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ORIGINAL RESEARCH

Prognostic Value of Sex After Revascularization for Left Main Coronary Disease

Extended PRECOMBAT Study

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ABSTRACT

BACKGROUND Female subjects have poorer outcomes in left main coronary artery (LMCA) disease compared with male subjects. However, limited information is available on the long-term prognostic impact of sex and sex-treatment interactions in patients with LMCA disease undergoing coronary revascularization.

OBJECTIVES The goal of this study was to investigate the long-term effects of sex and related differential outcomes after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in LMCA disease.

METHODS The extended PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial evaluated the >10-year clinical outcomes in patients with LMCA disease randomized to undergo PCI with drug-eluting stents (n = 300) or CABG (n = 300). The primary outcome was major adverse cardiac or cerebrovascular events (MACCE) (composite of death, myocardial infarction, stroke, or ischemia-driven target vessel revascularization) at 10 years.

RESULTS Of the 600 patients, 459 (76.5%) were male. The 10-year rates of MACCE were similar between male and female subjects in the overall cohort (27.3% vs 27.0%; adjusted hazard ratio [aHR]: 1.06; 95% confidence interval [CI]: 0.70-1.59), the PCI arm (30.6% vs 27.1%; aHR: 1.19; 95% CI: 0.69-2.05), and the CABG arm (24.0% vs 26.9%; aHR: 0.93; 95% CI: 0.53-1.62). The 10-year risks for MACCE did not significantly differ between PCI and CABG in both male (aHR: 1.37; 95% CI: 0.95-1.97) and female (aHR: 1.07; 95% CI: 0.56-2.07) subjects. There was no significant sex-treatment interaction regarding the adjusted risk of MACCE at 10 years (*P* for interaction = 0.52).

CONCLUSIONS In this 10-year follow-up of the PRECOMBAT trial, there was no sex-related impact on the long-term risk of MACCE after PCI and CABG for LMCA disease. (Ten-Year Outcomes of PRECOMBAT Trial; NCT03871127) (JACC: Asia 2022;2:19-29) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CI = confidence interval

DES = drug-eluting stents

HR = hazard ratio

LMCA = left main coronary artery

MACCE = major adverse cardiac or cerebrovascular events

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

TVR = target vessel revascularization

Knowledge regarding sex differences in the clinical presentation, pathophysiology, and outcomes of coronary artery disease (CAD) is evolving (1). In general, female subjects with stable CAD or acute coronary syndrome have worse clinical outcomes than male subjects (2,3). However, after multivariable adjustment of clinically relevant covariates, female sex was not found to be an independent risk factor for poorer outcomes, and sex-related differential outcomes were thought to be primarily attributed to differences in baseline characteristics (ie, older age, more comorbidities, less invasive procedures in female subjects) (1).

Sex differences, along with other important risk factors, can interact with the treatment effects of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in patients with multivessel CAD. The presence of significant interactions between sex and treatment with PCI or CABG can help clinicians decide on the optimum revascularization method for patients with complex CAD. Although prior studies have reported the differential effect of sex on the differences in treatment patterns and effects of PCI and CABG for multivessel or left main coronary artery (LMCA) disease (4-7), the prognostic effect of sex and its interaction with treatment strategy during long-term follow-up (10 years or longer) are still undetermined. Recently, the SYNTAXES (SYNTAX Extended Survival) study reported the time-dependent interaction of sex with treatment effects of PCI or CABG for multivessel disease, with female subjects showing favorable outcomes with CABG compared with PCI at 5 years of follow-up but no specific difference at 10 years (8).

To determine the impact of sex on long-term outcomes and sex-treatment interaction for LMCA disease, we investigated the association between sex and 10-year outcomes of each revascularization strategy using an extended follow-up of the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial (9).

METHODS

STUDY POPULATION, REVASCULARIZATION, AND FOLLOW-UP. The design and methods of the PRECOMBAT trial (NCT03871127) have been described previously (10,11). In brief, PRECOMBAT was a prospective, multicenter, open-label, randomized controlled trial (RCT) in which 600 patients with unprotected LMCA disease were randomly assigned to receive PCI with sirolimus-eluting stents (n = 300) or CABG (n = 300) in 13 hospitals in the Republic of Korea between April 2004 and August 2009. The clinical and anatomical eligibility of all participants were considered to be equally suitable for both PCI and CABG. PCI was performed with the standard interventional techniques according to the local practice. Surgical revascularization was performed with standard bypass techniques, and the internal-thoracic-artery graft was preferentially used for the left anterior descending coronary artery. Dual antiplatelet therapy (aspirin and clopidogrel) was administered before PCI and for at least 1 year thereafter.

This extended 10-year follow-up study of the PRECOMBAT trial was registered at ClinicalTrials.gov as an investigator-driven extension follow-up of the PRECOMBAT trial (NCT03871127) (9). The trial was approved by the respective ethics committee at each participating center, and the need for informed consent for obtaining information on the 10-year outcomes was waived. During long-term follow-up, guideline-directed medical therapy and management of risk factors for secondary prevention were highly recommended for all patients. Information on adverse clinical events and survival data (ie, vital status, cause of death, date of death) was obtained by reviewing the health care records and referring to the national death registry of the Korean National Health Insurance Service database, which was merged from the Statistics Korea database (12).

STUDY ENDPOINTS AND DEFINITIONS. The primary outcome was the 10-year incidence of major adverse cardiac and cerebrovascular events (MACCE), which was defined as a composite of death from any cause, nonfatal myocardial infarction (MI), nonfatal stroke, or ischemia-driven target vessel revascularization (TVR). Major secondary outcomes included the individual components of the primary endpoint and stent thrombosis (definite) or symptomatic graft occlusion.

All-cause mortality, the most unbiased method to report deaths in a clinical trial or observational study (13), was assessed in the current analysis. The protocol definition of MI was defined as the appearance of both new Q waves and creatine kinase-myocardial band to >5× the upper reference limit within 48 hours of PCI/CABG (periprocedural MI) or a rise of creatine kinase-myocardial band >1× upper reference limit plus new ischemic symptoms or signs >48 hours after PCI/CABG (spontaneous MI) (9). Stroke was defined as a focal neurologic deficit resulting from

TABLE 1 Baseline Characteristics of Patients According to Sex in the Overall and Each Revascularization Cohort

	Overall			PCI Arm			CABG Arm		
	Male (n = 459)	Female (n = 141)	*P* Value	Male (n = 228)	Female (n = 72)	*P* Value	Male (n = 231)	Female (n = 69)	*P* Value
Age, y	62.2 ± 9.6	62.5 ± 10.1	0.71	61.9 ± 9.8	61.3 ± 10.5	0.62	62.4 ± 9.5	63.8 ± 9.6	0.28
Body mass index, kg/m^2	24.5 ± 2.8	24.6 ± 3.2	0.78	24.5 ± 2.5	24.8 ± 3.3	0.37	24.6 ± 3.0	24.4 ± 3.2	0.67
Diabetes									
Any	145 (31.6)	47 (33.3)	0.70	72 (31.6)	30 (41.7)	0.12	73 (31.6)	17 (24.6)	0.27
Requiring insulin	14 (3.1)	5 (3.5)	0.78	7 (3.1)	3 (4.2)	0.71	7 (3.0)	2 (2.9)	>0.99
Hypertension	239 (52.1)	78 (55.3)	0.50	122 (53.5)	41 (56.9)	0.61	117 (50.6)	37 (53.6)	0.67
Hyperlipidemia	189 (41.2)	58 (41.1)	0.99	97 (42.5)	30 (41.7)	0.90	92 (39.8)	28 (40.6)	0.91
Current smoker	167 (36.4)	5 (3.5)	<0.001	88 (38.6)	1 (1.4)	<0.001	79 (34.2)	4 (5.8)	<0.001
Previous PCI	59 (12.9)	17 (12.1)	0.80	29 (12.7)	9 (12.5)	0.96	30 (13.0)	8 (11.6)	0.76
Previous MI	27 (5.9)	6 (4.3)	0.53	12 (5.3)	1 (1.4)	0.20	15 (6.5)	5 (7.2)	0.79
Previous heart failure	2 (0.4)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	NA	2 (0.9)	0 (0.0)	>0.99
Chronic renal failure	4 (0.9)	1 (0.7)	>0.99	3 (1.3)	1 (1.4)	>0.99	1 (0.4)	0 (0.0)	>0.99
Peripheral artery disease	14 (3.1)	8 (5.7)	0.20	10 (4.4)	5 (6.9)	0.37	4 (1.7)	3 (4.3)	0.20
Chronic lung disease	14 (3.1)	2 (1.4)	0.38	5 (2.2)	1 (1.4)	>0.99	9 (3.9)	1 (1.4)	0.46
Clinical presentation			0.21			0.22			0.76
Stable angina	231 (50.3)	66 (46.8)		125 (54.8)	35 (48.6)		106 (45.9)	31 (44.9)	
Unstable angina	201 (43.8)	71 (50.4)		92 (40.4)	36 (50.0)		109 (47.2)	35 (50.7)	
Recent MI	27 (5.9)	4 (2.8)		11 (4.8)	1 (1.4)		16 (6.9)	3 (4.3)	
LVEF	59.4 ± 12.7	60.5 ± 11.4	0.37	58.4 ± 15.6	61.2 ± 11.8	0.18	60.3 ± 9.4	59.8 ± 11.1	0.71
Electrocardiographic findings			0.55			0.12			0.41
Sinus rhythm	441 (97.1)	134 (96.4)		217 (96.9)	69 (95.8)		224 (97.4)	65 (97.0)	
Atrial fibrillation	8 (1.8)	2 (1.4)		5 (2.2)	0 (0.0)		3 (1.3)	2 (3.0)	
Others	5 (1.1)	3 (2.2)		2 (0.9)	3 (4.2)		3 (1.3)	0 (0.0)	
EuroSCORE	2.5 ± 1.7	3.6 ± 1.9	<0.001	2.4 ± 1.7	3.5 ± 2.0	<0.001	2.6 ± 1.8	3.8 ± 1.8	<0.001
Left main disease location			0.77			0.47			0.77
Ostium or shaft	294 (64.9)	89 (63.6)		155 (68.0)	45 (63.4)		139 (61.8)	44 (63.8)	
Distal bifurcation	159 (35.1)	51 (36.4)		73 (32.0)	26 (36.6)		86 (38.2)	25 (36.2)	
Extent of diseased vessel			0.44			0.20			0.39
Left main only	44 (9.6)	17 (12.1)		20 (8.8)	7 (9.7)		24 (10.4)	10 (14.5)	
Left main plus 1-vessel disease	79 (17.2)	24 (17.0)		34 (14.9)	16 (22.2)		45 (19.5)	8 (11.6)	
Left main plus 2-vessel disease	141 (30.7)	50 (35.5)		74 (32.5)	27 (37.5)		67 (29.0)	23 (33.3)	
Left main plus 3-vessel disease	195 (42.5)	50 (35.5)		100 (43.9)	22 (30.6)		95 (41.1)	28 (40.6)	
SYNTAX score									
Mean	24.8 ± 10.2	24.7 ± 10.7	0.87	24.6 ± 9.5	23.2 ± 10.0	0.30	25.1 ± 10.9	26.2 ± 11.3	0.50
Category			0.91			0.99			0.89
Low (≤22)	185 (42.9)	55 (41.4)		101 (45.3)	30 (44.8)		84 (40.4)	25 (37.9)	
Intermediate (23-32)	150 (34.8)	49 (36.8)		78 (35.0)	24 (35.8)		72 (34.6)	25 (37.9)	
High (≥33)	96 (22.3)	29 (21.8)		44 (19.7)	13 (19.4)		52 (25.0)	16 (24.2)	

Values are mean ± SD or n (%).

CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

vascular lesions on the brain that lasted >24 hours as confirmed by imaging and a neurologist. Ischemia-driven TVR was defined as PCI or CABG in the treated vessel that was driven by ischemia (ie, stenosis of at least 50% the diameter of the target vessel with ischemic signs or symptoms or if the stenosis was at least 70% of the diameter of the target vessel regardless of ischemic signs or symptoms). An independent clinical events committee adjudicated all primary and secondary endpoints with source document verification.

STATISTICAL ANALYSIS. This study was a prespecified subgroup analysis of the extended follow-up of the PRECOMBAT trial. All principal analyses were performed according to the intention-to-treat principle. Descriptive statistics for demographic characteristics and potential risk factors were calculated separately in male and female subjects as mean ± SD or number (proportion). Continuous variables were compared by using the Student *t*-test or Wilcoxon rank sum test, and categorical variables were compared by using the chi-square test or Fisher

TABLE 2 Medications and Procedural Characteristics According to Sex in the Overall Cohort and Each Revascularization Cohort

	Overall			PCI Arm			CABG Arm		
	Male (n = 459)	Female (n = 141)	*P* Value	Male (n = 228)	Female (n = 72)	*P* Value	Male (n = 231)	Female (n = 69)	*P* Value
Medication at discharge									
Antiplatelet therapy	451 (98.3)	141 (100.0)	0.25	226 (99.1)	72 (100.0)	>0.99	225 (97.4)	69 (100.0)	0.39
Aspirin	446 (98.9)	139 (98.6)	0.67	225 (99.6)	70 (97.2)	0.15	221 (98.2)	69 (100.0)	0.58
Thienopyridine	431 (95.6)	134 (95.0)	0.82	222 (98.2)	71 (98.6)	>0.99	209 (92.9)	63 (91.3)	0.61
Others	89 (19.4)	34 (24.1)	0.22	68 (29.8)	27 (37.5)	0.22	21 (9.1)	7 (10.1)	0.79
Statin	330 (73.2)	101 (71.6)	0.72	165 (73.0)	50 (69.4)	0.56	165 (73.3)	51 (73.9)	0.92
Beta-blocker	230 (51.0)	73 (51.8)	0.87	135 (59.7)	47 (65.3)	0.40	95 (42.2)	26 (37.7)	0.50
RAS blocker	151 (33.5)	39 (27.7)	0.20	89 (39.4)	23 (31.9)	0.26	62 (27.6)	16 (23.2)	0.47
Calcium-channel blocker	239 (53.0)	81 (57.4)	0.35	135 (59.7)	49 (68.1)	0.21	104 (46.2)	32 (46.4)	0.98
Medical therapy at 5 y									
Antiplatelet therapy	375 (81.7)	121 (85.8)	0.316	195 (85.5)	64 (88.9)	0.60	180 (77.9)	57 (82.6)	0.50
Aspirin	361 (92.1)	115 (94.3)	0.55	186 (93.9)	59 (92.2)	0.57	175 (90.2)	56 (96.6)	0.18
Thienopyridine	246 (62.8)	75 (61.5)	0.80	143 (72.2)	42 (65.6)	0.31	103 (53.1)	33 (56.9)	0.61
Others	70 (15.3)	21 (14.9)	0.92	55 (24.1)	17 (23.6)	0.93	15 (6.5)	4 (5.8)	0.84
Statin	187 (47.7)	64 (52.5)	0.36	96 (48.5)	34 (53.1)	0.52	91 (46.9)	30 (51.7)	0.52
Beta-blocker	197 (50.3)	59 (48.4)	0.72	114 (57.6)	31 (48.4)	0.20	83 (42.8)	28 (48.3)	0.46
RAS blocker	150 (38.3)	53 (43.4)	0.31	81 (40.9)	29 (45.3)	0.54	69 (35.6)	24 (41.4)	0.42
Calcium-channel blocker	217 (55.4)	68 (55.7)	0.94	122 (61.6)	41 (64.1)	0.73	95 (49.0)	27 (46.6)	0.75
Procedure or operative variables									
No. of stents per patient				3 (2-3)	2 (1-3)	0.12			
Total stent length per patient				63.6 (37.5)	61.0 (46.2)	0.65			
Mean stent diameter per patient				3.3 ± 0.2	3.2 ± 0.2	0.22			
Off-pump CABG							131 (63.9)	35 (56.5)	0.36
No. of total conduits per patient							3 (2-3)	2 (2-3)	0.30
No. of arterial conduits							2 (2-3)	2 (1-2)	0.08
No. of venous conduits							0 (0-1)	1 (0-1)	0.25
Use of LIMA							195 (93.3)	59 (93.7)	>0.99
Complete revascularization	320 (69.7)	96 (68.1)	0.713	156 (68.4)	49 (68.1)	0.954	164 (71.0)	47 (68.1)	0.65

Values are n (%), median (interquartile range), or mean ± SD.
LIMA = left internal mammary artery; RAS = renin-angiotensin system; other abbreviations as in Table 1.

exact test (expected frequency, <5). For primary and secondary outcomes, the cumulative event rates were calculated by using Kaplan-Meier estimates, with time from the date of randomization, according to sex or treatment, and were compared by using the log-rank test.

Sex differences in 10-year clinical outcomes were then assessed by using marginal and interaction analyses. In the marginal analyses, Cox regression models were used with the marginal effects of sex and PCI/CABG only. The assumptions of the Cox model were assessed statistically based on Schoenfeld residuals and graphically by using log-log plots, and were found to be approximately satisfied for all variables. In addition to sex and PCI/CABG, the interaction term was included in the interaction analyses. Sex- and treatment-specific hazard ratios (HRs) were estimated from the interaction models, and HRs for overall sex and treatment effects were estimated from the marginal models. Multivariable models were adjusted for potential confounders identified by the investigators using a literature search and based on known clinical knowledge available across all trials. The following baseline variables were applied for adjustment: age, medically treated diabetes, clinical presentation, ejection fraction, left main bifurcation involvement, SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score, and EuroSCORE (European System for Cardiac Operative Risk Evaluation). Finally, to determine the independent association between the primary composite outcome and risk factor in male and female subjects, a multivariable Cox proportional hazards regression model was used with clinically relevant variables, with *P* values <0.10 in univariate analysis.

All reported *P* values are 2-sided, and those <0.05 were considered statistically significant. No

TABLE 3 10-Year Clinical Outcomes According to Sex in the Overall Cohort and Each Revascularization Arm

	Overall			PCI Arm			CABG Arm		
	Male (n = 459)	Female (n = 141)	*P* Value	Male (n = 228)	Female (n = 72)	*P* Value	Male (n = 231)	Female (n = 69)	*P* Value
Primary outcome									
MACCE[a]	122 (27.3)	37 (27.0)	0.71	68 (30.6)	19 (27.1)	0.85	54 (24.0)	18 (26.9)	0.48
Secondary outcomes									
Death	66 (14.8)	16 (11.8)	0.70	34 (15.4)	8 (11.6)	0.62	32 (14.3)	8 (12.0)	0.94
MI	15 (3.5)	2 (1.4)	0.58	8 (3.8)	1 (1.4)	0.36	7 (3.2)	1 (1.4)	0.91
Stroke	8 (2.0)	3 (2.3)	0.91	5 (2.5)	0 (0.0)	0.21	3 (1.5)	3 (4.7)	0.20
TVR	49 (11.6)	18 (13.5)	0.53	33 (15.7)	12 (17.3)	0.52	16 (7.5)	6 (9.5)	0.87
Stent thrombosis (definite) or symptomatic graft occlusion	9 (2.1)	5 (3.9)	0.22	3 (1.4)	1 (1.4)	0.40	6 (2.9)	4 (6.4)	0.72

Values n (%) were derived from the Kaplan-Meier estimates, and *P* values were calculated by using the log-rank test. aThe primary endpoint of major adverse cardiac or cerebrovascular events (MACCE) was a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target vessel revascularization (TVR).

Abbreviations as in Table 1.

adjustment for multiple testing was undertaken. Because of the potential for type I error arising from multiple comparisons, all findings of this study should be interpreted as exploratory. All statistical analyses were performed by using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

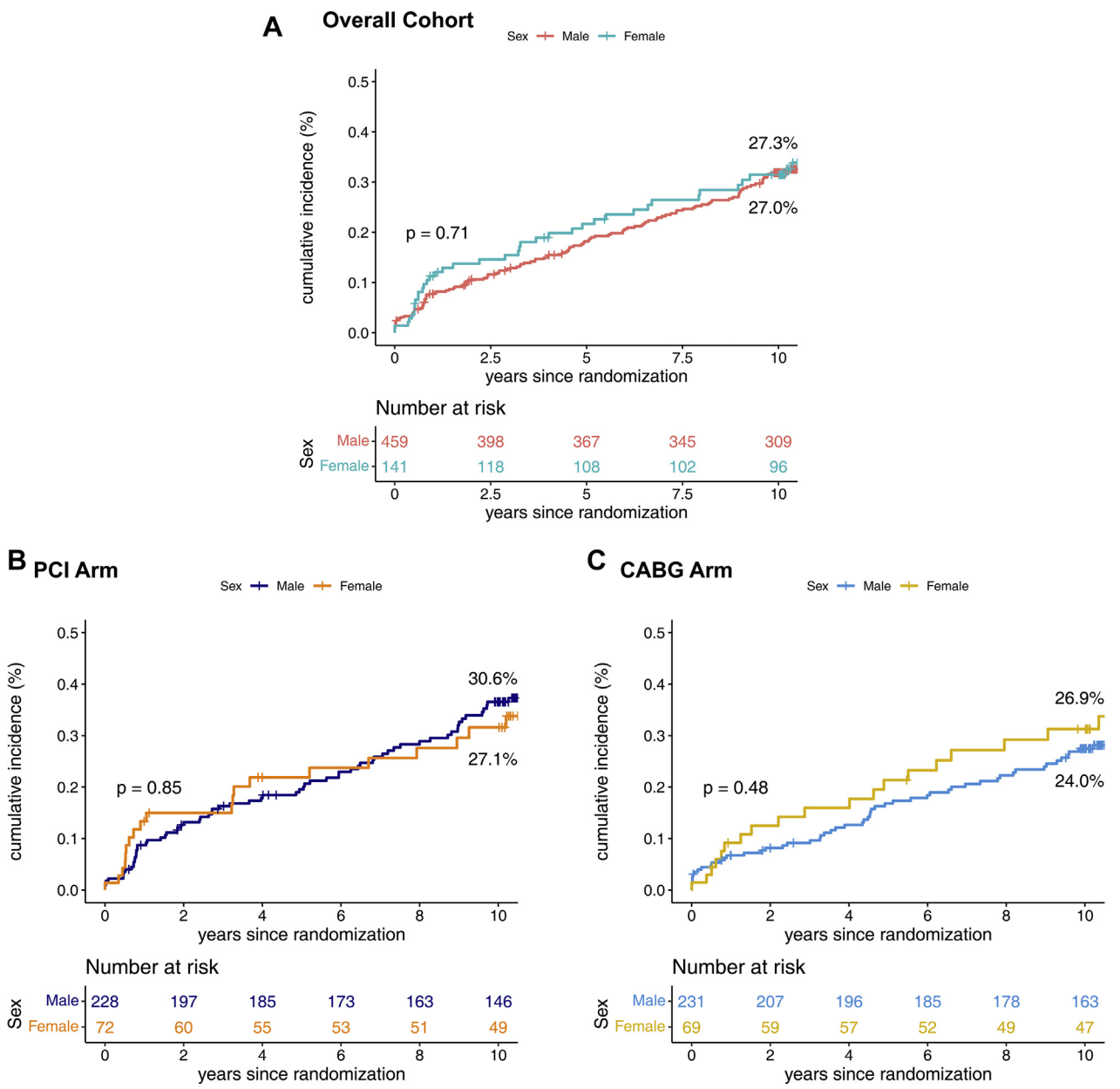
RESULTS

BASELINE CHARACTERISTICS. A total of 600 patients with unprotected LMCA disease were enrolled in the PRECOMBAT trial between April 2004 and August 2009. Among them, 459 (76.5%) were male, and 141 (23.5%) were female. The baseline clinical and angiographic characteristics between male and female subjects in the overall cohort and in each arm of PCI or CABG are summarized in **Table 1**. Compared with male subjects, female subjects had a low proportion of current smokers and a higher EuroSCORE. There were no significant differences in the anatomical characteristics between the 2 sexes. Moreover, there were no significant differences in cardiovascular medications at discharge and during follow-up, or in the procedural characteristics of PCI or CABG, between the 2 sexes (**Table 2**). Most baseline characteristics were not significantly different between PCI and CABG in either male or female subjects (Supplemental Table 1).

CLINICAL OUTCOMES ACCORDING TO SEX. The median duration of follow-up in all patients was 11.3 years (interquartile range: 10.2-13.0 years). Ten-year follow-up for all clinical endpoint events was achieved in 288 patients (96.0%) randomized to undergo PCI and 288 patients (96.0%) randomized to undergo CABG. Vital status was verified in all patients. The distributions of follow-up durations in male and female subjects according to treatment arm are shown in Supplemental Figure 1. The 10-year rates of primary and secondary outcomes between male and female subjects in the overall cohort and in each revascularization arm of PCI or CABG are shown in **Table 3 and Figure 1**. At 10 years, the incidences of MACCE were not significantly different between male and female subjects in the overall cohort (27.3% vs 27.0%; $P = 0.713$), the PCI arm (30.6% vs 27.1%; $P = 0.853$), or the CABG arm (24.0% vs 26.9%; $P = 0.476$). In the landmark analysis, the trend was consistent in the early period of <5 years and the late period beyond 5 years (Supplemental Figure 2). The 10-year incidences of mortality or TVR were also not significantly different between male and female subjects (Supplemental Figure 3). After multivariable adjustment for potentially confounding clinical covariates, sex was not independently associated with an increased risk of MACCE in the overall cohort (HR: 1.06; 95% confidence interval [CI]: 0.70-1.59), the PCI arm (HR: 1.19; 95% CI: 0.69-2.05), or the CABG arm (HR: 0.93; 95% CI: 0.53-1.62) (**Table 4, Central Illustration**). This trend was also observed for key secondary outcomes of all-cause mortality and TVR.

CLINICAL OUTCOMES ACCORDING TO REVASCULARIZATION STRATEGY IN MALE AND FEMALE SUBJECTS. The 10-year rates of primary and secondary outcomes between the PCI and CABG groups stratified according to sex category are summarized in **Table 5 and Figure 2**. After multivariable adjustment of clinically relevant covariates, the 10-year risk for MACCE did not significantly differ between PCI and CABG in both male (HR: 1.37; 95% CI: 0.95-1.97) and female (HR: 1.07; 95% CI: 0.56-2.07)

FIGURE 1 **10-Year Event Curves for the Primary Endpoint Between Male and Female Subjects**



Event curves are shown in the overall cohort **(A)**, the percutaneous coronary intervention (PCI) arm **(B)**, and the coronary artery bypass grafting (CABG) arm **(C)**. *P* values are derived from the log-rank test. Primary endpoint was major adverse cardiac or cerebrovascular events, which was defined as a composite of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or ischemia-driven target vessel revascularization.

subjects (**Central Illustration**). The rates of all-cause mortality were similar after PCI and CABG, but the TVR rates were higher after PCI, both in male and female subjects. Finally, there were no significant interactions between sex and treatment with PCI or CABG in terms of MACCE (*P* for interaction = 0.52) and key secondary outcomes of all-cause mortality (*P* for interaction = 0.86) and TVR (*P* for interaction = 0.93). The frequency and crude HR of MACCE at 5 years and 5 to 10 years are also presented in Supplemental Tables 2 and 3. In male subjects, the mortality rate was similar after PCI and CABG at 5

TABLE 4 Unadjusted and Adjusted Interaction Analyses: Hazard Ratios for Sex Stratified According to Treatment Strategy

	Unadjusted Hazard Ratio (95% CI)				Adjusted Hazard Ratio (95% CI)[a]			
	Marginal Analysis	Interaction Analysis			Marginal Analysis	Interaction Analysis		
	Overall	PCI	CABG	*P* for Interaction	Overall	PCI	CABG	*P* for Interaction
MACCE								
Female	Referent	Referent	Referent	0.51	Referent	Referent	Referent	0.52
Male	0.98 (0.68-1.42) *P* = 0.93	1.10 (0.66-1.83) *P* = 0.71	0.86 (0.51-1.47) *P* = 0.59		1.06 (0.70-1.59) *P* = 0.78	1.19 (0.69-2.05) *P* = 0.53	0.93 (0.53-1.62) *P* = 0.80	
Death								
Female	Referent	Referent	Referent	0.84	Referent	Referent	Referent	0.86
Male	1.28 (0.74-2.20) *P* = 0.84	1.35 (0.62-2.92) *P* = 0.44	1.20 (0.55-2.61) *P* = 0.64		1.69 (0.92-3.10) *P* = 0.09	1.78 (0.76-4.15) *P* = 0.18	1.60 (0.72-3.58) *P* = 0.25	
TVR								
Female	Referent	Referent	Referent	0.93	Referent	Referent	Referent	0.93
Male	0.82 (0.48-1.41) *P* = 0.47	0.83 (0.43-1.62) *P* = 0.59	0.79 (0.31-2.02) *P* = 0.63		0.54 (0.29-1.02) *P* = 0.06	0.55 (0.27-1.16) *P* = 0.12	0.53 (0.20-1.42) *P* = 0.20	

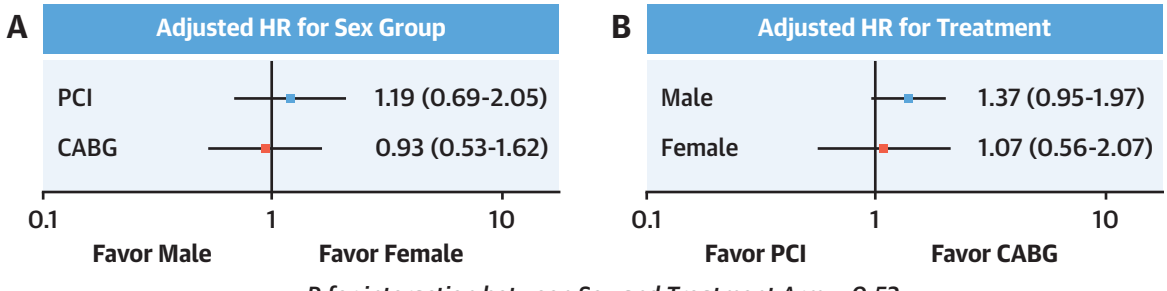
[a]Hazard ratios were adjusted for age, medically treated diabetes, clinical presentation, ejection fraction, left main bifurcation involvement, SYNTAX score, and EuroSCORE.
CI = confidence interval; other abbreviations as in Tables 1 and 3.

years but tended to be higher in PCI at 5 to 10 years without statistical significance (HR: 1.60; 95% CI: 0.89-2.87). In female subjects, the mortality rate after PCI and CABG was similar at 5 years and 5 to 10 years (Supplemental Figure 4). By multivariable analysis, in female subjects, peripheral artery disease was independently associated with MACCE at 10 years (Supplemental Table 4).

DISCUSSION

In this extended follow-up of the PRECOMBAT trial of patients with unprotected LMCA disease, we determined the long-term prognostic effect of sex on 10-year clinical and comparative outcomes after PCI with drug-eluting stents (DES) and CABG. The major findings of the study are as follows: 1) female subjects had a lower proportion of current smokers and higher EuroSCORE, whereas other clinical and anatomical characteristics were similar between the 2 sexes; 2) sex was not independently associated with higher risks of MACCE, all-cause mortality, or TVR; and 3) the 10-year rates of MACCE were similar after PCI and CABG in both male and female subjects, thus showing no significant interaction between sex and the relative treatment effect.

CENTRAL ILLUSTRATION Adjusted Hazard Ratios for the Primary Endpoint According to Sex and Treatment



P for interaction between Sex and Treatment Arm = 0.52

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Adjusted hazard ratios (95% CI) were stratified according to sex group **(A)** and treatment group **(B)**. Adjusted variables included age, medically treated diabetes, clinical presentation, ejection fraction, left main bifurcation involvement, SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score, and EuroSCORE (European System for Cardiac Operative Risk Evaluation). Primary end point was major adverse cardiac or cerebrovascular events, which was defined as a composite of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or ischemia-driven target vessel revascularization.
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

TABLE 5 Unadjusted and Adjusted Interaction Analyses: Hazard Ratios for Treatment Strategy Stratified According to Sex

	Unadjusted Hazard Ratio (95% CI)			Adjusted Hazard Ratio (95% CI)[a]		
	Male	Female	*P* for Interaction	Male	Female	*P* for Interaction
MACCE						
CABG	Referent	Referent		Referent	Referent	
PCI	1.32 (0.92-1.89) *P* = 0.13	1.03 (0.54-1.97) *P* = 0.92	0.51	1.37 (0.95-1.97) *P* = 0.09	1.07 (0.56-2.07) *P* = 0.83	0.52
Death						
CABG	Referent	Referent		Referent	Referent	
PCI	1.07 (0.66-1.73) *P* = 0.78	0.95 (0.36-2.54) *P* = 0.92	0.84	1.08 (0.66-1.78) *P* = 0.76	0.98 (0.36-2.64) *P* = 0.96	0.86
TVR						
CABG	Referent	Referent		Referent	Referent	
PCI	2.17 (1.19-3.94) *P* = 0.01	2.05 (0.77-5.47) *P* = 0.15	0.93	2.20 (1.20-4.02) *P* = 0.01	2.09 (0.78-5.62) *P* = 0.15	0.93

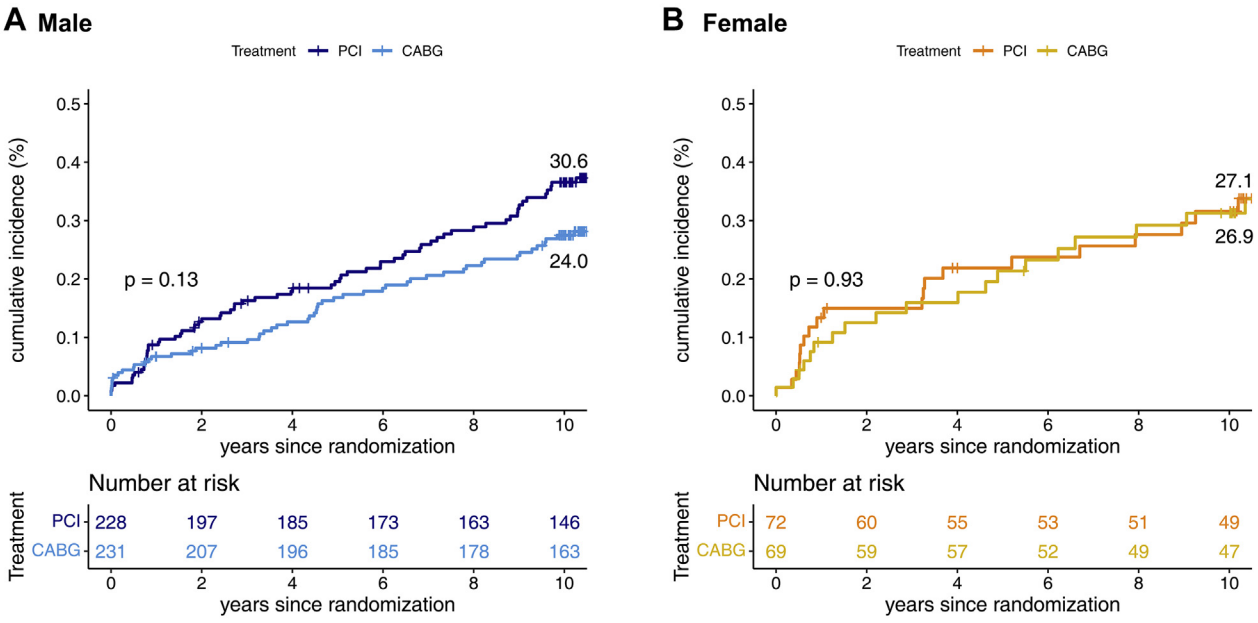
[a]Hazard ratios were adjusted for age, medically treated diabetes, clinical presentation, ejection fraction, left main bifurcation involvement, SYNTAX score, and EuroSCORE.
Abbreviations as in Tables 1, 3, and 4.

Sex differences in patients with atherosclerotic coronary artery disease include genetics, hormonal effects, prevalence of comorbidity, and anatomical complexity (20). The results are conflicting on whether female sex is an independent risk factor for worse short- or long-term clinical outcomes in patients with stable or acute CAD (14,15). The higher rates of mortality and complication in female subjects could be attributed to the differences in background characteristics and clinical covariates, as female subjects were shown to have unfavorable clinical characteristics such as older age and a higher number of comorbidities (16). In terms of angiographic characteristics, female subjects have smaller vessel lumen diameters than male subjects, which can lead to a higher rate of target lesion revascularization (17). Female subjects are also more likely to have atypical symptoms and receive delayed medical attention as well as reperfusion therapy (1,15,18). Until recently, many studies have suggested that sex is not an independent predictor of clinical outcomes in patients with CAD. A study using the KAMIR (Korean Acute Myocardial Infarction Registry) showed that although female subjects had a higher observed rate of mortality, female sex was not an independent risk factor after multivariable adjustment (19). In a prospective, large-sized, observational registry of patients with stable CAD, sex did not influence the risk of the composite outcome of cardiovascular death or fatal MI at 5 years' follow-up (20).

There has been a debate on whether biological sex should be considered a key factor when choosing revascularization strategy in patients with complex CAD. Several studies have thus evaluated the interaction effect of sex on the relative outcomes of treatment strategy with PCI or CABG for multivessel or LMCA (4-8,21). In prior reports, there was no significant sex-related interaction effect on clinical outcomes for up to 5 years (4-6,11), but other studies reported conflicting findings (22). The EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) study reported that women receiving PCI had a higher trend of worse outcomes, which was associated with comorbidities and higher rate of periprocedural complications (6). In the 5-year report of the NOBLE (Nordic-Baltic-British Left Main Revascularization) trial, treatment effects favoring CABG over PCI tended to be higher in women than in men, albeit not statistically significant (P = 0.22) (23). A meta-analysis of 10 RCTs showed that mortality at 5 years was significantly lower after CABG than after PCI and that this pattern was consistent regardless of sex (P for interaction = 0.82) (5). In a recent report of the SYNTAX extended follow-up study, female subjects reported more favorable 5-year outcomes after CABG than after PCI; however, the mortality rate of female subjects in the CABG group rapidly increased between 5 and 10 years of follow-up, and was similar to that of the PCI group at 10 years (8).

In our current prespecified subgroup analysis of the extended 10-year report of the PRECOMBAT trial, sex was not associated with adverse outcomes in patients who had undergone coronary revascularization. These study results also indicate that there was no significant interaction with the treatment strategy of PCI or CABG in patients with LMCA disease. Although the discrepant findings among trials is not yet fully elucidated, the female group in

FIGURE 2 **10-Year Event Curves of the Primary Endpoint Between PCI and CABG**



Event curves are shown in the male cohort **(A)** and female cohort **(B)**. *P* values are derived from the log-rank test. Primary endpoint was major adverse cardiac or cerebrovascular events, which was defined as a composite of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or ischemia-driven target vessel revascularization. Abbreviations as in Figure 1.

the PRECOMBAT study was substantially younger and tended to have fewer comorbidities (eg, hypertension, peripheral artery disease, heart failure) and less severe anatomical complexities (eg, lower prevalence of bifurcation lesions, lower SYNTAX score) compared with the SYNTAX and EXCEL study groups. Similarly, the discordant observations on the prognostic effect of sex between prior trials and ours might be explained in part by differences in baseline clinical or anatomical characteristics, interventional or operative practice, or race or ethnic groups.

Coronary heart teams play an important role in guiding the optimal revascularization strategy for patients with LMCA disease. However, the results of the current RCT-based studies show that sex-based decision-making is still limited for predicting long-term outcomes and optimal decision-making of revascularization strategy for patients with LMCA disease. Therefore, a more integrative approach with clinical factors such as operative risks (especially stroke), predicted longevity, and patient preferences for physical recovery profile, as well as more applicable and practical risk score tools, may be required to aptly tailor the decision-making process for patients with LMCA disease (24,25).

STUDY LIMITATIONS. First, although the current analysis was prespecified in the protocol, all findings should be interpreted as hypothesis-generating only considering the inherent limitations of subgroup analyses without adjustment of multiple testing. Second, the PRECOMBAT trial was an RCT with strict inclusion and exclusion criteria. Therefore, results may not be readily applicable in a real-world population with different clinical and anatomical characteristics. Third, this study was not statistically powered to compare the subgroups of sex for MACCE or its individual components. Therefore, our findings should be further tested through subsequent clinical trials that are adequately powered for this purpose. Finally, because the PRECOMBAT trial used first-generation DES, patients receiving PCI with current-generation DES may show better results; our current findings should therefore be further compared with long-term (beyond 5 years) follow-up data of the recent EXCEL and NOBLE trials that used contemporary DES.

CONCLUSIONS

In this 10-year report of the PRECOMBAT trial, we did not find differential prognostic effects of sex on the

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long-term risk of MACCE. Moreover, the rates of MACCE were similar after PCI and CABG both in male and female subjects without a significant interaction between sex and the relative treatment effect. The prognostic value and clinical adaptation of the sex-specific factor in patients with LMCA for use in coronary heart team discussions regarding the optimal revascularization strategy should be further validated in larger sized clinical studies in the contemporary revascularization setting.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with LMCA disease, PCI and CABG showed a similar incidence of MACCE and mortality in both male and female subjects at 10 years. There was no significant interaction between sex and treatment with PCI or CABG for MACCE (P for interaction = 0.52) and mortality (P for interaction = 0.86).

TRANSLATIONAL OUTLOOK: Long-term results from large-sized RCTs such as EXCEL and NOBLE would further bolster our understanding of the long-term effects of sex and its interaction with treatment (contemporary PCI and CABG) in patients with LMCA disease.

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KEY WORDS coronary artery bypass surgery, left main coronary artery disease, mortality, percutaneous coronary intervention, sex

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