

ORIGINAL ARTICLE

Paclitaxel-Eluting Stents versus Bare-Metal Stents in Acute Myocardial Infarction

Gregg W. Stone, M.D., Alexandra J. Lansky, M.D., Stuart J. Pocock, Ph.D., Bernard J. Gersh, M.B., Ch.B., D.Phil., George Dangas, M.D., Ph.D., S. Chiu Wong, M.D., Bernhard Witzensichler, M.D., Giulio Guagliumi, M.D., Jan Z. Peruga, M.D., Bruce R. Brodie, M.D., Dariusz Dudek, M.D., Martin Möckel, M.D., Andrzej Ochala, M.D., Alison Kellock, B.S., Helen Parise, Sc.D., and Roxana Mehran, M.D., for the HORIZONS-AMI Trial Investigators*

ABSTRACT

BACKGROUND

There is no consensus regarding the safety and efficacy of drug-eluting stents, as compared with bare-metal stents, in patients with ST-segment elevation myocardial infarction who are undergoing primary percutaneous coronary intervention (PCI).

METHODS

We randomly assigned, in a 3:1 ratio, 3006 patients presenting with ST-segment elevation myocardial infarction to receive paclitaxel-eluting stents (2257 patients) or otherwise identical bare-metal stents (749 patients). The two primary end points of the study were the 12-month rates of target-lesion revascularization for ischemia (analysis powered for superiority) and a composite safety outcome measure of death, reinfarction, stroke, or stent thrombosis (powered for noninferiority with a 3.0% margin). The major secondary end point was angiographic evidence of restenosis at 13 months.

RESULTS

Patients who received paclitaxel-eluting stents, as compared with those who received bare-metal stents, had significantly lower 12-month rates of ischemia-driven target-lesion revascularization (4.5% vs. 7.5%; hazard ratio, 0.59; 95% confidence interval [CI], 0.43 to 0.83; $P=0.002$) and target-vessel revascularization (5.8% vs. 8.7%; hazard ratio, 0.65; 95% CI, 0.48 to 0.89; $P=0.006$), with noninferior rates of the composite safety end point (8.1% vs. 8.0%; hazard ratio, 1.02; 95% CI, 0.76 to 1.36; absolute difference, 0.1 percentage point; 95% CI, -2.1 to 2.4 ; $P=0.01$ for noninferiority; $P=0.92$ for superiority). Patients treated with paclitaxel-eluting stents and those treated with bare-metal stents had similar 12-month rates of death (3.5% and 3.5%, respectively; $P=0.98$) and stent thrombosis (3.2% and 3.4%, respectively; $P=0.77$). The 13-month rate of binary restenosis was significantly lower with paclitaxel-eluting stents than with bare-metal stents (10.0% vs. 22.9%; hazard ratio, 0.44; 95% CI, 0.33 to 0.57; $P<0.001$).

CONCLUSIONS

In patients with ST-segment elevation myocardial infarction who were undergoing primary PCI, implantation of paclitaxel-eluting stents, as compared with bare-metal stents, significantly reduced angiographic evidence of restenosis and recurrent ischemia necessitating repeat revascularization procedures. No safety concerns were apparent at 1 year. (ClinicalTrials.gov number, NCT00433966.)

From Columbia University Medical Center and New York–Presbyterian Hospital and the Cardiovascular Research Foundation (G.W.S., A.J.L., G.D., A.K., H.P., R.M.), and New York–Presbyterian Hospital and Weill Cornell Medical Center (S.C.W.) — all in New York; London School of Hygiene and Tropical Medicine, London (S.J.P.); Mayo Clinic, Rochester, MN (B.J.G.); Charité Campus Benjamin Franklin (B.W.) and Charité Campus Virchow-Klinikum (M.M.) — both in Berlin; Ospedali Riuniti di Bergamo, Bergamo, Italy (G.G.); Medical University, Lodz (J.Z.P.), Jagiellonian University, Krakow (D.D.), and Silesian Medical Academy, Katowice (A.O.) — all in Poland; and LeBauer Cardiovascular Research Foundation and Moses Cone Hospital, Greensboro, NC (B.R.B.). Address reprint requests to Dr. Stone at Columbia University Medical Center, Cardiovascular Research Foundation, 111 E. 59th St., 11th Fl., New York, NY 10022, or at gs2184@columbia.edu.

*The investigators, institutions, and research organizations participating in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial are listed in the Appendix.

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BY ENLARGING LUMINAL DIMENSIONS and sealing dissection planes at the site of coronary-artery occlusion in patients with evolving ST-segment elevation myocardial infarction, bare-metal stents reduce the risk of early and late recurrent ischemia and reocclusion of the infarct-related artery, as compared with balloon angioplasty alone, decreasing the need for subsequent revascularization of the target lesion with repeat percutaneous coronary intervention (PCI) or coronary-artery bypass grafting.^{1,2} Nonetheless, restenosis occurs in more than 20% of patients in whom bare-metal stents are implanted during primary PCI, and implantation of bare-metal stents, as compared with balloon angioplasty, has not reduced the rates of death or reinfarction among patients with ST-segment elevation myocardial infarction.^{1,2} As compared with bare-metal stents, drug-eluting stents reduce neointimal hyperplasia and have been shown in large, randomized trials to be safe and effective for the treatment of simple lesions in patients with stable coronary-artery disease.^{3,4} As would be expected, however, the rates of target-lesion revascularization, stent thrombosis, and death are increased when drug-eluting stents are used in higher-risk patients and those with more complex lesions.^{5,6} Specifically, when drug-eluting stents are implanted in ruptured plaques with a large necrotic core (the lesion substrate responsible for most cases of ST-segment elevation myocardial infarction),⁷ they may impair vascular healing responses, potentially resulting in increased rates of stent thrombosis.^{8,9} Reduced rates of target-lesion revascularization with drug-eluting stents, as compared with bare-metal stents, in patients with ST-segment elevation myocardial infarction have been reported in small-to-moderate-size randomized trials¹⁰; none, however, were powered for safety end points, and the routine performance of follow-up angiography may have exaggerated the benefits of drug-eluting stents in many of these studies.^{11,12}

To address these limitations, we performed a large-scale, international, prospective, randomized trial comparing paclitaxel-eluting stents with bare-metal stents in patients with evolving ST-segment elevation myocardial infarction. The study was powered for safety as well as efficacy, with follow-up angiographic assessment performed only after the primary clinical end point had been evaluated.

METHODS

STUDY DESIGN

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial was a prospective, open-label, multicenter, controlled trial involving patients with ST-segment elevation myocardial infarction who were undergoing primary PCI as a management strategy. The study incorporated two factorial randomized phases to allow a comparison of the direct thrombin inhibitor bivalirudin alone with heparin plus glycoprotein IIb/IIIa inhibitors and a comparison of paclitaxel-eluting stents with bare-metal stents.^{13,14} The trial was designed by the principal investigator, executive committee, and pharmacology committee and was sponsored and managed by the Cardiovascular Research Foundation, a nonprofit foundation affiliated with Columbia University, with grant support from Boston Scientific Corporation and the Medicines Company. Other than supplying financial support and the drugs and devices, the funding companies were not involved with study processes, including site selection and management, data collection, and analysis. The principal investigator had unrestricted data access after the database was locked, controlled the decision to submit the findings for publication, prepared the manuscript, and vouches for the integrity of the data.

PATIENT POPULATION AND RANDOMIZATION

Consecutive patients 18 years of age or older who presented within 12 hours after the onset of symptoms and who had ST-segment elevation of 1 mm or more in two or more contiguous leads, new left bundle-branch block, or true posterior myocardial infarction were considered for enrollment. The clinical exclusion criteria, which have been described previously, were contraindications to study medications, conditions that increase the risk of hemorrhage, and an inability to take clopidogrel for 6 months after the procedure.^{13,14} The study was approved by the institutional review board or ethics committee at each participating center, and all patients gave written informed consent.

Eligible patients were randomly assigned in a 1:1 ratio to treatment with unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor or to treatment with bivalirudin alone (Fig. 1); the timing and dosing for each regimen have been de-

scribed previously.^{13,14} After the first randomization, emergency coronary angiography with left ventriculography was performed, and patients were then assigned, at the discretion of the physician, to treatment with PCI or coronary-artery bypass grafting (CABG) or to medical management. Among patients undergoing PCI, anatomical eligibility for randomization to stent implantation was assessed after the restoration of patency in the infarct-related vessel (by means of spontaneous reperfusion, guidewire recanalization, or inflation of an undersized angioplasty balloon).

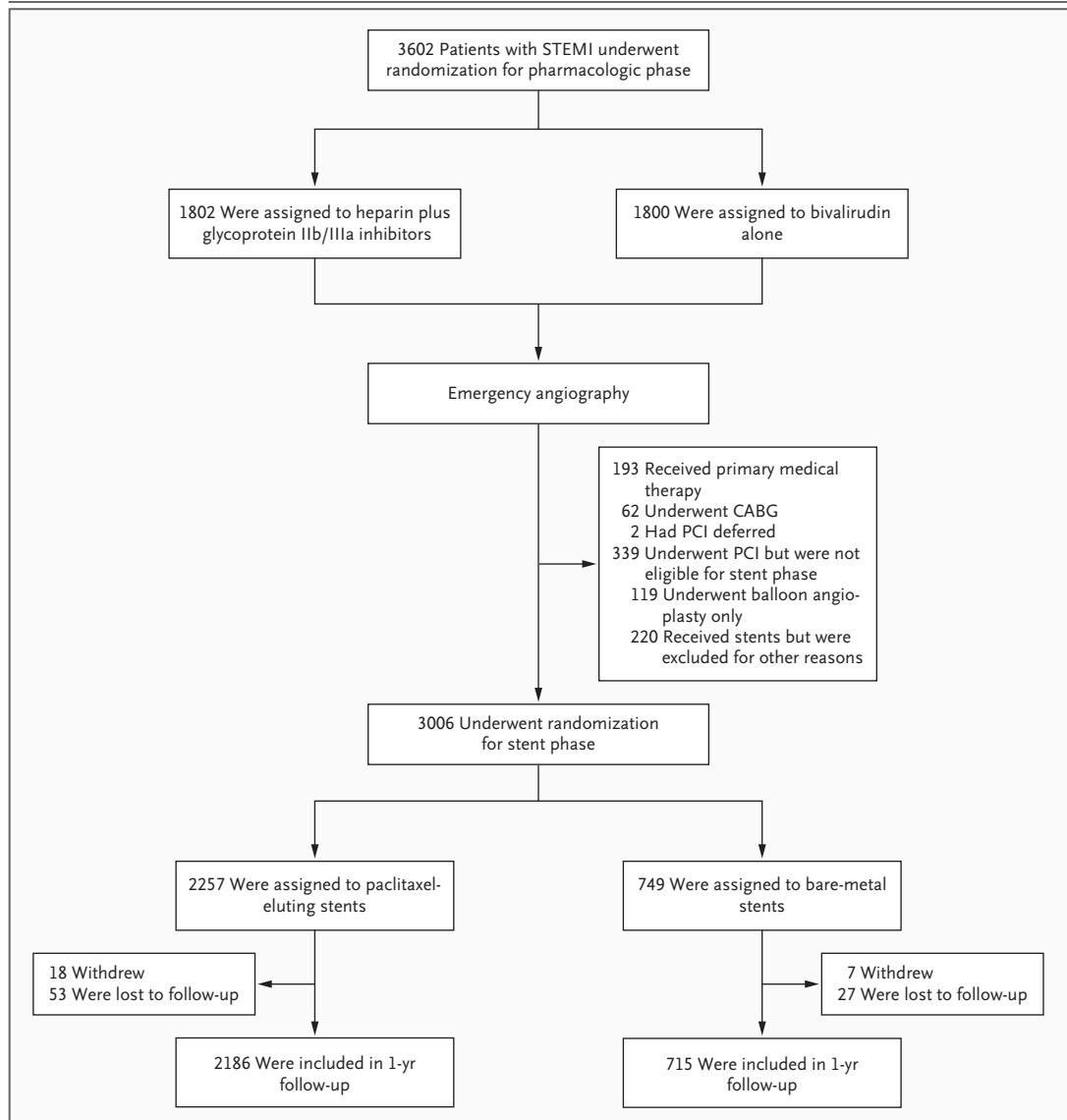


Figure 1. Randomization, Treatment, and Follow-up at 1 Year.

Patients with ST-segment elevation myocardial infarction (STEMI) were included if they presented within 12 hours after the onset of symptoms. Of the 3226 patients undergoing primary stenting, 220 were not randomly assigned to a stent group for the following reasons: the absence of any eligible vessels (85 patients), excessive tortuosity or calcification (35), bifurcation lesion with planned dual-branch stenting (24), unprotected left main coronary artery lesion (13), anticipated stent length of more than 100 mm (8), infarct lesion due to stent thrombosis (11), coronary-artery bypass grafting (CABG) likely to be performed within 30 days (37), lesions otherwise ineligible (29), and other or unspecified reasons (28). More than one reason was present for some patients. PCI denotes percutaneous coronary intervention.

Patients were considered to be eligible for random assignment to paclitaxel-eluting stents or bare-metal stents if an acute-infarct-related artery was present in which all lesions requiring PCI had a visually estimated reference-vessel diameter between 2.25 mm and 4.0 mm, without excessive tortuosity or severe calcification. Angiographic exclusion criteria were planned stenting of an unprotected left main artery (i.e., a left main artery without a patent bypass graft to either the left anterior descending artery or the left circumflex artery), a bifurcation lesion that required planned implantation of stents in both the main vessel and a side branch (bifurcation lesions were included if a single-stent strategy was intended, even if multiple stents were ultimately required), an anticipated stent length of more than 100 mm, infarction due to stent thrombosis, and an anticipated need for bypass grafting within 30 days. Patients with multiple lesions and vessels requiring intervention were included in the study if all the lesions were eligible for study stents.

Patients who were eligible for random assignment to stent implantation were assigned in a 3:1 ratio to receive either paclitaxel-eluting stents (TAXUS Express, Boston Scientific) or otherwise identical bare-metal stents (Express, Boston Scientific) (Fig. 1). Randomization was performed with the use of a computerized, interactive voice-response system and a dynamic (minimization) allocation scheme that balanced the assignment for the pharmacologic assignment (unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor or bivalirudin alone), the presence or absence of diabetes mellitus, lesion length (>26 mm, requiring overlapping stents, vs. ≤26 mm), and location of the study site (in the United States or outside the United States).

PROTOCOL PROCEDURES

Stents with a diameter between 100 and 110% of the distal reference-vessel diameter were implanted, and implantation was performed with a minimum pressure of 14 atm. Direct stenting (i.e., without balloon predilation) was permitted according to the discretion of the physician if the infarct-related vessel was patent (i.e., had a Thrombolysis in Myocardial Infarction [TIMI] flow grade of 2 or 3) at baseline. Study stents were available in diameters ranging from 2.25 to 4.0 mm and in lengths ranging from 8 to 32 mm.

Aspirin (324 mg administered in chewable

form or 500 mg administered intravenously) was given in the emergency room, after which 300 to 325 mg was given orally every day during the hospitalization and 75 to 81 mg every day thereafter indefinitely. A loading dose of clopidogrel (either 300 mg or 600 mg, at the discretion of the investigator) was administered before catheterization, followed by 75 mg orally every day for at least 6 months (with a recommendation of 1 year or longer).

Clinical follow-up examinations were performed at 30 days, 6 months, and 12 months, and then yearly for a total of 5 years. The primary clinical end points of the first randomization (pharmacologic phase) were prespecified at 30 days, whereas the primary end points of the second randomization (stent phase) were prespecified at 12 months. Routine angiographic follow-up at 13 months (after ascertainment of the primary 12-month clinical end points) was prespecified for 1800 patients randomly assigned to receive a stent in whom implantation of the stent was successful (diameter stenosis <10% with a TIMI flow grade of 3 and a National Heart, Lung, and Blood Institute classification for coronary-artery dissection of type A or less adjacent to the stent), stent thrombosis did not occur, and bypass grafting was not performed within 30 days after implantation of the stent.

STATISTICAL ANALYSIS

Two primary 12-month clinical end points were prespecified: ischemia-driven revascularization of the target lesion and a composite safety end point of major adverse cardiovascular events, consisting of death, reinfarction, stroke, and stent thrombosis. The components of the safety end point have been defined previously.^{13,14} Target-lesion revascularization was considered to be ischemia-driven if there was stenosis of at least 50% of the diameter of the target lesion, as documented by a positive functional study, ischemic changes on an electrocardiogram, or symptoms referable to the target lesion, or in the absence of documented ischemia, if there was stenosis of at least 70% as assessed by quantitative coronary analysis at the independent core laboratory. Stent thrombosis was defined as the definite or probable occurrence of a thrombotic event, according to the Academic Research Consortium classification.¹⁵ An independent clinical events committee whose members were unaware of the treatment assign-

ments adjudicated all primary end-point events by reviewing original source documents and procedural angiograms. Angiographic analysis was performed at the core laboratory with the use of validated methods by technicians who were unaware of the treatment assignments and clinical outcomes.¹⁶

The trial was powered to show the superiority of paclitaxel-eluting stents as compared with bare-metal stents for the 12-month primary efficacy end point of target-lesion revascularization and the major secondary efficacy end point of binary restenosis as assessed by angiography at 13 months, with a two-sided alpha level of 0.05. Assuming 1-year rates of ischemia-driven target-lesion revascularization of 5.0% in the paclitaxel-eluting-stent group and 9.0% in the bare-metal-

stent group, with assignment of 2250 patients and 750 patients to the two groups, respectively, and 95% of the patients available for the 1-year follow-up, we calculated that the trial would have 95% power to show the superiority of paclitaxel-eluting stents for the primary efficacy end point. Assuming that 1200 patients had follow-up angiograms at 13 months that could be evaluated, the trial would have 96% power to show a reduction in binary restenosis from 26.0% with bare-metal stents to 15.6% with paclitaxel-eluting stents. The trial was also powered to show the noninferiority of paclitaxel-eluting stents as compared with bare-metal stents for the primary composite safety end point of major adverse cardiovascular events, on the basis of the upper boundary of the two-sided 95% confidence inter-

Table 1. Baseline Characteristics of the Study Patients and Medication Use.

| Variable | Paclitaxel-Eluting Stents (N=2257) | Bare-Metal Stents (N=749) | P Value |
|--|------------------------------------|---------------------------|---------|
| Age — yr | | | 0.26 |
| Median | 59.9 | 59.3 | |
| Range | 30.9–92.3 | 26.0–89.0 | |
| Male sex — no. (%) | 1738 (77.0) | 569 (76.0) | 0.56 |
| Diabetes — no./total no. (%) | | | |
| Any | 364/2256 (16.1) | 114/749 (15.2) | 0.55 |
| Insulin-requiring | 98/2256 (4.3) | 31/749 (4.1) | 0.81 |
| Hypertension — no./total no. (%) | 1155/2256 (51.2) | 389/749 (51.9) | 0.73 |
| Hyperlipidemia — no./total no. (%) | 953/2256 (42.2) | 308/749 (41.1) | 0.59 |
| Current smoker — no./total no. (%) | 1041/2246 (46.3) | 388/748 (51.9) | 0.009 |
| Prior myocardial infarction — no./total no. (%) | 206/2256 (9.1) | 82/749 (10.9) | 0.14 |
| Prior percutaneous coronary intervention — no./total no. (%) | 214/2255 (9.5) | 58/749 (7.7) | 0.15 |
| Prior coronary-artery bypass grafting — no./total no. (%) | 50/2256 (2.2) | 14/749 (1.9) | 0.57 |
| Time from symptom onset to balloon inflation — min | | | 0.36 |
| Median | 221 | 225 | |
| Interquartile range | 160–329 | 162–350 | |
| Time from arrival at hospital to balloon inflation — min | | | 0.92 |
| Median | 100 | 97 | |
| Interquartile range | 74–134 | 71–138 | |
| Killip class II, III, or IV — no./total no. (%) | 199/2254 (8.8) | 60/748 (8.0) | 0.50 |
| Renal insufficiency — no./total no. (%) [*] | 328/2102 (15.6) | 107/696 (15.4) | 0.88 |
| Anemia — no./total no. (%) [†] | 235/2130 (11.0) | 54/715 (7.6) | 0.008 |
| Thrombocytopenia — no./total no. (%) [‡] | 91/2186 (4.2) | 30/733 (4.1) | 0.93 |
| Left ventricular ejection fraction — % [§] | | | 0.49 |
| Median | 50 | 50 | |
| Interquartile range | 44–59 | 43–58 | |

Table 1. (Continued.)

| Variable | Paclitaxel-Eluting Stents (N=2257) | Bare-Metal Stents (N=749) | P Value |
|---|------------------------------------|---------------------------|---------|
| Use of antithrombin during PCI — no./total no. (%) | | | |
| Unfractionated heparin | 1123/2255 (49.8) | 375/749 (50.1) | 0.90 |
| Bivalirudin | 1141/2252 (50.7) | 379/745 (50.9) | 0.92 |
| Use of glycoprotein IIb/IIIa inhibitor during PCI — no./total no. (%) | 1171/2253 (52.0) | 385/748 (51.5) | 0.81 |
| Medications at discharge — no./total no. (%) | | | |
| Beta-blockers | 2048/2213 (92.5) | 680/738 (92.1) | 0.72 |
| Angiotensin-converting-enzyme inhibitors or receptor blockers | 1840/2212 (83.2) | 614/738 (83.2) | 0.99 |
| Statins | 2123/2212 (96.0) | 708/738 (95.9) | 0.96 |
| Use of aspirin — no./total no. (%) | | | |
| At discharge | 2192/2213 (99.1) | 728/738 (98.6) | 0.35 |
| At 30 days¶ | 2115/2148 (98.5) | 700/712 (98.3) | 0.78 |
| At 6 mo¶ | 2043/2096 (97.5) | 682/694 (98.3) | 0.23 |
| At 1 yr¶ | 2019/2080 (97.1) | 662/679 (97.5) | 0.56 |
| Use of thienopyridine — no./total no. (%) | | | |
| At discharge | 2200/2213 (99.4) | 730/738 (98.9) | 0.16 |
| At 30 days¶ | 2127/2154 (98.7) | 696/712 (97.8) | 0.06 |
| At 6 mo¶ | 1989/2100 (94.7) | 607/694 (87.5) | <0.001 |
| At 1 yr¶ | 1522/2083 (73.1) | 434/679 (63.9) | <0.001 |

* Renal insufficiency was defined as a creatinine clearance of less than 60 ml per minute as calculated with the use of the Cockcroft–Gault equation.

† Anemia was defined, according to the World Health Organization criteria, as a hematocrit value at initial presentation of less than 39% for men and less than 36% for women.

‡ Thrombocytopenia was defined as less than 150,000 platelets per cubic millimeter.

§ The left ventricular ejection fraction was assessed visually on the contrast-enhanced left ventriculogram obtained at baseline.

¶ Patients were considered to have used aspirin or a thienopyridine if they had taken the drug on more than 50% of the days since the previous study visit.

val for the difference in percentages, with a non-inferiority margin of 3.0%. Assuming a 7.5% rate of the safety end point of major adverse cardiovascular events in both stent groups, we calculated that the study would have 80% power to show the noninferiority of paclitaxel-eluting stents as compared with bare-metal stents for the primary safety end point.

Data were analyzed according to the group assignment, regardless of the treatment received. Categorical outcomes were compared by means of the chi-square test or Fisher’s exact test. Continuous variables were compared by means of the Wilcoxon rank-sum test. The primary event analyses were performed with the use of time-to-event data (with data censored at the time of a patient’s withdrawal from the study or at the

last follow-up examination); the results of these analyses are shown with the use of Kaplan–Meier methods and were compared by means of the log-rank test. As a secondary analysis, time-updated Cox proportional-hazards regression with adjustment for covariates was performed to adjust for baseline imbalances and differences in medication use between the groups over time.

RESULTS

PATIENTS AND PROCEDURES

Between March 25, 2005, and May 7, 2007, a total of 3602 patients with ST-segment elevation myocardial infarction who were undergoing primary PCI at 123 centers in 11 countries were randomly assigned to treatment with heparin plus a glyco-

protein IIb/IIIa inhibitor (1802 patients) or to treatment with bivalirudin alone (1800 patients) (Fig. 1). PCI was subsequently performed in 3345 patients (92.9%), of whom 3226 (96.4%) underwent attempted stenting. Among those patients undergoing primary stenting, 3006 (93.2%) were randomly assigned to receive either paclitaxel-eluting stents (2257 patients) or bare-metal stents (749). A total of 220 patients received stents but were not randomly assigned to a study group for a variety of reasons (Fig. 1).

The baseline features of the groups were well matched, except that there was a slightly higher percentage of current smokers in the group assigned to receive bare-metal stents and a slightly higher percentage of patients with baseline anemia in the group assigned to receive paclitaxel-eluting stents (Table 1). The median age of the patients was 59.7 years, and 76.7% of the patients were men. The angiographic characteristics and procedural results were also similar between the groups except that the lesions in the patients assigned to receive paclitaxel-eluting stents were slightly longer, necessitating the use of slightly longer stents (Table 2). Compliance with taking aspirin was high in both groups throughout the 12-month follow-up period. The rate of thienopyridine use was slightly higher at 6 and 12 months among patients in whom paclitaxel-eluting stents had been implanted than among those in whom bare-metal stents had been implanted.

CLINICAL OUTCOMES

The rate of the primary efficacy end point, ischemia-driven target-lesion revascularization at 12 months, was 4.5% in the paclitaxel-eluting-stent group as compared with 7.5% in the bare-metal-stent group (hazard ratio with paclitaxel-eluting stents, 0.59; 95% confidence interval [CI], 0.43 to 0.83), which represented a benefit for 3 additional patients per 100 who were treated for 1 year with paclitaxel-eluting stents as compared with bare-metal stents (95% CI, 0.9 to 5.1; $P=0.002$) and a 41% relative hazard reduction with paclitaxel-eluting stents as compared with bare-metal stents (Table 3 and Fig. 2). The rate of ischemia-driven target-vessel revascularization at 12 months was also lower among patients treated with paclitaxel-eluting stents than among those treated with bare-metal stents (5.8% vs. 8.7%; hazard ratio, 0.65; 95% CI, 0.48 to 0.89; $P=0.006$). The 12-month rates of the primary safety end point of major

adverse cardiovascular events were similar between patients who received paclitaxel-eluting stents and those who received bare-metal stents (8.1% and 8.0%, respectively; hazard ratio with paclitaxel-eluting stents, 1.02; 95% CI, 0.76 to 1.36; absolute difference, 0.1 percentage point; 95% CI, -2.1 to 2.4; $P=0.01$ for noninferiority; $P=0.92$ for superiority). The individual rates of death, reinfarction, stroke, and stent thrombosis were also similar in the two groups through 12 months of follow-up. The point estimates for the two primary end points were not significantly changed after correction for the baseline differences in smoking and anemia and follow-up use of thienopyridine agents (hazard ratio for ischemic target-lesion revascularization with paclitaxel-eluting stents, 0.62; 95% CI, 0.44 to 0.87; $P=0.006$; hazard ratio for major adverse cardiovascular events, 1.03; 95% CI, 0.76 to 1.40; $P=0.84$). In logistic-regression analyses, there were no significant interactions between the initial pharmacologic group assignment (heparin plus a glycoprotein IIb/IIIa inhibitor or bivalirudin alone) and the assigned stent type with respect to the occurrence of the two primary end points ($P=0.17$ for ischemic target-lesion revascularization and $P=0.89$ for major adverse cardiovascular events).

ANGIOGRAPHIC OUTCOMES

Angiographic follow-up data at 13 months were available for 910 patients who received paclitaxel-eluting stents (1081 lesions) and for 293 patients who received bare-metal stents (332 lesions) and were analyzed at the core angiographic laboratory. The rate of the major secondary efficacy end point, analysis-segment binary restenosis (which includes measurements within the stent and 5 mm proximal and distal to the stent) in all lesions, was 10.0% among lesions in the paclitaxel-eluting-stent group as compared with 22.9% among lesions in the bare-metal-stent group, a difference of 56% (relative risk with paclitaxel-eluting stents, 0.44; 95% CI, 0.33 to 0.57; $P<0.001$). Among the 1062 lesions in the paclitaxel-eluting-stent group and the 328 in the bare-metal-stent group in which stents were implanted (Table 4), in-stent late luminal loss was less with paclitaxel-eluting stents than with bare-metal stents (0.41 ± 0.64 mm vs. 0.82 ± 0.70 mm, $P<0.001$), and the rate of analysis-segment binary restenosis was lower (9.6% vs. 23.2%, $P<0.001$). There were no significant differences in the rates of reocclusion of the infarct-

Table 2. Angiographic and Procedural Outcomes.*

| Variable | Paclitaxel-Eluting Stents (N=2257) | Bare-Metal Stents (N=749) | P Value |
|---|------------------------------------|---------------------------|---------|
| Lesions treated | | | 0.12 |
| Total no. | 2525 | 820 | |
| No. per patient | 1.1±0.4 | 1.1±0.4 | |
| ≥2 lesions treated — no. of patients/total no. (%) | 248/2236 (11.1) | 67/742 (9.0) | 0.11 |
| ≥2 vessels treated — no. of patients/total no. (%) | 101/2236 (4.5) | 23/742 (3.1) | 0.09 |
| Type of stent — no. of lesions/total no. (%) | | | |
| Paclitaxel-eluting | 2485/2525 (98.4) | 1/820 (0.1) | — |
| Other drug-eluting | 0/2525 | 1/820 (0.1) | — |
| Bare-metal | 28/2525 (1.1) | 813/820 (99.1) | — |
| Site of infarct lesion — no. of lesions/total no. (%) | | | |
| Left anterior descending coronary artery | 1006/2525 (39.8) | 347/820 (42.3) | 0.21 |
| Left circumflex coronary artery | 374/2525 (14.8) | 132/820 (16.1) | 0.37 |
| Right coronary artery | 1138/2525 (45.1) | 338/820 (41.2) | 0.05 |
| Left main coronary artery | 7/2525 (0.3) | 3/820 (0.4) | 0.71 |
| Saphenous-vein graft | 30/2498 (1.2) | 6/811 (0.7) | 0.27 |
| Implantation of at least one stent attempted — no. of lesions/total no. (%) | 2501/2525 (99.0) | 815/820 (99.4) | 0.36 |
| Direct stenting attempted — no. of lesions/total no. (%)† | 734/2501 (29.3) | 264/815 (32.4) | 0.10 |
| No. of stents implanted per patient | 1.5±0.9 | 1.4±0.7 | <0.001 |
| Total stent length per patient — mm | 30.8±17.8 | 27.3±14.9 | <0.001 |
| Maximum balloon diameter per lesion — mm | 3.20±0.61 | 3.18±0.58 | 0.84 |
| Maximum pressure per lesion — atm | 14.9±3.5 | 14.9±3.3 | 0.98 |
| Aspiration catheter used — no. of patients/total no. (%) | 255/2246 (11.4) | 80/745 (10.7) | 0.64 |
| Baseline TIMI flow grade — no. of vessels/total no. (%)‡ | | | |
| 0 or 1 | 1424/2348 (60.6) | 442/770 (57.4) | 0.11 |
| 2 | 320/2348 (13.6) | 117/770 (15.2) | 0.28 |
| 3 | 604/2348 (25.7) | 211/770 (27.4) | 0.36 |
| Baseline quantitative angiographic findings for lesions | | | |
| Reference-vessel diameter — mm | 2.89±0.51 | 2.90±0.50 | 0.75 |
| Minimal luminal diameter — mm | 0.35±0.45 | 0.35±0.45 | 0.81 |
| Stenosis — % of vessel diameter | 87.6±15.4 | 87.4±15.4 | 0.83 |
| Lesion length — mm | 17.5±10.1 | 16.2±8.8 | 0.006 |
| Final TIMI flow grade — no. of vessels/total no. (%) | | | |
| 0 or 1 | 40/2346 (1.7) | 7/771 (0.9) | 0.12 |
| 2 | 252/2346 (10.7) | 72/771 (9.3) | 0.27 |
| 3 | 2054/2346 (87.6) | 692/771 (89.8) | 0.10 |
| Final quantitative angiographic findings for lesions | | | |
| Reference-vessel diameter — mm | 2.93±0.51 | 2.95±0.50 | 0.57 |
| Minimal luminal diameter — mm | 2.36±0.55 | 2.37±0.52 | 0.38 |
| Stenosis — % of vessel diameter | 19.9±11.6 | 19.5±11.1 | 0.33 |

* Plus-minus values are means ±SD. TIMI denotes Thrombolysis in Myocardial Infarction.

† Direct stenting refers to the implantation of a stent without balloon predilation.

‡ TIMI flow is graded on a scale of 0 to 3, with a higher grade indicating better flow.

Table 3. Clinical Outcomes at 1 Year.*

| Outcome | Cumulative No. of Events | | Kaplan–Meier Estimate of Cumulative Event-Rate | | P Value |
|--|------------------------------------|---------------------------|--|---------------------------|---------|
| | Paclitaxel-Eluting Stents (N=2257) | Bare-Metal Stents (N=749) | Paclitaxel-Eluting Stents (N=2257) | Bare-Metal Stents (N=749) | |
| Ischemia-driven target-lesion revascularization† | 98 | 54 | 4.5 | 7.5 | 0.002 |
| PCI | 88 | 48 | 4.0 | 6.6 | 0.004 |
| CABG | 10 | 7 | 0.5 | 1.0 | 0.12 |
| Ischemia-driven target-vessel revascularization‡ | 126 | 63 | 5.8 | 8.7 | 0.006 |
| PCI | 109 | 56 | 5.0 | 7.7 | 0.006 |
| CABG | 18 | 8 | 0.8 | 1.1 | 0.48 |
| Major adverse cardiovascular events§ | 181 | 59 | 8.1 | 8.0 | 0.92 |
| Death | 78 | 26 | 3.5 | 3.5 | 0.98 |
| Cardiac | 54 | 20 | 2.4 | 2.7 | 0.67 |
| Noncardiac | 24 | 6 | 1.1 | 0.8 | 0.55 |
| Reinfarction | 81 | 33 | 3.7 | 4.5 | 0.31 |
| Q-wave | 45 | 14 | 2.0 | 1.9 | 0.83 |
| Non-Q-wave | 39 | 19 | 1.8 | 2.7 | 0.16 |
| Death or reinfarction | 152 | 52 | 6.8 | 7.0 | 0.83 |
| Stroke | 23 | 5 | 1.0 | 0.7 | 0.39 |
| Stent thrombosis¶ | 70 | 25 | 3.2 | 3.4 | 0.77 |
| Definite | 58 | 22 | 2.6 | 3.0 | 0.60 |
| Probable | 12 | 3 | 0.5 | 0.4 | 0.65 |

* CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

† Ischemia-driven target-lesion revascularization (the primary efficacy end point) refers to a procedure to treat recurrent ischemia due to restenosis at the site of the original target lesion (including a 5-mm proximal or distal margin outside the stent).

‡ Ischemia-driven target-vessel revascularization refers to a procedure to treat recurrent ischemia due either to restenosis within or just outside the stent or to a lesion anywhere else in the same epicardial coronary artery or its branches.

§ The composite primary safety end point of major adverse cardiovascular events comprised death, myocardial infarction, stroke, and stent thrombosis.

¶ Stent thrombosis was defined according to the Academic Research Consortium classification.¹⁵

related artery (TIMI flow grade of 0 or 1), ulceration, ectasia, or aneurysm formation between the two stent groups.

DISCUSSION

In this international, prospective, controlled trial involving patients with ST-segment elevation myocardial infarction who were undergoing primary PCI, in which more than 93% of the patients who received stents were randomly assigned to a study-stent group, treatment with paclitaxel-eluting stents as compared with otherwise identical bare-metal stents resulted in a significantly reduced rate of angiographically assessed restenosis and in a significantly decreased rate of recurrent ischemia necessitating repeat revascularization by means of

PCI or CABG. Moreover, paclitaxel-eluting stents were noninferior to bare-metal stents with respect to the primary composite safety end point of major adverse cardiovascular events at 12 months, with similar rates of the individual components of the composite safety end point (i.e., death, reinfarction, stroke, and stent thrombosis). The HORIZONS-AMI trial thus provides data indicating that paclitaxel-eluting stents can be used in patients with evolving ST-segment elevation myocardial infarction.

A meta-analysis of previous small-to-moderate-size randomized trials showed that for each 1000 patients with ST-segment elevation myocardial infarction who received drug-eluting stents as compared with bare-metal stents, approximately 76 fewer required target-vessel revascularization within 1 year.¹⁰ In contrast, in our trial, in which more

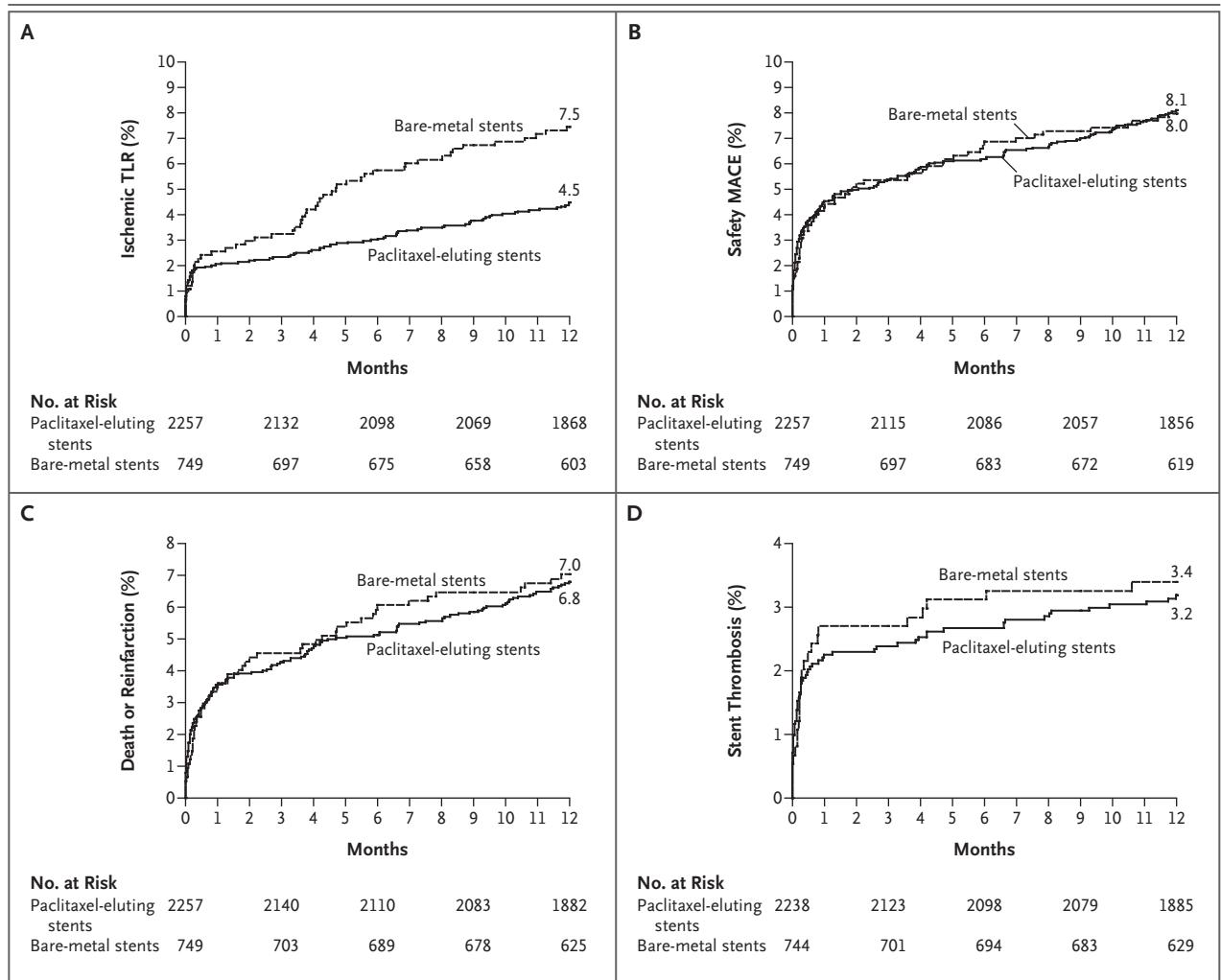


Figure 2. Kaplan–Meier Time-to-Event Curves for Primary End Points and Three Components of the Primary Composite Safety End Point. Time-to-event curves through 1 year are shown for ischemia-driven target-lesion revascularization (TLR) (Panel A), the composite safety end point of major adverse cardiovascular events (MACE), consisting of death, reinfarction, stroke, and stent thrombosis (Panel B), death or reinfarction (Panel C), and stent thrombosis (definite or probable, defined according to the Academic Research Consortium classification) (Panel D). Treatment with paclitaxel-eluting stents as compared with bare-metal stents resulted in a lower 12-month rate of ischemia-driven target-lesion revascularization (4.5% vs. 7.5%; hazard ratio, 0.59; 95% CI, 0.43 to 0.83; $P=0.002$), a noninferior 12-month rate of the safety composite end point of major adverse cardiovascular events (8.1% vs. 8.0%; hazard ratio, 1.02; 95% CI, 0.76 to 1.36; $P=0.01$ for noninferiority; $P=0.92$ for superiority), and nonsignificantly different 12-month rates of death or reinfarction (6.8% vs. 7.0%; hazard ratio, 0.97; 95% CI, 0.70 to 1.32; $P=0.83$) and of stent thrombosis (3.2% vs. 3.4%; hazard ratio, 0.93; 95% CI, 0.59 to 1.47; $P=0.77$).

than 3000 patients were randomly assigned to a stent group, approximately 30 fewer per 1000 patients who received paclitaxel-eluting stents as compared with a bare-metal stents required target-vessel revascularization within 1 year. Since relatively few patients were excluded from our trial because of anatomical complexity, the most likely explanation for the differences between these findings is that routine angiographic follow-up was performed before the assessment of the pri-

mary clinical end point in most of the earlier randomized trials, a protocol-specific process that artificially increases the rates of revascularization (the “oculostenotic reflex”).^{11,12} In contrast, routine angiographic follow-up in the present trial was not performed until 1 month after ascertainment of the primary 12-month clinical end points, thereby permitting a more accurate and realistic determination of treatment-related effects. Also, in the present study, the 41% rela-

Table 4. Angiographic Findings at 13 Months.*

| Finding | Paclitaxel-Eluting Stents | Bare-Metal Stents | P Value |
|--|---------------------------|-------------------|---------|
| TIMI flow grade — no. of vessels/total no. (%) | | | |
| 0 or 1 | 27/964 (2.8) | 11/302 (3.6) | 0.45 |
| 2 | 67/964 (7.0) | 15/302 (5.0) | 0.22 |
| 3 | 870/964 (90.2) | 276/302 (91.4) | 0.55 |
| Quantitative coronary angiography of lesions† | | | |
| Reference-vessel diameter — mm | | | |
| | 2.91±0.48 | 2.90±0.48 | 0.94 |
| Minimal luminal diameter — mm | | | |
| In-stent | 2.36±0.75 | 1.98±0.82 | <0.001 |
| In-segment | 2.09±0.68 | 1.84±0.76 | <0.001 |
| Late loss — mm | | | |
| In-stent | 0.41±0.64 | 0.82±0.70 | <0.001 |
| In-segment | 0.30±0.56 | 0.59±0.64 | <0.001 |
| Stenosis — % of vessel diameter | | | |
| In-stent | 18.7±22.8 | 32.6±24.9 | <0.001 |
| In-segment | 28.6±19.4 | 37.4±22.1 | <0.001 |
| Binary restenosis — no. of lesions/total no. (%) | | | |
| In-stent | 87/1062 (8.2) | 69/328 (21.0) | <0.001 |
| In-segment | 102/1062 (9.6) | 76/328 (23.2) | <0.001 |
| Aneurysm formation — no. of lesions/total no. (%)† | | | |
| | 4/1059 (0.4) | 3/328 (0.9) | 0.37 |
| Ulceration — no. of lesions/total no. (%)† | | | |
| | 5/1060 (0.5) | 2/328 (0.6) | 0.67 |
| Ectasia — no. of lesions/total no. (%)† | | | |
| | 7/1059 (0.7) | 3/328 (0.9) | 0.71 |

* Plus–minus values are means ±SD. TIMI denotes Thrombolysis in Myocardial Infarction.

† Data are for stented lesions only; no stent was implanted in 15 lesions in the paclitaxel-eluting–stent group and 4 lesions in the bare-metal–stent group.

tive hazard reduction in the rate of clinically assessed restenosis (ischemia-driven target-lesion revascularization) at 12 months with paclitaxel-eluting stents as compared with bare-metal stents was somewhat less than the 56% relative reduction in the rate of angiographically assessed restenosis at 13 months. This difference may be due to the occasional occurrence of restenosis that does not provoke ischemia or symptoms in an infarcted myocardial territory. This possibility, coupled with the elimination of unnecessary revascularization procedures because we did not perform routine angiographic follow-up before assessing the primary clinical end point, explains the relatively low 1-year rate of ischemia-driven target-lesion revascularization after implantation of bare-metal stents that was observed in the present trial. Longer-term follow-up will show whether the marked reduction in angiographical-

ly assessed restenosis with paclitaxel-eluting stents as compared with bare-metal stents results in greater incremental clinical benefits beyond 12 months.

The results of the present study are otherwise consistent with those of earlier, smaller, randomized studies, in which 1-year mortality rates were similar between patients with ST-segment elevation myocardial infarction who were treated with drug-eluting stents and those who were treated with bare-metal stents.¹⁰ In contrast, in large, nonrandomized, observational studies of data from state registries in Massachusetts, New York, and New Jersey, in which multivariable and propensity-score adjustments were used to correct for measured baseline differences, the results suggested that drug-eluting stents, as compared with bare-metal stents, significantly reduce mortality among patients with ST-segment elevation

myocardial infarction.¹⁷⁻¹⁹ However, scrutiny of the hazard curves in these registry studies indicates that much of the relative survival benefit with drug-eluting stents occurred within 30 days after stent implantation, before the known benefits of drug-eluting stents in reducing restenosis are apparent. The inability to adjust for unmeasured confounders (including coexisting conditions and other factors that make noncompliance with clopidogrel therapy likely in patients selected to receive bare-metal stents) probably explains the observed reduction in mortality with drug-eluting stents in these nonrandomized studies. In contrast, the results of randomized trials that now include more than 6500 patients strongly suggest that survival within 1 year after implantation is similar, but not improved, with drug-eluting stents as compared with bare-metal stents among patients with ST-segment elevation myocardial infarction. Similarly, the present trial confirms and extends the results of earlier randomized studies¹⁰ that showed similar rates of stent thrombosis and reinfarction at 1 year with drug-eluting stents and bare-metal stents in patients with ST-segment elevation myocardial infarction.

Several limitations of the present study deserve comment. First, logistic complexities necessitated an open-label design. Potential bias was mitigated by high rates of compliance with the protocol procedures and the use of blinded clinical-event adjudication and core-laboratory assessments. Second, although the rate of use of thienopyridine agents was slightly greater between 6 and 12 months in the group that received paclitaxel-eluting stents than in the group that received bare-metal stents, the point estimates for the primary efficacy and safety end points were not significantly altered after multivariable adjustment for this imbalance. Third, although the nearly identical rates of the safety end point of major adverse cardiovascular events in the two stent groups suggest that paclitaxel-eluting stents are safe in patients with evolving ST-segment elevation myocardial infarction at 1 year, longer-term follow-up is required to characterize the late safety and efficacy profiles of paclitaxel-eluting stents in patients with ST-segment elevation myocardial infarction, especially as the use of dual antiplatelet agents declines over time after stent implantation. This point is particularly germane because the increased risk of stent thrombosis with drug-eluting stents as compared with bare-metal stents may

emerge only beyond 1 year after stent implantation³ and because at least one previous study²⁰ (but not all^{17-19,21}) has suggested that the incremental benefits of drug-eluting stents in patients with ST-segment elevation myocardial infarction diminish with late follow-up. Fourth, although the present trial had relatively few exclusion criteria, the results apply only to patients who were enrolled; specifically, patients with unprotected left main coronary artery disease, patients with bifurcation lesions requiring planned dual-stent treatment, and patients who were unlikely to comply with at least 6 months of dual antiplatelet therapy were excluded, and relatively few patients with cardiogenic shock were enrolled. Further studies are also required to determine which patients and lesions are most likely to benefit from drug-eluting stents, the long-term safety of drug-eluting stents after discontinuation of thienopyridine treatment, and the relative cost-effectiveness of such stents in patients with ST-segment elevation myocardial infarction, all of which are important considerations in deciding which type of stent to use during primary PCI. Finally, our findings apply only to paclitaxel-eluting stents; future large-scale trials are required to determine the relative safety and efficacy of other drug-eluting stents in patients with ST-segment elevation myocardial infarction, especially stents that are more potent inhibitors of neointimal proliferation.^{22,23}

In conclusion, the present trial shows that in patients with evolving ST-segment elevation myocardial infarction who are undergoing primary PCI with stent implantation, the use of paclitaxel-eluting stents, as compared with bare-metal stents, reduces angiographic restenosis and recurrent ischemia necessitating repeat revascularization procedures within the first year. No safety concerns were apparent at 1 year.

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APPENDIX

The following investigators and institutions participated in the HORIZONS-AMI Trial: **Executive Committee:** G.W. Stone (principal investigator and chair), Columbia University Medical Center and the Cardiovascular Research Foundation, New York; B.R. Brodie, LeBauer Cardiovascular Research Foundation and Moses Cone Hospital, Greensboro, NC; D.A. Cox, Mid Carolina Cardiology, Charlotte, NC; C.L. Grines, William Beaumont Hospital, Royal Oak, MI; B.D. Rutherford, St. Luke's Hospital, Kansas City, MO. **Pharmacology Committee:** D. Bhatt, Cleveland Clinic Foundation, Cleveland; G. Dangas, Columbia University Medical Center and the Cardiovascular Research Foundation, New York; F. Feit, New York University, New York; M. Ohman, Duke University Medical Center, Durham, NC. **European Steering Committee:** H. Bonnier, Catharina Hospital, Eindhoven, the Netherlands; A. Colombo, Colombus Hospital, Milan; E. Garcia, Hospital Universitario Gregorio Marañon, Madrid; E. Grube, Heart Center Siegburg, Siegburg, Germany; G. Guagliumi, Ospedali Riuniti di Bergamo, Bergamo, Italy; A. Kastrati, Deutsches Herzzentrum, Technische Universität, Munich, Germany; P. Serruys, Thoraxcenter, Rotterdam, the Netherlands; H. Suryapranata, Hospital De Weezenlanden, Zwolle, the Netherlands. **Country Leaders:** *the Netherlands:* H. Bonnier, H. Suryapranata; *Italy:* A. Colombo, G. Guagliumi; *Spain:* E. Garcia; *Germany:* E. Grube, A. Kastrati; *Israel:* Y. Almagor; *United Kingdom:* A. Banning; *Argentina:* J. Belardi, L. Grinfeld; *Poland:* D. Dudek; *Austria:* K. Huber; *Norway:* D. Nilsen; *Sweden:* G. Olivecrona; *Denmark:* L. Rasmussen. **Clinical Endpoints Committee:** Cardiovascular Research Foundation Data Center, New York, S.C. Wong (chair). **Field Officers:** M. Farkouh (chair), M. Attubato, G. Dangas, F. Feit, R. Mehran. **Site Management and Data Monitoring:** J. Tyson and Associates (United States), D-Target (Europe), Tango (South America). **Data Management:** E-trials, Morrisville, NC, D. Winsted (manager). **Data Coordination and Analysis:** Cardiovascular Research Foundation Data Center, New York, R. Mehran (director), L. Gambone, I. Bihl (operations), H. Parise (statistics). **Data Safety and Monitoring Board:** B.J. Gersh (chair), Mayo Clinic, Rochester, MN; D. Faxon, Brigham and Women's Hospital, Boston; S. King, Fuqua Heart Center, Atlanta; S.J. Pocock, London School of Hygiene and Tropical Medicine, London; D.O. Williams, Rhode Island Hospital, Providence. **Qualitative and Quantitative Coronary Angiographic Core Laboratory Analysis:** Cardiovascular Research Foundation, New York, A.J. Lansky (director), E. Cristea (operations). **Qualitative and Quantitative Electrocardiographic Core Laboratory Analysis:** Cardiovascular Research Foundation, New York, J. Reiffel (director). **Intravascular Ultrasound Core Laboratory Analysis:** Cardiovascular Research Foundation, New York, G. Mintz (director). **Biomarker Substudy Core Laboratory:** BioSite, San Diego, CA.

For a full list of participating countries (with total enrollment), hospitals, and principal investigators, see the Supplementary Appendix (available with the full text of this article at NEJM.org).

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