Sirolimus-Eluting versus Uncoated Stents in Acute Myocardial Infarction

Christian Spaulding, M.D., Patrick Henry, M.D., Ph.D., Emmanuel Teiger, M.D., Ph.D.,
Kevin Beatt, M.B., B.S., Ph.D., Ezio Bramucci, M.D., Didier Carrié, M.D., Michel S. Slama, M.D.,
Bela Merkely, M.D., Ph.D., Andrejs Erglis, M.D., Ph.D., Massimo Margheri, M.D., Olivier Varenne, M.D., Ph.D.,
Ana Cebrian, Ph.D., Hans-Peter Stoll, M.D., David B. Snead, Ph.D., and Christoph Bode, M.D.,
for the TYPHOON Investigators*

ABSTRACT

BACKGROUND

Sirolimus-eluting stents reduce rates of restenosis and reintervention, as compared with uncoated stents. Data are limited regarding the safety and efficacy of such stents in primary percutaneous coronary intervention (PCI) for acute myocardial infarction with ST-segment elevation.

METHODS

We performed a single-blind, multicenter, prospectively randomized trial to compare sirolimus-eluting stents with uncoated stents in primary PCI for acute myocardial infarction with ST-segment elevation. The trial included 712 patients at 48 medical centers. The primary end point was target-vessel failure at 1 year after the procedure, defined as target-vessel–related death, recurrent myocardial infarction, or target-vessel revascularization. A follow-up angiographic substudy was performed at 8 months among 174 patients from selected centers.

RESULTS

The rate of the primary end point was significantly lower in the sirolimus-stent group than in the uncoated-stent group (7.3% vs. 14.3%, P=0.004). This reduction was driven by a decrease in the rate of target-vessel revascularization (5.6% and 13.4%, respectively; P<0.001). There was no significant difference between the two groups in the rate of death (2.3% and 2.2%, respectively; P=1.00), reinfarction (1.1% and 1.4%, respectively; P=1.00), or stent thrombosis (3.4% and 3.6%, respectively; P=1.00). The degree of neointimal proliferation, as assessed by the mean (±SD) in-stent late luminal loss, was significantly lower in the sirolimus-stent group (0.14±0.49 mm, vs. 0.83±0.52 mm in the uncoated stent group; P<0.001).

CONCLUSIONS

Among selected patients with acute myocardial infarction, the use of sirolimus-eluting stents significantly reduced the rate of target-vessel revascularization at 1 year. (ClinicalTrials.gov number, NCT00232830.)

From Assistance Publique–Hôpitaux de Paris (AP–HP) Cochin Hospital, Paris 5 Medical School Rene Descartes University and INSERM U780, Paris (C.S., O.V.); AP–HP Lariboisiere Hospital, Paris 7 Medical School University Denis Diderot, Paris (P.H.); AP–HP Henri Mondor Hospital, Paris 12 Medical School, Créteil (E.T.); Hospital Rangueil, Toulouse (D.C.); and AP–HP Antoine Béclère Hospital, Paris 12 Medical School Paris Sud University, Clamart (M.S.S.) — all in France; Mayday University Hospital, London (K.B.); Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia (E.B.), and Azienda Universitaria Ospedaliera Careggi, Florence (M.M.) — both in Italy; Semmelweis University, Budapest (B.M.); Pauls Stradins University Hospital, Riga, Latvia (A.E.); Cordis (Johnson & Johnson), Waterloo, Belgium (A.C., H.-P.S.) and Warren, NJ (D.B.S.); and the University of Freiburg, Freiburg, Germany (C.B.). Address reprint requests to Dr. Spaulding at Cochin Hospital, 27 rue du Faubourg St. Jacques, 75014 Paris, or at christian. spaulding@cch.ap-hop-paris.fr.

*Members of the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) are listed in the Appendix.

THE USE OF SIROLIMUS-ELUTING CORO-
nary-artery stents significantly reduces the
incidence of restenosis after percutaneous
coronary intervention (PCI), as compared with
the use of uncoated stents.[1-3] However, most ran-
domized trials evaluating sirolimus-eluting stents
have excluded patients with acute myocardial in-
farction with ST-segment elevation. Small series
of patients with acute myocardial infarction have
shown that the implantation of a sirolimus-elut-
ing stent is associated with a low rate of resteno-
sis.[4,5] In the Single High-Dose Bolus Tirofiban and
Sirolimus-Eluting Stent vs. Abciximab and Bare-
Metal Stent in Myocardial Infarction (STRATEGY)
trial, the use of sirolimus-eluting stents reduced
cardiovascular events, as compared with the use
of uncoated stents, in a small group of patients
undergoing primary PCI. However, the design of
the trial specified the use of different glycopro-
tein IIb/IIIa inhibitors in each of the two groups
to mitigate the greater cost of the drug-eluting
stents, which raised the possibility that the ben-
efit was influenced by the specific antiplatelet
regimen.[6]

We therefore designed a prospective, random-
ized, multicenter trial comparing the effective-
ness of sirolimus-eluting stents with that of un-
coated stents in primary PCI for acute myocardial
infarction with ST-segment elevation.

METHODS

ENROLLMENT AND ASSIGNMENT OF PATIENTS

We enrolled patients at 48 centers in 15 countries
to participate in the Trial to Assess the Use of the
Cypher Stent in Acute Myocardial Infarction Treat-
ed with Balloon Angioplasty (TYPHOON). The
study protocol was approved by the ethics com-
mittee at each participating institution and was
conducted according to the principles of the Dec-
laration of Helsinki. All patients gave written in-
formed consent before enrollment. The study was
conducted from October 2003 to October 2005.

Patients were eligible for the trial if their symp-
toms began less than 12 hours before catheter-
ization and if the electrocardiogram showed ST-
segment elevation (at least 1 mm in two or more
standard leads or at least 2 mm in two or more
contiguous precordial leads). Clinical criteria for
exclusion included the administration of fibrino-
lytic agents for the index infarction, overt acute
heart failure, a previously documented left ven-

tricular ejection fraction of less than 30%, previ-
ous myocardial infarction, and an estimated life
expectancy of less than 12 months.

DIAGNOSTIC ANGIOGRAPHY AND PRIMARY INTERVENTION

Patients were premedicated with aspirin (at least
100 mg) and unfractionated heparin (5000 to
10,000 IU). A loading dose of 300 mg of clopido-
grel was administered either before or immedi-
ately after PCI. Coronary angiography was per-
formed through the femoral or radial artery with
the use of standard techniques.

SELECTION AND RANDOMIZATION

The trial protocol required visualization of the
culprit lesion before randomization, in order to
determine whether the angiographic criteria for
inclusion or exclusion were met. Randomization
was therefore performed either immediately after
coronary angiography if the infarct-related vessel
was spontaneously patent or after reestablish-
ing coronary-artery blood flow by the placement
of a guidewire or by balloon angioplasty.

Criteria for angiographic exclusion included
previous PCI of the infarct-related vessel, exces-
sive tortuosity or calcification, ostial or multiple
lesions, massive thrombus in the infarct-related
artery, bifurcation or left main coronary-artery
disease, and severe multivessel disease requiring
surgical revascularization. Patients were finally
included and randomly assigned to a treatment
group if the target lesion had a maximum length
of 30 mm and was located in a native coronary
artery with a reference-vessel diameter of 2.25
mm to 3.50 mm.

Random assignments to the treatment groups
were generated in blocks of four or six and were
distributed in sealed envelopes to each partici-
pating center. Patients were randomly assigned
to the groups in a 1:1 ratio. Patients received ei-
ther a sirolimus-eluting stent (Cypher or Cypher
Select, Cordis, Johnson & Johnson) or any com-
mercially available uncoated stent. Patients, but
not investigators, were unaware of the treatment
assignment.

STENT IMPLANTATION

Direct implantation of a stent without previous
balloon angioplasty was allowed if the culprit le-
sion was adequately visualized either spontane-
ously or after guidewire placement. In the case of

insufficient stent expansion, the stent was dilated after placement with another angioplasty balloon that was shorter than the total length of the stent. Oversizing and additional high-pressure dilation after the initial procedure were not recommended. If more than one stent was implanted, the same type of stent (sirolimus-eluting or uncoated) was recommended. Intervention in non-infarct-related arteries during the initial procedure was discouraged.

Heparin was administered throughout the procedure in order to maintain an activated clotting time of 250 seconds or longer. Administration of platelet glycoprotein IIb/IIIa–receptor inhibitors was left to the investigator's discretion.

FOLLOW-UP

Clinical follow-up was performed at 30 days and at 6 and 12 months after the procedure. Combined antiplatelet therapy included daily administration of aspirin (100 mg) and either clopidogrel (75 mg) or ticlopidine (250 mg). Dual antiplatelet therapy was recommended for at least 6 months, and aspirin therapy was recommended indefinitely. Noninvasive testing to assess for evidence of ischemia was recommended before repeated revascularization. Patients were unaware of their treatment assignments throughout the follow-up period.

Angiographic follow-up at 8 months was planned for 200 patients at 12 centers. In these selected centers, consecutive patients were enrolled in the angiographic substudy until the total number of patients reached 210.

QUANTITATIVE CORONARY ANGIOGRAPHY

Technicians at an independent angiographic core laboratory (BioImaging, Leiden, the Netherlands), who were unaware of treatment assignment, analyzed all angiographic images with the use of edge-detection techniques.[7] Binary restenosis was defined as stenosis of more than 50% of the luminal diameter. Late luminal loss was calculated as the difference between the minimum luminal diameter immediately after the procedure and at 8 months. Flow in the infarct-related vessel was graded according to the Thrombolysis in Myocardial Infarction (TIMI) trial classification.[8]

PRIMARY AND SECONDARY END POINTS

The primary end point of the study was target-vessel failure, defined as the composite of target-vessel revascularization, recurrent infarction, or target-vessel–related death at 1 year. The clinical events committee reviewed and adjudicated all serious clinical events, including stent thrombosis.

Target-vessel revascularization was defined as repeated PCI or bypass grafting of the target vessel, driven by clinical symptoms of myocardial ischemia, a positive stress test, electrocardiographic evidence of ischemic changes at rest attributable to the target vessel, or an in-lesion stenosis of more than 70% of the reference luminal diameter by visual estimate.
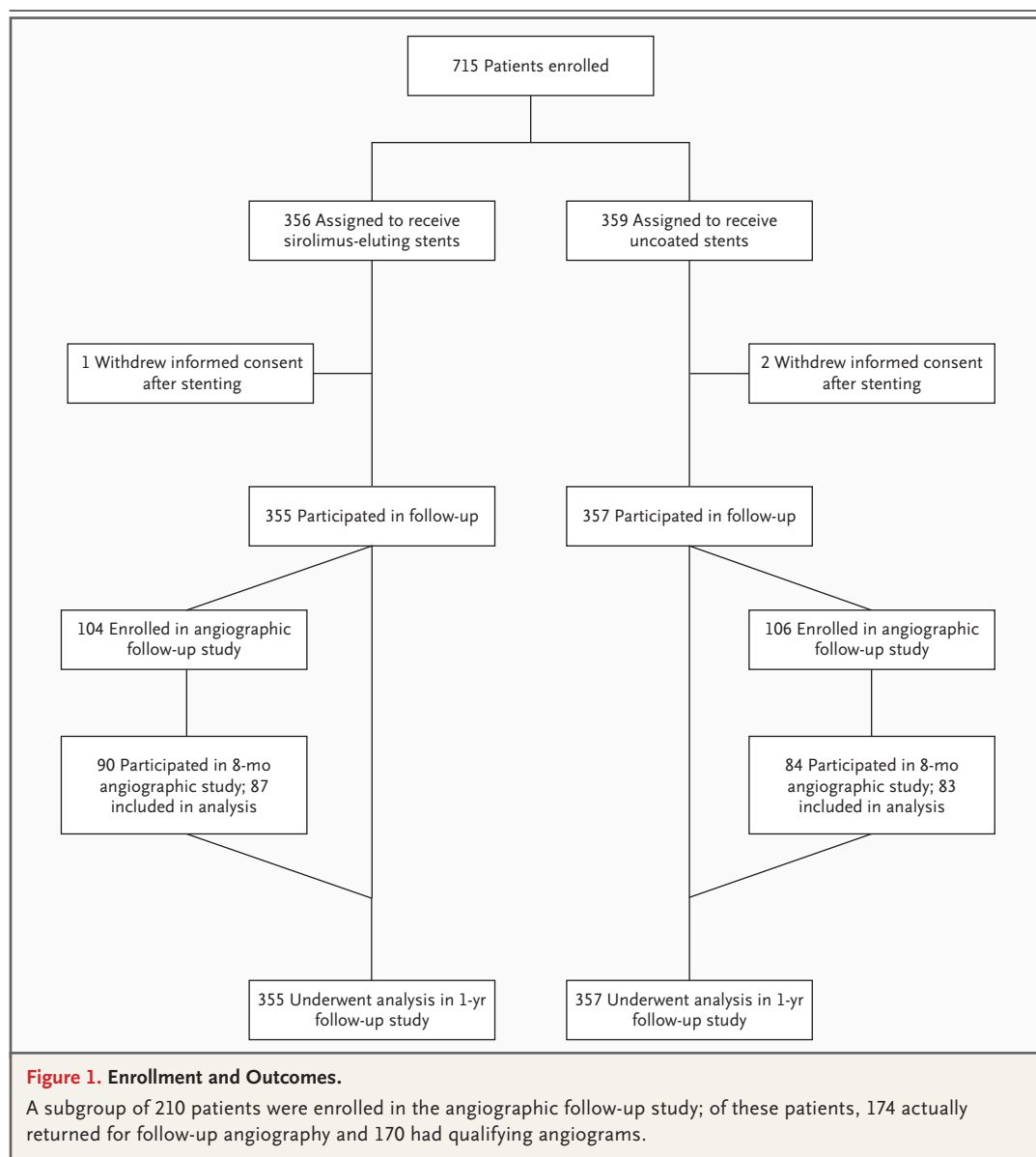
Recurrent infarction was defined as the recurrence of clinical symptoms or the occurrence of electrocardiographic changes accompanied by a new elevation in levels of creatine kinase, creatine kinase MB enzyme, or both. The level of creatine kinase required for the diagnosis of reinfarction depended on the interval from the index infarction: the creatine kinase level had to be at least 1.5 times the previous value if new symptoms appeared within 48 hours and at least 3 times the upper limit of normal if new symptoms appeared after 48 hours.

Death from cardiac causes included death from acute myocardial infarction, cardiac perforation, or pericardial tamponade; an arrhythmia or conduction abnormality; complications of the interventional procedure at baseline; stroke (including bleeding) within 30 days after the procedure or in connection with the procedure; and all deaths that could not be clearly attributed to a noncardiac cause.

The secondary end points of the trial included the rate of successful treatment of the lesion, defined by residual stenosis of less than 50% of the reference luminal diameter on quantitative coronary analysis and a TIMI flow grade of 3, and in-stent late luminal loss on quantitative coronary analysis at 8 months.

DEFINITION OF STENT THROMBOSIS

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, and late if it occurred after 30 days. Acute and subacute stent thrombosis were defined as angiographic proof of vessel occlusion, any recurrent Q-wave myocardial infarction in the territory of the stented vessel, or any death from cardiac causes. Late stent thrombosis was defined as any

Figure 1. Enrollment and Outcomes.

A subgroup of 210 patients were enrolled in the angiographic follow-up study; of these patients, 174 actually returned for follow-up angiography and 170 had qualifying angiograms.

recurrent myocardial infarction with angiographic proof of vessel occlusion.

STUDY DESIGN AND ADMINISTRATION

Our study was proposed to the industry sponsor by four of the academic investigators: Drs. Henry, Spaulding, Teiger, and Slama. The same investigators wrote the final version of the protocol in collaboration with the industry sponsor, and the steering committee approved the design. Dr. Spaulding designed the statistical-analysis plan in collaboration with the sponsor.

Data were collected with the use of an elec-

tronic case-report form through a secured Internet-based Web site. A clinical research organization (Hesperion, Allschwil, Switzerland) performed all study monitoring, data management, and statistical analysis. The industry sponsor had no direct role in the collection or analysis of data. The steering committee had unrestricted access to the data and made all decisions about publication independently of the sponsor. Dr. Spaulding assumes overall responsibility for the integrity of the data, the accuracy of the data analyses, and the completeness of the material reported.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Sirolimus-Eluting Stent (N=355)	Uncoated Stent (N=357)	P Value
Age — yr	58.0±11.8	60.5±12.4	0.008
Male sex — no. (%)	279 (78.6)	279 (78.2)	0.93
Diabetes — no. (%)	55 (15.5)	61 (17.1)	0.61
Hypertension — no. (%)	137 (38.6)	152 (42.6)	0.29
Hyperlipidemia — no. (%)	144 (40.6)	156 (43.7)	0.40
Current smoker — no. (%)	170 (47.9)	186 (52.1)	0.29
Previous PCI of noninfarct vessel — no. (%)	9 (2.5)	21 (5.9)	0.04
Previous stroke — no. (%)	7 (2.0)	7 (2.0)	1.00
Time from onset of chest pain to admission — min			0.66
Median	234	228	
Interquartile range	108–300	120–288	
Time from admission to angiography — min			0.78
Median	38	37	
Interquartile range	10–45	10–45	
Time from hospitalization to angioplasty — min			0.97
Median	60	60	
Interquartile range	30–71	30–73	
Systolic blood pressure at admission — mm Hg	131±23	131±24	0.95
Infarct-related vessel — no. (%)			0.006
Left anterior descending coronary artery	177 (49.9)	146 (40.9)	0.02
Right coronary artery	130 (36.6)	157 (44.0)	0.06
Left circumflex coronary artery	48 (13.5)	54 (15.1)	0.59
Extent of coronary disease — no. (%)			0.04
1 vessel	198 (55.8)	178 (49.9)	0.12
2 vessels	118 (33.2)	121 (33.9)	0.87
3 vessels	39 (11.0)	58 (16.2)	0.05
Ejection fraction — %	52±11	53±12	0.65

* Plus–minus values are means ±SD.

STATISTICAL ANALYSIS

The planned enrollment of 700 patients provided a statistical power of 80% to detect a 47% reduction in the rate of the primary end point at 1 year (from 17% in the uncoated-stent group to 9% in the sirolimus-stent group) with a 5% rate of false positive results in a two-sided test. The estimated enrollment for the angiographic substudy was based on an assumed in-stent late luminal loss of 0.43 mm in the sirolimus-stent group and 0.76 mm in the uncoated-stent group at 8 months, with an SD of 0.7 mm for both groups.[2,9] After correction for loss to follow-up, we estimated that the enroll-

ment of 200 patients provided 80% power with a false positive rate of 5% in a two-sided test.

All analyses were based on the intention to treat. The differences between the treatment groups were evaluated by analysis of variance or Wilcoxon rank-sum scores for continuous variables, if appropriate. Fisher's exact test was used for the analysis of categorical variables. The rate of survival free from target-vessel failure during the 1-year follow-up period was analyzed by the Kaplan–Meier method, and the difference in survival curves between the groups was assessed with the log-rank test. To test whether initial dif-

Table 2. Procedural Results and Use of Medication during the Trial.*

Variable	Sirolimus-Eluting Stent (N=355)	Uncoated Stent (N=357)	P Value
Characteristics of stent implantation			
No. of stents implanted	1.1±0.4	1.1±0.4	0.34
Total length of stent — mm	22.1±8.6	20.3±8.2	0.005
Maximal size of stent — mm	3.0±0.3	3.1±0.4	0.001
Maximal pressure — atm	13.8±2.7	13.2±2.5	0.002
Direct stenting — no. (%)			
Attempted	165 (46.5)	169 (47.3)	0.82
Successful	162 (45.6)	165 (46.2)	0.88
Glycoprotein IIb/IIIa–receptor inhibitors — no. (%)	246 (69.3)	263 (73.7)	0.25
Abciximab	128 (36.1)	127 (35.6)	0.94
Other	118 (33.2)	136 (38.1)	0.18
Quantitative coronary analysis†			
Before procedure			
No. evaluated	347	347	
TIMI flow — no. (%)			
Grade 0 or 1	230 (66.3)	234 (67.4)	0.81
Grade 2	70 (20.2)	53 (15.3)	0.11
Grade 3	47 (13.5)	60 (17.3)	0.21
Diameter of reference vessel — mm	2.78±0.50	2.84±0.61	0.36
Minimal luminal diameter — mm	0.20±0.33	0.19±0.35	0.82
Stenosis — % of luminal diameter	93.2±12.3	93.6±12.3	0.72
Immediately after procedure			
No. evaluated	350	347	
TIMI flow — no. (%)			
Grade 0 or 1	2 (0.6)	2 (0.6)	1.00
Grade 2	11 (3.1)	14 (4.0)	0.55
Grade 3	337 (96.3)	331 (95.4)	0.58
Diameter of reference vessel — mm	2.84±0.49	2.90±0.52	0.09
Minimal luminal diameter — mm			
In stent	2.49±0.39	2.58±0.44	0.01
In lesion	2.28±0.46	2.34±0.52	0.13
Stenosis — % of luminal diameter			
In stent	13.5±7.6	12.4±8.4	0.05
In lesion	19.2±8.8	19.3±9.1	0.92
Acute gain — mm			
In stent	2.42±0.47	2.41±0.53	0.92
In lesion	2.18±0.51	2.10±0.59	0.38
Successful treatment of lesion — no. (%)‡	321 (95.5)	326 (95.9)	0.85
No. evaluated	336	340	

Table 2. (Continued.)

Variable	Sirolimus-Eluting Stent (N=355)	Uncoated Stent (N=357)	P Value
Medications used during the trial§			
During hospital stay — no. (%)			
No. evaluated	355	357	
Aspirin	351 (98.9)	353 (98.9)	1.00
Clopidogrel	349 (98.3)	351 (98.3)	1.00
Ticlopidine	5 (1.4)	5 (1.4)	1.00
Beta-blockers	322 (90.7)	323 (90.5)	1.00
Statins	322 (90.7)	329 (92.2)	0.51
ACE inhibitors	262 (73.8)	275 (77.0)	0.34
Heparin	208 (58.6)	217 (60.8)	0.59
Follow-up at 1 mo — no. (%)			
No. evaluated	340	346	
Aspirin	334 (98.2)	336 (97.1)	0.45
Clopidogrel	334 (98.2)	337 (97.4)	0.60
Ticlopidine	3 (0.9)	2 (0.6)	0.68
Beta-blockers	303 (89.1)	311 (89.9)	0.80
Statins	318 (93.5)	322 (93.1)	0.88
ACE inhibitors	259 (76.2)	269 (77.7)	0.65
Follow-up at 6 mo — no. (%)			
No. evaluated	334	339	
Aspirin	312 (93.4)	318 (93.8)	0.88
Clopidogrel	253 (75.7)	249 (73.5)	0.54
Ticlopidine	1 (0.3)	1 (0.3)	1.00
Beta-blockers	294 (88.0)	290 (85.5)	0.36
Statins	311 (93.1)	316 (93.2)	1.00
ACE inhibitors	238 (71.3)	246 (72.6)	0.73
Follow-up at 1 yr — no. (%)			
No. evaluated	334	331	
Aspirin	299 (89.5)	307 (92.7)	0.17
Clopidogrel	170 (50.9)	168 (50.8)	1.00
Ticlopidine	1 (0.3)	1 (0.3)	1.00
Beta-blockers	281 (84.1)	279 (84.3)	1.00
Statins	308 (92.2)	306 (92.4)	1.00
ACE inhibitors	238 (71.3)	237 (71.6)	0.93
Duration of thienopyridine (clopidogrel or ticlopidine) treatment — mo	9.7±2.9	9.5±3.1	0.37

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting–enzyme.
† Differences in the numbers of patients who were evaluated with respect to quantitative coronary analysis and the successful treatment of lesions are due to angiograms that could not be evaluated.
‡ Successful treatment of lesions was defined as the achievement of a final residual stenosis of less than 50% of the luminal diameter and a coronary blood flow of grade 3, according to the TIMI classification, as assessed by the core laboratory.
§ Differences in the numbers of patients who were evaluated are due to the deaths of patients before each follow-up and to missing data.

ferences between the two treatment groups influenced the difference in outcome, multiple logistic-regression analysis was performed, controlling for all variables that were found to be significantly different at baseline. All statistical analyses were performed with the use of SAS software, version 8.2 (SAS Institute), and all reported P values are two-sided.

RESULTS

STUDY PATIENTS

Between October 2003 and September 2004, 2019 patients were screened and 715 were randomly assigned to the two treatment groups (356 to the sirolimus-stent group and 359 to the uncoated-stent group) (Fig. 1). The most frequent reason for exclusion was fibrinolytic therapy for the index infarction. After randomization and treatment with the assigned stent, one patient in the sirolimus-stent group and two in the uncoated-stent group withdrew their consent to participate in the study.

BASELINE CHARACTERISTICS AND MEDICATIONS USED

Patients in the uncoated-stent group were slightly older and had a higher rate of previous PCI involving a nontarget coronary vessel, a lower rate of

culprit lesions in the left anterior descending coronary artery, and a higher rate of triple-vessel disease (Table 1). In both groups, the median time from the onset of chest pain to hospital admission was less than 4 hours, and the median interval between arrival at the hospital and inflation of the balloon catheter was 60 minutes. The rate of use of glycoprotein IIb/IIIa–receptor inhibitors and the specific agents used did not vary significantly between the two groups (Table 2).

CLINICAL OUTCOME AT 1 YEAR

The primary end point of the study — target-vessel failure at 1 year — occurred in 7.3% of patients in the sirolimus-stent group and in 14.3% in the uncoated-stent group (P=0.004) (Table 3). This difference was due almost entirely to significant differences in the rates of target-vessel revascularization. There was no significant difference between the sirolimus-stent group and the uncoated-stent group in the rates of death (2.3% and 2.2%, respectively; P=1.00), recurrent myocardial infarction (1.1% and 1.4%, respectively; P=1.00), or in-stent thrombosis (3.4% and 3.6%, respectively; P=1.00). The actuarial rate of survival free from target-vessel failure was significantly higher in the sirolimus-stent group than in the uncoated-stent group (92.5% vs. 85.2%, P<0.001) (Fig. 2).

Table 3. Clinical Events at 1 Year.*

Event	Sirolimus-Eluting Stent (N=355)	Uncoated Stent (N=357)	P Value
	number (percent)		
Target-vessel failure	26 (7.3)	51 (14.3)	0.004
Clinically driven target-vessel revascularization	20 (5.6)	48 (13.4)	<0.001
PCI	20 (5.6)	47 (13.2)	<0.001
CABG	0	2 (0.6)	0.50
Death	8 (2.3)	8 (2.2)	1.00
Cardiac causes	7 (2.0)	5 (1.4)	0.58
Noncardiac causes	1 (0.3)	3 (0.8)	0.62
Recurrent myocardial infarction	4 (1.1)	5 (1.4)	1.00
Stent thrombosis	12 (3.4)	13 (3.6)	1.00
Acute	2 (0.6)	3 (0.8)	1.00
Subacute	9 (2.5)	8 (2.2)	0.81
Late	1 (0.3)	2 (0.6)	1.00
Angiographically proven stent thrombosis	7 (2.0)	12 (3.4)	0.35

* CABG denotes coronary-artery bypass grafting.

Multivariate analysis of the primary end point was performed to control for all significant variables in Tables 1 and 2, including the use of clopidogrel, at 6 months. On the basis of this adjusted analysis, patients in the sirolimus-stent group were less than half as likely as those in the uncoated-stent group to have target-vessel failure (odds ratio, 0.41; P=0.001).
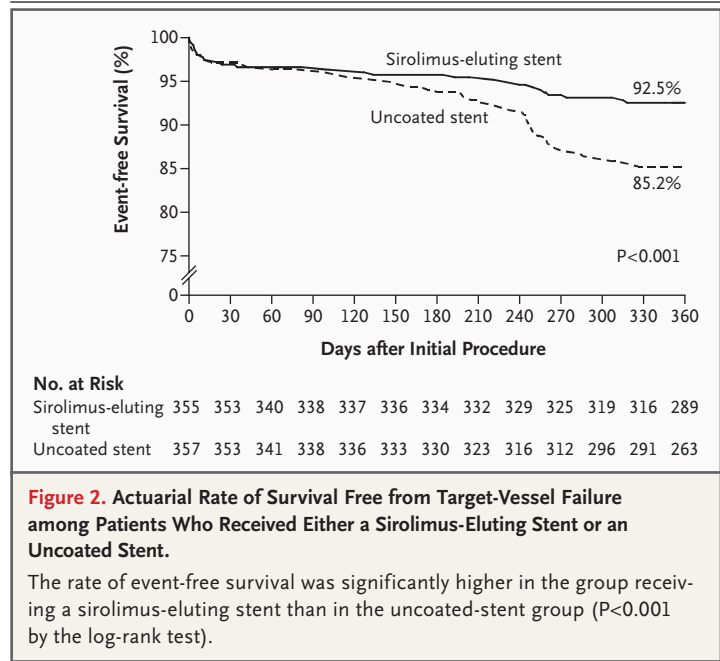
ANGIOGRAPHIC FOLLOW-UP STUDY

Of the 210 patients included in the angiographic substudy, 174 underwent angiography at 8 months (82.8%) and 170 had qualifying angiograms (81.0%) (Fig. 1 and Table 4). Patients in the angiographic study, as compared with those not in the study, tended to have higher rates of target-vessel failure (13.3% vs. 9.8%, P=0.19) and revascularization (12.4% vs. 8.4%, P=0.12), although these differences were not significant. However, the reduction in target-vessel failure in the sirolimus-stent groups was similar whether or not follow-up angiography was performed. At 8 months, sirolimus-eluting stents, as compared with uncoated stents, were associated with significant mean reductions in in-stent late luminal loss (0.14±0.49 mm vs. 0.83±0.52 mm, P<0.001) and in-stent restenosis (3.5% vs. 20.3%, P=0.001).

Figure 2. Actuarial Rate of Survival Free from Target-Vessel Failure among Patients Who Received Either a Sirolimus-Eluting Stent or an Uncoated Stent.

The rate of event-free survival was significantly higher in the group receiving a sirolimus-eluting stent than in the uncoated-stent group (P<0.001 by the log-rank test).

DISCUSSION

In our trial, the use of sirolimus-eluting stents during primary PCI was associated with a reduction in the incidence of target-vessel failure at 1 year, as compared with the use of uncoated stents (7.3% vs. 14.3%, P=0.004). This difference was mainly driven by a reduction in the incidence of target-vessel revascularization. The results of the angiographic follow-up study suggest that the mechanism of benefit involves the suppression of neointimal proliferation among patients receiving sirolimus-eluting stents. The average in-stent late luminal loss in the sirolimus-stent group in our study was similar to that in previous studies of patients undergoing elective procedures.[2,3,10]

Rates of stent thrombosis were similar in the sirolimus-stent and uncoated-stent groups (3.4% and 3.6%, respectively; P=1.00). These rates were higher than those in previous studies. Reported rates of stent thrombosis vary according to the clinical presentation and the definition used. In recent trials of sirolimus-eluting stents that included only elective cases and used the same defi-

nition that we used in our trial, cumulative rates of stent thrombosis ranged from 0 to 1.1%.[1-3,10] A higher rate (2.0%) was reported for sirolimus-eluting stents in the Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization (SIRTAX) trial (a comparison of the Cypher stent and the Taxus stent), which included both patients with and those without acute myocardial infarction.[11] Elsewhere in this issue of the *Journal*, Laarman et al.[12] report the results of the Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) trial, which showed a lower overall rate of stent thrombosis (1%) than did our study. However, angiographic proof was required for the diagnosis of stent thrombosis, and adjudication was not performed by an independent clinical events committee. The rates of stent thrombosis in the STRATEGY trial were 0% in the group receiving sirolimus-eluting stents and 3% in the group receiving uncoated stents.[6] The 1-month rate of stent thrombosis in trials and registries with uncoated stents in acute myocardial infarction ranges from 0.9 to 4.3%.[9,13-19]

Procedural factors may have contributed to in-stent thrombosis in our study. Suboptimal procedural regimens of aspirin and heparin were allowed, with minimal aspirin doses of 100 mg and a minimal activated clotting time of 250 seconds, in contrast to recent recommendations.[20] Further-

Table 4. Angiographic Measurements Obtained at the Time of the Index Procedure and at Follow-up at 8 Months.*

Variable	No. of Patients†	Sirolimus-Eluting Stent	Uncoated Stent	P Value
Patients studied — no.				
Initial angiographic subgroup	210	104	106	
Follow-up angiography completed	174	90	84	
Follow-up angiography qualifying for analysis	170	87	83	
Before procedure				
Diameter of reference vessel — mm	79	2.75±0.48	2.80±0.59	0.67
Minimal luminal diameter — mm	203	0.16±0.29	0.20±0.35	0.49
Stenosis — % of luminal diameter	203	94.6±11.1	93.30±13.0	0.45
Immediately after procedure				
Diameter of reference vessel — mm	200	2.92±0.46	2.93±0.50	0.95
Minimal luminal diameter — mm				
In stent	200	2.52±0.41	2.57±0.44	0.44
In lesion	200	2.30±0.48	2.30±0.54	0.92
Stenosis — % of luminal diameter				
In stent	207	13.4±6.4	11.4±9.1	0.08
In lesion	207	18.6±8.1	19.4±9.1	0.50
Acute gain — mm				
In stent	195	2.36±0.50	2.38±0.54	0.84
In lesion	195	2.14±0.52	2.11±0.6	0.70
Follow-up at 8 mo				
Diameter of reference vessel — mm	144	2.85±0.54	2.79±0.56	0.54
Minimal luminal diameter — mm				
In stent	144	2.42±0.59	1.78±0.61	<0.001
In lesion	144	2.14±0.61	1.76±0.61	<0.001
Stenosis of luminal diameter — %				
In stent	159	16.4±13.2	37.1±16.1	<0.001
In lesion	159	24.6±13.8	37.9±16.5	<0.001
Late luminal loss — mm				
In stent	138	0.14±0.49	0.83±0.52	<0.001
In lesion	138	0.17±0.47	0.56±0.60	<0.001
Proximal edge	131	0.21±0.47	0.29±0.51	0.38
Distal edge	137	0.03±0.35	0.09±0.50	0.46
Binary restenosis — no. (%)‡				
In stent	159	3 (3.5)	15 (20.3)	0.001
In lesion	159	6 (7.1)	15 (20.3)	0.02
Proximal edge	153	3 (3.5)	3 (4.1)	1.00
Distal edge	158	0	1 (1.4)	0.47

* Plus–minus values are means ±SD.
† The number listed for each angiographic variable is the number of angiograms that could be evaluated for the study patients.
‡ The percentages in this category are the number of patients divided by the number of angiograms that could be evaluated.

more, incomplete stent deployment favoring in-stent thrombosis cannot be ruled out, since the mean residual stenosis after the procedure was higher in both groups than that in previous studies.[1,2] Finally, our definition of acute and sub-

acute thrombosis was broad and included both death and repeated myocardial infarction if angiographic proof of stent patency was not available. In contrast, the definition of late thrombosis required angiographic proof of stent thrombosis.

Accordingly, 30-day rates of stent thrombosis may have been overestimated and those of late thrombosis underestimated.

In comparison with our study, trials and registries of primary PCI in patients with acute myocardial infarction with ST-segment elevation have reported lower rates of repeated revascularization. In fact, our rates are similar to those of previous studies in patients in stable condition.[9,13-18] This finding may be related to the effect of angiographic follow-up in a subgroup of patients, since revascularization rates tended to be higher among patients undergoing follow-up angiography. Nevertheless, the significant difference in the rates of target-vessel failure was maintained in the subgroup of patients without angiographic follow-up. Furthermore, noninvasive testing was performed on a routine basis at 6 months, an approach that may have led to an increased rate of ischemia-driven revascularization. Another factor may have been the speed of intervention (median interval from arrival at the hospital to inflation of the balloon catheter, 60 minutes), which left patients with a relatively large amount of viable myocardium at risk. In the PASSION trial, the revascularization rate in the group receiving uncoated stents was surprisingly low, and the incidence of the primary end point was lower than the expected rate. The enrollment of fewer patients with diabetes and more patients with larger target vessels in the PASSION trial may account for these differences.[12]

Our results cannot be generalized to all patients with acute myocardial infarction, since high-risk patients were excluded. Furthermore, our findings cannot be extended to other drug-eluting stents. Despite adjudication of events by an independent clinical events committee, the single-blind study design is an obvious limitation. This is especially true since the beneficial effect of sirolimus-eluting stents on the primary end point was almost entirely due to a reduction in target-vessel revascularization, which was performed by investigators who were not specifically blinded to the study assignment of each patient. Although an analysis that was adjusted for differences between treatment groups in baseline characteristics did not change the findings, other variables might have influenced them. Finally, an assessment of long-term safety and durability will require longer follow-up of a larger cohort of patients.

In summary, in our study, patients with acute myocardial infarction with ST-segment elevation who received sirolimus-eluting stents had a significantly lower rate of target-vessel failure than those who received uncoated stents. This difference was due almost entirely to a significant reduction in the rate of target-vessel revascularization. An angiographic follow-up study showed significant reductions in in-stent restenosis and in-stent late luminal loss.

APPENDIX

The following investigators and institutions participated in the TYPHOON study: **Steering Committee:** C. Spaulding, C. Bode, E. Bramucci, P. Henry, E. Teiger, D. Carrie, M. Slama, K. Beatt; **Sponsor:** *Cordis, Warren, NJ* — D. Donohoe (medical director), D. Snead, R. Dalal, S. Sun; *Cordis, Waterloo, Belgium* — H.-P. Stoll (program director), A. Cebrian (program coordination), L. Wheeler; **Data and Safety Monitoring Board:** B. Meier, Switzerland; B. Lancelin, France; J.-F. Neumann, Germany; **Clinical Events Committee:** A. Caspi (chair), Israel; G. Maurer, Austria; S. Cook, Switzerland; **Data Management and Monitoring:** *Hesperion, Clinical Development Services, Allschwil, Switzerland* — V. Charlon (director); C. Berge; P. Rush; **Electronic Data Capture:** *PPD GlobalView Web Services, New Hope, MN*; **Core Angiographic Laboratory:** *Bio Imaging Technologies, Leiden, the Netherlands* — A. Van Weert (director); **Clinical Sites:** *Royal Perth Hospital, Perth, Australia* — R. Clugston, M. Bonner; *Hôpital Cantonal de Genève, Geneva* — E. Camenzind, N. Masson; *Nemocnice Ceske, Budejovice, Czech Republic* — L. Pesl; *Poruba School of Medicine, Poruba, Czech Republic* — R. Stipal, L. Pleva; *Medizinische Universitätsklinik Freiburg, Freiburg, Germany* — C. Bode, M. Zehender, S. Richter; *Universitätskliniken des Saarlandes, Homburg Saar, Germany* — G. Nickenig, N. Werner; *Medizinische Klinik und Poliklinik Johannes-Gutenberg-Universität, Mainz, Germany* — F. Post; *Købenbavns Amtssygehus Gentofte, Hellerup, Denmark* — U. Abildgaard, A. Galloe; *Virgen de la Arrixaca, Murcia, Spain* — M. Valdés, E. Pinar; *Hôpital Européen Georges Pompidou, Paris* — N. Danchin; *Institut Mutualiste Montsouris, Paris* — A. Dibie, F. Larrazet, F. Philippe; *Clinique du Millénaire, Montpellier, France* — X. De Boisgelin, G. Levy; *Hôpital Lariboisiere, Paris* — P. Henry, G. Sideris, R. Fressonnet; *Hôpital Bichat, Paris* — J.-M. Juliard, P. Aubry; *Hôpital Tenon, Paris* — P. Michel, E. Garbarz; *Hôpital Béclère, Clamart, France* — M. Slama, P. Colin; *Hôpital Cochin, Paris* — C. Spaulding, O. Varenne; *Henri Mondor Hospital, Paris* — E. Teiger, J. Dubois-Randé, S. Champagne; *Centre Hospitalier Universitaire Toulouse–Hôpital Rangueil, Toulouse, France* — D. Carrié, J. Roncalli, J. Cahuzac; *Clinique Les Fleurs, Marseille, France* — P. Commeau, P. Barragan; *Hôpital Guillaume et René Laennec, Centre Hospitalier Universitaire Nord, St. Herblain, France* — P. Guerin, A. Tirouvanziam; *Clinique St. Augustin, Bordeaux, France* — O. Darremont, J. Leymarie; *Centre Hospitalier Ré-*

gional d'Orleans–Hôpital de la Source, Orleans, France — O. Dibon; Clinique Pasteur, Toulouse, France — J. Fajadet, B. Farah, B. Assoun; Centre Cardiologique du Nord, Saint Denis, France — P. Guyon, B. Chevalier; Clinique Victor Pauchet, Amiens, France — A. Py, E. Dadez; Centre Hospitalier Universitaire de Rennes, Rennes, France — H. Le Breton, M. Bedossa; Centre Hospitalier Universitaire Mulhouse, Mulhouse, France — L. Jacquemin, R. ElBelghit; Institut Hospitalier Jacques Cartier, Massy, France — M. Morice, T. Lefèvre; Centre Hospitalier Universitaire Avignon, Avignon, France — M. Pansieri, M. Metge; Clinique de la Casamance, Aubagne, France — B. Valeix; Clinique Médico-Chirurgicale Les Fontaines, Melun, France — P. Dupouy, E. Aptecar; Cardiovascular Center, Semmelweis University, Budapest, Hungary — B. Merkely, G. Szabó; Wolfson Medical Center, Holon, Israel — Y. Rozenman, V. Witzling; Assaf Harofeh Medical Center, Zrifin, Israel — R. Krakover, I. Zyssman; Soroka Medical Center, Beer Sheva, Israel — R. Ilia, C. Cafri; Souraski Medical Center, Tel Aviv, Israel — H. Miller, A. Finkelstein; Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy — E. Bramucci, M. Ferlini, U. Canosi; San Filippo Neri Hospital, Rome — G. Richichi, V. Pasceri; Azienda Ospedale Luigi Sacco, Milan — P. Viecca; Azienda Ospedaliera Careggi, Florence, Italy — M. Margheri, C. Giglioli; Pauls Stradins University Hospital, Riga, Latvia — A. Erglis; I. Narbute; University Medical Center Utrecht, Utrecht, the Netherlands — P. Stella; P. Elsman; Slaskie Centrum Chorób Serca, Zabrze, Poland — L. Poloński; Hospital Fernando Fonseca, Amadora, Portugal — P. Farto e Abreu; Hospital Garcia Orta, Almada, Portugal — H. Pereira; Hammersmith Hospital, London — K. Beatt; and Southampton General Hospital, Southampton, United Kingdom — K. Dawkins.

REFERENCES

1. Morice M-C, 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. 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, randomized controlled trial (E-SIRIUS). Lancet 2003;362:1093-9.

4. Saia F, Lemos PA, Lee CH, et al. Sirolimus-eluting stent implantation in ST-elevation acute myocardial infarction: a clinical and angiographic study. Circulation 2003;108:1927-9.

5. Lemos PA, Lee CH, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol 2003;41:2093-9.

6. Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109-17.

7. Serruys PW, Foley DP, de Feyter PJ, eds. Quantitative coronary angiography in clinical practice. Dordrecht, the Netherlands: Kluwer Academic, 1994.

8. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. N Engl J Med 1985;312:932-6.

9. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:1949-56.

10. Morice MC, Colombo A, Meier B, et al. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. JAMA 2006;295:895-904.

11. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.

12. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med 2006;355:1105-13.

13. Spaulding C, Cador R, Benhamda K, et al. One-week and six-month angiographic controls of stent implantation after occlusive and nonocclusive dissection during primary balloon angioplasty for acute myocardial infarction. Am J Cardiol 1997;79:1592-5.

14. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957-66.

15. Maillard L, Hamon M, Khalife K, et al. A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. J Am Coll Cardiol 2000;35:1729-36.

16. Antoniucci D, Santoro GM, Bolognese L, Valenti R, Trapani M, Fazzini PF. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction: results from the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial. J Am Coll Cardiol 1998;31:1234-9.

17. Rodriguez A, Bernardi V, Fernandez M, et al. In-hospital and late results of coronary stents versus conventional balloon angioplasty in acute myocardial infarction (GRAMI trial). Am J Cardiol 1998;81:1286-91.

18. Saito S, Hosokawa G, Tanaka S, Nakamura S. Primary stent implantation is superior to balloon angioplasty in acute myocardial infarction: final results of the primary angioplasty versus stent implantation in acute myocardial infarction (PASTA) trial. Catheter Cardiovasc Interv 1999;48:262-8.

19. Monassier JP, Hamon M, Elias J, et al. Early versus late coronary stenting following acute myocardial infarction: results of the STENTIM I Study (French Registry of Stenting in Acute Myocardial Infarction). Cathet Cardiovasc Diagn 1997;42:243-8.

20. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). (Available at http://www.acc.org/clinical/guidelines/percutaneous/update/index.pdf.)

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