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10-Year Outcomes of Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease

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ABSTRACT

BACKGROUND Comparative outcomes of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for left main coronary artery (LMCA) disease were previously reported. However, data on very long-term (>10 years) outcomes are limited.

OBJECTIVES The authors compare 10-year outcomes after PCI and CABG for LMCA disease.

METHODS In this observational study of the MAIN-COMPARE (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease) registry, the authors evaluated 2,240 patients with unprotected LMCA disease who underwent PCI (n = 1,102) or underwent CABG (n = 1,138) between January 2000 and June 2006. Adverse outcomes (death; a composite outcome of death, Q-wave myocardial infarction, or stroke; and target-vessel revascularization) were compared with the use of propensity scores and inverse-probability-weighting adjustment. The follow-up was extended to at least 10 years of all patients (median 12.0 years).

RESULTS In the overall cohort, there was no significant difference in adjusted risks of death and the composite outcome between the groups up to 10 years. The risk of target-vessel revascularization was significantly higher in the PCI group. In the cohort comparing drug-eluting stents and concurrent CABG, the 2 study groups did not differ significantly in the risks of death and the composite outcome at 5 years. However, after 5 years, drug-eluting stents were associated with higher risks of death (hazard ratio: 1.35; 95% confidence interval: 1.00 to 1.81) and the composite outcome (hazard ratio 1.46; 95% confidence interval: 1.10 to 1.94) compared with CABG.

CONCLUSIONS In patients with significant LMCA disease, as compared with CABG, PCI showed similar rates of death and serious composite outcomes, but a higher rate of target-vessel revascularization at 10 years. However, CABG showed lower mortality and serious composite outcome rates compared with PCI with drug-eluting stents after 5 years.(Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease [MAIN-COMPARE]; NCT02791412) (J Am Coll Cardiol 2018;■:■-■) © 2018 by the American College of Cardiology Foundation.

Owing to the large area of jeopardized myocardium and expected highest ischemic risk, coronary artery bypass grafting (CABG) has been recommended as the revascularization strategy of choice for unprotected left main coronary artery (LMCA) disease (1,2). However, over the last 2 decades, there are marked advances in percutaneous coronary intervention (PCI),

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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

LMCA = left main coronary artery

PCI = percutaneous coronary intervention

involving drug-eluting stents (DES), adjunctive antithrombotic drugs, periprocedural management, and expertise of the interventional cardiologists (3). Indeed, many studies reported favorable outcomes of PCI in LMCA disease (3-8).

Recently, 2 large trials comparing CABG and PCI with contemporary DES (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]) showed conflicting results and raised further uncertainty on the optimal revascularization strategy for LMCA disease (9,10). Moreover, both trials reported a trend toward late catch-up or crossover in the rates of death or the composite endpoint of death, stroke, or myocardial infarction favoring CABG over PCI during the late period of follow-up. Therefore, longer-term follow-up is necessary to examine additional differences between PCI and CABG over time.

The MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry was designed to compare outcomes of PCI and CABG for unprotected LMCA disease in multiple centers of Korea; the risks of death and composite of death, Q-wave myocardial infarction, or stroke were similar between PCI and CABG at 3 years and 5 years of follow-up (11,12). We now report the very long-term (10-year) results of the MAIN-COMPARE study with a systematic linkage to data from a national population registry of vital statistics.

METHODS

STUDY DESIGN AND POPULATION. The design and enrollment characteristics of the MAIN-COMPARE study have been published previously (11,12). Briefly, the MAIN-COMPARE study included consecutive patients with unprotected LMCA disease (defined as stenosis of >50%) who underwent either CABG or PCI as the index procedure at 12 major cardiac centers in Korea between January 2000 and June 2006. Patients with prior CABG, concomitant valvular or aortic surgery, or ST-segment elevation myocardial infarction or cardiogenic shock were excluded. Local ethics committee at each hospital approved the use of clinical data for this study, and all patients provided written informed consent.

The choice of revascularization strategy was at the discretion of the treating physicians and/or patients after consideration of several clinical and anatomic factors or surgical risk for CABG. Clinical and anatomic conditions favoring either PCI or CABG were described previously (11,12). All PCI procedures were performed with standard interventional techniques, and the use of intravascular ultrasound and use of a specific type of stent were at the operator's discretion. PCI was performed exclusively with bare-metal stents (BMS) between January 2000 and May 2003, and exclusively with DES between May 2003 and June 2006. Antiplatelet therapy and periprocedural anticoagulation followed standard regimens. Surgical revascularization was performed with the use of standard bypass techniques (11,12). The internal thoracic artery was preferentially utilized for revascularization of left anterior descending artery. On-pump or off-pump surgery was performed at the discretion of the surgeon. During the follow-up, medical therapy for secondary prevention and patient management were performed in accordance with accepted guidelines and established standard of care.

ENDPOINTS AND FOLLOW-UP. The study endpoints were death from any cause; the composite of all-cause death, Q-wave myocardial infarction, or stroke; and target-vessel revascularization. Q-wave myocardial infarction was defined as the documentation of a new pathological Q-wave after the index revascularization. Stroke, as detected by neurological deficits, was confirmed by a neurologist and imaging modalities. Target-vessel revascularization was defined as repeat 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 unaware of the type of revascularization treatment.

Clinical follow-up was recommended at 1 month, 6 months, 1 year, and annually thereafter. In this report, the follow-up period was extended through December 31, 2016, to ensure that all patients had the opportunity for at least 10-year follow-up evaluation. During the extended follow-up period, if a patient was unwilling or unable to return to the enrolling center, follow-up was maintained by the enrolling investigator through telephone contact or medical records obtained from other hospitals as necessary. For validation of complete follow-up data, the long-term follow-up was based on merging the MAIN-COMPARE database with other national population registries of vital statics. Data 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.

STATISTICAL ANALYSIS. As described in detail previously (11,12), comparative treatment analyses between PCI and CABG 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).

Inverse probability weighting that was based on the propensity score was used as the primary tool to adjust for differences in the baseline characteristics between the PCI and CABG groups (12–14). For each comparison (the entire cohort, wave 1, and wave 2), a separate propensity score was derived. We examined the similarity of the baseline characteristics between treatment groups before and after inverse probability weighting (15). The cumulative event curves were estimated with the use of a weighted Kaplan-Meier method.

To characterize the time-dependent nature of the relative risks of the treatment groups over time and to compensate for the violation of the proportional-hazards assumption for the treatment group variable (as evidenced by the crossing survival curves), we performed weighted piecewise Cox regression models with robust standard errors according to a pre-specified time point at 5 years after index treatment. Previous publications suggested no difference of mortality and hard clinical endpoints between PCI and CABG for LMCA disease up to 5 years (12,16–18). Although it still unknown whether difference of treatment effect between PCI and CABG diverge or emerge over time beyond 5 years, the findings of EXCEL and NOBLE trials suggested a trend toward late catch-up or crossover of events favoring CABG over time (9,10) and a significant benefit of CABG became evident from 5 years to 10 years of follow-up (19,20). Thus, a decision of a pre-specified time set of 5 years was made a priori on the basis of such findings from the available published reports. Hazard ratios (HRs) were calculated separately for events that occurred within 5 years after the index treatment and those that occurred between 5 years and the end of follow-up. All available follow-up data were used for the long-term outcome analyses without censoring clinical events beyond 10 years.

We also performed a test for the interaction between treatment and time. Additionally, sensitivity analyses were conducted with the use of the propensity-score matching (Online Appendix). We also conducted pre-specified subgroup analyses on the basis of key clinical and anatomical characteristics: sex, age group (<65 years vs. ≥65 years), presence or absence of diabetes, left main disease location (ostial or shaft vs. distal bifurcation), and extent of diseased vessel (isolated left main or left main and single-vessel coronary artery disease vs. left main and 2- or 3-vessel coronary artery disease). Tests for interaction were performed to assess for heterogeneity of treatment effect among subgroups.

All reported p values are 2-sided, and all the statistical analyses were performed with the use of SAS software, version 9.3 or higher (SAS Institute, Cary, North Carolina) and the R programming language (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

STUDY POPULATION. Between January 2000 and June 2006, a total of 2,240 patients with unprotected LMCA disease was enrolled. Among them, 1,102 patients underwent PCI with stent implantation (318 [29%] treated with BMS and 784 [71%] treated with DES), and 1,138 underwent CABG. Details of procedural or operative characteristics have been published previously (11,12). In patients who received DES, 607 (77%) received sirolimus-eluting stents and 177 (23%) received paclitaxel-eluting stents. The mean number of stents implanted in LMCA and per-patient was 1.2 ± 0.5 and 1.9 ± 1.1, respectively. In patients who underwent CABG, 478 (42.0%) underwent off-pump surgery, and 1120 (98.4%) received at least 1 arterial conduit that, in 1,096 patients (97.9%), was used in revascularization of the left anterior descending artery. The mean number of grafts used was 2.9 ± 1.0 (2.2 ± 0.9 arterial grafts and 0.7 ± 0.8 venous grafts).

Table 1 shows baseline characteristics of the study patients. Before adjustment with the use of inverse probability weighting, there were differences between the 2 groups in several of the baseline variables. Overall, patients undergoing CABG were older and had higher clinical and anatomic risk factor profiles as compared with those undergoing PCI. As expected, with regard to the distribution of propensity scores in the treatment groups, patients in the PCI group had a lower probability of being selected for CABG than did those in the CABG group (Online Figure 1). After adjustment with the use of inverse probability weighting, all the clinical covariates were well balanced (Table 1). In general, as compared with patients enrolled in wave 1, patients

TABLE 1 Baseline Characteristics of the Patients

	Unadjusted Data				Data Adjusted With the Use of Inverse Probability Weighting			After Propensity-Score Matching		
	PCI (n = 1,102)	CABG (n = 1,138)	p Value	Standardized Difference (%)	PCI (n = 1,102)	CABG (n = 1,138)	p Value	PCI (n = 659)	CABG (n = 659)	Standardized Difference (%)*
Age, yrs	61.3 ± 11.7	62.9 ± 9.4	<0.001	15.09	62.1 ± 11.0	62.1 ± 10.1	0.89	62.6 ± 11.2	63.2 ± 9.7	4.96
Median	62	64			63	63		63	64	
Interquartile range	52-70	57-70			54-70	56-69		55-71	57-70	
Male	779 (70.7)	830 (72.9)	0.24	4.99	797 (72.3)	820 (72.1)	0.90	472 (71.6)	457 (69.4)	4.99
Diabetes mellitus										
Any diabetes	327 (29.7)	395 (34.7)	0.01	10.80	338 (30.6)	356 (31.3)	0.73	197 (29.9)	206 (31.3)	2.96
Requiring insulin	75 (6.8)	93 (8.2)	0.22	5.19	84 (7.6)	89 (7.9)	0.82	44 (6.7)	47 (7.1)	1.80
Hypertension	546 (49.5)	562 (49.4)	0.94	0.32	525 (47.7)	551 (48.4)	0.71	335 (50.8)	335 (50.8)	0.00
Hyperlipidemia	315 (28.6)	371 (32.6)	0.04	8.73	340 (30.8)	339 (29.8)	0.60	201 (30.5)	200 (30.4)	0.33
Current smoker	282 (25.6)	339 (29.8)	0.03	9.39	313 (28.4)	330 (29.0)	0.76	188 (28.5)	179 (27.2)	3.05
Previous PCI	200 (18.1)	125 (11.0)	<0.001	20.42	165 (15.0)	172 (15.1)	0.93	99 (15.0)	97 (14.7)	0.85
Previous MI	89 (8.1)	132 (11.6)	0.005	11.85	99 (9.0)	111 (9.8)	0.54	67 (10.2)	54 (8.2)	6.84
Previous CHF	27 (2.5)	38 (3.3)	0.21	5.30	32 (2.9)	33 (2.9)	0.95	17 (2.6)	17 (2.6)	0.00
Chronic lung disease	22 (2.0)	23 (2.0)	0.97	0.18	25 (2.3)	20 (1.7)	0.36	8 (1.2)	10 (1.5)	2.62
Cerebrovascular disease	78 (7.1)	83 (7.3)	0.84	0.83	71 (6.5)	74 (6.5)	0.96	48 (7.3)	48 (7.3)	0.00
Peripheral arterial disease	16 (1.5)	62 (5.4)	<0.001	22.03	46 (4.2)	43 (3.9)	0.66	15 (2.3)	10 (1.5)	5.56
Renal failure	30 (2.7)	34 (3.0)	0.71	1.59	34 (3.1)	35 (3.1)	0.98	16 (2.4)	21 (3.2)	4.59
Ejection fraction	60.6 ± 10.8	57.2 ± 11.9	<0.001	30.16	59.8 ± 11.0	59.0 ± 11.2	0.12	59.7 ± 11.1	59.4 ± 11.5	2.33
Median	62	60			61	61		61	62	
Interquartile range	57-67	52-66			56-67	55-66		55-67	55-67	
ECG findings			0.53	4.80			0.92			5.86
Sinus rhythm	1,078 (97.8)	1,105 (97.1)			1,076 (97.7)	1,109 (97.4)		644 (97.7)	641 (92.3)	
Atrial fibrillation	22 (2.0)	31 (2.7)			24 (2.2)	28 (2.5)		15 (2.3)	17 (2.6)	
Other	2 (0.2)	2 (0.2)			1 (0.1)	1 (0.1)		0 (0.0)	1 (0.2)	
Clinical indication			<0.001	29.77			0.96			4.43
Silent ischemia	33 (3.0)	25 (2.2)			30 (2.7)	32 (2.8)		23 (3.5)	19 (2.9)	
Chronic stable angina	353 (32.0)	226 (19.9)			289 (26.1)	296 (26.0)		166 (25.2)	173 (26.3)	
Unstable angina	608 (55.2)	775 (68.1)			677 (61.4)	692 (60.1)		401 (60.9)	402 (61.0)	
NSTEMI	108 (9.8)	112 (9.8)			107 (9.7)	118 (10.4)		69 (10.5)	65 (9.9)	
Left main disease location			0.04	8.66			0.87			1.52
Ostium or shaft	557 (50.6)	526 (46.2)			522 (47.3)	543 (47.7)		316 (48.0)	321 (48.7)	
Distal bifurcation	545 (49.5)	612 (53.8)			580 (52.7)	595 (52.3)		343 (52.0)	338 (51.3)	
Extent of diseased vessel			<0.001	83.15			0.98			5.39
Left main only	278 (25.2)	71 (6.2)			175 (15.9)	186 (16.4)		81 (12.3)	71 (10.8)	
Left main plus 1-vessel disease	264 (24.0)	119 (10.5)			192 (17.4)	201 (17.6)		114 (17.3)	112 (17.0)	
Left main plus 2-vessel disease	287 (26.0)	299 (26.3)			288 (26.1)	291 (25.6)		212 (32.2)	223 (33.8)	
Left main plus 3-vessel disease	273 (24.8)	649 (57.0)			448 (40.1)	460 (40.4)		252 (38.2)	253 (38.4)	
RCA disease	396 (35.9)	804 (70.7)	<0.001	74.22	584 (53.0)	597 (52.5)	0.81	350 (53.1)	353 (53.6)	0.91
Restenotic lesion	32 (2.9)	14 (1.2)	0.005	11.78	22 (2.0)	22 (1.9)	0.88	17 (2.6)	12 (1.8)	5.17

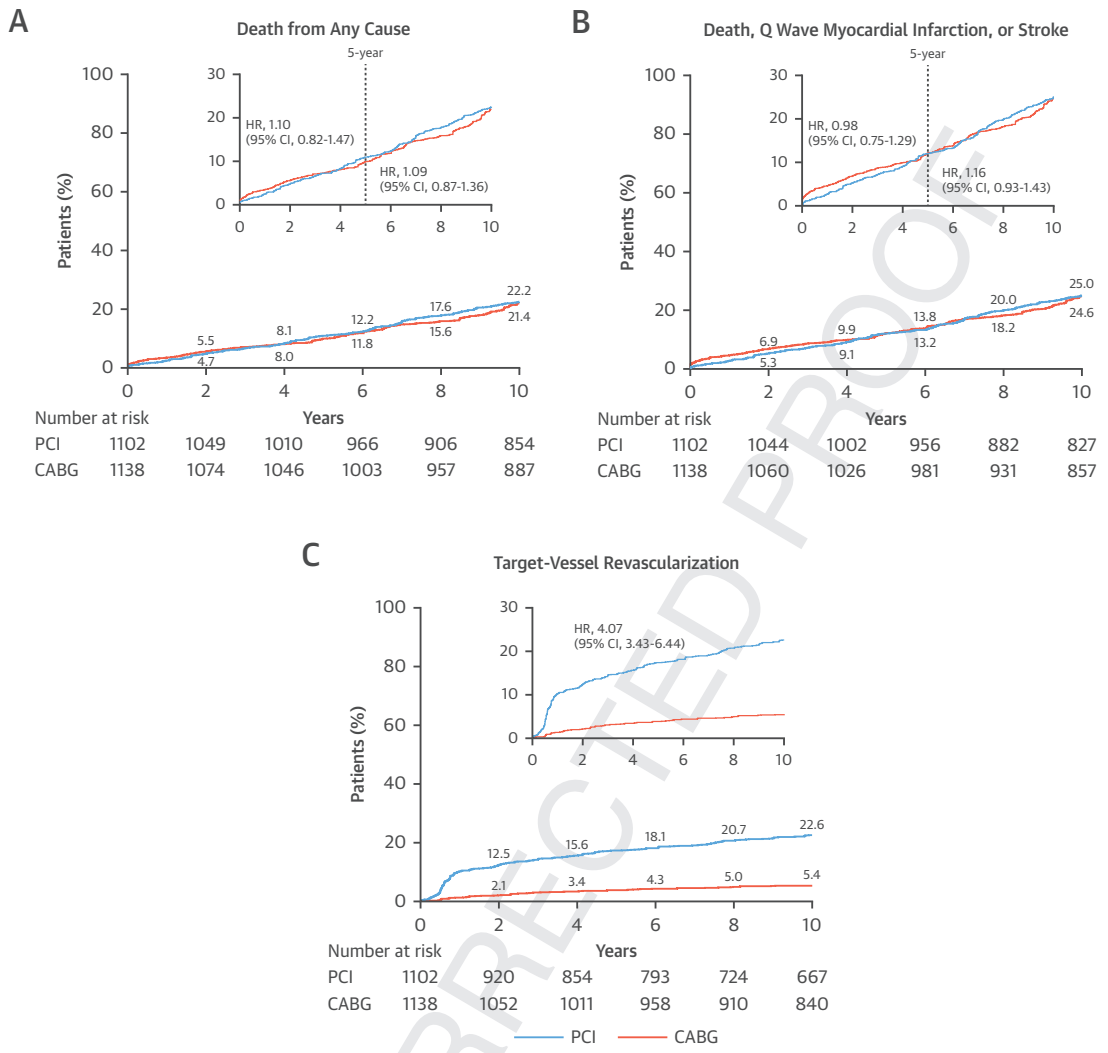
Values are mean ± SD or n (%). *The standardized differences are reported as percentages; a difference of <10.0% indicates a relatively small imbalance.

CABG = coronary-artery bypass grafting; CHF = congestive heart failure; ECG = electrocardiogram; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

enrolled in wave 2 had a higher risk profile of clinical and anatomic characteristics (Online Tables 1 and 2). After propensity-score adjustment, baseline characteristics between PCI and CABG groups were also well balanced in each cohort of wave 1 and wave 2. After propensity-score matching, 659 pairs of patients who underwent PCI and CABG were derived from the overall cohort (193 pairs in the wave 1 cohort and 432 pairs in the wave 2 cohort). After matching, the standardized differences were <10.0% for all variables, indicating only small differences between the 2 groups (**Table 1**, Online Tables 1 and 2).

LONG-TERM OUTCOMES. The median duration of follow-up among all patients was 12.0 years (interquartile range: 10.7 to 13.5 years); the maximum follow-up was 17.6 years. The follow-up status for major clinical events was ascertained for 2,211 patients (98.7%) of the overall population. The

FIGURE 1 Adjusted 10-Year Event Rates With the Use of Inverse Probability Weighting in the Overall Cohort of Patients Who Underwent PCI or CABG



(A) Death from any cause. **(B)** Death, Q-wave myocardial infarction, or stroke. **(C)** Target-vessel revascularization. In each **panel**, the **inset** shows the same data on an enlarged y-axis. HRs are for the PCI group, as compared with the CABG group. CABG = coronary artery bypass grafting; CI = confidence interval; DES = drug-eluting stent(s); HR = hazard ratio; PCI = percutaneous coronary intervention.

unadjusted Kaplan-Meier event curves in the overall cohort, and wave 1 and wave 2 cohorts are shown in Online Figures 2 to 4, respectively. Observed 10-year rates of death and composite of death, Q-wave myocardial infarction, or stroke were similar between PCI and CABG. Similar findings were observed in wave 2 of DES and concurrent CABG, but the rates of death and composite outcome were significantly lower in the BMS group than in the concurrent CABG group in wave 1.

In the overall population, the adjusted risks for clinical events with the use of inverse probability weighting are shown in Figure 1 and Table 2. There were no significant differences between the PCI and CABG groups with respect to the risks of death and composite of death, Q-wave myocardial infarction, or stroke stratified by the time period of before and after 5 years. The risk of target-vessel revascularization was consistently higher in the PCI group. In the cohort comparing BMS and concurrent CABG, no significant between-group differences were noted for the rates of death and the composite outcome at 5 years (Figure 2, Table 2). However, the HRs for each of these endpoints show a nonsignificant

TABLE 2 HRs for Clinical Outcomes Before and After 5-Year of Follow-Up

	Overall Cohort		Wave 1*		Wave 2*	
	HR† (95% CI)	p Value	HR† (95% CI)	p Value	HR† (95% CI)	p Value
Analyses with the use of inverse probability weighting	N = 2,240 (PCI n = 1,102; CABG n = 1,138)		N = 766 (BMS n = 318; CABG n = 448)		N = 1,474 (DES n = 784; CABG n = 690)	
Death		0.64		0.05		0.15
0∼5 yrs	1.10 (0.82-1.47)	0.53	1.65 (0.91-2.98)	0.10	1.02 (0.71-1.46)	0.91
>5 yrs	1.09 (0.87-1.36)	0.48	0.68 (0.46-1.02)	0.06	1.35 (1.00-1.81)	0.05
p value interaction with treatment and time‡		0.08		0.85		0.05
Composite outcome, death, Q-wave myocardial infarction, or stroke		0.43		0.06		0.03
0∼5 yrs	0.98 (0.75-1.29)	0.91	1.46 (0.84-2.53)	0.18	0.91 (0.66-1.27)	0.59
>5 yrs	1.16 (0.93-1.43)	0.19	0.67 (0.46-1.00)	0.05	1.46 (1.10-1.94)	0.009
p value interaction with treatment and time‡		0.009		0.95		0.004
Target-vessel revascularization						
All period	4.07 (3.43-6.44)	<0.001	4.45 (2.81-7.05)	<0.001	5.82 (3.77-9.01)	<0.001
p value interaction with treatment and time‡		0.47		0.11		0.82
Analyses with the use of propensity-score matching	N = 1,318 (PCI n = 659; CABG n = 659)		N = 386 (BMS n = 193; CABG n = 193)		N = 864 (DES n = 432; CABG n = 432)	
Death		0.27		0.29		0.25
0∼5 yrs	0.91 (0.66-1.24)	0.55	1.29 (0.67-2.46)	0.45	1.04 (0.70-1.54)	0.86
>5 yrs	1.21 (0.94-1.55)	0.14	0.74 (0.48-1.14)	0.17	1.30 (0.95-1.78)	0.09
p value interaction with treatment and time‡		0.003		0.92		0.21
Composite outcome, death, Q-wave myocardial infarction, or stroke		0.03		0.17		0.03
0∼5 yrs	0.85 (0.63-1.14)	0.27	1.18 (0.65-2.12)	0.59	0.92 (0.63-1.34)	0.66
>5 yrs	1.34 (1.06-1.70)	0.02	0.67 (0.44-1.04)	0.07	1.48 (1.10-2.00)	0.01
p value interaction with treatment and time‡		<0.001		0.89		0.03
Target-vessel revascularization						
All periods	4.70 (3.26-6.76)	<0.001	6.05 (3.12-11.76)	<0.001	5.07 (3.11-8.27)	<0.001
p value interaction with treatment and time‡		0.77		0.08		0.93

*Wave 1 shows comparisons between BMS versus concurrent CABG, and wave 2 shows comparisons between DES versus concurrent CABG. †HRs are for the PCI group, as compared with the CABG group. ‡Time period was scaled by log (time).

BMS = bare-metal stent(s); CI = confidence interval; DES = drug-eluting stent(s); HR = hazard ratio; other abbreviations as in Table 1.

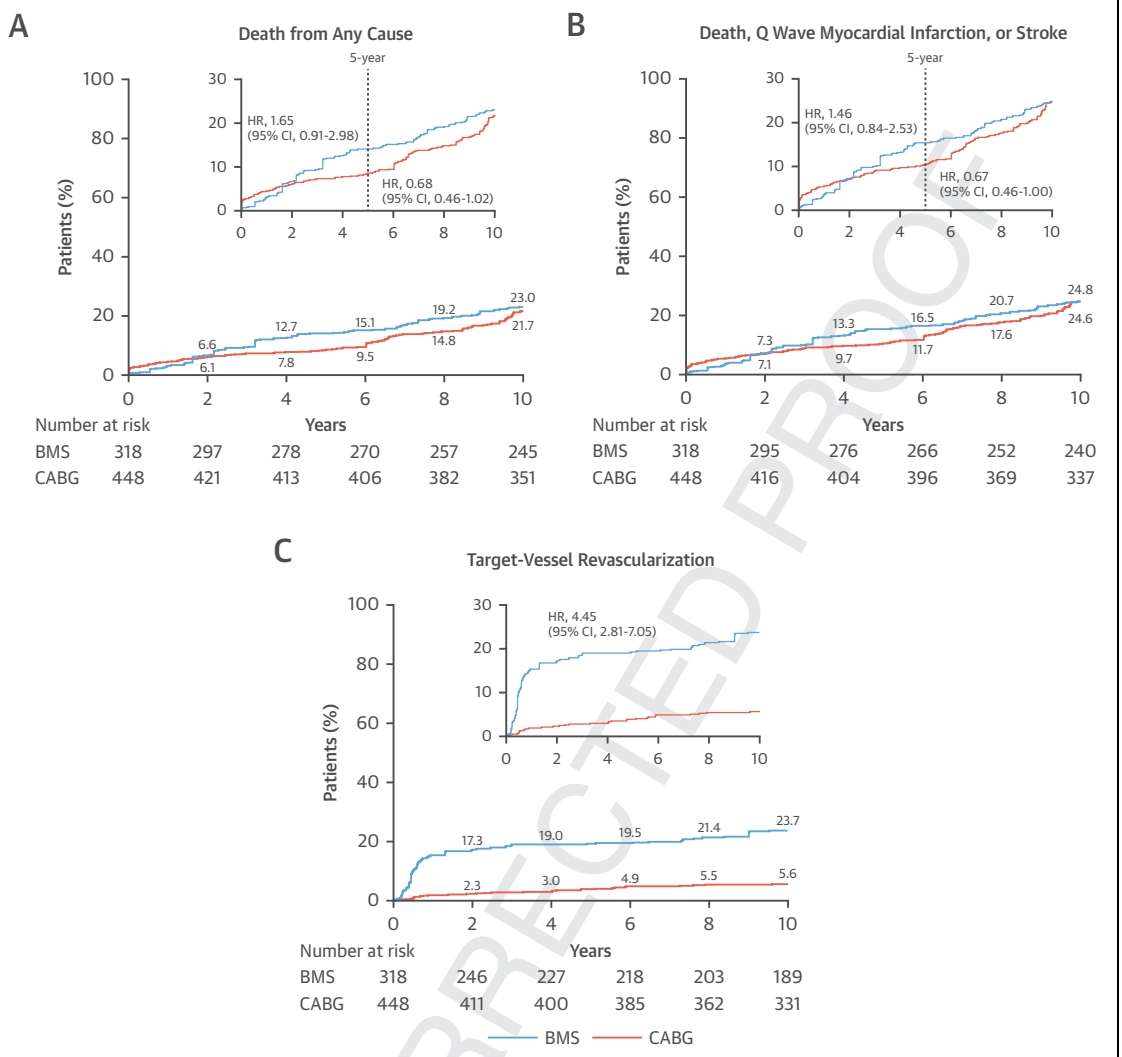
trend toward lower risk among patients treated with BMS.

In comparison of DES and the contemporary CABG group, there was no significant difference between the 2 groups in the risks of death (HR: 1.02; 95% confidence interval [CI]: 0.71 to 1.46) and composite risk of death, Q-wave myocardial infarction, or stroke (HR: 0.91; 95% CI: 0.66 to 1.27) up to 5 years (Central Illustration, Table 2). However, after 5 years, there was a continuous separation of the curves, with a significantly higher risk of death (HR: 1.35; 95% CI: 1.00 to 1.81) and a serious composite outcome (HR: 1.46; 95% CI: 1.10 to 1.94) in patients with DES than in patients with concurrent CABG. The risk of target-vessel revascularization was also significantly higher in the DES group than in the CABG group.

SENSITIVITY AND SUBGROUP ANALYSES. In the sensitivity analyses using the propensity-score matching, overall findings were similar (Table 2, Online Figures 5 to 7). In the matched cohort of PCI and CABG, there were no significant differences in the rates of death and composite of death, Q-wave myocardial infarction, or stroke before and after 5 years. The risk of target-vessel revascularization was higher in the PCI group. In the matched cohort of DES and concurrent CABG, the rate of death was similar up to 5 years. After 5 years, the risk of death tended to be higher in the DES group. With respect to the risk of a serious composite outcome, the 5-year rate of composite outcomes was similar between DES and CABG. However, the risk of composite outcomes was significantly higher in the DES group after 5 years. Each risk of Q-wave myocardial infarction or stroke with the use of inverse probability weighting and propensity-score matching is shown in Online Table 3.

The results of subgroup analyses using the inverse-probability-of-treatment weighting reflected the broad consistency of the relative effect of PCI and CABG (Online Figures 8 to 10). An exception was the nominally significant interactions of treatment with the left main disease location (ostial or shaft vs.

FIGURE 2 **Adjusted 10-Year Event Rates With the Use of Inverse Probability Weighting in the Wave 1 Cohort of Patients Who Underwent BMS or Concurrent CABG**



(A) Death from any cause. **(B)** Death, Q-wave myocardial infarction, or stroke. **(C)** Target-vessel revascularization. In each **panel**, the **inset** shows the same data on an enlarged y-axis. HRs are for the BMS group, as compared with CABG group. BMS = bare-metal stent(s); other abbreviations as in Figure 1.

distal bifurcation) with respect to the rates of death and composite outcome.

DISCUSSION

In this largescale, multicenter cohort of patients with LMCA disease, there was no significant difference in the rates of death and a composite endpoint of death, Q-wave myocardial infarction, or stroke between the PCI and the CABG groups up to 10 years. However, in the cohort comparing DES and concurrent CABG, PCI with DES implantation was associated with higher risks of death and serious composite outcomes compared with CABG after 5 years: the treatment benefit of CABG has diverged over time during continued follow-up. The rate of target-vessel failure was consistently higher in the PCI group.

Our findings should be evaluated in the context of results from recent other studies. In the EXCEL study, PCI was noninferior to CABG with respect to primary composite of death, stroke, or myocardial infarction at 3 years (9). The primary events were less common after PCI within 30 days, whereas fewer primary endpoint events occurred in the CABG group between

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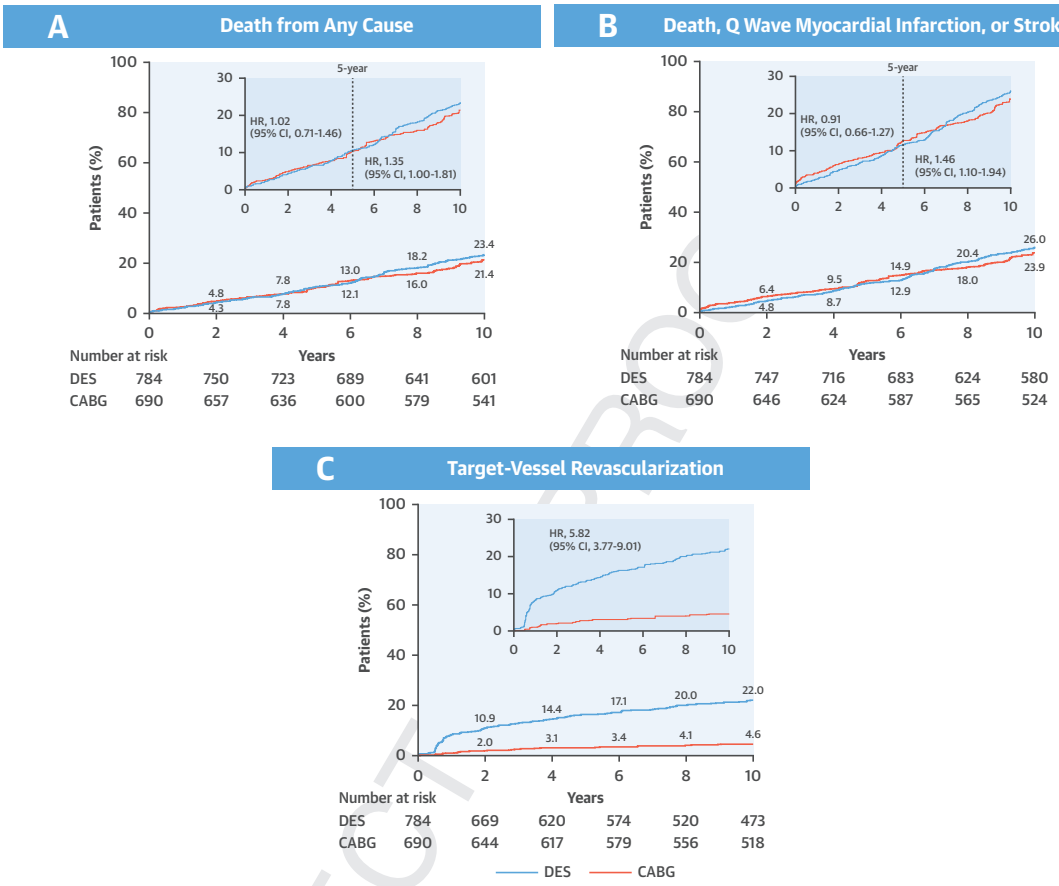
CENTRAL ILLUSTRATION **Long-Term Outcomes of PCI vs. CABG for Left Main Disease**



Park, D.-W. et al. J Am Coll Cardiol. 2018;■(■):■–■.

Adjusted 10-year event rates with the use of inverse probability weighting in the wave 2 cohort of patients who underwent DES or concurrent CABG. **(A)** Death from any cause. **(B)** Death, Q-wave myocardial infarction, or stroke. **(C)** Target-vessel revascularization. In each **panel**, the **inset** shows the same data on an enlarged y-axis. HRs are for the DES group, as compared with the CABG group. CABG = coronary artery bypass grafting; CI = confidence interval; DES = drug-eluting stent(s); HR = hazard ratio; PCI = percutaneous coronary intervention.

30 days and 3 years. Also, all-cause mortality tended to be higher after PCI than after CABG at complete 3-year follow-up (8.0% vs. 5.8%; p = 0.08). In the NOBLE study, CABG was better than PCI for major adverse cardiac or cerebrovascular events up to 5 years (10), when the advantages of CABG over PCI diverged over time. But, a recent meta-analysis suggested no mortality benefit of CABG over PCI in patients with left main disease up to 5 years (18). As noted in prior studies (9-12), the relative benefit of CABG and PCI has been different substantially over time, but until recently, long-term studies up to 10 years were limited (21). Limited follow-up could penalize the CABG group, because the long-term advantages of CABG does not become fully evident until 5 to 10 years after revascularization (20,22). In this 10-year final report of the MAIN-COMPARE study, a significant benefit of CABG over DES for reduction of mortality and serious composite outcomes began to accrue after 5 years. Given the inherent limitations of observational studies, our findings should be confirmed or refuted through long-term follow-up of the EXCEL and NOBLE studies, which will add additional valuable information on comparative long-term outcomes.

In our analyses, CABG showed treatment benefits over PCI only in the cohort of DES era, but not in comparison of BMS and concurrent CABG. In the BMS era, owing to higher-risk of restenosis and lack of appropriate stent technology and experience,

PCI was selectively performed for elective low-risk patients (23,24). With adoption of DES, the role of PCI for left main disease was substantially expanded and widely performed for a broader range of clinical and anatomical complexity (25,26). Thus, a differential treatment effect of PCI and CABG in each cohort of BMS and DES era might be mainly derived from considerable difference in clinical and anatomic characteristics of patients enrolled, but not owing to difference of stent used. From the clinical viewpoint, our study suggests that clinical equipoise may be present for either PCI or CABG in patients with less complex clinical and anatomic characteristics. These findings are supported by a recent randomized trial (16). By contrast, our data suggest that CABG is associated with superior long-term outcomes compared with multivessel PCI in patients with high clinical and anatomical complexity. Given that PCI with contemporary DES is widely considered for a broader range of clinical and angiographic complexities, further studies are required to determine whether PCI is an acceptable alternative to CABG in such patients. Moreover, although ongoing research may incrementally improve the PCI or CABG procedure, the largest improvements in outcomes are likely to be realized by appropriate selection of patients for optimal revascularization methods.

STUDY LIMITATIONS. First, this was a nonrandomized, observational study, and thus potential selection and ascertainment bias should be acknowledged. Second, although a large number of baseline covariates and potential confounders were accounted for using rigorous propensity-score analyses, unmeasured confounders (i.e., frailty or detailed information of concomitant atherosclerotic burden) could influence the observed findings. Unfortunately, the SYNTAX score (a measure of the extent and complexity of coronary artery disease) could not be measured because this score was not developed and not practically feasible in the enrollment period of study patients. Third, long-term medication use and compliance with guidelines-directed medical management after PCI and CABG substantially varied. Further study is required to determine the extent to which these differences contributed to the observed results. Finally, our study evaluated the first generation of DES. Previously, our reports did not find any meaningful difference in clinical outcomes among several types of first- and second-generation DES for LMCA disease (7,17,27,28). However, our findings should be compared with those of the extended follow-up of EXCEL and NOBLE trials using contemporary DES.

CONCLUSIONS

This longest follow-up study of patients with LMCA disease showed no difference in the rates of death and a composite endpoint of death, Q-wave myocardial infarction, or stroke between PCI and CABG at 10 years. However, in the cohort comparing DES and concurrent CABG among patients with more complex clinical and anatomic characteristics, a long-term benefit of CABG over PCI on mortality and hard clinical endpoints was detected after 5 years.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Longer-term follow-up is necessary to examine additional differences between PCI and CABG over time in patients with significant LMCA disease.

COMPETENCY IN PATIENT CARE: In patients with LMCA disease, as compared with CABG, PCI showed similar rates of death and serious composite outcomes, but a higher rate of target-vessel revascularization at 10 years. However, in the late cohort comparing DES and concurrent CABG, CABG showed lower mortality and serious composite outcome rates compared with DES especially after 5 years.

TRANSLATIONAL OUTLOOK: Further research is needed to clarify the mechanisms underlying differences in very long-term vascular outcomes after PCI and CABG for LMCA disease.

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KEY WORDS ■, ■, ■

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.