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ORIGINAL RESEARCH

Ten-year Outcomes After Drug-Eluting Stents or Bypass Surgery for Left Main Coronary Disease in Patients With and Without Diabetes Mellitus: The PRECOMBAT Extended Follow-Up Study

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BACKGROUND: Several trials reported differential outcomes after percutaneous coronary intervention with drug-eluting stents (DES) and coronary-artery bypass grafting (CABG) for multivessel coronary disease according to the presence of diabetes mellitus (DM). However, it is not well recognized how DM status affects very-long-term (10-year) outcomes after DES and CABG for left main coronary artery disease.

METHODS AND RESULTS: In the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial, patients with LMCA were randomly assigned to undergo PCI with sirolimus-eluting stents (n=300) or CABG (n=300). The primary outcome was the incidence of major adverse cardiac or cerebrovascular events (MACCE; a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization). Outcomes were examined in patients with (n=192) and without (n=408) medically treated diabetes. The follow-up was extended to at least 10 years for all patients (median, 11.3 years). The 10-year rates of MACCE were not significantly different between DES and CABG in patients with DM (36.3% versus 26.7%, respectively; hazard ratio [HR], 1.35; 95% CI, 0.83–2.19; *P*=0.23) and without DM (25.3% versus 22.9%, respectively; HR, 1.15; 95% CI, 0.79–1.67; *P*=0.48) (*P*-for-interaction=0.48). There were no significant between-group differences in composite of death, MI, or stroke, and all-cause mortality, regardless of DM status. TVR rates were consistently higher after DES than CABG.

CONCLUSIONS: In this 10-year extended follow-up of PRECOMBAT, we found no significant difference between DES and CABG with respect to the incidences of MACCE, serious composite outcome, and all-cause mortality in patients with and without DM with LMCA disease. However, owing to the limited number of patients and no adjustment for multiple testing, overall findings should be considered hypothesis-generating, highlighting the need for further research.

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Key Words: coronary artery bypass grafting ■ drug-eluting stents ■ left main coronary artery disease ■ percutaneous coronary intervention

See Editorial by Ben-Dor and Waksman.

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CLINICAL PERSPECTIVE

What Is New?

- It is still unknown whether the presence of medically treated diabetes mellitus can influence the very long-term (beyond 10 years) outcomes after percutaneous coronary interaction with drug-eluting stents and coronary artery bypass grafting in patients with left main coronary artery disease.

What Are the Clinical Implications?

- In this 10-year extended follow-up of the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial specifically targeting patients with left main coronary artery disease, we observed that the 10-year rates of primary composite of major adverse cardiac or cerebrovascular events, mortality, and serious composite of death, myocardial infarction, or stroke were similar between percutaneous coronary interaction and coronary artery bypass grafting in patients with and without diabetes mellitus.
- Therefore, there was no substantial interaction between diabetes mellitus status and revascularization type on 10-year clinical outcomes.
- Further larger studies are required to support our conclusion that the presence of diabetes mellitus should not penalize the specific revascularization strategy for left main coronary artery disease in a heart team's discussion for optimal decision making in contemporary clinical practice.

Nonstandard Abbreviations and Acronyms

DES	drug-eluting stent
DM	diabetes mellitus
LMCA	left main coronary artery
PRECOMBAT	Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease

Among various forms of obstructive coronary artery disease (CAD), the left main coronary artery (LMCA) disease is associated with high morbidity and mortality due to the large, jeopardized amount of myocardium at risk.[1,2] Although coronary artery bypass graft surgery (CABG) has been the first choice of coronary revascularization for LMCA disease, great strides have been made regarding percutaneous coronary intervention (PCI) in the treatment of complex CAD including LMCA disease. Furthermore, recent evidence has demonstrated that PCI with drug-eluting stents (DES) is a safer and more effective modality for patients with LMCA disease and low-to-intermediate anatomic complexity as compared with CABG.[3–6]

Diabetes mellitus (DM) is a major risk and prognostic factor in patients with obstructive CAD.[7,8] Patients with DM, compared with those without DM, usually have more diffuse, complex, and rapidly progressive forms of atherosclerotic CAD, which is associated with increased cardiovascular events and mortality.[9] Therefore, the guidelines on myocardial revascularization recommend that CABG is still preferred to PCI for patients with DM and multivessel or complex anatomic CAD including LMCA disease.[10] However, until recently, there have been limited data regarding the impact of DM on the relative treatment effects of PCI and CABG as well as on decision making for specific revascularization strategies in patients with LMCA disease. In addition, given that a detrimental effect of DM on cardiovascular outcomes might be less prominent within a limited follow-up duration, there is scarce extended (>10 years) follow-up data to fully elucidate the extent to which DM influences the comparative outcomes after PCI and CABG over a long time period.[11,12] We therefore determined whether an interaction exists between the presence of medically treated DM and long-term effects of PCI with DES versus CABG, using data from the extended 10-year follow-up of the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial.[5]

METHODS

Study Design, Patient Population, and Follow-Up

Anonymized data and materials have been made publicly available from the corresponding author upon reasonable requests. The protocol, trial design, patient eligibility criteria, and methods of the PRECOMBAT trial have been described previously,[13,14] and the primary results of the 10-year extended follow-up was recently reported.[5] The PRECOMBAT trial was a prospective, multicenter, unblinded randomized trial, in which patients with unprotected LMCA disease were randomly assigned to undergo PCI with sirolimus-eluting stents (n=300) or CABG (n=300) in 13 hospitals in Korea from April 2004 to August 2009. Patients were assessed for

clinical and anatomic eligibility by the cardiologists and surgeons at each participating site, which was considered equally suitable for both PCI and CABG. Randomization was performed using an interactive web-based response system and stratified according to the participating centers. Details of the PCI and CABG procedures have been described previously.[5,13,14] The trial was approved by the investigational review board or ethics committee at each participating center. All patients provided written informed consent before enrollment.

All participating centers agreed to participate in the extended 10-year follow-up study.[5] During follow-up, guideline-directed medical therapy and management of risk factors for secondary prevention were highly recommended for all patients. To adequately maintain glycemic control, all patients were treated following the newest guidelines and managed by endocrinologists. Information on adverse clinical events and survival data (vital status, cause of death, and date of death) was obtained through a review of electronic healthcare records and national death registry checks of the Korean National Health Insurance Service database, which was merged from the Statistics Korea database. The National Health Insurance Service is a single-payer program of a universal health coverage system in Korea and provides mandatory health care for all Korean citizens, with an enrollment rate of more than 97%.[15] The trial is registered at clinicaltrials.gov with the identifier NCT03871127.

Study End Points and Definitions

The primary outcome was a composite of major adverse cardiac and cerebrovascular events (MACCE; a composite of death from any cause, nonfatal myocardial infarction [MI], nonfatal stroke, or ischemia-driven target vessel revascularization [TVR]).[5] Major secondary outcomes included the individual components of the primary end point; serious composite outcome of death, MI, or stroke; any revascularization; and stent thrombosis or symptomatic graft occlusion.

The definitions of these outcome measures have been previously described in detail.[5,13,14] In brief, death was considered to have a cardiovascular cause unless an unequivocal, non-cardiovascular cause could be established. Protocol definition of MI was the appearance of both new Q-waves and creatine kinase-myocardial band to >5× the upper reference limit within 48 hours after PCI/CABG (periprocedural MI), or a rise in creatine kinase-myocardial band >1× the upper reference limit plus new ischemic symptoms or signs >48 hours after PCI/CABG (spontaneous MI). Stroke was defined as a focal neurological deficit resulting from vascular lesions of the brain lasting >24 hours, confirmed by a neurologist and imaging. Revascularization events were classified as either ischemia-driven or non–ischemia-driven by pre-specified criteria.[5] All primary and secondary outcome events were centrally adjudicated by an independent clinical-events committee, with source documents at each hospital.

Medically treated DM was defined as DM for which the patient was receiving oral hypoglycemic agents or insulin at the time of enrollment.

Statistical Analysis

Outcomes of patients randomized to PCI versus CABG were evaluated and stratified by the presence of medically treated DM. Although no formal statistical hypothesis was defined a priori, subgroup analysis according to DM status with formal interaction testing was pre-specified in the statistical analysis plan in the PRECOMBAT 10-year follow-up study protocol. Primary 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.

A descriptive analysis was performed, and data was presented as the mean (SD) or number (proportion). Continuous variables were compared with Student's *t* test or the Wilcoxon rank-sum test, and categorical variables were compared with the $\chi 2$ test or Fisher's exact test. Cumulative event rates were calculated using the Kaplan-Meier estimates, with event or censoring times calculated from the date of randomization. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses and were compared by the log-rank test. A Cox proportional-hazards model was used to compare the rates of primary and secondary end points between groups, and hazard ratios (HRs) were presented with 95% CIs. For these models, all available follow-up data were used for long-term outcome analyses without censoring clinical events beyond 10 years; thus, patients lost to follow-up were included in the analyses for all outcomes by censoring at the date of last follow-up. The assumptions of the Cox model were assessed statistically based on Schoenfeld residuals and graphically by log-log plots; they were found to be approximately satisfied for all variables.

As sensitivity analyses, we performed the as-treated analyses (in which patients were compared based on the treatment they actually received) and the per-protocol analyses (which included only patients who actually received their randomly assigned treatment). Analyses according to conventional Synergy Between PCI with TAXUS and Cardiac Surgery (SYNTAX) score tertiles (low, <23; intermediate, 23–32; high, >32) were also performed using 10-year Kaplan-Meier event estimates.

Table 1. Baseline Characteristics of Patients According to DM Status and Revascularization Assignment

	Overall Patients (n=600)			Patients With DM(n=192)			Patients Without DM (n=408)		
	DM(n=192)	No DM (n=408)	*P* Value	PCI (n=102)	CABG (n=90)	*P* Value	PCI (n=198)	CABG (n=210)	*P* Value
Age, y	63.2±8.8	61.8±10.1	0.07	63.2±8.8	63.2±8.7	0.99	61.0±10.4	62.5±9.8	0.15
Male sex	145 (75.5)	314 (77.0)	0.78	72 (70.6)	73 (81.1)	0.13	156 (78.8)	158 (75.2)	0.46
Body mass index, kg/m^2	24.8±3.1	24.4±2.8	0.14	24.6±2.7	25.0±3.5	0.36	24.6±2.7	24.3±2.8	0.29
Hypertension	115 (59.9)	202 (49.5)	0.02	67 (65.7)	48 (53.3)	0.11	96 (48.5)	106 (50.5)	0.76
Hyperlipidemia	83 (43.2)	164 (40.2)	0.54	51 (50.0)	32 (35.6)	0.06	76 (38.4)	88 (41.9)	0.53
Current smoker	60 (31.2)	112 (27.5)	0.39	30 (29.4)	30 (33.3)	0.67	59 (29.8)	53 (25.2)	0.36
Previous MI	12 (6.2)	21 (5.1)	0.72	3 (2.9)	9 (10.0)	0.09	10 (5.1)	11 (5.2)	>0.99
Previous PCI	23 (12.0)	53 (13.0)	0.83	12 (11.8)	11 (12.2)	>0.99	26 (13.1)	27 (12.9)	>0.99
Previous heart failure	2 (1.0)	0 (0.0)	0.89	0 (0.0)	2 (2.2)	0.42	0	0	NA
Chronic renal failure	3 (1.6)	2 (0.5)	0.39	2 (2.0)	1 (1.1)	>0.99	2 (1.0)	0 (0.0)	0.45
Peripheral artery disease	10 (5.2)	12 (2.9)	0.25	7 (6.9)	3 (3.3)	0.44	8 (4.0)	4 (1.9)	0.33
Chronic lung disease	6 (3.1)	10 (2.5)	0.84	0 (0.0)	6 (6.7)	0.03	6 (3.0)	4 (1.9)	0.68
Clinical presentation			0.13			0.19			0.01
Stable angina	92 (47.9)	205 (50.2)		45 (44.1)	47 (52.2)		115 (58.1)	90 (42.9)	
Unstable angina	85 (44.3)	187 (45.8)		51 (50.0)	34 (37.8)		77 (38.9)	110 (52.4)	
Recent MI	15 (7.8)	16 (3.9)		6 (5.9)	9 (10.0)		6 (3.0)	10 (4.8)	
Ejection fraction, %	57.5±13.0	60.8±11.7	<0.001	58.8±10.1	58.7±9.9	0.95	63.1±6.8	61.4±7.7	0.02
Left main disease location			0.37			0.36			0.53
Ostial or shaft	118 (61.8)	265 (65.9)		35 (34.7)	38 (42.2)		64 (32.3)	73 (35.8)	
Distal bifurcation	73 (38.2)	137 (34.1)		66 (65.3)	52 (57.8)		134 (67.7)	131 (64.2)	
Extent of diseased vessel			0.02			0.88			0.81
LM only	11 (5.7)	50 (12.3)		5 (4.9)	6 (6.7)		22 (11.1)	28 (13.3)	
LM+1-vessel disease	27 (14.1)	76 (18.6)		13 (12.7)	14 (15.6)		37 (18.7)	39 (18.6)	
LM+2-vessel disease	71 (37.0)	120 (29.4)		39 (38.2)	32 (35.6)		62 (31.3)	58 (27.6)	
LM+3-vessel disease	83 (43.2)	162 (39.7)		45 (44.1)	38 (42.2)		77 (38.9)	85 (40.5)	
Euroscore	2.7±1.9	2.7±1.8	0.94	2.8±1.8	2.7±1.9	0.61	2.5±1.8	2.9±1.8	0.04
SYNTAX Score									
Mean	26.4±9.8	24.0±10.5	0.01	26.6±9.3	26.2±10.4	0.82	23.1±9.6	25.0±11.2	0.07
Conventional category			0.01			0.79			0.04

(*Continued*)

Table 1. (Continued)

	Overall Patients (n=600)			Patients With DM(n=192)			Patients Without DM (n=408)		
	DM(n=192)	No DM (n=408)	*P* Value	PCI (n=102)	CABG (n=90)	*P* Value	PCI (n=198)	CABG (n=210)	*P* Value
<23 (low-risk)	60 (33.1)	180 (47.0)		31 (31.0)	29 (35.8)		100 (52.6)	80 (41.5)	
23–32 (intermediate-risk)	73 (40.3)	126 (32.9)		42 (42.0)	31 (38.3)		60 (31.6)	66 (34.2)	
>32 (high-risk)	48 (26.5)	77 (20.1)		27 (27.0)	21 (25.9)		30 (15.8)	47 (24.4)	
Complete revascularization	128 (66.7)	288 (70.6)	0.38	67 (65.7)	61 (67.8)	0.88	138 (69.7)	150 (71.4)	0.78

CABG indicates coronary artery bypass grafting; DM, diabetes mellitus; LM, left main disease; MI, myocardial infarction; NA, not analyzable; PCI, percutaneous coronary intervention; and SYNTAX, synergy between percutaneous coronary intervention with TAXUS and cardiac surgery

All reported *P* values were two-sided, and $P<0.05$ was considered significant for all tests. No adjustment for multiple testing was undertaken. Because of the potential for type I error due to multiple comparisons, all findings of this study should be interpreted as exploratory. All statistical analyses were performed using R 3.6.1. (R Foundation for Statistical Computing; Vienna, Austria).

RESULTS

Study Population and Baseline Characteristics

From April 2004 through August 2009, in the PRECOMBAT trial, a total of 600 of patients with unprotected LMCA disease were randomly assigned to PCI with sirolimus-eluting stents (300 patients) or to CABG (300 patients). A total of 192 patients (32.0%) had DM, of which 19 (9.9%) patients were treated with insulin and 173 (90.1%) patients with oral hypoglycemic agents without insulin. Of the patients with DM, 102 and 90 patients were randomized to PCI and CABG, respectively. Of the patients without DM, 198 and 210 patients were allocated to PCI and CABG, respectively.

The baseline characteristics of the patients according to DM status and revascularization assignment are summarized in Table 1. In general, patients with DM had a greater number of comorbidities compared with patients without DM, including hypertension, lower ejection fraction, a higher extent of diseased vessels, and a higher SYNTAX score. Most of the baseline characteristics were not significantly different between PCI and CABG in both populations with and without DM, except that there were slightly imbalances in baseline characteristics between PCI versus CABG in the DM (chronic lung disease) and non-DM group (clinical presentation, ejection fraction, Euroscore, and SYNTAX score category). The procedural or operative data according to DM status are provided in Tables 2 and Table 3. The mean stent number and length per patient were significantly higher in patients with DM than in patients without DM. However, the number and length of stent implanted to the LMCA and bifurcation treatment were not significantly different between patients with DM and patients without DM. With respect to operative aspects, there were no significant difference in CABG characteristics between diabetic and non-diabetic groups.

Follow-Up and 10-Year Outcomes According to DM Status

The median duration of follow-up was 11.3 years (interquartile range, 10.2–13.0). The 10-year follow-up for

Table 2. Procedural Characteristics According to DM Status in Patients Who Allocated to PCI Group

	DM (n=102)	No DM (n=198)	*P* Value
PCI procedures			
Total stent number in LMCA	1.8±0.8	1.6±0.9	0.09
Total stent length in LMCA	39.2±22.2	35.7±21.0	0.20
Total stent number per patient	3.0±1.4	2.5±1.4	0.01
Total stent length per patient, mm	74.0±42.2	60.2±38.1	0.01
Intravascular ultrasound-guided PCI	77 (77.0)	155 (77.5)	0.99
Distal LMCA bifurcation treatment			0.77
Single-stent technique	74 (72.5)	139 (70.2)	
Two-stent technique	28 (27.5)	59 (29.8)	

DM indicates diabetes mellitus; LMCA, left main coronary artery; and PCI, percutaneous coronary intervention.

all clinical end point events was achieved in 288 (96.0) patients randomized to each of PCI and CABG.

Clinical outcomes according to DM status and treatment assignment are shown in Table 4. Compared with patients without DM, patients with DM had higher 10-year rates of the primary composite end point of MACCE (Figure 1). The 10-year rates of all-cause mortality; serious composite of death, MI, or stroke; ischemic-driven TVR; and any revascularization also tended to be higher in patients with DM versus those without DM (Figure S1).

As shown in Table 4 and Figure 2, there were no significant differences with respect in the primary end point of MACCE in patients with DM randomized to PCI versus CABG (hazard ratio [HR], 1.35; 95% CI, 0.83–2.19; *P*=0.23). There were also no significant differences in the secondary outcomes of death, MI, stroke, and its composite outcomes in the diabetic population between the PCI and CABG groups (Figure S2). However, the rates of ischemic-driven TVR and any revascularization were significantly higher after PCI than after CABG in patients with DM. Similarly, there were no significant differences in primary end point of MACCE (HR, 1.15; 95% CI, 0.79–1.67; *P*=0.48) and secondary outcomes of death, MI, stroke, and its composite in patients without DM randomized to PCI versus CABG. The rates of TVR and any revascularization was consistently higher after PCI even in the non-diabetic population. Therefore, there were no significant interactions between DM status and revascularization treatment for any of the 10-year study end points including MACCE (*P*=0.48); serious composite of death, MI, or stroke (*P*=0.70); all-cause mortality (*P*=0.76); and ischemic-driven TVR (*P*=0.60).

Table 3. Operative Characteristics According to DM Status in Patients Who Allocated to CABG Group

	DM (n=90)	No DM (n=210)	*P* Value
CABG procedures			
Number of grafts per patient	2.8±0.9	2.7±0.9	0.35
Number of arterial grafts	2.1±0.9	2.1±0.9	0.84
Number of vein graft	0.7±0.9	0.6±0.9	0.10
Use of left internal mammary artery	70 (93.3)	163 (94.2)	0.99
Off-pump surgery	52 (57.8)	103 (49.0)	0.21

CABG indicates coronary artery bypass grafting surgery; and DM, diabetes mellitus.

Sensitivity and Key Subgroup Analysis

We performed an as-treated analysis comparing patients who were actually treated with PCI or were actually treated with CABG (Table S1). There was no significant difference in the risk for the primary outcome of MACCE after PCI and CABG in patients with DM and without DM. This finding was also consistent in a per-protocol comparing patients randomly assigned to PCI who actually received PCI and patients assigned to CABG who actually underwent CABG (Table S2). In these sensitivity analyses including the as-treated and per-protocol populations, there were no significant interactions between DM status and treatment effect of PCI versus CABG on 10-year rates of primary and any secondary outcomes.

We also analyzed the differences in outcomes after PCI and CABG according to SYNTAX category (stratified by a low score of <23, an intermediate score of 23–32, and a high score of >32) in the diabetic and non-diabetic populations (Figure S3). In general, there was a stepwise increase in the 10-year event rates after PCI and CABG with increasing levels of SYNTAX scores. In patients with DM, there was no significant interaction between the SYNTAX categories and the relative treatment effect of PCI and CABG with regard to primary and key secondary outcomes. However, in patients without DM, there was a tendency for a higher relative risk of primary composite outcomes in higher SYNTAX categories (*P*-for-interaction=0.011). This was mainly driven by ischemia-driven TVR, which had occurred more often after PCI than after CABG in higher SYNTAX categories (*P*-for-interaction=0.001).

Table 4. Ten-Year Clinical Outcomes According to DM Status and Revascularization Assignment*

Event rates, n (%)	Overall			Patients With DM				Patients Without DM				
	DM (n=102)	No DM (n=408)	*P* Value	PCI (n=102)	CABG (n=90)	Hazard Ratio† (95% CI)	*P* Value	PCI (n=198)	CABG (n=210)	Hazard Ratio† (95% CI)	*P* Value	*P*-Int‡
Primary outcome												
MACCE§	61 (31.8)	98 (24.0)	0.04	37 (36.3)	24 (26.7)	1.35 (0.83–2.19)	0.23	50 (25.3)	48 (22.9)	1.15 (0.79–1.67)	0.48	0.48
Secondary outcome												
Death from any cause	32 (16.7)	50 (12.3)	0.18	18 (17.6)	14 (15.6)	1.12 (0.56–2.26)	0.35	24 (12.1)	26 (12.4)	1.02 (0.60–1.73)	0.94	0.76
Cardiac death	20 (10.4)	27 (6.6)	0.15	12 (11.8)	8 (8.9)	1.31 (0.53–3.20)	0.56	10 (5.1)	17 (8.1)	0.64 (0.30–1.36)	0.24	0.22
Non-cardiac cause	7 (21.9)	12 (24.0)	0.22	3 (16.7)	4 (28.6)	0.66 (0.15–2.95)	0.59	8 (4.0)	4 (1.9)	2.11 (0.64–7.01)	0.22	0.23
Undetermined	5 (15.6)	11 (22.0)	0.67	3 (16.7)	2 (14.3)	1.32 (0.22–7.90)	0.76	6 (3.0)	5 (2.4)	1.27 (0.39–4.17)	0.40	0.98
Myocardial infarction	5 (2.6)	12 (2.9)	1.00	3 (2.9)	2 (2.2)	0.94 (0.19–4.66)	0.94	6 (3.0)	6 (2.9)	0.69 (0.24–1.93)	0.47	0.85
Q-wave MI	4 (2.1)	4 (1.0)	0.22	2 (2.0)	2 (2.2)	0.89 (0.13–6.32)	0.91	2 (1.0)	2 (1.0)	1.07 (0.15–7.57)	0.95	0.90
Non Q-wave MI	1 (0.5)	8 (1.9)	0.22	1 (0.9)	0 (0.0)	NA	NA	4 (2.0)	4 (1.9)	1.07 (0.27–4.26)	0.93	0.99
Stroke	2 (1.0)	9 (2.2)	0.51	1 (1.0)	1 (1.1)	0.48 (0.04–5.34)	0.55	4 (2.0)	5 (2.4)	0.84 (0.22–3.12)	0.79	0.64
Death, MI or stroke	39 (20.3)	65 (15.9)	0.23	22 (21.6)	17 (18.9)	1.04 (0.58–1.88)	0.88	31 (15.7)	34 (16.2)	0.92 (0.58–1.45)	0.71	0.70
Ischemia-driven TVR	26 (13.5)	41 (10.0)	0.26	19 (18.6)	7 (7.8)	2.55 (1.07–6.08)	0.03	26 (13.1)	15 (7.1)	1.75 (0.97–3.15)	0.06	0.60
Any revascularization	34 (17.7)	54 (13.2)	0.19	24 (23.5)	10 (11.1)	2.12 (1.04–4.34)	0.04	35 (17.7)	19 (9.0)	2.01 (1.20–3.41)	0.01	0.81
Stent thrombosis (definite) or symptomatic graft occlusion	4 (2.1)	10 (2.5)	1.00	4 (3.9)	2 (2.2)	1.81 (0.33–9.90)	0.69	2 (1.0)	8 (3.8)	0.26 (0.06–1.23)	0.09	0.34

CABG indicates coronary artery bypass grafting; DM, diabetes mellitus; MACCE, major adverse cardiac or cerebrovascular events; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; and TVR, target-vessel revascularization.

*Event rates (%) shown are the incidences as estimated with the use of a Kaplan-Meier survival analysis of data from the intention-to-treat population.

†Hazard ratios are for the PCI group as compared with the CABG group. For these models, all available follow-up data were used for long-term outcome analyses without censoring clinical events beyond 10 years. The CIs that are reported in this table have not been adjusted for multiple testing and therefore should not be used to infer definitive treatment effects.

‡Formal interaction testing was performed to determine whether the presence of diabetes mellitus influenced the relative risk of PCI vs CABG for the occurrence of primary or secondary end points at 10 years.

§The primary end point of MACCE was a composite of death from any cause, MI, stroke, or ischemia-driven TVR.

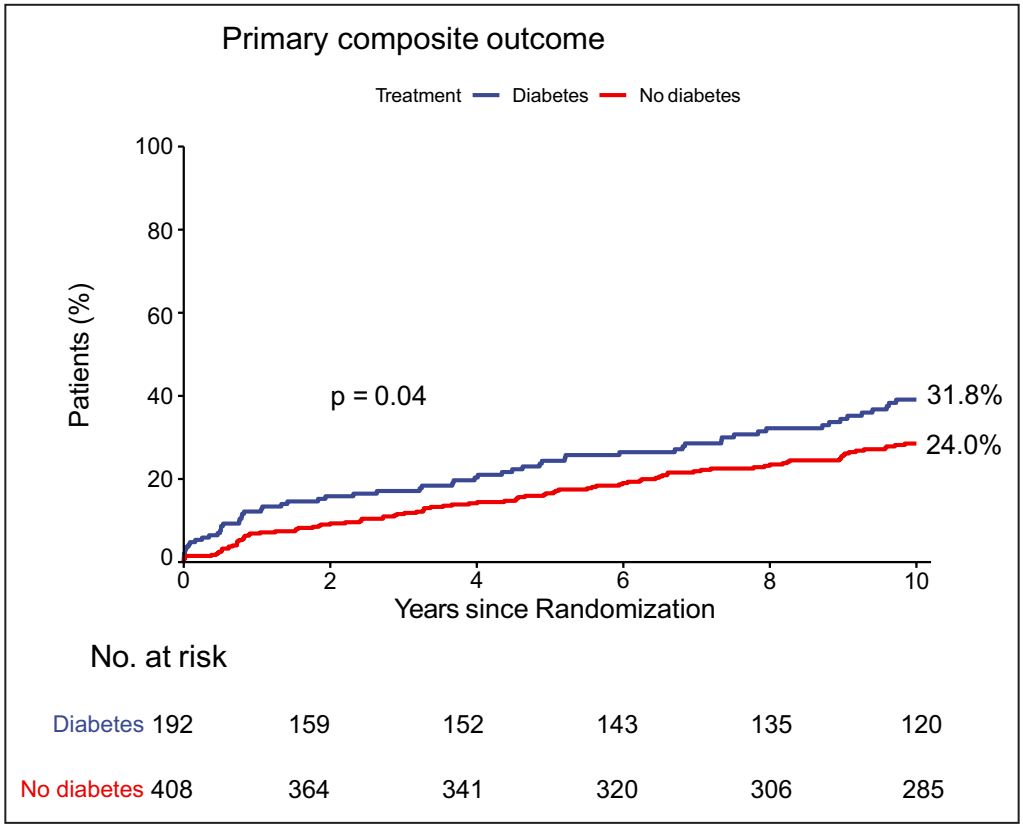

Figure 1. Kaplan-Meier curves for the 10-year primary composite outcome, according to the presence or absence of diabetes mellitus.
The 10-y event curves after percutaneous coronary intervention and coronary artery bypass grafting are shown for primary composite outcome of death from any cause, myocardial infarction, stroke, or ischemic-driven target-vessel revascularization.

DISCUSSION

The key findings from the present pre-specified PRECOMBAT sub-study, the longest follow-up study to date examining the impact of DM on clinical outcomes after PCI with DES versus CABG in patients with unprotected LMCA disease, are as follows: (1) compared with patients without DM, patients with DM had a higher risk of primary composite outcome of MACCE at 10 years; (2) the 10-year rates of MACCE, death, MI, stroke, and its composite outcomes were not significantly different after PCI or CABG in patients with and without DM, but the risk of TVR and repeat revascularization was consistently higher after PCI, irrespective of DM; and (3) thus, there was no interaction between DM status and treatment of PCI with DES compared with CABG for the 10-year primary and secondary outcomes.

DM is a leading cause of CAD and may be a predisposition to more severe forms of atherosclerotic CAD. Therefore, over the past several decades, CABG has been considered to be the preferred revascularization option in patients with DM with multivessel or complex CAD.[7,16] As a result, DM has been regarded as a key determinant for predicting poor prognosis and selecting optimal myocardial revascularization among several clinical risk factors.[17] However, with marked advancements in PCI devices (from balloon angioplasty to bare-metal stents and DES), technologies, experiences, and adjunctive drug therapies, PCI outcomes have been dramatically improved over time, even in patients with DM with complex CAD.[18] This has narrowed the revascularization gap in favor of CABG over PCI for patients with DM. Recent long-term report from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry reported that the clinical impact of DM favoring CABG over PCI has diminished over time from the bare-metal stent to the DES.[19] Despite this, currently, no specific recommendations exist concerning the optimal revascularization strategy in patients with DM with LMCA disease.[10]

Given that PCI outcomes are rapidly improving and optimal medical therapy for DM is also continuously evolving,[20] attenuating the treatment gap of the revascularization methods of CABG over PCI, the clinical role of DM for an important decision-maker for specific

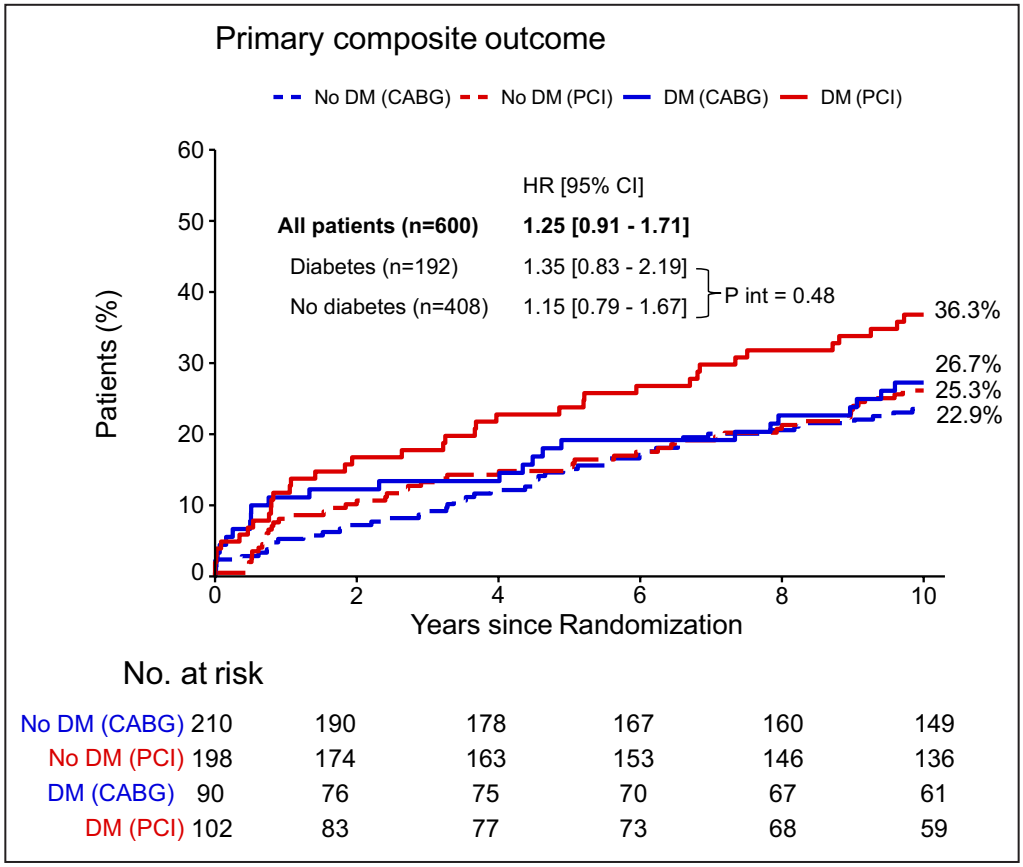

Figure 2. Cumulative incidences of primary composite outcome, according to diabetes mellitus status and treatment assignment.
The 10-y event curves after percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are shown for primary composite outcome of death from any cause, myocardial infarction, stroke, or ischemic-driven target-vessel revascularization. Hazard ratios are for the PCI group, as compared with the CABG group. DM indicates diabetes mellitus; and HR, hazard ratio.

revascularization approach is questioned in recent trials comparing CABG and PCI with DES for LMCA or multivessel disease.[21] Recently, the pre-specified substudy of EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) examined the impact of DM on clinical outcomes after PCI with everolimus-eluting stents versus CABG for patients with LMCA disease.[22] In this study, DM was a critical determinant of long-term outcomes after myocardial revascularization. However, the relative 30-day and 3-year outcomes of PCI versus CABG were consistent in diabetic and non-diabetic strata, and thus there was no significant interaction between DM status and the comparative treatment effect. However, the follow-up durations of this study were relatively short to establish the full effects of DM and revascularization methods on hard clinical end point and survival, particularly considering the diverging or converging Kaplan–Meier curves in specific subgroups. In our longest (beyond 10-year) follow-up of PRECOMBAT trial targeting specifically patients with LMCA, we observed that although DM was a risk factor associated with a higher clinical event, there was no differential effect of DM on comparative outcomes after PCI and CABG; the 10-year rates of the primary end points of MACCE, serious composite outcomes, and mortality were similar between PCI and CABG in patients with DM and patients without DM. These findings may suggest that the presence of DM should not penalize the specific revascularization strategy for LMCA disease in terms of optimal decision making in contemporary clinical practice.

By contrast, discordant findings favoring CABG over PCI in patients with DM were still observed for patients with multivessel CAD.[17] A recent large-sized pooled analysis showed that 5-year all-cause mortality was significantly better after CABG than after PCI in patients with multivessel disease, including in those with DM, but not in those without DM (*P*-for-interaction=0.045).[23] In this study, such finding was not consistent in the cohort with LMCA disease (*P*-for-interaction=0.13). Additionally, the FREEDOM (Future Revascularization

Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) follow-on study demonstrated that CABG was associated with lower all-cause mortality than PCI with DES in the long-term follow-up to 8 years.[12] Although we did not fully explain the underlying mechanism with regard to such differential impact of DM on the relative outcomes after PCI and CABG between patients with LMCA disease and those with multivessel disease, the results might be largely influenced by the status of complete revascularization.[24] Therefore, the choice between CABG and PCI with DES may depend on whether complete revascularization can be achieved with PCI. In addition, optimizing guideline-directed medication therapy after both CABG and PCI is essential for patients to derive the most benefits from revascularization.

Lastly, in the original protocol of PRECOMBAT trial, routine follow-up angiography was recommended at 8 to 10 months after the procedure for all patients who underwent PCI, but not for patients who underwent CABG.[13] This practice patterns might do not fit with those of the contemporary clinical settings. The systematic performance of repeat angiography in the PCI group may lead to more follow-up angiography-induced TVR, which may bias the rate of TVR in the PCI group. In prior report, the between-group difference in the rate of clinically driven TVR with documented ischemic symptoms or signs, appeared to be smaller than the difference in the rate of ischemia-driven TVR.[13]

There were several limitations that should be noted. First, owing to the relatively small number of patients, our trial did not have sufficient statistical power to detect clinically significant differences in clinical end points in each subgroup according to DM status. In addition, analyses for outcome measures were not adjusted for multiple comparisons. Thus, the present findings should be interpreted as hypothesis-generating only, and further investigation in dedicated trials of patients with DM are warranted. Second, detailed information on cardiovascular and DM medications after PCI and CABG during the long-term follow-ups was not available. Although the extent to which variability in medication use contributed to the results is uncertain, unmeasured confounding effects owing to differences in subsequent medication use cannot be ruled out. Third, there was a lack of detailed information on optimal glycemic control and new onset of DM occurring in the long-term follow-up, which could affect the relative outcomes after CABG and PCI. Fourth, the number of patients treated with insulin was too small; therefore, clinically and statistically relevant analyses were not possible. Fifth, we cannot fully exclude the possibility that clinical events were underreported because of the non-prespecified 10-year follow-up and lack of routine annual follow-up between 5 and 10 years. Sixth, we only evaluated the first-generation DES and thus our findings should be further evaluated through long-term follow-up of the recent EXCEL and NOBLE trials using contemporary DES. Finally, the study was conducted on Korean subjects only; thus, observed findings may not be applicable to other ethnic groups.

CONCLUSIONS

In this longest follow-up of a clinical trial specifically targeting patients with LMCA disease, we observed that the 10-year rates of primary composite of MACCE, serious composite of death, MI, or stroke, and all-cause mortality were similar between PCI and CABG in patients with and without DM. Therefore, there was no substantial interaction between DM status and revascularization type on 10-year clinical outcomes. However, owing to the limited number of patients and no adjustment for multiple testing, these findings must be interpreted conservatively and considered provisional, highlighting the need for further research.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2
Figures S1–S3

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Supplemental Material

Table S1. Ten-year clinical outcomes according to diabetes status and revascularization group in the as-treated analysis*.

	Patients with DM				Patients without DM				
Event rates, n (%)	**PCI (n = 109)**	**CABG (n = 82)**	**Hazard Ratio† (95% CI)**	**P**	**PCI (n = 218)**	**CABG (n = 190)**	**Hazard Ratio† (95% CI)**	**P**	**P-Int‡**
Primary outcome									
MACCE§	37 (36.3)	24 (26.7)	1.35 (0.83–2.19)	0.23	50 (25.3)	48 (22.9)	1.15 (0.79–1.67)	0.48	0.67
Secondary outcome									
Death from any cause	20 (18.3)	11 (13.4)	1.58 (0.79–3.18)	0.20	27 (12.4)	23 (12.1)	1.05 (0.62–1.79)	0.85	0.46
Cardiac death	14 (12.8)	5 (6.1)	2.38 (0.94–6.05)	0.07	13 (6.0)	14 (7.4)	0.81 (0.38–1.72)	0.58	0.12
Non-cardiac cause	3 (2.8)	4 (4.9)	0.58 (0.13–2.60)	0.48	8 (3.7)	4 (2.1)	1.74 (0.52–5.78)	0.37	0.28
Undetermined	3 (2.8)	2 (2.4)	1.24 (0.21–7.41)	0.82	6 (2.8)	5 (2.6)	1.06 (0.32–3.46)	0.93	0.89
Myocardial infarction	1 (0.9)	4 (4.9)	0.16 (0.02–1.35)	0.09	7 (3.2)	5 (2.6)	0.76 (0.28–2.10)	0.60	0.14
Q-wave MI	1 (0.9)	3 (3.7)	0.25 (0.03–2.39)	0.23	2 (0.9)	2 (1.0)	0.88 (0.12–6.25)	0.90	0.45
Non-Q-wave MI	0 (0.0)	1 (1.2)	NA	NA	5 (2.3)	3 (1.6)	1.46 (0.35-6.12)	0.52	0.99
Stroke	2 (1.8)	0 (0.0)	1.87 (0.17–21)	0.51	3 (1.4)	6 (3.2)	0.43 (0.11–1.73)	0.24	0.34

Death, MI or stroke	23 (21.1)	15 (18.3)	1.17 (0.64–2.14)	0.60	35 (16.1)	30 (15.8)	0.96(0.60–1.51)	0.85	0.71
Ischemia-driven TVR	20 (18.3)	6 (7.3)	2.87 (1.15–7.16)	0.02	32 (14.7)	9 (4.7)	2.69 (1.40–5.18)	<0.001	0.82
Any revascularization	26 (23.9)	8 (9.8)	2.58 (1.21–5.52)	0.01	43 (19.7)	11 (5.8)	3.00 (1.67–5.36)	<0.001	0.63
Stent thrombosis (definite) or symptomatic graft occlusion	3 (2.8)	3 (3.7)	0.91 (0.18–4.63)	0.92	5 (2.3)	5 (2.6)	0.86 (0.25–2.99)	0.82	0.95

*Event rates (%) shown are the incidences as estimated with the use of a Kaplan-Meier survival analysis of data from the as-treated population.

†Hazard ratios are for the PCI group as compared with the CABG group. For these models, all available follow-up data were used for long-term outcome analyses without censoring clinical events beyond 10 years. The CIs that are reported in this table have not been adjusted for multiple testing and therefore should not be used to infer definitive treatment effects.

‡Formal interaction testing was performed to determine whether the presence of diabetes mellitus influenced the relative risk of PCI versus CABG for the occurrence of primary or secondary end points at 10 years.

§The primary end point of MACCE was a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization.

CABG, coronary artery bypass grafting; MI, myocardial infarction; MACCE, major adverse cardiac or cerebrovascular events; NA, not available; PCI, percutaneous coronary intervention; TVR, target-vessel revascularization.

Table S2. Ten-year clinical outcomes according to diabetes status and revascularization group in the per-protocol analysis*.

	Patients with DM				Patients without DM				
Event rates, n (%)	**PCI (n = 95)**	**CABG (n = 75)**	**Hazard Ratio† (95% CI)**	**P**	**PCI (n = 181)**	**CABG (n = 173)**	**Hazard Ratio† (95% CI)**	**P**	**P-Int‡**
Primary outcome									
MACCE§	37 (38.9)	21 (28.0)	1.61 (0.94–2.76)	0.08	53 (29.3)	40 (23.1)	1.33 (0.88–2.00)	0.18	0.53
Secondary outcome									
Death from any cause	18 (18.9)	11 (14.7)	1.41 (0.69–2.88)	0.35	23 (12.7)	22 (12.7)	1.04 (0.60–1.81)	0.90	0.56
Cardiac death	12 (12.6)	5 (6.7)	1.95 (0.69–5.52)	0.21	10 (5.5)	14 (8.1)	0.68 (0.30–1.53)	0.35	0.12
Non-cardiac cause	3 (3.2)	4 (5.3)	0.60 (0.13–2.69)	0.51	8 (4.4)	4 (2.3)	1.9 (0.57–6.33)	0.29	0.25
Undetermined	3 (3.2)	2 (2.7)	1.25 (0.21–7.46)	0.81	5 (2.8)	4 (2.3)	1.20 (0.32–4.47)	0.79	0.98
Myocardial infarction	1 (1.1)	2 (2.7)	0.29 (0.03–2.79)	0.28	6 (3.3)	5 (2.9)	0.70 (0.24–2.03)	0.51	0.43
Q-wave MI	1 (1.1)	2 (2.7)	0.39 (0.04–4.36)	0.45	2 (1.1)	2 (1.2)	0.96 (0.14–6.84)	0.97	0.58
Non-Q-wave MI	0 (0.0)	0 (0.0)	NA	NA	4 (2.2)	3 (1.7)	1.29 (0.29–5.74)	0.33	>0.99
Stroke	1 (1.1)	0 (0.0)	1.02 (0.06–16.66)	0.99	2 (1.1)	4 (2.3)	0.47 (0.09–2.57)	0.39	0.73

Death, MI or stroke	20 (21.1)	13 (17.3)	1.17 (0.61–2.23)	0.47	29 (16.0)	28 (16.2)	0.93 (0.57–1.51)	0.76	0.62
Ischemia-driven TVR	18 (18.9)	5 (6.7)	3.21 (1.19–8.64)	0.02	25 (13.8)	8 (4.6)	2.53 (1.26–5.08)	0.01	0.99
Any revascularization	23 (24.2)	7 (9.3)	2.67 (1.19–5.97)	0.02	34 (18.8)	10 (5.8)	3.02 (1.61–5.67)	0.00	0.77
Stent thrombosis (definite) or symptomatic graft occlusion	3 (3.2)	2 (2.7)	1.25 (0.21–7.51)	0.81	2 (1.1)	5 (2.9)	0.38 (0.07–1.94)	0.24	0.55

*Event rates (%) shown are the incidences as estimated with the use of a Kaplan-Meier survival analysis of data from the per-protocol population.

†Hazard ratios are for the PCI group as compared with the CABG group. For these models, all available follow-up data were used for long-term outcome analyses without censoring clinical events beyond 10 years. The CIs that are reported in this table have not been adjusted for multiple testing and therefore should not be used to infer definitive treatment effects.

‡Formal interaction testing was performed to determine whether the presence of diabetes mellitus influenced the relative risk of PCI versus CABG for the occurrence of primary or secondary end points at 10 years.

§The primary end point of MACCE was a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization.

CABG, coronary artery bypass grafting; MI, myocardial infarction; MACCE, major adverse cardiac or cerebrovascular events; NA, not available; PCI, percutaneous coronary intervention; TVR, target-vessel revascularization.

Figure S1. The 10-year cumulative incidences of the key secondary outcomes, including A) composite of death, MI, and stroke, B) all-cause death, C) target vessel revascularization, according to the presence of diabetes.

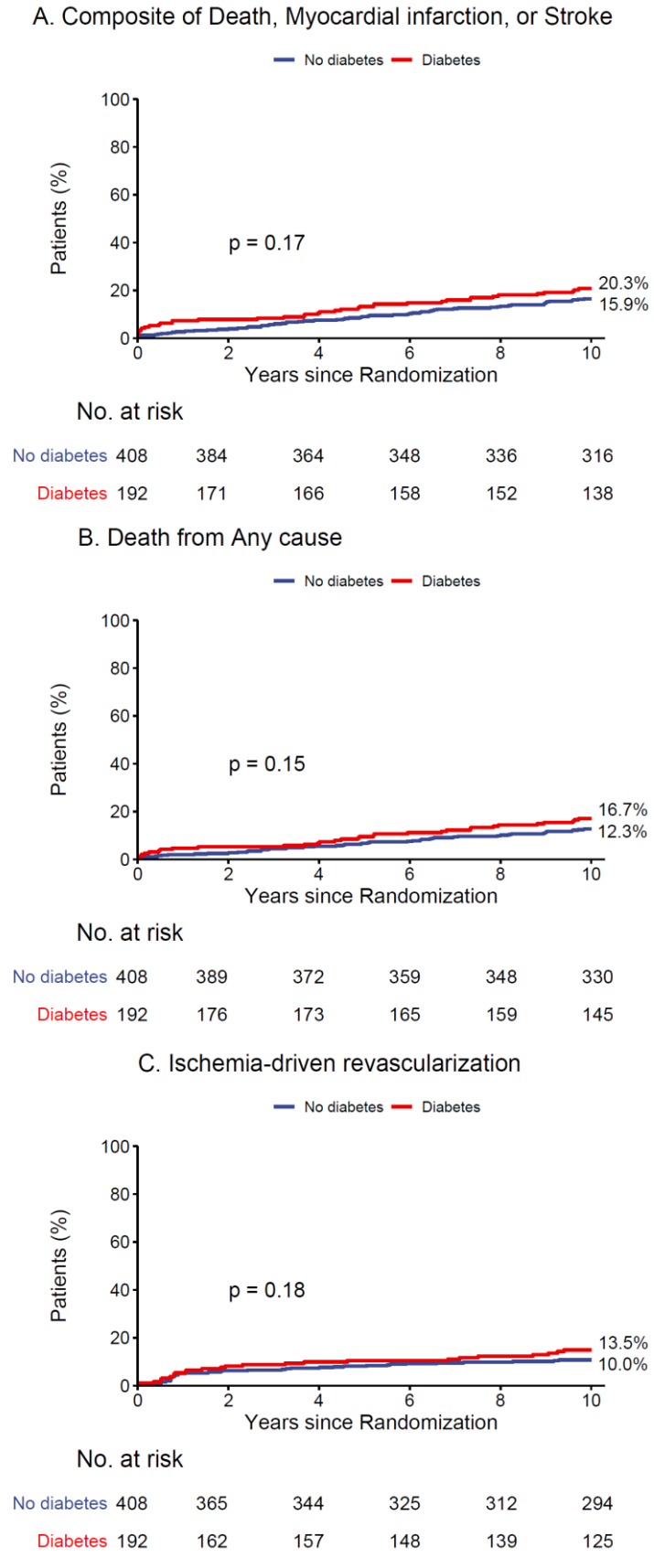
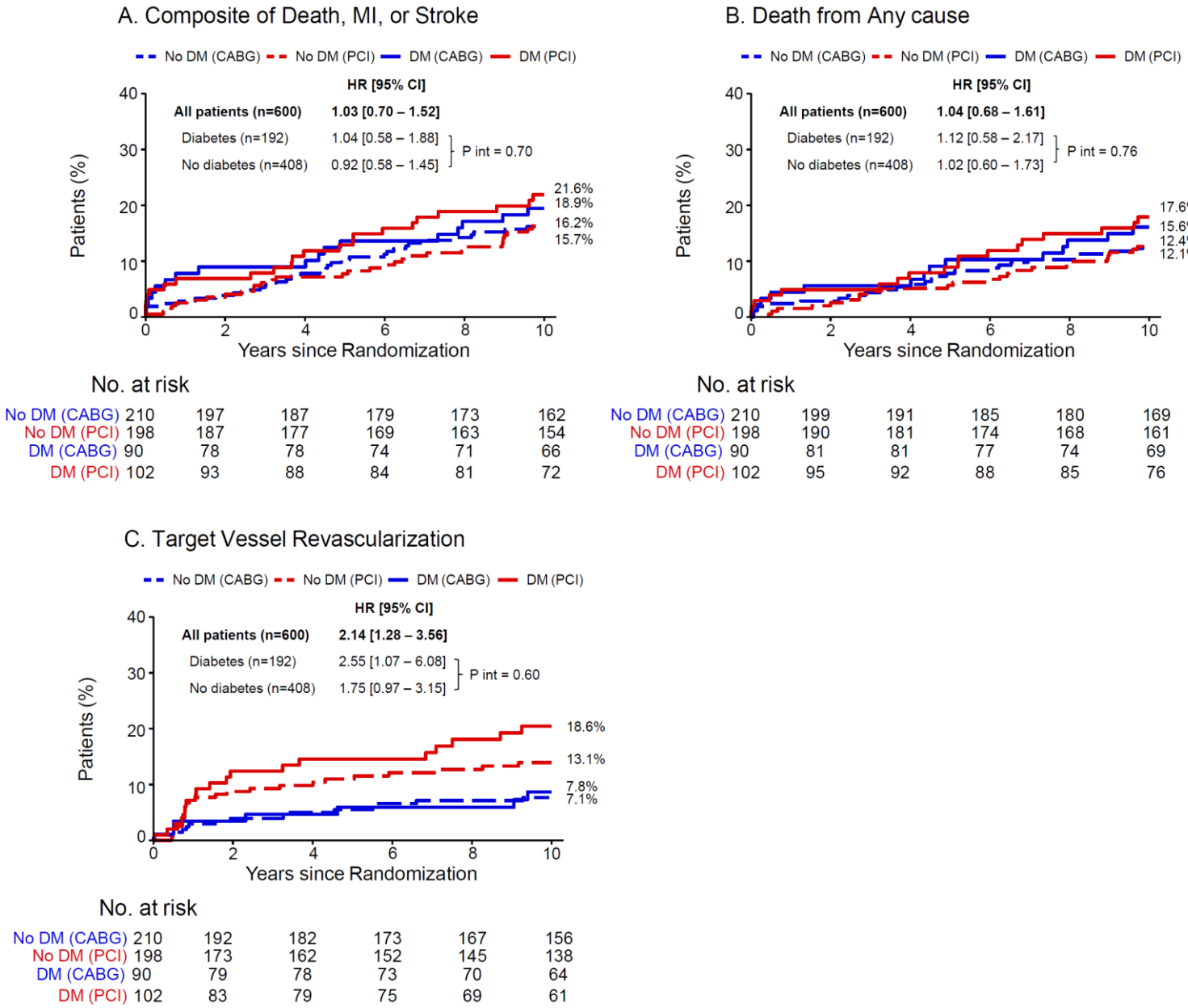


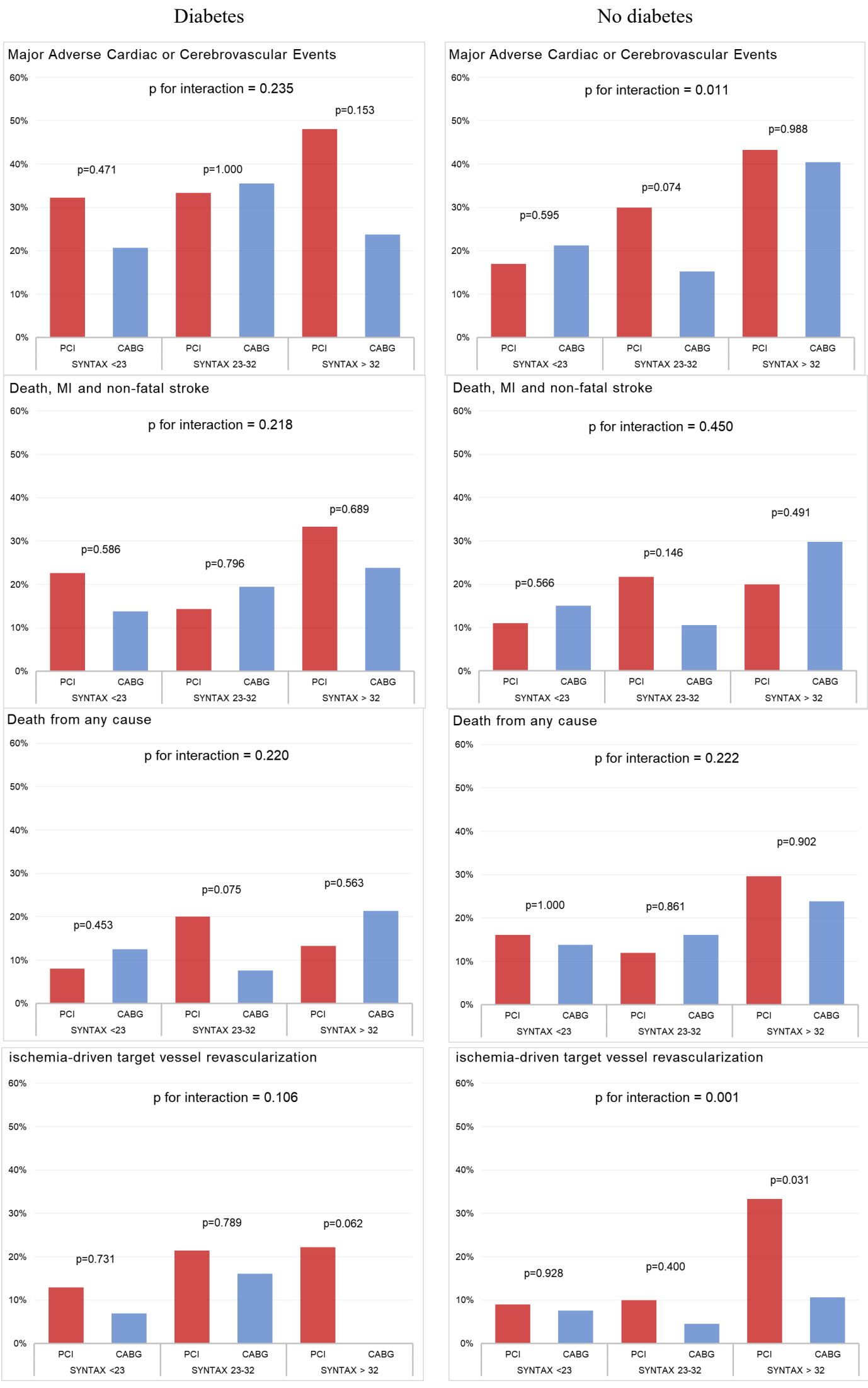
Figure S2. The 10-year cumulative incidences of the key secondary outcomes including A) composite of death, MI, and stroke, B) all-cause death, C) target vessel revascularization, according to the presence of diabetes and treatment assignment.



Hazard ratios are for the PCI group, as compared with the CABG group.

*P for interaction was used to determine the statistical interaction between the presence of diabetes and the relative treatment effect (PCI vs. CABG) for 10-year rates of key secondary outcomes.

Figure S3. Ten-year event rates of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) according to SYNTAX category stratified by diabetes status.



*P for interaction was used to determine the statistical interaction between the SYNTAX score category and the relative treatment effect (PCI vs. CABG) for 10-year rates of primary and key secondary outcomes.