JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 73, NO. 13, 2019

Bypass Surgery or Stenting for Left Main Coronary Artery Disease in Patients With Diabetes

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ABSTRACT

BACKGROUND The randomized EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial reported a similar rate of the 3-year composite primary endpoint of death, myocardial infarction (MI), or stroke in patients with left main coronary artery disease (LMCAD) and site-assessed low or intermediate SYNTAX scores treated with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Whether these results are consistent in high-risk patients with diabetes, who have fared relatively better with CABG in most prior trials, is unknown.

OBJECTIVES In this pre-specified subgroup analysis from the EXCEL trial, the authors sought to examine the effect of diabetes in patients with LMCAD treated with PCI versus CABG.

METHODS Patients (N = 1,905) with LMCAD and site-assessed low or intermediate CAD complexity (SYNTAX scores ≤32) were randomized 1:1 to PCI with everolimus-eluting stents versus CABG, stratified by the presence of diabetes. The primary endpoint was the rate of a composite of all-cause death, stroke, or MI at 3 years. Outcomes were examined in patients with (n = 554) and without (n = 1,350) diabetes.

RESULTS The 3-year composite primary endpoint was significantly higher in diabetic compared with nondiabetic patients (20.0% vs. 12.9%; $p < 0.001$). The rate of the 3-year primary endpoint was similar after treatment with PCI and CABG in diabetic patients (20.7% vs. 19.3%, respectively; hazard ratio: 1.03; 95% confidence interval: 0.71 to 1.50; $p = 0.87$) and nondiabetic patients (12.9% vs. 12.9%, respectively; hazard ratio: 0.98; 95% confidence interval: 0.73 to 1.32; $p = 0.89$). All-cause death at 3 years occurred in 13.6% of PCI and 9.0% of CABG patients ($p = 0.046$), although no significant interaction was present between diabetes status and treatment for all-cause death ($p = 0.22$) or other endpoints, including the 3-year primary endpoint ($p = 0.82$) or the major secondary endpoints of death, MI, or stroke at 30 days ($p = 0.61$) or death, MI, stroke, or ischemia-driven revascularization at 3 years ($p = 0.65$).

CONCLUSIONS In the EXCEL trial, the relative 30-day and 3-year outcomes of PCI with everolimus-eluting stents versus CABG were consistent in diabetic and nondiabetic patients with LMCAD and site-assessed low or intermediate SYNTAX scores.(Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization [EXCEL]; NCT01205776) (J Am Coll Cardiol 2019;73:1616–28) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00

https://doi.org/10.1016/j.jacc.2019.01.037

The number of people with diabetes mellitus is increasing, having risen from 108 million in 1980 to 422 million in 2014 (1). Patients with diabetes are at an increased risk for systemic atherosclerosis and advanced coronary artery disease (CAD), and diabetes is a predictor of adverse events after both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) (2,3). In patients with diabetes and complex anatomic disease, CABG has been associated with lower mortality rates compared with PCI (3–5). As a result, CABG has been recommended as the standard of care for patients with diabetes and complex CAD including left main coronary artery disease (LMCAD) (6); however, in a recent pooled analysis of 3 randomized trials (2 of which were performed more than a decade ago), patients with diabetes and low or intermediate anatomic complexity as signified by a SYNTAX score of ≤32 had similar 5-year rates after PCI and CABG of all-cause death, cardiac death, and the composite of death, myocardial infarction (MI), or stroke (7). Conversely, patients with high (≥33) SYNTAX scores had significantly higher adverse event rates with PCI compared with CABG. Since the performance of these trials, both PCI technology and technique, as well as surgical methods and outcomes, have continued to improve. The extent to which diabetes thus influences outcomes after contemporary revascularization strategies in patients with LMCAD is unknown.

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The EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was a large-scale study in which selected patients with LMCAD were randomized to PCI with everolimus-eluting stents (EES) versus CABG (8). Acknowledging the importance of diabetes, randomization was stratified by the presence of this variable to ensure a balanced baseline in the diabetic and nondiabetic strata. The present report describes the prespecified subgroup analysis examining the impact of diabetes on 30-day and 3-year outcomes after PCI versus CABG in patients with LMCAD.

ABBREVIATIONS AND ACRONYMS

BIMA = bilateral internal mammary artery

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CI = confidence interval

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

HR = hazard ratio

IDR = ischemia-driven revascularization

LMCAD = left main coronary artery disease

MI = myocardial infarction

PCI = percutaneous coronary intervention

URL = upper reference limit

METHODS

STUDY DESIGN. The protocol, patient eligibility criteria, and methods of the EXCEL trial have been reported previously (9). The EXCEL trial was a prospective, multinational, unblinded randomized trial

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Manuscript received December 4, 2018; accepted January 1, 2019.

in which 1,905 patients with de novo LMCAD and site-assessed SYNTAX scores ≤32 in whom equipoise was present for transcatheter versus surgical revascularization were randomly (1:1) assigned to undergo PCI with cobalt-chromium fluoropolymer-based EES (Abbott Vascular, Santa Clara, California) or CABG. Patients were assessed for eligibility at each participating site by a heart team that consisted of (at least) an interventional cardiologist and a cardiac surgeon (10). Randomization was stratified according to the presence of diabetes and site. The trial was approved by the investigational review board or ethics committee at each participating center. All patients provided written informed consent before enrollment. The trial was funded by Abbott Vascular but led by a broad academic group with equal representation of interventional cardiologists and cardiac surgeons (8,9). The trial is registered at clinicaltrials.gov, identifier NCT01205776.

ENDPOINTS AND DEFINITIONS. The primary endpoint was the 3-year rate of all-cause mortality, stroke, or MI. Major powered secondary outcomes included this endpoint at 30 days and the composite rate of death, stroke, MI, or ischemia-driven revascularization (IDR) at 3 years. Other secondary endpoints included the components of the primary and secondary endpoints as well as revascularization, stent thrombosis, symptomatic graft stenosis or occlusion, and a pre-specified composite of periprocedural major adverse events.

The definitions of these outcome measures have been previously described in detail (8,9). In brief, stroke was defined as a focal neurological deficit of central origin lasting >24 h, confirmed by a neurologist and imaging. Post-procedure MI was defined as the rise within 72 h after PCI or CABG of creatine kinase-myocardial band (CK-MB) to >10× the upper reference limit (URL), or >5× URL plus new pathological Q waves in at least 2 contiguous leads or new persistent non-rate-related left bundle branch block, or angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Spontaneous MI was defined as the occurrence >72 h after PCI or CABG of a rise and fall of cardiac biomarkers (CK-MB or troponin) >1× URL plus electrocardiogram changes indicative of new ischemia, or development of pathological Q waves in ≥2 contiguous electrocardiogram leads, or angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Revascularization events were classified as either ischemia-driven or non-ischemia-driven by pre-specified criteria (9). An independent clinical events committee adjudicated all primary and secondary endpoints with source document verification.

Patients with diabetes at baseline were categorized according to treatment as: 1) insulin-treated (with or without oral hypoglycemic agents); 2) oral hypoglycemic agent-treated without insulin; and 3) non-pharmacological therapy only, including dietary modification, exercise, and weight reduction. Using this classification, the following diabetes subgroups were defined and analyzed in the present study: 1) insulin-treated patients with or without oral hypoglycemic agents; and 2) non-insulin-treated patients (because only a small number of patients were treated without medications).

STATISTICAL ANALYSIS. Subgroup analysis according to diabetes status with formal interaction testing was pre-specified in the trial protocol, although no formal statistical hypothesis was defined a priori. All analyses were performed with data from the time of randomization in the intention-to-treat population, which included all patients according to the group to which they were randomly assigned, regardless of the treatment received. Data are summarized using descriptive statistics, presented as proportions (%, count/sample size) or mean ± SD. Continuous variables were compared using the Student's *t*-test; differences in categorical variables were assessed with the chi-square test or Fisher exact test, as appropriate. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses and were compared by the log-rank test. Multivariable predictors of 3-year outcomes were identified using stepwise selection with a significance level of <0.10 for entry and exit in a logistic regression model. p Values for interaction were generated by logistic regression chi-square test. Analyses according to SYNTAX score tertiles (low 0 to 22, intermediate 23 to 32, high ≥33) were performed using 3-year Kaplan-Meier event estimates. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS. Baseline diabetes status was known in 1,904 of 1,905 randomized patients. Diabetes was present in 554 of

1,904 patients (29.1%); 147 patients were treated with insulin, 358 were treated with oral hypoglycemic agents without insulin, and 49 were treated with nonpharmacological measures. Patients with diabetes had a significantly greater number of comorbidities compared with nondiabetic patients, including hypertension, hyperlipidemia, anemia, renal insufficiency, peripheral vascular disease, congestive heart failure, prior stroke, and a higher STS score, although were less likely to be current smokers (Table 1). By core laboratory analysis, diabetic patients also had a higher SYNTAX score, more frequently had diffuse or small vessel disease, and had a greater number of treated lesions.

As shown in Table 2, bilateral internal mammary artery (BIMA) grafting was performed significantly less frequently in patients with diabetes compared with patients without diabetes (19.6% vs. 32.4%; $p < 0.001$). Off-pump CABG technique, total bypass time, and the number of grafts did not differ between groups. Mean PCI duration was significantly longer in diabetic than in nondiabetic patients. There were no significant differences between the groups in other PCI procedural aspects. At hospital discharge, no differences in the administration of antiplatelet agents, statins, and beta-blockers were found between diabetic and nondiabetic patients after both PCI and CABG (Table 2). Medication use during follow-up is presented in Online Table 1.

THIRTY-DAY OUTCOMES. As shown in Table 3, the 30-day rates of major adverse events were not significantly different in diabetic compared with nondiabetic patients; however, in both diabetic and nondiabetic patients, the 30-day rate of the composite endpoint of death, stroke, or MI was higher after CABG than after PCI. The difference in outcome was driven mainly by higher rates of stroke and MI after CABG, whereas rates of all-cause death and ischemia-driven revascularization were similar between CABG and PCI. Major adverse events were also higher after CABG than PCI in both diabetic and nondiabetic patients. Acute renal failure within 30 days occurred more commonly in patients with diabetes compared with those without diabetes (2.7% vs. 1.1%; $p = 0.01$), and was more frequent after revascularization with CABG compared with PCI both in patients with (4.1% vs. 1.4%; $p = 0.005$) and without (1.9% vs. 0.3%; $p = 0.05$) diabetes ($p_{interaction} = 0.44$) (Online Table 2). Among CABG patients, sternal wound dehiscence occurred in 0.4% versus 1.2% of diabetic and nondiabetic patients, respectively ($p = 0.26$). Furthermore, sternal dehiscence did not occur more often after the use of BIMA compared with the single internal mammary artery technique (0% vs. 0.5%; $p = 0.68$). There were no significant interactions between diabetes status and treatment for any of the 30-day study endpoints.

TABLE 1 Baseline Characteristics of Patients According to Diabetes Status in the Overall Cohort

	No Diabetes (n = 1,350)	Diabetes (n = 554)	p Value
Age, yrs	65.7 ± 9.7	66.5 ± 9.2	0.17
Male	78.0 (10,53/1,350)	74.0 (410/554)	0.06
Body mass index, kg/m^2	28.0 ± 4.5	30.4 ± 5.5	<0.001
Hyperlipidemia treated with medication	65.7 (886/1,348)	80.5 (445/553)	<0.001
Hypertension treated with medication	68.2 (921/1,350)	87.5 (485/554)	<0.001
Current smoker	23.9 (321/1,343)	17.3 (95/548)	0.002
Prior myocardial infarction	17.1 (229/1,339)	18.4 (101/549)	0.50
Congestive heart failure	5.7 (77/1,345)	8.9 (49/553)	0.01
History of carotid artery disease	7.3 (98/1,345)	10.5% (58/551)	0.02
Prior stroke	3.0 (41/1,349)	5.1 (28/554)	0.03
Prior transient ischemic attack	2.8 (38/1,343)	3.5 (19/550)	0.47
Peripheral vascular disease	7.7 (103/1,344)	14.1 (78/552)	<0.001
Chronic kidney disease*	14.5 (191/1,320)	21.3 (117/549)	<0.001
Anemia†	20.1 (268/1,334)	36.1 (200/554)	<0.001
Recent myocardial infarction, within 7 days	15.1 (203/1,345)	14.3 (79/552)	0.66
Unstable angina without recent myocardial infarction	23.1 (311/1,345)	27.7 (153/552)	0.03
Prior percutaneous coronary intervention	15.3 (206/1,348)	21.7 (120/554)	<0.001
Left ventricular ejection fraction, %	57.4 ± 9.1	56.6 ± 9.8	0.19
Society of Thoracic Surgeons score	0.85 ± 0.81	0.96 ± 0.91	0.01
SYNTAX score			
Site-assessed	20.5 ± 6.3	20.8 ± 5.9	0.25
0–22	61.8 (833/1,348)	57.1 (316/553)	0.060
23–32	38.2 (515/1,348)	42.9 (237/553)	0.060
≥33	0 (0/1,348)	0 (0/553)	–
Core laboratory assessed	26.2 ± 9.4	27.3 ± 9.1	0.02
0–22	37.7 (491/1,302)	31.1 (167/537)	0.007
23–32	38.6 (502/1,302)	43.6 (234/537)	0.047
≥33	23.7 (309/1,302)	25.3 (136/537)	0.47
Coronary anatomy, core laboratory-assessed			
Left main distal bifurcation involvement	56.3 (568/1,009)	62.6 (253/404)	0.03
Number of lesions treated per patient	2.2 ± 0.9	2.3 ± 0.9	0.02
Number of treated non-left main diseased vessels	1.5 ± 1.0	1.7 ± 1.0	<0.001
0	18.8 (250/1,328)	14.6 (80/549)	0.03
1	32.8 (435/1,328)	27.1 (149/549)	0.02
2	31.3 (416/1,328)	37.2 (204/549)	0.01
3	17.1 (227/1,328)	21.1 (116/549)	0.04
Diffuse disease or small vessels	4.7 (62/1,321)	9.3 (51/549)	<0.001

Values are mean ± SD or % (n/N). *Estimated glomerular filtration rate <60 ml/min. †Hemoglobin <12 g/dl in women and <13 g/dl in men.

3-YEAR OUTCOMES. Clinical outcomes according to diabetes status and treatment group are shown in Table 4 and Figure 1. Compared with nondiabetic patients, diabetic patients had higher 3-year rates of the composite primary endpoint, including higher rates of all-cause death, cardiovascular death, MI, and IDR. The rates of the 3-year composite primary

TABLE 2 Procedural Characteristics and Discharge Medications According to Diabetes Status and Revascularization Assignment

	CABG (n = 956)			PCI (n = 948)		
	No Diabetes (n = 688)	Diabetes (n = 268)	p Value	No Diabetes (n = 662)	Diabetes (n = 286)	p Value
Procedural characteristics						
Assigned procedure performed	97.0 (667/688)	95.5 (256/268)	0.28	98.6 (653/662)	98.6 (282/286)	0.96
Time to procedure, days	6.8 ± 15.1	6.5 ± 11.9	0.69	3.4 ± 5.7	3.0 ± 4.1	0.73
Procedure duration, min	241.9 ± 70.9	246.2 ± 69.2	0.37	80.2 ± 41.8	87.7 ± 41.8	0.005
Off-pump CABG	30.1 (201/667)	27.3 (70/256)	0.40	–	–	–
Bypass time, min	81.6 ± 42.4	87.4 ± 51.0	0.21	–	–	–
Any internal mammary artery used	99.1 (658/664)	98.0 (250/255)	0.19	–	–	–
Both internal mammary arteries used	32.4 (215/664)	19.6 (50/255)	<0.001	–	–	–
No. of grafts	2.5 ± 0.8	2.6 ± 0.8	0.50	–	–	–
No. of stents implanted	–	–	–	2.4 ± 1.5	2.6 ± 1.5	0.08
Total stent length, mm	–	–	–	48.0 ± 35.4	51.7 ± 36.4	0.09
Distal LMCA bifurcation treated	–	–	–	56.7 (366/645)	58.2 (163/280)	0.68
2-stent approach	–	–	–	33.1 (121/366)	39.3 (64/163)	0.17
Crush or mini-crush	–	–	–	10.3 (12/117)	21.9 (14/64)	0.03
FFR used	–	–	–	9.0 (59/653)	8.9 (25/281)	0.95
IVUS used	–	–	–	77.3 (505/653)	77.0 (217/282)	0.90
Duration of hospital stay, days	12.5 ± 9.5	13.2 ± 9.9	0.66	5.4 ± 5.3	5.5 ± 5.1	0.33
Discharge medications						
Aspirin	98.9 (651/658)	98.8 (245/248)	>0.99	98.9 (641/648)	99.3 (278/280)	0.73
$P2Y_{12}$ inhibitor	33.7 (223/661)	30.4 (76/250)	0.34	98.3 (639/650)	97.2 (273/281)	0.25
DAPT	33.4 (221/661)	28.8 (72/250)	0.18	97.4 (633/650)	96.1 (270/281)	0.29
Statin	92.6 (612/661)	92.0 (230/250)	0.77	96.0 (624/650)	97.5 (274/281)	0.25
Beta-blocker	92.7 (613/661)	92.0 (230/250)	0.71	83.1 (540/650)	83.6 (235/281)	0.84
ACE inhibitor or ARB	40.7 (269/661)	46.0 (115/250)	0.15	54.8 (154/281)	57.5 (374/650)	0.44

Values are % (n/N) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; FFR = fractional flow reserve; IVUS = intravascular ultrasound; LMCA = left main coronary artery; PCI = percutaneous coronary intervention.

endpoint of death, stroke, or MI, or the secondary composite endpoint of death, stroke, MI, or IDR were not significantly different between CABG and PCI in either of the nondiabetic and diabetic cohorts. The 3-year rate of all-cause death was significantly higher after PCI compared with CABG in diabetic patients (13.6% vs. 8.0%; p = 0.046), but not in nondiabetic patients (5.5% vs. 5.0%; p = 0.71). IDR rates were lower after CABG compared with PCI in both diabetic and nondiabetic patients, whereas graft occlusion or stent thrombosis rates were lower after PCI compared with CABG. There were no significant interactions between diabetes status and treatment for any of the 3-year study endpoints, including mortality.

IMPACT OF INSULIN TREATMENT. Among diabetic patients, insulin use was associated with greater 3-year rates of MI and IDR (Online Table 3). The rate of the 3-year primary composite endpoint of death, stroke, or MI was similar after PCI and CABG in both insulin-treated and non-insulin-treated diabetic patients (**Figure 2**). There were no significant interactions between insulin use, revascularization modality, and 3-year outcomes among diabetic patients (Online Table 3).

SYNTAX SCORE SUBGROUPS. Analysis according to site-reported coronary complexity showed a stepwise increase in 3-year event rates with intermediate compared with low SYNTAX scores in diabetic patients, but similar event rates in nondiabetic patients (**Figure 3**, Online Table 4). In patients with diabetes and low SYNTAX scores (0 to 22), no significant 3-year event rate differences were observed between CABG and PCI, except for IDR (7.8% vs. 17.0%, respectively; p = 0.02); however, 3-year mortality was lower after CABG compared with PCI among the 237 diabetic patients with intermediate SYNTAX scores (9.6% vs. 19.6%; p = 0.04). However, the interaction between low versus intermediate site-assessed SYNTAX score and revascularization modality for 3-year death in diabetic patients was not significant (p = 0.32). Among nondiabetic patients, rates of adverse events were not significantly different after PCI and CABG irrespective of SYNTAX scores. The results according

TABLE 3 30-Day Clinical Outcomes According to Diabetes Status and Revascularization Assignment

	All (N = 1,904)			No Diabetes (n = 1,350)			Diabetes (n = 554)			
	No Diabetes (n = 1,350)	Diabetes (n = 554)	p Value	CABG (n = 688)	PCI (n = 662)	p Value	CABG (n = 268)	PCI (n = 286)	p Value	$p_{interaction}$
Death, stroke, or MI	6.0 (80)	7.5 (41)	0.24	7.2 (49)	4.7 (31)	0.06	9.8 (26)	5.3 (15)	0.05	0.61
Death, stroke, MI, or IDR	6.3 (84)	7.6 (42)	0.29	7.8 (53)	4.7 (31)	0.02	10.2 (27)	5.3 (15)	0.03	0.69
Death	0.9 (12)	1.3 (7)	0.46	0.9 (6)	0.9 (6)	0.96	1.5 (4)	1.1 (3)	0.63	0.68
Cardiovascular	0.8 (11)	1.3 (7)	0.36	0.7 (5)	0.9 (6)	0.73	1.5 (4)	1.1 (3)	0.63	0.58
Stroke	0.8 (10)	1.5 (8)	0.15	0.9 (6)	0.6 (4)	0.55	2.3 (6)	0.7 (2)	0.13	0.44
MI	4.9 (66)	5.5 (30)	0.65	6.1 (41)	3.8 (25)	0.06	6.8 (18)	4.2 (12)	0.20	0.98
Periprocedural	4.9 (65)	4.6 (25)	0.77	5.9 (40)	3.8 (25)	0.08	6.1 (16)	3.2 (9)	0.12	0.68
Spontaneous	0.1 (1)	0.9 (5)	0.003	0.1 (1)	0	0.32	0.8 (2)	1.1 (3)	0.72	0.99
All repeat revascularization	1.0 (13)	1.3 (7)	0.56	1.3 (9)	0.6 (4)	0.18	1.5 (4)	1.1 (3)	0.63	0.66
IDR	0.9 (12)	1.3 (7)	0.46	1.3 (9)	0.5 (3)	0.09	1.5 (4)	1.1 (3)	0.63	0.48
PCI	0.5 (7)	1.3 (7)	0.09	0.6 (4)	0.5 (3)	0.74	1.5 (4)	1.1 (3)	0.63	0.92
CABG	0.4 (5)	0	0.15	0.7 (5)	0	0.03	0	0	—	>0.99
Graft occlusion or stent thrombosis	0.7 (9)	0.9 (5)	0.59	1.2 (8)	0.2 (1)	0.02	1.1 (3)	0.7 (2)	0.59	0.26
Major adverse events*	15.3 (204)	15.1 (83)	0.92	23.1 (156)	7.3 (48)	<0.001	23.5 (62)	7.4 (21)	<0.001	0.97

Values are % (n) of Kaplan-Meier time-to-first event estimates. *The composite rate of death, stroke, myocardial infarction, TIMI major or minor bleeding, transfusion ≥2 U of blood, major arrhythmia (supraventricular tachycardia requiring cardioversion, ventricular tachycardia or fibrillation requiring treatment, or bradyarrhythmia requiring temporary or permanent pacemaker), ischemia-driven revascularization, any unplanned surgery or therapeutic radiologic procedure, renal failure (serum creatinine increase by ≥0.5 mg/dl from baseline or need for dialysis), sternal wound dehiscence, infection requiring antibiotics, or prolonged intubation (>48 h).

IDR = ischemia-driven revascularization; MI = myocardial infarction; other abbreviations as in Table 2.

to core lab adjudication were similar to those from the site-reported analysis (Online Table 5, Online Figure 1).

MULTIVARIABLE ANALYSIS. As shown in Online Tables 6 and 7, diabetes was an independent predictor for the composite endpoint of death, stroke, or MI after both CABG (hazard ratio [HR]: 1.55; 95% confidence interval [CI]: 1.04 to 2.31; p = 0.03) and PCI (HR: 1.53; 95% CI: 1.04 to 2.26; p = 0.03). Diabetes was also an independent predictor of stroke after CABG and all-cause death after PCI.

DISCUSSION

The present pre-specified EXCEL substudy examined the impact of diabetes on clinical outcomes after PCI with EES versus CABG in patients with LMCAD and site-assessed low or intermediate SYNTAX scores (**Central Illustration**). Compared with nondiabetic

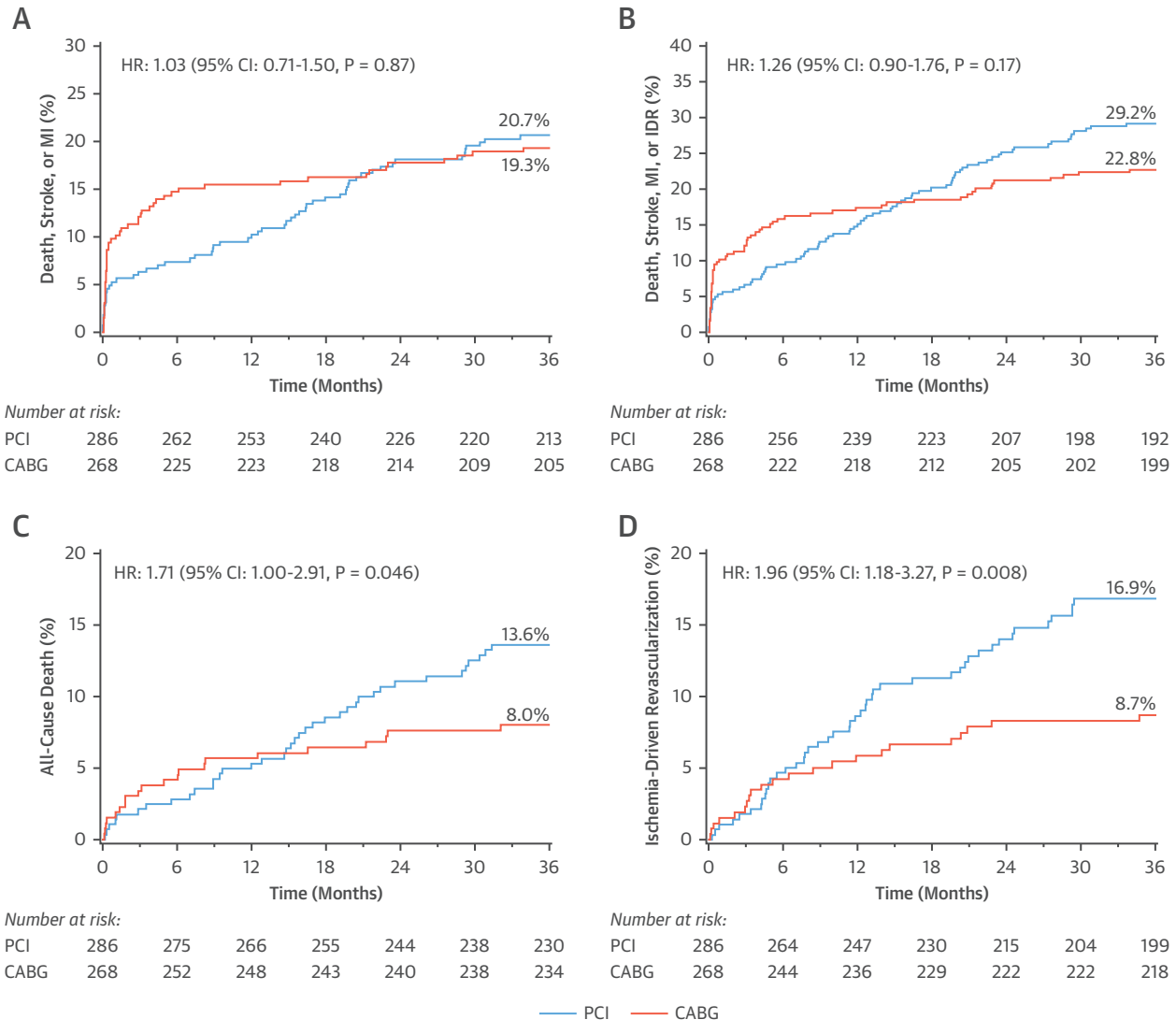
TABLE 4 3-Year Clinical Outcomes According to Diabetes Status and Revascularization Assignment

	All (N = 1,904)			No Diabetes (n = 1,350)			Diabetes (n = 554)			
	No Diabetes (n = 1,350)	Diabetes (n = 554)	p Value	CABG (n = 688)	PCI (n = 662)	p Value	CABG (n = 268)	PCI (n = 286)	p Value	$p_{interaction}$
Death, stroke, or MI	12.9 (170)	20.0 (109)	<0.001	12.9 (86)	12.9 (84)	0.89	19.3 (51)	20.7 (58)	0.87	0.82
Death, stroke, MI, or IDR	18.9 (248)	26.1 (142)	<0.001	17.5 (116)	20.2 (132)	0.28	22.8 (60)	29.2 (82)	0.17	0.65
Death	5.3 (69)	10.9 (59)	<0.001	5.0 (33)	5.5 (36)	0.71	8.0 (21)	13.6 (38)	0.046	0.22
Cardiovascular	3.1 (41)	6.2 (33)	0.002	3.1 (20)	3.2 (21)	0.85	5.4 (14)	7.0 (19)	0.48	0.68
Stroke	2.3 (30)	3.6 (19)	0.11	2.3 (15)	2.3 (15)	0.99	5.1 (13)	2.3 (6)	0.08	0.17
MI	7.3 (96)	10.5 (56)	0.03	7.5 (50)	7.1 (46)	0.73	10.8 (28)	10.3 (28)	0.76	0.99
Periprocedural	5.0 (67)	4.7 (26)	0.80	6.1 (41)	4.0 (26)	0.09	6.1 (16)	3.5 (10)	0.17	0.81
Spontaneous	2.4 (30)	6.4 (33)	<0.001	1.6 (10)	3.2 (20)	0.06	5.6 (14)	7.2 (19)	0.50	0.38
All repeat revascularizations	9.2 (117)	13.1 (68)	0.01	7.0 (45)	11.3 (72)	0.008	9.1 (23)	16.9 (45)	0.01	0.68
IDR	9.0 (115)	12.9 (67)	0.01	7.0 (45)	11.0 (70)	0.01	8.7 (22)	16.9 (45)	0.008	0.51
PCI	7.6 (97)	11.1 (58)	0.01	6.1 (39)	9.1 (58)	0.04	8.3 (21)	13.8 (37)	0.058	0.77
CABG	2.0 (26)	2.2 (11)	0.89	0.9 (6)	3.1 (20)	0.005	0.4 (1)	3.8 (10)	0.009	0.37
Graft occlusion or stent thrombosis	2.6 (34)	4.0 (21)	0.12	4.8 (31)	0.5 (3)	<0.001	6.7 (17)	1.5 (4)	0.002	0.32

Values are % (n) of Kaplan-Meier time-to-first event estimates.

Abbreviations as in Tables 2 and 3.

FIGURE 1 **3-Year Outcomes of PCI Versus CABG in Diabetic and Nondiabetic Patients**

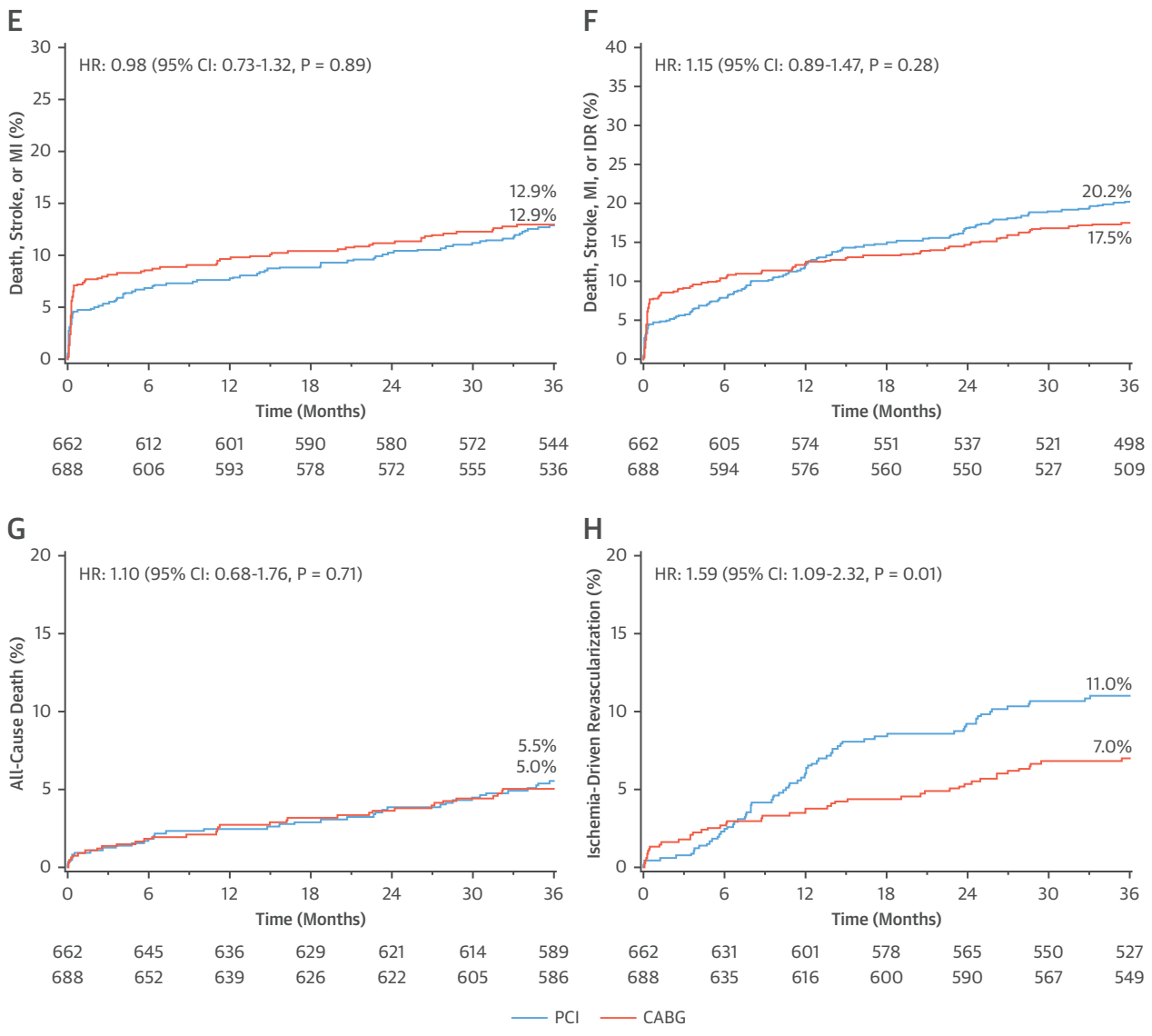


Kaplan-Meier estimates of the composite endpoint of all-cause death, stroke, or myocardial infarction (MI); the composite endpoint of all-cause death, stroke, MI, or ischemia-driven repeat revascularization; all-cause death; and IDR in patients with **(A to D)** and without **(E to H)** diabetes. p Values are by log-rank test. CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; IDR = ischemia-driven revascularization; PCI = percutaneous coronary intervention.

Continued on the next page

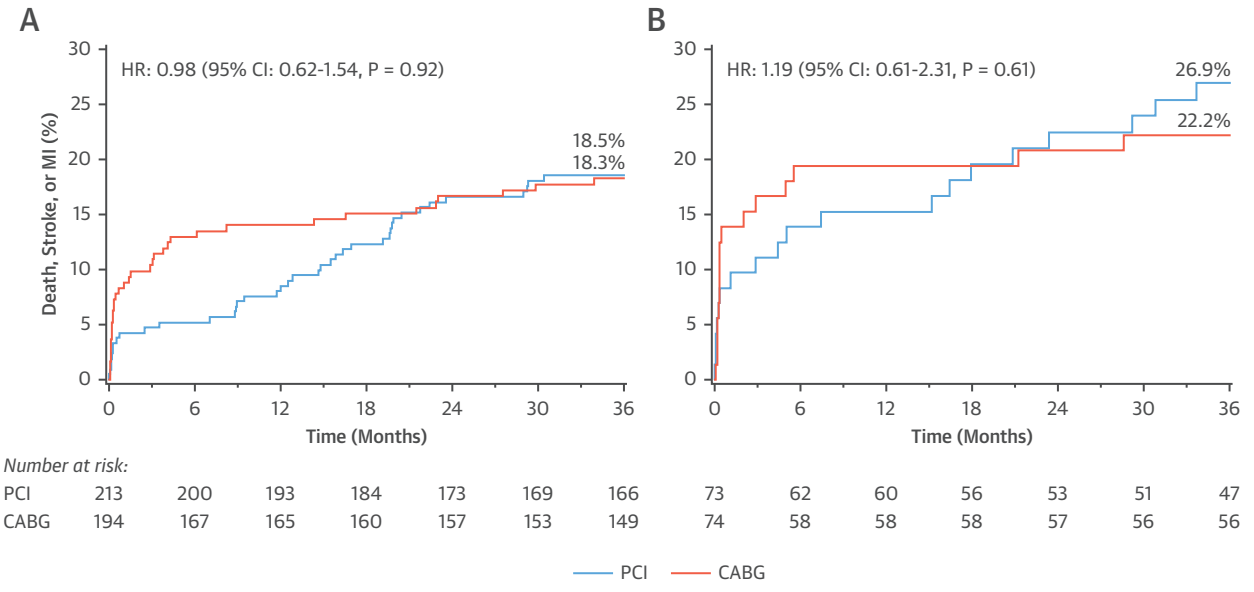
patients, diabetic patients with LMCAD were at a nearly 2-fold higher risk for all-cause death, stroke, or MI at 3 years. There was no significant difference in the 3-year composite primary endpoint of death, stroke, or MI or the powered 3-year secondary endpoint of death, stroke, MI, or IDR after PCI or CABG either in the diabetic or nondiabetic strata. Thirty-day adverse events were significantly less after PCI compared with CABG both in diabetic and nondiabetic patients. Conversely, all-cause mortality at 3 years was greater after PCI compared with CABG among diabetic patients with higher site-assessed SYNTAX scores, although the interaction between site-assessed SYNTAX score and revascularization modality for 3-year death in diabetic patients was not significant. IDR at 3 years was higher with PCI, whereas graft failure or thrombosis rates were higher after CABG, both irrespective of diabetic status.

FIGURE 1 Continued



Our findings confirm that diabetes is a critical determinant of long-term outcomes after myocardial revascularization (3,4). Currently, no specific recommendation exists concerning the optimal revascularization strategy in diabetic patients with LMCAD (6). Given the clinical and anatomic complexity that is frequently present in this high-risk subgroup, the selection between CABG and PCI in diabetic patients requires careful consideration. Large-registry data show a substantial increase in the number of patients with diabetes and LMCAD undergoing PCI over the last 20 years, although outcomes data are scarce (11). Before the present report, comparative effectiveness data for PCI with drug-eluting stents (DES) versus CABG in diabetic patients were limited to small subgroup analyses from clinical trials. In a pooled analysis of individual patient data from the PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) and the SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trials, Cavalcante et al. (12) found no difference in the occurrence of major adverse events between CABG and PCI with first-generation DES in LMCAD patients with or without diabetes at 5-year follow-up. The present results in which second-generation EES and

FIGURE 2 **3-Year Outcomes in Patients with Diabetes Stratified by Insulin Treatment**



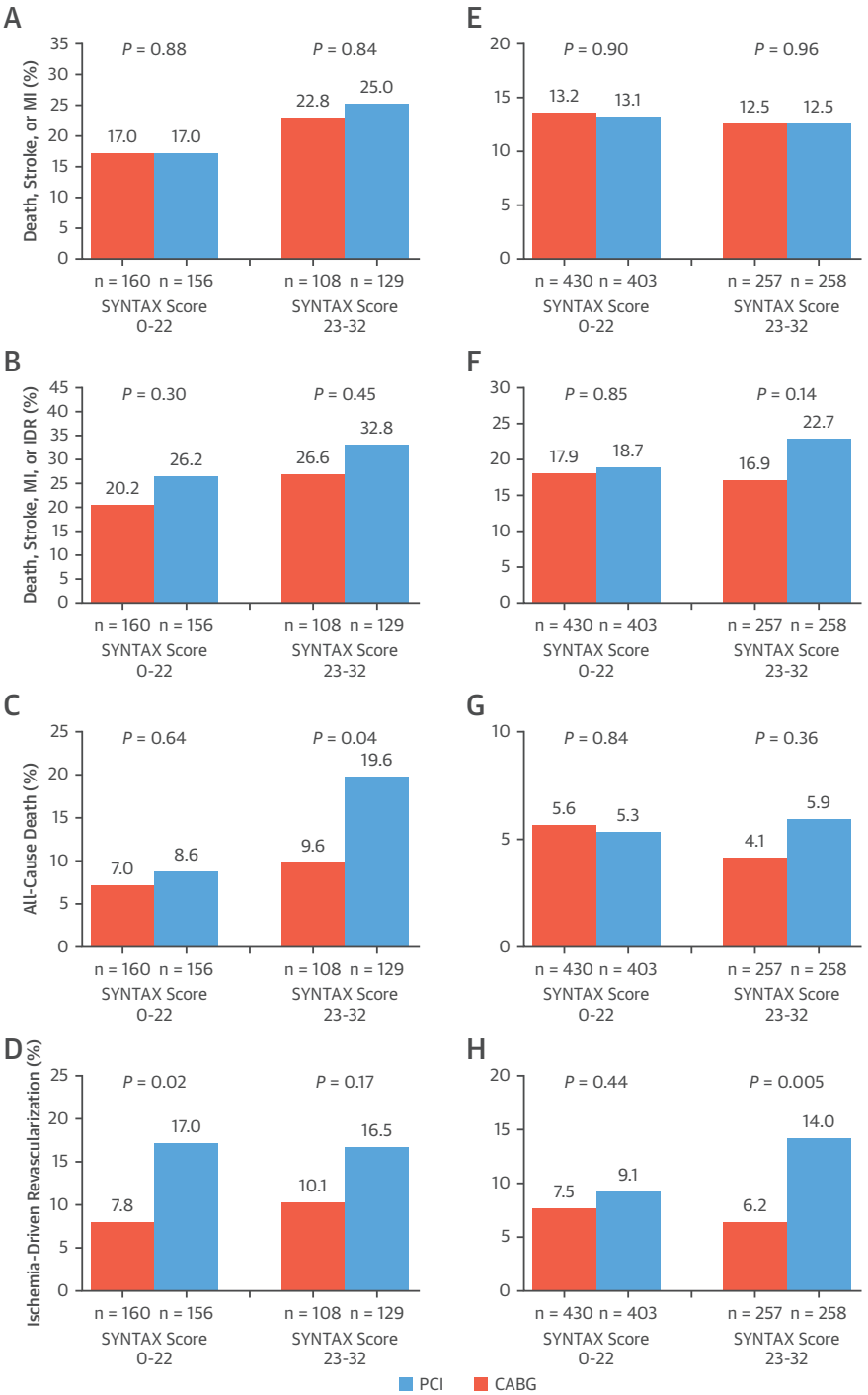
Kaplan-Meier estimates of the composite endpoint of all-cause death, stroke, or MI among non–insulin-treated **(A)** and insulin-treated **(B)** patients. The p values are by log-rank test. Abbreviations as in Figure 1.

contemporary CABG techniques were evaluated are consistent with these findings and indicate that both revascularization strategies result in comparable rates of major adverse events at 3 years.

Although PCI resulted in substantially fewer major adverse events at 30 days in both diabetic and nondiabetic patients, an important consideration affecting the selection of revascularization procedure is long-term survival. In this regard, a large propensity-matched analysis of 4,048 patient-pairs from the New York State outcomes registries suggested that the apparent survival benefit of CABG over PCI in diabetic patients in the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) and SYNTAX trials (3,4) might be lost when PCI was performed with EES (13); however, registries are particularly sensitive to the occurrence of selection bias, and these results must be interpreted with caution (14). Among the 554 diabetic patients randomized in the EXCEL trial, a significant difference in mortality between CABG and PCI was observed in those with higher SYNTAX scores; however, the EXCEL trial was not powered for mortality in the entire population, let alone the diabetic subgroup, and no interaction was noted between diabetic status, revascularization, and 3-year mortality. In a recently published pooled analysis of individual randomized patient data (15) from the SYNTAX, PRECOMBAT, EXCEL, and NOBLE (PCI vs. CABG in the Treatment of Unprotected Left Main Stenosis) trials (8,16-18), there was no significant difference in 5-year mortality after treatment of 4,478 patients with LMCAD with PCI versus CABG (10.7% vs. 10.5%; HR: 1.07; 95% CI: 0.87 to 1.33; p = 0.52), either in patients with (n = 1,120; HR: 1.34; 95% CI: 0.93 to 1.31) or without (n = 3,358; HR: 0.94; 95% CI: 0.72 to 1.23) diabetes. In this analysis, CABG did, however, result in superior survival to PCI in diabetic patients with multivessel disease (but without LMCA involvement), again suggesting that in general patients with diabetes and complex CAD may preferentially benefit by CABG.

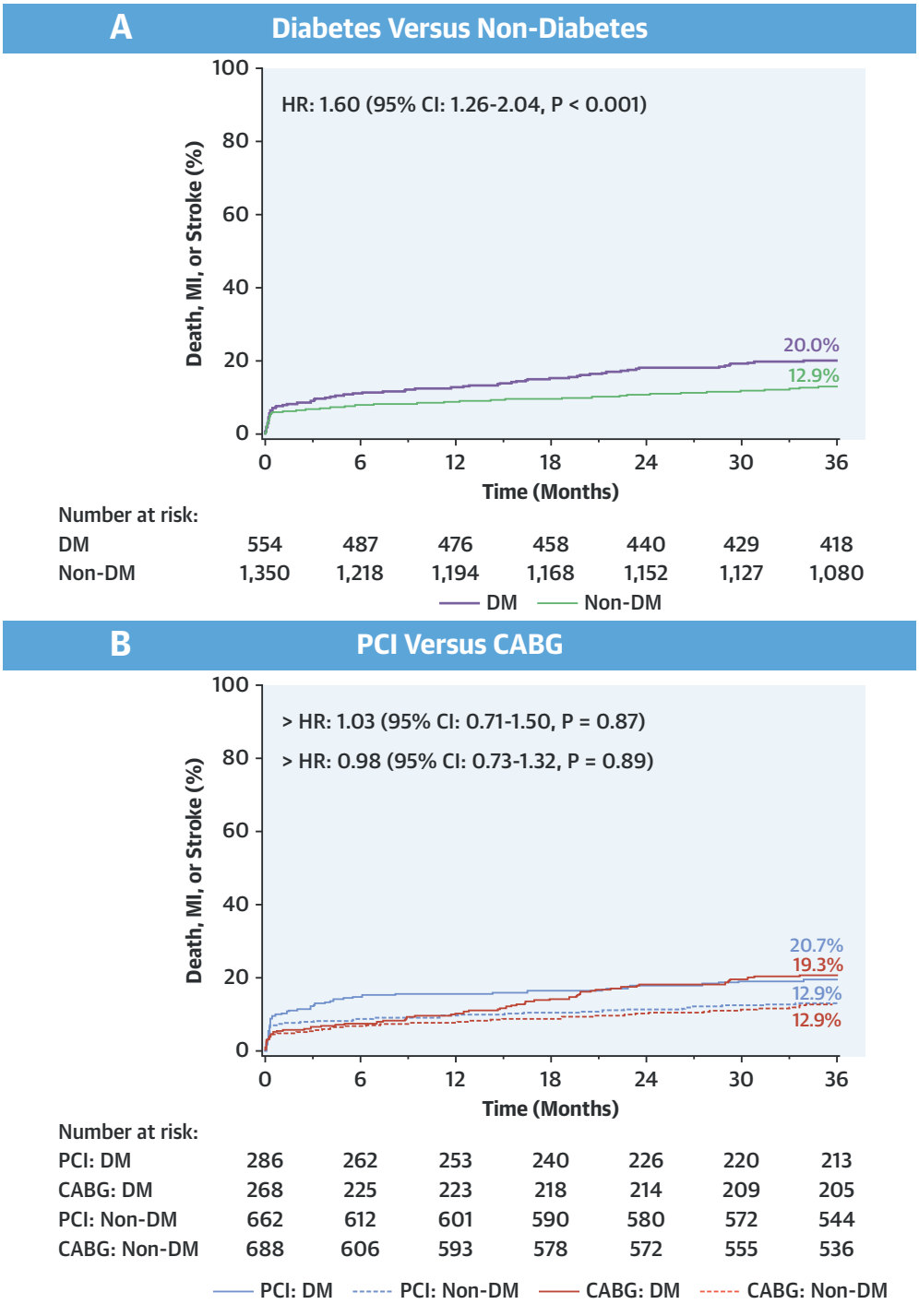
Finally, despite the fact that evidence supports the recommendation of increasing use of BIMA grafts during CABG in diabetic patients who are at low risk of deep sternal wound infection (6,19,20), rates of BIMA usage are still relatively low (only 19.6% of diabetic patients in the present trial). No significant differences in sternal wound dehiscence were observed in diabetic patients treated with a single internal mammary artery versus BIMA in the EXCEL trial. It is also noteworthy that adherence rates to

FIGURE 3 **3-Year Outcomes for Diabetic and Nondiabetic Patients According to Anatomic Lesion Complexity as Measured by the Site-Assessed SYNTAX Score**



Kaplan-Meier estimates of the composite endpoint of all-cause death, stroke, or MI; the composite endpoint of all-cause death, stroke, MI, or ischemia-driven repeat revascularization (IDR); all-cause death; and IDR in diabetic patients **(A to D)** and nondiabetic patients **(E to H)**. Treatment by SYNTAX score interactions in the diabetic and the nondiabetic groups: The composite endpoint of all-cause death, stroke, or MI ($p_{int} = 0.81$ and $p_{int} = 0.98$); the composite endpoint of all-cause death, stroke, MI, or IDR ($p_{int} = 0.87$ and $p_{int} = 0.31$); all-cause death ($p_{int} = 0.32$ and $p_{int} = 0.40$); and IDR ($p_{int} = 0.63$ and $p_{int} = 0.10$). p Values are by log-rank test. Rates are separated according to the site-reported SYNTAX score values, indicating low (0 to 22) and intermediate (23 to 32) anatomic lesion complexity. SYNTAX = Synergy Between PCI With TAXUS and Cardiac Surgery; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Impact of Diabetes Mellitus on 3-Year Outcomes After Left Main Revascularization**



Milojevic, M. et al. J Am Coll Cardiol. 2019;73(13):1616-28.

The incidence rates of the primary composite endpoint of death, stroke, or MI among diabetic and non-diabetic patients **(A)** and according to the type of revascularization procedure **(B)** are shown. Over the 3-year follow-up period, PCI with EES compared with CABG was associated with similar risk of the primary composite endpoint among both diabetic and nondiabetic patients. CABG = coronary artery bypass grafting; CI = confidence interval; DM = diabetes mellitus; EES = everolimus-eluting stents; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.

guideline-directed medication therapy after CABG have reached 90% in the EXCEL trial (21) but remain lower than after PCI. Of note, approximately one-third of CABG patients were discharged on dual antiplatelet therapy, which, although less than after PCI, represents a higher percentage than in some other studies. This may reflect appropriate use after CABG in patients presenting with acute coronary syndromes, as well as the potential for dual antiplatelet therapy to enhance graft patency (22), the topic of several ongoing randomized controlled trials (Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis [TARGET], NCT02053909; Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery [POPular CABG], NCT02352402; Study Comparing Ticagrelor With Aspirin for Prevention of Vascular Events in Patients Undergoing CABG [TiCAB], NCT01755520). Optimizing guideline-directed medication therapy after both CABG and PCI is essential for patients to derive the most benefits from revascularization.

STUDY LIMITATIONS. Although randomization was stratified by diabetes status, and the diabetes subgroup analysis was pre-specified in the EXCEL trial design, the present study was not powered to detect a difference in the primary endpoint of death, stroke, or MI between PCI and CABG in the diabetic cohort, and secondary outcome measures were not adjusted for multiple comparisons. Hence, the results of the present study should be interpreted as hypothesis-generating only, and further investigation in dedicated trials of diabetic patients are warranted (23,24). In addition, the EXCEL trial enrolled patients with LMCAD and site-assessed low or intermediate SYNTAX scores who were eligible to undergo both PCI and CABG. Therefore, these findings cannot be extrapolated either to patients with unacceptable high surgical risk or patients with coronary anatomy unsuitable for PCI. A major focus of diabetes management is optimal glycemic control. Recently, the use of gliflozins has been shown to reduce the risk of major cardiovascular events in patients with type 2 diabetes (25). Unfortunately, the use of specific oral hypoglycemic agents and data on long-term glycemic control were not collected in the present study. Finally, follow-up in the EXCEL trial is complete only through 3 years; longer-term surveillance is necessary to examine whether additional differences emerge over time.

CONCLUSIONS

In the large-scale EXCEL trial, among both diabetic and nondiabetic patients with LMCAD and site-assessed low-to-intermediate (≤32) SYNTAX scores, PCI using EES and CABG resulted in similar rates of the primary composite endpoint of death, stroke, or MI at 3-year follow-up, although fewer adverse events at 30 days occurred after PCI. For diabetic patients with LMCAD and relatively noncomplex coronary anatomy, PCI may be a reasonable approach, whereas CABG should be considered for diabetic patients with more complex CAD.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Patients with diabetes mellitus and LMCAD undergoing myocardial revascularization are at higher risk of mortality and major adverse events than those without diabetes. In a randomized trial, there was no difference in the 3-year composite endpoint of all-cause death, stroke, or myocardial infarction between PCI and CABG, irrespective of baseline diabetes status.

TRANSLATIONAL OUTLOOK: Although CABG remains the standard of care for diabetic patients with complex CAD, further studies are needed to ascertain the characteristics of patients with diabetes who can be appropriately managed by percutaneous intervention.

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KEY WORDS coronary artery bypass grafting, diabetes, left main disease, percutaneous coronary intervention, SYNTAX score

APPENDIX For supplemental tables and a figure, please see the online version of this paper.