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CORONARY

Long-Term Outcomes After PCI or CABG for Left Main Coronary Artery Disease According to Lesion Location

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the impact of lesion site (ostial or shaft vs. distal bifurcation) on long-term outcomes after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for left main coronary artery (LMCA) disease.

BACKGROUND Long-term comparative data after PCI and CABG for LMCA disease according to lesion site are limited.

METHODS Patients from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry were analyzed, comparing adverse outcomes (all-cause mortality [a composite outcome of death, Q-wave myocardial infarction, or stroke] and target vessel revascularization) between PCI and CABG according to LMCA lesion location during a median follow-up period of 12.0 years.

RESULTS In overall population, the adjusted risks for death and serious composite outcome were higher after PCI than after CABG for distal bifurcation disease, which was mainly separated beyond 5 years. These outcomes were not different for ostial or shaft disease. When comparing drug-eluting stents (DES) and CABG, the adjusted risks for death and serious composite outcome progressively diverged beyond 5 years after DES compared with CABG for distal bifurcation disease (death: hazard ratio: 1.78; 95% confidence interval: 1.22 to 2.59; composite outcome: hazard ratio: 1.94; 95% confidence interval: 1.35 to 2.79). This difference was driven mainly by PCI with a 2-stent technique for distal bifurcation. In contrast, the adjusted risks for these outcomes were similar between DES and CABG for ostial or shaft disease.

CONCLUSIONS Among patients with distal LMCA bifurcation disease, CABG showed lower mortality and serious composite outcome rates compared with DES beyond 5 years. However, there were no between-group differences in these outcomes among patients with ostial or shaft LMCA disease. (J Am Coll Cardiol Intv 2020;13:2825–36) © 2020 by the American College of Cardiology Foundation.

Historically, coronary artery bypass grafting (CABG) has been regarded as the first choice for patients with unprotected left main coronary artery (LMCA) diseases. With major advances in percutaneous coronary intervention (PCI), however, recent randomized controlled studies have shown that CABG and PCI have similar efficacies for LMCA disease in the medium term (3 to 5 years)

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CABG = coronary artery bypass grafting

CI = confidence interval

DES = drug-eluting stent(s)

HR = hazard ratio

IPTW = inverse probability treatment weighting

LMCA = left main coronary artery

MI = myocardial infarction

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiographic

TVR = target vessel revascularization

(1–3). Nevertheless, choosing between CABG and PCI is still under considerable debate, and a specific subset of patients with LMCA disease with high-risk clinical and anatomic characteristics (e.g., diabetes, concomitant multivessel disease, low ejection fraction, and high SYNTAX [Synergy Between PCI With Taxus and Cardiac Surgery] score) may benefit from CABG despite the remarkable improvements in procedural techniques and stent profiles (4,5).

The lesion site in LMCA disease is an important anatomic characteristic for deciding between PCI and CABG, because PCI for distal LMCA bifurcation lesions usually demands more complex procedural considerations and techniques than for ostial or shaft disease (6,7). Thus, current guidelines consider the LMCA lesion site as the key factor in the choice of revascularization strategy (8,9). However, data on the very long term (beyond 5 years) effect of LMCA lesion site on the relative treatment effect after CABG and PCI are still limited (10), and available long-term reports show conflicting results (1,2,11–13), with some reporting a trend of late catch-up or crossover in the incidences of primary composite outcomes or mortality in favor of CABG over PCI (1,2,13).

Therefore, to characterize the influence of LMCA lesion location on the very long term clinical outcomes of the 2 revascularization strategies, we compared 10-year outcomes after CABG and PCI in nonbifurcation or distal bifurcation LMCA disease using the extended follow-up data of the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry (13).

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METHODS

STUDY DESIGN AND PARTICIPANTS. The design of the MAIN-COMPARE study and the characteristics of its study population were previously reported (14,15). Briefly, the MAIN-COMPARE study was a prospective, multicenter registry that included consecutive patients with unprotected LMCA disease (diameter stenosis more than 50%) who underwent either PCI or CABG at 12 expert centers in Korea between January 2000 and June 2006. Patients with prior CABG, concomitant valvular or aortic surgery, ST-segment elevation myocardial infarction (MI), or cardiogenic shock as initial presentation were excluded. The final 10-year report of the MAIN-COMPARE study was recently published (13).

The decision between PCI or CABG was made at the discretion of attending cardiologists or cardiac surgeons, with careful consideration of both clinical and anatomic factors as well as patient preference. Clinical and anatomic conditions favoring either PCI or CABG were described previously (14,15), and all procedures or operations were carried out according to standard techniques and management (13). Because of device availability, bare-metal stents (BMS) were used only between January 2000 and May 2003 and drug-eluting stents (DES) were used only between May 2003 and June 2006 in the study population. During follow-up, medical therapy for secondary prevention and patient management were performed in accordance with relevant guidelines and established standard of care. The local ethics committee at each hospital approved the use of clinical data for this study, and all patients provided written informed consent.

Baseline angiograms were analyzed at an independent angiography core laboratory (Asan Medical Center, Seoul, Korea) (16). Quantitative coronary angiographic (QCA) analyses were performed by the analysts at the core laboratory, who were blinded to the revascularization treatment and clinical outcomes. For the present analysis, the overall population was stratified into 2 groups: patients with: 1) isolated disease (QCA diameter stenosis ≥50%) of LMCA ostial or shaft location; and 2) those with distal LMCA bifurcation disease (QCA diameter stenosis ≥50%) irrespective of concomitant ostial or shaft LMCA disease. In this registry, the SYNTAX score was retrospectively calculated for each patient by scoring all coronary lesions with diameter stenosis >50% stenosis in vessels with diameters >1.5 mm. The interoperator variabilities for SYNTAX score measurement have been previously described in detail (16), and the SYNTAX score was conventionally categorized into low (≤22), intermediate (23 to 32), and high (≥33) risk.

OUTCOMES AND FOLLOW-UP. The principal outcomes of the study were all-cause death; the composite outcome of all-cause death, Q-wave MI, and stroke; and target vessel revascularization (TVR) (13). Death of any cause was primarily considered. Q-wave MI was defined as the documentation of a new pathological Q wave with ischemic symptoms or signs after the index procedure. Stroke was defined as a sudden onset of neurological deficit confirmed by a neurologist and imaging studies. TVR was defined as any repeated revascularization of the treated vessels, including any segment of the left anterior descending

TABLE 1 Baseline Characteristics of the Patients According to Lesion Site

	Ostial or Shaft Disease (n = 1,083)						Distal Bifurcation Disease (n = 1,157)					
	Unadjusted Data			Data Adjusted With the Use of IPTW			Unadjusted Data			Data Adjusted With the Use of IPTW		
	PCI (n = 557)	CABG (n = 526)	p Value	PCI (n = 557)	CABG (n = 526)	SMD*	PCI (n = 545)	CABG (n = 612)	p Value	PCI (n = 545)	CABG (n = 612)	SMD*
Wave			0.80			0.03			<0.001			0.09
BMS era (January 2000 to May 2003)	218 (39.1)	202 (38.4)		209 (37.6)	204 (38.8)		100 (18.3)	246 (40.2)		150 (27.6)	193 (31.6)	
DES era (May 2003 to June 2006)	339 (60.9)	324 (61.6)		347 (62.4)	322 (61.2)		445 (81.7)	366 (59.8)		395 (72.4)	419 (68.4)	
Age, yrs	59.7 ± 12.1	62.7 ± 9.9	<0.001	61.6 ± 11.6	62.2 ± 11.1	0.04	63.0 ± 11.0	63.2 ± 8.9	0.78	62.8 ± 11.2	63.0 ± 8.9	0.01
Male	361 (64.8)	374 (71.1)	0.03	385 (69.0)	373 (70.9)	0.04	418 (76.7)	456 (74.5)	0.39	410 (75.3)	468 (76.5)	0.03
Hypertension	255 (45.8)	236 (44.9)	0.76	251 (45.1)	218 (41.4)	0.08	291 (53.4)	326 (53.3)	0.97	279 (51.1)	326 (53.3)	0.04
Diabetes	157 (28.2)	170 (32.3)	0.14	175 (31.4)	148 (28.1)	0.07	170 (31.2)	225 (36.8)	0.05	181 (33.2)	220 (35.9)	0.06
Hyperlipidemia	135 (24.2)	156 (29.7)	0.05	150 (26.9)	125 (23.7)	0.08	180 (33.0)	215 (35.1)	0.45	195 (35.8)	193 (31.6)	0.09
Current smoking	128 (23.0)	150 (28.5)	0.04	150 (27.0)	137 (26.0)	0.02	154 (28.3)	189 (30.9)	0.33	162 (29.8)	187 (30.5)	0.02
Prior MI	31 (5.6)	50 (9.5)	0.01	34 (6.2)	34 (6.4)	0.01	58 (10.6)	82 (13.4)	0.15	53 (9.7)	68 (11.2)	0.05
Prior PCI	84 (15.1)	45 (8.6)	0.001	69 (12.4)	58 (11.1)	0.04	116 (21.3)	80 (13.1)	<0.001	98 (18.0)	111 (18.1)	0.002
CHF	16 (2.9)	19 (3.6)	0.49	19 (3.5)	30 (5.7)	0.11	11 (2.0)	19 (3.1)	0.25	12 (2.2)	14 (2.3)	0.003
Cerebrovascular disease	32 (5.7)	29 (4.6)	0.87	27 (4.9)	19 (3.6)	0.06	46 (8.4)	54 (8.8)	0.82	45 (8.3)	44 (7.2)	0.04
PVD	6 (1.1)	24 (4.6)	<0.001	9 (1.6)	13 (2.5)	0.07	10 (1.8)	38 (6.2)	<0.001	20 (3.7)	25 (4.1)	0.02
Chronic kidney disease	9 (1.6)	19 (3.6)	0.05	15 (2.7)	15 (2.9)	0.009	21 (3.9)	15 (2.5)	0.17	19 (3.4)	27 (4.5)	0.06
Clinical presentation			0.03			0.25			<0.001			0.14
Silent ischemia	19 (3.4)	14 (2.7)		18 (3.2)	34 (6.4)		14 (2.6)	11 (1.8)		10 (1.8)	12 (1.9)	
Stable angina	176 (31.6)	125 (23.8)		166 (29.7)	142 (26.9)		177 (32.5)	101 (16.5)		137 (25.2)	148 (24.2)	
Unstable angina	309 (55.5)	331 (62.9)		299 (53.7)	311 (59.0)		299 (54.9)	444 (72.5)		331 (60.7)	400 (65.4)	
NSTEMI	53 (9.5)	56 (10.6)		75 (13.4)	40 (7.6)		55 (10.1)	56 (9.2)		67 (12.4)	52 (8.5)	
LVEF, %†	60.7 ± 10.5	56.1 ± 12.9	<0.001	58.8 ± 12.1	58.9 ± 11.2	0.008	60.5 ± 11.1	58.0 ± 11.1	<0.001	59.7 ± 10.9	59.3 ± 10.1	0.03
SYNTAX score‡			<0.001			0.06			<0.001			0.05
0–22	239 (42.9)	41 (7.8)		156 (38.7)	144 (40.5)		169 (31.0)	59 (9.6)		122 (29.2)	127 (31.2)	
23–32	89 (16.0)	69 (13.1)		89 (22.1)	71 (19.9)		136 (25.0)	95 (15.5)		120 (28.7)	110 (27.0)	
≥33	74 (13.3)	245 (46.6)		158 (39.2)	141 (39.6)		112 (20.6)	252 (41.2)		175 (42.1)	170 (41.8)	
Extent of diseased vessel			<0.001			0.06			<0.001			0.04
LMCA only	218 (39.1)	45 (8.6)		144 (25.8)	129 (24.6)		60 (11.0)	26 (4.2)		41 (7.5)	42 (6.8)	
LMCA + 1VD	134 (24.1)	58 (11.0)		108 (19.4)	107 (20.3)		177 (32.5)	61 (10.0)		90 (16.5)	105 (17.1)	
LMCA + 2VD	105 (18.9)	141 (26.8)		136 (24.4)	119 (22.7)		299 (54.9)	158 (25.8)		171 (31.4)	184 (30.0)	
LMCA + 3VD	100 (18.0)	282 (53.6)		169 (30.4)	171 (32.5)		55 (10.1)	367 (60.0)		243 (44.6)	281 (46.0)	
RCA disease	170 (30.5)	353 (67.1)	<0.001	249 (44.8)	248 (47.2)	0.05	226 (41.5)	451 (73.7)	<0.001	310 (56.8)	356 (58.2)	0.03
Restenotic lesion	10 (1.8)	6 (1.1)	0.37	8 (1.5)	5 (1.0)	0.05	22 (4.0)	8 (1.3)	0.004	14 (2.5)	12 (2.0)	0.03

Values are n (%) or mean ± SD. *An SMD of <0.1 indicates a relatively small imbalance. †LVEF was available in 1,826 patients. ‡The SYNTAX score reflects a comprehensive angiographic assessment of the coronary vasculature, with a score of 22 or less indicating low anatomic complexity and scores of 23 to 32 indicating intermediate anatomic complexity (0 is the lowest score, and there is no upper limit). The SYNTAX score was measured by angiography core laboratory assessment and was available in 1,580 patients who had available angiograms of sufficient image quality for accurate assessment.

1VD = one-vessel disease; 2VD = 2-vessel disease; 3-VD = 3-vessel disease; BMS = bare-metal stent; CABG = coronary artery bypass grafting; CHF = congestive heart failure; DES = drug-eluting stent; IPTW = inverse probability weighting; LMCA = left main coronary artery disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; RCA = right coronary artery; SMD = standardized mean difference; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

coronary artery, left circumflex coronary artery, or both. All clinical events were confirmed by source documentation collected at each hospital and centrally adjudicated by an independent group of clinicians unaware of the type of index procedure.

The detailed methods for data acquisition and management during the extended follow-up of the MAIN-COMPARE study have been reported elsewhere (13). Follow-up data beyond 10 years were completed by medical records review and telephone contact. Complete information on vital status and date of death was obtained from the National Population Registry of the Korea National Statistical Office by using the unique 13-digit personal identification numbers assigned to all Korean citizens.

STATISTICAL ANALYSIS. As described in detail previously (13), comparative treatment analyses between PCI and CABG according to LMCA lesion location (ostial or shaft or distal bifurcation) were

performed in the overall cohort, the early cohort of the BMS era (wave 1 of the registry: BMS vs. concurrent CABG between January 2000 and May 2003), and the late cohort of the DES era (wave 2 of the registry: DES vs. concurrent CABG between May 2003 and June 2006).

Summary statistics are presented as percentages for categorical variables and as mean ± SD for continuous variables. Baseline characteristics of the patients were compared between the PCI and CABG groups by using the Pearson chi-square test for categorical variables and Student's *t*-test for continuous variables.

Inverse probability treatment weighting (IPTW) on the basis of propensity scores of the patients was used as the primary tool for adjusting the differences in the baseline characteristics between the PCI and CABG groups (17,18). The separated propensity scores were calculated in each group of ostial or shaft LMCA disease and distal LMCA disease. We examined the similarities in the baseline characteristics between the treatment groups before and after IPTW (19), and the standardized mean differences were analyzed to assess the balance between the PCI and CABG groups; the standardized mean differences of <0.1 for a given covariate indicated a relatively small imbalance. The cumulative event curves were estimated using the weighted Kaplan-Meier method and IPTW (20). In addition, we performed sensitivity analyses with the use of propensity score matching with a caliper width equal to 0.1 of the SD of the logit of the propensity score. All available follow-up data were used for the long-term outcome analyses without censoring clinical events beyond 10 years.

As shown in the primary 10-year report of the MAIN-COMPARE registry (13), to characterize the time-dependent nature of the relative risks of the treatment groups and to compensate for the violation of the proportional hazards assumption for the treatment group variables, we performed weighted piecewise Cox regression models with robust standard errors according to a pre-specified time point at 5 years after the index revascularization; thus, hazard ratios (HRs) were also separately calculated from the index procedure to 5 years and from 5 years to the end of follow-up. As previously defined (13), a decision of a pre-specified time set of 5 years was made a priori on the basis of the available published long-term reports (21–24). Similarly, we also performed a test for the interaction between treatment group and time intervals.

All reported p values are 2-sided, and those <0.05 were considered to indicate statistical significance. No adjustments were made for multiple comparisons. All statistical analyses were performed using IBM SPSS Statistics for Windows version 22.0 (IBM, Armonk, New York) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BASELINE CHARACTERISTICS. A total of 2,240 patients with unprotected LMCA disease were enrolled in the MAIN-COMPARE registry between January 2000 and June 2006. Among them, 1,083 patients (48.3%) had isolated ostial or shaft LMCA disease (PCI in 557 patients and CABG in 526 patients), and 1,157 patients (51.7%) had distal LMCA bifurcation disease (PCI in 545 patients and CABG in 612 patients). Details of procedural and operative characteristics have been published previously (13–15). In brief, in the PCI group, 318 patients (29%) were treated with BMS and 784 (71%) with DES, among whom 607 (77%) received sirolimus-eluting stents and 177 (23%) received paclitaxel-eluting stents. The mean numbers of stents implanted in the LMCA and per patient were 1.2 ± 0.5 and 1.9 ± 1.1, respectively. In the CABG group, 478 patients (42.0%) underwent off-pump surgery, and 1,120 (98.4%) received at least 1 arterial conduit. The mean number of grafts used was 2.9 ± 1.0 (2.2 ± 0.9 arterial grafts and 0.7 ± 0.8 venous grafts).

The baseline demographic, clinical, and anatomic characteristics of the patients according to LMCA lesion site are shown in **Table 1**. In general, patients undergoing CABG were more likely to have a higher clinical and anatomic risk profile (i.e., higher incidence of diabetes, peripheral artery disease, or unstable angina), lower ejection fraction, and higher anatomic complexity. This pattern was more prominent in patients with distal bifurcation LMCA disease than in those with ostial or shaft disease. After adjustment with the use of ITPW, all baseline covariates except for clinical presentation were well balanced between the 2 groups, with standardized mean differences of <0.1.

10-YEAR COMPARATIVE OUTCOMES BY LESION LOCATION. The median duration of follow-up in the overall population was 12.0 years (interquartile range: 10.7 to 13.5 years). Follow-up status for major clinical events was verified in 2,211 patients (98.7%), and vital status was verified in all patients. The observed (unadjusted) 10-year cumulative incidence of clinical outcomes and Kaplan-Meier event curves in the overall cohort and wave 1 and wave 2 cohorts are shown in Supplemental Table 1 and Supplemental Figures 1 to 3, respectively.

The IPTW-adjusted 10-year incidences and risks for clinical outcomes after PCI and CABG stratified

TABLE 2 Adjusted Hazard Ratios for Long-Term Outcomes After PCI Versus CABG According to Lesion Location With the Use of Inverse Probability Weighting*

	Overall Cohort: PCI vs. CABG		Wave 1 Cohort: BMS vs. Concurrent CABG		Wave 2 Cohort: DES vs. Concurrent CABG	
Outcomes	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Ostial or shaft disease (n = 1,083)						
Death of any cause†	0.87 (0.62–1.20)	0.40	0.71 (0.45–1.14)	0.16	1.04 (0.66–1.64)	0.87
0–5 yrs	1.32 (0.74–2.38)	0.35	1.17 (0.54–2.56)	0.69	1.41 (0.64–3.13)	0.40
>5 yrs	0.71 (0.47–1.07)	0.10	0.62 (0.34–1.11)	0.11	0.83 (0.48–1.44)	0.52
p value for interaction‡		0.09		0.22		0.28
Composite of death, Q-wave MI, and stroke†	0.88 (0.65–1.19)	0.40	0.69 (0.45–1.06)	0.09	1.09 (0.71–1.66)	0.70
0–5 yrs	1.20 (0.72–2.00)	0.47	1.15 (0.56–2.33)	0.72	1.25 (0.63–2.50)	0.53
>5 yrs	0.74 (0.50–1.10)	0.14	0.58 (0.33–1.01)	0.05	0.98 (0.58–1.67)	0.95
p value for interaction‡		0.14		0.16		0.58
TVR†	6.12 (3.61–10.39)	<0.001	4.54 (2.21–9.32)	<0.001	7.54 (3.58–15.86)	<0.001
0–5 yrs	6.25 (3.03–12.50)	<0.001	7.14 (2.70–16.67)	<0.001	5.88 (2.27–14.29)	<0.001
>5 yrs	6.04 (2.76–13.25)	<0.001	3.04 (1.07–8.67)	0.04	12.92 (4.19–39.85)	<0.001
p value for interaction‡		0.97		0.25		0.28
Distal bifurcation disease (n = 1,157)						
Death of any cause†	1.33 (1.03–1.71)	0.03	1.19 (0.71–2.00)	0.50	1.39 (1.03–1.87)	0.03
0–5 yrs	1.19 (0.79–1.82)	0.42	1.75 (0.83–3.70)	0.57	0.98 (0.61–1.59)	0.94
>5 yrs	1.44 (1.06–1.96)	0.02	0.84 (0.44–1.61)	0.61	1.78 (1.22–2.59)	0.003
p value for interaction‡		0.46		0.13		0.05
Composite of death, Q-wave MI, and stroke†	1.33 (1.04–1.70)	0.02	1.15 (0.69–1.90)	0.32	1.42 (1.07–1.88)	0.02
0–5 yrs	1.11 (0.76–1.64)	0.59	1.67 (0.83–3.45)	0.15	0.91 (0.58–1.43)	0.70
>5 yrs	1.52 (1.13–2.05)	0.006	0.79 (0.41–1.52)	0.49	1.94 (1.35–2.79)	<0.001
p value for interaction‡		0.20		0.11		0.008
TVR†	3.77 (2.48–5.72)	<0.001	3.11 (1.59–6.10)	0.001	4.19 (2.39–7.35)	<0.001
0–5 yrs	4.76 (2.86–7.69)	<0.001	3.45 (1.59–7.69)	0.002	5.88 (2.78–12.50)	<0.001
>5 yrs	2.33 (1.09–4.98)	0.03	2.32 (0.58–9.36)	0.24	2.32 (0.93–5.80)	0.07
p value for interaction‡		0.13		0.62		0.13

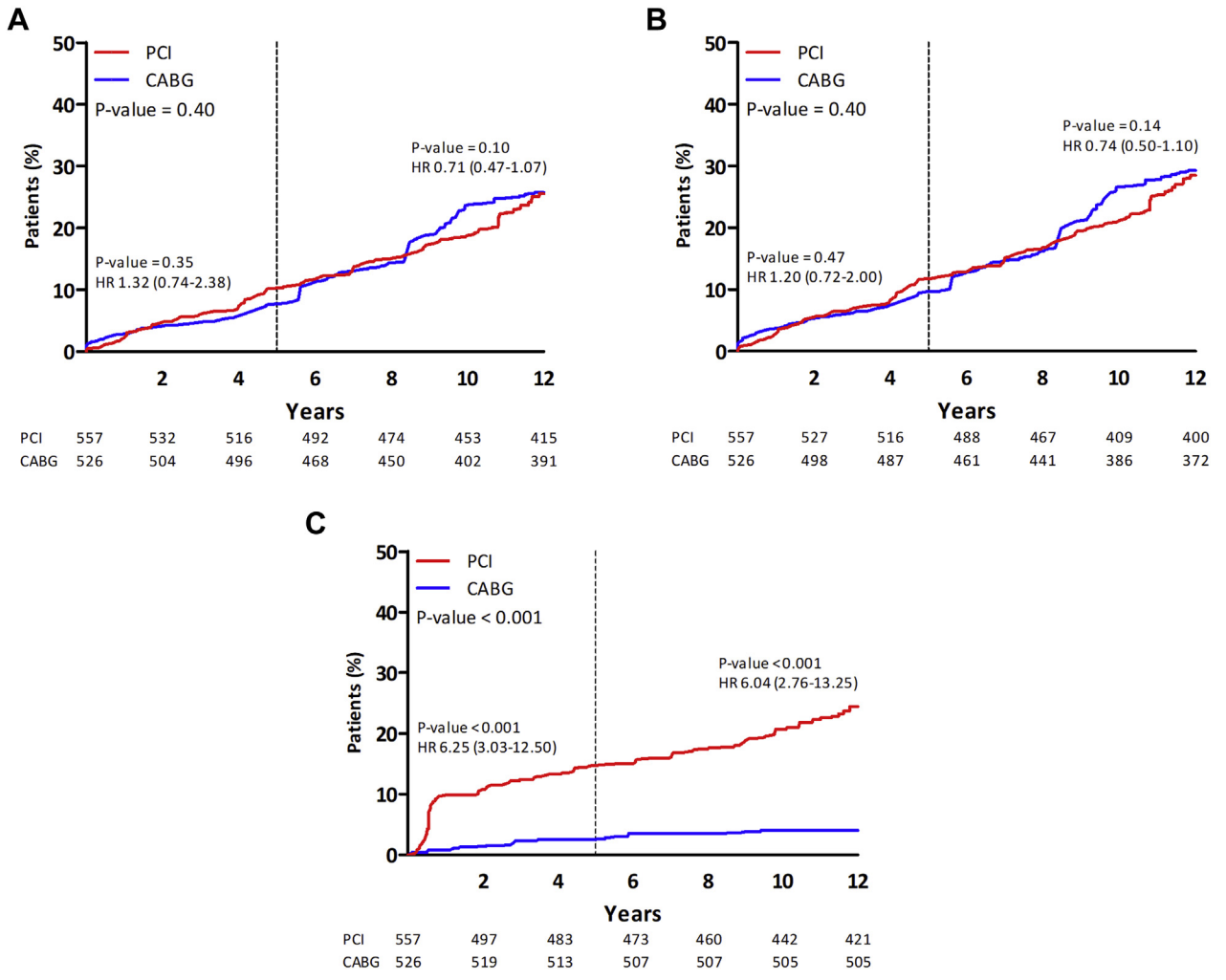
*Hazard ratio is the risk of PCI for different outcomes compared with CABG. †The outcome is calculated using a Cox regression model with assumption of constant hazard during the entire follow-up period. ‡p value for interaction for revascularization strategy (PCI vs. CABG) and time intervals (0 to 5 years vs. >5 years).

CI = confidence interval; HR = hazard ratio; TVR = target vessel revascularization; other abbreviations as in Table 1.

by LMCA lesion location are shown in Supplemental Table 2 and **Table 2**. In patients with ostial or shaft LMCA disease, the risks for death and the composite outcome of death, Q-wave MI, and stroke were similar between PCI and CABG during the entire follow-up period (**Figure 1**). However, in patients with distal LMCA bifurcation disease, the risks for death and the composite outcome of death, Q-wave MI, and stroke were significantly higher after PCI than after CABG. This difference was remarkable beyond 5 years (for death: HR: 1.44; 95% confidence interval [CI]: 1.06 to 1.96; p = 0.02; for the composite outcome: HR: 1.52; 95% CI: 1.13 to 2.05; p = 0.006) (**Figure 2**). The adjusted risk for Q-wave MI or stroke is shown in Supplemental Table 3: the risk for Q-wave MI was significantly higher after PCI than CABG for distal LMCA bifurcation disease but not for ostial or shaft disease.

When stratified analyses were performed in each time period of the BMS era and the DES era, such time-dependent differential outcomes after PCI and CABG according to lesion location were more prominent. In the cohort comparing between BMS and concurrent CABG, there were no statistically significant between-group differences in mortality and composite outcome irrespective of LMCA lesion location (**Figure 3**). In contrast, in the cohort comparing between DES and concurrent CABG, the relative comparative outcomes were substantially different according to LMCA lesion location (**Central Illustration**). In patients with ostial or shaft disease, there were no significant differences between DES and CABG in the risks for mortality and the composite outcome during extended follow-up. In contrast, in patients with distal bifurcation diseases, the risks for mortality and serious composite outcome was significantly higher after DES than after CABG, in which these difference were pronounced after 5 years (for death: HR: 1.78; 95% CI: 1.22 to 2.59; p = 0.003;

FIGURE 1 Adjusted Event Curves in the Overall Cohort of Patients Who Underwent PCI or CABG for Ostial or Shaft Left Main Coronary Artery Disease



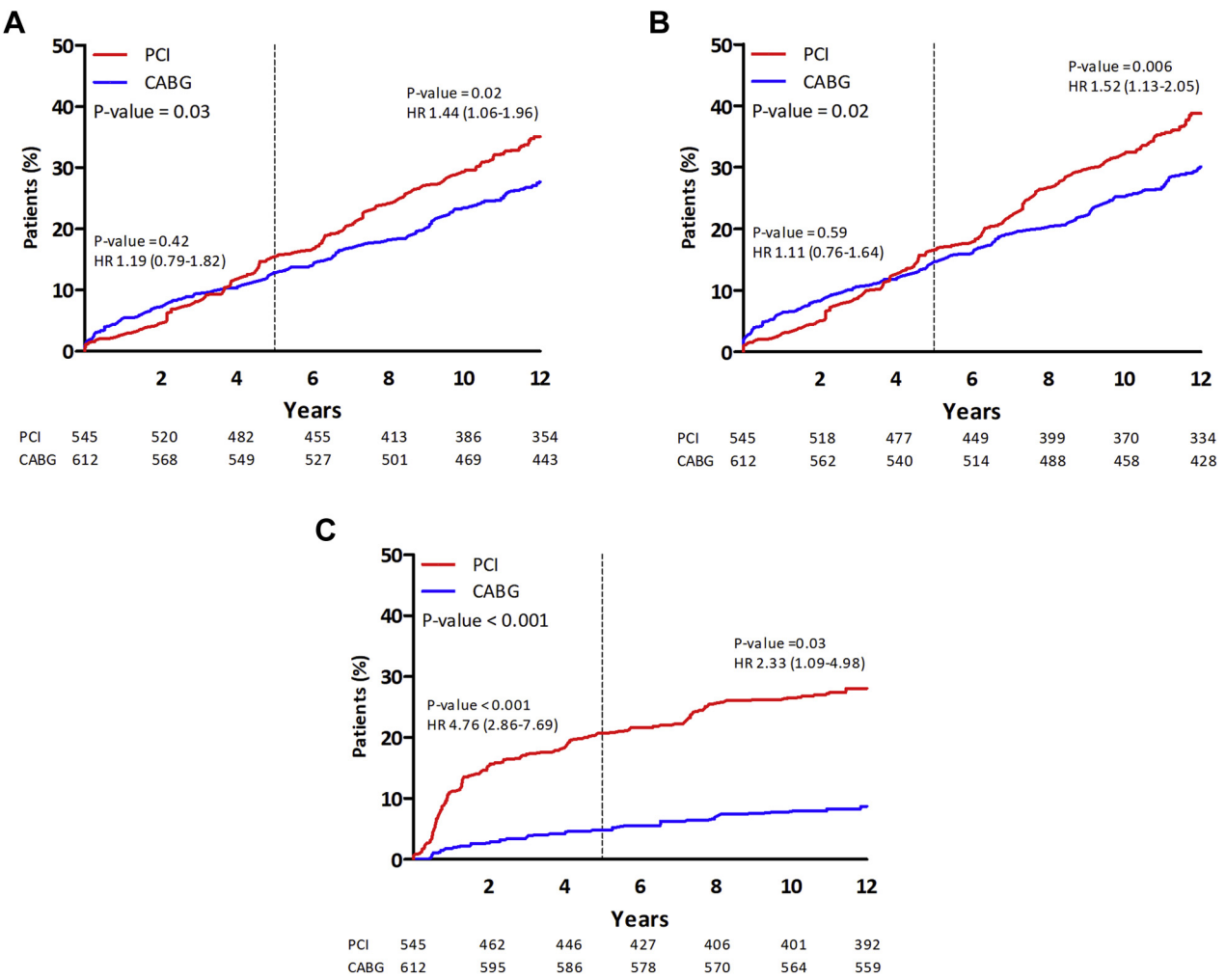
(A) All-cause death; **(B)** composite outcome of all-cause death, Q-wave myocardial infarction, and stroke; **(C)** target vessel revascularization. CABG = coronary artery bypass grafting; HR = hazard ratio; PCI = percutaneous coronary intervention.

for composite outcome: HR: 1.94; 95% CI: 1.35 to 2.79; $p < 0.001$). Statistically significant interactions were present between lesion location and revascularization type for the endpoints of death ($p = 0.05$) and serious composite outcome ($p = 0.008$). The risk for TVR was consistently higher in the PCI group than in the CABG group, irrespective of LMCA lesion location or stent type.

When we performed sensitivity analyses by use of propensity score matching, we identified a matched cohort of 246 pairs in patients with ostial or shaft LMCA disease and a matched cohort of 310 pairs patients with distal LMCA bifurcation disease (Supplemental Table 4). Overall findings in the matched cohort were consistent with the results from IPTW analyses (Supplemental Table 5).

In addition, we separately examined the comparative outcomes among patients with distal bifurcation lesions treated with a 1-stent technique or 2-stent technique with reference to CABG (Supplemental Table 6). In overall, PCI with a 1-stent technique showed comparable risks for death or serious composite outcome with CABG. However, PCI with a 2-stent technique showed higher risks for death and composite outcome, especially after 5 years from index revascularization.

FIGURE 2 **Adjusted Event Curves in the Overall Cohort of Patients Who Underwent PCI or CABG for Distal Bifurcation Left Main Coronary Artery Disease**



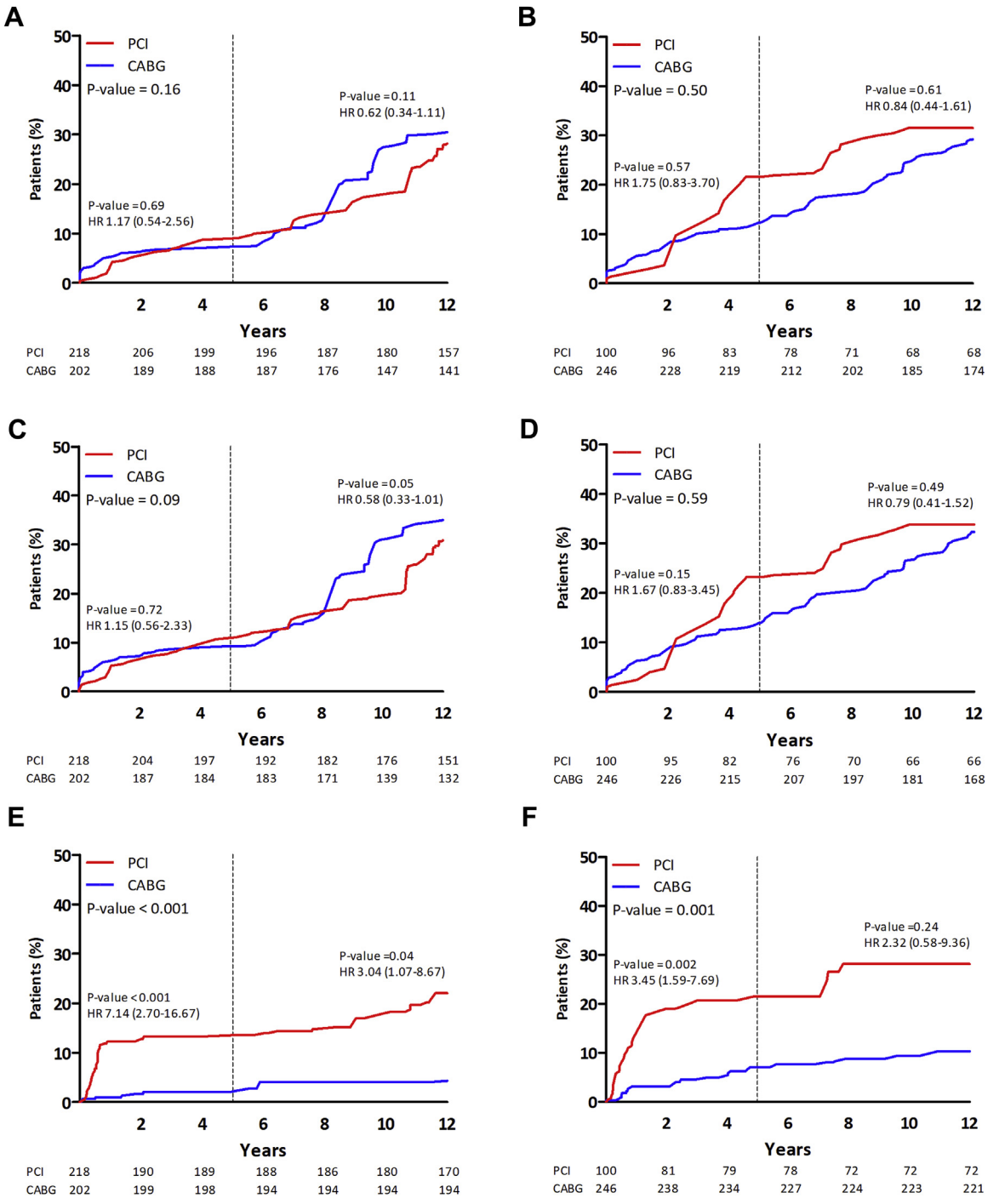
(A) All-cause death; **(B)** composite outcome of all-cause death, Q-wave myocardial infarction, and stroke; **(C)** target vessel revascularization. Abbreviations as in Figure 1.

DISCUSSION

In this longest to date follow-up study among patients with unprotected LMCA disease who underwent PCI or CABG, we determined whether major clinical outcomes differed between the 2 revascularization strategies according to LMCA lesion site (ostial or shaft and distal bifurcation). The major findings of the present analysis are that: 1) among patients with distal bifurcation disease, those in the PCI group showed gradually increasing risks for death and the composite outcome of death, Q-wave MI, and stroke beyond 5 years after index revascularization compared with the CABG group; 2) in contrast, among patients with ostial or shaft LMCA disease, there were no significant intergroup differences in mortality and the composite outcome; 3) this trend was more prominent in the comparison between DES and concurrent CABG, with the risks for mortality and the composite outcome significantly diverging over time to favor CABG over PCI after 5 years in patients with distal bifurcation disease; and 4) TVR rates were consistently higher in the PCI group than in the CABG group irrespective of lesion location and stent type.

Recent long-term reports on the trials and registries comparing PCI with DES and CABG for LMCA disease showed a distinct trend of late catch-up, crossover, or divergency in clinical outcomes in favor of CABG over PCI (1,2,13). PCI is relatively simple for ostial or shaft LMCA diseases, but it poses

FIGURE 3 Adjusted Event Curves in the Wave 1 Cohort of Patients Who Underwent Bare-Metal Stent Implantation or Concurrent CABG According to Lesion Location



Left panels show the outcomes of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) for ostial or shaft lesions: **(A)** all-cause death; **(C)** composite outcome of all-cause death, Q-wave myocardial infarction, and stroke; and **(E)** target vessel revascularization. **Right panels** show the outcomes of PCI versus CABG for distal bifurcation lesions: **(B)** all-cause death; **(D)** composite outcome of all-cause death, Q-wave myocardial infarction, and stroke; and **(F)** target vessel revascularization). Abbreviations as in Figure 1.

technical challenges and often requires complex 2-stent techniques for distal LMCA bifurcations; therefore, time-dependent differential outcomes by lesion site in extended follow-up after PCI and CABG are expected. However, until recently, there have been limited data on the very long-term comparative outcomes between the 2 revascularization strategies according to the LMCA involvement site. In this context, our study has clinically valuable information regarding the very long term impact of LMCA lesion location and decision making for optimal revascularization strategy according to this critical anatomic factor.

A recent subgroup analysis of the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial showed that at 3 years, PCI and CABG had no significant differences in the composite outcome of death, MI, and stroke and mortality in both distal LMCA bifurcation disease (n = 1,559) and isolated LM ostial or shaft disease (n = 293) (10). However, this study might be limited by a relatively small number of patients (n = 293 for isolated ostial or shaft disease) and short follow-up duration. The 3-year report of the large DELTA registry showed similar rates of clinical outcomes between PCI and CABG for ostial or mid-shaft LMCA lesions (25); for distal LMCA bifurcation, however, data on comparative long-term outcomes are still limited. The primary 10-year results of the MAIN-COMPARE registry showed that after 5 years, DES were significantly associated with higher rates of mortality and serious composite outcome compared with concurrent CABG (13). In this major subgroup analysis, we confirmed that late-occurring events penalizing DES over CABG beyond 5 years were likely driven by the differences in the relative treatment effect in patients with distal LMCA bifurcation disease, not those with ostial or shaft LMCA disease.

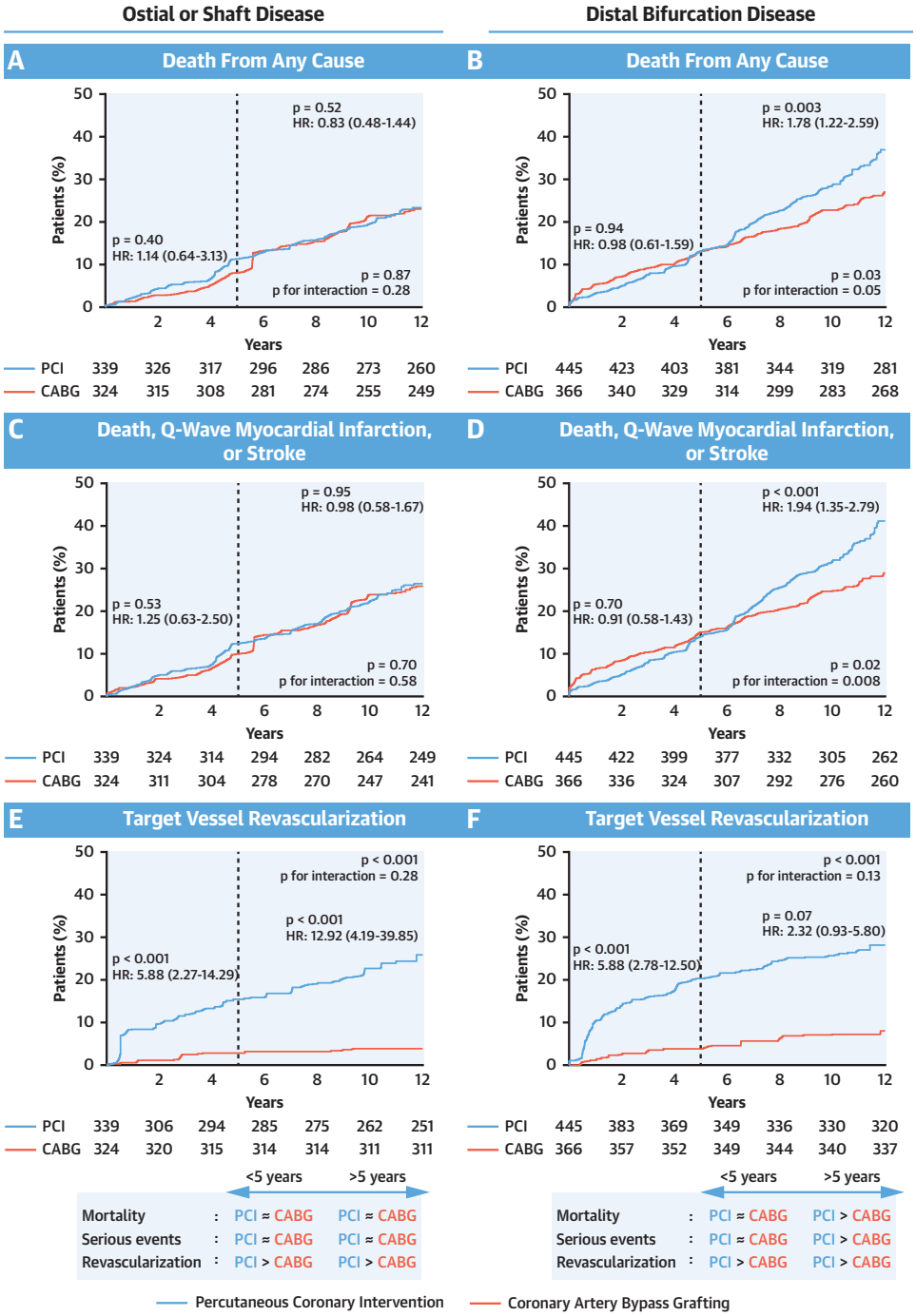
Given that the present study demonstrated time-dependent changes of relative risks in clinical outcomes after LMCA revascularization, the plausible mechanisms underlying the differential treatment effects after CABG and PCI during the late follow-up period should be considered. The caliber of the ostium or shaft is relatively larger in the LMCA than in non-LMCA vessels, and patients with ostial or shaft lesions have less complex anatomic characteristics and require less complex PCI techniques, which is associated with better clinical outcomes compared with distal LMCA diseases (26). In bypass surgery, a graft is placed on the mid coronary vessel, well beyond the area of disease; in contrast, stents are used to directly relieve the offending lesion, which might be more vulnerable to future restenosis and de novo lesion progression, especially in complex distal LMCA lesions. Such theoretical advantages of CABG over PCI may have affected the substantial, time-dependent deterioration in the outcomes of patients with distal LMCA diseases who underwent PCI, whereas those who underwent CABG had relatively stable outcomes.

In the present study, CABG showed treatment benefits over PCI only in the cohort of the DES era and not in the comparison between BMS and concurrent CABG. Although the exact mechanism for such discrepancy is unclear, it might have been derived from the inclusion of patients who had unmeasured but favorable lesion characteristics in the early era of left main PCI (13). In the BMS era, because of the higher risk for restenosis and the lack of appropriate stent technology and experience, PCI was highly selected for very low risk patients (27). Therefore, although we performed propensity score analyses, unmeasured confounders associated with the benign features of BMS-treated patients in the early PCI era were not fully adjusted and may have led to such differential findings between BMS and DES era.

Our findings might be different from the recent 10-year report of the SYNTAX and PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial (11,28). There were no significant differences between PCI and CABG with respect to major adverse cardiac or cerebrovascular events, serious composite outcome, or mortality over 10 years and no late-catch up phenomenon favoring CABG over PCI in the SYNTAX trial with paclitaxel-eluting stents and in the PRECOMBAT trial with sirolimus-eluting stents. These discrepant findings might be partly explained by a different study design, different patient inclusion criteria and characteristics, as well as unmeasured confounders in an observational study. Recently, the discrepancy in the long-term incidence of all-cause mortality among several studies has been highly debated. Further studies are required to resolve this conflicting issue and reasonably explain the discordant findings.

Another important finding of our study was that major differences in long-term outcomes for distal bifurcation LMCA diseases were prominent between CABG and PCI with a 2-stent technique, but not for PCI with a single stent. Distal bifurcation LMCA diseases requiring a 2-stent technique might have more complex anatomic features, favoring CABG over PCI with respect to long-term outcomes. Meanwhile, distal bifurcation lesions necessitating PCI with a 1-stent technique showed comparable outcomes with

CENTRAL ILLUSTRATION **Adjusted Event Curves in the Wave 2 Cohort of Patients Who Underwent Drug-Eluting Stent Implantation or Concurrent Coronary Artery Bypass Grafting According to Lesion Location**



Hyun, J. et al. J Am Coll Cardiol Intv. 2020;13(24):2825–36.

Left panels show the outcomes of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) for ostial or shaft lesions: **(A)** all-cause death; **(C)** composite outcome of all-cause death, Q-wave myocardial infarction, and stroke; and **(E)** target vessel revascularization. **Right panels** show the outcomes of PCI versus CABG for distal bifurcation lesions: **(B)** all-cause death; **(D)** composite outcome of all-cause death, Q-wave myocardial infarction, and stroke; and **(F)** target vessel revascularization). HR = hazard ratio (with 95% confidence interval).

CABG. Although this finding is hypothesis generating, further studies are required to determine whether the long-term adverse events following the use of a single stent for distal LMCA lesions can be comparable with CABG.

STUDY LIMITATIONS. First, as this was an observational cohort study with inherent methodological limitations, the present findings should be considered hypothetical and hypothesis-generating only.

Second, although propensity score analysis was performed to balance the baseline differences and avoid potential selection bias, unmeasured confounders might have influenced the observed results.

Third, the exact mechanism underlying the favorable clinical outcomes of CABG over PCI (especially DES) beyond 5 years could not be explained.

Fourth, this study did not evaluate whether different anatomic types and detailed stenting strategies for distal bifurcation LMCA disease influenced the outcomes between PCI and CABG.

Fifth, long-term medication use after PCI and CABG varied, which reflects differences in practice with respect to the 2 different treatments. Unfortunately, we did not capture detailed information on concurrent cardiovascular medications during extended follow-up. Thus, unmeasured confounding owing to differences in subsequent medication care cannot be ruled out.

Finally, we evaluated the clinical outcomes of BMS and first-generation DES in the PCI group. Therefore, the direct application of said results to contemporary PCI practice with newer generation DES may be limited. Our findings should be further evaluated through extended follow-up of the EXCEL and LeftMain/NOBLE (PCI vs. CABG in the Treatment of Unprotected Left Main Stenosis) trials.

CONCLUSIONS

In this very long term follow-up of real-world patients who underwent LMCA revascularization, there were differential comparative outcomes after PCI and CABG according to LMCA lesion site. Especially in patients with distal LMCA diseases, CABG showed better clinical outcomes with regard to mortality and serious compositive outcome compared with PCI with DES beyond 5 years. Such time-dependent differential risk was not evident in patients with ostial or shaft LMCA disease.

AUTHOR DISCLOSURES

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PERSPECTIVES

WHAT IS KNOWN? Very long term comparative data after PCI and CABG for LMCA disease are highly debated. Also, long-term comparative outcomes according to LMCA lesion site is limited.

WHAT IS NEW? In patients with ostial or shaft LMCA diseases, there were no significant differences in mortality and serious composite outcomes between DES and CABG over 10 years. However, in patients with distal LMCA diseases, DES had higher risks than CABG in terms of mortality and serious composite outcomes after 5 years.

WHAT IS NEXT? Further evidence from extended follow-up of the large, randomized trials EXCEL and LeftMain/NOBLE is required to provide more compelling evidence on the long-term effects of contemporary DES and CABG in LMCA disease according to LMCA lesion site.

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KEY WORDS cardiovascular events, coronary artery bypass grafting, left main coronary artery disease, mortality, percutaneous coronary intervention

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