

ORIGINAL INVESTIGATIONS

Coronary Artery Bypass Surgery Improves Outcomes in Patients With Diabetes and Left Ventricular Dysfunction



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ABSTRACT

BACKGROUND The role of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients with diabetes mellitus (DM) and multivessel coronary artery disease (CAD) has been established by large trials; however, these trials largely excluded patients with left ventricular dysfunction (LVD).

OBJECTIVES The aim of this study was to determine whether treatment with PCI or CABG leads to improved outcomes in patients with DM, CAD, and LVD.

METHODS In this propensity-matched study, outcomes were compared for patients with CAD, DM, and LVD treated with PCI or CABG between 2004 and 2016. The primary outcome was major adverse cardiac and cerebrovascular events, defined as the composite of death, stroke, myocardial infarction, and repeat revascularization. Secondary outcomes were the individual components of the primary outcome.

RESULTS PCI compared with CABG was associated with a higher risk for major adverse cardiac and cerebrovascular events in cohorts with ejection fraction (EF) 35% to 49% ($p < 0.001$) and $<35%$ ($p < 0.001$). Treatment with PCI was associated with an increased risk for death in both the EF 35% to 49% and the EF $<35%$ cohorts. Stroke rate did not differ between PCI and CABG in either EF cohort. PCI was associated with an increased rate of MI in the EF $<35%$ cohort, and repeat revascularization occurred more frequently in patients treated with PCI in both the EF 35% to 49% cohort and the EF $<35%$ cohort.

CONCLUSIONS At long-term follow-up, patients with CAD, DM, and LVD treated with CABG exhibited a significantly lower incidence of major adverse cardiac and cerebrovascular events and better long-term survival over PCI, without a higher risk for stroke. (J Am Coll Cardiol 2018;71:819-27) © 2018 by the American College of Cardiology Foundation.

Patients with diabetes mellitus (DM) are at a 2- to 4-fold increased risk for developing coronary artery disease (CAD). Multivessel CAD is the main cause of mortality in this population of patients (1). Furthermore, patients with DM and moderate (ejection fraction [EF] 35% to 49%) or severe

(EF $<35%$) left ventricular dysfunction (LVD) represent a growing clinical challenge.

Many randomized trials and observational studies have shown that both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients with CAD are associated with



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Manuscript received September 12, 2017; revised manuscript received November 14, 2017, accepted December 11, 2017.

**ABBREVIATIONS
AND ACRONYMS****CABG** = coronary artery bypass grafting**CAD** = coronary artery disease**CI** = confidence interval**DM** = diabetes mellitus**EF** = ejection fraction**HR** = hazard ratio**LVD** = left ventricular dysfunction**LVEF** = left ventricular ejection fraction**MACCE** = major adverse cardiac and cerebrovascular event**MI** = myocardial infarction**PCI** = percutaneous coronary intervention

improved survival compared with medical treatment (2,3). Several randomized trials comparing survival after PCI and CABG in patients with DM have been performed, but the proportion of patients with LVD was not reported or these patients were underrepresented in these trials (4-6). The most notable of these trials is the FREEDOM (Future Revascularization in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial. The FREEDOM trial demonstrated that in patients with CAD and DM, CABG resulted in a reduced rate of death and myocardial infarction (MI) compared with PCI. However, in these trials, patients with LVD were underrepresented. In fact, only 3% of patients enrolled in the FREEDOM trial had LVD; consequently, there was no evidence of a statistically significant interaction between

LVD and the treatment benefit of CABG in the subgroup analysis. Several studies examining the role of CABG in patients with CAD and LVD have been performed (7-9). Results of the STICHES (Surgical Treatment for Ischemic Heart Failure—Extension Study) trial have provided valuable insight into the long-term survival of patients with LVD treated with medical therapy or CABG (7). There was no evidence of a statistically significant interaction between DM and the treatment benefit of CABG in STICHES, but this comparison was underpowered, as <40% of STICHES participants had DM. As a result, the subgroup analysis in patients with both DM and LVD did not reach statistical significance for all-cause mortality (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.67 to 1.04).

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Furthermore, because randomized trial participants are highly selected and tend to have better prognoses than patients managed outside trial settings, the extent to which trial results translate into clinical practice is uncertain. The purpose of this study was to review the long-term results of PCI and CABG in nontrial patients with CAD, DM, and LVD by performing a propensity-matched study using a database that captures all cardiac catheterizations in an entire Canadian province. We also sought to analyze the rate of death, stroke, MI, and repeat revascularization after PCI and CABG.

METHODS

DATA SOURCE. The APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) database, in addition to linkage to the

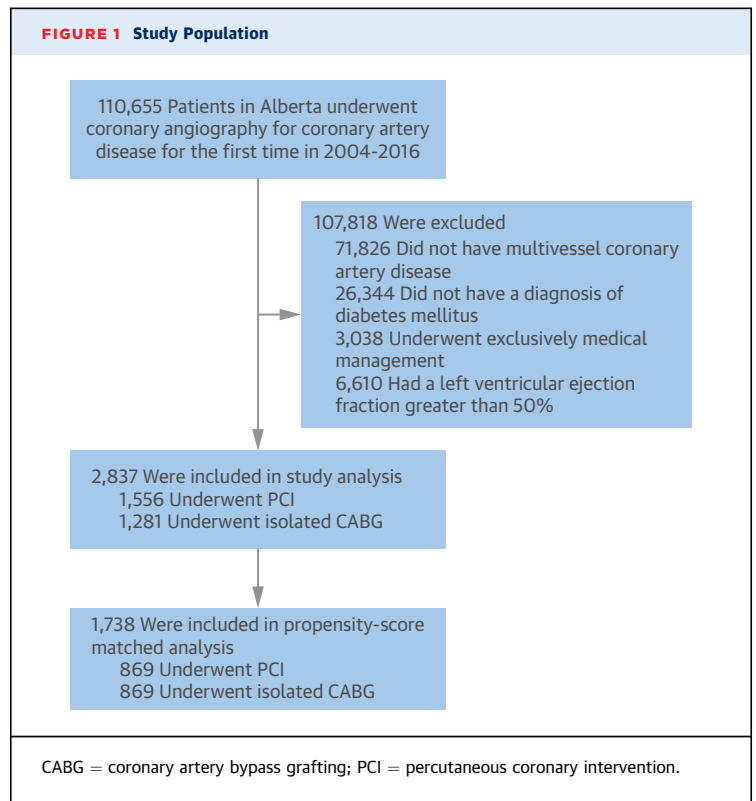
discharge abstract database and other administrative ambulatory databases to detect events after discharge and at other hospitals, was used to obtain all data. The APPROACH database is a prospective data collection initiative that acquires detailed clinical information on all patients undergoing coronary angiography in Alberta, a Canadian province with a population of approximately 4.3 million. Patients are enrolled into the registry at the time of angiography from all 3 hospital sites that provide cardiac catheterization in the province of Alberta since 1995. These patients are followed prospectively for outcomes, including subsequent revascularization and death. Details of this database have been previously described (10).

STUDY COHORT. In this study, DM was identified from cardiac catheterization requisitions through data collection and defined as having a glycosylated hemoglobin level >6.5% from the APPROACH database. Left ventricular EF (LVEF) was measured at the time of catheterization and/or echocardiography. If both modalities were performed, LVEF was defined from the coronary angiogram. Included in this study were patients with multivessel CAD, DM, and LVD who underwent isolated CABG without a concomitant procedure or PCI in Alberta between January 1, 2004, and March 31, 2016 (Figure 1). Patients undergoing concomitant cardiac surgery, transplant recipients, and those undergoing emergency surgery were excluded from this cohort. Drug-eluting stents became available in Alberta on a limited basis in 2003 and were more widely available by 2004. Once availability was widespread, drug-eluting stents became the preferred choice over bare-metal stents for high-risk cases such as those described in this study. Outcomes were measured over a 12-year span, with a mean follow-up duration of 5.5 years.

OUTCOMES. The primary outcome of this study was the combined endpoint of major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of death, stroke, MI, and repeat revascularization. Secondary outcomes assessed included rates of death, stroke, MI, and repeat revascularization. All outcomes were collected during admission for the index procedure and after discharge, being identified on the basis of admitting diagnosis for any readmission. MI was defined as being diagnosed at readmission with a primary diagnosis of non-ST-segment elevation MI or ST-segment elevation MI at any time after the index procedure. Stroke included both hemorrhagic and ischemic mechanisms and was defined as occurring during the index hospitalization or being the primary diagnosis of readmission at any time after the index procedure. Repeat

revascularization was identified as any unstaged revascularization after the index procedure. Distinction between events that occurred during the index hospitalization and those that occurred after discharge could not be obtained from the data.

STATISTICAL ANALYSIS. Baseline categorical variables were compared between the 2 groups using chi-square tests for categorical data and Student's *t*-tests to compare continuous baseline characteristics of PCI- versus CABG-treated patients. As in all non-randomized studies, the direct comparisons of distinct groups may be misleading because the groups generally differ systematically. To obtain a comparable distribution of demographic characteristics, comorbidities, and clinical variables among low-EF patients who underwent PCI compared with patients with low EFs who underwent CABG, we used the Rosenbaum and Rubin propensity-score-matching technique (11). The propensity score was calculated as the probability of having undergone CABG conditional on the observed baseline (measured at recruitment) characteristics. This technique allows a large number of confounding variables and has been used to create a stratum of subjects who can be matched on the propensity score whereby exposure (CABG) is not confounded with measured baseline covariates. The propensity score was calculated using logistic regression (C-statistic = 0.812) (Online Figure 1). The following variables were included in the model: age, sex, pulmonary disease, cerebrovascular disease, renal disease, congestive heart failure, current smoker, prior smoker, dialysis, hypertension, hyperlipidemia, liver or gastrointestinal disease, malignancy, peripheral vascular disease, prior MI, prior PCI, prior CABG, prior lytic therapy, prior acute coronary syndrome, prior ST-segment elevation MI, prior non-ST-segment elevation MI, and indication for catheterization, including MI, stable angina, unstable angina, or other. Greedy matching techniques were applied to match patients 1:1 who were treated with CABG to patients whose index treatment was PCI by matching the participants with the nearest propensity score, namely, within 3 decimal places of the propensity score for each case. Overlap of propensity scores between PCI and CABG patients was evaluated using histograms (Online Figures 2 and 3), chi-square values (Online Figures 4 and 5), and probability values (Online Figures 6 and 7). Differences in baseline factors between groups were calculated before and after propensity adjustment to assess balance. After the match, Kaplan-Meier curves and log-rank tests were used to determine if there were statistically significant differences in the primary and secondary outcomes between PCI and CABG patients at follow-up available in APPROACH.



Similarly, Cox regression analysis was used to test whether there were statistically significant differences in the primary and secondary outcomes between PCI and CABG patients following adjustment for all clinical and comorbid variables.

RESULTS

STUDY POPULATION. The study sample included 2,837 consecutive patients with multivessel CAD (involving 2 or 3 coronary arteries or left main CAD), DM, and LVD (EF <50%) who underwent cardiac catheterization in the province of Alberta between January 1, 2004, and March 31, 2016 (Figure 1). Of these patients, 1,556 underwent PCI and 1,281 underwent CABG. Baseline demographic data before and after propensity score matching are summarized in Table 1. Significant statistical differences between groups prior to propensity score matching included a higher prevalence of male sex, as well as chronic obstructive pulmonary disease, symptomatic heart failure, smoking history, hypertension, and dyslipidemia among patients who underwent CABG. Patients undergoing PCI had a higher prevalence of prior CABG surgery, prior lytic therapy, prior acute coronary syndrome, and prior ST-segment elevation MI. In terms of the indication for the index cardiac

TABLE 1 Baseline Characteristics Before and After Propensity Matching

	Before Matching			After Matching		
	PCI (n = 1,556)	CABG (n = 1,281)	p Value	PCI (n = 869)	CABG (n = 869)	p Value
Age, yrs	64.6 ± 11.4	65.6 ± 9.5	0.007	65.1 ± 10.8	65.1 ± 9.5	0.94
Female	25	20	<0.001	23	21	0.45
Pulmonary disease	14	17	0.02	17	17	0.75
Cerebrovascular disease	6	6	0.86	7	7	0.77
Renal disease	8	6	0.18	7	7	0.57
Symptomatic heart failure	19	27	<0.001	23	27	0.023
Smoker, current	19	19	0.89	18	20	0.24
Smoker, ever	18	27	<0.001	22	27	0.016
Dialysis	3	2	0.23	3	3	0.57
Hypertension	79	85	<0.001	83	85	0.40
Hyperlipidemia	71	84	<0.001	80	82	0.16
Liver/gastrointestinal disease	1	1	0.10	1	2	0.53
Malignancy	4	3	0.17	4	3	0.51
Peripheral vascular disease	8	9	0.62	9	8	0.48
Prior PCI	4	4	0.51	4	4	1.00
Prior CABG	5	1	<0.001	3	2	0.25
Prior lytic therapy	7	2	<0.001	4	3	0.69
Prior ACS	78	56	<0.001	67	60	0.01
Prior STEMI	43	14	<0.001	18	18	0.76
Prior NSTEMI	29	29	0.77	35	30	0.012
Indication for catheterization			<0.001			0.67
Myocardial infarction	49	37		42	40	
Stable angina	16	33		25	30	
Unstable angina	31	20		27	21	
Other	4	10		6	9	

Values are mean ± SD or %.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

catheterization, more CABG patients had stable angina, while more PCI patients had unstable angina or current MI. The PCI and CABG groups were quite different, and thus, comparing these groups before propensity matching would not be a valid comparison. **Table 1** summarizes the baseline characteristics after propensity matching 1,738 patients and demonstrates that the groups were evenly balanced on prognostic factors. Of these 1,738 patients, 973 (56%) had EFs of 35% to 49%, and 765 (44%) had EFs <34%. Variables of statistical significance following propensity matching include symptomatic heart failure, favoring PCI, and prior acute coronary syndrome, favoring CABG surgery.

PRIMARY OUTCOME. In patients with EFs of 35% to 49%, the frequency of MACCE with PCI versus CABG was 51% versus 28% ($p < 0.001$) at 5 years (**Central Illustration**). In patients with EFs <35%, MACCE frequencies for PCI versus CABG treatment were 61% versus 29% ($p < 0.001$) at 5 years (**Central Illustration**). Cox proportional hazard analysis demonstrated that over a mean follow-up period of 50 months, PCI was

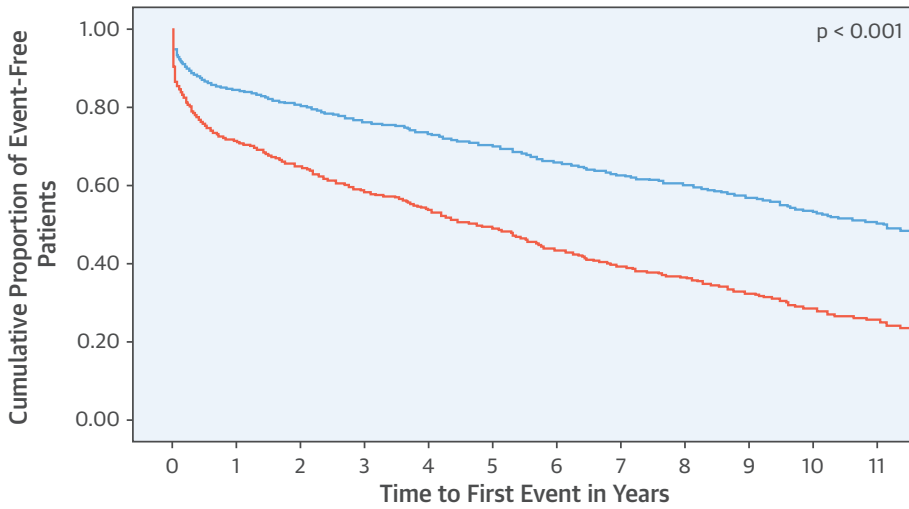
associated with a significantly higher risk for a MACCE compared with CABG in both the EF 35% to 49% (HR: 1.97; 95% CI: 1.64 to 2.35; $p < 0.001$) and EF <35% (HR: 2.28; 95% CI: 1.79 to 2.90; $p < 0.001$) cohorts (**Table 2**).

SECONDARY OUTCOMES. In patients with EFs of 35% to 49%, the mortality rate with PCI versus CABG was 26% versus 16% ($p = 0.001$) at 5 years (**Figure 2**). In patients with EFs <35%, the mortality rate for PCI versus CABG was 35% versus 19% ($p = 0.002$) at 5 years (**Figure 3**). Cox proportional hazard analysis demonstrated that over a mean follow-up period of 63 months, PCI was associated with a significantly higher risk for death compared with CABG in both the EF 35% to 49% (HR: 1.34; 95% CI: 1.07 to 1.68; $p = 0.01$) and EF <35% (HR: 1.62; 95% CI: 1.20 to 2.22; $p = 0.002$) cohorts (**Table 2**). The risk for stroke, MI, and repeat revascularization after PCI and CABG is summarized in **Table 2**. A Kaplan-Meier analysis of these outcomes was performed and is depicted in **Figure 2** for the EF 35% to 49% cohort and **Figure 3** for the EF <35% cohort. In patients with EFs of 35% to 49%, the frequency of stroke with PCI versus CABG was 4% versus 3% ($p = 0.663$) at 5 years (**Figure 2**). In patients with EFs <35%, stroke frequencies for PCI versus CABG treatment were 4% versus 3% ($p = 0.630$) at 5 years (**Figure 3**). Cox proportional hazard analysis demonstrated that over a mean follow-up period of 62 months, stroke rates did not differ between PCI and CABG in either the EF 35% to 49% (HR: 1.01; 95% CI: 0.57 to 1.78; $p = 0.98$) or EF <35% cohort (HR: 0.87; 95% CI: 0.39 to 1.91; $p = 0.72$) (**Table 2**). The risk for MI at a mean follow-up of 53 months did not differ between PCI and CABG in the EF 35% to 49% cohort (HR: 1.23; 95% CI: 0.87 to 1.76; $p = 0.25$); however, PCI was associated with a greater risk for MI in the EF <35% cohort (HR: 2.27; 95% CI: 1.38 to 3.75; $p = 0.001$). The rate of revascularization at a mean follow-up of 54 months after index procedure was significantly greater in those treated with PCI over CABG in both the EF 35% to 49% (HR: 5.46; 95% CI: 3.80 to 7.78; $p < 0.001$) and EF <35% (HR: 7.31; 95% CI: 4.08 to 13.1; $p < 0.001$).

SENSITIVITY ANALYSIS. Several significant differences between the PCI and CABG groups existed after propensity matching, including symptomatic heart failure, prior acute coronary syndrome, past smoking history, and diagnosis of ST-segment elevation MI. To determine if these differences would influence the results of this study, sensitivity analyses were performed. We adjusted for the variables that remained significantly different, and our results remained unchanged. Furthermore, because the study occurred over a significant amount of time, models were also

CENTRAL ILLUSTRATION CABG Improves Outcomes in Patients With Diabetes and LVD

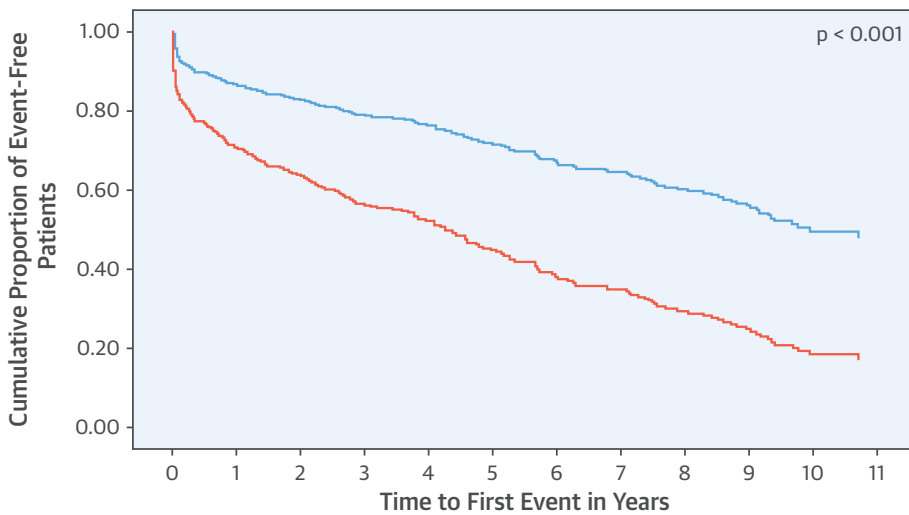
A MACCE



Number at Risk

PCI	457	314	287	247	193	169	140	100	74	58	35	19
CABG	516	446	421	385	340	295	247	214	183	146	103	68

B MACCE



Number at Risk

PCI	412	237	170	84	73	58	41	32	21	15	8	3
CABG	353	264	206	146	133	115	95	88	72	59	33	20

First Treatment Post Index Cath — CABG — PCI

Nagendran, J. et al. J Am Coll Cardiol. 2018;71(8):819-27.

Freedom from major adverse cardiac and cerebrovascular events (MACCE) during the study period in the ejection fraction (EF) 35% to 49% (A) and EF <math>< 35\%</math> (B) cohorts. Percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG) was associated with a higher risk for the composite endpoint of MACCE in both the EF 35% to 49% ($p < 0.001$) and EF <math>< 35\%</math> ($p < 0.001$) cohorts. cath = catheterization; LVD = left ventricular dysfunction.

TABLE 2 Risk of Primary and Secondary Outcomes in the Propensity-Matched Cohort

Outcome	Hazard Ratio, PCI:CABG	95% CI		p Value
		Lower	Upper	
EF 35%–49%				
MACCE	1.97	1.64	2.35	<0.001
Death	1.34	1.07	1.68	0.01
Stroke	1.01	0.57	1.78	0.98
Myocardial infarction	1.23	0.87	1.76	0.25
Repeat revascularization	5.46	3.80	7.78	<0.001
EF <35%				
MACCE	2.28	1.79	2.90	<0.001
Death	1.62	1.20	2.22	0.002
Stroke	0.87	0.39	1.91	0.72
Myocardial infarction	2.27	1.38	3.75	<0.001
Repeat revascularization	7.31	4.08	13.10	<0.001

CI = confidence interval; EF = ejection fraction; MACCE = major adverse cardiac and cerebrovascular event (a composite of death, stroke, myocardial infarction and repeat revascularization); other abbreviations as in Table 1.

adjusted for year of procedure to determine if there were changes over the years of the study period, and no changes were noted in any of the results. The results of the adjusted model can be found in [Online Table 1](#).

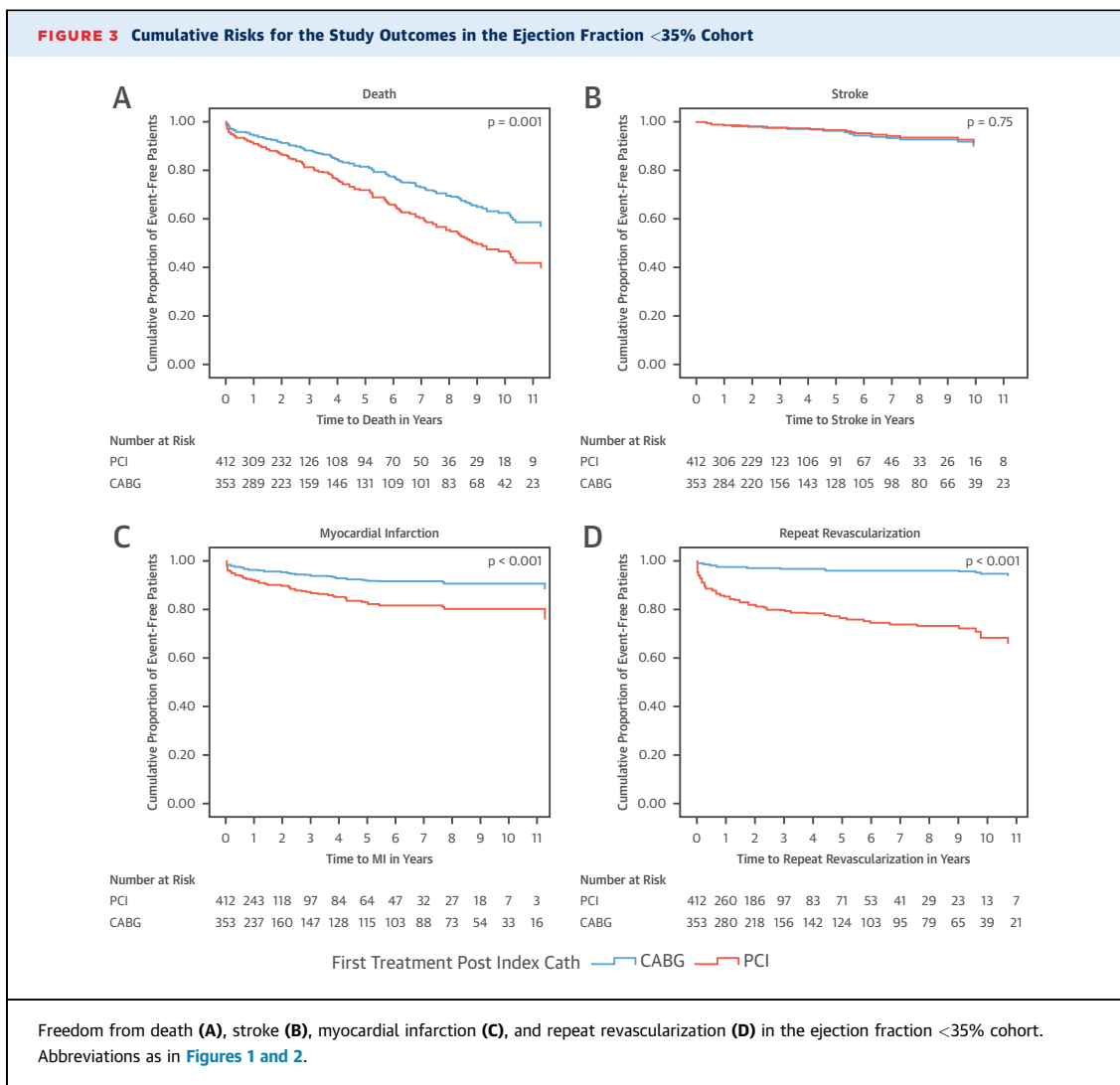
DISCUSSION

Although previous studies have established the role of both PCI and CABG in patients with normal EFs, CAD, and DM (12), the present work provides data on patients with CAD, DM, and LVD. First, the results showed that in both moderate and severe LVD, PCI is associated with an increased risk for MACCE compared with CABG (**Central Illustration**). Second, the results showed that in patients with CAD, DM, and moderate or severe LVD, PCI is associated with poorer long-term survival compared with CABG. Third, PCI is associated with an increased risk for MI in severe LVD and an increased risk for repeat revascularization in both moderate and severe LVD. Finally, the results showed that there was no significant difference in incidence of stroke between PCI and CABG in both the moderate and severe LVD cohorts.

These results are consistent with those of several studies examining revascularization in patients with CAD and DM (3–6,13). Kapur et al. (3) showed a trend toward improved outcomes in patients treated with CABG in 510 patients with DM, but the mean LVEF was 60%, and only 1% of patients had severe LVD. The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial enrolled 452 patients with DM and multivessel CAD, demonstrating a significant survival benefit

when treated with CABG (12). The mean LVEF was not reported in that study, while only 3% of patients had severe LVD (EF <30%). Kamalesh et al. (2) performed a small, underpowered study suggesting an advantage to treatment with CABG in 207 veterans with DM and CAD. In their study cohort, 7% had LVEFs <35%, but the mean LVEF was not reported. Most recently, in the FREEDOM trial by Farkouh et al. (4), CABG was demonstrated to provide significantly reduced rates of death and MI compared with PCI in 1,900 patients. These patients had a mean LVEF of 66%, with 3% having LVEFs <40%. Ahn et al. (14) recently compared long-term survival after CABG versus complete and incomplete PCI by performing a retrospective pooled analysis of SYNTAX, PRECOMBAT, and BEST. They found no significant difference in median 5-year survival between patients undergoing CABG and those undergoing PCI with complete revascularization, with subgroup analysis of multivessel CAD and DM showing consistent findings. The main limitation continues to be the underrepresentation of patients with LVD. Addressing the lack of LVD in these revascularization studies was the objective of the present study: to examine the effect of LVD specifically in patients with DM undergoing revascularization.

In the present study, it is worth noting that the 5-year mortality rate of patients with EFs <35% undergoing CABG was 19%. The very acceptable CABG survival data contrasts with results from the Surgical Treatment for Ischemic Heart Failure (STICH) trial, in which the 5-year mortality of patients undergoing CABG was much higher at 36% (7). This finding may suggest the possibility of more stringent selection of patients for CABG, but in the context of a propensity-matched analysis, this bias should be mitigated and compared with validity to the PCI mortality of 35% at 5 years in this study. Another difference between STICH and the present study is that the higher CABG mortality in STICH may have been due to the inclusion of patients with dyskinetic myocardium at baseline. In our cohort, the presence of a dyskinetic segment of myocardium was not a specific inclusion criterion. Hence patients undergoing CABG may have had LVD secondary to hypokinetic or akinetic segments, representing recruitable hibernating myocardium, which may have led to improved long-term survival in this study. Furthermore, comparisons between our study population and that of STICH are further limited because patients with recent MI as a precipitant of LVD were excluded in STICH, whereas patients with acute coronary syndromes accounted for >60% of our study population. The inclusion of patients with



with DM with normal EFs, while the stroke risk in CABG patients remained unchanged.

STUDY LIMITATIONS. Although patients in both intervention cohorts were propensity matched to account for variation in baseline characteristics, propensity matching cannot control for every confounding variable. This is especially true regarding variables not reported in the APPROACH database, which may still influence clinical decision making, such as patient frailty or goals of care designation. It has been noted that propensity-score matching allows one to analyze an observational study so that it mimics some of the characteristics of a randomized controlled trial (15). Despite propensity matching in this study, the PCI and CABG groups differed in prevalence of symptomatic heart failure

(23% vs. 27%, $p = 0.02$) and prior acute coronary syndromes (67% vs. 60%, $p = 0.01$) that may have introduced a small systematic bias favoring one arm over the other.

Second, data were collected over a 12-year time span. During this time, both treatment arms were subject to change in technologies and clinical practice, potentially influencing our study results. The introduction and increased use of drug-eluting stents in PCI, and advancements in anesthesia, post-operative care, and surgical technique in CABG may have affected long-term survival (16). Although we did not have information on the type of stent deployed in patients undergoing PCI, a prior systematic review (13) suggested little difference in outcomes other than repeat revascularization between drug-eluting and bare-metal stents.

CONCLUSIONS

Although the published research currently supports the use of CABG over PCI for patients with DM with multivessel disease, the randomized trials have largely enrolled only those with normal ventricular function. Thus, our finding that CABG is associated with better outcomes than PCI in patients with CAD, DM, and LVD addresses a gap in the research. This study provides the first data to suggest that patients who have CAD, DM, and LVD benefit from CABG, as it offers a long-term overall survival benefit, reduced risk for MI and repeat revascularization, and no increased rate of stroke compared with PCI for this subgroup of patients. Apart from those patients who have prohibitive surgical risk or technical factors limiting surgical revascularization, CABG should be considered first-line therapy for the treatment of multivessel CAD in patients with DM and LVD.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: In patients with diabetes mellitus, multivessel CAD, and LVD, CABG surgery generally improves clinical outcomes more than catheter-based revascularization.

TRANSLATIONAL OUTLOOK: Because factors such as frailty may confound this propensity-matched analysis, further studies are needed to compare the outcomes of CABG and PCI in subgroups of patients defined by specific comorbidities.

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KEY WORDS diabetes mellitus, ischemic cardiomyopathy, revascularization

APPENDIX For a supplemental table and figures, please see the online version of this article.