ORIGINAL RESEARCH

Long-Term (10-Year) Outcomes of Stenting or Bypass Surgery for Left Main Coronary Artery Disease in Patients With and Without Diabetes Mellitus

Kyusup Lee, MD*; Jung-Min Ahn, MD*; Yong-Hoon Yoon, MD; Do-Yoon Kang, MD; Seo-Young Park, PhD; Euihong Ko, MD; Hanbit Park, MD; Sang-Cheol Cho, MD; Sangwoo Park, MD; Tae Oh Kim, MD; Pil Hyung Lee, MD; Seung-Whan Lee, MD, PhD; Seong-Wook Park, MD, PhD; Duk-Woo Park 🆔, MD, PhD; Seung-Jung Park, MD, PhD

BACKGROUND: Data are still limited regarding whether there are differential long-term outcomes after percutaneous coronary intervention versus coronary artery bypass grafting (CABG) for left main coronary artery disease with or without diabetes mellitus (DM).

METHODS AND RESULTS: Using the 10-year data from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry, we sought to examine the effect of DM on comparative outcomes after percutaneous coronary intervention or CABG in patients with unprotected left main coronary artery disease. The outcomes of interest were all-cause mortality; a composite of death, Q-wave myocardial infarction, or stroke; and target-vessel revascularization. The primary adjusted analyses were performed with the use of propensity scores and inverse-probability weighting. Of 2240 patients with left main coronary artery revascularization, 722 (32%) had DM. In the overall population, the adjusted 10-year risks of death and composite outcome were similar between percutaneous coronary intervention and CABG, irrespective of DM status ($P_{interaction}$: 0.41, mortality; 0.40, composite outcome). However, in the cohort of bare-metal stents and concurrent CABG, we observed differential outcomes after stenting and CABG by DM status ($P_{interaction}$: 0.09, mortality; 0.04, composite outcome), favoring CABG in patients with DM. In the cohort of drug-eluting stents and concurrent CABG, the better effect of CABG over stenting was narrowed in patients with DM without a significant interaction ($P_{interaction}$: 0.63, mortality; 0.47, composite outcome).

CONCLUSIONS: In this cohort of patients with longest follow-up who underwent left main coronary artery revascularization, the clinical impact of DM favoring CABG over percutaneous coronary intervention has diminished over time from the bare-metal stent to the drug-eluting stent era.

REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02791412.

Key Words: coronary artery bypass grafting ■ diabetes mellitus ■ left main disease ■ stents

See Editorial by Ziada and Powers

Correspondence to: Duk-Woo Park, MD, PhD, Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea. E-mail: dwpark@amc.seoul.kr

CLINICAL PERSPECTIVE

What Is New?

- Extended follow-up and large population are important to assess the role of diabetes mellitus (DM) in left main coronary artery (LMCA) disease.
- In LMCA disease with DM, percutaneous coronary intervention showed comparable rates of mortality and serious composite outcome at 10 years.
- Unlikely in the bare-metal stent era, in which there was a significant interaction between DM status and revascularization method on mortality and serious composite outcome, no interaction was observed between diabetic status and treatment in the drug-eluting stent era.

What Are the Clinical Implications?

- Even though DM was related to higher 10-year mortality and composite outcome in patients with LMCA disease after myocardial revascularization, its role to guide clinical decision making regarding the choice of coronary revascularization strategy is limited in LMCA disease.
- In the drug-eluting stent era, percutaneous coronary intervention would be a reasonable option for myocardial revascularization in patients with LMCA disease, even in those with DM. Decision making between percutaneous coronary intervention and coronary artery bypass grafting in patients with LMCA disease should take into consideration several clinical or anatomic aspects and patient preference.

Nonstandard Abbreviations and Acronyms

BMS	bare-metal stent
CABG	coronary artery bypass grafting
CAD	coronary artery disease
DES	drug-eluting stent
DM	diabetes mellitus
IPTW	inverse probability of treatment weighting
LMCA	left main coronary artery
MAIN-COMPARE	Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization
MI	myocardial infarction
PCI	percutaneous coronary intervention
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
TVR	target-vessel revascularization

As compared with patients without diabetes mellitus (DM), patients with DM usually have more diffuse and complex anatomic features of coronary artery disease (CAD), which is associated with high morbidity and mortality.[1] Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are recommended for revascularization treatments for patients with DM with obstructive CAD.[2] In particular, CABG has been considered to be the preferred revascularization strategy in patients with DM and multivessel or complex CAD.[3–6]

Among various anatomic subtypes of atherosclerotic CAD, the optimal choice of revascularization strategies is more crucial for patients with left main coronary artery (LMCA) disease because of the large amount of myocardium at risk. The current US and European guidelines recommend that most patients with LMCA disease undergo CABG.[7,8] However, the updated evidence supports that PCI is a safe and effective modality for patients with LMCA disease and low-to-intermediate anatomic complexity as compared with CABG,[6,9,10] although some trials show conflicting results, supporting better effect with CABG over PCI.[11] Until recently, data were limited regarding the influence of DM on the relative outcomes after PCI or CABG and on decision making of particular revascularization strategies in patients with LMCA disease. In addition, given that the effects of DM and myocardial revascularization on mortality and major cardiovascular events is not fully revealed within a limited follow-up duration, longer-term evaluation of 5 to 10 years is essential to better define differences in outcomes between PCI and CABG.

We therefore sought to determine differences in very long-term (10-year) comparative outcomes between PCI and CABG according to the presence of DM using data from the extended follow-up of the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry.[12]

METHODS

Data Sources

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

The study population consisted of 2240 consecutive patients with unprotected LMCA disease who underwent PCI (n=1102) or CABG (n=1138) between January 2000 and June 2006 at 12 major cardiac centers in Korea, within the MAIN-COMPARE registry. The design, inclusion criteria, and primary results of the MAIN-COMPARE study have been published previously.[12–14] Patients who had prior bypass surgery, those who underwent concomitant valvular or aortic surgery, and those who had an ST-segment–elevation myocardial infarction (MI), or presented with cardiogenic shock were excluded.

The choice of treatment strategy between PCI and CABG was at the discretion of the attending cardiologists or cardiac surgeons with careful consideration of clinical risk factors, anatomic complexity, patient preference, and surgical risk. All procedures and surgery were guided by standard techniques and management. Because of device availability, PCI was performed exclusively with bare-metal stents (BMSs) between January 2000 and May 2003 and exclusively with DESs between May 2003 and June 2006. Antiplatelet therapy and periprocedural anticoagulation were performed in accordance with the accepted guidelines. During follow-up, patient management including medical treatment was performed in accordance with accepted guidelines and established standards of care. This study was approved by the local ethics committee of each hospital, and all patients provided written informed consent for the use of their clinical data for the registry study.

Study Outcomes and Follow-Up

The end points of the study were death; a composite of death, Q-wave MI, or stroke; and target-vessel revascularization (TVR). Death was defined as death from any cause. Q-wave MI was defined as documentation of a new pathological Q-wave after the index revascularization. Stroke was defined as a focal neurological deficit of central origin lasting >24 hours, confirmed by a neurologist and imaging. TVR was defined as any percutaneous or surgical revascularization of the treated vessel, including any segments of the left anterior descending artery and/or left circumflex artery. All clinical events were confirmed by source documentation collected at each hospital and centrally adjudicated by an independent group of clinicians.

Clinical follow-up was recommended at 1 month, 6 months, 1 year, and annually thereafter. In the 10-year MAIN-COMPARE study, the follow-up period was extended through December 31, 2016, to ensure that all patients had the opportunity to be followed up for at least 10 years. Complete information on vital status and date of death were obtained through December 31, 2016, from the National Population Registry of the Korea National Statistical Office on the basis of the unique 13-digit personal identification number that all Korean citizens have. The detailed methods for data acquisition and management during extended follow-up have been reported elsewhere.[12]

Statistical Analysis

Continuous variables were presented as mean±SD and compared using the Student t test or Mann–Whitney U test. Categorical variables were presented as counts (percentages) and compared using the chi-square or Fisher exact test, as appropriate. Event rates were estimated on Kaplan–Meier estimates in time-to-first-event analyses and were compared using the log-rank test.

Outcomes of patients who received PCI versus CABG were evaluated, stratified by the presence of medically treated DM. Crude and adjusted risks for adverse outcomes were compared by univariate and multivariable Cox proportional hazards regression analyses. Multiple regression analyses using Cox proportional hazard models were performed with CABG group as the reference category and with PCI group as the indicator variable. Variables with P values of ≤0.1 and clinically relevant covariates irrespective of their statistical relevance in univariate analyses were candidates for inclusion in multivariate Cox proportional hazards models. The final models were determined by backward elimination. When left ventricular ejection fraction was included in the multivariable model, multiple imputation with m=10 was performed, and the results of the Cox regression analyses on 10 imputed data sets were combined using Rubin's rules.

Inverse probability of treatment weighting (IPTW) based on the propensity score (probability of receiving PCI) was used as the primary tool to adjust for differences in the baseline characteristics between the PCI and CABG groups.[15] IPTW gives different weights to patients based on their characteristics, to create a "virtual" data set that mimics the data that would have been observed if the treatment was randomly assigned. To handle the missingness of left ventricular ejection fraction in 18.5% of the patients, we used the missingness pattern approach. That is, we fitted the separate propensity score model for the patients with complete data and those with missing left ventricular ejection fraction. The propensity score was estimated using a nonparsimonious logistic regression model, with the PCI group as the dependent variable and all the baseline characteristics outlined in Table 1 as covariates. Once each patient's propensity score was estimated, stabilized weights were calculated using the method described in the previous literature.[16] We examined the similarity of the baseline characteristics between the treatment groups before and after IPTW.[17] After confirming the comparability of the 2 groups in

Table 1. Baseline Characteristics of the Patients

Characteristics	Overall (n=2240)			Diabetes Mellitus (n=722)			No Diabetes Mellitus (n=1518)		
	PCI (n=1102)	CABG (n=1138)	*P* Value	PCI (n=327)	CABG (n=395)	*P* Value	PCI (n=775)	CABG (n=743)	*P* Value
Age, y	61.3±11.7	62.9±9.4	<0.001	63.5±10.0	63.6±8.7	0.87	60.4±12.2	62.6±9.8	<0.001
Male	779 (70.7)	830 (72.9)	0.26	228 (69.7)	294 (74.4)	0.19	551 (71.1)	536 (72.1)	0.69
Treatment of diabetes mellitus						0.85			
Required insulin				75 (22.9)	93 (23.5)				
Required OHA				252 (77.1)	302 (76.5)				
Wave			<0.001			<0.001			<0.001
Wave 1 BMS vs Concurrent CABG	318 (28.9)	448 (39.4)		76 (23.2)	139 (35.2)		242 (31.2)	309 (41.6)	
Wave 2 DES vs Concurrent CABG	784 (71.1)	690 (60.6)		251 (76.8)	256 (64.8)		553 (68.8)	434 (58.4)	
Hypertension	546 (49.5)	562 (49.4)	0.97	197 (60.2)	228 (57.7)	0.54	349 (45.0)	334 (45.0)	>0.99
Hyperlipidemia	315 (28.6)	371 (32.6)	0.044	110 (33.6)	139 (35.2)	0.72	205 (26.5)	232 (31.2)	0.046
Current smoker	282 (25.6)	339 (29.8)	0.030	72 (22.0)	107 (27.1)	0.14	210 (27.1)	232 (31.2)	0.09
Prior MI	89 (8.1)	132 (11.6)	0.006	32 (9.8)	55 (13.9)	0.11	57 (7.4)	77 (10.4)	0.048
Prior PCI	200 (18.1)	125 (11.0)	<0.001	80 (24.5)	50 (12.7)	<0.001	120 (15.5)	75 (10.1)	0.002
Congestive heart failure	27 (2.5)	38 (3.3)	0.21	14 (4.3)	23 (5.8)	0.35	13 (1.7)	15 (2.0)	0.62
Prior stroke	78 (7.1)	83 (7.3)	0.91	33 (10.1)	38 (9.6)	0.93	45 (5.8)	45 (6.1)	0.92
Peripheral vascular disease	16 (1.5)	62 (5.4)	<0.001	4 (1.2)	33 (8.4)	<0.001	12 (1.5)	29 (3.9)	0.008
Chronic kidney disease	30 (2.7)	34 (3.0)	0.80	17 (5.2)	26 (6.6)	0.53	13 (1.7)	8 (1.1)	0.43
Clinical indication			<0.001			0.001			<0.001
Silent ischemia	33 (3.0)	25 (2.2)		13 (4.0)	11 (2.8)		20 (2.6)	14 (1.9)	
Chronic stable angina	353 (32.0)	226 (19.9)		97 (29.7)	72 (18.2)		256 (33.0)	154 (20.7)	
Unstable angina	608 (55.2)	775 (68.1)		173 (52.9)	266 (67.3)		435 (56.1)	509 (68.5)	
NSTEMI	108 (9.8)	112 (9.8)		44 (13.5)	46 (11.6)		64 (8.3)	66 (8.9)	
Acute coronary syndrome	716 (65.0)	887 (77.9)	<0.001	217 (66.4)	312 (79.0)	<0.001	499 (64.4)	575 (77.4)	<0.001
LVEF, %	60.6±10.8	57.2±11.9	<0.001	58.8±11.9	55.6±13.0	0.002	61.3±10.2	58.0±11.2	<0.001
SYNTAX score (n=1580)			<0.001			<0.001			<0.001
0–22	408 (49.8)	100 (13.1)		94 (37.8)	25 (9.6)		314 (55.1)	75 (15.0)	
23–32	225 (27.5)	164 (21.6)		75 (30.1)	52 (19.9)		150 (26.3)	112 (22.4)	
≥33	186 (22.7)	497 (65.3)		80 (32.1)	184 (70.5)		106 (18.6)	313 (62.6)	
Involved location			0.045			0.21			0.17
Ostium and/or midshaft	557 (50.5)	526 (46.2)		157 (48.0)	170 (43.0)		400 (51.6)	356 (47.9)	
Distal bifurcation	545 (49.5)	612 (53.8)		170 (52.0)	225 (57.0)		375 (48.4)	387 (52.1)	
Disease extent			<0.001			<0.001			<0.001
LM only	278 (25.2)	71 (6.2)		56 (17.1)	13 (3.3)		222 (28.6)	58 (7.8)	
LM+single-vessel disease	264 (24.0)	119 (10.5)		73 (22.3)	30 (7.6)		191 (24.6)	89 (12.0)	
LM+double-vessel disease	287 (26.0)	299 (26.3)		102 (31.2)	92 (23.3)		185 (23.9)	207 (27.9)	
LM+triple-vessel disease	273 (24.8)	649 (57.0)		96 (29.4)	260 (65.8)		177 (22.8)	389 (52.4)	
Restenotic lesion	32 (2.9)	14 (1.2)	0.008	10 (3.1)	3 (0.8)	0.042	22 (2.8)	11 (1.5)	0.10

Values are presented as n (%) or mean±SD. BMS indicates bare-metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; OHA, oral hypoglycemic agent; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.

the data with IPTW, we ran the Cox proportional hazard model and made statistical inference using robust standard errors (Huber sandwich estimator).[18]

For all crude, multivariable-adjusted, and IPTW analyses, treatment effects were evaluated in all the patients and in each group of patients with and without DM. To test the statistical significance of the difference in treatment effect of revascularization methods between the patients with and without DM, the interaction term between diabetic status and the treatment

method was included in the multivariate and weighted Cox models using the IPTW method that were built on the basis of the data from all the patients. As described previously,[12] these analyses were performed in the overall cohort, wave 1 cohort of the BMS era (BMS versus concurrent CABG between January 2000 and May 2003), and wave 2 cohort of the DES era (DES versus concurrent CABG between May 2003 and June 2006). As the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score was available only for a subset of patients (n=1580; 70.5%), we performed sensitivity analyses in the group with the baseline SYNTAX score. All reported P values were 2-sided, and P<0.05 were considered statistically significant. R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

RESULTS

Baseline Characteristics

Detailed information on procedural characteristics of patients in the MAIN-COMPARE registry have been described previously[13]: (1) the mean number of stents implanted in LMCA lesions and per patient was 1.2±0.5 and 1.9±1.1, respectively; (2) mean total length and mean stent diameter was 28.0±20.7 and 3.5±0.4 mm, respectively; (3) among CABG patients, 42% underwent off-pump surgery; and (4) 98% underwent revascularization of the left anterior descending artery with an arterial conduit; and (5) mean number of grafts used was 2.9±1.0 (2.2±0.9 arterial grafts and 0.7±0.8 venous grafts).

Among 2240 patients with LMCA disease treated with PCI (n=1102) or CABG (n=1138), 722 (32.2%) had medically treated DM. As expected, compared with patients without DM, patients without DM had higher risks of clinical and anatomic risk-factor profiles and had higher 10-year incidence rates of clinical outcomes (Table S1 and Figure S1). Of the patients with DM, 327 (45.3%) received PCI and 395 (54.7%) underwent CABG. Of the 1518 patients without DM, 775 (51.1%) received PCI and 743 (48.9%) underwent CABG.

The baseline demographic, clinical, and angiographic characteristics of the patients who underwent PCI and CABG in the overall population and in the group with or without DM are shown in Table 1. In general, compared with the patients who received PCI, those who underwent CABG had a significantly greater prevalence of comorbidities (old age, hyperlipidemia, prior MI, peripheral vascular disease, unstable angina, and lower ejection fraction) and a higher proportion of SYNTAX scores of ≥33, distal bifurcation involvement, and LMCA plus triple-vessel disease. This pattern was similar in the group with or without DM. These baseline characteristics in

the BMS era (wave 1 cohort) and DES era (wave 2 cohort) are shown in Tables S2 and S3. Compared with the patients enrolled in the wave 1 period, those enrolled in the wave 2 period had higher-risk clinical and anatomic characteristics.

Ten-Year Clinical Outcomes

The median follow-up duration among all the patients was 12.0 years (interquartile interval, 10.7–13.5 years). The observed rates of clinical outcomes after PCI and CABG in the overall group and in the group with or without DM at 10 years are shown in Table 2 and Figure 1. The 10-year rates of all-cause mortality and the composite of death, Q-wave MI, or stroke were not significantly different between PCI and CABG in either of the cohorts with and without . The TVR rates were lower after CABG than after PCI in the patients both with and without DM. These findings were unchanged after multivariable and IPTW adjustment for differences in baseline characteristics (Table 2 and Figure 2). No significant interactions were found between diabetes mellitus status and treatment method in any of the adjusted 10-year risks of study outcomes ($P_{interaction}$=0.41 for mortality, $P_{interaction}$=0.40 for composite outcome, and $P_{interaction}$=0.82 for TVR).

The results of the analyses stratified by stent type are shown in Table 3. In the wave 1 cohort of BMS and concurrent CABG, patients with DM fared nominally better with CABG than with PCI with respect to the adjusted risks of death and composite outcome, and vice versa for patients without DM (Figure 3). Significant interaction was present between DM status and revascularization type for composite outcome of death, Q-wave MI, or stroke ($P_{interaction}$=0.04), and a nonsignificant trend was observed for mortality ($P_{interaction}$=0.09). In the wave 2 cohort of DES and concurrent CABG, these differential outcomes according to DM status, favoring CABG in patients with DM, has diminished without significant interactions ($P_{interaction}$=0.63 for mortality and 0.47 for composite outcome; Figure 4).

Sensitivity Analysis in the Patients With Baseline SYNTAX Scores

Of the 2240 patients enrolled in the registry, 1580 (70.5%) had a baseline SYNTAX score, which were measured retrospectively by a core laboratory. The 10-year clinical outcomes in this subcohort and in each group stratified by stent type are shown in Tables S4, S5, and Figure S2. These sensitivity analyses revealed consistent findings with the relative effect of PCI and CABG according to DM status, in which the interaction effect of DM was more prominent. In the BMS era, statistically significant interactions were present between diabetic status and

Table 2.   10-Year Rates and Hazard Ratios for Clinical Outcomes*

Outcomes	Event Rates at 10-Year (n/%)		Crude		Multivariate Adjusted†			IPTW Adjusted		
	PCI	CABG	HR (95% CI)	P Value	HR (95% CI)	P Value	$P_{interaction}$	HR (95% CI)	P Value	$P_{interaction}$
Overall patients										
Death	229 (21.0)	259 (22.9)	0.91 (0.78–1.06)	0.23	1.00 (0.82–1.22)	0.99	0.42	1.06 (0.84–1.35)	0.61	0.41
Death, Q-wave MI, or stroke	257 (23.6)	295 (26.1)	0.89 (0.77–1.03)	0.12	0.99 (0.82–1.19)	0.91	0.42	1.06 (0.86–1.32)	0.58	0.40
TVR	219 (21.1)	62 (6.0)	3.85 (2.95–5.02)	<0.001	4.71 (3.31–6.71)	<0.001	0.95	5.05 (3.42–7.45)	<0.001	0.82
Patients with DM										
Death	95 (29.4)	113 (28.8)	1.01 (0.80–1.29)	0.92	1.08 (0.85–1.38)	0.54		1.23 (0.92–1.65)	0.17	
Death, Q-wave MI, or stroke	100 (30.9)	126 (32.1)	0.97 (0.77–1.23)	0.81	1.25 (0.97–1.61)	0.09		1.23 (0.93–1.62)	0.16	
TVR	72 (24.5)	24 (6.9)	3.97 (2.58–6.10)	<0.001	4.07 (2.65–6.26)	<0.001		4.86 (3.04–7.78)	<0.001	
Patients without DM										
Death	134 (17.5)	146 (19.8)	0.89 (0.73–1.08)	0.24	1.03 (0.84–1.27)	0.75		1.07 (0.85–1.36)	0.57	
Death, Q-wave MI, or stroke	157 (20.5)	169 (22.9)	0.88 (0.73–1.06)	0.17	1.00 (0.82–1.20)	0.97		1.07 (0.86–1.33)	0.55	
TVR	147 (19.9)	38 (5.5)	3.88 (2.77–5.44)	<0.001	4.50 (3.16–6.41)	<0.001		4.97 (3.37–7.32)	<0.001	

CABG indicates coronary artery bypass grafting; DM, diabetes mellitus; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TVR, target-vessel revascularization.

*Event rates were derived from the Kaplan–Meier estimates. Hazard ratio is the risk of PCI for clinical outcomes compared with that of CABG.

†Multivariate models were adjusted for age, sex, wave, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, chronic renal failure, left ventricular ejection fraction, clinical presentation, involved location of the left main coronary artery, and extent of disease.
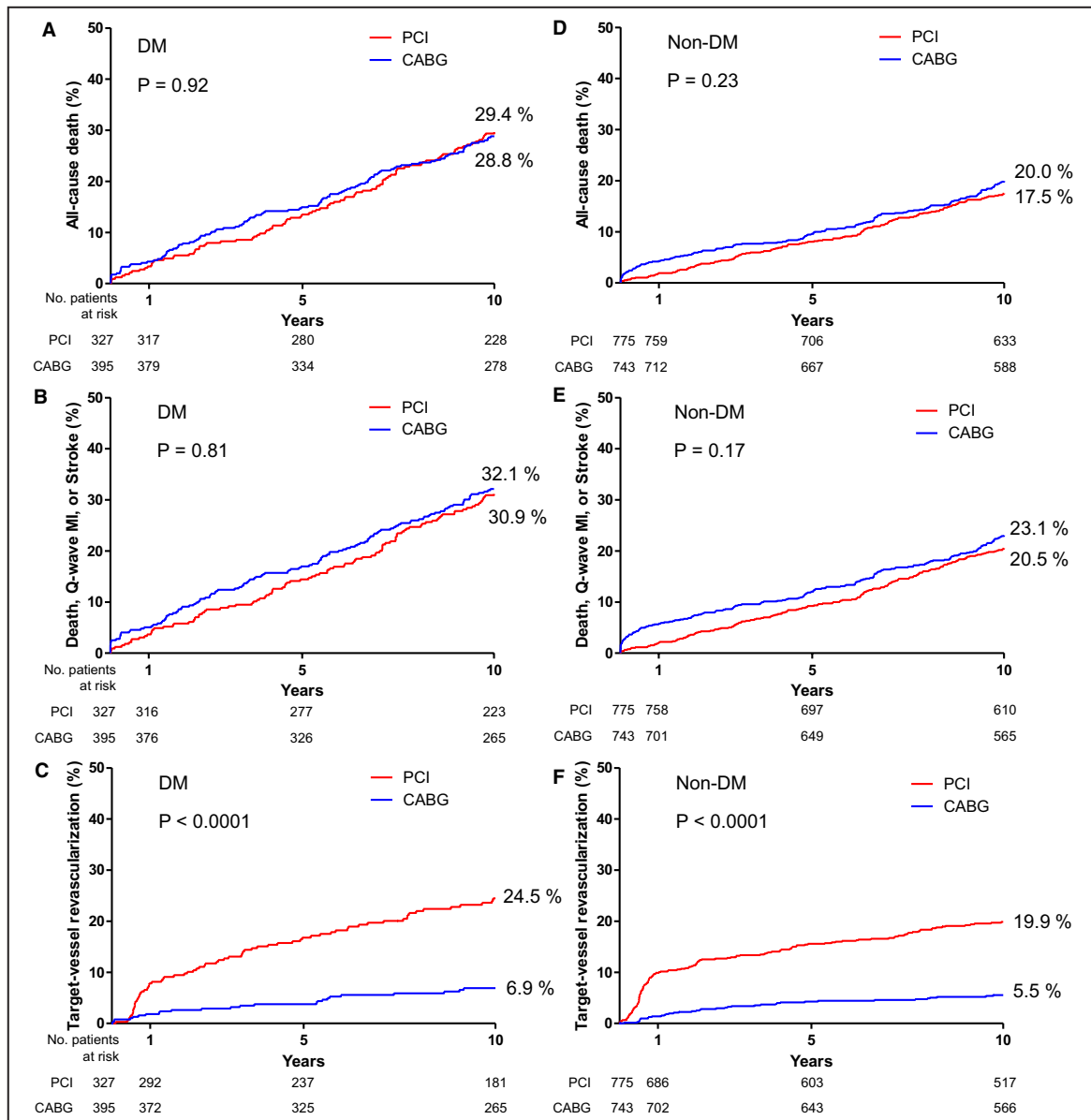
Figure 1.   Kaplan–Meier curves for 10-year outcomes after PCI or CABG in patients with or without DM.
The left panel (**A** through **C**) shows cumulative event curves for patients with DM and the right panel (**D** through **F**) showed event curves for patients without DM. The upper panel (**A** and **D**) indicates all-cause death, the middle panel (**B** and **E**) indicates a composite of death, Q-wave MI, or stroke; and the lower panel (**C** and **F**) indicates target-vessel revascularization. CABG indicates coronary artery bypass grafting; DM, diabetes mellitus; MI, myocardial infarction; non-DM, non–diabetes mellitus; and PCI, percutaneous coronary intervention.

revascularization type for the adjusted 10-year rates of mortality ($P_{interaction}$=0.007) and composite outcome ($P_{interaction}$<0.001; Figure S3). By contrast, this interaction effect of DM and revascularization type on the outcomes was absent in the DES era (Figure S4).

DISCUSSION

The major findings from the present analysis, which is the longest follow-up study to date that evaluates the relative treatment effects of PCI and CABG for LMCA

revascularization stratified by the presence of DM, are as follows: (1) compared with patients without DM, patients with DM had a nearly 1.5-fold higher risk of death and the composite outcome of death, Q-wave MI, or stroke at 10 years; (2) overall, there was no significant difference in the adjusted 10-year risks of mortality and serious composite outcome after PCI or CABG in patients both with and without DM, but the risk of TVR was consistently higher after PCI; (3) a significant interaction was present between DM status and treatment with BMS compared with CABG in the 10-year risks
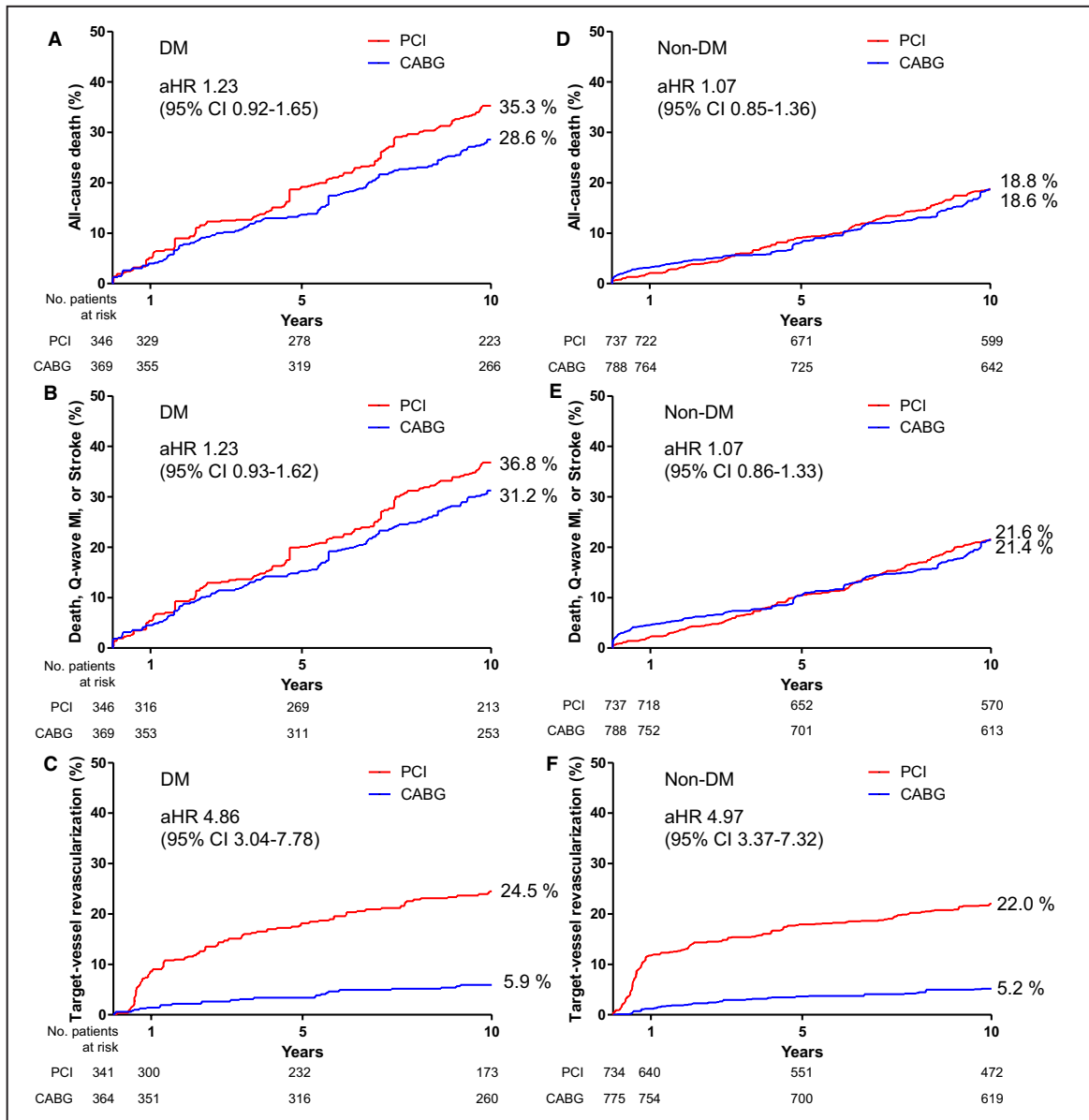
Figure 2.   Adjusted event curves for 10-year outcomes after PCI or CABG in patients with or without DM using inverse probability weighting.*

The left panel (**A** through **C**) shows cumulative event curves for patients with DM, and the right panel (**D** through **F**) shows event curves for patients without DM. The upper panel (**A** and **D**) indicates all-cause death, the middle panel (**B** and **E**) indicates a composite of death, Q-wave MI, or stroke; and the lower panel (**C** and **F**) indicates target-vessel revascularization. *Inverse probability of treatment weighting gives different weights to patients based on their characteristics, to create a "virtual" data set that mimics the data that would have been observed if the treatment was randomly assigned. This figure was drawn with individuals after weighting to study population. The adjusted survival curves were estimated with the use of the inverse-probability-weighting approach of Cole and Hernan.[33] aHR indicates adjusted hazard ratio; CABG, coronary artery bypass grafting; DM, diabetes mellitus; MI, myocardial infarction; non-DM, non–diabetes mellitus; and PCI, percutaneous coronary intervention.

of mortality and composite outcome, favoring CABG in patients with DM; and (4) no interaction was found between DM status and treatment with DES compared with CABG for the 10-year clinical outcomes.

Several studies have found that patients with DM are more likely to have more complex and multivessel CAD,

with a more diffuse and aggressive form of atherosclerosis.[1,19] Thus, among several important clinical risk factors, DM has been regarded as a major determinant for predicting worse clinical outcomes and has a pivotal role for the choice of optimal coronary revascularization.[20,21] However, the follow-up durations of prior studies were still

Table 3. 10-Year Rates and Hazard Ratios for Clinical Outcomes Stratified by Stent Type*

Outcomes	Event Rates at 10-Year (n/%)		Crude		IPTW Adjusted		
	PCI	CABG	HR (95% CI)	P Value	HR (95% CI)	P Value	$P_{interaction}$
Wave 1 (BMS vs concurrent CABG)							
Overall patients							
Death	59 (18.6)	103 (23.2)	0.72 (0.55–0.94)	0.014	0.78 (0.54–1.13)	0.19	0.09
Death, Q-wave MI, or stroke	65 (20.5)	118 (26.5)	0.68 (0.53–0.88)	0.003	0.74 (0.52–1.05)	0.09	0.04
TVR	65 (21.3)	29 (7.1)	3.28 (2.19–4.91)	<0.001	4.98 (2.92–8.50)	<0.001	0.23
Patients with DM							
Death	20 (26.7)	36 (26.1)	0.88 (0.56–1.38)	0.57	1.34 (0.79–2.26)	0.28	
Death, Q-wave MI, or stroke	22 (29.4)	41 (29.7)	0.85 (0.55–1.32)	0.48	1.38 (0.85–2.23)	0.19	
TVR	14 (20.8)	11 (8.7)	2.78 (1.36–5.68)	0.005	2.98 (1.35–6.56)	0.007	
Patients without DM							
Death	39 (16.1)	67 (21.8)	0.68 (0.49–0.94)	0.02	0.79 (0.54–1.14)	0.21	
Death, Q-wave MI, or stroke	43 (17.8)	77 (25.1)	0.64 (0.47–0.87)	0.004	0.74 (0.52–1.06)	0.10	
TVR	51 (21.6)	18 (6.4)	3.60 (2.20–5.90)	<0.001	4.91 (2.90–8.31)	<0.001	
Wave 2 (DES vs concurrent CABG)							
Overall patients							
Death	170 (21.9)	156 (22.8)	1.02 (0.84–1.23)	0.87	1.32 (0.96–1.82)	0.08	0.63
Death, Q-wave MI, or stroke	192 (24.8)	177 (25.9)	1.01 (0.84–1.22)	0.89	1.37 (1.02–1.83)	0.036	0.47
TVR	154 (21.1)	33 (5.3)	4.43 (3.09–6.35)	<0.001	5.09 (2.93–8.84)	<0.001	0.55
Patients without DM							
Death	75 (30.2)	77 (30.3)	1.04 (0.78–1.38)	0.81	1.17 (0.82–1.66)	0.39	
Death, Q-wave MI, or stroke	78 (31.4)	85 (33.4)	1.00 (0.76–1.32)	0.98	1.14 (0.81–1.61)	0.44	
TVR	58 (25.5)	13 (5.9)	4.85 (2.76–8.51)	<0.001	6.68 (3.69–12.08)	<0.001	
Patients without DM							
Death	95 (18.1)	78 (18.4)	1.06 (0.81–1.38)	0.68	1.33 (0.97–1.84)	0.08	
Death, Q-wave MI, or stroke	114 (21.7)	92 (21.4)	1.07 (0.84–1.36)	0.60	1.38 (1.03–1.85)	0.03	
TVR	96 (9.1)	20 (5.0)	4.31 (2.70–6.89)	<0.001	5.03 (2.90–8.71)	<0.001	

BMS indicates bare-metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stents; DM, diabetes mellitus; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TVR, target-vessel revascularization.

*Event rates were derived from the Kaplan–Meier estimates. Hazard ratio is the risk of PCI for clinical outcomes compared with CABG.

too short to establish the full effect of the revascularization method on survival and hard clinical end point, particularly considering the diverging or converging Kaplan–Meier curves in specific subgroups. In addition, the detriment effect of DM on major cardiovascular events or mortality might be particularly noticeable with longer follow-up duration. In this regard, the main strength of this study was that we evaluated whether there were clinically relevant differences in long-term outcomes beyond 10 years after PCI or CABG according to DM status. Thus, our study may provide important clinical insights for the selection of the most effective therapy for this high-risk subset of patients with DM and LMCA disease.

The key findings of the present study do not support the role of DM as an important modifier for the comparative effect of PCI and CABG for LMCA disease. To evaluate the clinical usefulness of important risk factors, we should consider not only their prognostic ability to predict the future risk of adverse events, but also their discriminating capacity to better guide decision making between PCI and CABG.[22] As expected, in our study, DM was an important predictor of adverse events after LMCA revascularization. However, the role of specific risk factors for optimal decision making should be considered in the context of the interaction effect, as they guide decision making between PCI and CABG.[23] If a significant interaction is present, the clinical or anatomic factor aids decision making between CABG and PCI. In a recent pooled analysis of individual patient data, the presence of DM
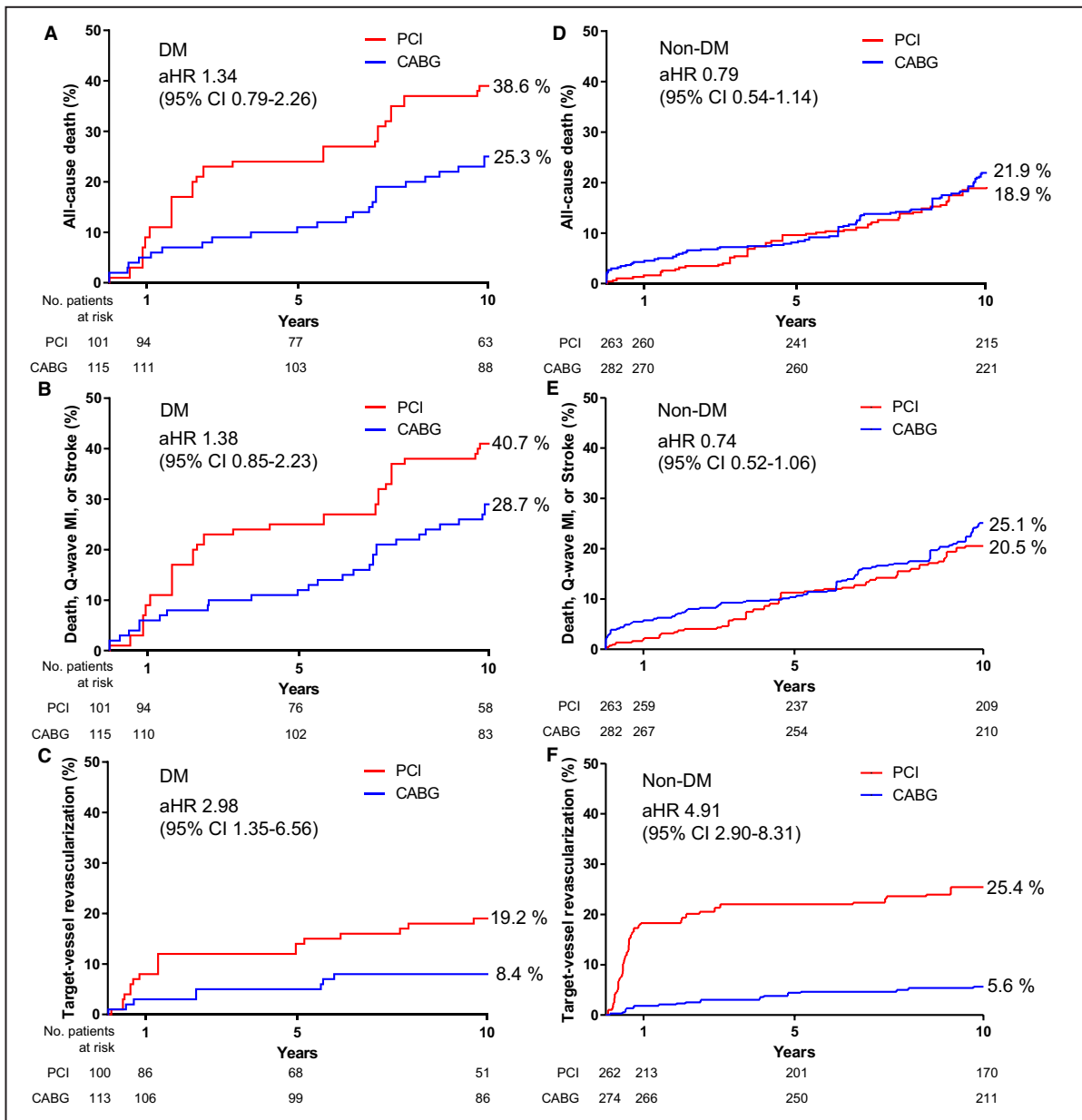
Figure 3.   Adjusted event curves for 10-year outcomes after BMS or concurrent CABG in Patients with or without DM using inverse probability weighting.

The left panel (**A** through **C**) shows cumulative event curves for patients with DM, and the right panel (**D** through **F**) shows event curves for patients without DM. The upper panel (**A** and **D**) indicates all-cause death; the middle panel (**B** and **E**) indicates a composite of death, Q-wave MI, or stroke; and the lower panel (**C** and **F**) indicates target-vessel revascularization. aHR indicates adjusted hazard ratio; CABG, coronary artery bypass grafting; DM, diabetes mellitus; MI, myocardial infarction; non-DM, non–diabetes mellitus; and PCI, percutaneous coronary intervention.

was reported to have a significant interaction effect for 5-year mortality favoring CABG over PCI in patients with multivessel CAD ($P_{interaction}$=0.045), but not in those with LMCA disease ($P_{interaction}$=0.13).[6] These findings also confirmed the impact of DM with respect to the primary composite end point ($P_{interaction}$=0.82) and mortality ($P_{interaction}$=0.22) in the subgroup analysis of the EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery

for Effectiveness of Left Main Revascularization) trial with low-to-intermediate SYNTAX scores.[24] Consistent with such findings, in our extended follow-up study, DM had no significant interaction effect with PCI and CABG for LMCA revascularization in establishing 10-year clinical outcomes. However, a recent 5-year report of the EXCEL trial showed a late catch-up of primary end point and an increased risk of mortality with a contemporary DES as compared
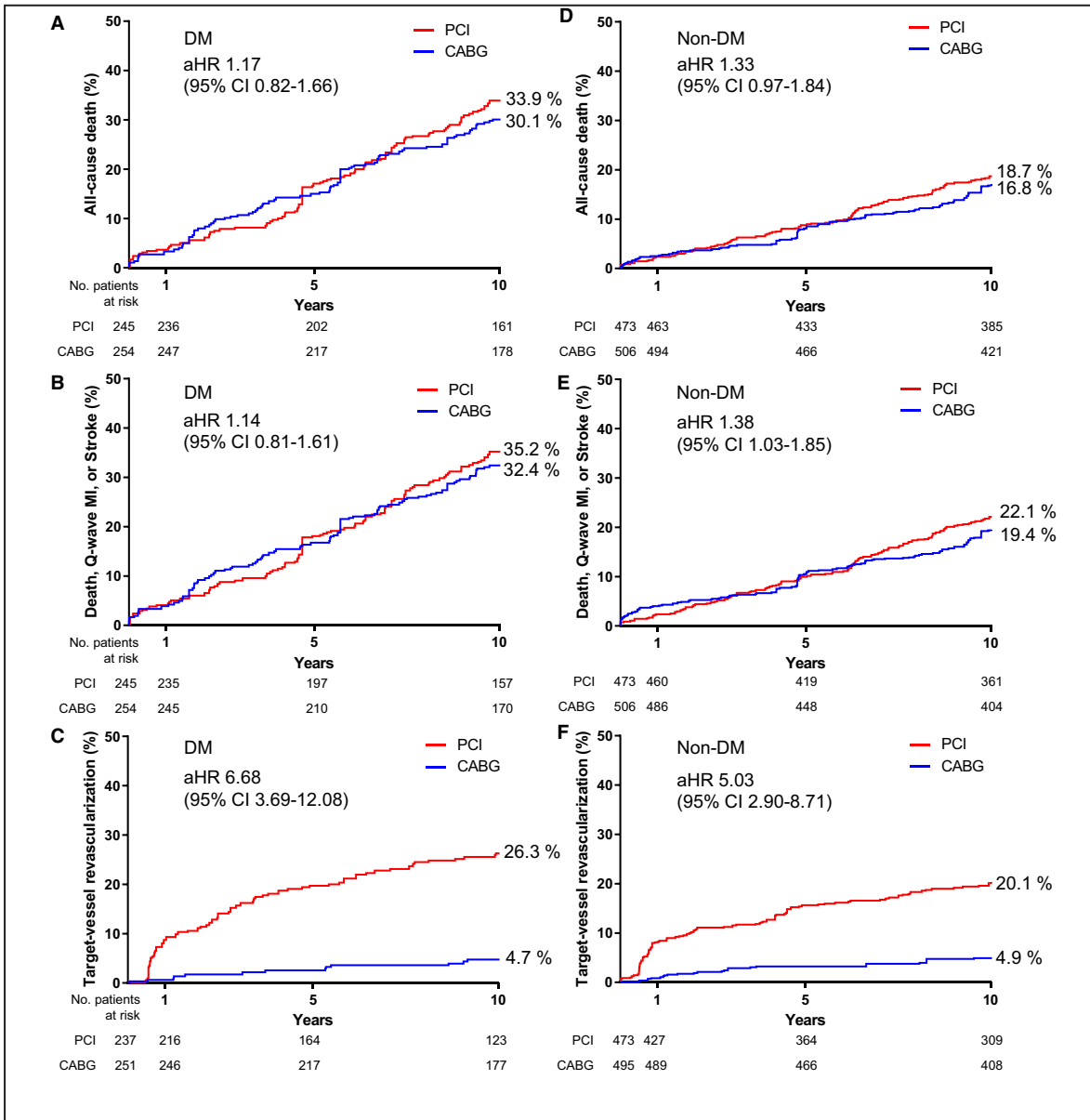
Figure 4.   Adjusted event curves for 10-year outcomes after DES or concurrent CABG in patients with or without DM using inverse probability weighting.

The left panel (**A** through **C**) shows cumulative event curves for patients with DM, and the right panel (**D** through **F**) shows event curves for patients without DM. The upper panel (**A** and **D**) indicates all-cause death; the middle panel (**B** and **E**) indicates a composite of death, Q-wave MI, or stroke; and the lower panel (**C** and **F**) indicates target-vessel revascularization. aHR indicates adjusted hazard ratio; BMS, bare-metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; DM, diabetes mellitus; MI, myocardial infarction; and non-DM, non–diabetes mellitus; and PCI, percutaneous coronary intervention.

with CABG.[25] Further study is required to determine the impact of DM on comparative outcomes during the extended follow-up.

By contrast, DM was still an important effect modifier in patients with multivessel disease and the benefit of CABG over PCI was shown in patients with multivessel CAD and DM. The extended follow-up (≈8 years) report of the FREEDOM (Future Revascularization Evaluation in Patients

With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial shows that CABG leads to lower all-cause mortality than PCI in patients with DM with multivessel disease.[26] A recently published SYNTAX study[27] also showed that CABG provided a significant survival benefit in patients with 3-vessel disease but not in patients with LMCA disease at 10 years. Similarly, the discrepancy between impact of DM on LMCA disease versus multivessel disease

has been found in coronary revascularization with PCI or CABG. The benefit of CABG in patients with DM might be attributed to complete revascularization in more diffuse and complex multivessel CAD.[28–30]

The relative benefits of CABG versus PCI with stents in terms of outcomes are highly debated, particularly each time stent design is enhanced. Our study population included both the BMS and DES eras, so we could demonstrate the secular change of DM impact on comparative outcomes after PCI or CABG for LMCA disease. In the BMS era, a comparison of PCI with BMS and concurrent CABG found a significant interaction between DM and revascularization type for 10-year clinical outcomes, in which CABG had an advantage over PCI with respect to mortality and serious composite outcomes in DM patients. This pattern was much more prominent after full adjustment of detailed information on angiographic complexity in the patient cohort with baseline SYNTAX scores. By contrast, moving on to the DES era, DM did not appear to modify the treatment effects of PCI and CABG for LMCA disease. Given that improvements in stent design have led to inclusion of higher-risk patients with more complex disease and also this higher-risk profile is already reflected in the contemporary clinical practice, these findings may be more clinically relevant and applicable. Notably, the clinical usefulness of DM as an important decision-making factor for a specific treatment option was not obvious in recent trials that compared CABG and PCI with DES for LMCA revascularization.[22] The remarkable improvements in stent platform and technology, procedural technique and experience, and adjunctive pharmacology have narrowed the treatment gap in favor of CABG over PCI for patients with DM.[31] In addition, the advanced and rapidly evolving optimal medical therapy (ie, high-potency statins, newer P2Y12 inhibitors, and more aggressive blood pressure targets) and DM management probably attenuate the treatment gap between CABG and PCI.[32]

Our study has several limitations. First, this was a nonrandomized, observational registry study with inherent methodological limitations; thus, its overall findings must be considered hypothetical and hypothesis generating only. Second, because the treatment choice was left to the physician or patient, our findings are subject to selection bias. Although propensity-score analyses were performed to adjust for potential selection bias, the unmeasured confounders might have affected the results. Third, owing to the relatively limited number of patients, this study is not sufficiently powered to compare between insulin-treated and non–insulin-treated DM and comparative outcomes after PCI and CABG. Fourth, the SYNTAX score was not available in

29.5% of patients. Therefore, our findings should be further evaluated through extended follow-up of the EXCEL and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trials using contemporary DES.

CONCLUSIONS

In conclusion, in this longest-term follow-up study of patients with LMCA disease, the 10-year rates of mortality and serious composite outcome of death, Q-wave MI, or stroke were similar between PCI and CABG in patients with or without DM. However, we observed the differential effect of DM on comparative outcomes of PCI and CABG over time from the BMS to the DES era. These findings may suggest that the presence of DM should not penalize the specific revascularization strategy for LMCA disease in the heart-team discussion for optimal decision making in contemporary clinical practice.

REFERENCES

1. Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–2515.

2. Castelvecchio S, Menicanti L, Garatti A, Tramarin R, Volpe M, Parolari A. Myocardial revascularization for patients with diabetes: coronary artery bypass grafting or percutaneous coronary intervention? *Ann Thorac Surg*. 2016;102:1012–1022.

3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972.

4. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, Danchin N, Flather M, et al. Coronary artery

bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet*. 2009;373:1190–1197.

5. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375–2384.

6. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391:939–948.

7. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130:1749–1767.

8. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165.

9. Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM III, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med*. 2016;375:2223–2235.

10. Park DW, Park SJ. Percutaneous coronary intervention of left main disease: pre- and post-EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) era. *Circ Cardiovasc Interv*. 2017;10:e004792.

11. Makikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2016;388:2743–2752.

12. Park DW, Ahn JM, Yun SC, Yoon YH, Kang DY, Lee PH, Lee SW, Park SW, Seung KB, Gwon HC, et al. 10-year outcomes of stents versus coronary artery bypass grafting for left main coronary artery disease. *J Am Coll Cardiol*. 2018;72:2813–2822.

13. Seung KB, Park D-W, Kim Y-H, Lee S-W, Lee CW, Hong M-K, Park S-W, Yun S-C, Gwon H-C, Jeong M-H. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med*. 2008;358:1781–1792.

14. Park D-W, Seung KB, Kim Y-H, Lee J-Y, Kim W-J, Kang S-J, Lee S-W, Lee CW, Park S-W, Yun S-C. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization) registry. *J Am Coll Cardiol*. 2010;56:117–124.

15. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550–560.

16. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661–3679.

17. Rosenbaum PR. Model-based direct adjustment. *J Am Stat Assoc*. 1987;82:387–394.

18. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer; 2000.

19. Silvain J, Vignalou JB, Barthelemy O, Kerneis M, Collet JP, Montalescot G. Coronary revascularization in the diabetic patient. *Circulation*. 2014;130:918–922.

20. Bhatt DL. CABG the clear choice for patients with diabetes and multivessel disease. *Lancet*. 2018;391:913–914.

21. Kappetein AP, Head SJ. CABG or PCI for revascularisation in patients with diabetes? *Lancet Diabetes Endocrinol*. 2013;1:266–268.

22. Park S-J, Park D-W. Diabetes in myocardial revascularization for left main coronary artery disease: predictor or decision maker?. *J Am Coll Cardiol*. 2019;73:1629–1632.

23. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639–650.

24. Milojevic M, Serruys PW, Sabik JF, Kandzari DE, Schampaert E, van Boven AJ, Horkay F, Ungi I, Mansour S, Banning AP, et al. Bypass surgery or stenting for left main coronary artery disease in patients with diabetes. *J Am Coll Cardiol*. 2019;73:1616–1628.

25. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice MC, Puskas J, Kandzari DE, Karmpaliotis D, Brown WM III, Lembo NJ, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med*. 2019;381:1820–1830.

26. Farkouh ME, Domanski M, Dangas GD, Godoy LC, Mack MJ, Siami FS, Hamza TH, Shah B, Stefanini GG, Sidhu MS, et al. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM follow-on study. *J Am Coll Cardiol*. 2019;73:629–638.

27. Thuijs DJFM, Kappetein AP, Serruys PW, Mohr F-W, Morice M-C, Mack MJ, Holmes DR Jr, Curzen N, Davierwala P, Noack T, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019;394:1325–1334.

28. Doenst T, Haverich A, Serruys P, Bonow RO, Kappetein P, Falk V, Velazquez E, Diegeler A, Sigusch H. PCI and CABG for treating stable coronary artery disease: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73:964–976.

29. Gersh BJ, Frye RL. Methods of coronary revascularization—things may not be as they seem. *N Engl J Med*. 2005;352:2235–2237.

30. Head SJ, Mack MJ, Holmes DR Jr, Mohr FW, Morice M-C, Serruys PW, Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg*. 2012;41:535–541.

31. Lee PH, Ahn JM, Chang M, Baek S, Yoon SH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, et al. Left main coronary artery disease: secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol*. 2016;68:1233–1246.

32. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31–39.

33. Cole SR, Hernan MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed*. 2004;75:45–49.

Supplemental Material

Table S1. Baseline Characteristics of Patients According to Diabetes Mellitus.

Variable	All patients (n = 2240)	Diabetes (n = 722)	No diabetes (n = 1518)	P
Age, years	62.2 ± 10.6	63.6 ± 9.3	61.5 ± 11.1	<0.001
Male	1609 (71.8)	522 (72.3)	1087 (71.6)	0.73
Hypertension	1108 (49.5)	425 (58.9)	683 (45.0)	<0.001
Hyperlipidemia	686 (30.6)	249 (34.5)	437 (28.8)	0.006
Current smoker	621 (27.7)	179 (24.8)	442 (29.1)	0.033
Prior MI	221 (9.9)	87 (12.0)	134 (8.8)	0.017
Prior PCI	325 (14.5)	130 (18.0)	195 (12.8)	0.001
Congestive heart failure	65 (2.9)	37 (5.1)	28 (1.8)	<0.001
Prior stroke	161 (7.2)	71 (9.8)	90 (5.9)	0.001
Peripheral vascular disease	78 (3.5)	37 (5.1)	41 (2.7)	0.003
Chronic kidney disease	64 (2.9)	43 (6.0)	21 (1.4)	<0.001

Acute coronary syndrome	1603 (71.6)	529 (73.3)	1074 (70.8)	0.22
LV EF, %	58.8 ± 11.5 (n = 1826)	57.1 ± 12.6 (n = 602)	59.7 ± 10.8 (n = 1224)	<0.001
SYNTAX score (n = 1580)				<0.001
0-22	508 (32.2)	119 (23.3)	389 (36.4)	
23-32	389 (24.6)	127 (24.9)	262 (24.5)	
≥ 33	683 (43.2)	264 (51.8)	419 (39.1)	
Left main Distal bifurcation	1157 (51.7)	395 (54.7)	762 (50.2)	0.046
Disease extent				<0.001
LM only	349 (15.6)	69 (9.6)	280 (18.4)	
LM + 1VD	383 (17.1)	103 (14.3)	280 (18.4)	
LM + 2VD	586 (26.2)	194 (26.9)	392 (25.8)	
LM + 3VD	922 (41.2)	356 (49.3)	566 (37.3)	

Values are presented as n (%) or mean ± standard deviation.

MI, myocardial infarction; PCI, percutaneous coronary intervention; LV EF, left ventricular ejection fraction; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; LM, left main; VD, vessel disease.

Table S2. Baseline Characteristics of Patients in the Era of Bare-Metal Stents (Wave 1).

Variable	Overall (n = 766)			Diabetes (n = 215)			No diabetes (n = 551)		
	BMS (n = 318)	CABG (n = 448)	P	BMS (n = 76)	CABG (n = 139)	P	BMS (n = 242)	CABG (n = 309)	P
Age (years)	58.6 ± 12.6	61.3 ± 9.6	0.002	62.2 ± 10.3	62.0 ± 8.9	0.91	57.4 ± 13.1	60.9 ± 9.9	0.001
Male	223 (70.1)	331 (73.9)	0.25	54 (71.1)	103 (74.1)	0.63	169 (69.8)	228 (73.8)	0.31
Treatment of diabetes mellitus			0.17			0.51			
Insulin-requiring	11 (3.5)	25 (5.6)		11 (14.5)	25 (18.0)				
OHA-requiring	307 (96.5)	423 (94.4)		65 (85.5)	114 (82.0)				
Hypertension	128 (40.3)	219 (48.9)	0.018	37 (48.7)	75 (54.0)	0.46	91 (37.6)	144 (46.6)	0.034
Hyperlipidemia	74 (23.3)	118 (26.3)	0.33	22 (28.9)	31 (22.3)	0.28	52 (21.5)	87 (28.2)	0.07
Current smoker	89 (28.0)	161 (35.9)	0.021	21 (27.6)	41 (29.5)	0.77	68 (28.1)	120 (38.8)	0.008
Prior MI	26 (8.2)	57 (12.7)	0.046	9 (11.8)	20 (14.4)	0.60	17 (7.0)	37 (12.0)	0.052
Prior PCI	40 (12.6)	46 (10.3)	0.32	16 (21.1)	19 (13.7)	0.16	24 (9.9)	27 (8.7)	0.64

Congestive heart failure	7 (2.2)	16 (3.6)	0.27	3 (3.9)	6 (4.3)	0.90	4 (1.7)	10 (3.2)	0.24
Prior stroke	12 (3.8)	35 (7.8)	0.022	6 (7.9)	14 (10.1)	0.60	6 (2.5)	21 (6.8)	0.02
Peripheral vascular disease	2 (0.6)	31 (6.9)	<0.001	0	16 (11.5)	0.001	2 (0.8)	15 (4.9)	0.006
Chronic kidney disease	4 (1.3)	10 (2.2)	0.32	1 (1.3)	7 (5.0)	0.27	3 (1.2)	3 (1.0)	1.00
Clinical indication			0.002			0.70			0.002
Silent ischemia	6 (1.9)	12 (2.7)		2 (2.6)	6 (4.3)		4 (1.7)	6 (1.9)	
Chronic stable angina	86 (27.0)	70 (15.6)		19 (25.0)	26 (18.7)		67 (27.7)	44 (14.2)	
Unstable angina	203 (63.8)	327 (73.0)		49 (64.5)	95 (68.3)		154 (63.6)	232 (75.1)	
NSTEMI	23 (7.2)	39 (8.7)		6 (7.9)	12 (8.6)		17 (7.0)	27 (8.7)	
LV EF, % (n = 612)	61.4 ± 10.2	59.2 ± 11.5		59.6 ± 11.8	58.5 ± 11.9	0.57	61.9 ± 9.6	59.6 ± 11.3	0.018
SYNTAX score (n = 430)			<0.001			<0.001			<0.001
0-22	102 (60.0)	39 (15.0)		18 (45.0)	7 (9.7)		84 (64.6)	32 (17.0)	
23-32	37 (21.8)	60 (23.1)		11 (27.5)	18 (25.0)		26 (20.0)	42 (22.3)	
≥ 33	31 (18.2)	161 (61.9)		11 (27.5)	47 (65.3)		20 (15.4)	114 (60.6)	

Involved location			<0.001			<0.001			<0.001
Ostium and/or midshaft	218 (68.6)	202 (45.1)		55 (72.4)	56 (40.3)		163 (67.4)	146 (47.2)	
Distal bifurcation	100 (31.4)	246 (54.9)		21 (27.6)	83 (59.7)		79 (32.6)	163 (52.8)	
Disease extent			<0.001			<0.001			<0.001
LM only	133 (41.8)	45 (10.0)		22 (28.9)	7 (5.0)		111 (45.9)	38 (12.3)	
LM + single vessel disease	82 (25.8)	65 (14.5)		23 (30.3)	16 (11.5)		59 (24.4)	49 (15.9)	
LM + double vessel disease	70 (22.0)	139 (31.0)		17 (22.4)	47 (33.8)		53 (21.9)	92 (29.8)	
LM + triple vessel disease	33 (10.4)	199 (44.4)		14 (18.4)	69 (49.6)		19 (7.9)	130 (42.1	
Restenotic lesion	5 (1.6)	8 (1.8)	1.00	1 (1.3)	1 (0.7)	1.00	4 (1.7)	7 (2.3)	0.76

Values are presented as n (%) or mean ± SD.

CABG, coronary artery bypass grafting; LM, left main; LV EF, left ventricle ejection fraction; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; OHA, oral hypoglycemic agent; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.

Table S3. Baseline Characteristics of Patients in the Era of Drug-Eluting Stents (Wave 2).

Variable	Overall (n = 1474)			Diabetes (n = 507)			No diabetes (n = 967)		
	DES (n = 784)	CABG (n = 690)	P	DES (n = 251)	CABG (n = 256)	P	DES (n = 533)	CABG (n = 434)	P
Age (years)	62.5 ± 11.1	64.0 ± 9.1	0.003	63.9 ± 10.0	64.5 ± 8.4	0.48	61.8 ± 11.5	63.8 ± 9.5	0.003
Male	556 (70.9)	499 (72.3)	0.55	174 (69.3)	191 (74.6)	0.19	382 (71.7)	308 (71.0)	0.81
Treatment of diabetes mellitus			0.26			0.79			
Insulin-requiring	64 (8.2)	68 (9.9)		64 (25.5)	68 (26.6)				
OHA-requiring	720 (91.8)	622 (90.1)		187 (74.5)	188 (73.4)				
Hypertension	418 (53.3)	343 (49.7)	0.17	160 (63.7)	153 (59.8)	0.36	258 (48.4)	190 (43.8)	0.15
Hyperlipidemia	241 (30.7)	253 (36.7)	0.016	88 (35.1)	108 (42.2)	0.10	153 (28.7)	145 (33.4)	0.12
Current smoker	193 (24.6)	178 (25.8)	0.60	51 (20.3)	66 (25.8)	0.14	142 (26.6)	112 (25.8)	0.77
Prior MI	63 (8.0)	75 (10.9)	0.062	23 (9.2)	35 (13.7)	0.11	40 (7.5)	40 (9.2)	0.34
Prior PCI	160 (20.4)	79 (11.4)	<0.001	64 (25.5)	31 (12.1)	<0.001	96 (18.0)	48 (11.1)	0.003

Congestive heart failure	20 (2.6)	22 (3.2)	0.46	11 (4.4)	17 (6.6)	0.27	9 (1.7)	5 (1.2)	0.49
Prior stroke	66 (8.4)	48 (7.0)	0.29	27 (10.8)	24 (9.4)	0.61	39 (7.3)	24 (5.5)	0.26
Peripheral vascular disease	14 (1.8)	31 (4.5)	0.003	4 (1.6)	17 (6.6)	0.006	10 (1.9)	14 (3.2)	0.18
Chronic kidney disease	26 (3.3)	24 (3.5)	0.86	16 (6.4)	19 (7.4)	0.64	10 (1.9)	5 (1.2)	0.37
Clinical indication			<0.001			<0.001			0.002
Silent ischemia	27 (3.4)	13 (1.9)		11 (4.4)	5 (2.0)		16 (3.0)	8 (1.8)	
Chronic stable angina	267 (34.1)	267 (34.1)		78 (31.1)	46 (18.0)		189 (35.5)	110 (25.3)	
Unstable angina	405 (51.7)	448 (64.9)		124 (49.4)	171 (66.8)		281 (52.7)	277 (63.8)	
NSTEMI	85 (10.8)	73 (10.6)		38 (15.1)	34 (13.3)		47 (8.8)	39 (9.0)	
LV EF, % (n = 1214)	60.3 ± 11.0	55.8 ± 12.0	<0.001	58.6 ± 11.9	54.1 ± 13.3	<0.001	61.1 ± 10.4	56.9 ± 11.9	<0.001
SYNTAX score (n = 1103)			<0.001			<0.001			<0.001
0-22	260 (43.1)	60 (12.0)		74 (35.7)	18 (9.5)		186 (47.0)	42 (13.5)	
23-32	188 (31.2)	104 (20.8)		64 (30.9)	34 (18.0)		124 (31.3)	70 (22.5)	
≥ 33	155 (25.7)	336 (67.2)		69 (33.3)	137 (72.5)		86 (21.7)	199 (64.0)	

Involved location			0.15			0.38			0.22
Ostium and/or midshaft	339 (43.2)	324 (47.0)		102 (40.6)	114 (44.5)		237 (44.5)	210 (48.4)	
Distal bifurcation	445 (56.8)	366 (53.0)		149 (59.4)	142 (55.5)		296 (55.5)	224 (51.6)	
Disease extent			<0.001			<0.001			<0.001
LM only	145 (18.5)	26 (3.8)		34 (13.5)	6 (2.3)		111 (20.8)	20 (4.6)	
LM + single vessel disease	182 (23.2)	54 (7.8)		50 (19.9)	14 (5.5)		132 (24.8)	40 (9.2)	
LM + double vessel disease	217 (27.7)	160 (23.2)		85 (33.9)	45 (17.6)		132 (24.8)	115 (26.5)	
LM + triple vessel disease	240 (30.6)	450 (65.2)		82 (32.7)	191 (74.6)		158 (29.6)	259 (59.7)	
Restenotic lesion	27 (3.4)	6 (0.9)	0.001	9 (3.6)	2 (0.8)	0.030	18 (3.4)	4 (0.9)	0.011

Values are presented as n (%) or mean ± SD.

CABG, coronary artery bypass grafting; LM, left main; LV EF, left ventricle ejection fraction; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; OHA, oral hypoglycemic agent; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.

Table S4. Ten-Year Rates and Hazard Ratios for Clinical outcomes in Patients with SYNTAX Score Data*.

| Outcomes | Event Rates at 10-Year, n (%) | | Crude | | IPTW | | |
	PCI (n = 510)	CABG (n = 1070)	HR (95% CI)	P	HR (95% CI)	P	P$_{Interaction}$
Overall patients							
Death	169 (20.8)	166 (21.9)	0.99 (0.82–1.19)	0.90	1.17 (0.85–1.61)	0.33	0.39
Death, Q-MI, or stroke	190 (23.3)	189 (25.0)	0.96 (0.81–1.15)	0.66	1.20 (0.89–1.61)	0.23	0.35
TVR	160 (20.9)	33 (4.7)	4.81 (3.39–6.84)	<0.001	7.33 (4.10–13.10)	<0.001	0.39
Diabetic patients							
Death	76 (30.9)	76 (29.2)	1.12 (0.85–1.49)	0.43	1.41 (0.99–2.01)	0.05	
Death, Q-MI, or stroke	79 (32.1)	85 (32.6)	1.08 (0.82–1.41)	0.60	1.45 (1.04–2.02)	0.03	
TVR	55 (24.5)	14 (6.1)	4.45 (2.60–7.61)	<0.001	5.25 (2.86–9.62)	<0.001	
Nondiabetic patients							

Death	93 (16.4)	90 (18.1)	0.94 (0.74–1.20)	0.63	1.18 (0.86–1.63)	0.31
Death, Q-MI, or stroke	111 (19.5)	104 (20.9)	0.93 (0.74–1.16)	0.51	1.21 (0.90–1.62)	0.22
TVR	105 (19.4)	19 (4.1)	5.27 (3.31–8.40)	<0.001	7.23 (4.05–12.90)	<0.001

CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PCI, percutaneous coronary intervention; Q-MI, Q-wave myocardial infarction; SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery; TVR, target-vessel revascularization.

*Event rates were derived from the Kaplan-Meier estimates. Hazard ratio is the risk of PCI for clinical outcomes compared to CABG.

Table S5. Ten-Year Rates and Hazard Ratios for Clinical outcomes in Patients with SYNTAX Score Data Stratified by Stent Type*.

Outcomes	Event Rates at 10-Year, n (%)		Crude		IPTW		
	PCI	CABG	HR (95% CI)	P	HR (95% CI)	P	P$_{Interaction}$
WAVE 1 (BMS vs. Concurrent CABG)	(n = 174)	(n = 260)					
Overall patients							
Death	39 (22.5)	56 (21.7)	0.94 (0.67–1.33)	0.74	0.73 (0.44–1.22)	0.23	0.007
Death, Q-MI, or stroke	41 (23.7)	63 (24.4)	0.85 (0.61–1.18)	0.34	0.64 (0.39–1.06)	0.08	<0.001
TVR	30 (18.0)	9 (3.7)	5.45 (2.77–10.72)	<0.001	10.41 (4.02–26.91)	<0.001	0.42
Diabetic patients							
Death	15 (38.1)	19 (26.4)	1.36 (0.76–2.42)	0.30	2.23 (1.18–4.22)	0.014	
Death, Q-MI, or stroke	16 (40.6)	20 (27.8)	1.32 (0.75–2.30)	0.34	2.61 (1.53–4.44)	<0.001	
TVR	5 (13.9)	4 (5.9)	4.05 (1.34–12.20)	0.013	6.73 (1.92–23.55)	0.003	
Nondiabetic patients							

Death	24 (18.0)	37 (19.9)	0.84 (0.55–1.27)	0.40	0.74 (0.45–1.23)	0.25	
Death, Q-MI, or stroke	25 (18.7)	43 (23.1)	0.73 (0.49–1.10)	0.13	0.65 (0.39–1.06)	0.08	
TVR	25 (19.2)	5 (2.8)	6.93 (2.86–16.78)	<0.001	9.94 (3.87–25.53)	<0.001	
WAVE 2 (DES vs. Concurrent CABG)	(n = 398)	(n = 748)					
Overall patients							
Death	130 (20.3)	110 (22.1)	1.00 (0.79–1.24)	0.95	1.49 (0.97–2.28)	0.07	0.53
Death, Q-MI, or stroke	149 (23.2)	126 (25.3)	0.99 (0.80–1.22)	0.92	1.61 (1.09–2.36)	0.02	0.32
TVR	130 (21.6)	24 (5.3)	4.42 (2.93–6.67)	<0.001	6.50 (3.27–12.90)	<0.001	0.58
Diabetic patients							
Death	61 (29.5)	57 (30.2)	1.05 (0.76–1.45)	0.78	1.21 (0.81–1.82)	0.36	
Death, Q-MI, or stroke	63 (30.5)	65 (34.5)	1.00 (0.73–1.37)	>0.99	1.19 (0.80–1.76)	0.40	
TVR	50 (26.3)	10 (6.2)	4.48 (2.39–8.37)	<0.001	4.94 (2.48–9.84)	<0.001	
Nondiabetic patients							
Death	69 (15.9)	53 (17.1)	1.01 (0.74–1.38)	0.94	1.50 (0.98–2.31)	0.06	

Death, Q-MI, or stroke	86 (19.8)	61 (19.6)	1.03 (0.78–1.37)	0.82	1.63 (1.11–2.40)	0.01
TVR	80 (19.5)	14 (4.8)	4.55 (2.63–7-87)	<0.001	6.50 (3.27–12.90)	<0.001

BMS, bare-metal stents; CABG, coronary artery bypass grafting; CI, confidence interval; DES, drug-eluting stents; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PCI, percutaneous coronary intervention; Q-MI, Q-wave myocardial infarction; SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery; TVR, target-vessel revascularization.

*Event rates were derived from the Kaplan-Meier estimates. Hazard ratio is the risk of PCI for clinical outcomes compared to CABG.

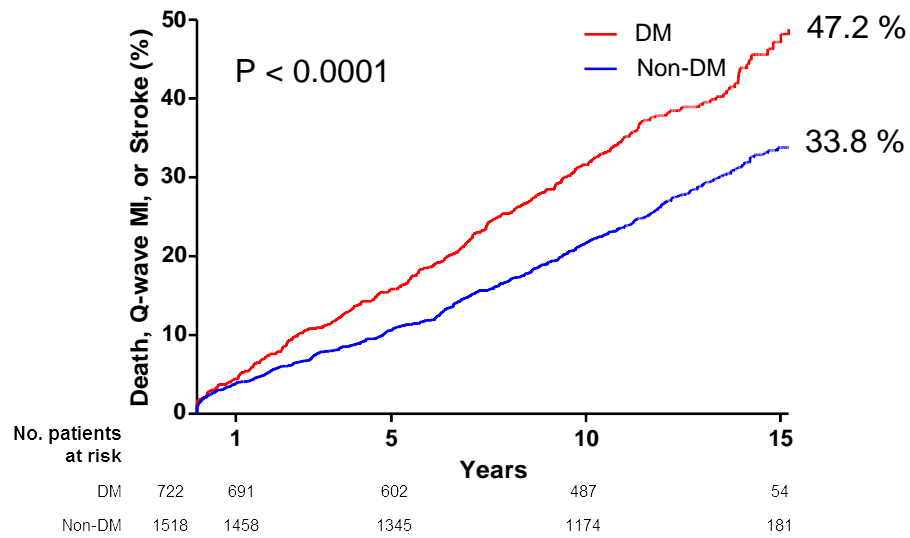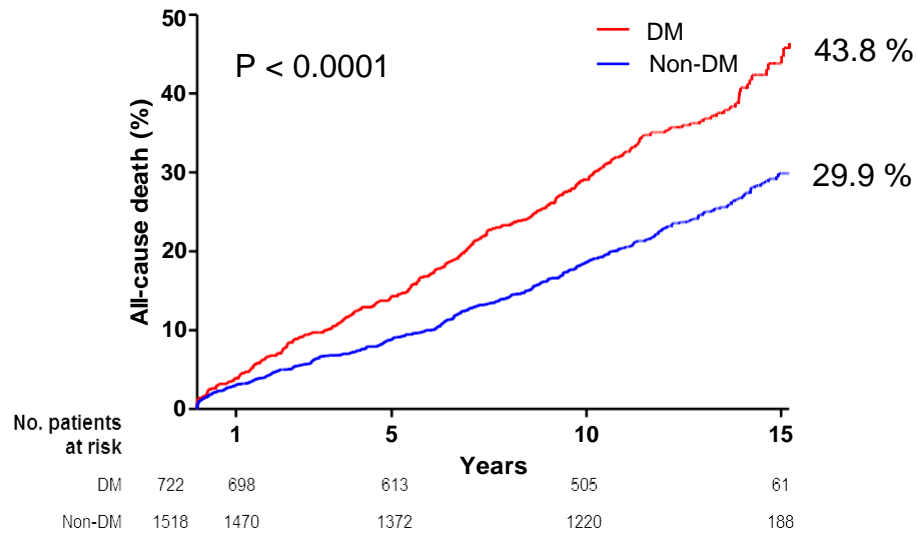**Figure S1. Kaplan-Meier Curves for 10-Year Clinical Outcomes in Patients with or without Diabetes.**
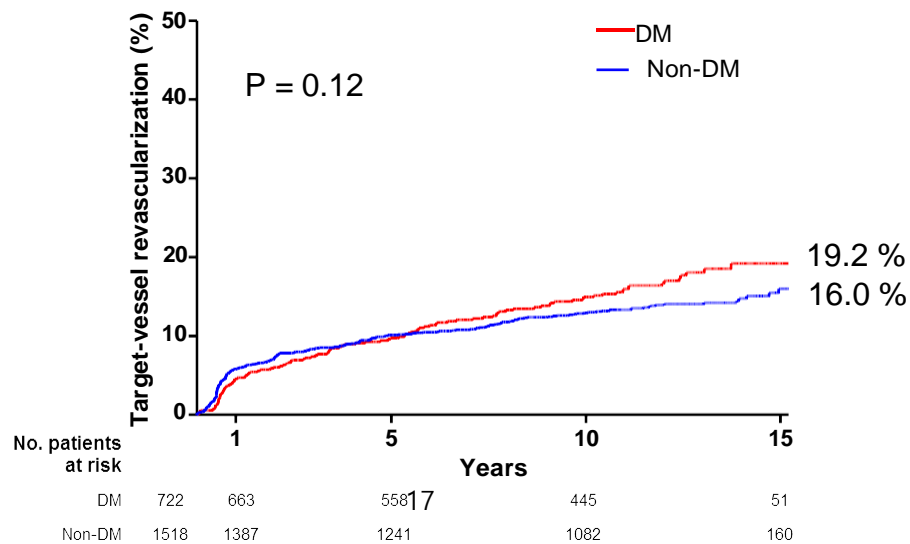
Figure S2. Adjusted Event Curves for 10-Year Outcomes After PCI or CABG Stratified by Diabetes Using Inverse Probability Weighting Among the Cohort with SYNTAX Score Data.
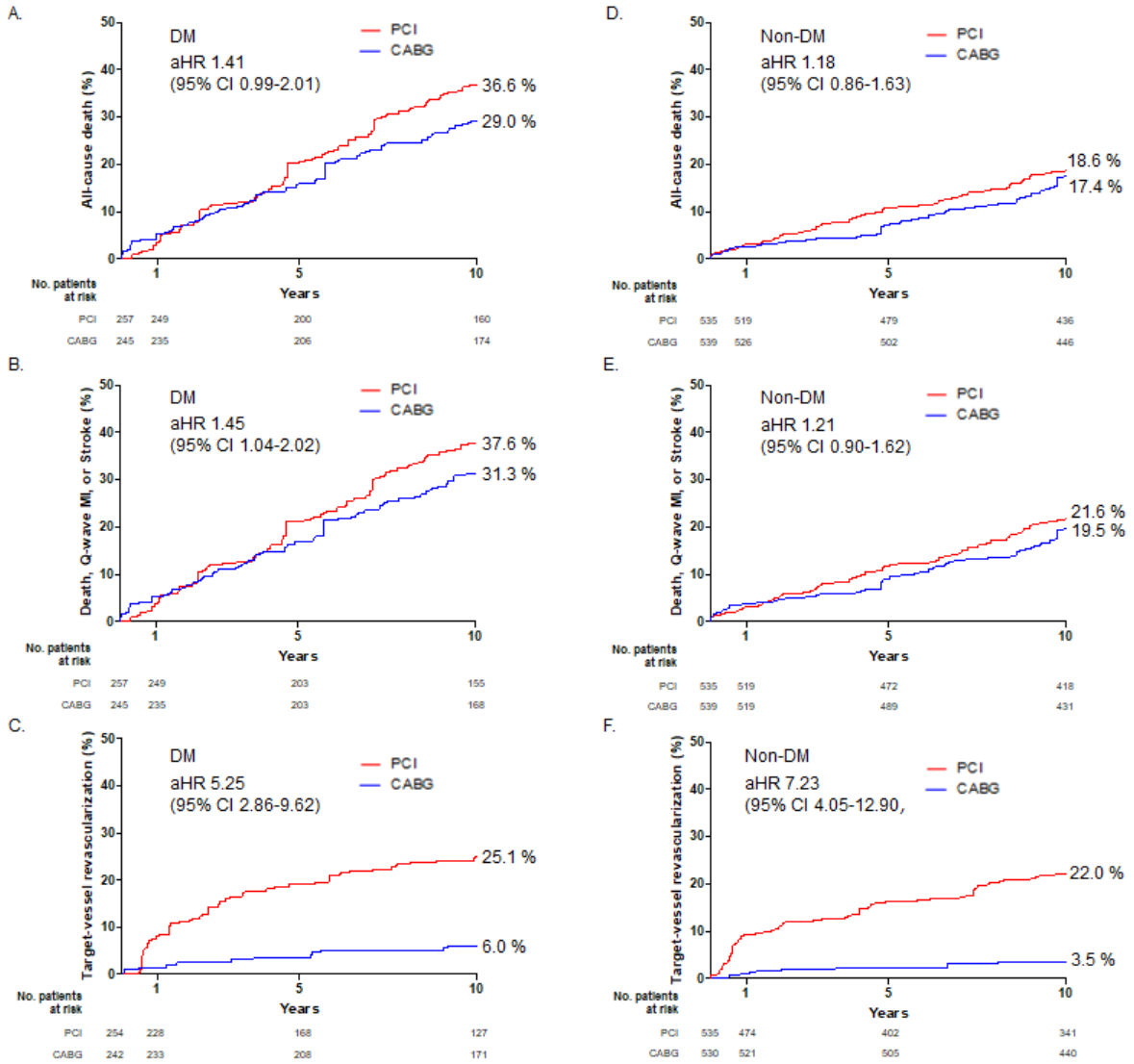
Figure S3. Adjusted Event Curves for 10-Year Outcomes After BMS or Concurrent CABG Stratified by Diabetes Using Inverse Probability Weighting Among the Cohort with SYNTAX Score Data.
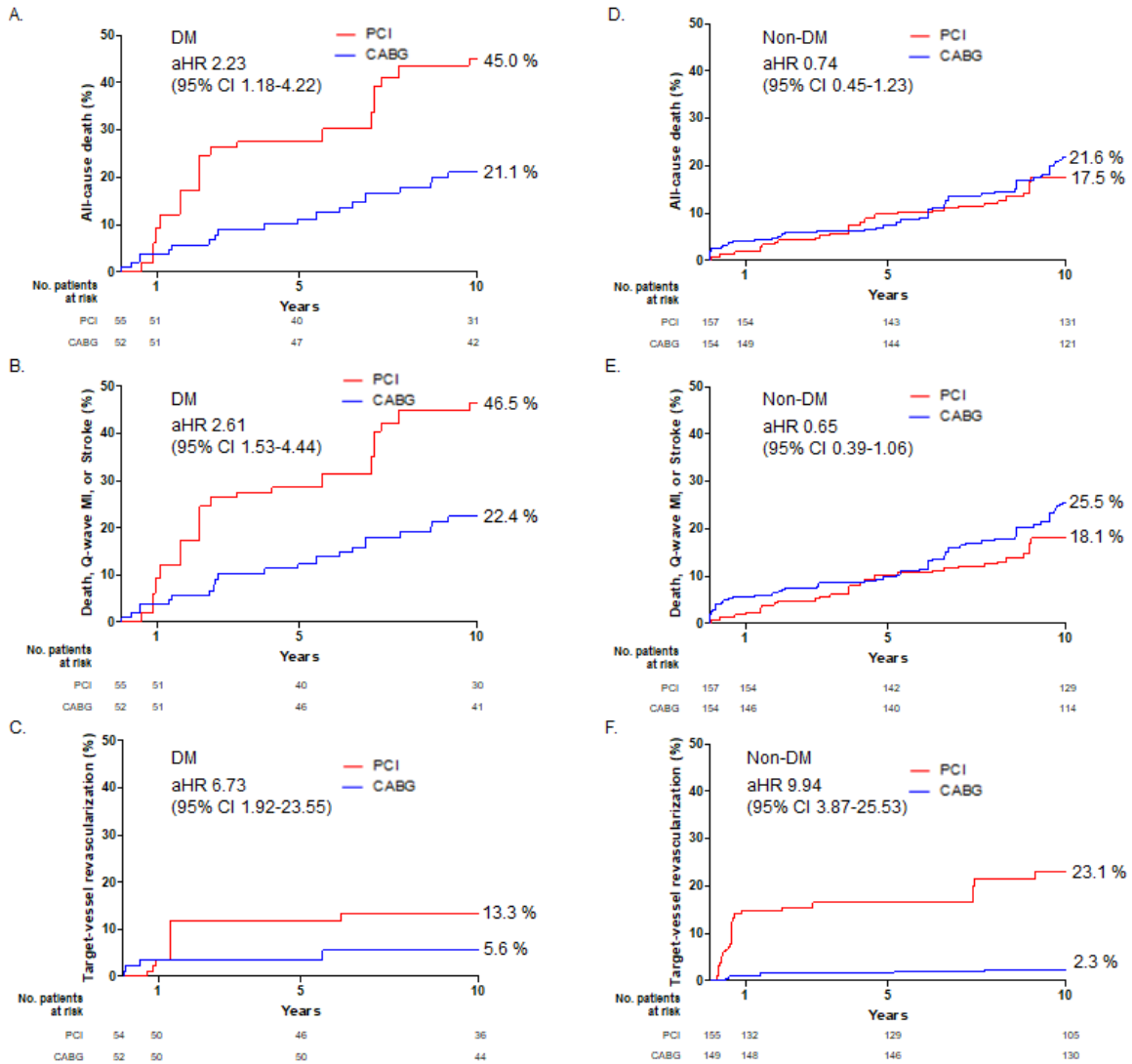
Figure S4. Adjusted Event Curves for 10-Year Outcomes After DES or Concurrent CABG Stratified by Diabetes Using Inverse Probability Weighting Among the Cohort with SYNTAX Score Data.