

ORIGINAL ARTICLE

Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents

Laura Mauri, M.D., Wen-hua Hsieh, Ph.D., Joseph M. Massaro, Ph.D.,
Kalon K.L. Ho, M.D., Ralph D'Agostino, Ph.D., and Donald E. Cutlip, M.D.

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.

From Brigham and Women's Hospital (L.M.), Harvard Clinical Research Institute (L.M., W.H., J.M.M., K.K.L.H., R.D., D.E.C.), Beth Israel Deaconess Medical Center (K.K.L.H., D.E.C.), Harvard Medical School (L.M., K.K.L.H., D.E.C.), and Boston University (J.M.M., R.D.) — all in Boston. Address reprint requests to Dr. Cutlip at Beth Israel Deaconess Medical Center, Baker 4, 185 Pilgrim Rd., Boston, MA 02215, or at don.cutlip@hcri.harvard.edu.

This article (10.1056/NEJMoa067731) was published at www.nejm.org on February 12, 2007.

N Engl J Med 2007;356:1020-9.
Copyright © 2007 Massachusetts Medical Society.

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.^{1,2} However, repeated percutaneous and surgical revascularization procedures are needed to treat restenosis in 14% of patients.³ The use of drug-eluting stents has reduced the occurrence of such procedures by 50 to 70%.^{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.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.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,¹⁰⁻¹² and there has been concern that late stent thrombosis may contribute to increased late mortality.^{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.

METHODS

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 2006.¹⁵ 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.^{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)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],⁴ C-SIRIUS in Canada [NCT00381420],¹⁷ and E-SIRIUS in Europe [NCT00235144]¹⁸). These databases were managed by the Harvard Clinical Research Institute, except for the RAVEL trial, which was managed by

Cardialysis 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

Table 1. Baseline Characteristics of the Study Patients.*

Variable	Sirolimus-Stent Trials		Paclitaxel-Stent Trials	
	Sirolimus Stent (N=878)	Bare-Metal Stent (N=870)	Paclitaxel Stent (N=1400)	Bare-Metal Stent (N=1397)
Age (yr)	61.9±11.1	61.9±10.7	62.8±11.0	62.2±10.7
Male sex (%)	71.6	71.5	71.5	71.7
Diabetes mellitus (%)				
Any diabetes	22.2	26.8	25.4	25.7
Requiring insulin	5.8	7.1	7.6	8.2
Hyperlipidemia (%)	70.8	71.8	70.1	70.1
Hypertension (%)	63.8	63.3	72.1	70.6
Current smoker (%)	21.2	24.5	23.8	22.2
Target vessel (%)				
Left anterior descending coronary artery	46.6	46.7	40.2	39.8
Circumflex artery	24.0	23.7	27.2	26.5
Right coronary artery	29.0	29.1	32.6	33.8
Left main coronary artery	0.3	0.3	0	0
Saphenous-vein graft	0	0.1	0	0
Reference-vessel diameter (mm)	2.7±0.4	2.7±0.5	2.7±0.5	2.7±0.5
Lesion length (mm)	13.8±5.7	13.9±5.9	14.7±7.7	14.6±7.9
No. of stents	1.4±0.7	1.4±0.6	1.2±0.5	1.2±0.5
Total stent length (mm)	22.9±9.0	22.4±8.1	23.9±11.0	23.5±10.9
Use of glycoprotein IIb/IIIa inhibitor (%)	44.2	43.4	45.6	45.4

* Plus-minus values are means ±SD.

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 siroli-

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

Definition	Sirolimus Stent <i>no. of events (%)</i>	Bare-Metal Stent <i>no. of events (%)</i>	Absolute Difference (95% CI) %	P Value	Paclitaxel Stent <i>no. of events (%)</i>	Bare-Metal Stent <i>no. of events (%)</i>	Absolute Difference (95% CI) %	P Value
Overall								
Protocol	10 (1.2)	5 (0.6)	0.6 (−0.4 to 1.5)	0.20	16 (1.3)	10 (0.8)	0.5 (−0.3 to 1.4)	0.24
Any ARC criterion	30 (3.6)	28 (3.3)	0.3 (−1.5 to 2.0)	0.80	39 (3.2)	41 (3.5)	−0.3 (−1.8 to 1.2)	0.84
ARC definite or probable	13 (1.5)	15 (1.7)	−0.2 (−1.5 to 1.0)	0.70	22 (1.8)	18 (1.4)	0.4 (−0.7 to 1.4)	0.52
ARC definite	10 (1.2)	7 (0.8)	0.4 (−0.7 to 1.4)	0.47	16 (1.3)	14 (1.1)	0.2 (−0.7 to 1.0)	0.71
Early (0 to 30 days)								
Protocol	4 (0.5)	1 (0.1)			7 (0.5)	7 (0.5)		
Any ARC criterion	4 (0.5)	3 (0.3)			7 (0.5)	7 (0.5)		
ARC definite or probable	4 (0.5)	3 (0.3)			7 (0.5)	7 (0.5)		
ARC definite	3 (0.3)	0			5 (0.4)	6 (0.4)		
Late (31 to 360 days)								
Protocol	1 (0.1)	4 (0.5)			3 (0.2)	2 (0.1)		
Any ARC criterion	2 (0.2)	11 (1.3)			12 (0.9)	13 (0.9)		
ARC definite or probable	1 (0.1)	8 (1.0)			5 (0.4)	4 (0.3)		
ARC definite	1 (0.2)	4 (0.5)			5 (0.3)	3 (0.2)		
Very late (>360 days)								
Protocol	5 (0.6)	0			6 (0.6)	1 (0.2)		
Any ARC criterion	24 (2.9)	14 (1.7)			20 (1.8)	21 (2.1)		
ARC definite or probable	8 (0.9)	4 (0.4)			10 (0.9)	7 (0.6)		
ARC definite	6 (0.7)	3 (0.3)			6 (0.6)	5 (0.5)		

* 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.

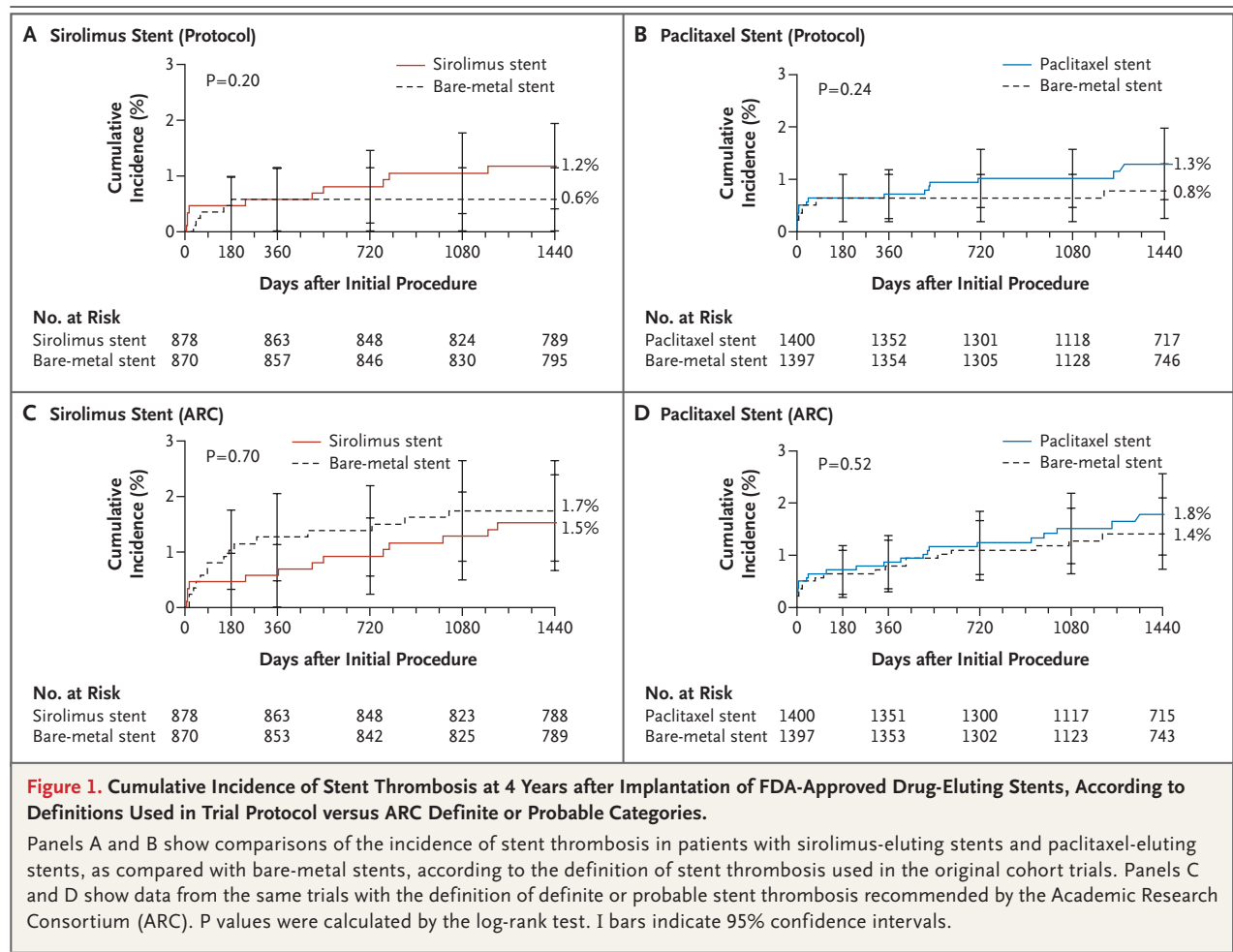
mus-stent group and $P=0.93$ for the paclitaxel-stent group for definite or probable events, as compared with the corresponding bare-metal-stent groups).

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



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 as-

certained 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-

Table 3. Clinical Outcomes in Patients after Definite or Probable Stent Thrombosis.*

Variable	Sirolimus-Stent Trials		Paclitaxel-Stent Trials	
	Sirolimus Stent (N=13)	Bare-Metal Stent (N=15)	Paclitaxel Stent (N=22)	Bare-Metal Stent (N=18)
	<i>no. of events (%)</i>			
Death	4 (30.8)	5 (33.3)	7 (31.8)	5 (27.8)
Myocardial infarction				
Any event	13 (100)	13 (86.7)	17 (77.3)	14 (77.8)
Fatal event	4 (30.8)	4 (26.7)	4 (18.2)	3 (16.7)
Q-wave	8 (61.5)	5 (33.3)	7 (31.8)	5 (27.8)
Non-Q-wave	5 (38.5)	9 (60.0)	10 (45.5)	10 (55.6)

* 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.

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.²³ Our analysis demonstrates that recent reports of higher mortality in meta-analyses of trials involving sirolimus-

eluting stents, as compared with bare-metal stents,^{13,14} 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.^{4,5} Although intracoro-

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

Variable	Sirolimus-Stent Trials		Paclitaxel-Stent Trials	
	Sirolimus Stent (N=13)	Bare-Metal Stent (N=15)	Paclitaxel Stent (N=22)	Bare-Metal Stent (N=18)
Intervening target-lesion revascularization (no.)	0	6	1	5
Time from target-lesion revascularization to stent thrombosis (days)				
Median	NA	138	331	313
Range	NA	15–484	331–331	137–669
Classification of stent thrombosis (no.)				
Definite	0	4	1	4
Probable	0	2	0	1
Target-lesion revascularization (no.)				
Bare-metal stent	0	0	0	1
Any drug-eluting stent	0	0	0	0
PTCA only	0	1	0	0
Brachytherapy with PTCA	0	5	1	4
Brachytherapy with bare-metal stent	0	0	0	0

* 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.

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

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,³⁰ 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

1. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
2. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;331:489-95.
3. Williams DO, Holubkov R, Yeh W, et al. Percutaneous coronary intervention in the current era compared with 1985-1986: the National Heart, Lung, and Blood Institute Registries. *Circulation* 2000;102:2945-51.
4. 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.
5. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221-31.
6. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001;103:1967-71.
7. Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004;109:1942-7.
8. Holmes DR Jr, Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004;109:634-40.
9. Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol* 2005;45:954-9.
10. 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.
11. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;48:2584-91.
12. 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-institutional cohort study. *Lancet* (in press).
13. Camenzind E, Steg G, Wijns W. Safety of drug-eluting stents: a meta-analysis of 1st generation DES programs. European Society of Cardiology 2006 Hot Line session. (Accessed February 9, 2007, at http://www.esccardio.org/knowledge/congresses/CongressReports/hotlinesandctus/707009_Camenzind.htm.)
14. 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.
15. Food and Drug Administration. Circulatory System Devices Panel Meeting. (Accessed February 9, 2007, at <http://www.fda.gov/ohrms/dockets/ac/cdrh06.html#circulatory>.)
16. 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.
17. 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.
18. 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.
19. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation* 2003;107:38-42.
20. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;108:788-94.
21. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA* 2005;294:1215-23.
22. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of Martingale-based residuals. *Biometrika* 1993;80:557-72.
23. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998-1008.
24. Waksman R, Bhargava B, Mintz GS, et al. Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis. *J Am Coll Cardiol* 2000;36:65-8.
25. Popma JJ, Suntharalingam M, Lansky AJ, et al. Randomized trial of 90Sr/90Y beta-radiation versus placebo control for treatment of in-stent restenosis. *Circulation* 2002;106:1090-6.
26. Stone GW, Ellis SG, O'Shaughnessy CD, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA* 2006;295:1253-63.
27. Holmes DR Jr, Teirstein P, Satler L, et al. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA* 2006;295:1264-73.
28. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;297:159-68.
29. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-30.
30. Mak KH, Belli G, Ellis SG, Moliterno DJ. Subacute stent thrombosis: evolving issues and current concepts. *J Am Coll Cardiol* 1996;27:494-503.

Copyright © 2007 Massachusetts Medical Society.