Sweden. The registry is sponsored by the Swedish Health Authorities and is independent of commercial funding. The technology is developed and administered by the Uppsala Clinical Research Center. Since 2001, SCAAR has been Internet-based, with recording of data online through a Web interface in the catheterization laboratory; data are transferred in an encrypted format to a central server at the Uppsala Clinical Research Center. All consecutive patients undergoing coronary angiography or PCI are included. We compiled a list of the most important recorded variables in accordance with international recommendations (Table 1). Information with respect to restenosis has been registered for patients undergoing subsequent coronary angiography for clinical reasons since the beginning of 2004. The Internet-based system provides each center with immediate and continuous feedback on processes and quality-of-care measures. Monitoring and verification of registry data have been performed in all hospitals since 2001 by comparing 50 entered variables in 20 randomly selected interventions per hospital and year with the patients’ hospital records. The overall correspondence in data during the study period was 95.2%. By December 31, 2005, information on approximately 255,000 procedures had been collected in SCAAR.

The long-term follow-up was based on merging the SCAAR database with other national registries on the basis of the unique 10-digit personal identification number of each Swedish citizen. Data on vital status and date of death were obtained from the national population registry through June 30, 2006. We obtained data regarding hospital admissions for myocardial infarction (as defined in the International Classification of Diseases, 10th revision, disease codes, I21 and I22)
from the Swedish Hospital Discharge Registry through December 31, 2005, except for one small county (with 417 patients) in which myocardial infarction could be evaluated only through December 31, 2004. The merging of the registries was performed by the Epidemiologic Center of the Swedish National Board of Health and Welfare and was approved by the local ethics committee at Uppsala University.

STATISTICAL ANALYSIS
We summarized baseline characteristics of the patients with medians and interquartile ranges for continuous variables and percentages for discrete variables. Cumulative event rates were estimated by the Kaplan–Meier method. The primary objective was to evaluate late-occurring events after the implantation of drug-eluting stents. The primary end point was the composite of death or myocardial infarction. Secondary end points were death, myocardial infarction, revascularization, and restenosis. To compensate for the non-randomized design of our observational study, we used propensity-score methods. The individual propensity scores, defined as the conditional probability of obtaining a drug-eluting stent based on available covariables, were estimated with a multiple logistic-regression model. All prespecified covariates were included in the respective models for the two study populations as well as several interaction terms (Table 1). The predictive ability of each propensity-score model was evaluated by means of the C statistic.

To provide separate descriptions of the early and late relative risks of events, we performed a “landmark analysis” with a prespecified landmark set at 6 months. Adjusted relative risks were estimated from models in which the propensity score and the stent group were entered as covariates. For plotting purposes, the models were then refitted with the stent group as a stratification variable, and adjusted cumulative event rates were estimated at the overall average propensity score. Further addition of any of the variables that had already been incorporated through the propensity score did not materially alter the results. Death was regarded as a censoring event in the analysis of myocardial infarction. This analysis led to results that were similar to those obtained when the cumulative incidence of myocardial infarction was estimated in a competing-risks framework (data not shown). All reported P values are two-sided. All analyses were performed with the use of the statistical program R, version 2.4.0.

RESULTS

CHARACTERISTICS OF THE PATIENTS
During 2003 and 2004, a total of 19,771 patients were treated with 37,750 stents in 24,215 PCI procedures in Sweden and were entered into the database. Table 1 shows the characteristics of the 6033 patients with drug-eluting stents and 13,738 patients with bare-metal stents. The factor with the largest influence on the choice of stent was the geographic region. The use of drug-eluting stents ranged from 0.4 to 62.5% among centers and from 0.6 to 40.8% among geographic regions. On average, as compared with patients who received bare-metal stents, patients with drug-eluting stents were slightly younger and were more likely to be women; they also had a higher prevalence of diabetes mellitus, hypertension, heart failure, and renal dysfunction, and stable angina was more likely to be the indication for the procedure. Among patients with drug-eluting stents, pretreatment with clopidogrel was more common, but the periprocedural use of glycoprotein IIb/IIIa inhibitors was less common. In the group with drug-eluting stents, more patients had undergone PCIs and coronary-artery bypass grafting (CABG), had multi-vessel and left main coronary artery disease, and had a higher number of implanted stents. Patients with bare-metal stents were older, were more likely to be men, and more often had primary PCIs for myocardial infarction with ST-segment elevation as the indication for receiving a stent. In the one-stent subgroup, the drug-eluting stents were generally longer and had smaller diameters than the bare-metal stents. Among the 3638 patients with drug-eluting stents in the one-stent subgroup, paclitaxel-eluting stents (Taxus Express, Boston Scientific) were used in 2608 patients (72%) and sirolimus-eluting stents (Cypher and Cypher Select, Cordis, Johnson & Johnson) in 1030 patients (28%).

DEATH AND MYOCARDIAL INFARCTION
During the entire study period, 3887 events occurred, including 2463 myocardial infarctions (1713 in the group with bare-metal stents and 750 in the group with drug-eluting stents) and 1424 deaths (999 in the group with bare-metal stents).
<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients with Stents</th>
<th>One-Stent Subgroup</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Bare-Metal Stent (N = 13,738)</td>
<td>Drug-Eluting Stent (N = 6033)</td>
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<td>Age</td>
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<td>Median — yr</td>
<td>66</td>
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<td>2,539</td>
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<td>2,427 (17.7)</td>
<td>1686 (27.9)</td>
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<td>3,636 (26.5)</td>
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<td>West</td>
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<td>Never smoked</td>
<td>1,694 (12.4)</td>
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<td>Diabetes — no. (%)</td>
<td>19,771</td>
<td>2,140 (15.6)</td>
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<td>Hypertension — no. (%)</td>
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<td>5,961 (43.6)</td>
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<td>Previous PCI — no. (%)</td>
<td>19,343</td>
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<td>Previous myocardial infarction — no. (%)</td>
<td>19,771</td>
<td>5,046 (36.7)</td>
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<td>19,763</td>
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<td>19,729</td>
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<td>Cancer &lt;3 yr before procedure — no. (%)</td>
<td>19,656</td>
<td>389 (2.8)</td>
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<td>Previous heart failure — no. (%)</td>
<td>19,771</td>
<td>963 (7.0)</td>
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<td>Previous stroke — no. (%)</td>
<td>19,771</td>
<td>801 (5.8)</td>
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<td>Glycoprotein IIb/IIIa inhibitors — no. (%)</td>
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Table 1. (Continued.)

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<th>Variable</th>
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<td>Bare-Metal Stent (N = 13,738)</td>
<td>Drug-Eluting Stent (N = 6033)</td>
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<td>No. of stents — no. (%)</td>
<td>19,757</td>
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<td>1</td>
<td>10,319 (75.2)</td>
<td>3638 (60.3)</td>
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<td>2</td>
<td>2,574 (18.8)</td>
<td>1680 (27.9)</td>
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<td>≥3</td>
<td>833 (6.1)</td>
<td>713 (11.8)</td>
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<td>19,271</td>
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<td>Not significant</td>
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<td>2-vessel disease</td>
<td>3,765 (28.3)</td>
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<td>3-vessel disease</td>
<td>2,199 (16.5)</td>
<td>1069 (17.9)</td>
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<td>Left main coronary artery disease (with or without other coronary disease)</td>
<td>491 (3.7)</td>
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<td>&lt;2.5 mm</td>
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<td>2.5 to &lt;3.0 mm</td>
<td>2,314 (22.5)</td>
<td>1203 (33.3)</td>
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<td>3.0 to &lt;3.5 mm</td>
<td>3,897 (37.9)</td>
<td>1311 (36.2)</td>
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<td>3.5 to &lt;4 mm</td>
<td>2,663 (25.9)</td>
<td>744 (20.6)</td>
</tr>
<tr>
<td>≥4 mm</td>
<td>1,061 (10.3)</td>
<td>32 (0.9)</td>
</tr>
<tr>
<td>Stent length — no. (%)</td>
<td>13,910</td>
<td></td>
</tr>
<tr>
<td>&lt;10 mm</td>
<td>864 (8.4)</td>
<td>182 (5.0)</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>3,074 (29.9)</td>
<td>792 (21.8)</td>
</tr>
<tr>
<td>15–16 mm</td>
<td>2,767 (26.9)</td>
<td>796 (21.9)</td>
</tr>
<tr>
<td>17–19 mm</td>
<td>1,313 (12.8)</td>
<td>341 (9.4)</td>
</tr>
<tr>
<td>20–23 mm</td>
<td>1,092 (10.6)</td>
<td>675 (18.6)</td>
</tr>
<tr>
<td>24–25 mm</td>
<td>716 (7.0)</td>
<td>382 (10.5)</td>
</tr>
<tr>
<td>26–30 mm</td>
<td>304 (3.0)</td>
<td>187 (5.2)</td>
</tr>
<tr>
<td>≥31 mm</td>
<td>153 (1.5)</td>
<td>272 (7.5)</td>
</tr>
<tr>
<td>Restenotic lesion — no. (%)</td>
<td>13,877</td>
<td>121 (1.2)</td>
</tr>
<tr>
<td>Treated vessel — no. (%)</td>
<td>13,951</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>3,463 (33.6)</td>
<td>557 (15.3)</td>
</tr>
<tr>
<td>Left main coronary artery</td>
<td>99 (1.0)</td>
<td>82 (2.3)</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>3,969 (38.5)</td>
<td>2260 (62.1)</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>2,386 (23.1)</td>
<td>619 (17.0)</td>
</tr>
<tr>
<td>CABG graft</td>
<td>397 (3.8)</td>
<td>119 (3.3)</td>
</tr>
</tbody>
</table>

* PCI denotes percutaneous coronary intervention, CABG coronary-artery bypass grafting, STEMI myocardial infarction with ST-segment elevation, and COPD chronic obstructive pulmonary disease. Percentages may not total 100 because of rounding.
† Values indicate the number of patients for whom data were available for each variable.
There was no significant difference between the two groups in the composite risk of death and myocardial infarction during the 3-year follow-up period (Fig. 1A and 1B). At 6 months, there was an indication of a lower unadjusted event rate in the group with drug-eluting stents than in the group with bare-metal stents, with 13.4 fewer events per 1000 patients. However, during continued follow-up, there was a higher unadjusted event rate in the group with drug-eluting stents, with 12.7 more events per 1000 patients per year.

Accordingly, in the landmark analysis, the adjusted event rate tended to be lower in the group with drug-eluting stents during the initial 6 months (Fig. 2A). Thereafter, there was a continuous separation of the curves, with a significantly higher rate of events in patients with drug-eluting stents (relative risk, 1.20; 95% confidence interval [CI], 1.05 to 1.37). In the one-stent subgroup, allowing for adjustment for characteristics of both stents and lesions, the outcome was similar, with a lower risk of death or myocardial infarction in the group with drug-eluting stents during the first 6 months (relative risk, 0.82; 95% CI, 0.69 to 0.98) and a higher risk after the first 6 months (relative risk,
1.23; 95% CI, 1.02 to 1.48) (Fig. 3A). There were no significant differences in early outcome (P = 0.40) or late outcome (P = 0.30) between patients with paclitaxel-eluting stents and those with sirolimus-eluting stents.

**RISK OF DEATH**

Propensity-score–adjusted Cox regression analysis showed a significantly higher risk of death in the group with drug-eluting stents than in the group with bare-metal stents (relative risk, 1.18; 95% CI, 1.04 to 1.35) (Fig. 1C). At 6 months, the risk of death was similar in the two groups (Fig. 2B). However, after 6 months, the risk of death was significantly higher in the group with drug-eluting stents, with a continuous separation of the events curves (relative risk, 1.32; 95% CI, 1.11 to 1.57).

**MYOCARDIAL INFARCTION**

At 6 months, the adjusted cumulative risk of myocardial infarction was lower in the group with drug-eluting stents (Fig. 1D, 2C, and 3C). However, between 6 and 12 months, the risk of myocardial infarction was higher in the group with drug-eluting stents. Accordingly, in the landmark analysis, the event curves diverged over time, and after 6 months, there was a nonsignificant trend toward an increased risk of myocardial infarction both in the overall population (relative risk, 1.12; 95% CI, 0.95 to 1.32) and in the one-stent subgroup (relative risk, 1.18; 95% CI, 0.93 to 1.49).

**NEW REVASCULARIZATION AND RESTENOSIS**

During follow-up, in the group with drug-eluting stents, 888 patients (14.7%) had new PCIs, 92 patients (1.5%) had coronary surgery, and 917 patients (15.2%) had new revascularization; in the group with bare-metal stents, 1989 patients (14.5%) had new PCIs, 403 patients (2.9%) had coronary surgery, and 2260 patients (16.5%) had new revascularization. Among the 2285 patients receiving a second stent, the median time to a repeated PCI was 138 days for both groups, but 558 of 710 patients (78.6%) in the group with drug-eluting stents received new drug-eluting stents, as compared with 869 of 1575 patients (55.2%) in the group with bare-metal stents. In a Cox regression analysis, as compared with the group with bare-metal stents, the group with drug-eluting stents had a lower adjusted risk of undergoing a new PCI (relative risk, 0.94; 95% CI, 0.83 to 1.06).
Our study compared the long-term outcome of drug-eluting stents versus bare-metal stents in a large cohort of unselected consecutive patients treated with coronary stents at all interventional centers in Sweden. The data are entered into SCAAR to be used as tools for the treatment of patients, which improves the reliability of such information. The validity was also supported by source-data verification, which had a 95% correspondence with patients’ hospital records. The long-term follow-up was complete, since it was based on merging the SCAAR database with the national registries of vital statistics and of hospital admissions. Although the nonrandomized comparison between the study groups was adjusted for all available confounders, there is always a possibility of selection bias because of unknown confounders. However, in our study, the major reason for the selection of drug-eluting stents or bare-metal stents was the large variation in acceptance of the indications for these devices among the hospitals and geographic regions. Therefore, the selection of either type of device was often at random in relation to patient-related factors, which led to the opportunity to compare the group with drug-eluting stents with a contemporary, at least partly nonselected control group of patients with bare-metal stents.

Comparisons between nonrandomized groups usually are based on Cox regression analyses with adjustment for differences in all available background factors between the groups. However, these analyses require proportional hazards over time in order to make formal statistical comparisons between the groups appropriate. Therefore, the time course of events over the entire follow-up period was illustrated with unadjusted and propensity-score–adjusted cumulative event rates.
For the matter of statistical inference, the groups were compared in landmark analyses with an offset at 6 months. We had two reasons for choosing a 6-month cutoff. First, the recommendation for the duration of clopidogrel treatment after stent placement is up to 6 months in most centers in Sweden. Second, despite initial differences in event rates between the main indications (myocardial infarction with ST-segment elevation, the acute coronary syndrome, and stable coronary artery disease), after 6 months the event rates became similar for all three main-indication groups. By this division in early and late risk, we also overcame the problem with nonproportional hazards, which allowed for the estimation of relative risks and confidence intervals. A similar approach was used by Eisenstein et al.14

Our study showed an increased long-term risk of death among patients with drug-eluting stents, as compared with patients with bare-metal stents, stemming from an increased risk of death after 6 months. When evaluating the event rates in the landmark analysis starting at 6 months, we found an approximate 30% increase in the risk of death, and it remained consistent over time. Concerning the composite of death and myocardial infarction, there was a trend toward a lower event rate during the initial 6 months and a consistently higher event rate thereafter. These findings were best demonstrated by the results in the one-stent subgroup, in which adjustment could be made for differences in lesion-related characteristics. Among patients with drug-eluting stents, this subgroup had a relatively lower composite event rate (18%) during the first 6 months but thereafter had a relatively higher rate (23%). This early gain and late loss in the composite event rate might have been related to the risk of stent-related thrombosis with drug-eluting stents that was initially lower and later higher than that with bare-metal stents. This finding corresponds to the results of a recent randomized trial.14

According to criteria recently proposed by the Academic Research Consortium, the late events in our study would correspond to “possible stent thrombosis.” The time course of these events also corresponds to the recent reports from the meta-analyses of randomized trials8,10,14 and registries.14 The likelihood that these events were caused by stent thrombosis is strengthened by the demonstration of incomplete neointimal coverage as a probable reason for late stent thromboses in patients with drug-eluting stents.12,13 Although stent thromboses seem to occur only in approximately 0.5% of patients treated with drug-eluting stents per year, this factor may still have an effect on the risk of death, since a fatal outcome has been reported in up to 45% of these patients.21 Our findings are a cause for worry, since they indicate a continuous increase of approximately 0.5% per year in the risk of death and an increase of 0.5 to 1.0% per year in the incidence of death or myocardial infarction after 6 months. If this increased risk is maintained during even longer periods than the 3 years of follow-up in our study, any initial gains in event rates will be superseded by the continuous loss in late events.

The increase in event rate was observed only after the first 6 months. Although no details on long-term use of clopidogrel are available, most patients were prescribed dual antiplatelet treatment for 6 months after implantation of drug-eluting stents but for only 1 to 3 months after implantation of bare-metal stents. Therefore, the early gain and late loss of clinical events in the group with drug-eluting stents might have been related to better protection with clopidogrel in the early phase and a prolonged need for such protection after 6 months. It has been proposed that the occurrence of late stent thrombosis may be due to delayed healing7,22 that may necessitate lifelong dual antiplatelet therapy. Such an interpretation is in accordance with the recently reported high rates of death and myocardial infarction in patients with drug-eluting stents after cessation of clopidogrel, from the Duke database.20

The average rate of use of drug-eluting stents increased substantially during the study period, but there remained a large variation among the centers and indications. Although geographic differences accounted for most of the differences in the use of drug-eluting stents, patient selection was also based on risk criteria for restenosis, as suggested by the higher percentage of clinical and angiographic high-risk features in patients with drug-eluting stents.23 The clinical restenosis rate was approximately 60% lower among patients with drug-eluting stents than among patients with bare-metal stents. However, the restenosis rate after the implantation of bare-metal stents (5.9%) and the absolute differences in the rates of restenosis (3%) and reintervention (1%) between the two groups were lower in our study than in randomized clinical trials and in other registry
data. The low incidence of restenosis and re-intervention after the implantation of bare-metal stents and the small difference after the implantation of drug-eluting stents do not support the need for drug-eluting stents in patients at low or intermediate risk for restenosis.

Despite our use of appropriate statistical adjustments, differences in baseline characteristics or selection criteria that might not have been recorded could remain. Potential alternative explanations for the crossing of event curves—for example, multiple selection biases, such as higher early-event rates in patients with bare-metal stents because of a higher proportion of patients with myocardial infarction with ST-segment elevation and higher late-event rates in patients with drug-eluting stents because of a higher proportion of high-risk patients. Also, changes in event rates over time might have been influenced by the smaller number of patients with drug-eluting stents early in the study period. Another limitation is the lack of information about the duration of clopidogrel treatment in individual patients.

In conclusion, we showed that patients with drug-eluting stents had an 18% increase in the relative long-term risk of death, as compared with patients with bare-metal stents—a decrease that corresponded to an absolute increase of 0.5% in the risk of death per year after the initial 6 months. The analysis of the composite of death and myocardial infarction indicated a lower event rate during the first 6 months but thereafter an increase of approximately 20%, which corresponded to an absolute increase of 0.5 to 1.0% per year. Although the rate of clinically observed restenosis was 60% lower among patients with drug-eluting stents, the absolute difference did not amount to more than 3%. Therefore, a generalized, unselective use of drug-eluting stents should be avoided until randomized studies with an adequate number of patients and long-term follow-up have ruled out any increased long-term risk. Such studies should also provide clear evidence about the duration of dual antiplatelet therapy and the risk-benefit ratio in subgroups of patients based on clinical and angiographic risk criteria.

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APPENDIX

The following persons and institutions have contributed to this work: SCAA Steering Committee: T. Nilsson, Karlstad (chair); P. Albertsson, Göteborg; J. Carlsson, Kalmar; P. Eriksson, Umeå; S. James, Uppsala; J. Jensen, Stockholm; T. Kellert, Örebro; B. Lagerqvist, Uppsala; H. Olsson, Karlstad; F. Scherstén, Helsingborg; I. Sjögren, Falun; U. Stenestrand, Linköping; B. Thorvinger, Lund; and P. Tornvall, Stockholm. Uppsala Clinical Research Center: L. Wallentin, director; R. Svensson, system developer; O. Felton, system developer; K. Spångberg, data manager; and E. Svensson, monitor. Epidemiologic Center, Swedish Board of Health and Welfare: M. Köster, statistician. SCAA Centers and Responsible Physicians: Borås, L. Robertson; Danderyd, T. Särev; Eskilstuna, F. Hjortevang; Falun, I. Sjögren; Gävle, L. Hellsten; Halmstad, P. Härdhammar; Helsingborg, L. Sandhall; Karolinska University in Huddinge, B. Lindwall; Kalmar, J. Carlsson; Karolinska University in Solna, J. Jensen; Karlswarna, C.-M. Pripp; Kristianstad, R. Uher; Linköping University, U. Stenestrand; Lands University, B. Thorvinger; Rybom, J.-W. Puskar; Malmö University, C.-G. Gustavsson; Sahlgrenska University in Göteborg, P. Albertsson; Skövde, A. Kallryd; St. Göran in Stockholm, H. Enhörning; Sunderby Hospital in Luleå, A. Johansson; Söder- sjukhuset in Stockholm, M. Aasa; Trollhättan, D. Ioanes; Umeå University, J. Nilsson; Uppsala University, O. Duvenoy; Västerås, U. Björklind; and Örebro University, T. Kellert.

REFERENCES

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Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents

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ABSTRACT

BACKGROUND
Definitions of stent thrombosis that have been used in clinical trials of drug-eluting stents have been restrictive and have not been used in a uniform manner.

METHODS
We applied a hierarchical classification of stent thrombosis set by the Academic Research Consortium (ARC) across randomized trials involving 878 patients treated with sirolimus-eluting stents, 1400 treated with paclitaxel-eluting stents, and 2267 treated with bare-metal stents. We then pooled 4 years of follow-up data. All events were adjudicated by an independent clinical-events committee.

RESULTS
The cumulative incidence of stent thrombosis according to the original protocol definitions was 1.2% in the sirolimus-stent group versus 0.6% in the bare-metal–stent group (P=0.20; 95% confidence interval [CI], −0.4 to 1.5) and 1.3% in the paclitaxel-stent group versus 0.8% in the bare-metal–stent group (P=0.24; 95% CI, −0.3 to 1.4). The incidence of definite or probable stent thrombosis as defined by the ARC was 1.5% in the sirolimus-stent group versus 1.7% in the bare-metal–stent group (P=0.70; 95% CI, −1.5 to 1.0) and 1.8% in the paclitaxel-stent group versus 1.4% in the bare-metal–stent group (P=0.52; 95% CI, −0.7 to 1.4). The incidence of definite or probable events occurring 1 to 4 years after implantation was 0.9% in the sirolimus-stent group versus 0.4% in the bare-metal–stent group and 0.9% in the paclitaxel-stent group versus 0.6% in the bare-metal–stent group.

CONCLUSIONS
The incidence of stent thrombosis did not differ significantly between patients with drug-eluting stents and those with bare-metal stents in randomized clinical trials, although the power to detect small differences in rates was limited.
The treatment of obstructive coronary artery disease with percutaneous placement of coronary stents is associated with significantly improved procedural safety and a lower rate of restenosis, as compared with balloon angioplasty alone.\textsuperscript{1,2} However, repeated percutaneous and surgical revascularization procedures are needed to treat restenosis in 14% of patients.\textsuperscript{3} The use of drug-eluting stents has reduced the occurrence of such procedures by 50 to 70%.\textsuperscript{4,5}

Clinical studies involving two drug-eluting stents that have been approved by the Food and Drug Administration (FDA) were designed primarily to test the effectiveness of this strategy. The studies also examined whether there was a safety penalty to this mechanism of action, including whether thrombotic occlusion within the stent occurred more frequently or at a later time than the expected rate of about 1% occurring within 30 days after the procedure in patients with bare-metal stents.\textsuperscript{6} Individual reports and meta-analysis of randomized trials showed no significant increase in risk associated with drug-eluting stents, as compared with bare-metal stents, at 1 year.\textsuperscript{7-9} However, these studies used relatively restrictive and nonuniform definitions of stent thrombosis and had limited power to detect low-frequency events. Furthermore, observational studies have reported an increased risk of thrombotic events in patients with drug-eluting stents after 1 year,\textsuperscript{10-12} and there has been concern that late stent thrombosis may contribute to increased late mortality.\textsuperscript{13,14}

We sought to increase the power to detect differences in stent thrombosis in data available from extended follow-up of randomized trials of drug-eluting stents and to evaluate the effect of stent thrombosis on late mortality. We implemented a new standardized, hierarchical definition of stent thrombosis for uniform evaluation of events in a pooled analysis of eight randomized trials of the two FDA-approved drug-eluting stents, as compared with their respective bare-metal stents.

STUDY DESIGN
We readjudicated the latest available data from eight trials of two approved drug-eluting stents according to standardized definitions of stent thrombosis requested by the FDA for presentation at an advisory panel on drug-eluting stents in December 2006.\textsuperscript{15} All the studies remained blinded at the patient level to investigators, patients, and adjudication committees.

The Academic Research Consortium (ARC) was formed before this request to implement consensus definitions for implementation in clinical trials of drug-eluting stents. Invited to attend discussions were representatives of international academic research organizations who were involved in designing these trials, representatives of the FDA, and representatives of manufacturers of drug-eluting stents that were involved in managing or planning clinical trials. The stent manufacturers included Abbott Vascular Devices, Biosensors International, Boston Scientific, Conor Medsystems, Cordis, Guidant, and Medtronic. Funding to cover the costs of the meetings was requested and received from each manufacturer but was not a requirement for participation. Meetings and final consensus definitions were controlled by the academic researchers.

Harvard Clinical Research Institute was contracted by Cordis and Boston Scientific to adjudicate clinical events and by Cordis to manage and analyze the data. The academic authors designed and performed the analyses and prepared the manuscript; the authors assume responsibility for the integrity and completeness of the data and analyses.

STUDY POPULATION
Patient-level data were pooled for four randomized, controlled, double-blind trials evaluating the sirolimus-eluting stent, as compared with the same stent without a drug or polymer coating (bare-metal stent) and separately for four randomized trials evaluating the paclitaxel-eluting stent, as compared with the corresponding bare-metal stent.\textsuperscript{4,5,16-21} Eligible patients received treatment of single, previously untreated coronary lesions, as previously described. The trial cohort of patients with sirolimus-eluting stents included those enrolled in the Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL; ClinicalTrials.gov number, NCT00233805)\textsuperscript{16} and the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of De Novo Native Coronary Artery Lesions (SIRIUS in the United States [NCT00232765],\textsuperscript{4} C-SIRIUS in Canada [NCT00381420],\textsuperscript{17} and E-SIRIUS in Europe [NCT00235144]\textsuperscript{18}). These databases were managed by the Harvard Clinical Research Institute, except for the RAVEL trial, which was managed by
Cardialis and transferred to the Harvard Clinical Research Institute. The trial cohort of patients with paclitaxel-eluting stents included those enrolled in the TAXUS-I,19 TAXUS-II (NCT00299026),20 TAXUS-IV (NCT00292474),5 and TAXUS-V (NCT00301522)21 trials. The individual databases were managed by Boston Scientific, and data for our study were transferred to the authors. Patients were prescribed aspirin indefinitely and clopidogrel for a minimum of 2 to 3 months in the trials involving sirolimus-eluting stents and for 6 months in the trials involving paclitaxel-eluting stents, regardless of study-group assignments.

END POINT DEFINITIONS
In the study protocol, stent thrombosis was defined according to the protocols used in the original clinical trials, as adjudicated by the independent clinical-event committees for each trial. These definitions uniformly regarded evidence of any myocardial infarction with angiographic confirmation of in-stent thrombus or unexplained death within 30 days after the procedure as stent thrombosis but varied when myocardial infarction was present without angiographic confirmation of target-vessel involvement. Thrombotic occlusion of the study stent subsequent to repeated percutaneous treatment of the target lesion did not qualify as stent thrombosis in these definitions, and none of the protocols reported late unexplained deaths as stent thrombosis. Stent thrombosis was then classified by the ARC definition as definite, probable, or possible and as early (0 to 30 days), late (31 to 360 days), or very late (>360 days). The definition of definite stent thrombosis required the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion. Probable stent thrombosis included unexplained deaths within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation. Possible stent thrombosis included all unexplained deaths occurring at least 30 days after the procedure. Intervening target-lesion revascularization was defined as any repeated percutaneous revascularization of the stented segment, including the 5-mm proximal and distal margins, that preceded stent thrombosis.

STATISTICAL ANALYSIS
We compared the time to stent thrombosis during 4 years of follow-up for patients with drug-eluting stents, as compared with those with bare-metal stents, using the unstratified log-rank test for each definition of stent thrombosis that was used: protocol, definite, definite or probable, and any ARC criterion. Data for patients who did not have stent thrombosis were censored either at 4 years or at the last known time of follow-up, whichever was earlier. Data for patients who died before the 4-year follow-up and without thrombosis were censored at the time of death. The treatment of death as a competing risk yielded results that were very similar to those of the approach reported here. The proportional-hazards assumption for each stent group was assessed with the use of the Kolmogorov-type supremum test.22 Kaplan–Meier estimates of the cumulative incidence of stent thrombosis are presented for each group during a 4-year period and during the specified ARC time intervals and are based on a risk set of the number of patients who were alive at the beginning of the interval. The time from target-lesion revascularization to stent thrombosis was calculated as days from the last target-lesion revascularization to stent thrombosis. Statistical analyses were performed with the use of SAS software, version 9.1. All reported P values are two-sided. Exact results of the log-rank test (as calculated by StatXact software, version 7.0.0) were confirmed to be similar to the log-rank results calculated by asymptotic methods, as reported here.

RESULTS

PATIENTS AND LESIONS
The cohorts included 878 patients treated with sirolimus-eluting stents, 870 patients treated with corresponding bare-metal stents, 1400 patients treated with paclitaxel-eluting stents, and 1397 treated with corresponding bare-metal stents. Follow-up differed between the sirolimus-stent group and the paclitaxel-stent group because of the later initiation of the trials in the paclitaxel-stent group but remained balanced across randomized study groups. The median duration of follow-up was 1804 days in both the sirolimus-stent group and the corresponding bare-metal-stent group, 1423 days in the paclitaxel-stent group, and 1430 days in the corresponding bare-metal-stent group.

Within each cohort, the patients were well matched with respect to clinical and lesion characteristics across the treatment groups (Table 1). Furthermore, the characteristics of the patients...
in the pooled trials of sirolimus-eluting stents and paclitaxel-eluting stents were similar: the frequency of diabetes mellitus was 26%, the mean reference-vessel diameter was 2.7 mm, and the mean lesion length was 14 mm.

**Definitions of Stent Thrombosis**

According to the protocol definitions, the cumulative incidence of stent thrombosis during 4 years of follow-up was not significantly different for either of the groups receiving drug-eluting stents, as compared with those receiving bare-metal stents, although there were numerically more events after 1 year for both sirolimus-eluting stents and paclitaxel-eluting stents (Table 2 and Fig. 1A and 1B). As assessed by each of the ARC categories, differences in the cumulative incidence of stent thrombosis during 4 years between patients with sirolimus-eluting stents and those with paclitaxel-eluting stents, as compared with patients with bare-metal stents, were less than those observed for the protocol definitions, owing to more late or very late events adjudicated for both bare-metal–stent groups. The most inclusive ARC category, including possible stent thrombosis, yielded an increase by a factor of 2 in the number of events in all four groups, mostly owing to very late unexplained deaths (Fig. 1C and 1D, and Fig. 2 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

The incidence of definite or probable events occurring 31 to 360 days after the procedure was 0.1% in the sirolimus-stent group versus 1.0% in the corresponding bare-metal–stent group and 0.4% in the paclitaxel-stent group versus 0.3% in the corresponding bare-metal–stent group. At year 4, the incidence of such events was 0.9% in the sirolimus-stent group versus 0.4% in the corresponding bare-metal–stent group and 0.9% in the paclitaxel-stent group versus 0.6% in the corresponding bare-metal–stent group (Fig. 1C and 1D). For both pooled cohorts, the proportional-hazards assumption for treatment group was not rejected over the 4 years (P=0.23 for the sirol-

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**Table 1. Baseline Characteristics of the Study Patients.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sirolimus-Stent Trials</th>
<th>Paclitaxel-Stent Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sirolimus Stent (N=878)</td>
<td>Bare-Metal Stent (N=870)</td>
</tr>
<tr>
<td>Age (yr)</td>
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<td>61.9±10.7</td>
</tr>
<tr>
<td>Male sex (%)</td>
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<td>71.5</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td></td>
<td></td>
</tr>
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<td>Any diabetes</td>
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</tr>
<tr>
<td>Requiring insulin</td>
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<td>Hyperlipidemia (%)</td>
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<tr>
<td>Hypertension (%)</td>
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<td>63.3</td>
</tr>
<tr>
<td>Current smoker (%)</td>
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<td>24.5</td>
</tr>
<tr>
<td>Target vessel (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>46.6</td>
<td>46.7</td>
</tr>
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<td>Circumflex artery</td>
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<td>23.7</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>29.0</td>
<td>29.1</td>
</tr>
<tr>
<td>Left main coronary artery</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Saphenous-vein graft</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Reference-vessel diameter (mm)</td>
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<td>2.7±0.5</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>13.8±5.7</td>
<td>13.9±5.9</td>
</tr>
<tr>
<td>No. of stents</td>
<td>1.4±0.7</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td>22.9±9.0</td>
<td>22.4±8.1</td>
</tr>
<tr>
<td>Use of glycoprotein IIb/IIa inhibitor (%)</td>
<td>44.2</td>
<td>43.4</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.
mus-stent group and \( P = 0.93 \) for the paclitaxel-stent group for definite or probable events, as compared with the corresponding bare-metal–stent groups).

**Clinical Outcomes**

In the 68 patients with definite or probable stent thrombosis, 21 patients died (30.9%) and 57 had myocardial infarction (83.8%) (Table 3). Outcome rates after stent thrombosis were similar among treatment groups. At 4 years, on the basis of the overall rates of death from any cause reported in the study by Stone et al.\(^23\) in this issue of the *Journal*, the proportions of deaths from stent thrombosis in our study were 7.0% in the sirolimus-stent group versus 11.1% in the corresponding bare-metal–stent group and 8.2% in the paclitaxel-stent group versus 6.1% in the corresponding bare-metal–stent group.

**Effect of Repeated Revascularization**

Percutaneous target-lesion revascularization during the 4-year follow-up period occurred in 8.4% of patients with sirolimus-eluting stents versus 29.0% of patients with bare-metal stents (\( P<0.001 \)) and in 7.7% of paclitaxel-eluting stents versus 15.6% of patients with bare-metal stents (\( P<0.001 \)). Either definite or probable stent thrombosis was not observed after target-lesion revascularization in the sirolimus-stent group and was observed in one patient in the paclitaxel-stent group. In the bare-metal–stent groups of both cohorts, stent thrombosis occurred somewhat more frequently among patients who underwent intervening target-lesion revascularization than in patients without such intervention (binary rates, 2.4% of patients with target-lesion revascularization vs. 1.5% of those without such intervention in the sirolimus-stent trial cohort and 2.3% of patients with target-lesion

---

**Table 2. Cumulative Incidence of Stent Thrombosis According to Definition and Time Interval.**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Sirolimus Stent</th>
<th>Bare-Metal Stent</th>
<th>Absolute Difference (95% CI)</th>
<th>Paclitaxel Stent</th>
<th>Bare-Metal Stent</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>10 (1.2)</td>
<td>5 (0.6)</td>
<td>0.6 (−0.4 to 1.5)</td>
<td>16 (1.3)</td>
<td>10 (0.8)</td>
<td>0.5 (−0.3 to 1.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Any ARC criterion</td>
<td>30 (3.6)</td>
<td>28 (3.3)</td>
<td>0.3 (−1.5 to 2.0)</td>
<td>39 (3.2)</td>
<td>41 (3.5)</td>
<td>−0.3 (−1.8 to 1.2)</td>
<td>0.84</td>
</tr>
<tr>
<td>ARC definite or probable</td>
<td>13 (1.5)</td>
<td>15 (1.7)</td>
<td>−0.2 (−1.5 to 1.0)</td>
<td>22 (1.8)</td>
<td>18 (1.4)</td>
<td>0.4 (−0.7 to 1.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>ARC definite</td>
<td>10 (1.2)</td>
<td>7 (0.8)</td>
<td>0.4 (−0.7 to 1.4)</td>
<td>16 (1.3)</td>
<td>14 (1.1)</td>
<td>0.2 (−0.7 to 1.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>Early (0 to 30 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>4 (0.5)</td>
<td>1 (0.1)</td>
<td></td>
<td>7 (0.5)</td>
<td>7 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ARC criterion</td>
<td>4 (0.5)</td>
<td>3 (0.3)</td>
<td></td>
<td>7 (0.5)</td>
<td>7 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC definite or probable</td>
<td>4 (0.5)</td>
<td>3 (0.3)</td>
<td></td>
<td>7 (0.5)</td>
<td>7 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC definite</td>
<td>3 (0.3)</td>
<td>0</td>
<td></td>
<td>5 (0.4)</td>
<td>6 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late (31 to 360 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
<td></td>
<td>3 (0.2)</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ARC criterion</td>
<td>2 (0.2)</td>
<td>11 (1.3)</td>
<td></td>
<td>12 (0.9)</td>
<td>13 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC definite or probable</td>
<td>1 (0.1)</td>
<td>8 (1.0)</td>
<td></td>
<td>5 (0.4)</td>
<td>4 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC definite</td>
<td>1 (0.2)</td>
<td>4 (0.5)</td>
<td></td>
<td>5 (0.3)</td>
<td>3 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very late (&gt;360 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>5 (0.6)</td>
<td>0</td>
<td></td>
<td>6 (0.6)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ARC criterion</td>
<td>24 (2.9)</td>
<td>14 (1.7)</td>
<td></td>
<td>20 (1.8)</td>
<td>21 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC definite or probable</td>
<td>8 (0.9)</td>
<td>4 (0.4)</td>
<td></td>
<td>10 (0.9)</td>
<td>7 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC definite</td>
<td>6 (0.7)</td>
<td>3 (0.3)</td>
<td></td>
<td>6 (0.6)</td>
<td>5 (0.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Percentages are the cumulative rates of the event from Kaplan–Meier estimates, rather than binary percentages; for time intervals, this value was calculated as the difference in cumulative incidence between the current interval and the preceding interval. To avoid bias from the exclusion of events before a given time point, \( P \) values were calculated only for the overall study period. ARC denotes Academic Research Consortium, and CI confidence interval.
revascularization vs. 1.1% of those without such intervention in the paclitaxel-stent trial cohort) (see Fig. 3 of the Supplementary Appendix). Events occurred 15 to 669 days after the target-lesion revascularization and were fatal in two patients.

**EFFECT OF INTRACORONARY BRACHYTHERAPY**

Brachytherapy was frequently used to treat restenosis among patients with definite or probable stent thrombosis at any time after target-lesion revascularization. The treatment was performed in 9 of 11 patients in the bare-metal–stent groups and in the 1 patient who underwent target-lesion revascularization in the paclitaxel-stent group. (Table 4).

**EFFECT OF DISCONTINUATION OF ANTIPLATELET THERAPY**

Information regarding compliance with dual antiplatelet therapy was limited, since it was not ascertained in the trials of sirolimus-eluting stents beyond the protocol-recommended durations of 2 to 3 months; in the trials of paclitaxel-eluting stents, compliance was determined within follow-up intervals but not with actual dates of discontinuance. The retrospective collection of data in the trials of sirolimus-eluting stents indicated that 2 of 9 patients (22.2%) with sirolimus-eluting stents and 6 of 12 patients (50.0%) with bare-metal stents who had definite or probable stent thrombosis (according to ARC criteria) after 30 days were receiving dual antiplatelet therapy.

**DISCUSSION**

On the basis of a uniform hierarchical classification for stent thrombosis, we did not find statistically significant differences in the overall incidence between either of the currently approved drug-eluting stents, as compared with their bare-
metal–stent controls, during the 4 years after implantation. Stent thrombosis, a low-frequency event with serious, life-threatening consequences and variable rates of confirmation, poses many difficulties for analysis. Restrictive and nonuniform definitions from protocols of previous clinical trials and confounding in observational studies provide further challenges. We used the ARC definition to allow uniform ascertainment of end points across a large cohort derived from randomized trials. Our clinical review suggested that the most restrictive category, definite stent thrombosis, although unbiased, may have missed true events of stent thrombosis by requiring angiographic or autopsy confirmation even when the clinical presentation was consistent with stent thrombosis. The most inclusive definition, possible stent thrombosis, introduced a large number of events, owing to insufficient information to specify the cause of death, particularly after 1 year. These events were equally distributed across groups and weakened any potential signal of harm. Thus, we believe the “definite or probable” category provided the best approximation of the true incidence of stent thrombosis.

Although clinical end points have primary importance for the patient, they may fail to discriminate between small differences in the risk of stent thrombosis, since the condition accounts for a small fraction of the total number of these events. In fact, death from stent thrombosis accounted for about 10% of the total number of deaths reported in these studies. Our analysis demonstrates that recent reports of higher mortality in meta-analyses of trials involving sirolimus-eluting stents, as compared with bare-metal stents, are not attributable to differences in the risk of stent thrombosis across treatments. However, the fact that stent thrombosis is an infrequent cause of death in these studies does not diminish its relevance or the relevance of accurate assessment, given the strong association with mortality and morbidity, regardless of stent type.

We found that definite or probable stent thrombosis was relatively more frequent after treatment for restenosis. A dilemma exists in these cases as to whether to attribute stent thrombosis to the initial treatment strategy or the intervening treatment for restenosis. The original protocol definitions did not allow any event occurring after revascularization to be classified as stent thrombosis. This approach departed from an intention-to-treat principle and introduced a bias against devices that reduce restenosis. The restenosis treatments applied according to the standard of care represent a part of the strategy of the use of bare-metal stents. Therefore, we included such events. Outcomes of death and myocardial infarction after stent thrombosis were similar for patients with bare-metal stents and those with drug-eluting stents, suggesting that stent thrombosis after a previous target-lesion revascularization carries equally dire consequences.

During these trials, investigators remained unaware of treatment assignments, but brachytherapy, the standard of care at the time, was more commonly used in the groups with bare-metal stents, in which restenosis occurred more frequently and more diffusely than in the groups with drug-eluting stents. Although intracoro-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sirolimus-Stent Trials</th>
<th>Paclitaxel-Stent Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sirolimus Stent (N=13)</td>
<td>Bare-Metal Stent (N=15)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (30.8)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Any event</td>
<td>13 (100)</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>Fatal event</td>
<td>4 (30.8)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Q-wave</td>
<td>8 (61.5)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Non–Q-wave</td>
<td>5 (38.5)</td>
<td>9 (60.0)</td>
</tr>
</tbody>
</table>

* The definition of definite or probable stent thrombosis is based on criteria set by the Academic Research Consortium (ARC). One patient with a bare-metal stent had both Q-wave and non–Q-wave myocardial infarctions at different times.
nary brachytherapy for restenosis treatment has been previously identified as a risk for late thrombosis, this risk has been mainly attributed to concurrent implantation of a new stent,24,25 which was not the case in any patients with definite or probable stent thrombosis in our study. Furthermore, the association of brachytherapy with thrombosis is probably confounded by the occurrence and severity of restenosis. Our data do not allow us to speculate whether the risk of subsequent thrombosis after target-lesion revascularization would be different with other methods of restenosis treatment. Although brachytherapy is the only approved treatment for restenosis associated with bare-metal stents, it has been largely supplanted by other treatments (in particular, by treatment with drug-eluting stents).26,27 Therefore, further analysis is needed to determine the frequency of late thrombosis when a strategy of bare-metal stenting is followed by drug-eluting stenting to treat restenosis.

Analyses in which events before a given time point (such as 6 months or 1 year) are excluded have indicated an increased late risk associated with drug-eluting stents.11,28 We aimed to avoid bias introduced by omitting or censoring early events from statistical comparisons but observed that the incidence from year 1 through year 4 ranged from 0.4 to 0.9%, with very late events occurring in all stent groups. A larger number of very late events occurred in patients with drug-eluting stents than in those with bare-metal stents, but nearly 40% of patients with very late stent thrombosis had bare-metal stents.

Early cessation of clopidogrel is commonly reported in patients with thrombosis associated with drug-eluting stents.29 However, we observed events in patients with both bare-metal stents and drug-eluting stents in the presence of both aspirin and clopidogrel. These findings are consistent with a recent observational study showing ongoing risk despite continued dual antiplatelet therapy12 and suggest that although a protective effect may exist,28 extended dual antiplatelet therapy alone may not be sufficient to eliminate the occurrence of late thrombosis in patients with either bare-metal stents or drug-eluting stents.

Our analysis includes all trials used to support the FDA approval of the two drug-eluting stents. Nonetheless, on the basis of the rates observed in these trials (i.e., assuming a thrombosis rate of 1% with the use of bare-metal stents and an absolute increase of 1% in the rate of thrombosis with drug-eluting stents), a randomized trial with

### Table 4. Intervening Target-Lesion Revascularization in Patients with Definite or Probable Stent Thrombosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sirolimus-Stent Trials</th>
<th>Paclitaxel-Stent Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sirolimus Stent (N = 13)</td>
<td>Paclitaxel Stent (N = 22)</td>
</tr>
<tr>
<td>Intervening target-lesion revascularization (no.)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Time from target-lesion revascularization to stent thrombosis (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NA</td>
<td>138</td>
</tr>
<tr>
<td>Range</td>
<td>NA</td>
<td>15–484</td>
</tr>
<tr>
<td>Classification of stent thrombosis (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Target-lesion revascularization (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bare-metal stent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any drug-eluting stent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PTCA only</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Brachytherapy with PTCA</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Brachytherapy with bare-metal stent</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* The definition of definite or probable stent thrombosis is based on criteria set by the Academic Research Consortium (ARC). PTCA denotes percutaneous transluminal coronary angioplasty, and NA not applicable.
a power of 90% to detect a doubling of the risk of stent thrombosis would require approximately 8000 subjects. The duration of such a study would depend on the expected duration of thrombosis risk beyond 1 year. Observations regarding variations of hazard rates over time are difficult to make with certainty, since such variations are also limited by the small number of events. Whether the incidence curves for the events associated with drug-eluting stents and those associated with bare-metal stents will remain convergent or separate beyond 4 years is unknown, and follow-up for longer than 4 years will be necessary to answer this question. Finally, this study reflects rates of stent thrombosis in a population of patients who were at moderate risk for the condition. The application of drug-eluting stents has been extended in practice beyond the population of patients who are reflected in these trials. Since the individual characteristics of patients, lesions, and procedural factors are known to contribute to the risk of stent thrombosis, higher rates would be expected in higher-risk groups or in situations in which maintenance of recommended antiplatelet therapy is not possible. Our findings may not be applicable to these subgroups of patients.

In summary, we used a standardized, hierarchical definition of stent thrombosis to compare risk across studies. We found that during 4 years of follow-up, overall rates of stent thrombosis were not significantly different for patients who had received one of two approved types of drug-eluting stents and those who had received bare-metal stents. However, both longer-term and larger studies are needed to better understand how these infrequent but deadly events can be prevented.

Cordis and Boston Scientific contracted with Harvard Clinical Research Institute to perform independent adjudication of clinical events and data management, the results of which were used in this analysis. No external funds were received for this analysis or in the preparation of the manuscript, and industry sponsors were not involved in the preparation of the manuscript or consulted before the submission of results for publication.

Drs. Mauri, Massaro, and D’Agostino report receiving reimbursement for travel expenses and lodging for preparation and presentation of part of these results during a recent FDA advisory panel meeting; Dr. Mauri, administering an educational grant from Cordis without payment; and Dr. Cutlip, receiving a consulting fee from Bristol-Myers Squibb for participating in an advisory meeting on stent thrombosis. No other potential conflict of interest relevant to this article was reported.

**REFERENCES**


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Analysis of 14 Trials Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

Adnan Kastrati, M.D., Julinda Mehilli, M.D., Jürgen Pache, M.D., Christoph Kaiser, M.D., Marco Valgimigli, M.D., Ph.D., Henning Kelbæk, M.D., Maurizio Menichelli, M.D., Manel Sabaté, M.D., Maarten J. Suttorp, M.D., Ph.D., Dietrich Baumgart, M.D., Melchior Seyfarth, M.D., Matthias E. Pfisterer, M.D., and Albert Schömig, M.D.

BACKGROUND
The long-term effects of treatment with sirolimus-eluting stents, as compared with bare-metal stents, have not been established.

METHODS
We performed an analysis of individual data on 4958 patients enrolled in 14 randomized trials comparing sirolimus-eluting stents with bare-metal stents (mean follow-up interval, 12.1 to 58.9 months). The primary end point was death from any cause. Other outcomes were stent thrombosis, the composite end point of death or myocardial infarction, and the composite of death, myocardial infarction, or reintervention.

RESULTS
The overall risk of death (hazard ratio, 1.03; 95% confidence interval [CI], 0.80 to 1.30) and the combined risk of death or myocardial infarction (hazard ratio, 0.97; 95% CI, 0.81 to 1.16) were not significantly different for patients receiving sirolimus-eluting stents versus bare-metal stents. There was a significant reduction in the combined risk of death, myocardial infarction, or reintervention (hazard ratio, 0.43; 95% CI, 0.34 to 0.54) associated with the use of sirolimus-eluting stents. There was no significant difference in the overall risk of stent thrombosis with sirolimus-eluting stents versus bare-metal stents (hazard ratio, 1.09; 95% CI, 0.64 to 1.86). However, there was evidence of a slight increase in the risk of stent thrombosis associated with sirolimus-eluting stents after the first year.

CONCLUSIONS
The use of sirolimus-eluting stents does not have a significant effect on overall long-term survival and survival free of myocardial infarction, as compared with bare-metal stents. There is a sustained reduction in the need for reintervention after the use of sirolimus-eluting stents. The risk of stent thrombosis is at least as great as that seen with bare-metal stents.
Restenosis after percutaneous coronary intervention (PCI) reduces the quality of life and increases the morbidity of patients with this complication; it may even increase the risk of death. Drug-eluting stents are highly effective in preventing restenosis after PCI. It has been anticipated that by reducing the rate of restenosis, drug-eluting stents may have the potential to improve the long-term prognosis of patients treated with these devices. However, initial randomized studies focused on restenosis itself and had insufficient power and duration to assess the incidence of less frequent adverse events, such as death.

Recent reports have identified pathologic responses of the vessel wall to drug-eluting stents that may serve as precursors to adverse clinical events. Such studies have raised concern that drug-eluting stents might actually worsen, rather than improve, long-term prognosis. However, efforts to examine this issue by combining data from previous randomized trials have been limited to published trial-level data and have not included all the relevant studies. The aim of this study was to assess the long-term outcome after implantation of sirolimus-eluting stents on the basis of data from individual patients from randomized clinical trials comparing this device with bare-metal stents.

**METHODS**

**Inclusion Criteria**

We included in our analysis the results of randomized clinical trials that compared sirolimus-eluting stents (Cypher or Cypher Select, Cordis) with bare-metal stents for management of coronary artery disease if results for a mean follow-up period of at least 1 year were reported or made available by the trials’ investigators or sponsors.

**Data Sources**

We searched the National Library of Medicine (PubMed, at www.pubmed.gov), the National Institutes of Health clinical trials registry (www.clinicaltrials.gov), and the Cochrane Central Register of Controlled Trials (www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html) for randomized trials comparing sirolimus-eluting stents with bare-metal stents in patients with coronary artery disease. We also searched Internet-based sources of information on the results of clinical trials in cardiology (www.cardiosource.com/clinicaltrials, www.theheart.org, www.clinicaltrialresults.com, and www.tctmd.com), as well as conference proceedings from meetings of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology. Relevant reviews and editorials published within the past year in major medical journals were identified and assessed for possible information on trials of interest. Searches were restricted to the period from January 2002 through September 2006.

We found and screened 16 randomized trials, the main characteristics of which are shown in Table 1. Two randomized trials, Reduction of Restenosis in Saphenous Vein Grafts with Cypher Sirolimus-Eluting Stent (RRISC) and Sirolimus-Eluting Stent in the Prevention of Restenosis in Small Coronary Arteries (SES-SMART), were not included in this analysis because each had a mean follow-up of less than 1 year; the findings of these trials are displayed in Table 1 of the Supplementary Appendix (available with the full text of this article at www.nejm.org).

**DATA COLLECTION AND QUALITY ASSESSMENT**

An electronic form containing the data fields to be completed for individual patients was sent to all principal investigators or sponsors of the trials. Data from nine randomized trials were provided by the principal investigators; data from the remaining five trials were provided by the sponsor, who had no role in the study design or analysis or in the writing of or decision to publish the manuscript.

The data requested for each patient included the date of randomization, treatment allocation, diabetes status, event status (including death, myocardial infarction, coronary reintervention [percutaneous or surgical], and stent thrombosis and the respective dates of occurrence), and the date of the last follow-up visit. All data were thoroughly checked for consistency (logical checking and checking against the original publications). Any queries were resolved and the final database entries verified by the responsible trial investigator.

We also evaluated each trial for the adequacy of allocation concealment, performance of the analysis according to the intention-to-treat principle, and blind assessment of the outcomes of interest. We used the criteria recommended by Altman and Schulz and by Jüni et al. to de-
Table 1. Main Characteristics of the Trials. *

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>No. of Patients with Diabetes</th>
<th>Mean Age yr</th>
<th>Double Blinding</th>
<th>Patient Profile</th>
<th>Primary End Point</th>
<th>Protocol-Mandated Follow-up Angiography</th>
<th>Length of Thienopyridine Therapy</th>
<th>Mean Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET</td>
<td>545</td>
<td>101</td>
<td>64.0</td>
<td>No</td>
<td>Unselected patients</td>
<td>Cost-effectiveness based on the composite of death, myocardial infarction, and reinvention</td>
<td>No</td>
<td>6</td>
<td>18.3</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>100</td>
<td>24</td>
<td>60.5</td>
<td>Yes</td>
<td>Small vessels, long lesions</td>
<td>Minimal luminal diameter on follow-up angiography</td>
<td>Yes</td>
<td>2</td>
<td>48.5</td>
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<tr>
<td>DECODE</td>
<td>83</td>
<td>83</td>
<td>60.0</td>
<td>No</td>
<td>Patients with diabetes</td>
<td>Late luminal loss on angiography</td>
<td>Yes</td>
<td>3</td>
<td>12.7</td>
</tr>
<tr>
<td>DIABETES</td>
<td>160</td>
<td>160</td>
<td>66.6</td>
<td>No</td>
<td>Patients with diabetes</td>
<td>Late luminal loss on angiography</td>
<td>Yes</td>
<td>12</td>
<td>25.3</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>352</td>
<td>81</td>
<td>62.3</td>
<td>Yes</td>
<td>Long lesions</td>
<td>Minimal luminal diameter on follow-up angiography</td>
<td>Yes</td>
<td>2</td>
<td>49.4</td>
</tr>
<tr>
<td>Pache et al.</td>
<td>500</td>
<td>154</td>
<td>66.6</td>
<td>No</td>
<td>Unselected patients</td>
<td>Binary restenosis on angiography</td>
<td>Yes</td>
<td>6</td>
<td>46.1</td>
</tr>
<tr>
<td>PRISON II</td>
<td>200</td>
<td>27</td>
<td>59.5</td>
<td>No</td>
<td>Total occlusions</td>
<td>Binary restenosis on angiography</td>
<td>Yes</td>
<td>6</td>
<td>24.6</td>
</tr>
<tr>
<td>RAVEL</td>
<td>238</td>
<td>44</td>
<td>60.8</td>
<td>Yes</td>
<td>Selected patients</td>
<td>Late luminal loss on angiography</td>
<td>Yes</td>
<td>2</td>
<td>58.1</td>
</tr>
<tr>
<td>RRISC</td>
<td>75</td>
<td>11</td>
<td>72.5</td>
<td>No</td>
<td>Venous bypass grafts</td>
<td>Late luminal loss on angiography</td>
<td>Yes</td>
<td>2</td>
<td>6.0</td>
</tr>
<tr>
<td>SCANDSTENT</td>
<td>322</td>
<td>58</td>
<td>62.7</td>
<td>No</td>
<td>Complex lesions</td>
<td>Minimal luminal diameter on follow-up angiography</td>
<td>Yes</td>
<td>12</td>
<td>12.2</td>
</tr>
<tr>
<td>SCORPIUS</td>
<td>193</td>
<td>193</td>
<td>64.9</td>
<td>No</td>
<td>Patients with diabetes</td>
<td>Late luminal loss on angiography</td>
<td>Yes</td>
<td>3</td>
<td>12.7</td>
</tr>
<tr>
<td>SES-SMART</td>
<td>257</td>
<td>64</td>
<td>63.4</td>
<td>No</td>
<td>Small vessels</td>
<td>Binary restenosis on angiography</td>
<td>Yes</td>
<td>2</td>
<td>8.0</td>
</tr>
<tr>
<td>SESAMI</td>
<td>320</td>
<td>65</td>
<td>61.6</td>
<td>No</td>
<td>Patients with acute myocardial infarction</td>
<td>Binary restenosis on angiography</td>
<td>Yes</td>
<td>12</td>
<td>12.3</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>1058</td>
<td>279</td>
<td>62.2</td>
<td>Yes</td>
<td>Relatively selected patients</td>
<td>Death, myocardial infarction, or reintervention</td>
<td>Yes</td>
<td>3</td>
<td>58.9</td>
</tr>
<tr>
<td>STRATEGY</td>
<td>175</td>
<td>26</td>
<td>62.6</td>
<td>No</td>
<td>Patients with acute myocardial infarction</td>
<td>Death, myocardial infarction, stroke, or binary restenosis on angiography</td>
<td>Yes</td>
<td>3</td>
<td>24.2</td>
</tr>
<tr>
<td>TYPHOON</td>
<td>712</td>
<td>116</td>
<td>59.3</td>
<td>No</td>
<td>Patients with acute myocardial infarction</td>
<td>Death from cardiac causes, myocardial infarction, or reintervention</td>
<td>Yes</td>
<td>6</td>
<td>12.1</td>
</tr>
</tbody>
</table>

* Two randomized trials that are listed in the table — RRISC and SES-SMART — were not included in the analysis because they each had a mean follow-up of less than 1 year. BASKET denotes Basel Stent Kosten Effektivitäts Trial (ISRCTN.org number, ISRCTN75663024), C-SIRIUS Canadian Study of the Sirolimus-Eluting Stent in the Treatment of Patients with Long De Novo Lesions in Small Native Coronary Arteries (ClinicalTrials.gov number, NCT00381420), DECODE Randomized Trial of Cypher versus Bare Metal Stents in Diabetics, DIABETES Diabetes and Sirolimus-Eluting Stent Trial, E-SIRIUS European Multicenter, Randomized, Double-Blind Study of the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Coronary Artery Lesions (NCT00235144), PRISON II Primary Stenting of Totally Occluded Native Coronary Arteries II (NCT00258596), RAVEL Randomized Trial of the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (NCT00233805), RRISC Reduction of Restenosis in Saphenous Vein Grafts with Cypher Sirolimus-Eluting Stent (NCT00263263). SCANDSTENT Stenting Coronary Arteries in Non-Stress/Benestent Disease Trial (NCT00151658), SCORPIUS German Multicenter, Randomized, Controlled, Open-Label Study of the Cypher Sirolimus-Eluting Stent in the Treatment of Diabetic Patients with De Novo Native Coronary Artery Lesions, SES-SMART Sirolimus-Eluting Stent in the Prevention of Restenosis in Small Coronary Arteries, SESAMI Randomized Trial of Sirolimus Stent vs. Bare Stent in Acute Myocardial Infarction (NCT002388210), SIRIUS Sirolimus-Eluting Balloon Expandable Stents in the Treatment of Patients with De Novo Coronary Artery Lesions (NCT00232765), STRATEGY Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs. Abciximab and Bare-Metal Stent in Myocardial Infarction (NCT00229515), and TYPHOON Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (NCT00232830).
cide whether the treatment allocation was adequately concealed. Some trials used a modified intention-to-treat principle (i.e., excluding patients who did not receive the study stent) (see Table 2 of the Supplementary Appendix).

**STUDY OUTCOMES**

The primary end point of this analysis was death from any cause. Secondary end points were the composite of death or myocardial infarction and the composite of death, myocardial infarction, or reintervention (major adverse cardiac events). We also assessed the occurrence of stent thrombosis (see Table 2 of the Supplementary Appendix for the end-point definitions used in individual trials). It is important to note that in eight trials, data for patients who underwent target-lesion revascularization were censored with respect to the subsequent assessment of stent thrombosis. The adjudication of events in each trial was performed by the same event committee over the entire follow-up period.

**STATISTICAL ANALYSIS**

We performed survival analyses with the use of the Mantel–Cox test stratified according to trial. Survival was defined as the interval from randomization until the event of interest. Data for patients who did not have the event of interest were censored at the date of the last follow-up visit. The log-rank test was used to calculate hazard ratios and their 95% confidence intervals (CIs).

Trials in which the event of interest was not observed in either study group were omitted from the analysis of that event. For trials in which only one of the groups had no event of interest, the estimate of treatment effect and its standard error were calculated after adding 0.5 to each cell of the 2×2 table for the trial.

We assessed the heterogeneity across trials by the Cochran test and by calculating the I² statistic (describing the percentage of total variation across trials that was due to heterogeneity rather than chance), as proposed by Higgins et al. We pooled hazard ratios from individual trials according to the method of DerSimonian and Laird for random effects.

Sensitivity analyses were performed by comparing the treatment effects obtained with each trial removed consecutively from the analysis with the overall treatment effects. In addition, we used a random-effects meta-regression analysis to estimate the extent to which including four covariates — the nature of the study with respect to blinding (double blinding or no double blinding), the length of follow-up, the protocol-mandated duration of dual antiplatelet therapy, and the presence of acute myocardial infarction — as

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sirolimus Stent</th>
<th>Bare-Metal Stent</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET</td>
<td>10/264</td>
<td>13/281</td>
<td></td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>2/50</td>
<td>3/50</td>
<td></td>
</tr>
<tr>
<td>DECODE</td>
<td>0/54</td>
<td>2/29</td>
<td></td>
</tr>
<tr>
<td>DIABETES</td>
<td>7/80</td>
<td>5/80</td>
<td></td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>10/175</td>
<td>11/177</td>
<td></td>
</tr>
<tr>
<td>Pache et al.</td>
<td>29/250</td>
<td>24/250</td>
<td></td>
</tr>
<tr>
<td>PRISON II</td>
<td>2/100</td>
<td>3/100</td>
<td></td>
</tr>
<tr>
<td>RAVEL</td>
<td>14/120</td>
<td>8/118</td>
<td></td>
</tr>
<tr>
<td>SCANDSTENT</td>
<td>1/163</td>
<td>3/159</td>
<td></td>
</tr>
<tr>
<td>SCORPIUS</td>
<td>5/95</td>
<td>4/98</td>
<td></td>
</tr>
<tr>
<td>SESAMI</td>
<td>3/160</td>
<td>7/160</td>
<td></td>
</tr>
<tr>
<td>SIRIUS</td>
<td>45/533</td>
<td>46/525</td>
<td></td>
</tr>
<tr>
<td>STRATEGY</td>
<td>10/87</td>
<td>12/88</td>
<td></td>
</tr>
<tr>
<td>TYPHOON</td>
<td>8/355</td>
<td>8/357</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>146/2486</td>
<td>147/2472</td>
<td>1.03 (0.80 to 1.30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probability of Survival (%)</th>
</tr>
</thead>
<tbody>
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<td>Years after Randomization</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

**Figure 1. Hazard Ratios for Individual Trials and for the Pooled Population and Kaplan–Meier Estimates for 5-Year Survival.**

In Panel A, hazard ratios are shown on a logarithmic scale. The size of each square is proportional to the weight of the individual study, measured as the inverse of the estimated variance of the log hazard ratio. In Panel B, Kaplan–Meier curves are shown for survival for the pooled population during a 5-year period in each of the stent groups.
inclusion criteria for the trial might have influenced the treatment effect. Using the Mantel–Cox model, we checked for statistically significant interaction between the treatment effect (sirolimus-eluting stent vs. bare-metal stent) and the presence of diabetes mellitus (the only prespecified subgroup that was analyzed).

All P values are two-sided. Results were considered to be statistically significant at a P value of less than 0.05. Statistical analysis was performed with the use of Stata software, version 9.2 (Stata). Survival curves are presented as simple, nonstratified Kaplan–Meier curves across all trials and constructed with the use of S-Plus software, version 4.5 (Insightful).

**Results**

Our analysis included 14 trials and 4958 patients, 1411 of whom had diabetes mellitus. Table 1 displays the main characteristics of these trials. The age of the patients in the trials ranged from 59.3 to 66.6 years, and the length of follow-up ranged from 12.1 to 58.9 months.

Figure 1A shows the absolute numbers of deaths in each trial according to treatment group, with the hazard ratio for each trial. There was no statistical evidence of heterogeneity across the 14 trials. In total, there were 146 deaths (83 from cardiac causes) in patients with sirolimus-eluting stents and 147 deaths (79 from cardiac causes) in patients with bare-metal stents. Overall, the use of sirolimus-eluting stents was associated with a hazard ratio for death of 1.03 (95% CI, 0.80 to 1.30; P = 0.80), as compared with that of bare-metal stents.

Sequential exclusion of each individual trial from the analysis of death yielded hazard ratios that ranged from 0.96 (95% CI, 0.74 to 1.25) to 1.06 (95% CI, 0.84 to 1.34) and were not significantly different from the overall hazard ratio (P = 0.76). No significant influence of prespecified covariates on the treatment effect was observed, including the length of follow-up (P = 0.44), the protocol-mandated duration of dual antiplatelet therapy (P = 0.69), the presence of patients with acute myocardial infarction in the trial (P = 0.56), or the presence of double blinding in the trial design (P = 0.70). Figure 1B shows the overall 5-year survival curves for the two treatment groups.

Figure 2A shows the absolute numbers of patients who died or had a myocardial infarction in each trial according to treatment group, with the hazard ratio for each trial. There was no statistical evidence of heterogeneity across the 14 trials. In total, 241 patients with sirolimus-eluting stents
either died or had a myocardial infarction, as compared with 252 patients with bare-metal stents. Overall, use of sirolimus-eluting stents was associated with a hazard ratio for death or myocardial infarction of 0.97 (95% CI, 0.81 to 1.16; P=0.76), as compared with use of bare-metal stents. Figure 2B shows the overall 5-year curves for survival free of myocardial infarction in the two study groups.

Figure 3A shows the absolute numbers of patients who died, had a myocardial infarction, or required reintervention in each trial according to treatment group, with the hazard ratio for each trial. In total, 331 patients with sirolimus-eluting stents died, had a myocardial infarction, or required reintervention, as compared with 649 patients with bare-metal stents. Overall, the use of sirolimus-eluting stents was associated with a hazard ratio for death, myocardial infarction, or reintervention of 0.43 (95% CI, 0.34 to 0.54; P<0.001), as compared with the use of bare-metal stents. Although the point estimates for individual trials all favored sirolimus-eluting stents, there was a significant heterogeneity across trials with a high I² value. Figure 3B shows the overall 5-year curves for survival free of myocardial infarction and reintervention in the two study groups.

No significant interaction between treatment groups and the diagnosis of diabetes was observed for any of the three end points of the study, including death (P=0.19), death or myocardial infarction (P=0.39), and death, myocardial infarction, or reintervention (P=0.49). We nonetheless performed a separate analysis of the rate of death in the subgroup of patients with diabetes. Figure 4A shows the absolute numbers of deaths in each trial by treatment group, with the hazard ratio for the subgroup of patients with diabetes in each trial. There was no significant heterogeneity across trials. In total, 59 patients with diabetes and sirolimus-eluting stents died, as compared with 56 patients with diabetes and bare-metal stents. The overall hazard ratio associated with sirolimus-eluting stents was 1.27 (95% CI, 0.83 to 1.95; P=0.26). Figure 4B shows the overall 5-year survival curves in the subgroup of patients with diabetes.

Stent thrombosis (as defined by the individual
Hazard Ratios for Death in a Subgroup of Patients with Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of events/total no. of patients</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET</td>
<td>5/69</td>
<td>1.44</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>1/12</td>
<td>1.07</td>
</tr>
<tr>
<td>DECODE</td>
<td>0/54</td>
<td>1.00</td>
</tr>
<tr>
<td>DIABETES</td>
<td>7/80</td>
<td>1.18</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>2/33</td>
<td>1.33</td>
</tr>
<tr>
<td>Pache et al.</td>
<td>9/72</td>
<td>1.27</td>
</tr>
<tr>
<td>PRISON II</td>
<td>1/11</td>
<td>1.00</td>
</tr>
<tr>
<td>RAVEL</td>
<td>6/19</td>
<td>1.00</td>
</tr>
<tr>
<td>SCANDSTENT</td>
<td>0/29</td>
<td>1.00</td>
</tr>
<tr>
<td>SCORPIUS</td>
<td>5/95</td>
<td>1.00</td>
</tr>
<tr>
<td>SESAMI</td>
<td>2/28</td>
<td>1.00</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>20/131</td>
<td>1.00</td>
</tr>
<tr>
<td>STRATEGY</td>
<td>2/15</td>
<td>1.00</td>
</tr>
<tr>
<td>TYPHOON</td>
<td>1/55</td>
<td>1.00</td>
</tr>
<tr>
<td>Overall</td>
<td>59/675</td>
<td>1.27 (0.83 to 1.95)</td>
</tr>
</tbody>
</table>

P(heterogeneity)=0.37
I²=7%
P(overall effect)=0.26

Figure 5B shows the curves of probability of stent thrombosis in the two study groups after the trial-defined minimum duration of recommended use of dual antiplatelet therapy (Table 1). The overall risk of stent thrombosis during 4 years after this time was 0.8% (95% CI, 0.5 to 1.5) in the sirolimus-stent group and 0.3% (95% CI, 0.1 to 0.6) in the bare-metal–stent group (P=0.16).

In 8 of the 14 trials, data for patients undergoing target-lesion revascularization were censored with respect to the subsequent assessment of stent thrombosis. This censoring resulted in the exclusion of five additional cases of stent thrombosis, all in the bare-metal–stent group. In contrast, in the other six trials, such censoring did not occur, which resulted in the inclusion of one case of stent thrombosis that occurred after target-lesion revascularization in the sirolimus-stent group.

**DISCUSSION**

In our study, we analyzed individual data for patients with coronary heart disease from 14 randomized trials comparing sirolimus-eluting stents with bare-metal stents. We found that the use of sirolimus-eluting stents was associated with rates of death alone or combined with myocardial infarction that were similar to those observed with the use of bare-metal stents. Sirolimus-eluting stents were also associated with a sustained reduction in the need for reintervention but with an overall risk of stent thrombosis that was at least as high as that seen with bare-metal stents.

Several previous analyses of trials comparing drug-eluting stents and bare-metal stents in patients with coronary artery disease have been reported. In these previous studies, aggregate data from published reports, rather than data from individual patients, were examined. The superiority of analysis of data from individual patients over meta-analysis of lumped study outcomes has been emphasized. In particular for survival data, the lack of adjustment for censoring leads to an imprecise estimate of the overall treatment effect and interstudy heterogeneity.

Access to data for individual patients also makes...
it possible to analyze the timing of events. We made an extensive effort to identify and incorporate all trials comparing sirolimus-eluting stents with bare-metal stents. As a result, we believe that we have reduced the likelihood of study-selection bias, the major risk of any meta-analysis, which may have been present in previous reports.

The effect of the use of sirolimus-eluting stents on long-term mortality has not previously been established. Contrary to the expectation that prevention of restenosis by sirolimus-eluting stents might lead to improved survival, recent reports suggested that sirolimus-eluting stents were associated with an increased rate of death as early as 2 years after the procedure. Although this finding was not statistically significant, it generated much concern among the medical community. Our study shows no difference in mortality between patients with sirolimus-eluting stents and those with bare-metal stents during a 5-year period. The same finding was true for the combined end point of death or myocardial infarction.

No significant increase in the overall rate of stent thrombosis was seen with sirolimus-eluting stents. However, this complication was significantly more frequent in patients with sirolimus-eluting stents after the first year following the procedure, a finding that was consistent with another recent report. This difference is chronologically associated with the end of the protocol-specified interval of dual antiplatelet therapy with thienopyridines and aspirin. Although an accurate assessment of this issue cannot be made without knowledge of the actual timing of discontinuation of thienopyridine therapy in individual patients, our findings, as well as other recently published observations, may suggest the need for a longer duration of dual antiplatelet therapy in patients receiving sirolimus-eluting stents.

As noted, there were another five cases of stent thrombosis that were censored from the analysis of the original trials because they occurred after target-lesion revascularization. One case of stent thrombosis that was included in our count would have been excluded if such censoring had been applied to all the trials. Whether such cases of stent thrombosis should be included in comparisons of this kind is open to question. Proponents of inclusion would argue that post-revascularization episodes of stent thrombosis are an inseparable part of the experience of receiving a stent and that such episodes are more common with bare-metal stents because target-lesion revascularization is required more often in patients with such stents. The argument for excluding such episodes is that they may have occurred not as a result of the original stent choice, but as a result of the subsequent revascularization procedure, and thus that they do not reflect the biologic effects of the specific stent type.

Our observation that there is no late difference in hard end points (death or myocardial infarction) despite an increase in late stent thrombosis...
associated with sirolimus-eluting stents may be explained by the small proportion of patients with this complication in the trials. Also, the negative effect of late stent thrombosis on clinical outcome might have been offset by the reduction in the need for reintervention with the sirolimus-eluting stent and, consequently, by the exposure of a lower number of patients to postprocedural complications, as suggested by recent analyses.43

We paid special attention to patients with diabetes through a prespecified subgroup analysis. Patients with diabetes are at increased risk for adverse events after PCI,44,45 and aortocoronary bypass surgery is often considered to be a better treatment option for them. The effect of drug-eluting stents on the long-term outcome of patients with diabetes is not known. In the Siroli-
mus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of De Novo Native Coronary Artery Lesions (SIRIUS) trial, the largest trial in our analysis, patients with diabetes continued to have a relatively high rate of restenosis even after receiving drug-eluting stents.21 In our study, there was no statistical interaction between the presence of diabetes and the effect of sirolimus-eluting stents on the outcome of patients, including the rate of death. However, when we analyzed mortality in the subgroup of patients with diabetes, there was a trend toward a higher hazard ratio in patients with sirolimus-eluting stents. This observation suggests that patients with diabetes should be observed and followed especially carefully after treatment with sirolimus-eluting stents. It also justifies further collection of data on the long-term outcome of patients with diabetes who are treated with such stents. In addition, it will be important to evaluate whether other available or new drug-eluting stents may offer better results to patients with diabetes.

In conclusion, the use of sirolimus-eluting stents did not have a significant effect on overall long-term survival or on survival free of myocardial infarction, as compared with bare-metal stents. There was a sustained reduction in the need for reintervention after the placement of sirolimus-eluting stents. The risk of stent thrombosis was at least as great as that seen with bare-metal stents.

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REFERENCES

14 TRIALS OF SIROLIMUS-ELUTING STENTS VERSUS BARE-METAL STENTS


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Pediatric Strabismus

Sean P. Donahue, M.D., Ph.D.

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A healthy 3-year-old boy presents with a 6-month history of strabismus in his left eye. The visible inward deviation of the eye began intermittently but is now constant. His visual acuity is 20/20 in the right eye but only 20/100 in the left eye. The physical examination is otherwise normal. How should he be treated?

As evolution proceeded, the location of the eyes within the head moved from a lateral to a frontal position. In animals for which panoramic vision is not crucial, this frontal migration resulted in increasing overlap of each eye’s visual field and conferred the advantage of stereopsis (depth perception). In mammals, inputs from the two eyes converge on binocular neurons in the visual cortex, which are thought to be the neural substrate for stereopsis. Maturation of these binocular neurons is dependent on proper ocular alignment early in life. Childhood strabismus disrupts this process and results in permanent loss of stereopsis if the eyes are not realigned early in development.

Untreated pediatric strabismus can also cause amblyopia (a decrease in best-corrected visual acuity in an otherwise structurally healthy eye). The neuroanatomic substrate for amblyopia is a shrinkage in the size of neurons driven by the amblyopic eye in the visual cortex and lateral geniculate nucleus. Although experimental studies of amblyopia have been performed primarily in kittens and non-human primates, similar pathologic features have been reported in humans with amblyopia caused by strabismus or anisometropia (a difference between the eyes in the refractive error). Perturbations in the visual system that occur after the age of 5 years do not cause amblyopia.

Pediatric strabismus must be treated early to maximize the potential for binocular vision and decrease the risk of amblyopia. Treatment goals include good vision in each eye (no amblyopia) and straight eyes (orthotropia). Both conditions are necessary to produce stereopsis, which is a third goal.

The eyes of most children are not orthotropic at birth but, rather, are mildly exotropic (deviating outward). Neonatal misalignment typically resolves by 3 months, and any strabismus occurring after this age is abnormal. Large-angle esotropia (greater than 15 degrees) is also abnormal in infants.

Strabismus is classified according to the type and magnitude of misalignment (see Glossary). Most patients with esotropia present before school age, generally between the ages of 2 and 3 years. Most esodeviations (inwardly directed ocular deviations) are intermittent initially but within a few weeks become constant. An intermittent deviation does not preclude the development of stereopsis; however, failure to realign the eyes of children whose eyes are constantly esotropic results in lifelong abnormal depth perception. Patients with exotropia usually present between the ages of 1 and 4 years; the condition nearly always remains intermittent and is
therefore associated with good binocular vision. Vertical ocular deviations occur in children, in isolation or associated with horizontal strabismus, but are much less common and are not discussed here.

LATER CHILDHOOD AND ADULT STRABISMUS

New-onset strabismus in a school-aged child is unusual and warrants neurologic evaluation. Most cases of strabismus in this age group represent the recurrence of a partially treated strabismus earlier in life, which recurs because of a relative deficiency in fusion (the ability to maintain binocular vision). Such recurrences are most likely in children in whom deviations in ocular alignment have remained untreated for a prolonged period.

Adult strabismus is fundamentally different from pediatric strabismus. It does not produce amblyopia, and binocular vision can be restored when the strabismus is corrected. Most adult strabismus represents deterioration of childhood strabismus, which can occur even after decades of good ocular alignment. Diplopia may or may not be present. Recurrence is more common in adults whose childhood strabismus resulted in a lack of binocular vision and stereopsis or who had partially treated or untreated amblyopia (since the poor acuity makes binocular vision less sustainable). These observations underscore the importance of aggressive treatment of childhood amblyopia and strabismus. Adults with recurrent childhood strabismus should be treated (typically with surgery), since correction can restore binocular vision and expand visual fields.

Strabismus may also occur in adults after an insult to the ocular motor system, involving the supranuclear, prenuclear, or nuclear pathways sub-serving eye movements or the cranial nerves themselves. Important causes include vascular disease, inflammatory disease, infiltrative processes (including Graves' disease), myasthenia, and direct orbital trauma. bothersome diplopia is invariably present. A detailed discussion of adult strabismus is beyond the scope of this review, but referral to a neuro-ophthalmologist or a specialist in adult strabismus is warranted in such cases.

STRA T EGIES AND E V IDENCE

E SO D E V I AT I ONS

Infantile Esotropia

Infantile esotropia occurs in the first 6 months of life, with large-angle crossing in an otherwise developmentally and neurologically normal child (Fig. 1). Eye movements are full, and the child often alternates fixation (i.e., uses each eye independently for viewing). Children with constant, large-angle esodeviations of more than 20 degrees do not “outgrow” the condition.

Treatment of infantile esotropia is surgical and involves recession (weakening) the medial rectus muscles of each eye while the infant is under general anesthesia. Complications are infrequent. Globe perforation occurs in less than 1% of cases and usually heals without sequelae. Endophthalmitis occurs in fewer than 1 of 10,000 patients but can be devastating. Similar risks are associated with all strabismus surgery.

The goal of surgery is alignment of the eyes within 8 prism diop ters (4 degrees) and can be achieved initially in most patients. This small-angle deviation allows for limited binocular visual function (i.e., gross stereopsis) and an increased likelihood of stable long-term alignment (“monofixation”). High-grade stereopsis after surgery is extremely unusual.

Early surgical realignment in infantile esotropia appears to result in better outcomes than does later intervention. The duration of misalignment may be the major predictor of the outcome. Among children with infantile esotropia who underwent surgery between 3.5 and 22 months

<table>
<thead>
<tr>
<th>Glossary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strabismus</strong>: An ocular misalignment</td>
</tr>
<tr>
<td><strong>Tropia</strong>: A manifest (constant) ocular misalignment (as in “heterotropia”)</td>
</tr>
<tr>
<td><strong>Phoria</strong>: A latent tendency to deviate; held in control by fusion (as in “heterophoria”)</td>
</tr>
<tr>
<td><strong>Comitant strabismus</strong>: A similar magnitude of deviation in all gaze positions</td>
</tr>
<tr>
<td><strong>Incomitant strabismus</strong>: A deviation of greater magnitude in one direction or at close range</td>
</tr>
<tr>
<td><strong>Prism diopter</strong>: A measure of ocular misalignment; one prism diopter equals 1 cm of deviation at 1 m (approximately 0.5 degree)</td>
</tr>
<tr>
<td><strong>Orthotropia</strong>: No ocular deviation (i.e., straight eyes)</td>
</tr>
<tr>
<td><strong>Esotropia</strong>: An inward deviation of the nonfixing eye</td>
</tr>
<tr>
<td><strong>Exotropia</strong>: An outward deviation of the nonfixing eye</td>
</tr>
<tr>
<td><strong>Hypertropia</strong>: A vertical deviation, in which the nonfixing eye is higher</td>
</tr>
<tr>
<td><strong>Hypotropia</strong>: A vertical deviation, in which the nonfixing eye is lower</td>
</tr>
<tr>
<td><strong>Amblyopia</strong>: A unilateral or bilateral decrease in best-corrected visual acuity in a structurally normal eye or eyes</td>
</tr>
<tr>
<td><strong>Binocular vision</strong>: Blending of the separate images seen by each eye into one composite image</td>
</tr>
<tr>
<td><strong>Stereopsis</strong>: Visual blending of two similar (not identical) images, one falling on each retina, into one with visual perception of depth</td>
</tr>
</tbody>
</table>
of age (45% of whom had some postoperative stereopsis), there was a significant correlation between the duration of ocular alignment before the development of esotropia and later stereopsis.

Recurrent strabismus is common in children with infantile esotropia. Overcorrection and undercorrection of the original deviation, as well as vertical misalignments, can develop throughout life, and multiple surgeries are often required. In one follow-up study, the risk of recurrent strabismus was more than three times as high in children with no postoperative stereopsis as in those with detectable stereopsis. Some children with accommodative esotropia remain esotropic when viewing near objects and require bifocals to achieve orthotropia in this setting.

Children with esotropia who have no hypermetropia, or whose esotropia cannot be corrected fully with eyeglasses, should undergo strabismus surgery. Surgery does not improve the esotropia that occurs without eyeglasses but is performed to correct any residual deviation that remains after treatment with eyeglasses. A randomized, multicenter trial showed a slight improvement in postoperative alignment for patients with esotropia who, before surgery, had fusion after a week of wearing eyeglass-mounted prisms to mimic the effect of surgery (prism adaptation), as compared with patients who had surgery without prism adaptation or who did not have fusion with the prisms. However, the benefit, although statistically significant, was modest, and this technique is not universally used.

Surgery in children with esotropia should be performed as early as possible to preserve stereopsis. Prospective observational data indicate a significant inverse correlation between the duration of misalignment before surgery and the likelihood of postoperative stereopsis; the data also suggest that the development of stereopsis can be disrupted at least through the age of 4.6 years. The period of susceptibility to the loss of stereopsis probably never completely closes, since adults with acquired strabismus and diplopia risk losing high-grade stereopsis slowly with an increasing duration of misalignment.

In a prospective study of 4-year-old children with hypermetropia of +4.0 diopters or more, eyeglass correction was associated with a 50% reduction in the incidence of accommodative esotropia. However, because accommodative esotropia develops in only 10 to 20% of such chil-
routine eyeglass treatment would result in substantial overtreatment. Eyeglasses are usually not covered by medical insurance, maintaining compliance is difficult, and some (although not all) data have suggested that use of eyeglasses may interfere with the normal reduction in hypermetropia with age.

Also, many children with accommodative esotropia have refractive errors of less than +4.0 diopters. A more prudent approach may be to treat only patients with risk factors for accommodative esotropia (e.g., a family history of strabismus or amblyopia in a first-degree relative, subnormal stereopsis, or anisometropia), although the cost-effectiveness of such a strategy has not been well studied.

**Exodeviations**

**Infantile Exotropia**

Any exotropia that occurs after the age of 4 months is abnormal (Fig. 3). Constant exotropia is usually associated with neurologic delay, craniofacial syndromes, and structural abnormalities in an eye, but in rare cases it occurs in otherwise healthy children. Surgery can realign the eyes and is indicated unless extreme developmental delay precludes psychosocial interactions. However, ocular, orbital, and neurologic abnormalities often preclude the development of stereopsis, and recurrence of strabismus is more common when these conditions are present.

**Intermittent Exotropia**

Intermittent exotropia is one of the most common problems in pediatric ophthalmology. Although no appreciable deviation is present when the patient views near objects, the deviation becomes manifest when the patient views distant objects or is fatigued. A family history of the condition is common, and parents report observing the child habitually closing the nondominant eye when outdoors.

Several options are available to treat intermittent exotropia. These approaches have generally not been evaluated in randomized trials but, rather, are supported largely by data from case series. Nonsurgical treatments are intended to improve control of the deviation (i.e., reduce its frequency) but do not affect its magnitude. If the deviation occurs infrequently (for a few seconds on rare occasions when the child is daydreaming or tired), observation alone is reasonable. Intermittent exotropia typically does not resolve completely, but control can improve. Options for more frequent or consistent deviations include intermittent patching, the use of overminus eyeglasses (lenses that overcorrect myopia), vision therapy (exercises to stimulate convergence), and surgery. Response rates of 30% (for overminus eyeglasses) to about 50% (for other nonsurgical therapies) are reported in various retrospective series, but the studies are limited by selection bias, because for children with deviations that are poorly controlled or have a large magnitude and for those who do not have a response to conservative measures, there is a rapid move to surgical treatment.

Patching for 1 to 2 hours daily for several months works by preventing, rather than treating, suppression of an eye; this approach is most effective in infants, and efficacy is limited in children over the age of 3 years. The use of overminus eyeglasses stimulates accommodative con-
vergence, which counteracts the exotropic drift. Vision therapy involves exercises to stimulate convergence (e.g., focusing on reading-distance targets for up to 30 minutes several times daily) and techniques to train the visual system to recognize the suppressed image. However, the techniques are not well described in the literature and are not typically used by ophthalmologists for managing intermittent exotropia. A recent randomized trial showed a modest benefit of intensive vision therapy in patients with a particular type of intermittent exotropia (convergence insufficiency, a deviation that is more prominent when near objects are viewed), but it is possible that the observed improvement was caused by other factors.

Surgical treatment for intermittent exotropia is indicated when conservative measures do not reduce the frequency of the deviation. Surgery usually involves either weakening both lateral rectus muscles or combining a procedure that weakens a lateral rectus muscle with a procedure that strengthens the medial rectus muscle. Surgery is not a cure for intermittent exotropia; the recurrence rate is approximately 30% within 5 years.

Early establishment of constant orthotropia is not as crucial in patients with intermittent exotropia as it is in those with constant deviations, since stereopsis can still develop. However, the risk of the development of reduced stereopsis, mild amblyopia, or superimposed vertical strabismus increase with the duration of the intermittent deviation, underscoring the fact that even intermittent deviations may result in suppression of vision in the exotropic eye.

**Amblyopia**

Amblyopia occurs in nearly 50% of children with esotropia but is unusual in children with intermittent exotropia. The restoration of proper ocular alignment decreases but does not eliminate the risk of amblyopia. Several multicenter, randomized trials have demonstrated that amblyopia does not resolve spontaneously and that treatment is effective, restoring visual acuity of 20/30 or better in both eyes in nearly 70% of children.

Although occlusion of the fellow eye has been the traditional approach to treatment, a randomized trial showed that pharmacologic paralysis of accommodation (“penalization”) with the use of atropine works nearly as well as occlusion, with a 6-month success rate of 74% with the use of atropine, as compared with 79% with occlusion.

Atropine eyedrops blur the healthy eye at near vision and force fixation of the amblyopic eye. After 4 months of treatment, either limited occlusion (for as short a period as 2 hours a day) or the use of atropine (administered twice weekly) has an efficacy similar to that of more intensive therapy, such as patching for 6 hours a day or daily administration of atropine. A longer duration of treatment is generally needed with atropine than with patching — and a longer duration with limited patching or atropine use than with more intensive therapy — but treatment rarely exceeds 1 year. Neither treatment has serious side effects.

Amblyopia of the previously healthy eye occurs infrequently (in less than 3% of patients treated with either approach, even when intensive therapy is used) and is easily treated. Recurrence is most common during the first year after the cessation of treatment; resuming therapy is effective. Amblyopia can be treated at least through the age of 14 years, although not as effectively as in children who are of preschool age or are in elementary school.

Amblyopia therapy should be completed before proceeding with strabismus surgery.
Benefits of Strabismus Surgery

In addition to its effects on visual function, strabismus surgery has other benefits. Children begin to develop negative attitudes toward classmates with strabismus as early as the age of 6 years; these attitudes adversely affect interpersonal relationships, self-image, schoolwork, and participation in sports and intensify in the teenage and adult years. Surgical correction of childhood strabismus reduces these difficulties. Straight eyes are also important in adults, since strabismus can have a negative effect on social interaction (e.g., during a job interview).

Areas of Uncertainty

Factors that precipitate infantile esotropia are unknown, and data from randomized trials to guide decisions about the timing and type of surgical intervention are lacking. Surgery before the age of 6 months may increase the likelihood of the development of stereopsis. However, the deviation cannot be measured accurately in such young children and may increase during the first few months, necessitating repeated surgery. The natural history and optimal management of intermittent exotropia have also not been well studied.

Guidelines from Professional Societies

Guidelines from professional societies for the management of strabismus and amblyopia are summarized in Table 1.

Summary and Recommendations

The child described in the vignette has new-onset esotropia and should receive a cycloplegic refraction. If eyeglasses are indicated because of hypermetropia, he should receive them and return in approximately 2 months for a reassessment of acuity and alignment and initiation of amblyopia treatment with the use of either atropine or patching. Although intermittent therapy is a reasonable option, I generally recommend full-time patching, since improvement is more rapid and compliance may be better. If eyeglasses are not indicated, amblyopia therapy should be started immediately. Strabismus surgery would not be indicated until the amblyopia was fully treated and only if the eyeglasses did not fully correct the esotropia.

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41. Satterfield D, Keltner JL, Morrison TL. Diopsys. No other potential conflict of interest relevant to this article was reported.

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A 48-Year-Old Man with Multiple Myeloma and a History of a Repaired Umbilical Hernia and Four Thromboembolic Events Was Admitted for Cramping Abdominal Pain Associated with Back Pain and a Weight Loss of 5 kg (11 lb) during the Previous Month. Physical Examination Showed a Distended Abdomen and No Lower-Extremity Edema. Laboratory Evaluation Was Notable for a Creatinine Level of 1.2 mg per Deciliter (108 μmol per liter), an Albumin Level of 3.3 g per Deciliter, and Normal Urinary Sediment. Contrast-Enhanced Computed Tomography Showed Well-Defined Cystic Retroperitoneal Masses in Which the Kidneys Appeared to Be Floating, Extending from Below the Liver into the Pelvis. Percutaneous Drainage Did Not Improve His Symptoms. Flow Cytometry of the Fluid Aspirated from a Cyst Showed No Evidence of Cystic Lymphoma, and the Cytologic Findings Were Consistent with Lymphangioma. Exploratory Laparotomy Revealed Large, Uncomplicated Retroperitoneal Cysts Surrounding Both Kidneys. Total Excision Was Not Possible, because the Walls of the Cysts Were Adherent to the Major Abdominal Vessels. Subsequently, the Patient Has Had Recurrent Ascites Requiring Frequent Percutaneous Drainage in Addition to Medical Therapy. Retroperitoneal Cystic Lymphangiomas Are Rare Malformations of the Lymphatic System. Complete Surgical Resection Is the Definitive Treatment for Symptomatic Lymphangiomas. If Resection Is Incomplete, Recurrence Is Frequent, as in This Case.

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Case 7-2007: A 59-Year-Old Woman with Diabetic Renal Disease and Nonhealing Skin Ulcers

Hasan Bazari, M.D., Michael R. Jaff, D.O., Michael Mannstadt, M.D., and Shaofeng Yan, M.D., Ph.D.

PRESENTATION OF CASE

Dr. Maha R. Farhat (Medicine): A 59-year-old woman was admitted to the hospital because of a nonhealing ulcer on the right heel and painful ulcers on the right thigh and hip.

The patient had been morbidly obese since early childhood; she had had type 2 diabetes mellitus and hypertension for 30 years and chronic renal insufficiency for 6. Painless ulcers had developed on the plantar surfaces of both heels 6 years earlier; those on the left side had healed with wound care and decreased weight bearing, but those on the right recurred when she resumed weight bearing. Four years before admission, she became unable to walk because of the ulcers, and moved to a long-term care facility. The chronic renal insufficiency progressed, and hemodialysis was begun 8 months before admission.

Three months before admission, a large area of purple discoloration and tenderness appeared along the back of her right lower thigh. This area subsequently ulcerated. Two months before admission, an ulcer developed over the greater trochanter of the right hip. Computed tomographic (CT) scanning of the thigh performed 3 months before admission was interpreted as showing cellulitis. Ultrasound imaging of the right leg was negative for deep venous thrombosis.

At approximately the same time, an ulcer on the right heel that had been present for about 2 years enlarged despite local care and attempts at primary closure. Approximately 2 months before admission, cultures of this ulcer yielded growth of *Pseudomonas aeruginosa* that was susceptible to ciprofloxacin and gentamicin, and intravenous therapy with these agents was started. Approximately 1 month before admission, a limited bone scan suggested the presence of osteomyelitis of the right calcaneus. Noninvasive vascular studies revealed an ankle–brachial index of 0.83 on the right and 0.90 on the left (normal, >0.96). Right calcaneal resection and placement of a vacuum-assisted closure dressing were performed 3 weeks before admission. Cultures of the resected bone grew the same species of *P. aeruginosa*, as well as *Escherichia coli*. Ciprofloxacin and gentamicin were continued.

On follow-up examinations, the heel ulcer did not improve; it became painful,
with a purulent discharge, and an area of redness and swelling developed around it. The ulcers on the right hip and thigh increased in size. She was referred to the vascular-surgery clinic of this hospital 10 days before admission. At that time, there was an ulcer, 3 cm deep, on the right hip; a black, necrotic area, 15 cm by 15 cm, on the right posterior thigh; and a decubitus ulcer, 5 cm by 5 cm, on the right heel with exposed bone. None of the ulcers were purulent. Noninvasive vascular study of both legs was recommended. During the next 10 days, her physicians became increasingly concerned about sepsis from the foot ulcer, and she was sent to the emergency department of this hospital.

On examination, her vital signs were normal and the right lower leg was painful on any movement; the ulcers were unchanged. Examination by vascular ultrasound imaging was limited because of pain but revealed right distal popliteal-artery and tibial-artery disease with poor perfusion of the right foot. She was admitted to the hospital for a below-the-knee amputation of the right leg.

She did not have fever, chills, or sweats. She had diabetic retinopathy, neuropathy, and carotid and coronary atherosclerosis; carotid endarterectomy had been performed in the past because of transient ischemic attacks. She had had episodes of congestive heart failure with pulmonary edema but had no history of venous or arterial thromboses. She had no known allergies. She was unmarried, had a 16-year-old daughter, and had worked as a teacher until becoming disabled because of the ulcers. She had a 5-pack-year history of cigarette smoking, but had stopped smoking 5 years before admission. She did not drink alcohol or use illicit drugs. Her medications, in addition to the antibiotics, included simvastatin, furosemide, lisinopril, metoprolol, insulin, calcium carbonate, sevelamer, famotidine, gabapentin, narcotics for the pain from her ulcers, and laxatives.

On examination, the patient was an obese woman who was lethargic but arousable and oriented. She was in moderate discomfort from pain in her right leg. The axillary temperature was 37.4°C, the blood pressure 137/58 mm Hg, and the pulse regular at 72 beats per minute. Auscultation of the lungs and heart were normal; the abdomen was obese, with no tenderness or organomegaly. The carotid and radial pulses were normal. The left dorsalis pedis pulse was diminished, and the right was not palpable. An ulcer, 5 cm by 5 cm, overlying the trochanter of the right hip exposed the subcutaneous tissue without purulence or erythema. On the right posterior-medial thigh, an exquisitely tender and violaceous indurated area, 15 cm by 15 cm, with black, dry ulcerations and surrounding tender erythema, extended from the popliteal fossa two thirds of the way up the thigh. An ulcer, 5 cm by 5 cm, on the right heel had cyanotic margins and a foul-smelling purulent base that exposed bone. An area of erythema that was tender to palpation spread from the heel about two thirds of the way up the lower leg. Laboratory test results are shown in Table 1.

During the evening, a repeated examination disclosed that the area of erythema on the lower leg now extended to the knee. The patient continued to have severe pain of the calf and posterior aspect of the thigh. A procedure was performed early the next morning.

**Differential Diagnosis**

*Dr. Hasan Bazari:* May we see the imaging studies?

*Dr. Michael R. Jaff:* The noninvasive vascular studies were performed with blood-pressure cuffs placed at the thigh, calf, ankle, foot, and toe levels. This examination tells us two things: the blood pressure at several levels of the leg, and the qualitative volume of arterial blood flowing to each level. These data are used to predict not only the presence and severity of peripheral arterial disease but also the segments of artery involved. The right thigh was not studied because of the ulceration. A normal plethysmographic pulse-volume recording is seen at the transmetatarsal region of the left foot (Fig. 1), with a rapid upstroke, rapid downstroke, dicrotic notch, and return to baseline.

The reported ankle–brachial indexes of 0.83 on the right and 0.90 on the left suggest minimal peripheral arterial disease. However, the arteries of the legs had diffuse calcification of the medial arterial layer, so that inflating the blood pressure cuff will not close the lumen, allowing for continuous arterial Doppler signals. In this setting, the ankle–brachial index is unreliable and cannot be used to determine the presence or severity of peripheral arterial disease. The plethysmographic waveforms, however, show significant peripheral arterial disease of both the femoral and the popliteal arteries at multiple levels of the right leg.
and at the level of the ankle, the metatarsals, and the digits (Fig. 1).

Dr. Bazari: This 59-year-old woman with obesity, type 2 diabetes mellitus, hypertension, and end-stage renal disease presented with ulcers on her legs and feet and concern for sepsis. A chronic ulcer on the right heel was complicated by osteomyelitis and *P. aeruginosa* infection. During the three months before admission, new lesions developed, which were described as areas of purple discoloration and tenderness that appeared on the hip and thigh, and subsequently turned black and ulcerated. Her vital signs were stable on admission, but spreading erythema and pain associated with the heel ulcer suggested progression of infection. The laboratory tests showed a low albumin level and a high globulin level. She had anemia of chronic kidney disease as expected. I am aware of the diagnosis in this case, but the differential diagnosis was initially broad.

### Ulcers on the legs and feet

The ulcers on the legs and feet may be related to this patient’s chronic diseases or may have another cause. The differential diagnosis for ulcers on the legs and feet is shown in Table 2.

### Vascular and Thrombotic Diseases

Ulcers due to arterial insufficiency typically occur on the toes, the heels, and the anterior shin and extend over the malleoli. Thromboangiitis obliterans (Buerger’s disease) is a thrombotic disease seen in young male smokers that leads to limb loss if there is delay in cessation of smoking; this patient does not fit the demographic for Buerger’s disease.

Atheroembolic disease can cause ulcers in the legs, especially in the setting of peripheral arterial disease; embolization characteristically occurs after a vascular procedure, such as angiography or cardiac or vascular surgery. This patient clearly had peripheral arterial disease, which was probably a major factor in the heel ulceration.

Venous ulcerations typically occur above the lateral or medial malleoli. The patients usually have a history of venous insufficiency, stasis dermatitis, and a history of deep venous thrombosis. The distribution of this patient’s ulcers is not characteristic of venous ulcers, there is no history of deep venous thrombosis, and there are no cutaneous findings to suggest venous stasis. Vasculitis and the antiphospholipid-antibody syndrome are unlikely in this patient, since she has no history of autoimmune disease and no systemic features of a vasculitis. I would have considered obtaining a hypercoagulable screen in the evaluation of this patient. Disseminated intravascular coagulation can lead to ischemia and loss of the arms and the legs; this typically occurs with disseminated infection or shock and would not be compatible with this patient’s course.

Heparin-induced thrombocytopenia is caused by antibodies against complexes of platelet factor 4 and heparin and is increasingly recognized as a cause of thrombosis leading to loss of limbs. This disorder is associated with both venous and arterial thrombi. I would have inquired whether heparin products had been used as prophylaxis or treatment in this patient. Skin necrosis can occur in patients with an underlying genetic or acquired deficiency in protein C or protein S who begin therapy with warfarin.

### Neuropathic Ulcers

Neuropathic ulcers occur under the metatarsal head, over the toe joints, under the heel, on the inner side of the first metatarsal head, and over the malleoli. We are not told about the neurologic

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**Table 1. Results of Laboratory Tests on Admission.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Range (Adults)</th>
<th>Value in Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>White-cell count (per mm³)</td>
<td>4500–11,000</td>
<td>13,000</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>36.0–46.0</td>
<td>32.5</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–350,000</td>
<td>509,000</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes (%)</td>
<td>40–70</td>
<td>81</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>11.3–13.3</td>
<td>14.7</td>
</tr>
<tr>
<td>Activated partial-thromboplastin time (sec)</td>
<td>22.1–35.1</td>
<td>28.1</td>
</tr>
<tr>
<td>Plasma sodium (mmol/liter)</td>
<td>135–145</td>
<td>139</td>
</tr>
<tr>
<td>Plasma carbon dioxide (mmol/liter)</td>
<td>23.0–31.9</td>
<td>24.9</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.5–10.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>2.6–4.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Magnesium (mmol/liter)</td>
<td>0.7–1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>8–25</td>
<td>27</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.6–1.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.3–5.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Globulin (g/dl)</td>
<td>2.6–4.1</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milliequivalents per liter, divide by 0.5. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4.*
Figure 1. Vascular Studies of the Legs.
Plethysmographic pulse-volume recordings at five levels of the legs show multilevel peripheral arterial disease, which is more severe on the right than on the left. The normal deflection represents a waveform similar to an intraarterial pressure waveform, with a rapid upstroke, narrow waveform, rapid downstroke, dicrotic notch, and then completion of the waveform as it bows down to the baseline; the tracing from the left calf is closer to normal than that from the right calf. As peripheral arterial disease worsens, the dicrotic notch is lost, the waveform widens, and the amplitude decreases. Plethysmography of the digits shows complete loss of pulsatility at the level of the right great toe, suggesting advanced ischemia at the foot and toes.
examination, but this patient probably had diabetic neuropathy. The ulcers on this patient's heels are typical of neuropathic ulcers.

**INFECTIONS**

Osteomyelitis is clearly established in this case by the radiologic and microbiologic findings. Although osteomyelitis can be a cause of ulceration, in this case it is a consequence of the ulceration rather than a primary cause. The patient was treated with ciprofloxacin and gentamicin for a prolonged period, but the wound did not heal. Indolent infections such as tuberculosis can cause chronic nonhealing ulcers, and in immunosuppressed patients, fungal infections such as cryptococcus and coccidioidomycosis can lead to skin lesions that ulcerate. If these organisms had caused the heel ulcer, they probably would have been found at the time of this patient's recent surgery.

**OTHER DISORDERS**

Necrobiosis lipoidica diabeticorum produces skin lesions that typically occur over the pretibial area and heal with shallow hypopigmented scars. Erythema nodosum is a form of panniculitis that is often associated with underlying systemic diseases such as sarcoidosis and inflammatory bowel disease. Weber–Christian disease is another panniculitide and is sometimes associated with pancreatic disease. Pyoderma gangrenosum is associated with inflammatory bowel disease and cancer, neither of which this patient had; it typically presents as a single, purple, furunculoid abscess on the trunk that ulcerates.\(^5\) The ulcers have a characteristic heaped-up border, unlike our patient's ulcers. None of these disorders are likely to explain the ulcer on the heel, but necrobiosis lipoidica or Weber–Christian disease could be considered for the more recent ulcers on the hip and thigh. However, although the patient has diabetes, the location of these lesions and their size and painfulness is atypical of necrobiosis lipoidica, and she has no history of pancreatic disease to suggest Weber–Christian disease.

**CALCYPHYLAXIS**

The ulcers on this patient's thigh and hip, which appeared spontaneously and without trauma, are characteristic of calciphylaxis, or calcific uremic arteriopathy, as shown in another patient in Figure 2. The lesions associated with calciphylaxis are characteristically exquisitely tender and plaque-like, with a dusky or purple discoloration, and progress to ulceration with the formation of eschars.\(^6\) In a patient who receives dialysis, the appearance of progressive cutaneous lesions that are painful and ulcerate should invoke the diagnosis of calciphylaxis.

Patients with renal disease often have arteriolar, ocular, periarticular, soft-tissue, and visceral calcifications — these do not represent calciphylaxis.\(^7\) Calciphylaxis is a poorly understood disorder, predominantly of the skin, that has characteristic calcifications in the media of small to medium-size blood vessels of the dermis and subcutaneous fat and is associated with ischemia and skin necrosis.\(^8\) The relationship between uremia

### Table 2. Differential Diagnosis of Ulcers on the Legs and Feet.

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular diseases</td>
<td>Arterial disease, Thromboangiitis obliterans (Buerger's disease), Cholesterol embolization, Venous disease with stasis, Lymphedema, Antiphospholipid-antibody syndrome, Vasculitis, Cryoglobulinemia, Wegener's granulomatosis, Rheumatoid arthritis, Disseminated intravascular coagulation, Heparin-induced thrombocytopenia, Warfarin-induced skin necrosis, Neuropathic ulcers, Infections, Osteomyelitis, Necrotizing fasciitis with organisms such as clostridia, group A streptococcus, and <em>Vibrio vulnificus</em></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Fungal infections</td>
<td><em>Cryptococcus neoformans</em></td>
</tr>
<tr>
<td><em>Coccidioides immitis</em></td>
<td></td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>Polycythemia vera, Essential thrombocytopenia, Therapy with hydroxyurea, Necrobiosis lipoidica diabeticorum, Pyoderma gangrenosum, Sweet's syndrome, Erythema nodosum, Cancer (squamous-cell carcinoma), Calciphylaxis</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
</tr>
</tbody>
</table>
and vascular calcification was first described in 1898 by Bryant and White. The term calciphylaxis was originally coined by Selye, who showed that deposition of calcium occurred in the tissues of rats that were sensitized with vitamin D analogues, parathyroid hormone, and nephrotoxic insults when they were challenged with iron, other metal salts, glucocorticoids, or physical trauma.

**DIAGNOSIS OF CALCIPHYLAXIS**

Calciphylaxis is rare, although the prevalence in one study was 4.1% of patients receiving long-term hemodialysis. It is more common in women and girls than in men and boys (male:female ratio, 1:3); the age range is 6 months to 83 years. Most patients have some degree of kidney disease, although calciphylaxis has been reported in patients with cirrhosis, Crohn’s disease, hyperparathyroidism, and cancer. The clinical features include hyperparathyroidism (in 80% of patients), hypercalcemia (in 20%), hyperphosphatemia (in 68%), and elevations in the calcium–phosphate product (in 33%). About a third of the patients have had renal transplants. The use of calcium-based phosphate binders and the use of vitamin D products to suppress the parathyroid hormone levels lead to higher levels of both calcium and calcium–phosphate products, causing premature vascular calcifications in patients with end-stage renal disease.

The presence of hypercalcemia, hyperphosphatemia, elevations in the calcium–phosphate product, hyperparathyroidism, and exposure to calcium and vitamin D products should raise the suspicion of calciphylaxis. However, it is possible that the clinical syndrome may present well after the optimal confluence of conditions for the initiation of calciphylaxis, and the measurements at the time of clinical presentation may not represent the conditions required for initiation of the syndrome. This patient’s serum calcium level was normal at 9.1 mg per deciliter (2.28 mmol per liter), but because of her albumin level of 2.4 g per deciliter, the ionized calcium level was probably at the upper limit of normal. She was also receiving calcium and vitamin D supplementation while she was receiving dialysis. She had a moderately elevated parathyroid hormone level. Some patients have low levels of protein C, protein S, or both, which may promote calciphylaxis by inducing a hypercoagulable state.

Clinical suspicion is the single most important feature of the diagnosis, and once one has seen a case, the evolution of the disease is unforgettable. The gold standard for the diagnosis of calciphylaxis is a biopsy of one of the lesions. Bone scanning has been recommended as an alternative to biopsy. It is unclear whether bone scans are as specifically diagnostic as a biopsy is, but they can be used when there is concern that a biopsy could lead to the formation of ulcers.

**SUMMARY**

In summary, the ulcer on this patient’s foot and those on the hip and thigh have characteristics that suggest two different causes. The heel ulcers probably began as neuropathic ulcers. The presence of severe arterial insufficiency, in addition to probable diabetic small-vessel disease and uremia, all contributed to the persistence of the ulcer on the right heel. Finally, this ulcer was complicated by osteomyelitis caused by two organisms, one of which — *P. aeruginosa* — is particularly virulent and was difficult to eradicate, probably because of the patient’s compromised vascular status. In contrast, the lesions on the hip and thigh, which developed several months after the patient began hemodialysis, are typical of calciphylaxis.

The procedures performed at the end of the
protocol were a guillotine amputation of the distal third of the right lower leg, done as an emergency because of the apparent progression of infection, and débridement of the ulcer on the right thigh.

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**CLINICAL DIAGNOSIS**

Ischemic ulcer of the heel due to atherosclerotic vascular disease.
Decubitus ulcers of the hip and thigh.

**DR. HASAN BAZARI’S DIAGNOSIS**

Calciphylaxis, causing ulcers on the hip and thigh.
Ischemic ulcer on the heel, with secondary osteomyelitis, due to diabetic nephropathy and atherosclerotic and diabetic vascular disease.

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**PATHOLOGICAL DISCUSSION**

*Dr. Shaofeng Yan:* Histologic examination of the amputation specimen of the right lower leg showed cutaneous ulceration of the heel with necrosis of collagen, muscle, and subcutaneous fat, as well as osteomyelitis. There was severe atherosclerosis of large vessels, as well as Monckeberg’s medial calcific sclerosis (Fig. 3A). These findings are common in patients with diabetes and can arise independently in the same or anatomically similar arterial segments. Both lesions compromise perfusion—the intimal atheroma by occlusion of the lumen, and the medial calcification by limiting distensibility.

The amputation of the right leg was followed during the ensuing days and weeks by two revisions of the amputation; three débridements of skin, soft tissue, and fascia of the right thigh; and finally, 6 weeks after admission, an above-the-knee amputation of the right leg. Histologic examination of both the amputation specimens and the lesion on the right thigh showed extensive areas of fat necrosis without marked acute inflammation. There is deeply basophilic amorphous material consistent with calcium deposition within the small arteries in the septa (Fig. 3B) and lobules (Fig. 3C) of the subcutaneous fat, highlighted by von Kossa’s stain (Fig. 3D). Microthrombi were present within the small vessels (Fig. 3E). These features are diagnostic of calciphylaxis.

Calciphylaxis is a small-vessel vasculopathy characterized by mural calcification, intimal pro-

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**Figure 3.** Histologic Examination of Specimens from Amputation of the Right Leg and Débridement.

A large artery from the guillotine below-the-knee amputation of the right leg (Panel A) shows severe atheroma and Monckeberg’s medial calcific sclerosis (hematoxylin and eosin). Basophilic calcium deposition is evident within a small artery in the septum of subcutaneous fat (Panel B, hematoxylin and eosin). Panel C shows calcium deposition within a small artery in a lobule of subcutaneous fat (hematoxylin and eosin). Calcium deposits are highlighted as fine, dark granules within the septum tissue (Panel D, von Kossa’s stain). Microthrombi are present within a small artery (Panel E, hematoxylin and eosin).
liferation, and microthrombosis. It commonly affects small arteries, ranging from 40 to 600 μm, with the average size approximately 100 μm. The pathological differential diagnosis of calciphylaxis includes dystrophic calcification, calcinosis cutis, and medial calcific sclerosis. Calcinosis cutis is characterized by calcification in skin tissue but not in vessels. Dystrophic calcification involves calcification of injured tissue in association with normal serum calcium and phosphate levels, whereas in cases of calciphylaxis, calcium deposition can occur in areas without an abundant inflammatory-cell infiltrate. Medial calcific sclerosis affects larger vessels than those affected by calciphylaxis.

**DISCUSSION OF MANAGEMENT**

Dr. Bazari: The management of calciphylaxis is based on assumptions about its causes; however, since no particular combination of factors reliably predicts the development of calciphylaxis, the effectiveness of all treatments remains unproved. When elevated levels of calcium, phosphate, and calcium–phosphate product are present, sevelamer hydrochloride should be substituted for calcium-based phosphate binders, dietary phosphate intake and calcium in the dialysis bath should be reduced, and vitamin D products both in medications and in dialysis supplements should be eliminated. The role of parathyroidectomy remains controversial. Calcimimetic agents can be used to control parathyroid hormone secretion. Bisphosphonates, sodium thiosulfate, tissue plasminogen activator, and hyperbaric-oxygen therapy have all been used with some success.

Sepsis is the leading cause of death in patients with calciphylaxis. Meticulous and aggressive management of wounds, use of antibiotics, and resection of necrotic tissue are key parts of the treatment, as they were in this patient.

Dr. Michael Mannstadt: Endocrinology was asked to consider the possible benefit of parathyroidectomy in this patient. Her serum calcium and phosphorus levels were normal. The elevation of intact parathyroid hormone was mild for the degree of renal insufficiency. Both 25-hydroxyvitamin D (a marker of vitamin D stores) and 1,25-dihydroxyvitamin D (the active metabolite of vitamin D) were within the normal range. Most reports of clinical improvement after parathyroidectomy have involved patients with markedly elevated parathyroid hormone levels, and even in that group it was not possible to predict who might benefit. Moreover, parathyroidectomy in this patient could precipitate severe adynamic bone disease and complicate efforts to control the calcium–phosphate metabolism. Our recommendation was to continue efforts to tightly control the calcium–phosphate product, continue sodium thiosulfate, avoid vitamin D analogues and warfarin, and consider hyperbaric-oxygen therapy. The patient declined to undergo hyperbaric-oxygen therapy because of claustrophobia.

During her hospital stay, the patient’s parathyroid hormone levels fluctuated, probably in response to fluctuating calcium levels around the time of her hemodialysis, but were as high as 466 pg per milliliter. Therapy was initiated with oral cinacalcet, a calcimimetic agent approved for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease who receive dialysis and also for the treatment of patients with parathyroid cancer. Cinacalcet activates the calcium-sensing receptor expressed by parathyroid cells and in so doing mimics the action of calcium to suppress secretion of parathyroid hormone, enabling control of hypersecretion at normal or even low blood levels of ionized calcium. The drug has an acceptable side-effect profile, and the patient was able to take 30 mg of cinacalcet without appreciable side effects. Subsequent levels of parathyroid hormone remained only slightly elevated.

Dr. Farhat: Calcium and vitamin D supplements were stopped, and sodium thiosulfate was added to her dialysate during hemodialysis three times a week. Several repeated débrimages were performed, as were medical applications of maggots to the wounds and the placement of a vacuum-assisted closure dressing. Her wounds eventually showed evidence of healing, and after 3 months in the hospital, she was discharged to a rehabilitation facility. She was making good progress in regaining strength and physical mobility.

**ANATOMIC DIAGNOSIS**

Calciphylaxis, extensive, involving the right leg.

Atherosclerotic vascular disease with ischemic ulcer on the heel and osteomyelitis.

Dr. Jaff reports receiving lecture fees from Bristol-Myers Squibb and Sanofi. No other potential conflict of interest relevant to this article was reported.


Drug-Eluting Coronary Stents — Promise and Uncertainty
Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., John A. Jarcho, M.D., and Jeffrey M. Drazen, M.D.

In this issue of the Journal, we publish five Original Articles and two Perspective articles on the subject of drug-eluting coronary stents.1-7 Our motivation is the recent concern that the implantation of drug-eluting stents, as compared with bare-metal stents, may be associated with a small increased risk of late stent thrombosis, a potentially fatal complication (Fig. 1). At a meeting of the Circulatory System Devices Advisory Panel of the Food and Drug Administration (FDA) on December 7 and 8, 2006, presentations were made on virtually every aspect of this complex clinical problem.8 In order to inform the medical community, we are publishing these articles, which are representative of the presentations and discussions that took place at the panel meeting. In some cases we provide two views of the same data sets, because different investigators looked at the same data using different analytic approaches. Readers will see that the details of analysis are critical for understanding the conclusions of each of these reports.

In addition to the data reported in the Original Articles, the two Perspective articles, by Dr. Andrew Farb and Ashley Boam of the FDA Center for Devices and Radiological Health and by Dr. William Maisel, who served as chair of the Circulatory System Devices Advisory Panel, synthesize a great deal of information on both the benefits and the potential risks of drug-eluting stents. These stents were approved for use in stable patients with relatively noncomplex coronary stenoses, but they have been used in many patients whose clinical features and coronary anatomy fall outside the original specifications. Such off-label use has made assessments of stent safety beyond the setting of clinical trials considerably more challenging. There is also the important matter of adjunctive antiplatelet therapy. Although a science advisory recommending 12 months of dual antiplatelet therapy after placement of a drug-eluting stent was published electronically in January, the optimal duration of therapy has not yet been precisely determined.

Figure 1. Potential Complications of Coronary Stenting: Restenosis in a Traditional Bare-Metal Stent and Late Thrombosis in a Drug-Eluting Stent. Arrows indicate blood flow. An animation showing restenosis and stent thrombosis can be viewed at www.nejm.org.
Millions of patients with coronary artery disease worldwide have received coronary-artery stents, and the enormous health benefits of this technology are not in dispute. Still, when a potentially serious albeit uncommon complication such as stent thrombosis is detected, it is mandatory that everything possible be done to aggressively examine the complication, assess the risk, understand the pathophysiological characteristics, and develop preventive measures. Although not all questions have been answered and areas of uncertainty remain, the FDA acted appropriately by taking expeditious action. We understand that these matters are far from resolved, but our hope is that the articles in this issue of the Journal will inform the medical community and help health professionals make the best decisions for their patients.

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Here we acknowledge, with special thanks, those who reviewed two or more papers between January and December 2006. Each year thousands of reviewers contribute their expertise to peer review, a process that contributes critically to the quality of the Journal. The editors and the authors of the papers submitted to the Journal are grateful for the help of all our reviewers.
Ethical Challenges Posed by the Solicitation of Deceased and Living Organ Donors

Douglas W. Hanto, M.D., Ph.D.

Given the shortage of transplantable organs, some potential recipients are going to great lengths to find organ donors on their own. For example, a patient with advanced liver cancer advertised on a personal Web site, billboards, and in the media for a liver, leading the family of a brain-dead donor to direct the donor’s liver to him. A patient undergoing dialysis solicited on a commercial Web site and received a kidney from a volunteer living donor. The solicitation for organs from deceased and living donors potentially circumvents the principles of justice and utility on which organ-allocation policies are based and has sparked a vigorous public debate. In this article, I review the medical, ethical, and public policy issues involved in solicitation and offer possible solutions.

Solicitation of Families of Deceased Donors

In the United States, organs from deceased donors are allocated in a nondirected fashion (see the Glossary) to patients on a waiting list according to the policies established by the United Network for Organ Sharing (UNOS). Exceptions have occurred when a family member or friend of a deceased donor is on the waiting list and the organ or organs are directed to that person (see the Glossary). These exceptions are permitted by the final rule governing the Organ Procurement and Transplantation Network (OPTN) and by the Uniform Anatomical Gift Act, which was revised in 1987. The transplantation community has interpreted the final rule as permitting the directed donation of organs from deceased donors to family members or friends but not under other circumstances. Another exception occurs when a donor’s family has responded to a public plea by a potential recipient and directs the donor’s organ or organs to that recipient. The solicitation of the families of deceased donors by recipients or their representatives results in a directed donation that allows recipients to “jump the list” and is viewed by most in the transplantation field as violating the fair principles of organ allocation.

Solicitation of Living Donors

No national organization or allocation policies regulate living organ donation. Living donations historically have all been directed between family members and friends, are considered ethically acceptable, and are performed according to policies established at individual transplantation centers. Volunteer living donors (“good Samaritan” donors) who present themselves to a transplantation center generally become anonymous nondirected donors to the next compatible patient on the waiting list at the given transplantation center; this method is generally considered to be the most fair. However, good Samaritan donors are rare (there were 85 such donors in 2004 and 79 in 2005 in the United States). The solicitation of a living donor for a specific recipient does not violate any existing national policies as long as there is no payment for the organ, but this form of donation is currently unregulated. Because the solicitation of living donors may involve unethical or even illegal practices, the Health Resources and Services Administration has directed UNOS to develop guidelines for the allocation of organs from living donors.

Arguments for and Against Solicitation

Donor Autonomy

In order for solicitation to work for the recipient of an organ from either a deceased or living donor, the donor or his or her family must be allowed to direct the donation. It has been argued that the donor who is voluntarily giving a kidney should be...
able to direct this gift to anyone he or she chooses (Table 1). Not everyone agrees. In order for the donor to donate, not just the recipient, but others such as a transplantation surgeon, nurses, and a hospital must be involved, and the ethical, legal, and social obligations of these other parties must be considered.23 Furthermore, justice and utility demand a balance between the donor, who claims autonomy, and the rights of all patients on the waiting list. If a donor’s choice interferes with justice and utility, it should neither be considered a fair application of autonomy nor be allowed.21

UNOS bars directed donation to groups on the basis of race, sex, religion, national origin, or similar characteristics.15,16 Others view a kidney as a private resource that can be donated to anyone of the donor’s choosing, even if the donation is discriminatory, and they believe that the graft becomes the property of the designated recipient.22

The argument that living kidney donors want to be able to direct their donation — and would be less likely to donate if this right were taken away — is not supported by the experience at the University of Minnesota, which requires that kidneys from good Samaritan donors go to the patient who is first on their center’s UNOS waiting list.29 A national conference report on nondirected living kidney donation provided support for a policy of nondirected donation to the list.20 On the basis of the results of a survey of adults in the United States about whether donors should be able to choose their recipients, Spital23 reported that 93% of the respondents who were willing to donate a kidney to a stranger said they would still donate if they could not direct their donation. Spital concluded that permitting directed, living kidney donation would result in a very small increase in the number of people willing to donate to a stranger, whereas not allowing it would not substantially decrease the number of donors.

What happens when a good Samaritan donor or the family of a deceased donor says “directed donation or no donation”? Many people believe that accepting directed donation in this circumstance abandons the principles of equity and justice.7,17,19,21 For example, a liver from a deceased donor might be directed to a patient waiting at home, whereas a critically ill patient in an intensive care unit in the same hospital where the donor died might die while waiting for an organ. If we accept directed donation in this circumstance, it is likely that we would also have to accept discriminatory directed donations from living donors and deceased donors.

**IS THE ALLOCATION SYSTEM FAIR?**

Claims that the current allocation system is not fair to all patients on the waiting list have been used to justify seeking an organ or organ donor outside the current system. UNOS is required by the Health Resources and Services Administration to allocate organs from deceased donors in a nondirected way that balances the principles of justice, equity, and utility. Broadly representative committees are involved in developing, soliciting public comment on, approving, and reviewing allocation policies that are updated as inequalities are identified. All policies are subject to public and governmental accountability and oversight. UNOS allocates organs from deceased donors in a nondirected fashion that appears to be the most fair to all recipients on the waiting list and is arguably a model that could be applied with some modifications to living-donor transplantation.

**DOES SOLICITATION INCREASE PUBLIC AWARENESS AND ORGAN DONATION?**

Media publicity regarding solicitation has increased public awareness of the organ-donor shortage and the suffering of patients. Anecdotal information suggests that some donors have come forward

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**Glossary**

| Directed donation: An organ or organs donated to a specific named person. This donation can be from a living donor, from a deceased donor (by means of an advance directive), or from the family of a deceased donor to a family member, friend, or stranger as a result of solicitation. |
| Nondirected donation: An organ or organs donated to patients on the transplantation waiting list. A nondirected donation does not name a specific recipient. It can be from a good Samaritan living donor, from a donor who has signed an organ-donor card or an advance directive, or from the family of a deceased donor. The organ or organs are allocated by UNOS according to established policies. |
| Solicit: To make a petition to, to approach with a request or plea, to strongly urge, to entice, or to seek to obtain by persuasion, entreaty, or formal application. |
| Public solicitation: Pleas for an organ or organ donor by potential recipients or their agents on Web sites, billboards, television or radio, or other forms of advertising. Public solicitation can involve deceased donors or living donors and, if successful, always results in a directed donation. If the donation is from a deceased person, the intent is to bypass the usual allocation processes. |

* Organ-donor cards are now legally binding because of “first-person consent” laws passed in several states that prevent families from overriding a person’s decision to be an organ donor.
and indicated they would not have thought to do so except for the personal stories reported by the media. Publicity and personal stories are misleading, however, because they suggest unique recipient needs. Directed donation that is based on an emotional appeal assumes that the recipient is for some reason exempt from the criteria that apply to all patients waiting for an organ.

**DOS SOLICITATION BYPASS FAIR-ALLOCATION POLICIES?**

The solicitation of organs from deceased donors bypasses the patient who is first on the waiting list; therefore, it violates the principles of utility and justice on which allocation policies are based. The trust in and fairness of the system will be undermined if the policies that have been agreed to are violated by the directed donation of organs from deceased donors to recipients other than the person at the top of the waiting list; a decrease in organ donation could result. Recall the public outcry when it was believed (incorrectly) that Mickey Mantle, a baseball player who received a liver transplant, had “jumped the list” and received a liver before others on the list because of his fame.

Should exceptions be allowed? The American Society of Transplant Surgeons has declared its support for directed donation from a deceased person to family members, friends, or persons with a preexisting community-based relationship to the donor. Some have argued that organ-procurement organizations are not detective agencies and that directed donation of organs from deceased donors should be permitted only for first-degree relatives; after that, the organ from a deceased donor should go to a person on the waiting list. However, many friends have strong emotional bonds and feel a greater obligation to help a friend who needs an organ than do some family members. Donors in this situation should not be excluded from sharing their gift. Transplantation centers and organ-procurement organizations currently permit directed donations from friends when there is confidence of a preexisting emotional relationship. I believe this practice should continue.

**POtENTIALLY DISCRIMINATORY PRACTICES**

A potential donor or a donor’s family may choose a person on a Web site or billboard on the basis of criteria that are discriminatory; there is no way to prevent this from happening. Most believe this practice is unethical and should not be permitted. For example, the family members of a murdered Ku Klux Klan sympathizer agreed to donate his organs only if they were transplanted into white recipients. Their decision led the Florida legislature to ban directed donation to persons belonging to specific groups, consistent with UNOS policy. The current organ-allocation system must be protected from discriminatory practices that could place certain classes of people at a disadvantage.

**DOES DIRECTED DONATION FAVOR ADVANTAGED PERSONS?**

Well-educated patients and those with public relations skills and financial resources arguably have easier access to the media and Internet than patients with fewer advantages. Thus, their stories, pictures, and demographic characteristics may be favored by potential living donors and the families of deceased donors. For example, many people volunteered to donate an organ to a well-known professional basketball player. In addition, there has been little proactive effort to make Web sites about solicitation available to all recipients on the waiting list. Recipients need to know about these Web sites, decide if they want to participate, and then must have the resources to write a story, pay fees, and screen donors who come forward. A patient’s access to the Internet, particularly broad-

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**Table 1. Summary of Arguments for and against Solicitation of Organ Donors.**

<table>
<thead>
<tr>
<th>For</th>
<th>Against</th>
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<tbody>
<tr>
<td>1. Donor autonomy requires that the donor or donor family be able to decide where the organs should be directed.</td>
<td>1. Donor autonomy is not absolute and must consider the fair rights of others.</td>
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<tr>
<td>2. The current allocation system may be unfair to certain patients.</td>
<td>2. Solicitation of deceased donors bypasses the fair policies of allocation and the person ethically entitled to the organ.</td>
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<tr>
<td>3. Solicitation results in more public awareness and willing donors.</td>
<td>3. Solicitation permits discriminatory practices.</td>
</tr>
<tr>
<td>4. Solicitation favors the well educated and those with financial resources.</td>
<td>4. Solicitation favors the well educated and those with financial resources.</td>
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<tr>
<td>5. Solicitation risks the exploitation of donors or recipients and may result in the undetected buying and selling of organs.</td>
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<tr>
<td>6. Solicitation may divert organs to unsuitable candidates for transplantation.</td>
<td>6. Solicitation may divert organs to unsuitable candidates for transplantation.</td>
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</table>
band services, varies according to location (e.g., access may be less available in rural communities) and to his or her age and socioeconomic class. Furthermore, because the Organ Donation and Recovery Improvement Act permits the recipient to reimburse the donor for travel and subsistence, recipients with the ability to pay would be more likely to complete the transaction successfully with a solicited living donor.

If solicitation becomes acceptable and common, patients might elect to solicit a living-donor stranger rather than approach a family member. Besides the ethical concerns about soliciting strangers to take risks that a patient is not willing to ask of a family member, soliciting donors could lead to a net decrease in the number of living organ donors because fewer family members might be approached.

**RISK OF EXPLOITATION AND THE BUYING AND SELLING OF ORGANS**

Solicitation may result in the exploitation of vulnerable populations such as the poor, psychologically unstable, and mentally impaired. One would hope that the psychosocial evaluation of potential donors by each transplantation center would uncover such instances, but this may not always be possible.

Furthermore, illegal demands for payment at the time of solicitation have already been made by prospective living donors. The potential for illegal transactions as a result of solicitation puts transplantation physicians and centers at risk for unknowingly participating in the buying and selling of organs. It is more likely that recipients who have substantial financial resources and are willing to risk violating the law will be able to buy a donor organ. Some have proposed that the donor and recipient should sign an affidavit certifying that no reward has been paid for the organ, but such an affidavit will not prevent these transactions. Although there may be exchanges of goods or favors between living related donors and recipients or between those with preexisting relationships, it appears more likely that the motives of families and friends will be purely altruistic. In contrast, the motives of strangers are apt to be much more complex. Unfortunately, no data have been obtained to directly address this issue.

Finally, years after the donation, a living donor could have a financial or other need and could contact the recipient with a request for assistance, placing the recipient and his or her family at risk of violating current laws that prohibit the buying and selling of organs. In many nondirected, living-donation programs, the donor and recipient are anonymous unless both wish to meet. This anonymity protects the donor from an unwanted relationship with the recipient, maintains the true altruism of the donation, and frees the recipient from any further obligation to the donor. Many believe this should be the preferred arrangement for such donations.

**DOES SOLICITATION DIVERT ORGANS TO UNSUITABLE CANDIDATES FOR TRANSPLANTATION?**

Solicitation by potential recipients who may not be appropriate candidates for transplantation may occur. For example, the young man with liver cancer described previously did not meet the added priority criteria for hepatocellular carcinoma because his disease was far advanced, and he was low on the waiting list. He received a liver outside of the normal allocation system but died of recurrent tumor less than 1 year after transplantation. Was that a fair or efficient use of a scarce resource? What happened to the patient on the waiting list who would have received that liver had the normal allocation policy been followed?

**CONCLUSIONS**

The solicitation of families of deceased donors by recipients or their agents to direct the donation to a recipient other than the person at the top of the waiting list should not be permitted. Solicitation of living donors and the directed donation that results may involve unethical and illegal practices that place recipients and donors at risk and should be rejected by the transplantation community. A nondirected donation from a deceased or living donor to the first patient on the waiting list is permissible and preferable and is unlikely to discourage donation. UNOS is best positioned to and should regulate living organ donation and allocation, and it should apply the same principles used for nondirected, deceased-donor organ allocation. The directed donation of organs from deceased and living donors to family members and persons with a preexisting emotional relationship should be permitted. A clear policy that defines the preexisting emotional relationships that are acceptable must be developed, and the final
rule, which technically permits any directed donation of deceased-donor organs to a named person, should be amended to be consistent with this policy.

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Pioglitazone in Nonalcoholic Steatohepatitis

TO THE EDITOR: Belfort and colleagues (Nov. 30 issue) report on the efficacy of 6 months of treatment with pioglitazone with respect to the histologic severity of nonalcoholic steatohepatitis. I agree with the authors’ conclusion that the results serve as “proof of concept” that pioglitazone leads to histologic improvement in patients with this condition.

These results apply to nonalcoholic steatohepatitis in patients with type 2 diabetes mellitus or impaired glucose tolerance; however, they may not apply to the general population of patients with nonalcoholic steatohepatitis. Indeed, although this condition is frequently associated with obesity and type 2 diabetes, only one third of people with nonalcoholic steatohepatitis have type 2 diabetes.2-4

Moreover, it would be interesting to know whether pioglitazone is equally effective in improving the hepatic histologic findings in patients with type 2 diabetes and in those with impaired glucose tolerance. In the study by Belfort and colleagues, information on the exact proportion of patients with type 2 diabetes and of those with impaired glucose tolerance is lacking. Patients with type 2 diabetes have a higher risk of fibrosis and cirrhosis than do patients who do not have diabetes.2-4 Thus, the efficacy of pioglitazone in reducing the severity of nonalcoholic steatohepatitis might be different among patients with type 2 diabetes than among those with impaired glucose tolerance.

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TO THE EDITOR: The study by Belfort et al. shows a significant effect of pioglitazone, as compared with placebo, for the treatment of nonalcoholic steatohepatitis. However, the average weight reduction was only 0.5 kg over a 6-month period in subjects in the placebo group; this may explain the lack of improvement in indicators of nonalcoholic steatohepatitis in these subjects. Thus, the ineffective diet and exercise program could have led to an overestimation of the effect of pioglitazone. Belfort and colleagues attempt to address this limitation by showing that there was no hepatic histologic improvement in 12 subjects who were assigned to placebo and who lost a mean (±SD) of 3.2±0.5 kg. This sample size may lack the power to detect differences. Also, the authors cite a meta-analysis that reported the variable ef-
The effects of pioglitazone on the liver were more strikingly demonstrated by Belfort et al. as a result of the antiinflammatory effect on the liver. The improvement in the pathological abnormalities is exacerbated by insulin resistance and suppresses cytokine-mediated inflammation. However, it is not clear whether the beneficial effect of pioglitazone occurs through improved insulin sensitivity or its direct antiinflammatory effect on the liver.

Recently we established an animal model of steatohepatitis in which the pathological abnormalities are exacerbated by insulin resistance and obesity-related diabetes. In this model, pioglitazone inhibits the activation of stellate cells, which play a central role in hepatic fibrosis, probably by down-regulating the hepatic expression of transforming growth factor β and inflammatory cytokines. The improvement in the pathological findings as a result of the antiinflammatory effects of pioglitazone on the liver were more striking than expected.

In their placebo-controlled trial, Belfort et al. showed consistent improvement in liver measurements after weight reduction. The standard treatment for nonalcoholic steatohepatitis and other obesity-related diseases is weight reduction, achieved through concurrent diet and exercise. It is impossible to predict what the real difference would have been if the subjects in the placebo group had lost weight. Future research regarding nonalcoholic steatohepatitis will require comprehensive programs of diet and exercise to estimate accurately the effects of drugs over standard treatment.

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TO THE EDITOR: In their placebo-controlled trial, Belfort et al. show that pioglitazone leads to improvement in subjects with nonalcoholic steatohepatitis by reducing insulin resistance and suppressing cytokine-mediated inflammation. However, it is not clear whether the beneficial effect of pioglitazone occurs through improved insulin sensitivity or its direct antiinflammatory effect on the liver.

Recently we established an animal model of steatohepatitis in which the pathological abnormalities are exacerbated by insulin resistance and obesity-related diabetes. In this model, pioglitazone inhibits the activation of stellate cells, which play a central role in hepatic fibrosis, probably by down-regulating the hepatic expression of transforming growth factor β and inflammatory cytokines. The improvement in the pathological findings as a result of the antiinflammatory effects of pioglitazone on the liver were more striking than expected.

We agree with Chavez-Tapia et al. that lifestyle modification and weight reduction are the cornerstones of treatment for both type 2 diabetes and nonalcoholic steatohepatitis. However, we did not compare the effect of weight reduction (in the...
placebo group) with the effect of pioglitazone treatment. The two groups received identical nutritional counseling to reflect the current standards of care. Against this background, we compared placebo with pioglitazone. Our results match those of the clinical-practice and lifestyle-intervention studies that show the difficulties of achieving and maintaining weight loss in patients with nonalcoholic steatohepatitis. In the meta-analysis of 13 trials by Wang et al., the studies were typically small (only 3 had >50 patients) and uncontrolled (10 were case series), and they frequently used a surrogate primary end point (i.e., liver aminotransferase levels in 8 of the 13 trials); steatosis was the only histologic improvement. As in our placebo group, improvement in aminotransferase levels does not necessarily translate into improved liver histologic scores. Recently, Huang et al. reported a trend toward a histologic benefit but not a significant benefit of a year-long, intense nutritional counseling program in patients with nonalcoholic steatohepatitis. Weight reduction in their study (−2.9 kg) was similar to that in our patients in the diet-plus-placebo group who had a response to the study treatment (−3.2 kg). Moderate weight loss may improve liver histologic results, but long-term controlled trials using histologic results as the primary end point are needed.

As suggested by Ota et al., pioglitazone not only may improve insulin resistance but may have direct antiinflammatory effects on the liver. In our study, pioglitazone ameliorated systemic inflammation by lowering plasma C-reactive protein, tumor necrosis factor α, transforming growth factor β, and intracellular adhesion molecule and vascular-cell adhesion molecule concentrations (unpublished data). Obesity and high-fat diets may activate the hepatic inhibitor of κB kinase β and nuclear factor-κB inflammatory pathways and promote insulin resistance. As Ota and colleagues suggest, more work is needed in this area.

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Bivalirudin in Acute Coronary Syndromes

TO THE EDITOR: The main message of the study of bivalirudin in patients with acute coronary syndromes, reported by Stone et al. (Nov. 23 issue) is that, as compared with heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin alone offers a similar degree of protection against ischemic events and a significant reduction in bleeding complications. Most of the benefit of bivalirudin alone was associated with the lower rate of catheterization-related hemorrhage (0.8% with bivalirudin alone vs. 2.5% in the other two groups). Given the importance of bleeding complications for the interpretation of the results, it is surprising that no details on the arterial access used during the trial were provided, although the numbers reported suggest a predominant use of the transfemoral approach. If this is true, considering that severe local arterial complications are rare when the radial artery is used for diagnostic or interventional procedures, probably little or no benefit should be expected from bivalirudin in the setting of transradial catheterization. We still need better antithrombotic strategies for high-risk acute coronary syndromes, but the reduction of vascular complications is best accomplished by a wider application of the transradial technique.

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TO THE EDITOR: Stone et al. suggest that bivalirudin alone, as compared with unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor or bivalirudin plus a glycoprotein IIb/IIIa inhibitor, is associated with similar rates of ischemia and a lower rate of bleeding in patients with acute coronary syndromes who are undergoing invasive procedures. Bivalirudin is a small synthetic peptide modeled after hirudin, a protein that is 65 amino acids in length and of nonhuman origin. Antibodies against lepirudin have been shown in several studies. In particular, lepirudin has been linked to at least nine cases of severe anaphylaxis, four of them with a fatal outcome. In contrast, no clinically relevant antihirudin antibodies formation has been reported to date. However, since bivalirudin and lepirudin have some identical amino acid sequences, the possible formation of such antibodies or cross-reactivity due to previous exposure to lepirudin is plausible. Thus, before bivalirudin can be widely used as a standard anticoagulant during coronary interventions, more data concerning its safety, especially in the setting of reexposure, are warranted.

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THE AUTHORS REPLY: Sanmartín questions whether the choice of a vascular access site affected the findings of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, noting that hemorrhagic complications are less frequent with radial arterial puncture than with femoral arterial puncture. Of the 13,819 patients from 17 countries enrolled in the ACUITY trial, radial-artery access was used in only 798 patients (5.8%), reflecting the well-recognized infrequency with which this vessel is selected for angiography and coronary intervention. Overall bleeding rates were lower with radial than with femoral access. Given the small number of patients in whom radial access was used, firm conclusions regarding the relative rates of bleeding among the three groups that underwent randomization cannot be achieved, although intuitively, the efficacy of bivalirudin monotherapy in reducing bleeding unrelated to the access site is independent of vascular access.

Bonvini and colleagues raise important issues regarding bivalirudin immunogenicity and potential cross-reactivity with recombinant hirudin. Recombinant hirudin is a protein of 65 amino acids derived from yeast cells with a defined tertiary and quaternary structure containing three disulfide cross-links. In contrast, bivalirudin is a smaller, synthetic peptide (20 amino acids) that lacks disulfide bonds, with a resultant minimal secondary structure. As such, bivalirudin would be expected to be less immunogenic than hirudin. Bivalirudin is also typically administered for less than the 2 to 3 days necessary for a B-cell response. Among 494 patients in clinical trials who received bivalirudin and who were tested for antibodies, treatment-emergent antibivalirudin antibodies developed in only 2 patients (0.4%), and neither patient had an allergic reaction. Regarding readministration, 13 patients received repeat courses of bivalirudin 3 months apart and underwent serial antibody testing. Antibivalirudin antibodies did not develop in any of the patients after either initial or repeat administration. In 52 patients with heparin-induced thrombocytopenia undergoing angioplasty with bivalirudin on two or more occasions, no allergic reactions or thrombocytopenia developed. In post-marketing surveillance of more than 1.3 million patient-exposures to bivalirudin, anaphylaxis or serious
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Treatment of Restenosis with a Paclitaxel-Coated Balloon Catheter

TO THE EDITOR: We question the conclusion by Scheller and colleagues (Nov. 16 issue) that paclitaxel-coated balloon catheters significantly reduce the incidence of adverse outcomes in patients undergoing percutaneous coronary intervention for in-stent stenosis. First, the trial was reported to be a double-blind study, but the investigators were aware of assignments to study groups because the paclitaxel-coated balloons were a different color from the uncoated balloons. The reduction in major cardiac events in patients who received treatment with a paclitaxel-coated balloon was driven primarily by a reduction in target-lesion revascularization, a subjective end point that was based on symptoms and angiographic appearance reported by investigators who were aware of study-group assignments. Two of the authors were also coinventors on a patent for the paclitaxel-coated balloon evaluated in the study.

Second, the clinical relevance of a reduction in restenosis is uncertain. In-stent stenosis is usually a nonfatal condition, and the use of drug-eluting stents to reduce restenosis may lead to a late increase in the rate of death from noncardiac causes. Adequately powered and blinded randomized clinical studies with extended follow-up are required to demonstrate both the efficacy and the safety of paclitaxel-coated balloon catheters.

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TO THE EDITOR: Although we agree with the opinion of Camenzind in the editorial accompanying the article by Scheller at al., we are concerned about the information shown in Figure 1, which we believe is not evidence-based. In Panel A, late luminal loss is graphically represented as a “normal” curve. Although late luminal loss is commonly expressed as a mean ±SD, the distribution of late luminal loss is not “normal” but “bimodal.” This also is true of drug-eluting stents. Thus, the relationships among late luminal loss, binary restenosis, and repeated revascularization are more complex than they appear in Panel A.

In Panel B, a J-curve relationship between late luminal loss and clinical events is represented. The hypothesized increase in the rate of death or infarction with negative late luminal loss has never been proved, and the sentence “Late thrombosis causing myocardial infarction or death is more likely to occur among patients with minimal or negative late luminal loss” is not evidence-based.

Late luminal loss is a simple bidimensional measure that is used as a surrogate for a complex three-dimensional phenomenon. It has inherent limitations. The use of late luminal loss as a
surrogate for stent endothelialization is inaccurate, since evidence correlating these measures is lacking.

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In their second comment, Sun and Eikelboom refer to an ongoing discussion of the safety of drug-eluting stents, which was not the subject of our study. We do agree that larger and longer trials will be necessary to confirm the benefits suggested by the initial report; this point was acknowledged in our discussion.

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THE EDITORIALIST REPLIES: With respect to the comments of Agostoni et al.: the figure in the editorial depicts a concept whose message is not dependent on the best mathematical fit of the distribution curve of late luminal loss. The intent was, rather, to illustrate the shift of the distribution curve to the left as a consequence of treatment approaches that inhibit restenosis. Thus, with such therapies, vascular widening develops in a larger portion of the treated population, which is reflected in a larger negative area of late luminal loss. This phenomenon reflects an abnormal healing response previously observed after brachytherapy for the treatment of restenosis; the clinical consequences of this response have been well documented.1,2

We are discovering that any potent, site-specific approach to treatment that interferes with arterial healing may create a potential local prothrombotic milieu and carry the clinical risk of myocardial infarction and death.4 The issue is important because angiographic findings have been traditionally used in interventional cardiology as surrogate end points for the clinical outcome. However, excellent luminal results (negative late luminal loss) may predict a worse clinical outcome (as shown by the J curve), suggesting that an established principle of therapeutics is seen with endovascular interventions: the more potent the treatment, the stronger the adverse effect.

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The Asthma Epidemic

TO THE EDITOR: Eder and colleagues (Nov. 23 issue)1 describe the high prevalence and incidence of asthma in the Western world. However, survey instruments that rely on physicians’ or patients’ reports of diagnosis for case ascertainment do not provide robust measurements of asthma and may be unreliable for estimating its prevalence.2 No single instrument can identify asthma with certainty. Exacerbations of asthma are episodic, are of limited duration, and share clinical features with other disorders, complicating accurate diagnosis. In addition, no theory has been confirmed to explain an asthma epidemic.

The authors should comment more analytically on the possibility that asthma is overdiagnosed by clinicians3,4 and that social marketing may contribute to the increased diagnosis of asthma and, in turn, to the perception of an epidemic.5 Multicenter clinical trials of treatments for asthma that have well-defined enrollment criteria typically recruit few subjects as compared with trials of treatments for cardiovascular diseases with a similar reported prevalence. The reasons for this disparity defy simple explanation if the prevalence of asthma is 5.8% in the United States and is substantially higher in many other Western nations.1

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THE AUTHORS REPLY: As we stated in our review article, the results of various epidemiologic studies suggest that “part of the increase in the prevalence of asthma is attributable to changes in diagnostic labeling. The magnitude of the resulting bias in different populations is, however, difficult to appraise.” Nevertheless, this bias is unlikely to completely explain the increase in the prevalence of asthma over time. First, there is evidence that the prevalence of objective markers associated with asthma, such as atopy, has increased over time, although these markers are admittedly not identical to asthma. Second, the bias will affect the rate of diagnosis of asthma by physicians in children with wheezing. In Aberdeen, Scotland, this rate has indeed increased: asthma was diagnosed in 28% of children with wheezing in 1964, in 49% of such children in 1989, and in 64% in 1999.1 Yet the prevalence of wheezing, not only the prevalence of the diagnosis of asthma by physicians, increased over time. Because most studies do not report the rate of diagnosed asthma among children with wheezing, the magnitude of the bias is difficult to appraise.

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Compulsory HPV Vaccination

TO THE EDITOR: In his Perspective article on the ethics and politics of compulsory vaccination against human papillomavirus (HPV) (Dec. 7 issue), Colgrove highlights the perception that HPV vaccination is a women’s health issue, yet he also alludes to the question of how much herd immunity may be necessary to protect unvaccinated women from cervical cancer. Exploration of the question of herd immunity exposes HPV vaccination as a men’s health issue as well — that is, men are responsible for half the cases of transmission of the virus, and vaccinating men, if found to be effective in reducing the transmission of HPV to women, could be an important mechanism for reducing the burden of cervical cancer. At least one recent study involving boys has reported noninferior immunogenic responses to all four types of HPV covered by the quadrivalent vaccine. We have insufficient data to evaluate how great an effect vaccinating boys could have on reducing transmission to women. Therefore, the possibility of vaccinating persons of both sexes should be further evaluated if we are to consider all policy options for preventing cervical cancer.

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TO THE EDITOR: The political implications of compulsory HPV vaccination deserve further attention. Unfortunately, Colgrove only briefly mentions Michigan’s proposed legislation regarding HPV vaccination, and he erroneously describes it as compulsory vaccination. What Michigan’s proposed legislation actually requires is that parents receive information on the connection between HPV and cervical cancer before making an informed decision about HPV vaccination for their adolescent daughters. This broad allowance for informed refusal — for any reason — is clearly outside the realm of traditional programs of compulsory vaccination, which permit only religious or medical exemptions. By allowing informed refusal, Michigan’s ingenious proposed legislation not only respects individual liberties but also ensures that all adolescent girls will be offered the vaccine and eliminates the opportunity for passive omission by parents and physicians. Other states considering HPV-vaccination legislation should take a serious look at Michigan’s proposed legislation and follow its lead in balancing individual liberties with the legitimate health concerns raised by HPV and cervical cancer.

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1. Michigan Senate bill 1417 (as passed on Sept. 20, 2006).

THE AUTHOR REPLIES: Basu makes an important point about the indirect effect that vaccinating boys against HPV might have on the incidence of cervical cancer among women. A policy of vaccinating one segment of the population for the primary purpose of reducing the incidence of a disease in another segment was also undertaken in the case of the rubella vaccine, which is routinely given to all children for the primary purpose of reducing the incidence of congenital defects in infants born to women who contract rubella during pregnancy.

Segraves is incorrect in stating that a vaccination law allowing informed refusal for any reason “is clearly outside the realm of traditional programs of compulsory vaccination, which permit only religious or medical exemptions.” Almost half the states that allow exemptions for medical or religious reasons also permit exemptions for personal or philosophical concerns. It is true that a law such as Michigan’s that contains an opt-out provision does not represent compulsion in a strict sense, but as used in common parlance, the term “compulsory” applies to school-based vaccination policies in the United States. Some states place administrative burdens on parents who seek exemptions — such as requirements to obtain a form from a local health department, to write a letter explaining their decision, or to renew the exemption annually — that may in practice make it difficult to claim an exemption.

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TO THE EDITOR: I retract the Image in Clinical Medicine presenting a complication of central venous catheterization that was published in the January 11, 2007, issue of the Journal,1 because the figures, which I had previously submitted elsewhere, have already been published.2,3

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Prolonged Bisphosphonate Release after Treatment in Children

TO THE EDITOR: Bisphosphonates are widely used in the management of osteoporosis. They are cleared rapidly from the circulation, with about half the administered dose taken up by the skeleton and the rest excreted unmetabolized by the kidneys.1 At the bone surface, bisphosphonates suppress bone resorption and are embedded in bone. The embedded bisphosphonate is released slowly from bone, presumably after the resumption of bone remodeling at previously exposed sites.

A terminal half-life of 10 years has been estimated for alendronate in the longest pharmacokinetic study in humans, up to 1.5 years, after intravenous administration. There is no direct evidence of release of bisphosphonates in patients who receive long-term, continuous oral treatment, the most common therapy for osteoporosis. Such information can help explain changes in bone remodeling and in bone mineral density after the cessation of long-term treatment and can be obtained by measuring the urinary excretion of bisphosphonates, the only route of their elimination from the body.

We measured drug excretion after the cessation of long-term treatment with daily oral pamidronate in seven young patients with severe osteoporosis — four with juvenile osteoporosis, two with osteogenesis imperfecta, and one with juvenile arthritis. All but one of the patients has been described previously2; all had normal renal function. At the start of treatment, the patients were between the ages of 10 and 14 years, and they received pamidronate for a mean period of 6.7 years (range, 4 to 10). Excretion of pamidronate was measured in 24-hour urine samples with the use of fluorometry and high-performance liquid chromatography at a mean interval of 7.7 years (range, 3 to 12) after treatment had been discontinued; the total mean observation period was 12.9 years (range, 7 to 19).

Pamidronate was detectable in urine samples from the patients up to 8 years after the cessation of treatment (Fig. 1A). There was a trend toward reduced excretion of the drug with time, but there was no relation between the cumulative dose of the bisphosphonate and its excretion in urine (Fig. 1B).

These results provide direct evidence of long-term release of a bisphosphonate and show that

the drug can persist in the body for many years after the discontinuation of treatment. The activity of the released bisphosphonate is unknown but may account for the stabilization of bone mineral density and fracture rates after the discontinuation of treatment in patients with osteoporosis. In addition, the findings suggest a need for caution in the selection of girls and young women for bisphosphonate treatment, since there is only anecdotal information about the safety of the drugs during fetal development.

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Figure 1. Twenty-Four-Hour Urinary Excretion of Pamidronate in Seven Young Patients with Osteoporosis.
Panel A shows the levels of pamidronate excreted after the cessation of daily oral treatment, and Panel B shows the levels of excretion according to the cumulative doses of the drug that were received. The dashed lines indicate the assay’s lower limit of detection.

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THE RENAISSANCE HOSPITAL:
HEALING THE BODY AND HEALING
THE SOUL


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his beautifully illustrated and thoroughly researched study surveys Florentine hospitals from their earliest appearances around the year 1000 to the reforms of Cosimo I in 1542. It concentrates, however, on the period after the Black Death from 1348 up to the 16th century, when sources such as hospital accounts, pharmacy books, and the tax registers of medical practitioners either became available for the first time or increased considerably in number. The book offers a holistic account of the hospital. Throughout, author John Henderson emphasizes the hospital’s dual concerns: healing the body and healing the soul. Renaissance hospitals, with their cloisters and high ceilings, and their practices, with the staff washing the feet of patients in imitation of Christ, are exposed in their duality, fulfilling currently perceived dicta of medical theory and spiritual ends.

To be sure, the hospital was not a Renaissance invention. In fact, more hospitals were founded in Florence from the mid-13th to the mid-14th century than at any other time. Nor were hospitals before the plague exclusively of the kind that offered lodging and food to pilgrims and the poor, without regard for medical care. In fact, Henderson traces the origins of the medicalization of the medieval hospital to the 1330s and 1340s, when physicians, surgeons, and other health practitioners first became regular members of the staff. Nonetheless, the Black Death and the periodic appearances of the disease thereafter spurred the transformation of the hospital from an enterprise that focused predominantly on hospitality to one that provided medical care.

As doctors and nurses became more central to hospital operations, charity and medical services became more specialized, with different founda-
and beauty. In addition to being masterful achievements in Renaissance architecture — one example being Filippo Brunelleschi’s Ospedale degli Innocenti (Hospital of the Innocents), built in phases during the years 1419 to 1427 — hospital chapels such as Santa Maria Nuova’s Sant'Egidio became centers of Renaissance art patronage. These hospitals also attracted the services of the most prestigious doctors in Florence, who often donated their time free of charge or at reduced rates. By the end of the 15th century, hospitals such as Santa Maria Nuova had become centers of medical training.

Far from being places of confinement, the hospitals received patients who often had struggled to be admitted. Nor were new hospitals (such as San Matteo) or older hospitals that were greatly expanded during the Renaissance (such as Santa Maria Nuova) places for beggars or the utterly destitute. Instead, patients of the Renaissance hospital ranged from the respectable poor, represented by artisans and shopkeepers, to members of Florence’s most renowned families. Finally, these institutions were hardly hellholes of death; only 5 to 12% of those admitted died during their stay.

In the last part of his survey, Henderson turns to medicine, in particular to a development that he sees as demonstrating a third phase in the medicalization of hospitals — the establishment of permanent pharmacies within wards and the appearance of new books and ordinances to advise and regulate the dispensation of drugs. At Santa Maria Nuova, these prescriptions were not derived solely from classical or Arabic theory but came from recipes “tried and tested” within the hospital itself. Henderson describes these concoctions in elaborate detail but ultimately shies away from evaluating their efficacy, even going so far as to suggest that such an endeavor would be misguided. Perhaps future scholars with stronger pharmaceutical backgrounds, who are less squeamish about using knowledge from the present to ask questions from the past, will be able to use Henderson’s carefully gathered evidence to investigate medical progress, or the lack thereof, within these Renaissance temples of care for the body and the soul.

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**SOLVING THE HEALTH CARE PROBLEM: HOW OTHER NATIONS SUCCEEDED AND WHY THE UNITED STATES HAS NOT**


*Status quo is a powerful determinant of both belief and behavior. Many of the things we do and the things we believe in transpire because they are what we have always done or believed. This is why incumbents win elections, why we always choose the same flavor of yogurt, why we take the same route to work, why we prescribe the same antihypertensive medications. For most Americans, our health care system is the way it is simply because this is the way it has been. The logic of changing doctors when you change insurance, changing insurance when you change jobs, and paying out of pocket when you do not have a job makes some sort of sense because this is simply the way things are.*

A visitor from Mars, or Europe perhaps, would find this status quo shocking, much the way American tourists abroad are sometimes shocked to find that they are not supposed to dispose of toilet paper in some toilets. In this regard, Pamela Behan has something of an outsider’s view of America. The title of her book, *Solving the Health Care Problem*, assumes that the lack of national health insurance is the biggest problem in U.S. health care, which is what you learn once you read the book. This is surely what most Europeans would call the biggest problem in U.S. health care. But I’m sure that many Americans, even thoughtful ones, might think that other issues — the cost of prescription drugs, inequitable funding for research, Food and Drug Administration oversight — are the biggest problems. Even the book’s subtitle — *How Other Nations Succeeded and Why the United States Has Not* — assumes that the adoption of national health insurance is the definition of success in solving the biggest health care problem. I happen to agree with Behan that national health insurance is what the United States needs, but the title of her book and her approach make assumptions that might put off some of the intellectuals and policymakers who play an influential role in the future of American health care.

The book lays out a very specific methodolo-
gy to answer the question that the subtitle poses. It chooses Canada and Australia as countries that are relatively similar to the United States, and it traces the paths these societies traveled to achieve national health insurance. Then it sketches the (unsuccessful) path that the United States has traveled. Approaching the problem as if it were a case–control study, the author attempts to compare these three experiences and calculate the differences, with the goal of explicating what the United States would need to do to obtain that holy grail.

Readers from the medical community are well aware of the limitations of case–control studies involving groups of human beings — even large, well-selected groups. But to compare three societies, with incalculable historical, political, and social differences that could conceivably outweigh their similarities, in the expectation of a clear finding is a tall order indeed. Aside from speculation, however, there are not many other research options out there, so Behan offers what is probably the most careful analysis that can be performed.

The first chapter of the book frames the basic research question in three brief pages; there is a casual mention that the last chapter “describes the study’s conclusion in layman’s terms, including the changes that may be needed to solve the problems of health care access and protection from its costs in the United States.” Were this an Agatha Christie mystery or a José Saramago novel, I wouldn’t dare peek at the last chapter. But in a book that intends to provide the all-embracing research details in the intervening chapters, nonacademicians are all but invited to skip to the plot’s climax. If suspense is important to your reading enjoyment, then stop reading this review now, because I will divulge the outcome. The answer is that in order to enact national health insurance, countries need to achieve four necessary conditions: both federal and financial authority in health care (that is, the national rather than the local government manages and funds the health care system), a multi-party system, a health care legislative legacy, and strong trade unions. Countries also need one of two sufficient conditions: labor-party power and lack of veto points (that is, the ability to block legislation — easily — from within or outside the system).

The United States comes up short on almost every one of these six counts. I found the discussion of the veto points the most interesting. For the past century, almost every legislative gesture was soundly defeated by an unelected body — the American Medical Association (AMA). Behan takes pains not to paint the AMA as the devil, since plenty of senators, representatives, and presidents added their own obstructionism. But the historical discussion reveals that the most consistent pressure came from within medicine itself.

The very nature of the American political system — the winner-take-all voting system, the free-market attitude toward lobbyists, the ability of legislators to compromise bills into nothingness — makes far-reaching social change almost impossible. The necessary and sufficient conditions needed to achieve universal health insurance seem constitutionally unachievable in American society. Behan’s sad conclusion is that “many of the chief blessings of democracy” — and health care as a right is clearly included here — “will, ironically, elude those pioneers of democracy, the American people.”

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OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION


In the past few years, various books and scholarly articles have portrayed pharmaceutical innovation as plagued by myriad problems, many of which could be addressed through greater (or at least alternative) regulatory intervention. In Overdose, prominent legal scholar Richard Epstein presents a different story. His comprehensive and ambitious discussion proceeds chronologically, starting with the research and development process, moving to Food and Drug Administration (FDA) approval and postapproval marketing, and ending with a discussion of tort liability. Throughout the book, Epstein asserts the theme suggested in his title — that regulatory intervention in
the pharmaceutical industry is already too extensive and that proposed interventions would exacerbate rather than ameliorate current difficulties.

Epstein begins by suggesting that the pharmaceutical industry may be the victim of unreasonable expectations because of its past success in picking the “low-hanging fruit” of drug innovation — that is, therapies that are relatively inexpensive to develop but nonetheless have high social value. He appears skeptical that current or future advances in basic science will generate additional low-hanging fruit. Moreover, according to Epstein, the scientific challenge is greatly aggravated by regulatory excess.

Epstein then focuses on strategies that various economists and policy analysts have suggested to address the inefficiencies created by drug patents. He deploys a series of powerful arguments against the practicality of schemes that would regulate pricing, “buy out” drug patents, or use public funding for all stages of drug development.

Epstein is perhaps most critical of what he argues is a tendency on the part of the FDA to be unduly risk-averse. In his view, the FDA’s excessive desire to avoid mistakes in drug approval (false positives) causes it to deny approval of many useful drugs (false negatives). In Epstein’s estimation, heterogeneity in patient reaction to drugs should lead the FDA to approve all drugs that show benefit for some identified subgroup. Patients, together with their physicians, can then determine “downstream” whether they fall into the particular subgroup that benefits. The theme of market-based differentiation also informs Epstein’s defense of “me-too” drugs — patented drugs that fall into the same therapeutic class as other patented drugs but may have somewhat different efficacy or side-effect profiles in particular patients.

The success of Epstein’s vision turns in large part on whether information that allows for downstream differentiation is available in most cases. Unfortunately, accurate information may be underproduced by ordinary marketplace mechanisms. Related to this issue is the fact that patients and physicians must be motivated to demand such information. Reductions in the availability of court-imposed damages after the fact (a move advocated by Epstein) may spur patients to demand more comprehensive information at the outset. But Epstein’s otherwise impressive account largely ignores an institutional factor that distorts information markets — insurance. Because insured patients bear only indirect financial responsibility for their purchasing decisions — and their physicians typically bear none at all — incentives to parse complicated information about future benefits and risks may be diminished. Certainly, patients and physicians appear to have had little interest in parsing cost–benefit profiles — profiles that might call into question the prices that can be charged for at least some me-too drugs.

Even in the optimistic scenario in which information markets on individualized risk and benefit would be robust and in which physicians and patients (or at least insurers) would pay close attention, the future for pharmaceutical firms might not be rosy. The FDA might approve many more drugs, but the markets for these drugs would be smaller. In the end, the biggest challenge to pharmaceutical companies’ current business models may not be government regulation but advances in science that balkanize potential markets.

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MEDICINE AND THE MARKET:
EQUITY V. CHOICE

By Daniel Callahan and Angela A. Wasunna. 320 pp.
Baltimore, Johns Hopkins University Press, 2006. $35.

The objective of this book is to provide a comprehensive discussion of the conflict between the use of markets (aimed at achieving efficiency) and the use of government funding and controls (aimed at achieving equity). Authors Daniel Callahan and Angela A. Wasunna attempt to cover the field in two dimensions: content areas (such as physician, hospital, and pharmaceutical services) and international variation in the use of market and government strategies. Their goals are ambitious, and they outline the key issues in both of these dimensions. They also provide an extensive list of others who have written about or taken up positions on this subject. Finally, they provide a comprehensive review of the health care systems of many countries as well as a useful bibliography.

When I read a book like this, I ask myself three
questions: Would an expert in the area view the information as accurate? Would a novice in the area come away with an understanding of the key issues? Would an expert gain new insights?

With regard to accuracy, I consider the book to be incomplete in many ways. I could not find any section that actually laid out the theoretical arguments concerning why market forces are desirable to achieve efficiency, why government action is needed to achieve equity, and where the two mechanisms conflict. There was no discussion of what constitutes perfect competition or how health care markets contain many sources of imperfection that cause market distortions. The authors allude to these areas but never address them in any depth. The descriptions of two areas that I know best — the Canadian health care system and the pharmaceutical industry — are incomplete. For Canada, I could not find a full discussion of the arguments in favor of or against the outlawing of a two-tiered system of public and private health care. And there was no reference to the pharmaceutical industry as an example of a price-discriminating monopoly, as an explanation of its behavior around the world.

Would a novice come away from this book with an understanding of the issues? I believe not. Novices might pick up a few “sound bites” and would certainly have a list of “who's who” in the field, but I doubt that they could adequately explain the true nature of the issues.

Does an expert come away from the book with a better understanding? In one regard, the answer is yes, in that the book describes the health care systems of many countries — particularly some of those in the developing world — that are not usually included in an international review. But these descriptions are so short that I consider them superficial.

I am extremely reluctant to write negative reviews that will appear in public, and so I apologize to these authors. It should be noted that the back cover of the book contains four positive assessments, written by knowledgeable people. So perhaps this reviewer’s opinion is not the prevailing one. Nonetheless, I cannot recommend this book highly.

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Correction
Case 38-2006: A 5-Year-Old Boy with Headache and Abdominal Pain (December 14, 2006;355:2575-84). At the beginning of the article, under “Presentation of Case,” Dr. Zanger’s first name should read “Kerstin” (not “Kirsten”). Also, in Table 1 (page 2576), the entries for the rows under “Cerebrospinal Fluid” were incorrect. At first admission, the red-cell count (per mm3) should have been 12,222 and the white-cell count (per mm3) 23; at second admission, the red-cell count should have been 1200 and the white-cell count 30; and at the current admission, the red-cell count should have been 4056 and the white-cell count 153. The reference range for white cells in the cerebrospinal fluid should be 0-5 cells per mm3. The text and the table have been corrected on the Journal’s Web site at www.nejm.org.

We regret the errors.

Notices
Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal’s Web site (www.nejm.org/meetings). The listings can be viewed in their entirety or searched by location, month, or key word.

StemConn 07
“Connecticut’s Stem Cell Research International Symposium” will be held in Hartford, CT, March 27 and 28.

Contact Connecticut’s Stem Cell Research International Symposium, c/o Connecticut United for Research Excellence (CURE), 300 George St., Suite 561, New Haven, CT 06511; or see http://www.stemconn.org; or call (203) 777 8747, extension 204; or e-mail info@stemconn.org.

Coagulation Testing Quality
The meeting will be held in Minneapolis, April 25–27.

Contact Sharon Preuss, Mayo Medical Laboratories Education Department, 3050 Superior Dr. NW, Rochester, MN 55901; or call (507) 284-8742; or fax (507) 284-8016; or e-mail press.sharon@mayo.edu; or see http://www.mayoreferenceservices.org/education.

15th Annual International Congress on Anti-Aging Medicine and Regenerative Biomedical Technologies
The congress will be held in Orlando, FL, April 26–28.

Contact American Academy of Anti-Aging Medicine, 1510 W. Montana St., Chicago, IL 60614; or call (800) 598-1267; or fax (561) 997-0287; or e-mail events@worldhealth.net; or see http://www.worldhealth.net.

Program in Palliative Care Education and Practice
The program will be held in Boston, April 17–24 (Part I) and Nov. 7–13 (Part II). It is presented by the Harvard Medical School Center for Palliative Care.

Contact Venus Watson, Dana–Farber Cancer Institute, 44 Binney St., SW411, Boston, MA 02115; or call (617) 582-7859; or fax (617) 632-6180; or e-mail pcallcare@partners.org.
A 21-Year-Old Woman with a History of Rheumatic Fever at 7 Years of Age presented with left-sided weakness. A large ischemic infarction involving the territory of the right middle cerebral artery was diagnosed. Cardiac evaluation revealed atrial fibrillation. Echocardiography showed normal aortic, pulmonic, and tricuspid valves, severe mitral stenosis with a valve area of 0.9 cm², and a large free-floating ball-valve thrombus in the dilated (to 5 cm in diameter) left atrium (Panels A and B, arrows), which partially obstructed the mitral valve intermittently (Panels C and D, arrows, and video). After initial stabilization, the patient was treated with digoxin, warfarin, and penicillin G benzathine at a dose of 1.2 million units every 21 days. After 6 months of physical therapy, she underwent an open mitral valvotomy with removal of the ball-valve thrombus and an increase in the mitral-valve area to 2.8 cm². Rheumatic heart disease remains a major health issue in India, with one recent study estimating the prevalence as 6.8 cases per 10,000 schoolchildren. Our patient is doing well after surgery, with minimal residual left hemiparesis and facial weakness.

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