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

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### 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.)

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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.<sup>1-6</sup> 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.<sup>7,8</sup> Impaired reendothelialization, late endothelial dysfunction, hypersensitivity reactions to the stent or its coating, and stent thrombosis have been suggested as potential causes.<sup>9-17</sup> 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.<sup>1-4</sup> 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 defined as an elevation of the creatine kinase MB level to three times the normal value in the absence of new, pathologic Q-waves; if no assay for creatine kinase MB was performed, elevation of the creatine kinase level to a value that was twice the normal value in the absence of new Q-waves was also considered a non-Q-wave myocardial infarction.

In the study protocols, stent thrombosis was defined as acute if it occurred within 24 hours after the index procedure, subacute if it occurred between 1 and 30 days after the procedure, and late if it occurred more than 30 days after the pro-

cedure. Acute and subacute stent thromboses were 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.\***

| Characteristic  | Sirolimus-Stent Group | Bare-Metal-Stent Group | P Value |
|---|-----------------------|------------------------|---------|
| Age — yr  |                       |                        |         |
| Median  | 61                    | 62                     | 0.91    |
| IQR   | 54–70                 | 54–70                  |         |
| Range   | 24–92                 | 32–89                  |         |
| Male sex — no./total no. (%)                              | 629/878 (71.6)        | 622/870 (71.5)         | 0.95    |
| Diabetes mellitus — no./total no. (%)                     | 195/878 (22.2)        | 233/868 (26.8)         | 0.02    |
| Insulin-dependent diabetes mellitus — no./total no. (%)   | 51/195 (26.2)         | 62/233 (26.6)          | 0.92    |
| Previous MI — no./total no. (%)                           | 287/865 (33.2)        | 308/862 (35.7)         | 0.26    |
| Previous PCI — no./total no. (%)                          | 201/878 (22.9)        | 184/869 (21.2)         | 0.39    |
| Previous coronary-artery bypass graft — no./total no. (%) | 66/878 (7.5)          | 64/870 (7.4)           | 0.90    |
| Hyperlipidemia — no./total no. (%)                        | 613/866 (70.8)        | 617/859 (71.8)         | 0.63    |
| Hypertension — no./total no. (%)                          | 557/873 (63.8)        | 548/866 (63.3)         | 0.82    |
| Current smoker — no./total no. (%)                        | 183/862 (21.2)        | 210/858 (24.5)         | 0.11    |
| Congestive heart failure — no./total no. (%)              | 36/869 (4.1)          | 49/861 (5.7)           | 0.14    |
| CCS angina classification III or IV — no./total no. (%)†  | 344/831 (41.4)        | 344/831 (41.4)         | 1.00    |
| Silent ischemia — no./total no. (%)                       | 152/783 (19.4)        | 155/793 (19.5)         | 0.95    |
| Ejection fraction — %                                     |                       |                        |         |
| Median  | 59                    | 60                     | 0.55    |
| IQR   | 50–64                 | 50–65                  |         |
| Range   | 25–91                 | 25–89                  |         |
| Coronary artery disease — no./total no. (%)               |                       |                        |         |
| Single-vessel   | 538/876 (61.4)        | 531/868 (61.2)         | 0.92    |
| Double-vessel   | 216/876 (24.7)        | 236/868 (27.2)         | 0.23    |
| Triple-vessel   | 122/876 (13.9)        | 101/868 (11.6)         | 0.15    |
| Procedure success — no./total no. (%)                     | 858/877 (97.8)        | 852/868 (98.2)         | 0.63    |
| Target vessel — no./total no. (%)                         |                       |                        |         |
| LAD   | 408/878 (46.5)        | 407/870 (46.8)         | 0.98    |
| LCx   | 210/878 (23.9)        | 207/870 (23.8)         | 0.90    |
| RCA   | 254/878 (28.9)        | 254/870 (29.2)         | 0.96    |
| LMCA  | 3/878 (0.3)           | 3/870 (0.3)            | 1.00    |
| SVG   | 0                     | 1/870 (0.1)            | 0.31    |
| Severe calcification — no./total no. (%)                  | 37/755 (4.9)          | 26/754 (3.4)           | 0.16    |
| Total occlusion — no./total no. (%)                       | 25/875 (2.9)          | 20/870 (2.3)           | 0.46    |
| Disease of branch vessel — no./total no. (%)              | 55/755 (7.3)          | 46/755 (6.1)           | 0.35    |
| Modified ACC–AHA lesion class — no./total no. (%)‡        |                       |                        |         |
| A   | 61/875 (7.0)          | 61/870 (7.0)           | 0.98    |
| B1  | 297/875 (33.9)        | 317/870 (36.4)         | 0.28    |
| B2  | 320/875 (36.6)        | 332/870 (38.1)         | 0.50    |
| C   | 197/875 (22.5)        | 161/870 (18.5)         | 0.04    |

**Table 1. (Continued.)**

| Characteristic                 | Sirolimus-Stent Group | Bare-Metal-Stent Group | P Value |
|--------------------------------|-----------------------|------------------------|---------|
| Reference-vessel diameter — mm |                       |                        |         |
| Median                         | 2.7                   | 2.7                    | 0.98    |
| IQR                            | 2.4–3.0               | 2.4–3.0                |         |
| Range                          | 1.5–4.5               | 1.7–5.4                |         |
| Lesion length — mm             |                       |                        |         |
| Median                         | 12.7                  | 13.1                   | 0.96    |
| IQR                            | 10.0–16.6             | 9.8–16.5               |         |
| Range                          | 3.2–41.5              | 3.4–48.9               |         |

\* Data for some characteristics were missing for some patients. IQR denotes interquartile range, MI myocardial infarction, PCI percutaneous coronary intervention, LAD left anterior descending coronary artery, LCx left circumflex coronary artery, RCA right coronary artery, LMCA left main coronary artery, and SVG saphenous-vein graft.

† Canadian Cardiovascular Society (CCS) angina classifications III and IV are defined as angina on mild exertion and angina at any level of physical exertion, respectively.

‡ Modified American College of Cardiology (ACC) and American Heart Association (AHA) lesion classes A, B1, B2, and C are defined as a low-risk lesion, a moderate-risk lesion with one or with two or more risk factors, and a high-risk lesion, respectively.

cedure 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.<sup>5</sup> 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.<sup>18</sup>

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](http://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.\***

| End Point                                 | Sirolimus-Stent Group (N=878) | Bare-Metal-Stent Group (N=870) | Adjusted Hazard Ratio (95% CI) | P Value |
|---|-------------------------------|--------------------------------|--------------------------------|---------|
|   | <i>number (percent)</i>       |                                |                                |         |
| Death                                     | 57 (6.7)                      | 46 (5.4)                       | 1.24 (0.84–1.83)               | 0.28    |
| Cardiovascular cause                      | 29 (3.5)                      | 23 (2.7)                       | 1.26 (0.73–2.18)               | 0.40    |
| Noncardiovascular cause                   | 28 (3.3)                      | 23 (2.8)                       | 1.22 (0.70–2.11)               | 0.49    |
| MI  | 55 (6.4)                      | 53 (6.2)                       | 1.03 (0.71–1.51)               | 0.86    |
| Q-wave                                    | 18 (2.1)                      | 11 (1.3)                       | 1.64 (0.78–3.47)               | 0.20    |
| Non-Q-wave                                | 37 (4.3)                      | 43 (5.0)                       | 0.85 (0.55–1.33)               | 0.48    |
| Death or Q-wave MI                        | 70 (8.2)                      | 55 (6.5)                       | 1.28 (0.90–1.82)               | 0.17    |
| Death or any MI                           | 100 (11.6)                    | 90 (10.5)                      | 1.11 (0.83–1.47)               | 0.48    |
| 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.

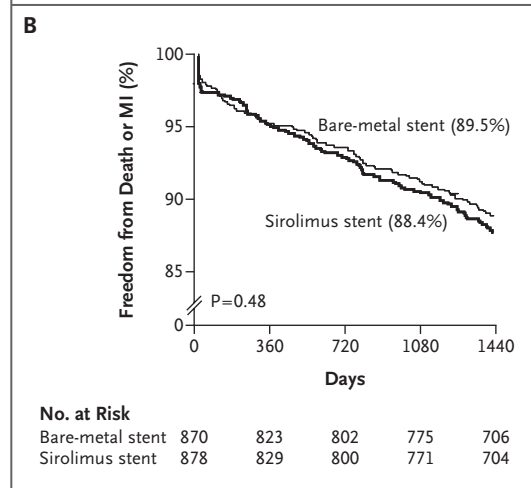
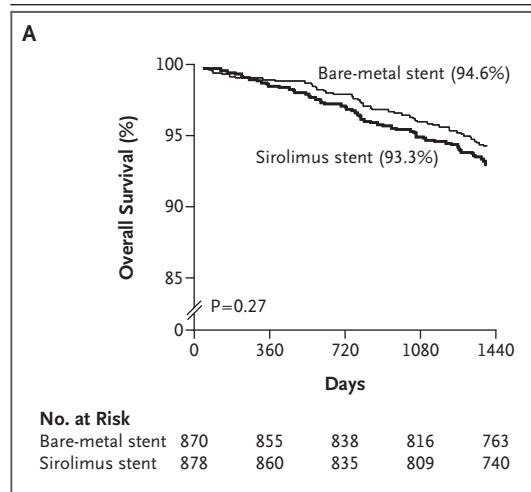
† Definitions of stent thrombosis according to the study protocols were as follows: acute, within 24 hours after the procedure; subacute, within 1 to 30 days after; and late, more than 30 days after.

‡ 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).

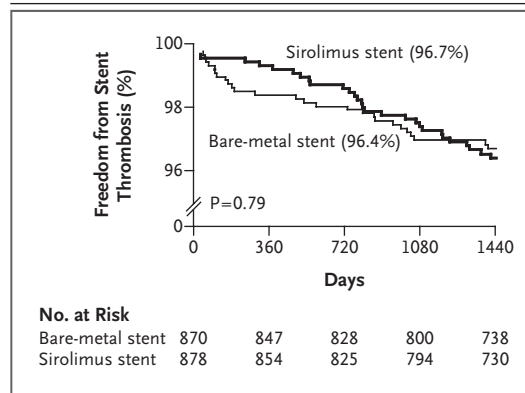


**Figure 1. Kaplan–Meier Survival Curves for Patients Who Received a Sirolimus-Eluting Stent and Those Who Received a Bare-Metal Stent.**

Panel A shows overall survival; Panel B shows freedom from death or myocardial infarction (MI). The survival rates at 1440 days are shown in parentheses. P values were calculated with the use of the log-rank test.

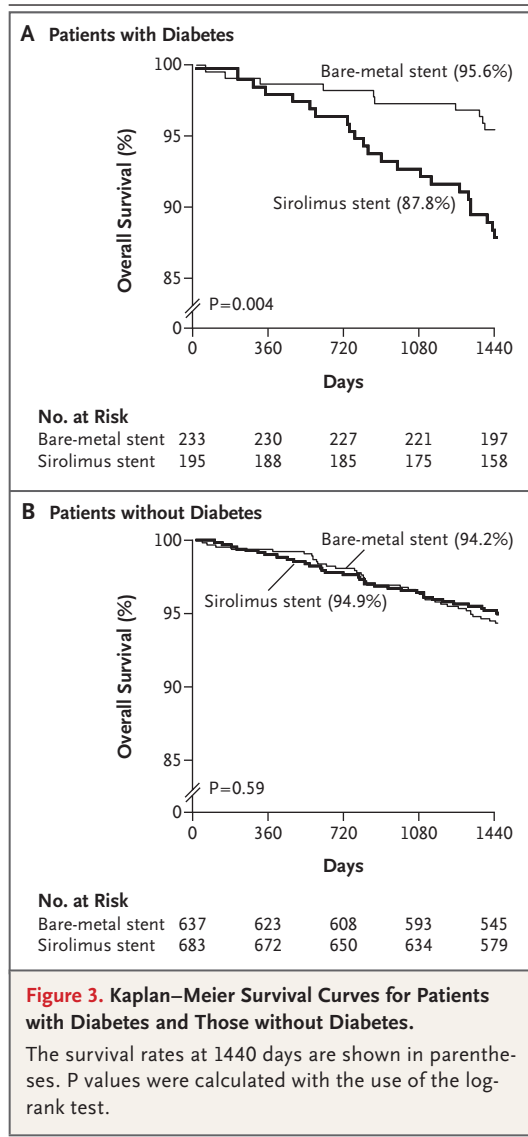
DISCUSSION

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



**Figure 2. Kaplan–Meier Curves for the Survival of Patients without Stent Thrombosis as Defined by the ARC.**

All first episodes of stent thrombosis were counted, including those that occurred after revascularization of the target lesion. The survival rates at 1440 days are shown in parentheses. The P value was calculated with the use of the log-rank test.



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.<sup>19</sup> 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.<sup>20</sup> 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.<sup>21,22</sup>

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.

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REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346:1773-80.
2. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349: 1315-23.
3. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004;43:1110-5.
4. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003;362:1093-9.
5. Daemen J, Ong AT, Stefanini G, et al. Three-year clinical follow-up of the unrestricted use of sirolimus-eluting stents as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. *Am J Cardiol* 2006; 98:895-901.
6. Urban P, Gershlick AH, Guagliumi G, et al. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. *Circulation* 2006;113:1434-41.
7. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006;27:2784-814.
8. Camenzind E. Do drug-eluting stents increase death? *European Society of Cardiology Congress News*. September 5, 2006.
9. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;48:193-202.
10. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004;109:701-5.
11. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519-21.
12. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006;47:175-81.
13. Hofma SH, van der Giessen WJ, van Dalen BM, et al. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. *Eur Heart J* 2006;27:166-70.
14. Babinska A, Markell MS, Salifu MO, Akoad M, Ehrlich YH, Kornecki E. Enhancement of human platelet aggregation and secretion induced by rapamycin. *Nephrol Dial Transplant* 1998;13:3153-9.
15. Sianos G, Hofma S, Ligthart JM, et al. Stent fracture and restenosis in the drug-eluting stent era. *Catheter Cardiovasc Interv* 2004;61:111-6.
16. Scheller B, Grandt A, Wnendt S, Lorenz G, Bohm M, Nickenig G. Comparative study of tacrolimus and paclitaxel stent coating in the porcine coronary model. *Z Kardiol* 2005;94:445-52.
17. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institution cohort study. *Lancet* (in press).
18. Steyerberg EW, Bossuyt PM, Lee KL. Clinical trials in acute myocardial infarction: should we adjust for baseline characteristics? *Am Heart J* 2000;139:745-51.
19. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation* 2005;112: 2175-83.
20. Daemen J, Garcia-Garcia HM, Kukreja N, et al. The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus. *Eur Heart J* 2007;28:26-32.
21. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 2005;45:2088-92.
22. Iakovou I, Schmidt T, Bonizzi E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293: 2126-30.

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