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ORIGINAL INVESTIGATIONS

Long-Term Survival After Surgical or Percutaneous Revascularization in Patients With Diabetes and Multivessel Coronary Disease

Derrick Y. Tam, MD, PhD,[a,b] Christoffer Dharma, MSc,[c] Rodolfo Rocha, MD, PhD,[d] Michael E. Farkouh, MD,[e] Husam Abdel-Qadir, MD, PhD,[b,c,f] Louise Y. Sun, MD, SM,[g] Harindra C. Wijeysundera, MD, PhD,[b,h] Peter C. Austin, PhD,[c] Jacob A. Udell, MD, MPH,[b,c,e,f] Mario Gaudino, MD,[i] Stephen E. Fremes, MD, MSc,[a,*] Douglas S. Lee, MD, PhD[b,c,e,*]

ABSTRACT

BACKGROUND There remains a paucity of real-world observational evidence comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in patients with diabetes and multivessel coronary artery disease (CAD).

OBJECTIVES This study compared early and long-term outcomes of PCI versus CABG in patients with diabetes.

METHODS Clinical and administrative databases in Ontario, Canada were linked to obtain records of all patients with diabetes with angiographic evidence of 2- or 3-vessel CAD who were treated with either PCI or isolated CABG from 2008 to 2017. A 1:1 propensity score match was performed to account for baseline differences. All-cause mortality and the composite of myocardial infarction, repeat revascularization, stroke, or death (termed major cardiovascular and cerebrovascular events [MACCEs]) were compared between the matched groups using a stratified log-rank test and Cox proportional hazards model.

RESULTS A total of 4,519 and 9,716 patients underwent PCI and CABG, respectively. Before matching, patients who underwent CABG were significantly younger (age 65.7 years vs. 68.3 years), were more likely to be men (78% vs. 73%) and had more severe CAD. Propensity score matching based on 23 baseline covariates yielded 4,301 well-balanced pairs. There was no difference in early mortality between PCI and CABG (2.4% vs. 2.3%; $p = 0.721$) after matching. The median and maximum follow-ups were 5.5 and 11.5 years, respectively. All-cause mortality (hazard ratio [HR]: 1.39; 95% CI: 1.28 to 1.51) and overall MACCEs (HR: 1.99; 95% CI: 1.86 to 2.12) were significantly higher with PCI compared with CABG.

CONCLUSIONS In patients with multivessel CAD and diabetes, CABG was associated with improved long-term mortality and freedom from MACCEs compared with PCI. (J Am Coll Cardiol 2020;76:1153–64) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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From the [a]Division of Cardiac Surgery, Department of Surgery, Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [b]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; [c]ICES, Toronto, Ontario, Canada; [d]Division of Cardiac Surgery, Department of Surgery, Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada; [e]Division of Cardiology, Department of Medicine, Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada; [f]Division of Cardiology, Department of Medicine, Women's College Hospital, University of Toronto, Toronto, Ontario, Canada; [g]Department of Anesthesiology and Pain Medicine, University of Ottawa Heart Institute; ICES, Ottawa, Ontario, Canada; School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada; [h]Division of Cardiology, Department of Medicine,

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ABBREVIATIONS AND ACRONYMS

ARD = absolute risk difference

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CI = confidence interval

CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database

HR = hazard ratio

LAD = left anterior descending

MACCE = major adverse cardiac and cerebrovascular event

PCI = percutaneous coronary intervention

Clinical trials in the late 1990s to early 2000s that compared percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) demonstrated improved outcomes with CABG in patients with diabetes in post hoc subgroup analyses. The BARI (Bypass Angioplasty Revascularization) trial showed a mortality benefit with CABG compared with balloon angioplasty, whereas the ARTS-I (Arterial Revascularization Therapy Study) trial demonstrated a higher incidence of repeated revascularization with PCI over CABG (1,2). Subgroup analyses of the BARI-2D trial showed that patients with diabetes who underwent surgical revascularization had fewer major adverse cardiac events than medical therapy (3). Similarly, a subgroup analysis of patients with diabetes in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial showed both a reduction in repeat revascularization and major adverse cardiac and cerebrovascular events (MACCEs) with CABG over PCI (4).

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The FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Diseases) trial was designed to compare PCI performed using drug-eluting stents with CABG in patients with diabetes and multivessel disease (5). The trial randomized 1,900 patients with diabetes to intervention with PCI with drug-eluting stents or CABG and demonstrated a mortality benefit and reduced risk of nonfatal myocardial infarction that favored CABG. The FREEDOM trial led to a change in the 2014 American Heart Association/American College of Cardiology guideline recommendations for the revascularization of stable ischemic heart disease, indicating that patients with diabetes and complex 3- or 2-vessel disease with proximal left anterior descending (LAD) artery involvement, who were good surgical candidates, should be treated with CABG (2012: Class IIa, Level of Evidence: B to 2014: Class I, Level of Evidence: B) (6). Similar recommendations were also made in 2014 in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery European guidelines, with a higher level of evidence in their recommendation for CABG over PCI in patients with diabetes and multivessel disease (Class I, Level of Evidence: A) (7). Recently, the FREEDOM follow-up study demonstrated improved survival with CABG at a mean 7.5 years of follow-up in the original FREEDOM cohort (8).

Despite strong evidence from randomized clinical trials that supported the use of CABG over PCI in patients with diabetes and multivessel disease, it remains unclear if the efficacy observed in randomized clinical trials translates to comparative effectiveness in the more heterogeneous population in real-world practice. Our objective was to compare the primary outcome of long-term mortality and the secondary outcome of a composite of long-term MACCEs at the population level between PCI and CABG in patients with diabetes and multivessel coronary artery disease (CAD).

METHODS

STUDY DESIGN. We conducted a retrospective analysis of records for all patients in Ontario, Canada, who had invasive coronary angiography from

Schulich Heart Centre, University of Toronto, Toronto, Ontario, Canada; and the [i]Department of Cardiothoracic Surgery, Weill Cornell Medical College, New York, New York. *Drs. Fremes and Lee contributed equally to this work. This study was supported by a Foundation Grant from the Canadian Institutes of Health Research (grant # FDN 148446). The opinions, results, and conclusions are those of the authors and no endorsement by the Ministry of Health and Long-Term Care or by ICES is intended or should be inferred. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the authors, and not necessarily those of CIHI. Dr. Tam was supported by a CIHR Fellowship. Dr. Rocha is supported by the Black Family Foundation Fellowship Award. Dr. Farkouh has received research grants from Amgen, Novo Nordisk, and Novartis. Dr. Abdel-Qadir has served on the endpoint adjudication committee for the THEMIS trial funded by AstraZeneca. Dr. Austin is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation. Dr. Fremes is supported by the Bernard S. Goldman Chair in Cardiovascular Surgery. Dr. Sun is supported by the University of Ottawa Heart Institute Research Corporation and the Tier 2 Clinical Research Chair in Big Data and Cardiovascular Outcomes at the University of Ottawa. Dr. Lee is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation; and is the Ted Rogers Chair in Heart Function Outcomes, a joint University-Hospital Chair of University of Toronto and University Health Network. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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October 1, 2008 to December 31, 2018 and who subsequently underwent revascularization with CABG or PCI within 90 days of the index angiography. Clinical registries of all patients who underwent angiography, CABG, and PCI were linked to multiple population-based health databases using patient-level encrypted health card numbers at ICES. As a prescribed entity under Ontario's Personal Health Information Protection Act, ICES is able to collect, to construct, and to store registries, as well as link and analyze individual health data without the need to obtain individual patient consent. Therefore, we were able to study all patients who underwent these revascularization procedures without participation bias. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. These datasets were linked using unique encoded identifiers and analyzed at ICES.

DATA SOURCES. Similar to previously published studies, coronary angiography records were obtained from the CorHealth Ontario Registry (9,10). Baseline demographics were obtained from the CorHealth Registry, Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD), or previously validated algorithms, where applicable (11). Hospitalizations and the primary admission diagnoses were determined via the CIHI-DAD, using the International Classification of Diseases-10th edition coding system, as previously described (12). Deaths were determined using the Registered Persons Database, which contains vital status information for all Ontarians. In-hospital deaths were determined using a combination of the Registered Persons Database and CIHI-DAD. Physicians' claims for procedures were determined using the Ontario Health Insurance Plan fee billing database. The Ontario Diabetes Database was used to identify patients with diabetes, as previously described (12). We used Statistics Canada's census data to determine sociodemographic information based on median neighborhood income of individuals, to serve as a proxy for socioeconomic status.

STUDY POPULATION AND DATA LINKAGES. Significant coronary artery narrowing in the CorHealth angiographic database was defined as ≥70% for all coronary arteries, with the exception of the left main artery, in which ≥50% was considered a significant narrowing (9). In our primary analysis, we included only patients with pre-existing diabetes and significant multivessel disease, defined as: 2-vessel disease consisting of proximal left anterior descending (LAD) artery and either circumflex disease or right coronary artery disease; or 3-vessel disease involving the LAD, circumflex, and right coronary artery. Patients with significant left main disease were excluded in the primary analysis to be consistent with the coronary anatomic inclusion criteria in the FREEDOM trial but were included in a secondary analysis to examine the robustness of our findings. In patients with >1 coronary angiogram, we used the first angiogram that demonstrated 1 of the preceding disease patterns as the index angiogram.

Since patients could undergo revascularization after some time passed after angiography (e.g., due to the need for surgical or interventional consultation after an elective angiogram), we assigned patients who underwent CABG within 90 days after angiography to the CABG cohort and those who underwent PCI within 90 days to the PCI cohort; whichever procedure occurred first was considered the index procedure. Those who did not undergo CABG or PCI within 90 days were considered medically managed and were excluded from the analysis. Patients who underwent another concomitant cardiac operation (e.g., valve procedures and aortic surgery) and those who underwent transaortic valve replacement following the index CABG or PCI were excluded to ensure that patients were comparable in terms of procedural risk. For all patients, we excluded those with a history of cardiac surgical procedures using a "look back" of 20 years before the index procedure date to identify patients who underwent previous cardiac surgery in the CIHI-DAD and the CorHealth cardiac surgery registry and patients who underwent a PCI procedure 6 months before the index coronary angiogram using the CIHI-DAD and the CorHealth PCI registry data. Finally, we excluded patients with cardiogenic shock, ST-segment elevation myocardial infarction, or those who underwent emergent or salvage procedures because these patients are primarily treated by PCI and are at high risk for mortality.

EARLY OUTCOMES. First, we examined 30-day mortality, defined as death that occurred in-hospital or within 30 days of the index revascularization procedure (PCI/CABG). Nonfatal early events, including in-hospital complications of new clinically diagnosed acute myocardial infarction and stroke, were obtained from the CIHI-DAD.

LONG-TERM OUTCOMES. Long-term outcomes included all events from the index procedure (defined as the

TABLE 1 Baseline Characteristics and Procedural Description

	Before Propensity Score Matching				After Propensity Score Matching		
	PCI (n = 4,519)	CABG (n = 9,716)	SMD	p Value	PCI (n = 4,301)	CABG (n = 4,301)	SMD
Age, yrs	68.3 ± 11.2	65.7 ± 9.4	0.26	<0.001	67.9 ± 11.1	67.5 ± 9.2	0.04
Charlson index	3.2 ± 1.9	3.1 ± 1.6	0.04	0.015	3.1 ± 1.9	3.1 ± 1.7	0.00
Hospital frailty risk score	2.4 ± 4.0	2.2 ± 3.4	0.08	<0.001	2.4 ± 4.0	2.3 ± 3.7	0.01
BMI, kg/m^2							
0–25	695 (15.4)	1,352 (13.9)	0.04	<0.001	653 (15.2)	642 (14.9)	0.01
26–30	1,132 (25.0)	2,180 (22.4)	0.06		1,065 (24.8)	1,035 (24.1)	0.02
≥31	1,060 (23.5)	2,226 (22.9)	0.01		1,011 (23.5)	1,011 (23.5)	0.00
Unknown	1,632 (36.1)	3,958 (40.7)	0.10		1,572 (36.5)	1,613 (37.5)	0.02
Creatinine level, mg/dl							
0–120	3,339 (73.9)	7,566 (77.9)	0.09	<0.001	3,207 (74.6)	3,183 (74.0)	0.01
121–180	525 (11.6)	887 (9.1)	0.08		478 (11.1)	491 (11.4)	0.01
≥181	243 (5.4)	456 (4.7)	0.03		229 (5.3)	221 (5.1)	0.01
Unknown	412 (9.1)	807 (8.3)	0.03		387 (9.0)	406 (9.4)	0.02
Male	3,276 (72.5)	7,573 (77.9)	0.13		3,161 (73.5)	3,174 (73.8)	0.01
Income quintile							
1	1,018 (22.6)	2,012 (20.8)	0.04	0.005	954 (22.2)	959 (22.4)	0.00
2	1,004 (22.3)	2,088 (21.6)	0.02		950 (22.2)	948 (22.1)	0.00
3	968 (21.5)	2,049 (21.2)	0.01		934 (21.8)	935 (21.8)	0.00
4	788 (17.5)	1,916 (19.8)	0.06		758 (17.7)	757 (17.7)	0.00
5	727 (16.1)	1,615 (16.7)	0.01		692 (16.1)	688 (16.0)	0.00
Rural status	572 (12.7)	1,314 (13.5)	0.03	0.156	554 (12.9)	569 (13.2)	0.01
History of smoking							
Current	737 (16.3)	1,871 (19.3)	0.08	<0.001	721 (16.8)	737 (17.1)	0.01
Former	1,349 (29.9)	2,932 (30.2)	0.01		1,297 (30.2)	1,297 (30.2)	0.00
Never	2,264 (50.1)	4,532 (46.6)	0.07		2,126 (49.4)	2,105 (48.9)	0.01
Unknown	169 (3.7)	381 (3.9)	0.01		157 (3.7)	162 (3.8)	0.01
Recent MI within 30 days	1,105 (24.5)	2,472 (25.4)	0.02	0.205	1,039 (24.2)	1,065 (24.8)	0.01
History of MI	1,237 (27.4)	2,281 (23.5)	0.09	<0.001	1,152 (26.8)	1,159 (26.9)	0.00
Hypertension	3,763 (83.3)	7,826 (80.5)	0.07	<0.001	3,558 (82.7)	3,570 (83.0)	0.01
Cerebrovascular disease	364 (8.1)	541 (5.6)	0.10	<0.001	322 (7.5)	319 (7.4)	0.00
COPD	1,012 (22.4)	1,730 (17.8)	0.11	<0.001	930 (21.6)	919 (21.4)	0.01
Hyperlipidemia	2,271 (50.3)	4,434 (45.6)	0.09	<0.001	2,145 (49.9)	2,142 (49.8)	0.00
Peripheral vascular disease	251 (5.6)	410 (4.2)	0.06	<0.001	230 (5.3)	229 (5.3)	0.00
Dementia	114 (2.5)	111 (1.1)	0.10	<0.001	90 (2.1)	85 (2.0)	0.01
History of cancer	513 (11.4)	790 (8.1)	0.11	<0.001	453 (10.5)	459 (10.7)	0.00
Dialysis	180 (4.0)	287 (3.0)	0.06	0.001	164 (3.8)	169 (3.9)	0.01
CCS class							
0	582 (12.9)	1,255 (13.0)	0.00	<0.001	556 (13.0)	563 (13.2)	0.01
1	435 (9.7)	945 (9.8)	0.00		416 (9.7)	424 (9.9)	0.01
2	1,100 (24.4)	2,239 (23.2)	0.03		1,056 (24.7)	980 (22.9)	0.04
3	761 (16.9)	1,457 (15.1)	0.05		713 (16.6)	742 (17.3)	0.02
4	133 (3.0)	268 (2.8)	0.01		125 (2.9)	124 (2.9)	0.00
High-risk features	355 (7.9)	652 (6.8)	0.04		328 (7.7)	332 (7.8)	0.00
Intermediate-risk features	692 (15.4)	1,805 (18.7)	0.09		667 (15.6)	687 (16.1)	0.01
Low-risk features	442 (9.8)	1,033 (10.7)	0.03		422 (9.9)	426 (10.0)	0.00
NYHA functional class							
I	2,125 (47.0)	4,868 (50.1)	0.06	0.014	2,048 (47.6)	2,066 (48.0)	0.01
II	504 (11.2)	1,030 (10.6)	0.02		472 (11.0)	468 (10.9)	0.00
III	261 (5.8)	539 (5.5)	0.01		244 (5.7)	233 (5.4)	0.01
IV	118 (2.6)	218 (2.2)	0.02		105 (2.4)	102 (2.4)	0.00
Unknown	1,511 (33.4)	3,061 (31.5)	0.04		1,432 (33.3)	1,432 (33.3)	0.00

Continued on the next page

TABLE 1 Continued

	Before Propensity Score Matching				After Propensity Score Matching		
	PCI (n = 4,519)	CABG (n = 9,716)	SMD	p Value	PCI (n = 4,301)	CABG (n = 4,301)	SMD
Extent of CAD							
2 vessel	1,566 (34.7)	1,442 (14.8)	0.47	<0.001	1,362 (31.7)	1,349 (31.4)	0.01
3 vessel	2,953 (65.3)	8,274 (85.2)	0.47		2,939 (68.3)	2,952 (68.6)	0.01
Left ventricular ejection fraction, %							
≥50	1,822 (40.3)	3,794 (39.0)	0.03	0.305	1,735 (40.3)	1,725 (40.1)	0.00
35–49	537 (11.9)	1,224 (12.6)	0.02		517 (12.0)	499 (11.6)	0.01
20–34	223 (4.9)	474 (4.9)	0.00		206 (4.8)	208 (4.8)	0.00
<20	49 (1.1)	83 (0.9)	0.02		44 (1.0)	39 (0.9)	0.01
Unknown	1,888 (41.8)	4,141 (42.6)	0.02		1,799 (41.8)	1,830 (42.5)	0.01
Stent type used*							
BMS	1,009 (23.3)	0 (0.0)	—		945 (22.9)	0 (0.0)	—
DES	3,545 (81.8)	0 (0.0)	—		3,395 (82.2)	0 (0.0)	—
No. of grafted vessels (CABG)*							
1	0 (0.0)	120 (1.2)	—		0 (0.0)	76 (1.8)	—
2	0 (0.0)	1,076 (11.1)	—		0 (0.0)	627 (14.6)	—
≥3	0 (0.0)	8,403 (86.5)	—		0 (0.0)	3,551 (82.6)	—
Unknown	0 (0.0)	117 (1.2)	—		0 (0.0)	47 (1.1)	—
No. of stented vessels (PCI)*							
1	2,538 (56.2)	0 (0.0)	—		2,408 (56.0)	0 (0.0)	—
2	1,464 (32.4)	0 (0.0)	—		1,393 (32.4)	0 (0.0)	—
≥3	209 (4.6)	0 (0.0)	—		205 (4.8)	0 (0.0)	—
Unknown	308 (6.8)	0 (0.0)	—		295 (6.9)	0 (0.0)	—

Values are mean ± SD or n (%). *Matching was not performed on the last 3 variables (stent type used, number of stented vessels, number of grafted vessels).

BMI = body mass index; BMS = bare-metal stent; CAD = coronary artery disease; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Study; COPD = chronic obstructive pulmonary disease; DES = drug-eluting stent; NYHA = New York Heart Association; MI = myocardial infarction; PCI = percutaneous coronary intervention; SMD = standardized mean difference.

date of either PCI or CABG) to date of last follow-up on March 31, 2020. All patients were followed for at least 1 year; the maximum follow-up was 11.5 years. Our primary study outcome was long-term, all-cause mortality. The secondary outcomes included long-term MACCEs and the individual components of MACCEs—new hospital admission for myocardial infarction, stroke, and repeat revascularization. Because revascularization procedures might be staged, PCI of a new vessel (i.e., not previously stented) within 90 days of the index procedure PCI was not counted as a repeat revascularization procedure. Repeat PCI was subcategorized based on the target of intervention (vessel with previous PCI, PCI after CABG, or PCI of a new vessel). However, if PCI was performed on the same vessel or CABG was performed after an index PCI, this was considered a repeat revascularization procedure.

STATISTICAL ANALYSES. Baseline characteristics were first compared in the overall sample between those who underwent CABG and those who underwent PCI. Student's *t*-test was used for normally distributed continuous variables, Wilcoxon rank-sum test was used for non-normally distributed continuous variables, and the chi-square test was used for categorical variables. Propensity score matching was performed to account for baseline differences in patient characteristics between PCI and CABG to minimize confounding. The propensity score for each patient was estimated using a multivariable logistic regression model in which the intervention performed (PCI vs. CABG) was regressed on 23 baseline characteristics that might influence the choice of intervention or that were prognostically important for the outcome. These baseline characteristics included age, sex, frailty, cardiac comorbidities, lung disease, peripheral vascular disease, cerebrovascular disease, cancer, dementia, renal function, Canadian Cardiovascular Society and New York Heart Association functional class, left ventricular function, the extent of CAD, and surrogates for socioeconomic status (neighborhood income quintile and rural status). Subjects were matched on the logit of the propensity score using 1:1 greedy nearest-neighbor matching with a caliper distance of 0.2 times the SD of the logit of the propensity score (13). Success of matching was assessed by computing the standardized mean difference (SMD) of each covariate with a cutoff of 0.10 to denote acceptable balance (14).

TABLE 2 Early Outcomes for Unmatched and Matched Cohorts

	Before Propensity Score Matching			After Propensity Score Matching		
	PCI (n = 9,716)	CABG (n = 4,519)	p Value	PCI (n = 4,301)	CABG (n = 4,301)	p Value
Early death	117 (2.6)	180 (1.9)	<0.001	104 (2.4)	99 (2.3)	0.721
		0.74 (0.22 to 1.29)			0.12 (−0.52 to 0.76)	
In-hospital stroke		−0.52 (−0.34 to −0.71)			−0.58 (−0.84 to −0.32)	
In-hospital MI	44 (1.0)	108 (1.1)	0.427	38 (0.88)	53 (1.2)	0.112
		−0.14 (−0.48 to 0.24)			−0.35 (−0.78 to 0.008)	

Values are n (%) or absolute risk difference (95% confidence intervals) in %. For outcomes (such as in-hospital stroke) with < 6 events per group, privacy legislation prevents the reporting of the actual number of events; as such, we instead report absolute risk differences between the PCI and CABG, which is compliant with Ontario privacy legislation. Risk difference <0 means that risk of the event was higher for CABG than that for PCI.

Abbreviations as in Table 1.

Early events were compared between the 2 cohorts using the McNemar test for binary outcomes and the paired Student's *t*-test and the Wilcoxon signed rank test for normally and non-normally distributed continuous variables, respectively. All tests were 2-sided, and p values <0.05 were considered significant.

For long-term mortality and MACCEs, a time-to-event analysis using Kaplan-Meier survival curves was conducted in the matched sample, using a log-rank p test stratified on the matched pairs to test the equality of the estimated survival curves (15). In addition, cause-specific hazard ratios (HRs) were estimated using a Cox proportional hazards model that incorporated a robust sandwich-type variance estimator to account for the matched nature of the data. This was shown to result in more accurate estimates of SEs compared with the conventional maximum-likelihood estimate of the SEs (16). For the individual components of MACCE (late myocardial infarction, stroke, and repeat revascularization), we estimated cumulative incidence functions to estimate the incidence of these events after accounting for death as a competing risk. In the matched sample, a Fine-Gray sub-distribution hazard model was used to regress the outcome on a single variable that denoted treatment status (17). For both models, robust variance estimators were used to estimate the SEs.

For outcomes with <6 events per group, privacy legislation prevented the reporting of the actual number of events. We instead reported absolute risk differences (ARDs) between PCI and CABG, which was compliant with Ontario privacy legislation. All curves were truncated to 8 years because of the small numbers at risk after that time point.

SECONDARY ANALYSIS. Our primary analysis excluded patients with left main disease because these patients were excluded in the FREEDOM trial. We performed a secondary analysis that compared outcomes in patients, which included those with left main disease. Therefore, the secondary analysis cohort included isolated left main, left main with 1- or 2-vessel disease, 2- or 3-vessel disease, and 3-vessel disease with left main involvement for the primary outcome of long-term mortality.

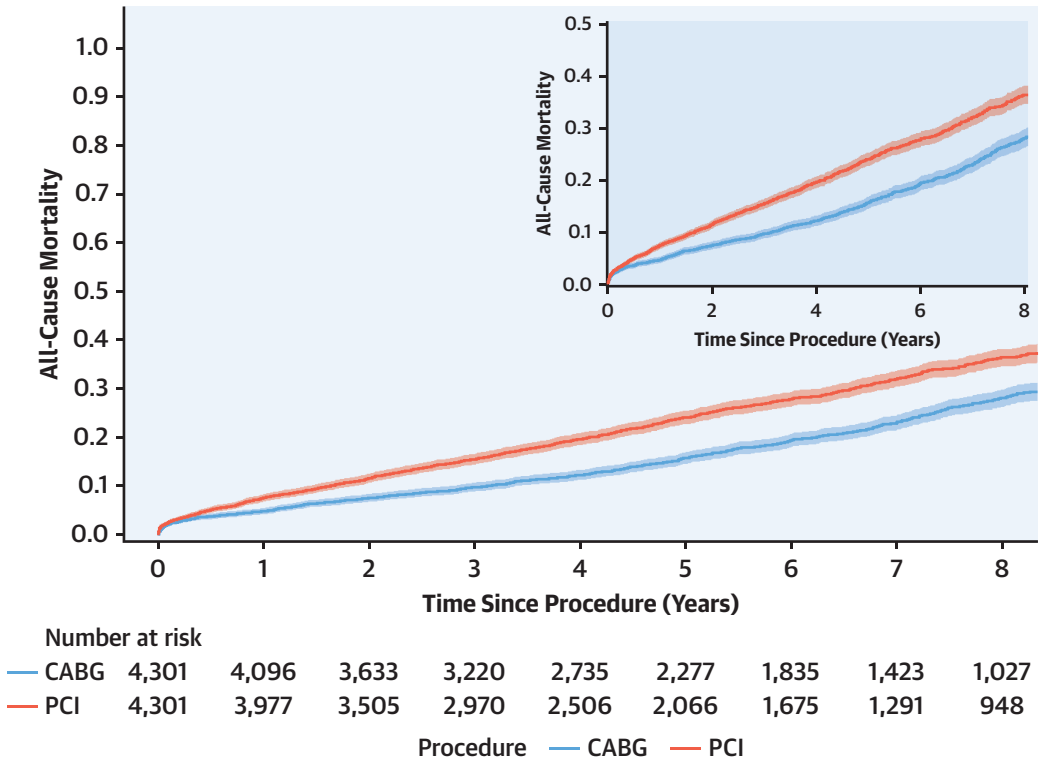
SENSITIVITY ANALYSES. In a series of sensitivity analyses, we excluded patients at higher risk for either PCI or CABG to ascertain the robustness of our primary outcome of long-term mortality. Specifically, we excluded patients who underwent PCI after a cardiac surgery consult, because these patients might be considered possible surgical turndowns, those with an initial diagnosis of acute coronary syndrome (i.e., non–ST-segment elevation myocardial infarction or unstable angina), and those with severe renal disease who required dialysis. Baseline characteristics were compared, and the primary outcome of long-term survival was compared as described previously. Two additional sensitivity analyses were conducted to examine the temporal robustness of the primary outcomes. In the first sensitivity analysis, patients who underwent PCI and received a bare-metal stent were excluded. In the second sensitivity analysis, we performed an exact match on year of procedure, such that pairs were only matched within the same year to account for potential era differences.

All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PRIMARY MATCHED ANALYSIS. In total, there were 4,519 patients in the PCI group and 9,716 patients in the CABG group (Supplemental Figure 1). There were significant differences in important baseline characteristics in the PCI and CABG cohorts before propensity matching (**Table 1**, Supplemental Figure 2). Those who underwent PCI were older, more often female, and had a higher burden of comorbidities but

FIGURE 1 Cumulative Incidence Curves for 8-Year Survival



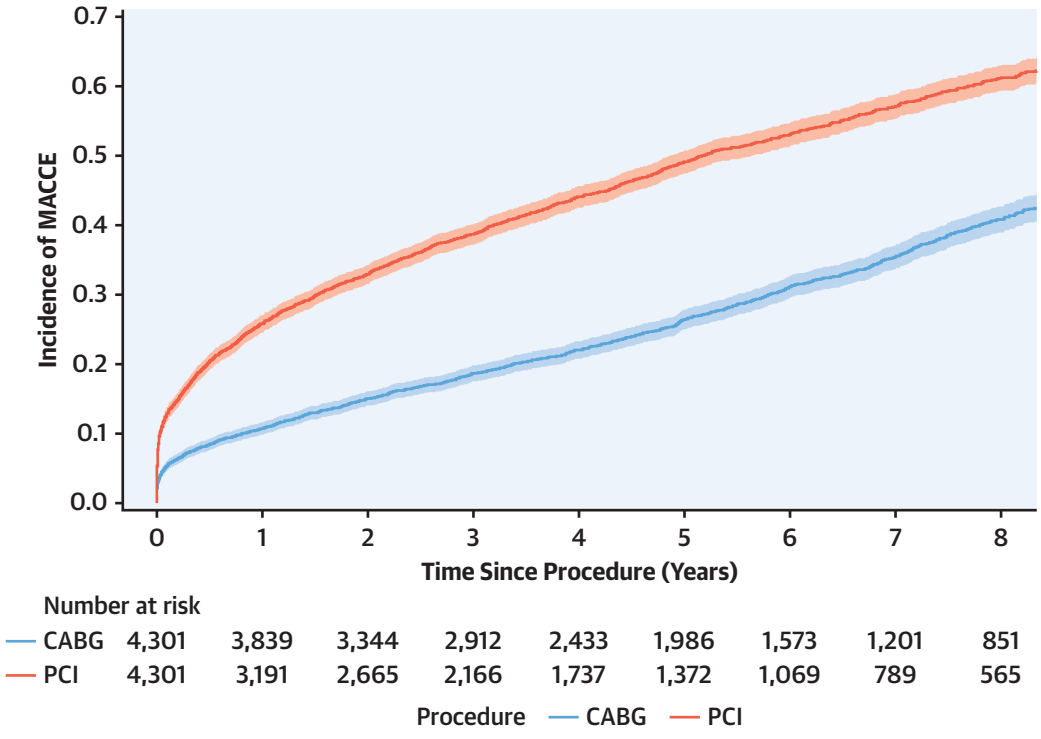
All-cause mortality was compared between percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) after propensity score matching in patients with diabetes and multivessel coronary artery disease (hazard ratio: 1.39; 95% confidence interval [CI]: 1.28 to 1.51; $p < 0.001$). The **shaded region around the curve** represents the 95% CIs.

had fewer diseased coronary vessels. Propensity score matching on 23 baseline covariates yielded 4,301 pairs of patients (i.e., 95% of PCI patients were matched to a CABG patient) who were well-matched with standardized mean differences of <0.10 for all covariates. The extent of CAD was similar between the groups after matching. Early deaths did not differ between the PCI and CABG groups (2.4% vs. 2.3%; ARD: 0.12; 95% confidence interval [CI]: −0.52% to 0.76%; $p = 0.721$) (**Table 2**). There was no difference in the rate of new in-hospital myocardial infarctions between the PCI and CABG groups (0.88% vs. 1.2%; ARD: −0.35%; 95% CI: −0.78% to 0.08%; $p = 0.112$). The rate of new in-hospital stroke was higher with CABG compared with PCI (ARD: −0.58%; 95% CI: −0.84% to −0.32%; $p < 0.001$). Early outcomes before and after propensity score matching are provided in **Table 2**.

At 8-year follow-up (maximum: 11.5 years; interquartile range: 2.7 to 7.5 years), all-cause mortality in the propensity score–matched cohorts was 27.0% for patients who underwent PCI and 19.4% for patients who underwent CABG surgery. The HR was 1.39 (95% CI: 1.28 to 1.51; $p < 0.0001$) over the entire follow-up period. Survival curves are shown in **Figure 1**. In addition, in long-term follow-up, 51.1% of patients who underwent PCI and 30.4% who underwent CABG surgery experienced MACCEs at 8 years (**Figure 2**). The HR was 1.99 (95% CI: 1.86 to 2.12) over the entire follow-up period, which again indicated a higher risk of adverse outcomes among those who underwent PCI ($p < 0.001$). Supplemental Table 1 shows the HRs and 95% CIs in the samples before and after propensity score matching.

When the components of MACCEs were analyzed separately, we found that the cumulative incidence of myocardial infarctions was 16.4% among those who underwent PCI compared with 7.2% in those who had CABG (Supplemental Figure 3). The sub-distribution HR was 2.32 (95% CI: 2.04 to 2.64), which indicated

FIGURE 2 Cumulative Incidence Curves for 8-Year Freedom From MACCEs



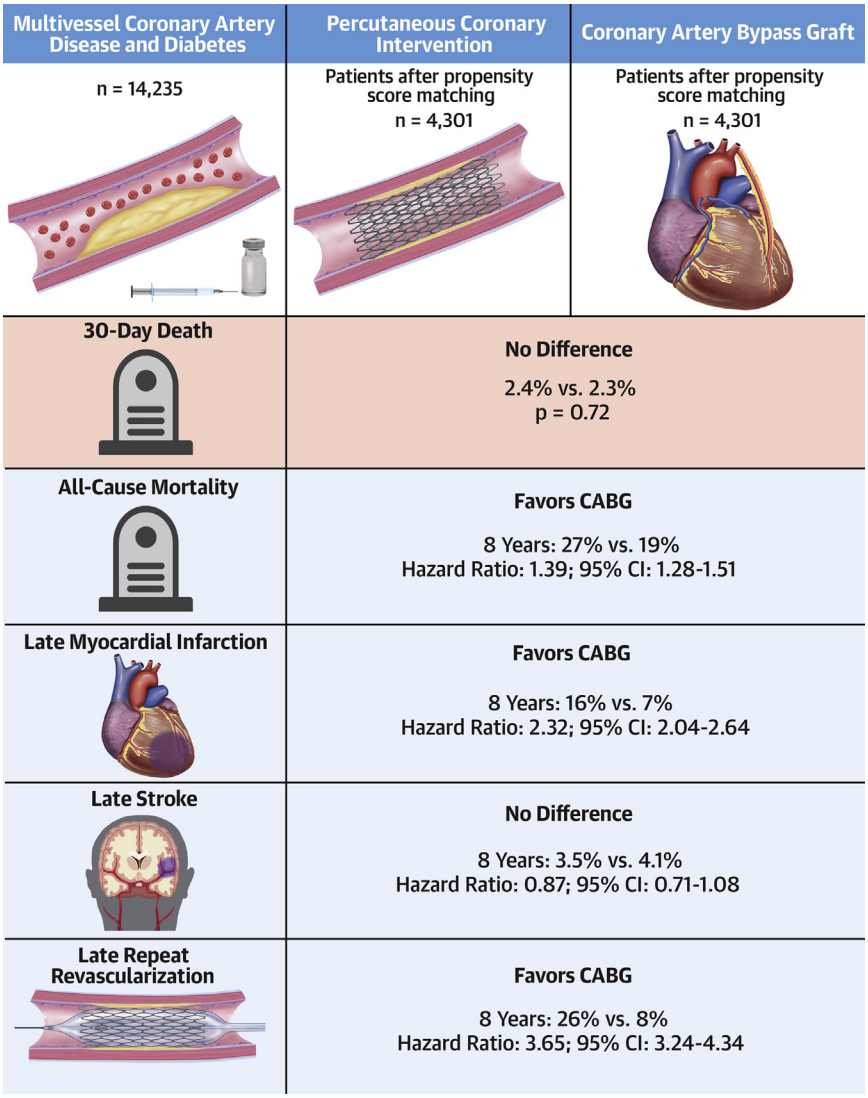
Major adverse cardiac and cerebrovascular events (MACCEs) were a composite of death, myocardial infarction, stroke, and repeat revascularization and were compared between PCI and CABG after propensity score matching in patients with diabetes and multivessel coronary artery disease (HR: 1.99; 95% CI: 1.86 to 2.12; $p < 0.001$). The **shaded region around the curve** represents the 95% CIs. Abbreviations as in **Figure 1**.

an increased risk of myocardial infarction in the PCI group ($p < 0.001$). Repeat revascularization occurred more frequently in the PCI group compared with the CABG group (25.9% vs. 7.8%) (Supplemental Figure 4). The risk of repeat revascularization was >3-fold higher in the PCI group (sub-distribution HR: 3.65; 95% CI: 3.24 to 4.34; $p < 0.001$). The details of the repeat revascularization procedures can be found in Supplemental Table 2. The cumulative incidence of stroke at 8 years was similar between PCI and CABG (3.5% vs. 4.1%) (Supplemental Figure 5) with a sub-distribution HR of 0.87 (95% CI: 0.71 to 1.08; $p = 0.203$) over the entire study period. Overall key findings from the primary analysis are presented in the **Central Illustration**.

SECONDARY ANALYSIS. In the secondary analysis, patients with left main disease were included in the sample. Propensity score matching on the same covariates as the primary analysis was performed, yielding 5,139 pairs of patients that were well-matched (SMD <0.10 for all covariates). Findings were consistent with the primary analysis; the risk of late mortality was significantly higher with PCI compared with CABG (Supplemental Figure 6) (HR: 1.47; 95% CI: 1.36 to 1.58; $p < 0.001$).

SENSITIVITY ANALYSIS. In the cohort of 4,519 patients with diabetes with 2- and 3-vessel disease who underwent PCI, only 375 patients (8.3%) were seen by a cardiac surgeon for consultation. These 375 patients were older and had more comorbidities compared with patients who underwent PCI without a cardiac surgical consult. After exclusion of patients who had pre-PCI cardiac surgical consultation and repeating the propensity score match, there were 3,968 pairs of patients. Again, late mortality was higher in the PCI group (HR: 1.43; 95% CI: 1.31 to 1.57) (Supplemental Figure 7). When patients with a diagnosis of acute coronary syndrome (i.e., non–ST-segment elevation myocardial infarction and unstable angina) were excluded, late

CENTRAL ILLUSTRATION **Summary of Early and Long-Term Outcomes**



Tam, D.Y. et al. J Am Coll Cardiol. 2020;76(10):1153–64.

A propensity score cohort-matched analysis of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) for patients with multivessel coronary artery disease and diabetes. CI = confidence interval.

mortality was higher in the PCI group (HR: 1.36; 95% CI: 1.19 to 1.56) (Supplemental Figure 8) in 2,337 pairs of well-matched patients. The full details of the sensitivity analysis that excluded those with a history of dialysis (Supplemental Figure 9), those who received bare-metal stents (Supplemental Figure 10), and exact match by year (Supplemental Figure 11) can be found in the Supplemental Appendix. Findings supported the robustness of the primary analysis.

DISCUSSION

There were several key findings from this analysis. First, long-term survival was significantly higher in patients with multivessel CAD and diabetes who underwent CABG compared with the long-term survival of those who underwent PCI. Freedom from MACCEs was also higher with CABG compared with that of PCI, and these findings were driven by lower mortality, new myocardial infarction, and reduced need for

repeat revascularization. There was no excess early mortality with CABG compared with PCI. Although the rate of early stroke was higher with CABG compared with PCI, the incidence of stroke was similar between the 2 treatments at 8-year follow-up. Finally, <10% of patients with diabetes with multivessel CAD who underwent PCI had a consultation with a cardiac surgeon.

Overall, these findings suggested that in patients with diabetes and multivessel CAD, revascularization with CABG might be the preferred approach. Although our primary analysis excluded patients with left main disease to be consistent with the FREEDOM trial, the findings were robust even when these patients were added into the study. Although the FREEDOM trial was the largest randomized clinical trial that compared PCI and CABG in patients with diabetes and multivessel disease, nearly 33,000 patients were screened, 3,309 were eligible, and ultimately only 1,900 were randomized (8). In the extended follow-up study of FREEDOM, mortality was higher in the PCI group (24.3%) compared with the CABG group (18.3%) at 8 years; these numbers were strikingly similar to the findings of our observational study (26.1% vs. 18.5% at 8 years). The findings of our observational study derived from registry data were consistent with that of the FREEDOM trial. Similar to the FREEDOM trial, we did not find any difference in early mortality, but we did detect an increase in peri-operative stroke in the CABG group, although there was no difference at 8 years. We noted that our patient cohort was similar to that of the FREEDOM study. Although our patients were, on average, 5 years older, the proportion of men (~80%) and proportion of patients with 3-vessel disease (~70%) were similar between the trial and our study.

Ramanathan et al. (18) examined outcomes following PCI and CABG in a cohort of patients with diabetes with multivessel CAD. They concluded that CABG was associated with a lower risk of MACCEs at 5 years, particularly in patients admitted with acute coronary syndrome rather than those admitted with stable ischemic heart disease. Although our analysis shared similar findings, there were several important differences between the 2 studies. Our primary analysis included >8,000 patients and our secondary analysis included patients with left main disease in addition to clinically significant 2- and 3-vessel disease. Furthermore, we used propensity score matching to create 2 well-balanced groups rather than multivariable analysis to compare long-term outcomes. Nonetheless, the similar conclusions of these 2 studies continue to support the use of CABG in patients with advanced multivessel CAD for long-term benefit.

Our analysis also found significant reductions in myocardial infarction and need for repeat revascularization events in the CABG cohort, which was consistent with findings from the FREEDOM trial and the diabetic subgroup of the SYNTAX trial (19). Our findings might be explained by the differing mechanisms of PCI and CABG in the revascularization of diseased vessels. In PCI, stents are placed to treat focal flow limiting lesions, whereas any distal nonflow limiting lesions are left untreated. In contrast, in CABG, the bypass graft is often placed distal to both the flow limiting and nonflow limiting lesions (20). Future events after revascularization might occur when an acute thrombosis of the nonflow limiting lesion occurs, which results in an acute myocardial infarction and potential need for subsequent revascularization. In PCI, the distal coronary bed is not protected, whereas in CABG, there is protection of the distal coronary bed if the bypass graft remains patent. In patients with diabetes, the coronary arteries are often diffusely diseased; thus, CABG may be more effective for protection against late thrombotic events compared with PCI (21). In addition, numerous studies have shown that the risk of stent re-stenosis is doubled in patients with diabetes compared with patients without diabetes; thus, patients with diabetes are at especially higher risk for myocardial infarction and need for repeat revascularization (22,23). Finally, there is some concern for higher rates of incomplete revascularization with PCI compared with CABG. Incomplete revascularization is associated with worse late survival and higher late MACCE events (24,25).

A concerning finding in our study was that only 10% of patients who underwent PCI had a consultation with a cardiac surgeon. According to both American and European guidelines, there is a Class I recommendation that CABG is preferred to PCI in patients with diabetes and multivessel disease (both 3-vessel and complex 2-vessel disease involving the proximal LAD) (26,27). These recommendations are further supported by the American College of Cardiology/American Heart Association appropriate use criteria for patients with diabetes and 2- and 3-vessel coronary disease, which suggests that CABG is more often appropriate compared with PCI in patients with stable ischemic heart disease (28). Furthermore, the heart team approach is recommended in patients with diabetes and complex multivessel CAD (Class I recommendation). Thus, although most of the patients in our analysis underwent CABG, it remains concerning that only 10% of those patients who

underwent PCI had ever seen a cardiac surgeon, despite guidelines recommending that a heart team approach be undertaken. Our study was the largest to-date, to the best of our knowledge, to examine the real-world clinical practice of revascularization in patients with diabetes and supported the generalizability of the FREEDOM trial results. However, we note that both PCI and CABG techniques continue to improve and evolve, and that the use of intravascular ultrasound, optical coherence tomography, and fractional flow reserve may improve outcomes, as shown in the SYNTAX II study that examined state-of-the-art PCI (29).

STUDY LIMITATIONS. This study must be interpreted in the context of some significant limitations. This was a retrospective observational study and thus might have been confounded by treatment allocation bias. Although we attempted to mitigate any potential bias by performing propensity score matching on 23 variables, we recognize that unmeasured or unknown confounders could exist. Another concern was that patients with a history of acute coronary syndrome or patients who underwent PCI after a cardiac surgery consult might be considered higher risk patients (i.e., surgical turndown patients), and thus, might be biased against PCI. However, we performed several sensitivity analyses that excluded these patients; findings were robust and still favored CABG. There was a paucity of detailed surgical information in the patients who underwent CABG (e.g., use of sequential grafts, target vessel bypassed, vessel size, and completeness of revascularization) because these details were not captured in our dataset. Finally, we noted that the definition of early myocardial infarction used in our analysis depended on a clinical diagnosis and differed from those used in clinical trials that relied on mostly biochemical markers. This might have underestimated the number of peri-procedural myocardial infarctions in both groups. Controversy remains surrounding the definition of clinically important myocardial infarction, and, in particular, using only biochemical markers (30).

CONCLUSIONS

CABG should be considered the preferred approach in patients with diabetes and multivessel CAD who are good surgical candidates. Further work is warranted to ensure that patients with diabetes with extensive CAD are treated within a heart team framework.

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ADDRESS FOR CORRESPONDENCE: Dr. Douglas S. Lee, Division of Cardiology, Peter Munk Cardiac Centre & University Health Network, University of Toronto, ICES, G1 06, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada. E-mail: dlee@ices.on.ca. Twitter: @DouglasLeeMD.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In routine clinical practice, patients with diabetes mellitus and multivessel coronary artery disease, CABG surgery is associated with greater survival than PCI over a follow-up interval of 5 to 10 years.

TRANSLATIONAL OUTLOOK: Further efforts are needed to individualize the selection of optimum revascularization strategies for diabetic patients with multivessel CAD through implementation of heart team collaboration.

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KEY WORDS coronary artery bypass grafting, diabetes, percutaneous coronary intervention, propensity score

APPENDIX For expanded Methods and Results sections and supplemental tables and figures, please see the online version of this paper.