

ORIGINAL ARTICLE

Drug-Eluting or Bare-Metal Stents for Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

Studies comparing percutaneous coronary intervention (PCI) with drug-eluting and bare-metal coronary stents in acute myocardial infarction have been limited in size and duration.

METHODS

We identified all adults undergoing PCI with stenting for acute myocardial infarction between April 1, 2003, and September 30, 2004, at any acute care, nonfederal hospital in Massachusetts with the use of a state-mandated database of PCI procedures. We performed propensity-score matching on three groups of patients: all patients with acute myocardial infarction, all those with acute myocardial infarction with ST-segment elevation, and all those with acute myocardial infarction without ST-segment elevation. Propensity-score analyses were based on clinical, procedural, hospital, and insurance information collected at the time of the index procedure. Differences in the risk of death between patients receiving drug-eluting stents and those receiving bare-metal stents were determined from vital-statistics records.

RESULTS

A total of 7217 patients were treated for acute myocardial infarction (4016 with drug-eluting stents and 3201 with bare-metal stents). According to analysis of matched pairs, the 2-year, risk-adjusted mortality rates were lower for drug-eluting stents than for bare-metal stents among all patients with myocardial infarction (10.7% vs. 12.8%, $P=0.02$), among patients with myocardial infarction with ST-segment elevation (8.5% vs. 11.6%, $P=0.008$), and among patients with myocardial infarction without ST-segment elevation (12.8% vs. 15.6%, $P=0.04$). The 2-year, risk-adjusted rates of recurrent myocardial infarction were reduced in patients with myocardial infarction without ST-segment elevation who were treated with drug-eluting stents, and repeat revascularization rates were significantly reduced with the use of drug-eluting stents as compared with bare-metal stents in all groups.

CONCLUSIONS

In patients presenting with acute myocardial infarction, treatment with drug-eluting stents is associated with decreased 2-year mortality rates and a reduction in the need for repeat revascularization procedures as compared with treatment with bare-metal stents.

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PERCUTANEOUS CORONARY INTERVENTION (PCI) for acute myocardial infarction reduces the rates of death and recurrent ischemia as compared with medical therapy.¹⁻³ In current clinical practice, both drug-eluting and bare-metal stents are commonly used. However, the randomized trials supporting the approval of drug-eluting stents excluded patients with acute myocardial infarction.^{4,5} Randomized studies comparing drug-eluting stents with bare-metal stents in patients with myocardial infarction have been relatively small (300 to 700 patients per study) and have had limited periods of follow-up (typically 1 year or less).⁶⁻¹¹ In these trials, drug-eluting stents reduced the need for repeat revascularization procedures to treat restenosis as compared with bare-metal stents, but there were no significant differences between the two types of stents in the rates of death or subsequent myocardial infarction at 1 year.

Observational studies comparing drug-eluting and bare-metal stents in patients with acute myocardial infarction have had conflicting results.^{12,13} One study suggested that among patients surviving myocardial infarction with ST-segment elevation, the mortality rate between 6 months and 2 years in those treated with drug-eluting stents was more than twice that in those treated with bare-metal stents.¹⁴

We conducted a study on an unselected, population-based cohort of patients presenting with myocardial infarction who were treated with either drug-eluting or bare-metal stents. We sought to determine whether higher rates of death and recurrent myocardial infarction could be attributed to the use of drug-eluting stents rather than bare-metal stents among all patients, and specifically among those with and those without ST-segment elevation. Because the type of stent used was not randomly assigned, we used propensity-score matching to minimize bias.

METHODS

STUDY POPULATION

In 2002, the Massachusetts Department of Public Health established a requirement that all Massachusetts hospitals that provide interventional cardiology services collect data on all PCI procedures. These data are prospectively collected by trained hospital personnel with the use of the National Car-

diovascular Data Registry data-collection instrument (www.accncdr.com/WebNCDR/Common) of the American College of Cardiology. The data are then submitted electronically to the Massachusetts Data Analysis Center at Harvard Medical School, where they are audited, adjudicated by a committee of interventionalists, and verified with the use of internal and external procedures.¹⁵ The Massachusetts Data Analysis Center also maintains a similar state-mandated cardiac-surgery database.

We performed our analysis with the use of the Massachusetts Data Analysis Center database. The study was designed and conducted by the authors and funded by the Massachusetts Department of Public Health. Dr. Normand vouches for the integrity, accuracy, and completeness of the data and the analyses. The study was approved by the Committee on Human Studies at Harvard Medical School.

ANALYSIS COHORT

We identified all adults (18 years of age or older) undergoing PCI with stenting for acute myocardial infarction between April 1, 2003, and September 30, 2004, at all acute care, nonfederal hospitals in Massachusetts. To preclude incomplete ascertainment of subsequent adverse events, subjects were excluded from this analysis if they were not Massachusetts residents at the time of the procedure or if they could not be linked to hospital-discharge billing records.

Study subjects were assigned to either the drug-eluting-stent group or the bare-metal-stent group according to the stent type used during the index admission. Patients receiving both drug-eluting and bare-metal stents during the index admission were excluded from the analysis.

STUDY OUTCOMES

The primary outcome was death from any cause within 2 years after the index procedure. In-hospital mortality information at the time of the index procedure was reported directly to the Massachusetts Data Analysis Center by the hospitals. This information was verified with the use of data from the Massachusetts Registry of Vital Records and Statistics, which also provided 2-year mortality data for all study participants at the time of analysis. The Social Security Death Index Interactive Search Web site (<http://ssdi.rootsweb.com/cgi-bin/ssdi.cgi>) was used to confirm mortality

Table 1. Characteristics of Patients before Propensity-Score Matching.*

Characteristic	Drug-Eluting Stent (N = 4016)	Bare-Metal Stent (N = 3201)	P Value	Myocardial Infarction with ST-Segment Elevation (N = 3379)	Myocardial Infarction with- out ST-Segment Elevation (N = 3838)	P Value
Age — yr	63.6±13.4	64.3±14.0	0.03	62.0±13.6	65.6±13.5	<0.001
Female sex — no. (%)	1324 (33.0)	1059 (33.1)	0.92	1031 (30.5)	1352 (35.2)	<0.001
Race or ethnic group — no./total no. (%)†			0.08			0.29
White	3562/4008 (88.9)	2822/3194 (88.4)		2998/3374 (88.9)	3386/3828 (88.5)	
Black	124/4008 (3.1)	77/3194 (2.4)		81/3374 (2.4)	120/3828 (3.1)	
Hispanic	138/4008 (3.4)	116/3194 (3.6)		121/3374 (3.6)	133/3828 (3.5)	
Other	184/4008 (4.6)	179/3194 (5.6)		174/3374 (5.2)	189/3828 (4.9)	
Insurance — no. (%)			<0.001			<0.001
Government	1679 (41.8)	1345 (42.0)		1222 (36.2)	1802 (47.0)	
Commercial	964 (24.0)	575 (18.0)		760 (22.5)	779 (20.3)	
Health maintenance organization	1144 (28.5)	1056 (33.0)		1112 (32.9)	1088 (28.3)	
None	229 (5.7)	225 (7.0)		285 (8.4)	169 (4.4)	
Diabetes mellitus — no. (%)	1023 (25.5)	721 (22.5)	0.004	613 (18.1)	1131 (29.5)	<0.001
Diabetes mellitus requiring insulin — no. (%)	349 (8.7)	207 (6.5)	<0.001	163 (4.8)	393 (10.2)	<0.001
Hyperlipidemia — no. (%)	2680 (66.7)	1989 (62.1)	<0.001	1828 (54.1)	2841 (74.0)	<0.001
Hypertension — no. (%)	2775 (69.1)	2081 (65.0)	<0.001	1971 (58.3)	2885 (75.2)	<0.001
Smoker — no. (%)						
Current	1170 (29.1)	1002 (31.3)	0.05	1211 (35.8)	961 (25.0)	<0.001
Former	1457 (36.3)	1117 (34.9)	0.22	1016 (30.1)	1558 (40.6)	<0.001
Previous myocardial infarction — no. (%)	896 (22.3)	741 (23.1)	0.40	487 (14.4)	1150 (30.0)	<0.001
Previous CABG — no. (%)	333 (8.3)	311 (9.7)	0.04	123 (3.6)	521 (13.6)	<0.001
Previous PCI — no. (%)	562 (14.0)	409 (12.8)	0.13	356 (10.5)	615 (16.0)	<0.001
Congestive heart failure — no. (%)	377 (9.4)	342 (10.7)	0.07	182 (5.4)	537 (14.0)	<0.001
Peripheral vascular disease — no. (%)	427 (10.6)	340 (10.6)	0.99	212 (6.3)	555 (14.5)	<0.001
Cerebrovascular disease — no. (%)	322 (8.0)	289 (9.0)	0.13	208 (6.2)	403 (10.5)	<0.001
Chronic lung disease — no. (%)	449 (11.2)	384 (12.0)	0.28	309 (9.1)	524 (13.7)	<0.001
History of neoplasm — no. (%)‡	87 (2.2)	97 (3.0)	0.02	77 (2.3)	107 (2.8)	0.17
History of gastrointestinal bleeding — no. (%)§	99 (2.5)	103 (3.2)	0.05	95 (2.8)	107 (2.8)	0.95
Chronic renal insufficiency — no. (%)	241 (6.0)	214 (6.7)	0.23	128 (3.8)	327 (8.5)	<0.001
Dialysis — no. (%)	66 (1.6)	42 (1.3)	0.25	25 (0.7)	83 (2.2)	<0.001

Cardiogenic shock — no. (%)	92 (2.3)	202 (6.3)	<0.001	246 (7.3)	48 (1.3)	<0.001
Indication — no. (%)			<0.001			
Myocardial infarction with ST-segment elevation	1558 (38.8)	1821 (56.9)		—	—	
Myocardial infarction without ST-segment elevation	2458 (61.2)	1380 (43.1)		—	—	
Procedure status — no. (%)			<0.001			<0.001
Urgent	1913 (47.6)	1133 (35.4)		515 (15.2)	2531 (65.9)	
Emergency or salvage	1495 (37.2)	1734 (54.2)		2744 (81.2)	485 (12.6)	
Duration of acute coronary syndrome — no./total no. (%)			<0.001			<0.001
0 to <6 hr	1439/3970 (35.8)	1508/3179 (47.1)		2356/3365 (69.7)	591/3784 (15.6)	
6 to 24 hr	894/3970 (22.3)	715/3179 (22.3)		597/3365 (17.7)	1012/3784 (26.7)	
>24 hr	1637/3970 (40.8)	956/3179 (29.9)		412/3365 (12.2)	2181/3784 (57.6)	
Ejection fraction <30% — no./total no. (%)	117/2294 (5.1)	144/1607 (9.0)	<0.001			<0.001
Left main coronary artery disease — no. (%)	193 (4.8)	183 (5.7)	0.08	106 (3.1)	270 (7.0)	<0.001

* Plus-minus values are means ±SD. Percentages may not sum to 100 because of rounding. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

† Race or ethnic group was self-assessed.

‡ A history of neoplasm was defined as the presence of any condition with a code of 140.0 through 239.9 of the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM), during the index admission.

§ A history of gastrointestinal bleeding was defined as the presence of any condition with an ICD-9-CM code of 531.0 through 534.99 or 578.0 through 578.99 during the index admission.

status as recorded by the Registry of Vital Records and Statistics and to resolve cases in which the Massachusetts vital statistics data disagreed with the Massachusetts Data Analysis Center data.

Secondary outcomes included recurrent myocardial infarction and repeat revascularization. Recurrent myocardial infarction occurring during the index hospitalization was determined from the mandatory recording of in-hospital events in the Massachusetts Data Analysis Center database according to the National Cardiovascular Data Registry definitions. Myocardial infarctions occurring during any subsequent hospital admission were identified by linking the Massachusetts Data Analysis Center data to hospital-discharge billing data collected by the Massachusetts Division of Health Care Finance and Policy. Repeat target-vessel revascularization was defined as PCI performed in a vessel treated during the index procedure or any coronary-artery bypass grafting (CABG) procedure performed after the index procedure. Information regarding CABG and PCI was obtained from the Massachusetts Data Analysis Center databases.

CONFOUNDING VARIABLES

We developed a list of potential confounders, including demographic factors, insurance status, medical history, and risk factors of the patient; characteristics of the lesion and the procedure; and medications received by the patients. Because some patients were treated for multiple lesions during their index admission, we created patient-specific, lesion-based variables, including maximum stenosis as a percentage of arterial diameter, any high-risk lesion, and any use of thrombectomy. Because some hospitals in Massachusetts have pilot programs that perform only primary PCI without performing surgery on site, we also included a variable that indicated whether the patient underwent the PCI in a pilot program. Data on the majority of the confounders were obtained from the Massachusetts Data Analysis Center database, and data on two confounders were obtained from hospital-discharge billing data for the index admission.

STATISTICAL ANALYSIS

Because the patients were not randomly assigned to receive drug-eluting stents, we used propensity-score matching to adjust for differences in baseline characteristics.¹⁶ We performed a one-to-one

matched analysis without replacement on the basis of the estimated propensity score of each patient. The log odds of the probability that a patient received a drug-eluting stent (the “logit”) was modeled as a function of the confounders that we identified and included in our data set. Using the estimated logits, we first randomly selected a patient in the group receiving drug-eluting stents and then matched that patient with the patient in the group receiving bare-metal stents with the closest estimated logit value. Patients in the group receiving bare-metal stents who had an estimated logit within 0.6 SD of the selected patients in the group receiving drug-eluting stents were eligible for matching. We selected 0.6 because this value has been shown to eliminate approximately 90% of the bias in observed confounders.¹⁷ If more than one patient in the group receiving bare-metal stents met this criterion, we randomly selected one patient for matching.

We analyzed the data according to three different propensity-score models: one for any myocardial infarction, one for myocardial infarction with ST-segment elevation, and one for myocardial infarction without ST-segment elevation. To assess the success of the matching procedure, we measured standardized differences (measured in percentage points) in observed confounders between the matched groups after matching.

Using the matched pairs, we performed paired t-tests to determine whether rates of death, myocardial infarction, and repeat revascularization differed between recipients of drug-eluting stents and recipients of bare-metal stents. Estimates of the adjusted differences in risks are presented, with 95% confidence intervals. All P values presented are two-sided.

Because matching on the propensity score cannot be expected to balance for unobserved confounders that are independent of observed confounders, we performed several sensitivity analyses. First, we examined differences between the two stent groups in mortality rates 2 days after stent placement. A large difference would indicate residual confounding, because such an early benefit would be unlikely.

Second, the initiation of this study coincided with the introduction of drug-eluting stents in Massachusetts in late April 2003. We observed that the use of drug-eluting stents increased during our observation period (Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org) and that the time

course of adoption varied according to whether the hospital performed PCI under a pilot program or a nonpilot program. In order to evaluate whether these temporal trends influenced the study results, we reestimated propensity scores that, in addition to our initial set of confounders, included time (measured as days since April 1, 2003), a quadratic term for time, and an interaction between time and type of hospital program (pilot or nonpilot). We then used these propensity scores to obtain a restricted matched cohort and compare risks after treatment with a drug-eluting stent and after treatment with a bare-metal stent.

Finally, we performed propensity-matched analyses of two subgroups of patients from the cohort of patients who had a myocardial infarction with ST-segment elevation. One of these subgroups excluded patients treated in hospitals with pilot programs, and the other excluded patients treated more than 24 hours after the onset of symptoms.

RESULTS

Between April 1, 2003, and September 30, 2004, there were 21,045 adult patients who underwent PCI with stenting in Massachusetts. Of these, 8440 patients (40%) presented with acute myocardial infarction (Fig. 2 in the Supplementary Appendix). We excluded 576 patients who were not residents of Massachusetts, 167 patients who were not linkable to hospital-discharge data, and 480 patients who were treated with both drug-eluting and bare-metal stents. The resulting cohort of 7217 patients underwent stenting by 119 operators at 21 hospitals. Of these patients, 4016 were treated with drug-eluting stents and 3201 were treated with bare-metal stents. Of the patients treated with drug-eluting stents, 71% received sirolimus-eluting stents only, 27% received paclitaxel-eluting stents only, and 2% received both types of drug-eluting stents. Of the 7217 patients included, 3379 underwent stenting for myocardial infarction with ST-segment elevation and 3838 underwent stenting for myocardial infarction without ST-segment elevation.

Before propensity-score matching, patients treated with drug-eluting stents and those treated with bare-metal stents differed significantly in clinical and procedural characteristics (Tables 1 and 2). Patients with diabetes mellitus, hyperlipidemia, hypertension, or myocardial infarction

Table 2. Characteristics of Procedures before Propensity-Score Matching.*

Characteristic	Drug-Eluting Stent (N=4016)	Bare-Metal Stent (N=3201)	P Value	Myocardial Infarction with ST-Segment Elevation (N=3379)	Myocardial Infarction without ST-Segment Elevation (N=3838)	P Value
No. of diseased vessels	1.79±0.80	1.82±0.81	0.11	1.75±0.79	1.85±0.82	<0.001
No. of vessels treated	1.18±0.43	1.10±0.32	<0.001	1.11±0.33	1.18±0.42	<0.001
No. of stents	1.52±0.91	1.42±0.78	<0.001	1.45±0.82	1.50±0.90	0.02
No. of lesions treated	1.40±0.69	1.31±0.60	<0.001	1.30±0.60	1.42±0.71	<0.001
Target vessel — no. of patients (%)						
Left main coronary artery	60 (1.5)	39 (1.2)	0.32	19 (0.6)	80 (2.1)	<0.001
Left anterior descending coronary artery	1759 (43.8)	1184 (37.0)	<0.001	1376 (40.7)	1567 (40.8)	0.92
Circumflex coronary artery	1319 (32.8)	832 (26.0)	<0.001	644 (19.1)	1507 (39.3)	<0.001
Right coronary artery	1595 (39.7)	1467 (45.8)	<0.001	1697 (50.2)	1365 (35.6)	<0.001
Saphenous vein graft	147 (3.7)	196 (6.1)	<0.001	63 (1.9)	280 (7.3)	<0.001
Arterial graft	5 (0.1)	5 (0.2)	0.72	4 (0.1)	6 (0.2)	0.66
High-risk lesion — no. (%)	1361 (33.9)	1275 (39.8)	<0.001	1502 (44.5)	1134 (29.5)	<0.001
Restenosis — no. (%)	201 (5.0)	90 (2.8)	<0.001	119 (3.5)	172 (4.5)	0.04
Thrombectomy — no. (%)	313 (7.8)	440 (13.7)	<0.001	555 (16.4)	198 (5.2)	<0.001
Pretreatment — no. (%)						
Aspirin	3941 (98.1)	3104 (97.0)	0.001	3304 (97.8)	3741 (97.5)	0.39
Glycoprotein IIb/IIIa inhibitor	1408 (35.1)	1219 (38.1)	0.008	1396 (41.3)	1231 (32.1)	<0.001
Clopidogrel or ticlopidine	1405 (35.0)	1035 (32.3)	0.02	943 (27.9)	1497 (39.0)	<0.001
Hospital has pilot program for PCI — no. (%) †	19 (0.5)	206 (6.4)	<0.001	224 (6.6)		

* Plus-minus values are means ±SD. PCI denotes percutaneous coronary intervention.

† The pilot programs were only for patients who had myocardial infarction with ST-segment elevation.

Table 3. Two-Year Adjusted Clinical Outcomes.

Initial Presentation	2-Year Outcome	Drug-Eluting Stent	Bare-Metal Stent	Absolute Risk Difference % (95% CI)	P Value*
		no./total no. (%)			
Any myocardial infarction					
	Death	276/2570 (10.7)	330/2570 (12.8)	-2.1 (-3.8 to -0.4)	0.02
	Recurrent myocardial infarction	227/2570 (8.8)	263/2570 (10.2)	-1.4 (-3.0 to 0.2)	0.09
	Repeat target-vessel revascularization	247/2570 (9.6)	373/2570 (14.5)	-4.9 (-6.7 to -3.1)	<0.001
Myocardial infarction with ST-segment elevation					
	Death	110/1298 (8.5)	150/1298 (11.6)	-3.1 (-5.4 to -0.8)	0.008
	Recurrent myocardial infarction	91/1298 (7.0)	104/1298 (8.0)	-1.0 (-3.0 to 1.0)	0.34
	Repeat target-vessel revascularization	132/1298 (10.2)	181/1298 (13.9)	-3.8 (-6.2 to -1.3)	0.003
Myocardial infarction without ST-segment elevation					
	Death	157/1228 (12.8)	192/1228 (15.6)	-2.9 (-5.5 to -0.2)	0.04
	Recurrent myocardial infarction	126/1228 (10.3)	163/1228 (13.3)	-3.0 (-5.6 to -0.5)	0.02
	Repeat target-vessel revascularization	120/1228 (9.8)	187/1228 (15.2)	-5.5 (-8.0 to -2.9)	<0.001

* P values were calculated by the paired t-test.

without ST-segment elevation were more likely to be treated with drug-eluting stents than with bare-metal stents. Also, the numbers of vessels and lesions treated were higher in patients treated with drug-eluting stents than in those treated with bare-metal stents. In contrast, patients with cardiogenic shock or myocardial infarction with ST-segment elevation, those undergoing emergency procedures, and those with high-risk lesions were more likely to be treated with bare-metal stents.

The unadjusted rates of death, myocardial infarction, and repeat revascularization at 2 years were significantly lower among patients receiving drug-eluting stents than among those receiving bare-metal stents (Table 1 in the Supplementary Appendix). Patients treated for myocardial infarction with ST-segment elevation had lower rates of death and myocardial infarction at 2 years than those treated for myocardial infarction without ST-segment elevation, but there was no difference between these two groups in the rate of repeat revascularization.

The propensity-score models included up to 63 variables, depending on the subgroup. The matching of patients presenting with any acute myocardial infarction yielded 2570 patients treated with drug-eluting stents matched with 2570 patients treated with bare-metal stents. The area

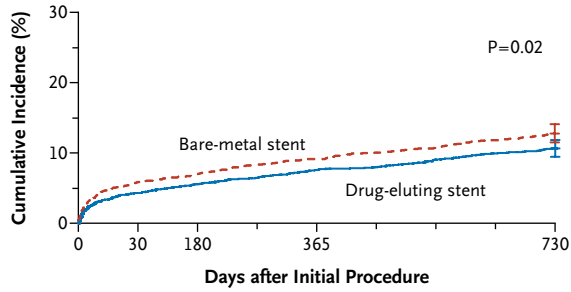
under the receiver-operating-characteristic curve (AUC) for this model was 0.68. Standardized differences were less than 10% for all matched variables (Tables 2 through 7 in the Supplementary Appendix), a result that supports the assumption of balance between treatment groups¹⁸ in observed confounders. Separate propensity-score matches were performed for patients who had myocardial infarction with ST-segment elevation (1298 matched pairs; AUC, 0.67) and for patients who had myocardial infarction without ST-segment elevation (1228 matched pairs; AUC, 0.66).

After propensity-score matching, we examined each of the study end points (Table 3 and Fig. 1, 2, and 3). With respect to the primary outcome, drug-eluting stents were associated with significantly lower mortality at 2 years than were bare-metal stents in the matched cohort of patients with any myocardial infarction (10.7% vs. 12.8%; risk difference, -2.1%; 95% confidence interval

Figure 1 (facing page). Clinical Outcomes after Stenting for Myocardial Infarction.

The graphs show the cumulative 2-year incidence of death (Panel A), myocardial infarction (Panel B), and repeat target-vessel revascularization (Panel C) in the matched sample of patients receiving bare-metal or drug-eluting stents. Error bars are 95% confidence intervals. P values were calculated by the paired t test.

A Death



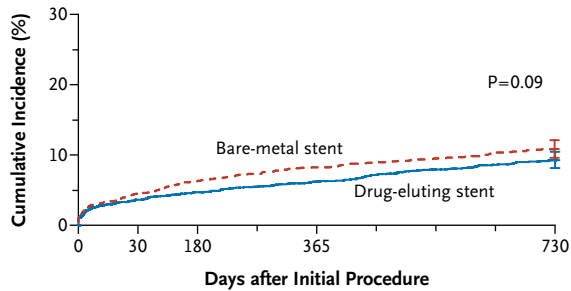
Drug-Eluting Stent

No. at risk	2570	2560	2492	2427	2375
Cumulative no. of events	10	78	143	195	276
Cumulative incidence (%)	0.4	3.0	5.6	7.6	10.7

Bare-Metal Stent

No. at risk	2570	2557	2465	2392	2334
Cumulative no. of events	13	105	178	236	330
Cumulative incidence (%)	0.5	4.1	6.9	9.2	12.8

B Recurrent Myocardial Infarction



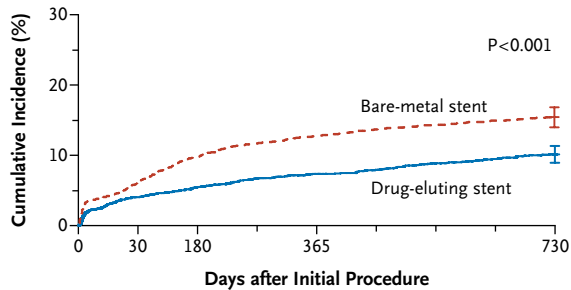
Drug-Eluting Stent

No. at risk	2570	2544	2429	2324	2243
Cumulative no. of events	26	69	117	155	227
Cumulative incidence (%)	1.0	2.7	4.7	6.2	9.3

Bare-Metal Stent

No. at risk	2570	2541	2394	2260	2167
Cumulative no. of events	29	77	155	202	263
Cumulative incidence (%)	1.1	3.0	6.2	8.2	10.8

C Repeat Target-Vessel Revascularization



Drug-Eluting Stent

No. at risk	2570	2567	2431	2298	2202
Cumulative no. of events	3	62	135	181	247
Cumulative incidence (%)	0.1	2.4	5.4	7.3	10.1

Bare-Metal Stent

No. at risk	2570	2570	2378	2170	2049
Cumulative no. of events	5	95	240	311	373
Cumulative incidence (%)	0.2	3.8	9.7	12.7	15.4

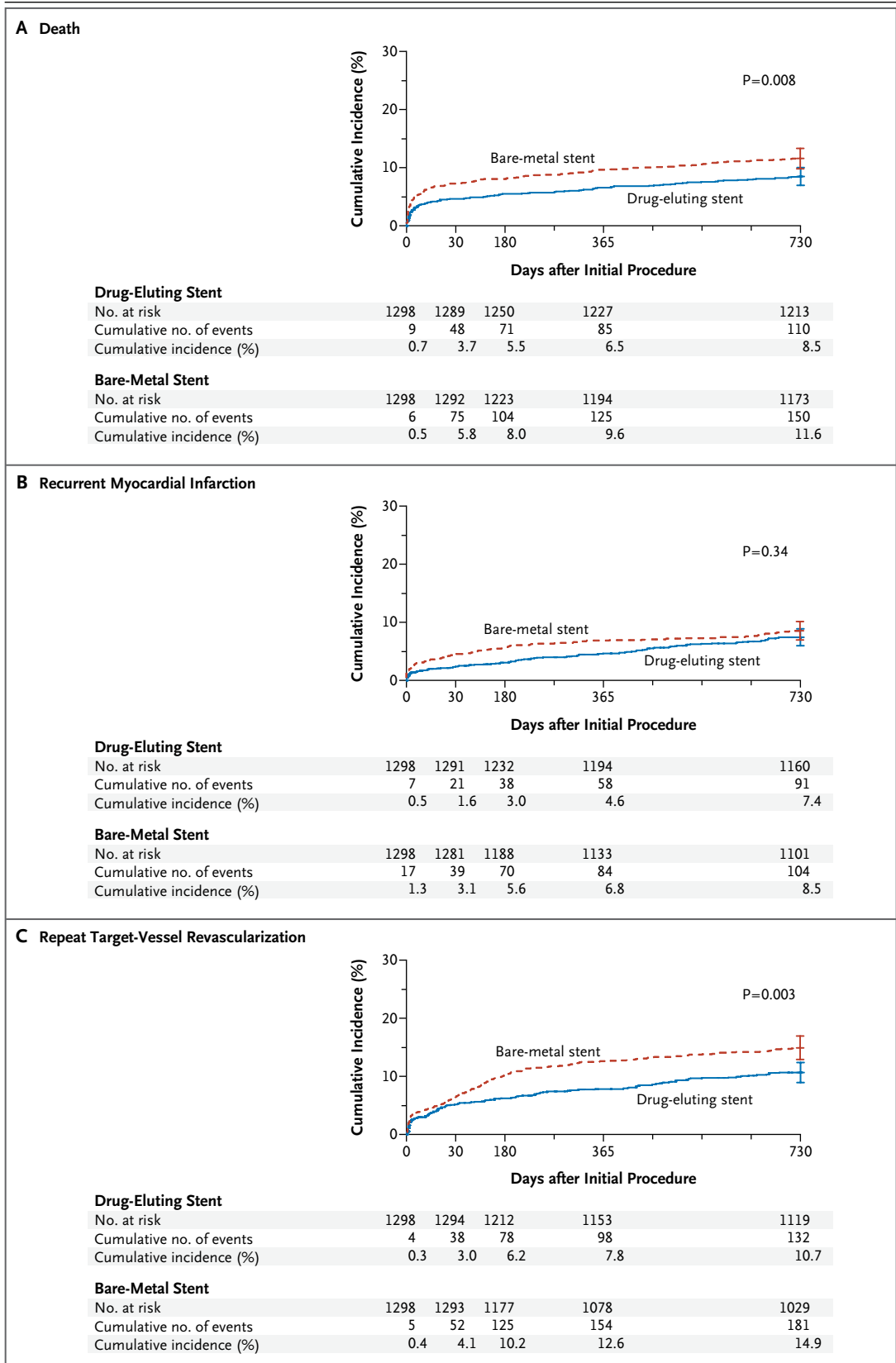


Figure 2 (facing page). Clinical Outcomes after Stenting for Myocardial Infarction with ST-Segment Elevation.

The graphs show the cumulative 2-year incidence of death (Panel A), myocardial infarction (Panel B), and repeat target-vessel revascularization (Panel C) in the matched sample of patients receiving bare-metal or drug-eluting stents. Error bars are 95% confidence intervals. P values were calculated by the paired t test.

[CI], -3.8% to -0.4% ; $P=0.02$). This difference was also significant in the matched cohort of patients who had myocardial infarction with ST-segment elevation (8.5% vs. 11.6% ; risk difference, -3.1% ; 95% CI, -5.4% to -0.8% ; $P=0.008$) and in the matched cohort of patients who had myocardial infarction without ST-segment elevation (12.8% vs. 15.6% ; risk difference, -2.9% ; 95% CI, -5.5% to -0.2% ; $P=0.04$).

After propensity-score matching, there was no significant difference in the rate of reinfarction at 2 years between patients receiving drug-eluting stents and those receiving bare-metal stents (8.8% vs. 10.2% ; risk difference, -1.4% ; 95% CI, -3.0% to 0.2% ; $P=0.09$), except for patients who had myocardial infarction without ST-segment elevation (10.3% vs. 13.3% ; risk difference, -3.0% ; 95% CI, -5.6% to -0.5% ; $P=0.02$). The rates of repeat target-vessel revascularization at 2 years in the matched cohort of patients with any myocardial infarction were significantly lower among patients receiving drug-eluting stents than among those receiving bare-metal stents (9.6% vs. 14.5% ; risk difference, -4.9% ; 95% CI, -6.7% to -3.1% ; $P<0.001$). A similar reduction in repeat target-vessel revascularization was evident for both subtypes of myocardial infarction.

Among all patients with myocardial infarction who received stents, the risk-adjusted mortality 2 days after stent placement was 0.7% in the group receiving drug-eluting stents and 1.2% in the group receiving bare-metal stents (risk difference, -0.5% ; 95% CI, -1.0% to 0.0% ; $P=0.06$). The corresponding risk differences were statistically significant for patients who had myocardial infarction with ST-segment elevation (risk difference, -0.9% ; $P=0.04$) but not for patients who had myocardial infarction without ST-segment elevation (risk difference, -0.3% ; $P=0.32$) (Table 8 in the Supplementary Appendix). Adjustment for the length of time after the introduction of drug-eluting stents tended to confirm the results of the primary analysis: event rates in the group receiving drug-eluting stents were either similar

to or lower than those in the group receiving bare-metal stents (Fig. 1 and Table 9 in the Supplementary Appendix). After the exclusion of patients who were treated at hospitals without cardiac surgery on site or of patients who presented more than 24 hours after the onset of symptoms, the risk differences for death after myocardial infarction with ST-segment elevation were consistent with the primary findings (Table 10 in the Supplementary Appendix).

DISCUSSION

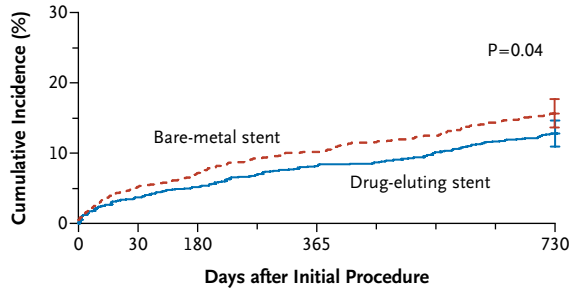
Coronary-artery stenting is commonly performed to treat myocardial infarction. Acute coronary syndromes and myocardial infarction (in contrast to stable angina)¹⁹ are the only clinical presentations in which PCI has been shown to reduce the rate of death to a rate lower than that achieved with medical therapy alone.¹⁻³ Despite the important role of stenting in patients with myocardial infarction and, in particular, in those who have myocardial infarction with ST-segment elevation, there has been little information regarding the long-term efficacy or safety of drug-eluting stents among these patients.

During the interval evaluated in our study, patients presenting with myocardial infarction accounted for 40% of stent procedures. These patients were split almost evenly between those with and those without ST-segment elevation. The rates of use of drug-eluting and bare-metal stents were nearly equal among all the patients that we studied, but because stent assignment was not random, we used propensity-score matching to adjust for imbalances in the measured characteristics of the patients, procedures, and hospitals in order to compare outcomes associated with the choice of stent.

Although our primary goal was to evaluate whether drug-eluting stents were associated with increased rates of myocardial infarction and death at long-term follow-up, we observed small absolute differences in mortality that favored drug-eluting stents in matched patient cohorts. These observations were consistent for all myocardial infarctions and for both subtypes of myocardial infarction.

Previous studies have reported an association between restenosis and the risk of death or myocardial infarction.^{20,21} A matched, population-based analysis of patients receiving drug-eluting stents or bare-metal stents (not restricted to patients with myocardial infarction) reported a

A Death



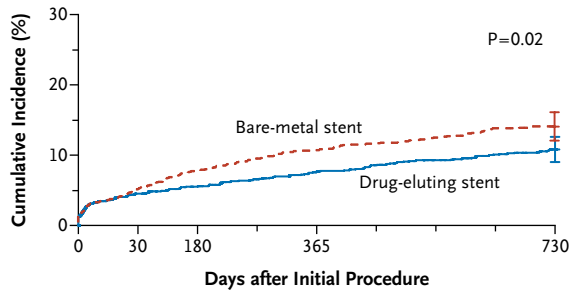
Drug-Eluting Stent

No. at risk	1228	1226	1200	1165	1128
Cumulative no. of events	2	28	63	100	157
Cumulative incidence (%)	0.2	2.3	5.1	8.1	12.8

Bare-Metal Stent

No. at risk	1228	1222	1193	1142	1103
Cumulative no. of events	6	35	86	125	192
Cumulative incidence (%)	0.5	2.9	7.0	10.2	15.6

B Recurrent Myocardial Infarction



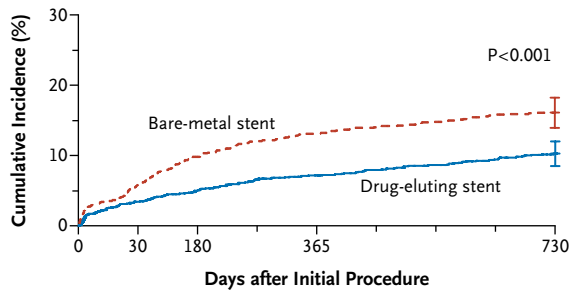
Drug-Eluting Stent

No. at risk	1228	1213	1162	1105	1052
Cumulative no. of events	15	41	66	91	126
Cumulative incidence (%)	1.2	3.4	5.5	7.6	10.8

Bare-Metal Stent

No. at risk	1228	1212	1157	1068	1006
Cumulative no. of events	16	40	92	126	163
Cumulative incidence (%)	1.3	3.3	7.7	10.7	14.1

C Repeat Target-Vessel Revascularization



Drug-Eluting Stent

No. at risk	1228	1228	1176	1107	1047
Cumulative no. of events	0	25	60	85	120
Cumulative incidence (%)	0.0	2.1	5.0	7.2	10.4

Bare-Metal Stent

No. at risk	1228	1227	1160	1037	967
Cumulative no. of events	1	37	116	154	187
Cumulative incidence (%)	0.1	3.0	9.8	13.2	16.2

Figure 3 (facing page). Clinical Outcomes after Stenting for Myocardial Infarction without ST-Segment Elevation.

The graphs show the cumulative 2-year incidence of death (Panel A), myocardial infarction (Panel B), and repeat target-vessel revascularization (Panel C) in the matched sample of patients receiving bare-metal or drug-eluting stents. Error bars are 95% confidence intervals. P values were calculated by the paired t test.

similar reduction in 2-year mortality rates.²² Within the first year of follow-up, drug-eluting stents reduced the need for procedures to treat restenosis. Performing fewer procedures may have resulted in small reductions in the rates of death and myocardial infarction.

Some of the observed benefit, however, was apparent within the first 6 months, before the maximum effect of restenosis prevention would be apparent. This result suggests that additional factors, such as the duration of dual antiplatelet therapy, which is known to provide benefit in acute coronary syndromes, might have had a role.^{23,24} We adjusted for use of and contraindications to dual antiplatelet therapy. However, we were unable to adjust for the duration of therapy, which during the study period was probably 1 month for bare-metal stents and 3 to 6 months for drug-eluting stents, according to the manufacturers' instructions for use, rather than the 12 months recommended in the United States since 2007.²⁵ We were also unable to assess and adjust for adherence to this therapy.

We found that among all patients with myocardial infarction, the absolute difference between those receiving drug-eluting stents and those receiving bare-metal stents in the rate of repeat revascularization of the treated vessel was approximately 5%, which was similar in magnitude to the absolute difference observed in populations of patients treated with stents for any indication.^{26,27} In fact, because the absolute rates of repeat revascularization are lower in patients who have had a myocardial infarction than in patients who have not had a myocardial infarction, the relative difference in the rate of repeat revascularization between patients receiving drug-eluting stents and those receiving bare-metal stents was actually larger among patients who had had a myocardial infarction than we have observed among all stent recipients.²⁶

Our findings should be interpreted in the context of our study design and its limitations. First, it has been postulated that the difference in the

biologic response to drug-eluting stents as compared with bare-metal stents may be greater in the presence of a thrombotic occlusion²⁸ and may lead to a higher risk of stent thrombosis or adverse clinical events with the placement of drug-eluting stents in patients with a thrombotic occlusion.²⁹ Although no difference in the rates of clinical sequelae of stent thrombosis was present, the rates of stent thrombosis could not be directly ascertained from our data.

Second, our data are observational. We used propensity-score matching to make the patient groups comparable according to the measured confounders, and we successfully eliminated the observed differences. However, residual confounding cannot be excluded. Our analysis of 2-day adjusted mortality rates in patients with ST-segment elevation showed a small but statistically significant difference in event rates between the two stent groups. Such a difference is unlikely to be related to the choice of stent and suggests that some residual confounding is present.

Possible sources of residual bias are differences in use of concomitant medical therapy or completeness of revascularization, if such differences are associated with the choice of stent. In addition, although we adjusted for the presence of cardiogenic shock, we did not have data on infarct size, an important predictor of death in patients with myocardial infarction. Finally, we did not have access to quantitative angiographic findings. This is a potential limitation, because drug-eluting stents were not available in the same range of vessel diameters as bare-metal stents. In particular, small-vessel stenting is known to be associated with higher risks both during the procedure and during follow-up.

Finally, the primary purpose of our analysis was to determine whether there was any harm associated with the use of drug-eluting stents as compared with bare-metal stents in an unselected population of patients with myocardial infarction. The observation of a reduction in mortality rates with drug-eluting stents was unanticipated and merits confirmation in randomized trials.³⁰

In conclusion, in patients with myocardial infarction treated with stenting, the use of drug-eluting stents is associated with reduced rates of death and repeat revascularization at 2 years of follow-up, as compared with the use of bare-metal stents. Large, randomized trials with long-term follow-up will be necessary to confirm this observation.

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REFERENCES

- Bavry AA, Kumbhani DJ, Quiroz R, Ramchandani SR, Kenchaiah S, Antman EM. Invasive therapy along with glycoprotein IIb/IIIa inhibitors and intracoronary stents improves survival in non-ST-segment elevation acute coronary syndromes: a meta-analysis and review of the literature. *Am J Cardiol* 2004;93:830-5.
- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13-20.
- Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;293:2908-17.
- 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.
- 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.
- Laarman GJ, Sutorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 2006;355:1105-13.
- Menichelli M, Parma A, Pucci E, et al. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). *J Am Coll Cardiol* 2007;49:1924-30.
- Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 2006;355:1093-104.
- van der Hoeven BL, Liem SS, Jukema JW, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. *J Am Coll Cardiol* 2008;51:618-26.
- Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 2007;28:2706-13.
- 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.
- Lemos PA, Saia F, Hofma SH, et al. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. *J Am Coll Cardiol* 2004;43:704-8.
- Slottow TL, Steinberg DH, Roy P, et al. Drug-eluting stents are associated with similar cardiovascular outcomes when compared to bare metal stents in the setting of acute myocardial infarction. *Cardiovasc Revasc Med* 2008;9:24-8.
- Steg PG. Increased all-cause mortality at 2-year follow-up after PCI with drug-eluting stents versus bare-metal stents in acute coronary syndromes: the GRACE Registry. Presented at the European Society of Cardiology World Congress, Vienna, September 1-5, 2007. abstract.
- Shahian DM, Silverstein T, Lovett AF, Wolf RE, Normand SL. Comparison of clinical and administrative data sources for hospital coronary artery bypass graft surgery report cards. *Circulation* 2007;115:1518-27.
- D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265-81.
- Gu XS, Rosenbaum PR. Comparison of multivariate matching methods: structures, distances, and algorithms. *J Comput Graph Stat* 1993;2:405-20.
- Cohen J. The t test for means. In: Cohen J, ed. *Statistical power analysis for the behavioral sciences*. Toronto: Academic Press, 1977:19-74.
- Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-16.
- Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 2006;151:1260-4.
- Doyle B, Rihal CS, O'Sullivan CJ, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. *Circulation* 2007;116:2391-8.
- Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med* 2007;357:1393-402.
- Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-33.
- Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-89.
- Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007;115:813-8.
- Mauri L, Silbaugh TS, Wolf RE, et al. Long-term clinical outcomes following drug-eluting and bare metal stenting in Massachusetts. *Circulation* (in press).
- Abbott JD, Voss MR, Nakamura M, et al. Unrestricted use of drug-eluting stents compared with bare-metal stents in routine clinical practice: findings from the National Heart, Lung, and Blood Institute Dynamic Registry. *J Am Coll Cardiol* 2007;50:2029-36.
- Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007;115:2426-34.
- Sianos G, Papafaklis MI, Daemen J, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol* 2007;50:573-83.
- Stone GW. HORIZONS-AMI: a prospective randomized comparison of bivalirudin vs. heparin plus glycoprotein IIb/IIIa inhibitors during primary angioplasty in acute myocardial infarction. Presented at the 19th annual Transcatheter Cardiovascular Therapeutic symposium, Washington, DC, October 20-25, 2007. abstract.

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