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Percutaneous Coronary Intervention Versus Coronary Bypass Surgery in United States Veterans With Diabetes

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Objectives This study sought to determine the optimal coronary revascularization strategy in patients with diabetes with severe coronary disease.

Background Although subgroup analyses from large trials, databases, and meta-analyses have found better survival for patients with diabetes with complex coronary artery disease when treated with surgery, a randomized trial comparing interventions exclusively with drug-eluting stents and surgery in patients with diabetes with high-risk coronary artery disease has not yet been reported.

Methods In a prospective, multicenter study, 198 eligible patients with diabetes with severe coronary artery disease were randomly assigned to either coronary artery bypass grafting (CABG) (n = 97) or percutaneous coronary intervention (PCI) with drug-eluting stents (n = 101) and followed for at least 2 years. The primary outcome measure was a composite of nonfatal myocardial infarction or death. Secondary outcome measures included all-cause mortality, cardiac mortality, nonfatal myocardial infarction, and stroke.

Results The study was stopped because of slow recruitment after enrolling only 25% of the intended sample size, leaving it severely underpowered for the primary composite endpoint of death plus nonfatal myocardial infarction (hazard ratio: 0.89; 95% confidence interval: 0.47 to 1.71). However, after a mean follow-up period of 2 years, all-cause mortality was 5.0% for CABG and 21% for PCI (hazard ratio: 0.30; 95% confidence interval: 0.11 to 0.80), while the risk for nonfatal myocardial infarction was 15% for CABG and 6.2% for PCI (hazard ratio: 3.32; 95% confidence interval: 1.07 to 10.30).

Conclusions This study was severely underpowered for its primary endpoint, and therefore no firm conclusions about the comparative effectiveness of CABG and PCI are possible. There were interesting differences in the components of the primary endpoint. However, the confidence intervals are very large, and the findings must be viewed as hypothesis generating only. (Coronary Artery Revascularization in Diabetes; NCT00326196) (J Am Coll Cardiol 2013;61:808–16) © 2013 by the American College of Cardiology Foundation

A randomized clinical trial specifically designed to compare percutaneous intervention and surgical bypass for severe coronary artery disease (CAD) in patients with type 2 diabetes has not yet been reported in the era of drug-coated stents. In the diabetic subset of the BARI (Bypass Angioplasty

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Revascularization Investigation) trial (1), coronary artery bypass grafting (CABG) was superior to percutaneous coronary intervention (PCI) at 5-year follow-up. However, this may not be relevant to the current era, when the use of drug-eluting stents, glycoprotein IIb/IIIa inhibitors, and newer oral antiplatelet agents has become standard (2). Surgical techniques have also evolved since the BARI trial, with increased use of arterial conduits and off-pump techniques (3). Although the impact of these technical advances in revascularization has been studied extensively in the general patient population with multivessel CAD (4–6), there is a paucity of randomized data concentrating on patients with diabetes. The BARI 2D trial was not designed to compare revascularization strategies, and the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease trial has completed enrollment but has not yet produced its results. The CARDIA (Coronary Artery Revascularization in Diabetes) trial randomized 510 subjects with diabetes between PCI (with either bare-metal or drug-coated stents) and surgery and resulted in a composite 1-year rate of death, stroke, and myocardial infarction (MI) that was similar between CABG and PCI, but that study was underpowered for this composite endpoint (7).

We conducted a prospective randomized multicenter study comparing CABG with PCI for severe CAD in subjects with diabetes, using currently available techniques for revascularization in the United States. The primary hypothesis of this study was that a strategy of initial surgical revascularization is superior to percutaneous intervention in preventing death or MI in patients with diabetes with severe ischemic heart disease.

Methods

The trial was conducted at U.S. Department of Veterans Affairs (VA) medical centers in the United States with a 1:1 randomization between treatment arms. Patients were enrolled at 22 sites between August 26, 2006, and March 24, 2010. Patients were eligible if they had diabetes and either multivessel disease including the left anterior descending coronary artery or isolated proximal left anterior descending coronary artery disease. Objective evidence of ischemia was required for stenoses between 50% and 70%. Ischemia was documented by stress testing, flow wire, intracoronary ultrasound, or dynamic changes on electrocardiography during a symptomatic episode. An interventional cardiologist and cardiothoracic surgeon reviewed each case and determined that either procedure was appropriate. The World Health Organization definition of diabetes was used (8). Exclusion criteria were age $<$ 18 years, women of childbearing potential, inability to give informed consent, concomitant cardiac surgery, congenital heart disease, life expectancy $<$ 2 years, lack of surgical conduit, CABG in the preceding year, class III decompensated or class IV heart failure, history of embolic stroke within 6 months, history of hemorrhagic stroke, history of gastrointestinal bleeding within 1 month, known sensitivity to glycoprotein IIb/IIIa inhibitors, chronic steroid use, bleeding diathesis, and acute ST-segment elevation MI. Angiographic exclusion criteria were chronic total occlusion in 2 or more territories, unprotected left main coronary artery disease, unavailability of both internal thoracic arteries, and PCI of a major vessel in a qualifying territory within 1 year.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CAD = coronary artery disease
CI = confidence interval
HbA_{1c} = glycosylated hemoglobin
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
VA = U.S. Department of Veterans Affairs

The study was funded by the VA Cooperative Studies Program and approved by the institutional review board at each site. An investigational device exemption was obtained, and all commercially available drug-eluting stents were allowed once they were approved by the U.S. Food and Drug Administration for use in the study. Treatment crossovers were discouraged but allowed. Patients could withdraw from the study at any time.

Randomization was performed by the coordinating center with stratification by site, insulin use (yes or no) and glycosylated hemoglobin (HbA_{1c}) ($\leq$8% vs. $>$8%). Staged PCI was considered 1 procedure if all interventions were declared at randomization and completed within 4 weeks. The choice of stent was at the operator's discretion, but a single stent type per patient was recommended. The left internal thoracic artery was used whenever possible, and the anterior descending artery was the recommended recipient. Cardiac risk factor management was left to the primary care provider, with recommendations to follow American College of Cardiology and American Heart Association guidelines. Periprocedural insulin infusions were recommended. HbA_{1c} $>$ 9% or failure to achieve blood glucose $<$ 180 mg/dl within 12 h on an insulin drip was an indication for referral to an endocrinologist, but routine consultations were discouraged. Recurrent coronary disease was treated at the physician's discretion.

Baseline and annual rest nuclear studies were performed to identify silent MIs. Follow-up visits were scheduled at 4 to 6 weeks after revascularization and then every 6 months. Electrocardiograms were obtained every 3 months, along with phone contact to determine health status. Interim hospitalizations for cardiac-related events were documented. Quality-of-life measures (Seattle Angina Questionnaire and EuroQol-5D) were obtained every 6 months. Adverse events were assessed from time of informed consent to 30 days after the end of a subject's participation. A data monitoring committee reviewed safety and outcome measures semiannually. A blinded core angiographic laboratory reviewed all coronary angiograms.

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A conservative definition of periprocedural MI was used in both arms. This required a 5-fold increase in creatine phosphokinase-MB plus diagnostic new Q waves on electrocardiography. During follow-up, new MIs were defined as either clinical (typical history with diagnostic electrocardiography changes and/or enzyme elevations) or silent (diagnostic changes on serial electrocardiograms or new fixed defect ≥20% of the myocardium on nuclear studies). Secondary endpoints included all-cause mortality, cardiac death, nonfatal MI, stroke, repeated revascularization, stent thrombosis, and cardiac-related hospitalization. Stent thrombosis was defined by the Academic Research Consortium guidelines (9). A 3-member endpoint committee blinded to treatment assignment adjudicated all MIs and strokes. Where records related to a death in follow-up were available, the endpoint committee reviewed them to assign a presumed cardiac versus noncardiac cause. At the end of the study, searches of VA death databases were undertaken to confirm the vital status of all patients at last follow-up and revealed 6 deaths not otherwise reported. No data concerning causality was available for these cases.

The primary endpoint was a composite of all-cause mortality or nonfatal MI. Expected event rates used to determine sample size were based on data from the VA cardiac surgery database, VA trials, and other non-VA trials. A total sample size of 790 (395 in each group) was projected for the study to have 90% power to detect a 40% reduction in the primary endpoint with CABG compared with PCI, using a 2-sided log-rank test at an alpha level of 0.05. The sample size calculation assumed 48 months of recruitment and minimum follow-up of 24 months.

All statistical analyses were conducted using intent-to-treat principles. The primary hypothesis was tested using the Kaplan-Meier method and a 2-sided log-rank test. The time of follow-up was from randomization to the last visit. Patients who did not have events were censored at their last visits. The rates for the primary endpoint were also compared according to pre-specified subgroups (insulin use vs. no insulin use, $HbA_{1c} \leq 8\%$ vs. $> 8\%$) using the same methods. Secondary endpoints were assessed using log-rank tests. Cox proportional hazards models were used to determine hazard ratios (HRs) and 95% of confidence intervals (CIs). SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores (10) were assigned by the angiographic core laboratory. Comparisons of demographic characteristics, clinical variables, SYNTAX scores, and medication use between the primary treatment groups and the PCI survivors versus nonsurvivors were undertaken using 2-sample student t tests for continuous variables and chi-square tests or Fisher exact tests as appropriate for discrete variables. All statistical analyses were 2 sided and were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina), with $p \leq 0.05$ as the criterion for significance.

Results

A total of 6,678 patients with diabetes presenting for cardiac catheterization were screened by study coordinators (Fig. 1). Of these, 6,080 (91%) did not meet angiographic requirements. Of the remaining patients, 207 (35%) were randomized. Of the randomized patients, 103 were assigned to surgery and 104 to PCI. In March 2010, the data monitoring committee recommended stopping enrollment in the study because of slow recruitment. At that time, no differences between treatment groups were evident in either the primary endpoint or all-cause mortality. Six randomized patients withdrew from the study before treatment once this was announced (5 surgery, 1 PCI). Three ineligible patients were randomized in error because of Health Insurance Portability and Accountability Act issues or confusion by local investigators regarding eligibility. A total of 198 patients were available for analysis (97 surgery, 101 PCI). Eleven patients assigned to surgery and 6 patients assigned to PCI crossed over to the opposite treatment arm. These patients were analyzed in their assigned treatment arms. Follow-up of the enrolled patients continued until October 2010.

Baseline characteristics were similar between the treatment arms (Table 1). There was, however, a higher rate of previous PCI in the PCI group and a trend toward a different distribution of left ventricular function scores. The maximal degree of stenosis and lesion length were also slightly greater in the PCI group, but not by a clinically significant degree. The average time from randomization to completion of treatment was 21.4 days for CABG and 7.4 days for PCI ($p < 0.001$).

After a mean follow-up period of 2 years, all-cause mortality was 5% for CABG and 21% for PCI (HR: 0.30; 95% CI: 0.11 to 0.80), while the risk for nonfatal MI was 15% for CABG and 6.2% for PCI (HR: 3.32; 95% CI: 1.07 to 10.30). These 2 components of the composite endpoint offset each other, giving a combined risk for death or nonfatal MI of 18.4% for CABG and 25.3% for PCI (HR: 0.89; 95% CI: 0.47 to −1.71) (Table 2, Fig. 2). Because the study was underpowered because of early termination, no differences were found in either the composite endpoint or its components for the predefined subgroups on the basis of HbA_{1c} or insulin use, with the exception of all-cause mortality (3.5% for CABG vs. 28.3% for PCI, $p = 0.05$) in the largest subgroup ($HbA_{1c} < 8\%$). The study findings were not altered after adjusting for previous PCI, degree of stenosis, and lesion length. The study results were also not altered by eliminating low-volume recruiting sites from the analysis. There was no clustering of PCI mortality by specific operator or performance site. An "as treated" analysis showed results similar to the intention-to-treat analysis, indicating that the crossover patients did not alter the study results.

The PCI arm was assessed for characteristics associated with greater risk for death. The nonsurvivors were slightly

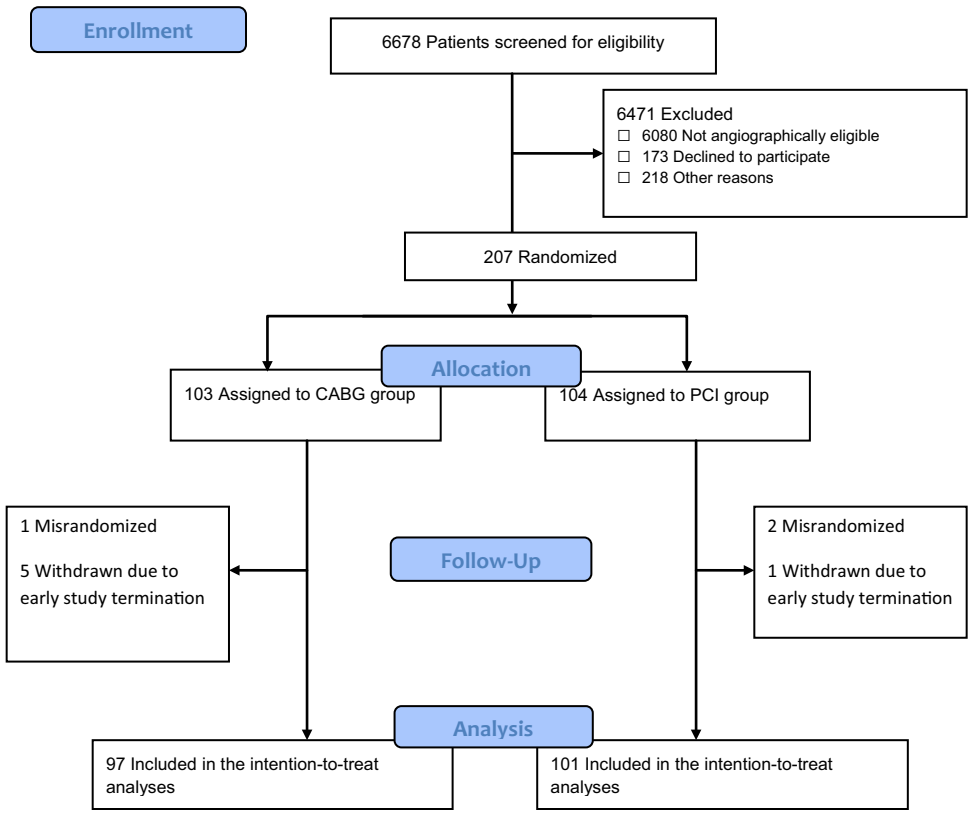

Figure 1 **CONSORT Flow Diagram**

Flow diagram of study screening and recruitment.

older (p = 0.01), and the distribution of ventricular function scores showed slightly worse ventricular function (p = 0.04). Although no other statistically significant differences were detected between PCI survivors and nonsurvivors, there were suggestions of greater clinical severity (previous MI, greater use of cardiac medications) and more severe CAD (more 3-vessel disease, more chronic total occlusions, more bifurcation disease, and a higher rate of previous coronary revascularization) in the nonsurvivors (Table 3). There were no differences between PCI survivors and nonsurvivors in the distributions of SYNTAX scores or stent brands used. The stents used were Taxus (Boston Scientific Corporation, Natick, Massachusetts; n = 35), Cypher (Cordis Corporation, Miami Lakes, Florida; n = 20), XIENCE/PROMUS (Abbott Vascular, Santa Clara, California; n = 18), Endeavor (Medtronic, Inc., Minneapolis, Minnesota; n = 2), mixed drug-eluting stents (n = 16), and mixed bare-metal stents (n = 1).

Discussion

Early termination of this study shortened follow-up to a mean of only 2 years, compared with the planned 3.7 years. With an accrual period of 44 months and maximum follow-up of 52 months, the study was stopped at a power of 9.7% for its primary endpoint. At 2 years, however, we found a relative risk reduction in all-cause mortality of 76% (HR: 0.30; 95% CI: 0.11 to 0.80) (Table 2) with surgery compared to PCI. The finding of improved survival among patients with diabetes treated with bypass surgery in our study is consistent with evidence from subset analyses of earlier studies. In BARI patients with diabetes treated with bypass surgery using an internal mammary artery graft had improved survival compared with PCI using balloon angioplasty (1). A meta-analysis of 10 studies comparing CABG with stent PCI showed a survival benefit for CABG-treated patients in the diabetic subgroup (11). This finding was repeated in the recently published ASCERT (ACCF-STS Database Collaboration on the Comparative Effectiveness of Revascularization Strategies) study, in which surgery carried a superior survival to PCI in all subgroups (12).

Other subset analyses have shown trends toward lower mortality with surgery in patients with diabetes that did not reach statistical significance. In BARI 2D, 5-year results showed a small survival advantage (13.6% vs. 16.4% all-cause mortality) for surgery versus intensive medical treatment, without reaching significance (13,14). SYNTAX compared percutaneous and surgical revascularization strategies for either left main or 3-vessel coronary disease (15).

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Table 1 Baseline Characteristics

Characteristic	CABG Group (n = 97)	PCI Group (n = 101)	p
Age (yrs)	62.1 ± 7.4	62.7 ± 7.1	0.61
Male	96 (99.0%)	100 (99.0%)	1.00
Current smoker	20 (20.6%)	28 (27.7%)	0.16
BMI (kg/m^2)	33.0 ± 5.7	32.8 ± 5.7	0.80
MI			
None	59 (62.8%)	55 (54.5%)	
Acute (<24 h)	1 (1.1%)	1 (1.0%)	
Recent (<4 days)	7 (7.4%)	9 (8.9%)	
Remote	27 (28.7%)	36 (35.6%)	0.74
CHF			
None	53 (56.4%)	64 (63.4%)	
Class I	11 (11.7%)	5 (5.0%)	
Class II	23 (24.5%)	23 (22.8%)	
Class III	7 (7.4%)	9 (8.9%)	0.85
Angina status			
None	30 (31.9%)	27 (26.7%)	
Class I	18 (19.1%)	17 (16.8%)	
Class II	26 (27.7%)	35 (34.7%)	
Class III	13 (13.8%)	15 (14.9%)	
Class IV	7 (7.4%)	7 (6.9%)	0.85
Previous PCI	19 (20.2%)	35 (34.7%)	0.03
Previous CABG	1 (1.1%)	3 (3.0%)	0.62
Hypertension	90 (95.7%)	97 (96.0%)	1.00
History of stroke	8 (8.5%)	7 (6.9%)	0.79
Peripheral vascular disease	16 (17.0%)	11 (10.9%)	0.30
Total cholesterol (mg/dl)	156.7 ± 38.1	152.1 ± 39.3	0.40
HDL (mg/dl)	30.8 ± 8.2	32.8 ± 9.5	0.13
LDL (mg/dl)	88.8 ± 31.2	82.7 ± 29.6	0.18
Triglycerides (mg/dl)	221.4 ± 149.4	224.0 ± 254.5	0.93
Glucose (mg/dl)	160.1 ± 58.1	157.3 ± 60.9	0.74
HbA_{1c} (%)	7.8 ± 1.6	8.0 ± 1.9	0.54
Duration of diabetes (yrs)	11.3 ± 9.2	11.2 ± 7.7	0.97
Chronic kidney disease (eGFR < 60 ml/min)	33 (35.1%)	26 (26.0%)	0.17
Left ventricular ejection fraction			
Normal (≥55%)	56 (63.6%)	44 (48.9%)	
Mild dysfunction (45%–54%)	18 (20.5%)	27 (30.0%)	
Moderate dysfunction (35%–44%)	9 (10.2%)	11 (12.2%)	
Severe dysfunction (25%–34%)	2 (2.3%)	8 (8.9%)	
Very severe dysfunction (<25%)	2 (2.3%)	0 (0.0%)	0.06
Aspirin use	81 (86.2%)	87 (86.1%)	1.00
Clopidogrel or ticlopidine use	20 (21.3%)	24 (23.8%)	0.73
Statin use	80 (85.1%)	91 (90.1%)	0.38
Beta-blocker use	79 (84.0%)	85 (84.2%)	1.00
ACE inhibitor use	72 (76.6%)	84 (83.2%)	0.29
Calcium-channel blocker use	28 (29.8%)	27 (26.7%)	0.75
Diuretic agent use	48 (51.1%)	58 (57.4%)	0.39
Long-acting nitrate use	27 (28.7%)	27 (26.7%)	0.87
PRN nitroglycerine use	43 (45.7%)	40 (39.6%)	0.47
Fibrate use	16 (17.0%)	12 (11.9%)	0.32
Insulin use	45 (47.9%)	48 (47.5%)	1.00
Sulfonylurea/meglitinide use	39 (41.5%)	46 (45.5%)	0.66
Thiazolidinedione use	17 (18.1%)	10 (9.9%)	0.15
Metformin use	45 (47.9%)	58 (57.4%)	0.20
Other antidiabetic medication use	6 (6.4%)	8 (7.9%)	0.78
Stenosis (%)	77.6 ± 9.0	82.0 ± 8.2	<0.001
Lesion length (mm)	13.4 ± 5.5	15.5 ± 7.1	0.02
Total number of native lesions	3.6 ± 1.3	3.6 ± 1.7	0.79
SYNTAX score	22.7 ± 10.6	21.5 ± 8.9	0.41
SYNTAX score			
Low risk (0–22)	47 (50.5%)	59 (62.1%)	
Moderate risk (23–32)	33 (35.5%)	24 (25.3%)	
High risk (>33)	13 (14.0%)	12 (12.6%)	0.24

Values are mean ± SD or n (percentage).

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass grafting; CHF = congestive heart failure; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRN; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

The diabetic subset analysis reported all-cause mortality of 8.7% for CABG and 13.6% for PCI (p = 0.113) (16). Cardiac mortality almost doubled for PCI (8.8% vs. 4.8%, p = 0.102). Unlike SYNTAX, our patient population did not include patients with left main disease (who may have better midterm outcomes with PCI) and had higher rates of risk factors such as HbA_{1c}, smoking, prior MI, and congestive heart failure.

Only 1 prospective randomized trial (CARDIA) has been published comparing CABG with PCI exclusively patients with diabetes, but it used a mix of bare-metal (30%) and drug-eluting stents (7). The rate of the composite outcome (death, MI, and stroke) at 1 year was 10.5% for CABG and 13% for PCI, failing to prove noninferiority for PCI (p = 0.39). All-cause mortality was identical at 3.2% and 3.2%. We observed a survival difference only after 1 year. Early trials comparing surgical revascularization with medical management showed that the impact of surgery on survival may not be apparent for 18 months (17). More recently, the ASCERT study also showed that surgical benefit is delayed beyond 1 year (12).

The higher risk for nonfatal MI after surgery than after PCI in this study resulted in offsetting components of the composite endpoint. A variable impact of revascularization on the risk for MI has previously been reported. At 10 years, surgical patients experienced a higher rate of MI than the medically treated group in the VA coronary surgery trial, yet survival was improved in certain groups, suggesting that transforming large MIs into smaller, nonfatal ones can affect survival (18).

Two factors influenced our reported incidence of MI. First, we chose a single definition for MI, which is consistent with what was subsequently adopted by the task force of the European Society of Cardiology, the American College of Cardiology Foundation, the American Heart Association, and the World Heart Federation in 2007 for infarction associated with bypass surgery (19). BARI 2D and other trials used divergent definitions of periprocedural MI for PCI and surgery. We deliberately adopted the

Table 2 Primary and Secondary Endpoints

Endpoint	1-Year Occurrence Rate (%)		2-Year Occurrence Rate (%)		HR	95% CI
	CABG (n = 97)	PCI (n = 101)	CABG (n = 97)	PCI (n = 101)		
Death or nonfatal MI	16.9 (54%)*	10.6 (63%)	18.4 (53%)	25.3 (31%)	0.89	0.47–1.71
All-cause death	5.0 (62%)	8.2 (70%)	5.0 (62%)	21.0 (33%)	0.30	0.11–0.80
Cardiac death	5.0 (62%)	4.5 (69%)	5.0 (62%)	10.8 (32%)	0.53	0.16–1.77
All nonfatal MI	13.4 (54%)	2.6 (62%)	15.0 (53%)	6.2 (47%)	3.32	1.07–10.30
Periprocedural MI	4.2 (91%)	0.0 (101%)	4.2 (91%)	0.0 (101%)	—	—
Clinical MI	7.8 (58%)	2.6 (62%)	7.8 (58%)	6.2 (47%)	—	—
Silent MI	1.4 (73%)	0.0 (101%)	5.3 (40%)	0.0 (101%)	—	—
Stroke	1.2 (82%)	1.0 (100%)	1.2 (82%)	1.0 (100%)	1.03	0.06–16.49
Repeat revascularization	11.3 (56%)	11.6 (55%)	19.5 (26%)	18.9 (31%)	0.93	0.42–2.07
Using universal definition of PCI periprocedural MI						
Death or nonfatal MI	16.9 (54%)	11.6 (63%)	18.4 (53%)	32.0 (26%)	0.72	0.39–1.35
All nonfatal MI	13.4 (54%)	4.8 (62%)	15.0 (53%)	16.3 (24%)	1.34	0.58–3.11
Periprocedural MI	4.2 (91%)	2.3 (75%)	4.2 (91%)	10.1 (26%)	0.72	0.20–2.57
Clinical MI	7.8 (58%)	2.6 (62%)	7.8 (58%)	6.2 (47%)	1.59	0.45–5.62
Silent MI	1.4 (73%)	0.0 (101%)	5.3 (40%)	0.0 (101%)	—	—
Using universal definition of PCI periprocedural MI and no silent MIs						
Death or nonfatal MI	14.7 (54%)*	11.6 (63%)	14.7 (54%)	32.0 (26%)	0.59	0.30–1.15
All nonfatal MI	11.2 (54%)	4.8 (62%)	11.2 (54%)	16.3 (24%)	1.01	0.41–2.48
Periprocedural MI	4.2 (91%)	2.3 (75%)	4.2 (91%)	10.1 (26%)	0.72	0.20–2.57
Clinical MI	7.8 (58%)	2.6 (62%)	7.8 (58%)	6.2 (47%)	1.59	0.45–5.62

*Number of patients at risk.
CI = confidence interval; HR = hazard ratio. All other abbreviations as in Table 1.

surgical definition for both groups to avoid the appearance of biasing the trial by the definition of periprocedural MI. This resulted in a moderate risk for periprocedural MIs in the surgery group (4%) and no periprocedural MIs for PCI. This was accepted with the expectation of capturing "harder" endpoints later in the study. An unintended consequence was to exclude periprocedural MIs that occurred with repeat revascularization (Table 2). At 2-year follow-up, the composite endpoint would have been 18.4% in the surgery arm and 32% in the PCI arm, using the 2007 universal definitions of MI (Table 2). This 42.5% relative risk reduction is virtually identical to our projections.

A second factor is our aggressive search for silent MIs. Other studies have included silent MIs when discovered but have not mandated serial electrocardiography and nuclear studies. We believed that it was critical to identify and accurately time as many silent MIs as possible in a diabetic cohort. All of the silent MIs were found in the surgery arm. Possible explanations include small number effects, a potential for surgical "denervation" to blunt symptoms, and transforming larger MIs into smaller, asymptomatic ones. Silent MIs accounted for one-third of the total nonfatal MIs in the surgery arm, an effect that has not been reported elsewhere. Our study might best be compared with others with silent MIs excluded. Table 2 shows the risk for MI at 2 years when silent MIs are eliminated. The study would have had power of 76.9% for the composite endpoint eliminating silent MIs and using the 2007 universal definition for periprocedural MIs.

We looked for specific patient or angiographic characteristics that contributed to a higher mortality with PCI. The PCI arm contained more patients with previous PCI, a slightly higher degree of average lesion stenosis, and slightly longer average lesion length. Survival curves were reanalyzed adjusting for these variables, with no effect on the results. There were also more normal ventricular function scores in surgical patients. Comparing the distribution of left ventricular function in PCI survivors versus nonsurvivors reached statistical significance ($p = 0.04$), as did greater age (61.8 vs. 66.4 years, $p = 0.01$). Among PCI patients, moderate to severely impaired ventricular function resulted in mortality of 28.3% as opposed to 11.4% with no or mild dysfunction (relative risk: 2.49). There were trends toward greater beta-blocker use ($p = 0.07$) and lower body mass index ($p = 0.12$) in the nonsurvivors. Surprisingly, SYNTAX score did not affect outcomes in our patients. At baseline, the PCI arm had a higher percentage of patients with low SYNTAX scores than the surgical arm (Table 1), and the balance of SYNTAX scores among PCI survivors and nonsurvivors was virtually identical (Table 3). Low numbers and short follow-up limit our ability to make definitive statements about subsets that fare worse with PCI.

Our patient population was deliberately chosen to maximize survival effects over time. Coordinators screened all patients with diabetes presenting for diagnostic catheterization. Patients who had no indications for revascularization or who did not have territories at risk in the anterior wall were excluded. Many patients eligible for PCI in BARI 2D

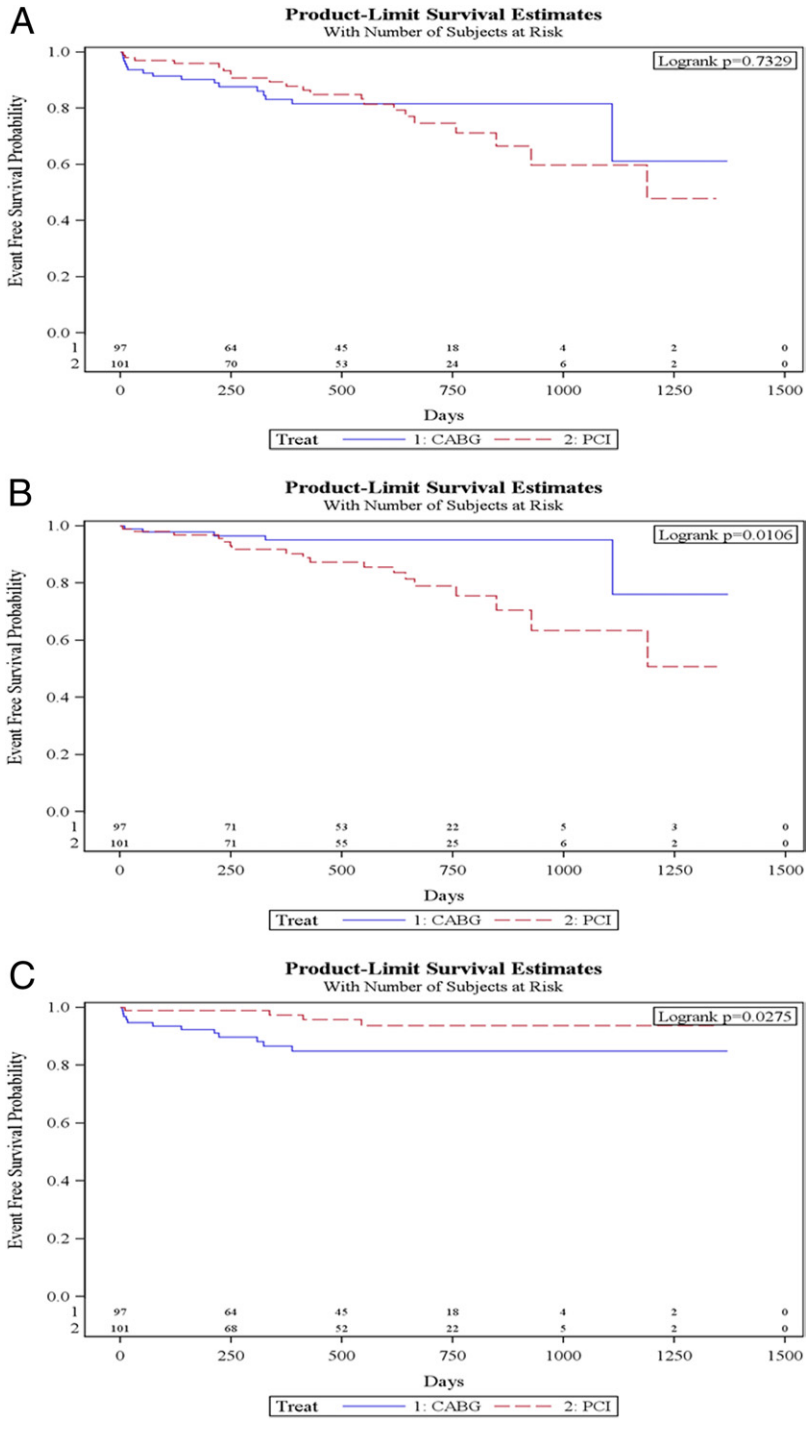

Figure 2 **Composite Endpoint, All-Cause Mortality, and Nonfatal MI**

(A) Time to first occurrence of nonfatal myocardial infarction (MI) or death by treatment group: Kaplan-Meier estimate of survival function. **(B)** Time to all-cause death by treatment group: Kaplan-Meier estimate of survival function. **(C)** Time to first occurrence of nonfatal MI by treatment group: Kaplan-Meier estimate of survival function.

were excluded by this screening. The remaining patients had left anterior descending coronary artery disease with or without disease in 1 or both other territories. There had to be at least 1 territory with either a ≥70% angiographic stenosis or objective evidence of ischemia. Evidence of ischemia included cardiac enzymes, stress testing, dynamic electrocardiographic changes, flow wire, or intracoronary ultrasound. This ensured that angiographically borderline

Table 3 Risk Factors for Adverse Outcome in PCI

Characteristic	Survivors (n = 83)	Nonsurvivors (n = 18)	p Value
Baseline variables			
Age (yrs)	61.8 ± 7.0	66.4 ± 6.6	0.01
Current smoker	22 (26.5%)	6 (33.3%)	0.31
BMI (kg/m^2)	33.2 ± 5.8	30.8 ± 5.9	0.12
MI			0.29
None	48 (57.8%)	7 (38.9%)	
Acute (<24 h)	1 (1.2%)	0 (0.0%)	
Recent (<4 days)	8 (9.6%)	1 (5.6%)	
Remote	26 (31.3%)	10 (55.6%)	
Previous PCI	28 (33.7%)	7 (38.9%)	0.79
Previous CABG	2 (2.4%)	1 (5.6%)	0.45
History of stroke	5 (6.0%)	2 (11.1%)	0.61
Total cholesterol (mg/dl)	154.3 ± 39.3	141.8 ± 38.5	0.22
HDL (mg/dl)	32.3 ± 8.8	34.8 ± 12.2	0.30
LDL (mg/dl)	84.5 ± 30.4	74.1 ± 24.7	0.20
Glucose (mg/dl)	158.5 ± 63.2	151.6 ± 50.5	0.67
HbA_{1c} (%)	8.0 ± 2.0	8.1 ± 1.9	0.86
Left ventricular ejection fraction			0.04
Normal (≥55%)	39 (54.2%)	5 (27.8%)	
Mild dysfunction (45%–54%)	22 (30.6%)	5 (27.8%)	
Moderate dysfunction (35%–44%)	6 (8.3%)	5 (27.8%)	
Severe dysfunction (25%–34%)	5 (6.9%)	3 (16.7%)	
Very severe dysfunction (<25%)	0 (0.0%)	0 (0.0%)	
Aspirin use	71 (85.5%)	16 (88.9%)	1.00
Clopidogrel or ticlopidine use	18 (21.7%)	6 (33.3%)	0.36
Statin use	74 (89.2%)	17 (94.4%)	0.69
Beta-blocker use	67 (80.7%)	18 (100.0%)	0.07
ACE inhibitor use	67 (80.7%)	17 (94.4%)	0.29
Insulin use	38 (45.8%)	10 (55.6%)	0.60
Oral antidiabetic medication use	66 (79.52%)	13 (72.22%)	0.53
Baseline angiography			
Chronic total occlusion	18 (23.1%)	5 (31.3%)	0.53
Bifurcation lesion	22 (29.7%)	8 (53.3%)	0.13
Stenosis	82.2 ± 8.5	80.9 ± 6.6	0.55
Lesion length (mm)	15.5 ± 7.2	15.8 ± 7.0	0.87
Total number of native lesions	3.6 ± 1.5	3.5 ± 1.9	0.77
>5 stents	13 (16.3%)	4 (23.5%)	0.49
Number of affected territories*			0.19
Single-vessel disease	10 (12.8%)	3 (18.8%)	
Double-vessel disease	21 (26.9%)	1 (6.3%)	
Triple-vessel disease	47 (60.3%)	12 (75.0%)	
Stenting			
Overlapping stents	28 (35.4%)	6 (35.3%)	1.00
>100 mm total stent length implanted	16 (20.0%)	3 (17.6%)	1.00
Stenting technique			0.75
Direct stenting	11 (13.9%)	1 (6.3%)	
Pre-dilation stenting	31 (39.2%)	8 (50.0%)	
Mix	37 (46.8%)	7 (43.8%)	
Successful revascularization rate	97.7	98.1	0.82
Follow-up			
Duration of aspirin therapy (days)	367 ± 15	376 ± 24	0.30
Duration of clopidogrel/ticlopidine (days)	365 ± 17	372 ± 25	0.33
Definite DES thrombosis	1 (1.2%)	2 (11.1%)	0.08

*7 patients (5 survivors and 2 non-survivors) had missing values due to the form changes after data collection.

DES = drug-eluting stent. All other abbreviations as in Table 1.

cases had a clear indication for revascularization. The Fractional Flow Reserve Versus Angioplasty for Multivessel Evaluation trial showed the importance of objective evidence of flow restriction in borderline stenoses (20). Our trial focused on high-risk patients, those with diabetes in whom aggressive coronary disease progression was combined with severe existing lesions. We expected to have the greatest difference in survival with revascularization compared with aggressive medical therapy, in contrast to BARI 2D, in which medical management was a reasonable option. Relaxing our entry criteria to include more patients would have also reduced the expected differences in survival and thus necessitated a much larger sample size to identify a survival effect of revascularization.

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Key Words: coronary artery bypass surgery ■ diabetes ■ percutaneous coronary intervention.

APPENDIX

For a complete listing of the members of the VA CARDS, please see the online appendix.