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Strategies for Multivessel Revascularization in Patients with Diabetes

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ABSTRACT

BACKGROUND

In some randomized trials comparing revascularization strategies for patients with diabetes, coronary-artery bypass grafting (CABG) has had a better outcome than percutaneous coronary intervention (PCI). We sought to discover whether aggressive medical therapy and the use of drug-eluting stents could alter the revascularization approach for patients with diabetes and multivessel coronary artery disease.

METHODS

In this randomized trial, we assigned patients with diabetes and multivessel coronary artery disease to undergo either PCI with drug-eluting stents or CABG. The patients were followed for a minimum of 2 years (median among survivors, 3.8 years). All patients were prescribed currently recommended medical therapies for the control of low-density lipoprotein cholesterol, systolic blood pressure, and glycated hemoglobin. The primary outcome measure was a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

From 2005 through 2010, we enrolled 1900 patients at 140 international centers. The patients' mean age was 63.1 ± 9.1 years, 29% were women, and 83% had three-vessel disease. The primary outcome occurred more frequently in the PCI group ($P=0.005$), with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group. The benefit of CABG was driven by differences in rates of both myocardial infarction ($P<0.001$) and death from any cause ($P=0.049$). Stroke was more frequent in the CABG group, with 5-year rates of 2.4% in the PCI group and 5.2% in the CABG group ($P=0.03$).

CONCLUSIONS

For patients with diabetes and advanced coronary artery disease, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction, with a higher rate of stroke. (Funded by the National Heart, Lung, and Blood Institute and others; FREEDOM ClinicalTrials.gov number, NCT00086450.)

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REVASCULARIZATION FOR PATIENTS WITH multivessel coronary artery disease is performed commonly throughout the world. In the United States alone, approximately 700,000 patients undergo multivessel coronary revascularization yearly. Of these patients, 25% have diabetes.^{1,2} In the Bypass Angioplasty Revascularization Investigation (BARI) trial, patients with diabetes and multivessel disease who underwent coronary-artery bypass grafting (CABG) lived longer than did patients undergoing balloon angioplasty, a finding that led to guideline recommendations for CABG as the preferred approach for revascularization in such patients.^{3,4} Outcomes from CABG improved with the advent of antithrombotic therapy and the use of arterial conduits.^{5,6} In subsequent years, despite major advances in percutaneous coronary intervention (PCI) and accompanying medical therapy, studies have consistently shown a trend toward more frequent major adverse cardiovascular and cerebrovascular events in patients with diabetes and multivessel coronary artery disease who underwent PCI than among those who underwent CABG. Most recently, in the era of drug-eluting stents, a small, underpowered, randomized trial, the Coronary Artery Revascularization in Diabetes (CARDia) study, and a subgroup analysis of the Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) study showed an increased rate of major adverse cardiovascular and cerebrovascular events at 12 months for patients with multivessel disease who underwent PCI with drug-eluting stents, as compared with CABG.^{7,8} In SYNTAX, there was further divergence of the event curves during long-term follow-up.⁹

In the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, we used contemporary PCI and CABG techniques and currently recommended ancillary medical therapies to determine whether CABG or PCI with drug-eluting stents is the superior approach to revascularization in patients with diabetes and multivessel coronary artery disease.

METHODS

PATIENT SELECTION AND RANDOMIZATION

The study enrolled patients with diabetes and angiographically confirmed multivessel coronary artery disease with stenosis of more than 70% in two or more major epicardial vessels involving at

least two separate coronary-artery territories and without left main coronary stenosis. A full description of the methods was published previously,¹⁰ and the protocol is available with the full text of this article at NEJM.org. Randomization was conducted in a 1:1 ratio with the use of permuted blocks with dynamic balancing within each study center.

MEASUREMENTS

Patients underwent routine assessment of angina and neurologic status and cardiac markers. All patients were screened for stroke with the National Institutes of Health (NIH) Stroke Scale¹¹ and the Rankin scale¹² at each follow-up visit for 12 months in order to detect strokes that might not have been reported. Minimum follow-up for all patients was 2 years, and the first enrolled patients were followed for 6.75 years. A core laboratory reading of all qualifying angiograms was conducted at the Cardiovascular Research Foundation in New York.

REVASCULARIZATION AND PHARMACOLOGIC THERAPY

Sirolimus-eluting and paclitaxel-eluting stents, which were provided to the patients free of charge, were the predominant types of drug-eluting stents that were used in the trial, according to the timing of the study. The study protocol recommended that only one type of drug-eluting stent should be used in a given patient. A newer generation of drug-eluting stents could be used in the trial as long as they were approved for use. The use of abciximab was recommended for patients undergoing PCI and also was provided to the patients free of charge. The use of dual antiplatelet therapy with aspirin and clopidogrel (also provided free of charge) was recommended for at least 12 months after stent implantation. For CABG surgery, arterial revascularization was encouraged. It was recommended that the following guideline-driven targets be used for lowering medical risk factors: low-density lipoprotein cholesterol, lower than 70 mg per deciliter; blood pressure, lower than 130/80 mm Hg; and glycated hemoglobin, lower than 7%. Regular communication with the treating physicians regarding control of risk factors was maintained throughout the course of the trial.

TRIAL OUTCOMES

The primary outcome was a composite of death from any cause, nonfatal myocardial infarction,

and nonfatal stroke. In the first 30 days after the primary or any repeat revascularization procedure, myocardial infarction was defined as the presence of new Q waves in 2 or more contiguous leads on electrocardiography, as compared with baseline. Following the first 30 days after any revascularization procedure, myocardial infarction was defined as either a typical increase in the troponin level or a more rapid rise and fall in the MB fraction of creatine kinase (CK-MB) with the presence of one or more of the following factors: ischemic symptoms, development of pathologic Q waves on electrocardiography, changes indicative of ischemia on electrocardiography, the need for repeated coronary-artery intervention, or pathologic findings of an acute myocardial infarction.

Stroke was defined as the presence of at least one of the following factors: a focal neurologic deficit of central origin lasting more than 72 hours or lasting more than 24 hours with imaging evidence of cerebral infarction or intracerebral hemorrhage, a nonfocal encephalopathy lasting more than 24 hours with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state, or retinal arterial ischemia or hemorrhage. Strokes were graded with the NIH 11-item Stroke Scale (with a score of >4 indicating a disabling stroke) and the Rankin scale (ranging from 1 to 5, with higher scores indicating greater disability). The definitions of all trial end points are listed in the Supplementary Appendix, available at NEJM.org.

Key secondary outcome measures included the rate of major adverse cardiovascular and cerebrovascular events 30 days and 12 months after the procedure (including components of the primary outcome as well as repeat revascularization) and annual all-cause and cardiovascular mortality. We also examined categories for the SYNTAX score (≤ 22 , 23 to 32, or ≥ 33 , with a score of ≥ 33 indicating extensive disease) and study-center location in North America, as compared with not in North America. An events committee provided central independent adjudication of all occurrences of the primary end points in an unblinded fashion.

TRIAL OVERSIGHT

The study was sponsored by the National Heart, Lung, and Blood Institute (NHLBI). Cordis, Johnson & Johnson, and Boston Scientific provided the

stents; Eli Lilly provided abciximab and an unrestricted research grant; and Sanofi-Aventis and Bristol-Myers Squibb provided clopidogrel.

The steering committee was solely responsible for the design and conduct of the study, along with the analysis of the data and the decision to submit the manuscript for publication. The committee vouches for the accuracy and completeness of the data analysis and attests to the fidelity of this report to the study protocol.

STATISTICAL ANALYSIS

We adopted two amendments to the study protocol with respect to the target sample size. The trial was originally designed to enroll 2400 patients during a 2-year period with minimum follow-up of 3 years per patient to ensure a power of 85% to detect a relative reduction of 18 to 23% in 4-year rates of the primary outcome, which were expected to range from 30 to 38% in the less effective study group. In December 2007, the protocol was amended to have a target enrollment of 2058 patients during a 4.25-year period with a minimum of 2.5 years of follow-up to ensure a power of 85% to detect a relative reduction of 24.6% in the rate of the primary outcome, with 1% crossover and loss to follow-up. In April 2009, the protocol was again amended to have a final target enrollment of 1900 patients during a 4.75-year period with a minimum of 2 years of follow-up. These calculations were based on an observed aggregate 4-year event rate of 14.85%, with an estimated power of 80% to detect a relative reduction of 27% in the 4-year event rates in the two study groups.

Clinical event rates for the primary outcome and for cardiovascular death were based on the time since randomization. The secondary trial end points of major adverse cardiovascular and cerebrovascular events at 30 days and 12 months were based on the time since the procedure. We calculated the time since the procedure according to the date of the initial index procedure for both single and staged procedures. We used the log-rank test to compare the distributions of the time to the first event for the primary and secondary outcomes according to study-group assignment using all available follow-up data. We used Cox proportional-hazards regression to determine hazard ratios for selected outcomes and to conduct prespecified subgroup analyses of the primary outcome, using a test of study-group assignment according to subgroup interaction.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	PCI (N=953)	CABG (N=947)	P Value†
Age at randomization — yr	63.2±8.9	63.1±9.2	0.78
Male sex — no. (%)	698 (73.2)	658 (69.5)	0.08
Glycated hemoglobin — %	7.8±1.7	7.8±1.7	0.86
Current smoker — no. (%)	141 (14.8)	157 (16.6)	0.31
Previous myocardial infarction — no. (%)	250 (26.2)	237 (25.0)	0.56
Recent acute coronary syndrome — no. (%)	304 (31.9)	279 (29.5)	0.25
Three-vessel disease — no./total no. (%)	780/948 (82.3)	793/939 (84.5)	0.22
Left ventricular ejection fraction			
Percent	65.7±12.1	66.6±10.5	0.13
<40% — no./total no. (%)	21/641 (3.3)	11/650 (1.7)	0.07
EuroSCORE‡			0.52
Mean	2.7±2.4	2.8±2.5	
Median (interquartile range)	1.9 (1.3–3.1)	2.0 (1.3–3.3)	
SYNTAX score§			0.77
Mean	26.2±8.4	26.1±8.8	
Median (interquartile range)	26.0 (20.5–31.0)	26.0 (19.5–31.5)	
Category — no./total no. (%)			
Low: ≤22	329/949 (34.7)	340/938 (36.2)	
Intermediate: 23–32	438/949 (46.2)	406/938 (43.3)	
High: ≥33	182/949 (19.2)	192/938 (20.5)	0.45
No. of lesions	5.65±2.16	5.74±2.19	0.33
Chronic total occlusion — no./total no. (%)¶	323/5564 (5.8)	329/5662 (5.8)	0.99
Bifurcation — no./total no. (%)¶	1242/5561 (22.3)	1177/5640 (20.9)	0.06
Use of insulin — no./total no. (%)	322/952 (33.8)	293/947 (30.9)	0.19
Use of thiazolidinedione — no./total no. (%)	73/952 (7.7)	82/947 (8.7)	0.45
Staged procedure — no./total no. (%)	321/939 (34.2)	NA	NA
Total no. of lesions stented across all stages	3.5±1.4	NA	NA
Total length of stents placed — mm	26.1±14.2	NA	NA
Surgery off-pump — no./total no. (%)	NA	165/893 (18.5)	NA
No. of graft vessels	NA	2.9±0.8	NA
Left internal thoracic-artery graft — no./total no. (%)	NA	848/898 (94.4)	NA

* Plus-minus values are means ±SD. NA denotes not applicable.

† P values were calculated with the use of Fisher's exact test for categorical variables, the Wilcoxon rank-sum test for the European System for Cardiac Operative Risk Evaluation (EuroSCORE) value, and Student's t-test for the remaining continuous variables.

‡ A score of 5 or more on the EuroSCORE is associated with decreased rates of survival.

§ A score of 33 or more on the Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) scale indicates extensive disease.

¶ Values in this category are based on the total number of lesions in 949 patients in the PCI group and 939 patients in the CABG group.

All between-group comparisons were conducted according to the intention-to-treat principle. Interim analyses were planned to be conducted when 25%, 50%, and 75% of data were available, with the fraction calculated on the basis of the accrual of potential follow-up data. A final P value of less than 0.044 was considered to indicate statistical significance for the primary outcome on

Table 2. Kaplan–Meier Estimates of Key Outcomes at 2 Years and 5 Years after Randomization.

Outcome	2 Years after Randomization		5 Years after Randomization		Patients with Event		P Value*
	PCI	CABG	PCI	CABG	PCI	CABG	
	number (percent)				number		
Primary composite†	121 (13.0)	108 (11.9)	200 (26.6)	146 (18.7)	205	147	0.005‡
Death from any cause	62 (6.7)	57 (6.3)	114 (16.3)	83 (10.9)	118	86	0.049
Myocardial infarction	62 (6.7)	42 (4.7)	98 (13.9)	48 (6.0)	99	48	<0.001
Stroke	14 (1.5)	24 (2.7)	20 (2.4)	37 (5.2)	22	37	0.03§
Cardiovascular death	9 (0.9)	12 (1.3)	73 (10.9)	52 (6.8)	75	55	0.12

* P values were calculated with the use of the log-rank test on the basis of all available follow-up data (i.e., more than 5 years).

† The primary composite outcome was the rate of death from any cause, myocardial infarction, or stroke.

‡ P=0.006 in the as-treated (non–intention-to-treat) analysis.

§ P=0.16 by the Wald test of the Cox regression estimate for study-group assignment in 1712 patients after adjustment for the average glucose level after the procedure.

the basis of three interim analyses (performed with 22%, 46%, and 74% of available data). A P value of less than 0.05 was considered to indicate significance for all other outcomes. All analyses were conducted with the use of SAS software, version 9.3 (SAS Institute) and S-PLUS 8.0 for Windows software (Insightful).

RESULTS

STUDY POPULATION

From April 2005 through April 2010, a total of 32,966 patients were screened (Fig. 1 in the Supplementary Appendix). Of the 3309 trial-eligible patients, 1900 (57.4%) provided written informed consent and underwent randomization. The clinical and angiographic characteristics of the patients were well balanced in the two study groups at baseline (Table 1). The mean age was 63.1±9.1 years, and 83% of patients had three-vessel disease. The mean SYNTAX score was 26.2±8.6 and did not differ significantly according to study group. Sirolimus-eluting and paclitaxel-eluting stents were used exclusively in 51% and 43% of patients, respectively, in the PCI group who actually underwent PCI. The median follow-up time was 3.8 years (interquartile range, 2.5 to 4.9).

CARDIAC MEDICATIONS

The use of thienopyridines in particular remained higher in the PCI group after 5 years of follow-up. However, the use of other evidence-based therapies such as statins, beta-blockers, and angiotensin-

converting-enzyme inhibitors and angiotensin-receptor blockers was similar in the two study groups (Table 1 in the Supplementary Appendix).

PRIMARY OUTCOME

The primary outcome occurred in 352 patients (205 in the PCI group and 147 in the CABG group) (Table 2). The rate of the primary outcome was lower in the CABG group than in the PCI group (P=0.005 by the log-rank test), with divergence of the curves starting at 2 years (Fig. 1A). At 30 days, the primary outcome had occurred in fewer patients in the PCI group than in the CABG group (26 vs. 42). However, 5-year event rates were 26.6% in the PCI group, as compared with 18.7% in the CABG group, for an absolute difference of 7.9 percentage points (95% confidence interval [CI], 3.3 to 12.5). There was increased all-cause mortality in the PCI group (P=0.049), with 5-year rates of 16.3% in the PCI group versus 10.9% in the CABG group, for an absolute difference of 5.4 percentage points (95% CI, 1.5 to 9.2) (Fig. 1B).

The distributions of time until myocardial infarction also differed in favor of the CABG group (P<0.001) (Table 2, and Fig. 2A in the Supplementary Appendix). At 5 years, 13.9% of patients in the PCI group had had a myocardial infarction, as compared with 6.0% in the CABG group. Periprocedural myocardial infarction occurred in 17 patients in the PCI group (17% of the 99 patients with myocardial infarction in that group) and 15 in the CABG group (31% of the 48 pa-

tients with myocardial infarction in that group). All the procedural myocardial infarctions in the trial were non-Q-wave events. Myocardial infarctions that occurred more than 30 days after the index procedures were reported in 81 of 99 patients (82%) in the PCI group and in 29 of 48 patients (60%) in the CABG group.

There were fewer strokes in the PCI group than in the CABG group ($P=0.03$) (Table 2, and Fig. 2B in the Supplementary Appendix). The

5-year rates were 2.4% in the PCI group and 5.2% in the CABG group. Of these strokes, the majority (87%) were ischemic and 13% were hemorrhagic. In the first 30 days after the procedure, 3 patients in the PCI group and 16 in the CABG group had a stroke (Table 3). The excess of strokes in the CABG group occurred in the first 30 days after randomization. An NIH Stroke Scale score of more than 4 (severely disabling) at the time of the event was reported in 27% of patients in the PCI group, as compared with 55% of those in the CABG group. A score on the Rankin scale of more than 1 at the time of the stroke was reported in 60% of patients in the PCI group, as compared with 70% in the CABG group.

SECONDARY OUTCOMES

Rates of cardiovascular death (63.7% of all deaths) did not differ significantly between the two study groups ($P=0.12$ by the log-rank test), nor did rates of major adverse cardiovascular and cerebrovascular events at 30 days ($P=0.68$ by the log-rank test). However, at 1 year after the procedure, there was a significant difference in rates of major adverse cardiovascular and cerebrovascular events, with 16.8% in the PCI group versus 11.8% in the CABG group ($P=0.004$) (Table 3, and Fig. 2C in the Supplementary Appendix). This difference was attributed largely to the preponderance of repeat revascularization events by 1 year in the PCI group, as compared with the CABG group, with repeat events in 12.6% and 4.8% of patients in the two groups, respectively (hazard ratio, 2.74; 95% CI, 1.91 to 3.89; $P<0.001$) (Fig. 2D in the Supplementary Appendix).

PRESPECIFIED SUBGROUP ANALYSES

The greater benefit of CABG versus PCI was consistent across all prespecified subgroups (Fig. 2). The analysis according to the category of SYNTAX score showed no significant subgroup interaction ($P=0.58$). At 5 years, the absolute difference in the rate of the primary outcome in the PCI group, as compared with the CABG group, was similar in the three SYNTAX subgroups (6 percentage points for a low SYNTAX score, 10 percentage points for an intermediate score, and 8 percentage points for a high score). The hazard ratios for the PCI group, as compared with the CABG group, according to SYNTAX subgroup were 1.14, 1.46, and 1.46, respectively. Similarly, for the rate of major adverse cardiovascular and cerebrovascular events at 1 year,

Table 3. Kaplan–Meier Estimates of Major Adverse Cardiovascular and Cerebrovascular Events at 30 Days and 12 Months after the Procedure.

Event	30 Days after Procedure			12 Months after Procedure		
	PCI	CABG	P Value	PCI	CABG	P Value
	number (percent)			number (percent)		
Major adverse cardiovascular and cerebrovascular events	45 (4.8)	47 (5.2)	0.68	157 (16.8)	106 (11.8)	0.004
Death	8 (0.8)	15 (1.7)	0.12	32 (3.4)	38 (4.2)	0.35
Myocardial infarction	17 (1.8)	15 (1.7)	0.82	54 (5.8)	30 (3.4)	0.02
Stroke	3 (0.3)	16 (1.8)	0.002	8 (0.9)	17 (1.9)	0.06
Repeat revascularization	31 (3.3)	10 (1.1)	0.002	117 (12.6)	42 (4.8)	<0.001

there was no differential treatment effect according to the category of SYNTAX score ($P=0.28$ for interaction).

We conducted the primary outcome analysis for PCI, as compared with CABG, using data for patients in whom only paclitaxel-eluting stents were used (394 patients) and in whom only sirolimus-eluting stents were used (469 patients), as compared with 898 patients who underwent CABG. In these two analyses, the absolute between-group rate differences at 5 years were nearly identical: 6.5 percentage points for paclitaxel-eluting stents and 6.7 percentage points for sirolimus-eluting stents.

SAFETY

A major bleeding event occurred within 30 days after the index revascularization procedure in 23 patients in the PCI group and 34 patients in the CABG group ($P=0.13$). Acute renal failure requiring hemodialysis within 30 days after the index revascularization procedure was observed in 1 patient in the PCI group and 8 patients in the CABG group ($P=0.02$).

DISCUSSION

In this study, we compared revascularization strategies for patients with diabetes and multivessel (predominantly three-vessel) coronary artery disease and found that patients who underwent CABG had significantly lower rates of the composite primary outcome of death from any cause, myocardial infarction, or stroke than did those undergoing PCI with a drug-eluting stent. This result was similar at all levels of angiographic complexity (according to the SYNTAX score¹³), ejection fraction, and renal function.

Our findings are consistent with reports from other smaller or retrospective studies of revascularization in patients with diabetes. A significant advantage of CABG over balloon angioplasty was reported in the mid-1990s in a retrospective analysis of the BARI trial.¹⁴ This study led to an NHLBI alert recommending that patients with diabetes and multivessel disease undergo CABG as the preferred mode of revascularization.¹⁵ However, clinical practice did not change appreciably on the basis of the alert or the subsequent trial publication.

Since that time, other trials, including the Arterial Revascularization Therapies Study (ARTS) (historical control),¹⁶ CARDia (underpowered randomized trial), and SYNTAX (subgroup analysis), have reported excess rates of major adverse cardiovascular and cerebrovascular events in patients with diabetes who were assigned to undergo PCI rather than CABG, although the differences observed in these studies were primarily the result of a higher rate of revascularization among patients undergoing PCI. In contrast, in our study, we found that the benefit of CABG was driven by reductions in rates of both myocardial infarction and death from any cause. Our definition of myocardial infarction is consistent with the recent consensus of the American College of Cardiology and the American Heart Association with respect to spontaneous myocardial infarction. However, we used even more stringent criteria for the definition of periprocedural myocardial infarction.¹⁷ The observation that CABG was associated with a higher rate of stroke has been observed in virtually every comparative trial of the two treatment strategies, as well as in a recent meta-analysis.¹⁸

Figure 2. Primary Composite Outcome, According to Subgroup.

Subgroup analyses were performed with the use of Cox proportional-hazards regression. Five-year composite event rates for death, myocardial infarction, or stroke are shown. LAD denotes left anterior descending artery, and LVEF left ventricular ejection fraction.

Our study has several strengths. We focused exclusively on patients with diabetes in a single, well-powered, randomized trial, in which we enrolled high-risk patients with a good distribution of SYNTAX scores and followed those patients for clinical cardiovascular events for a median of 3.8 years. Consistent with the BARI 2 Diabetes (BARI-2D) trial, optimal medical therapy was prescribed throughout the follow-up.¹⁹

A comprehensive meta-analysis of trials performed before the introduction of drug-eluting

stents showed excess mortality after PCI, as compared with CABG, in patients with diabetes.²⁰ Although our study was not powered to detect a difference in all-cause mortality, we observed a significantly ($P=0.049$) higher rate in the PCI-treated group. This was also observed in the small subgroup analysis of the BARI trial, and a similar trend toward higher mortality has been suggested by the other trials. The increased use of internal mammary grafting in these trials has been postulated to play a key role in the improved survival

with CABG. When considered together, the data provide a convincing signal that PCI results in increased long-term mortality, as compared with CABG, in patients with diabetes and multivessel coronary artery disease.

In long-term follow-up, the rate of myocardial infarction was significantly higher in the PCI group than in the CABG group, whereas the rate of stroke was significantly higher in the CABG group. The higher relative risk of stroke among patients undergoing CABG was evident only early in the postprocedural period.

Concomitant medical therapy is important to all patients with diabetes and coronary artery disease. In the PCI group, almost 90% of patients were receiving dual antiplatelet therapy at 12 months. Unlike in the SYNTAX trial, we observed similar rates of use of most other cardiovascular medications in the two study groups. An intensive medical program was promoted throughout the trial as the cornerstone of treatment.

Our study has some limitations. First, since some of the prespecified subgroups had very low prevalence, the statistical power was low to detect interactions between treatment and subgroup. Second, since the trial was not blinded, patients may have been treated differently on the basis of their surgical procedure. However, trial outcomes were objective and independently adjudicated, and the available data suggest no group differences in the appropriateness of the medical therapy received. Clearly, there is wide variability as to the types of patients enrolled, as shown by the distribution of SYNTAX scores at baseline. This variation reflects real-world practice and is a strength, rather than a weakness, of the study.

In conclusion, we found that CABG was superior to PCI with drug-eluting stents in patients with diabetes and advanced (predominantly three-vessel) coronary artery disease in that CABG

significantly reduced rates of death and myocardial infarction, with a higher rate of stroke.

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APPENDIX

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