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ORIGINAL RESEARCH

Time-Dependent Impact of Sex on the Long-Term Outcomes After Left Main Revascularization

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BACKGROUND: There are still limited data about the differential effect of sex on long-term outcomes after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for left main coronary artery disease. This extended follow-up study of the MAIN-COMPARE (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease) registry evaluated clinical outcomes beyond 10 years.

METHODS AND RESULTS: Of 2240 patients with unprotected left main coronary artery disease (PCI=1102 and CABG=1138), all-cause mortality, the composite of death, Q-wave myocardial infarction, or stroke, and target vessel revascularization were separately evaluated in both sexes. Of 2240 patients, 631 (28.2%) were women and 1609 (71.8%) were men. Women had lower 10-year incidences of death and serious composite outcomes than men. The adjusted 10-year risks of adverse outcomes were similar in men. However, the adjusted 10-year risks were different according to a prespecified period in women. In the short-term (0–1 year) period, PCI had a significantly lower risk for serious composite outcomes (adjusted hazard ratio [HR], 0.41; 95% CI, 0.19–0.91; *P*=0.03) compared with CABG. The adjusted risks for death and serious composite outcomes were significantly higher after PCI than after CABG, during the midterm (1–5 years) period (death; adjusted HR, 3.99; 95% CI, 2.01–7.92; *P*<0.001 and composite outcome; adjusted HR, 2.93; 95% CI, 1.59–5.39; *P*=0.001). Beyond 5 years, adjusted risks were similar after PCI and CABG in women.

CONCLUSIONS: In this 10-year extended follow-up study of patients undergoing left main coronary artery revascularization, we observed a time-dependent impact of sex on the long-term outcomes after PCI and CABG, especially in women, with significant interactions. However, these results warrant confirmation on larger series of studies.

REGISTRATION: URl: https://www.clinicaltrials.gov; Unique identifier: NCT02791412.

Key Words: coronary artery bypass surgery ■ left main coronary artery disease ■ outcomes ■ percutaneous coronary intervention ■ sex

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Over the past 2 decades, percutaneous coronary intervention (PCI) has been accepted as an effective revascularization strategy for selected patients with left main coronary artery (LMCA) disease attributable to improved devices, accumulation of experiences, and proper long-term medications after procedures.[1,2] Although there are still ongoing debates about the relative long-term outcomes of PCI and coronary artery bypass grafting (CABG) for LMCA disease,[3–7] the decision making for optimal revascularization strategy is of paramount importance considering several clinical profiles, comorbidity, anatomic

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CLINICAL PERSPECTIVE

What Is New?

- Differential treatment effect of percutaneous coronary intervention or coronary artery bypass grafting for left main coronary artery disease was observed according to specific periods for a long time, especially in women but not in men.
- Women undergoing percutaneous coronary intervention had a significantly lower risk for serious composite outcomes during the short-term (0–1 year) period, but they had significantly higher risks for death and serious composite outcomes during the midterm (1–5 years) period than women undergoing coronary artery bypass grafting.
- There were no significant differences in mortality and serious composite outcomes between percutaneous coronary intervention and coronary artery bypass grafting in men.

What Are the Clinical Implications?

- This extended follow-up of the MAIN-COMPARE (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease) registry provides important insights on sex-related long-term outcomes, which could aid in decision making for optimal revascularization strategy in patients with LMCA disease.

Nonstandard Abbreviations and Acronyms

EXCEL	Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
IPTW	inverse probability treatment weighting
LMCA	left main coronary artery
MAIN-COMPARE	Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease
NOBLE	Nordic–Baltic–British Left Main Revascularization
PRECOMBAT	Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease
STICH	Surgical Treatment for Ischemic Heart Failure
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
SYNTAXES	Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival
TVR	target vessel revascularization

complexity, physical performance, and preference of patients.[8,9]

Among several important clinical factors, sex-specific differences in baseline characteristics and outcomes have been recognized,[10] and several clinical trials and registries reported the differential effect of sex on the relative treatment patterns and the effects of PCI and CABG for multivessel or LMCA disease.[11–15] Given that the difference in treatment effect of 2 competing revascularization strategies in both men and women were discordant according to period, geography, and ethnicity of the study subjects, there is no uniform consensus with regard to the interaction between sex and periprocedural complications or long-term cardiovascular events after PCI or CABG. In addition, a recent SYNTAXES (Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival) report revealed time-dependent interaction of sex with treatment effect of PCI or CABG in patients with multivessel disease.[16] Herein, we investigated the association between sex and long-term (beyond 10 years) outcomes of PCI versus CABG for patients with LMCA disease, using the extended follow-up of the MAIN-COMPARE (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease) registry.[5]

METHODS

Data Sources

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

Study Design and Population

The study design, characteristics, primary results, and final 10-year outcomes of the MAIN-COMPARE study (NCT02791412) have been reported previously.[5,17,18] In brief, the MAIN-COMPARE study included consecutive patients with significant LMCA disease who underwent PCI or CABG in 12 major centers in Korea between January 2000 and June 2006. Patients with previous CABG, concomitant valve or aortic surgery, or ST-segment–elevation myocardial infarction (MI) or cardiogenic shock at presentation were excluded. The use of clinical data for this study was approved by the institutional review committees at each hospital, and all patients provided written informed consent.

Detailed information on PCI and CABG procedures were reported.[5,17] Selection of either PCI or CABG as treatment strategy for LMCA disease was at the discretion of attending cardiologists or cardiac surgeons, with careful consideration of clinical and anatomic factors and patient preference. Bare-metal stents and drug-eluting stents were exclusively used from January 2000 to May 2003 and from May 2003 to June 2006, respectively, in the study, because of the availability of those devices. The methods for data acquisition and management during the extended follow-up period have been described previously.[5] Follow-up was performed in accordance with the local law and regulations of each participating institution, and it was extended through December 31, 2016 to ensure the availability of 10-year follow-up for all study subjects. Complete information on vital status was also reconfirmed from the National Population Registry of the Korea National Statistical Office.

Study Outcomes

The key study outcomes were all-cause death; the composite of death, Q-wave MI, or stroke; and target vessel revascularization (TVR) 10 years after index revascularization. In the current study, all-cause mortality was assessed, which was the most unbiased method to report deaths in a clinical trial or observational study.[19] Q-wave MI was defined as periprocedural or spontaneous MI accompanied with any new pathologic Q wave. Stroke was confirmed by neurologists with clinical symptoms and neurologic imaging. TVR was defined as any repeat revascularization of the target vessels including any segments in LMCA, the left anterior descending artery, and/or left circumflex artery. All clinical outcomes were confirmed by the source documentation obtained from each hospital, and central adjudication was performed for all clinical events by an independent group of clinicians.

Statistical Analysis

The study methods have been described in detail previously.[5] The primary objective was to evaluate whether female and male patients would respond to revascularization differently during an extended long-term follow-up. Patient demographics and procedural characteristics are presented as mean with standard deviation in continuous variables and as number with percentage in categorical variables. Comparisons between groups were performed using the Pearson χ^2 test for categorical variables and the Student *t* test for continuous variables.

To compensate for the nonrandomized design of this study, primary analysis was performed using inverse probability treatment weighting (IPTW) based on propensity scores. The propensity score was defined as the conditional probability of receiving PCI relative to CABG on the basis of available variables, and it was estimated with a multiple logistic regression model. All prespecified variables were included in the respective models (Table 1). Separate propensity scores were used to adjust differences in the baseline characteristics of both treatment groups (PCI versus CABG) in women and men. Appropriateness of adjustment was evaluated using standardized mean differences after IPTW.[20] The cumulative event curves were estimated using the Kaplan-Meier method in time-to-first-event analyses with IPTW.[21] The weighted Cox proportional hazard model was used to assess the relative risk of differential outcomes between the CABG and PCI arms. The assumption of proportional hazards in the Cox model for all-cause mortality and composite outcomes were not met in log of negative log of estimated survivor functions. Thus, we performed logistic regression for clinical outcomes, with follow-up time as a log-transformed offset variable. Piecewise hazard models were used separately for 0 to 1 year, 1 to 5 years, and 5 to 10 years to assess short-term, midterm, and long-term effects of different treatment modalities (PCI versus CABG), respectively, in women and men. This time period separation was made for the following reasons: (1) to avoid a significant bias toward positive results for the selection of time period based on relevant outcomes, (2) in accordance with a prespecified time point of 5 years in the previous report of the MAIN-COMPARE registry that divided 10 years into 0 to 5 and 5 to 10 years,[5] and (3) to show differential effect of PCI and CABG in women that showed dramatic changes during the early period, 0 to 1 year was additionally included as the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) extended follow-up trial assessed.[3] Interactions of sex and the 2 treatment arms were evaluated using the separate periods and the entire follow-up period. Patients with missing vital status and clinical events were included in the analysis and censored at the last date of contact or observation. All reported *P* values were 2-sided, and values <0.05 were considered statistically significant. No adjustments were made for multiple comparisons. Because of the potential for type I error attributable to multiple comparisons, all findings of this study should be interpreted as exploratory. All statistical analyses were performed with the use

Table 1. Baseline Characteristics of Patients According to Sex and Revascularization Strategies

Characteristics	Women			Men		
	CABG, N=308	PCI, N=323	*P* value	CABG, N=830	PCI, N=779	*P* value
Wave			0.028			<0.001
BMS era, Jan 2000–May 2003	117 (38.0)	95 (29.4)		331 (39.9)	223 (28.6)	
DES era, May 2003–Jun 2006	191 (62.0)	228 (70.6)		499 (60.1)	556 (71.4)	
Age, y	63.5 ± 9.3	59.8 ± 13.4	<0.001	62.7 ± 9.4	62.0 ± 10.8	0.133
Diabetes	101 (32.8)	99 (30.7)	0.622	294 (35.4)	228 (29.3)	0.010
Hypertension	168 (54.5)	177 (54.8)	>0.99	394 (47.5)	369 (47.4)	>0.99
Dyslipidemia	112 (36.4)	107 (33.1)	0.441	259 (31.2)	208 (26.7)	0.053
Current smoker	23 (7.5)	14 (4.3)	0.132	316 (38.1)	268 (34.4)	0.139
Previous PCI	36 (11.7)	49 (15.2)	0.244	89 (10.7)	151 (19.4)	<0.001
Previous MI	24 (7.8)	17 (5.3)	0.260	108 (13.0)	72 (9.2)	0.020
Previous CHF	6 (1.9)	10 (3.1)	0.507	32 (3.9)	17 (2.2)	0.071
Chronic lung disease	3 (1.0)	5 (1.5)	0.773	20 (2.4)	17 (2.2)	0.891
Cerebrovascular disease	11 (3.6)	23 (7.1)	0.072	72 (8.7)	55 (7.1)	0.268
Peripheral arterial disease	11 (3.6)	1 (0.3)	0.007	51 (6.1)	15 (1.9)	<0.001
Renal failure	9 (2.9)	7 (2.2)	0.727	25 (3.0)	23 (3.0)	>0.99
Ejection fraction	59.7 ± 10.9	62.1 ± 9.7	0.003	56.7 ± 12.2	60.1 ± 11.0	<0.001
Clinical indication			0.161			<0.001
Silent ischemia	2 (0.6)	7 (2.2)		23 (2.8)	26 (3.3)	
Chronic stable angina	70 (22.7)	90 (27.9)		156 (18.8)	263 (33.8)	
Unstable angina	209 (67.9)	201 (62.2)		566 (68.2)	407 (52.2)	
NSTEMI	27 (8.8)	25 (7.7)		85 (10.2)	83 (10.7)	
Left main disease location			0.005			0.642
Ostium or shaft	152 (49.4)	196 (60.7)		374 (45.1)	361 (46.3)	
Distal bifurcation	156 (50.6)	127 (39.3)		456 (54.9)	418 (53.7)	
Extent of diseased vessel			<0.001			<0.001
Left main only	22 (7.1)	107 (33.1)		49 (5.9)	171 (22.0)	
Left main plus 1-vessel disease	37 (12.0)	65 (20.1)		82 (9.9)	199 (25.5)	
Left main plus 2-vessel disease	70 (22.7)	78 (24.1)		229 (27.6)	209 (26.8)	
Left main plus 3-vessel disease	179 (58.1)	73 (22.6)		470 (56.6)	200 (25.7)	
Restenotic lesion	7 (2.3)	12 (3.7)	0.408	7 (0.8)	20 (2.6)	0.013

Values are n (%) or mean±SD.

BMS indicates bare-metal stent; CABG, coronary artery bypass grafting; CHF, congestive heart failure; DES, drug-eluting stent; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; and PCI, percutaneous coronary intervention.

of R software version 3.4.4 (The R Foundation for Statistical Computing) and SAS (SAS Institute).

RESULTS

Study Population and Baseline Characteristics

Of the 2240 patients enrolled in the MAIN-COMPARE registry, 631 (28.2%) were women and 1609 (71.8%) were men: women were treated with either PCI (323 patients [51.2%]) or CABG (308 patients [48.8%]), and men were treated with either PCI (779 patients [48.4%]) or CABG (830 patients [51.6%]). In general, compared with men, women had higher prevalence rates of hypertension and dyslipidemia, and the rate of current smokers was low (Table S1). On procedural or operative characteristics, women were treated with shorter total stent length in the PCI arm and received fewer conduits in the CABG arm compared with men (Table S2).

Baseline demographics, clinical, and anatomical characteristics between the CABG and PCI groups stratified by sex are summarized in Table 1. In both female and male groups, patients who underwent CABG were more likely to have a higher risk for clinical and anatomic risk factor profiles than those who underwent PCI. After adjustment for the use of IPTW, all of the clinical covariates were well balanced (Table 2). The standard mean differences were <0.1 for almost all variables, indicating that the PCI and CABG arms in both sexes were balanced after adjustment.

Table 2. Adjusted Baseline Characteristics of Patients Using Inverse Probability Weighting According to Sex and Revascularization Strategies

Characteristics	Women			Men		
	CABG, N=308	PCI, N=323	SMD	CABG, N=830	PCI, N=779	SMD
Wave			0.04			0.02
BMS era, Jan 2000–May 2003	0.36	0.35		0.34	0.33	
DES era, May 2003–Jun 2006	0.64	0.66		0.66	0.67	
Age, y	62.67	61.84	0.07	62.65	62.47	0.02
Diabetes	0.30	0.29	0.01	0.32	0.31	0.01
Hypertension	0.54	0.54	0.01	0.46	0.46	0.01
Dyslipidemia	0.36	0.33	0.07	0.29	0.29	0.01
Current smoker	0.06	0.05	0.04	0.37	0.37	0.01
Previous PCI	0.14	0.14	0.003	0.15	0.16	0.03
Previous MI	0.07	0.06	0.06	0.10	0.10	0.01
Previous CHF	0.01	0.04	0.18	0.03	0.03	0.01
Chronic lung disease	0.01	0.02	0.08	0.03	0.02	0.03
Cerebrovascular disease	0.07	0.06	0.04	0.07	0.07	0.004
Peripheral arterial disease	0.02	0.00	0.14	0.04	0.04	0.01
Renal failure	0.03	0.03	0.01	0.04	0.03	0.03
Ejection fraction	61.33	61.13	0.02	58.37	58.89	0.05
Clinical indication	0.00	0.00	0.06	0.00	0.00	0.01
Silent ischemia	0.02	0.02		0.03	0.03	
Chronic stable angina	0.23	0.25		0.27	0.27	
Unstable angina	0.66	0.65		0.60	0.60	
NSTEMI	0.08	0.09		0.11	0.11	
Left main disease location			0.04			0.002
Ostium or shaft	0.53	0.54		0.46	0.46	
Distal bifurcation	0.48	0.46		0.54	0.54	
Extent of diseased vessel	0.00	0.00	0.09	0.00	0.00	0.03
Left main only	0.17	0.21		0.14	0.14	
Left main plus 1-vessel disease	0.18	0.17		0.18	0.18	
Left main plus 2-vessel disease	0.25	0.24		0.27	0.28	
Left main plus 3-vessel disease	0.40	0.38		0.41	0.40	
Restenotic lesion	0.03	0.03	0.02	0.01	0.02	0.03

BMS indicates bare-metal stent; CABG, coronary artery bypass grafting; CHF, congestive heart failure; DES, drug-eluting stent; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and SMD, standardized mean difference.

Comparative 10-Year Clinical Outcomes in Women and Men

The median follow-up duration was 11.9 years (interquartile range, 10.3–13.4 years) for the study population. The follow-up status for major clinical events was ascertained for 2211 patients (98.7%) of the overall population. In general, women had lower crude rates of all-cause mortality and serious composite outcomes at 10 years compared with men, in which the significant difference at 10 years was driven mainly by a higher event rate in men during the late period between 5 and 10 years (Figure S1 and Table S3). The crude rate of TVR at 10 years was not significantly different between women and men. However, after adjustment for baseline characteristics, there were no significant differences in clinical outcomes between women and men (Figure S2 and Table S3).

The unadjusted Kaplan-Meier event rates and curves after PCI and CABG stratified by sex group are shown in Figure 1 and Table 3. The observed 10-year rates of mortality and the composite of death, Q-wave MI, or stroke were similar between the PCI and CABG groups for both sexes. However, there was a crossover in outcomes after PCI versus CABG over time in women but not in men (Figure 1). The rate of TVR was consistently higher after PCI than after CABG, irrespective of the sex. The IPTW-adjusted Kaplan-Meier event rates and curves for clinical outcomes are shown in Figure 2 and Table 3. In men, the adjusted rates of

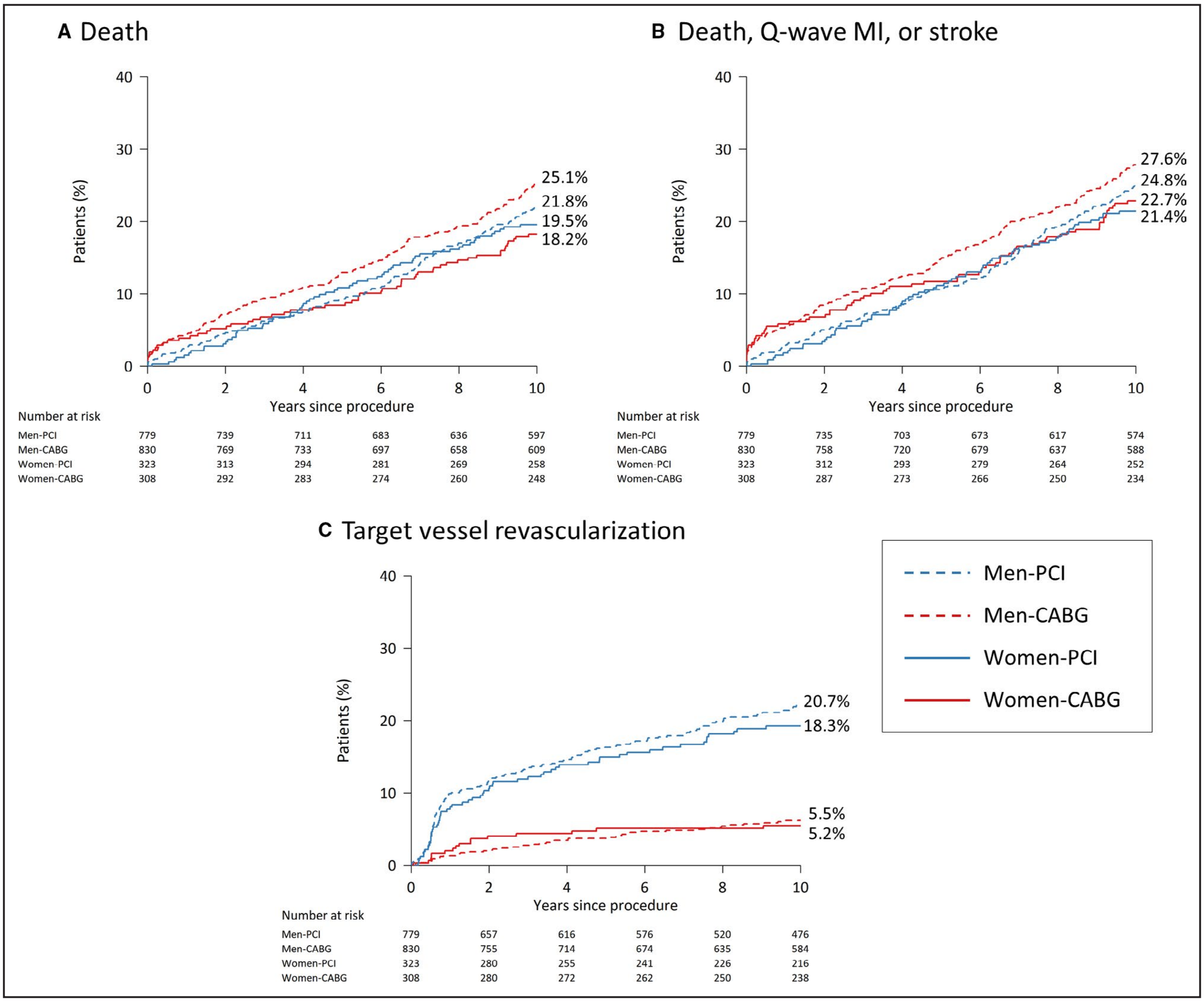

Figure 1. Crude 10-year Kaplan-Meier curves for clinical events stratified by sex and revascularization strategies in the overall cohort.
A, Death. **B**, Death, Q-wave myocardial infarction (MI), or stroke. **C**, Target vessel revascularization. CABG, indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

all-cause mortality and composite outcome of death, Q-wave MI, or stroke were not significantly different between the PCI and CABG groups during the 10-year follow-up. On the contrary, in women, the adjusted 10-year rates of death and serious composite outcomes were higher after PCI than they were after CABG (death: 24.4% in PCI versus 17.0% in CABG, and composite outcome: 26.2% in PCI versus 20.8% in CABG). In addition, there was a crossover in the adjusted outcomes after PCI versus CABG over time in women but not in men (Figure 2). Especially, over time, the risks for death and composite outcomes have diverged during the late period of follow-up, favoring CABG over PCI in women.

Differential effects of PCI and CABG were observed in women in the piecewise Cox models over 3 periods. In the short-term (0- to 1-year) period, after undergoing PCI, women had a significantly lower risk for serious composite outcomes compared with women after undergoing CABG (adjusted hazard ratio [HR], 0.41; 95% CI, 0.19–0.91; P=0.028). On the other hand, significantly higher risks for death and serious composite outcomes were observed in women who underwent PCI than in women who underwent CABG during the midterm (1 to 5 years) period (for death: adjusted HR, 3.99; 95% CI, 2.01–7.92, P<0.001, and for serious composite outcome: adjusted HR, 2.93; 95% CI, 1.59–5.39; P=0.001) with significant interactions between sex and treatment modalities (for death: P<0.001, for serious composite outcome: P=0.002). There were no significant differences in these outcomes beyond 5 years after PCI and CABG in women (Table 4 and Figure 3). Male patients experienced similar adverse events in all clinical outcomes regardless of time

Table 3. Clinical Outcomes at 10 y*

	Unadjusted outcomes					Adjusted outcomes with the use of inverse probability treatment weighting				
	CABG	PCI	Odds Ratio	*P* value	*P*-int†	CABG	PCI	Odds ratio	*P* value	*P*-int†
Death										0.096
Women	56 (18.2)	63 (19.5)	1.16 (0.76–1.79)	0.489	0.303	17.0	24.3	1.52 (0.99–2.34)	0.058	
Men	208 (25.1)	170 (21.8)	0.90 (0.70–1.15)	0.405		24.0	24.2	1.01 (0.78–1.29)	0.964	
Death, Q-wave MI, or stroke										0.379
Women	70 (22.7)	69 (21.4)	0.94 (0.63–1.41)	0.770	0.936	20.7	26.0	1.25 (0.83–1.87)	0.281	
Men	229 (27.6)	193 (24.8)	0.93 (0.73–1.18)	0.531		26.1	26.7	1.01 (0.80–1.29)	0.923	
TVR										0.774
Women	16 (5.2)	59 (18.3)	7.69 (3.76–15.87)	<0.001	0.422	4.4	18.6	6.67 (3.17–14.08)	<0.001	
Men	46 (5.5)	161 (20.7)	8.77 (5.78–13.33)	<0.001		5.4	22.0	7.58 (5.05–11.24)	<0.001	

CABG indicates coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TVR, target vessel revascularization.
*Event rates (percent) shown are the incidences estimated using the Kaplan-Meier survival analysis.
†*P* value for the interaction (*P*-int) between sex (women vs men) and revascularization strategy (PCI vs CABG).

period. The rate of TVR was consistently higher in the PCI group, irrespective of sex.

DISCUSSION

In this longest follow-up cohort study of patients with unprotected LMCA disease who underwent PCI or CABG, we performed an analysis to assess the long-term prognostic effect of sex on the relative clinical outcomes of 2 competing revascularization modalities. The major findings of the study are: (1) Compared with women, men experienced higher rates of mortality and serious composite of death, Q-wave MI, or stroke at 10 years. (2) In men, there were no differences between PCI and CABG arms on mortality and serious composite outcomes over time up to 10 years. (3) In women, the adjusted 10-year risks of death and composite outcomes were significantly lower up to 1 year after PCI than they were after CABG, whereas they were significantly higher after PCI over CABG from 1 year to 5 years. This trend has emerged during the late period of follow-up. (4) TVR rates were consistently higher after PCI than they were after CABG, regardless of sex.

Women and men who developed atherosclerotic coronary artery disease are different in terms of genetics, hormonal effect, prevalence of comorbidity, and anatomic complexity.[22] Traditionally, female sex has been considered as a disadvantage in risk-assessment scoring systems developed for cardiac surgery,[23,24] but the relationship between cardiac surgery and sex on clinical outcomes are still controversial. The 10-year results of the STICH (Surgical Treatment for Ischemic Heart Failure) trial showed no disadvantage during the early period after CABG in women, and thus, sex should not influence treatment decisions about CABG in these patients.[25] The results from other large-sized registries showed inconsistent results of worse clinical outcomes in women than in men.[26,27] Also, several studies elucidated differential effect of sex on PCI outcomes, and the results are conflicting; some studies showed similar outcomes of PCI in women and men,[15,28–30] other studies reported higher periprocedural risk but lower long-term mortality in women than in men,[31] and recent pooled analysis of patient-level data showed that women had a higher risk of major adverse cardiac events and target-lesion revascularization compared with men 5 years after undergoing PCI.[32]

On the decision-making for optimal revascularization strategy for patients with multivessel or LMCA disease, there has been a continuing debate on biological sex being considered as one of the key factors for discriminating treatment modalities. The relative treatment effect of PCI or CABG can differ between women and men. However, data on the interaction between

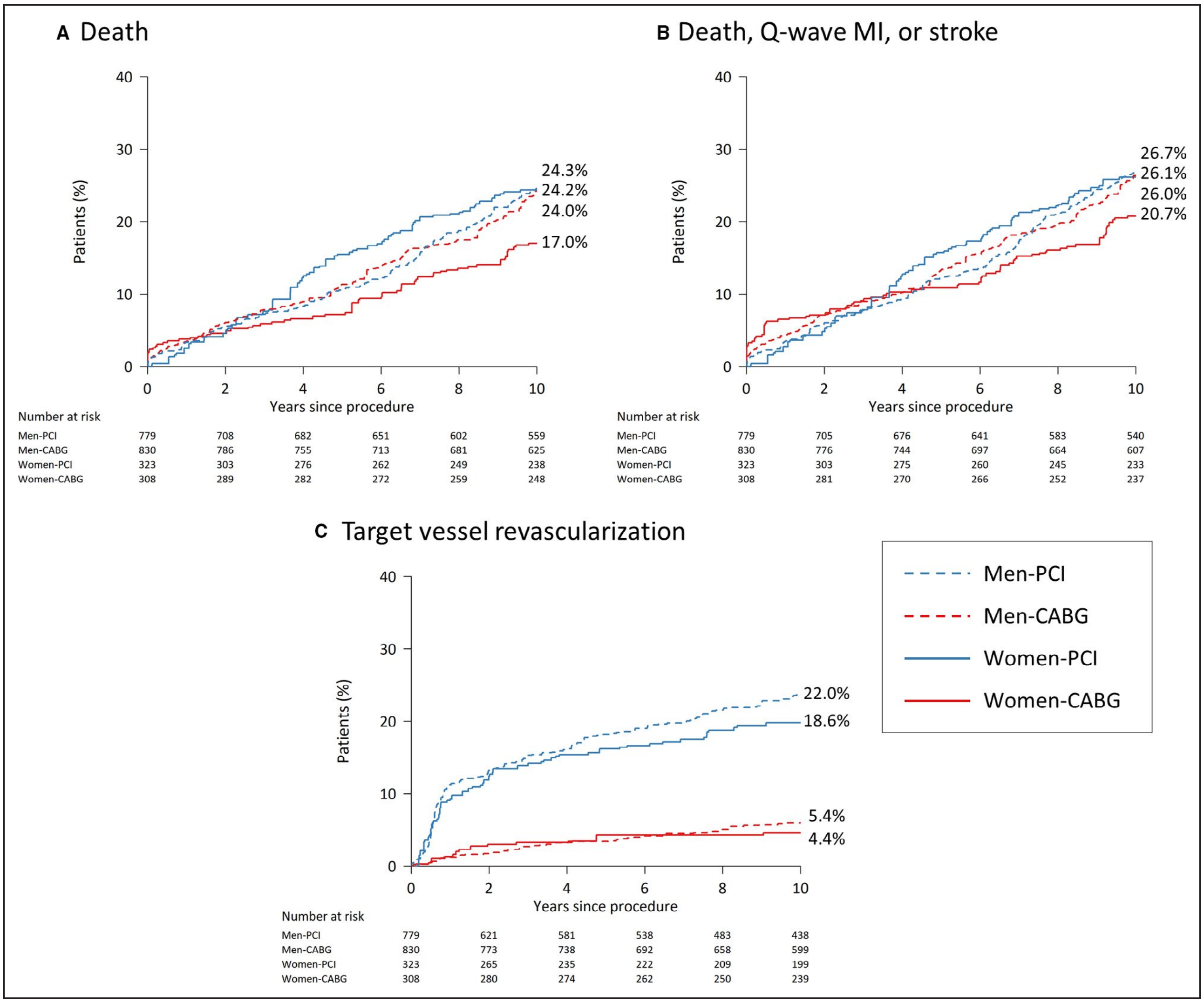

Figure 2. Adjusted 10-year Kaplan-Meier curves for clinical events stratified by sex and revascularization strategies in the overall cohort.

A, Death. **B**, Death, Q-wave myocardial infarction (MI), or stroke. **C**, Target vessel revascularization. CABG indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

sex and those 2 revascularization modalities are limited to date, especially in patients with LMCA disease. Most randomized studies showed similar outcomes between CABG and PCI, regardless of sex.[6,12–14] The 10-year follow-up report 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 showed no significant interaction between sex and PCI with first-generation drug-eluting stents or CABG (*P* for interaction=0.95). The EXCEL trial revealed that women undergoing PCI with second-generation drug-eluting stents had a trend toward worse outcomes, a finding related to associated clinical comorbidities and increased periprocedural complications.[14] In the 5-year report of the NOBLE (Nordic–Baltic–British Left Main Revascularization) trial, treatment effect favoring CABG over PCI was more prominent in women than in men, without significant interaction (*P* for interaction=0.22).[4] The meta-analysis of 10 randomized trials showed that 5-year mortality was lower after CABG than it was after PCI, which was consistent in both sexes (*P* for interaction=0.82).

Because of the late catch-up phenomenon of CABG over PCI after midterm follow-up (3–5 years), the analysis of an extended follow-up period >5 years is important to provide a relevant massage on the effect of PCI and CABG in LMCA disease. An early report of the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial for up to 5 years showed worse outcomes after PCI in women, and a lower anatomical SYNTAX score was required to achieve similar

Table 4. Crude and Adjusted Risks Over Prespecified 3 Time Periods After PCI or CABG, According to Sex Category

	Unadjusted Outcomes					Adjusted outcomes with the use of inverse probability treatment weighting				
	Crude event rates at 10 y, n (%)					Adjusted event rates at 10 y, %				
	CABG	PCI	HR (95% CI)*	*P* value	*P*-int†	CABG	PCI	HR (95% CI)*	*P* value	*P*-int†
Outcomes at 1 year										
Death					0.474					0.477
Women	12 (3.9)	5 (1.6)	0.39 (0.14–1.11)	0.077		3.8	2.4	0.65 (0.27–1.61)	0.355	
Men	23 (2.8)	15 (1.9)	0.69 (0.36–1.32)	0.265		3.5	3.4	0.95 (0.56–1.62)	0.863	
Death, Q-wave MI, or stroke					0.347					0.171
Women	18 (5.8)	6 (1.9)	0.31 (0.12–0.78)	0.013		6.5	2.8	0.41 (0.19–0.91)	0.028	
Men	25 (3)	16 (2.1)	0.68 (0.36–1.27)	0.224		4.3	3.5	0.79 (0.48–1.31)	0.363	
TVR					0.283					0.700
Women	6 (2)	26 (8.1)	4.14 (1.70–10.05)	0.002		1.3	9.2	7.34 (2.53–21.28)	<0.001	
Men	8 (1)	71 (9.1)	9.79 (4.71–20.33)	<0.001		1.2	11.0	9.46 (4.94–18.13)	<0.001	
Outcomes from 1–5 y										
Death					0.008					<0.001
Women	14 (4.6)	30 (9.3)	2.08 (1.10–3.92)	0.024		3.4	12.9	3.99 (2.01–7.92)	<0.001	
Men	70 (8.4)	51 (6.6)	0.77 (0.54–1.11)	0.157		7.8	7.3	0.94 (0.65–1.34)	0.711	
Death, Q-wave MI, or stroke					0.083					0.002
Women	19 (6.2)	30 (9.3)	1.52 (0.86–2.70)	0.154		4.6	12.9	2.93 (1.59–5.39)	0.001	
Men	78 (9.4)	62 (8.0)	0.84 (0.61–1.18)	0.318		8.9	8.8	1.00 (0.72–1.39)	>0.99	
TVR					0.675					0.537
Women	9 (2.9)	21 (6.5)	2.27 (1.04–4.96)	0.040		2.9	6.5	2.37 (1.07–5.24)	0.034	
Men	18 (2.2)	47 (6.1)	2.80 (1.62–4.82)	<0.001		2.0	6.5	3.24 (1.87–5.62)	<0.001	
Outcomes from 5–10 y										
Death					0.591					0.535
Women	30 (9.8)	28 (8.7)	0.89 (0.53–1.49)	0.657		9.8	8.9	0.90 (0.54–1.52)	0.700	
Men	101 (12.3)	98 (12.7)	1.04 (0.79–1.38)	0.764		12.8	13.8	1.09 (0.83–1.43)	0.547	
Death, Q-wave MI, or stroke					0.523					0.498
Women	36 (11.7)	34 (10.6)	0.90 (0.57–1.44)	0.672		11.5	10.6	0.92 (0.58–1.49)	0.745	
Men	113 (13.8)	113 (14.7)	1.08 (0.83–1.40)	0.588		12.8	13.8	1.11 (0.86–1.44)	0.412	
TVR					0.145					0.161
Women	1 (0.3)	12 (3.7)	11.65 (1.52–89.61)	0.018		0.2	3.0	12.29 (1.14–132.26)	0.039	
Men	17 (2.1)	38 (4.9)	2.42 (1.36–4.28)	0.003		2.1	4.6	2.14 (1.21–3.80)	0.009	

CABG indicates coronary artery bypass grafting; HR, hazard ratio, MI, myocardial infarction; PCI, percutaneous coronary intervention; and TVR, target vessel revascularization.

*HR is the risk of different outcomes in PCI compared with CABG.

†*P* value for the interaction (*P*-int) between sex (women vs men) and revascularization strategy (PCI vs CABG).

outcomes between PCI and CABG in women.[10,33] Thus, SYNTAX score II added female sex to the original SYNTAX score I, as a factor favoring CABG over PCI.[10] However, a recent 10-year report from SYNTAXES demonstrated the interaction between sex and treatment with PCI or CABG that was observed at the 5-year follow-up (*P* for interaction=0.03) was no longer present at 10 years (*P* for interaction=0.95), in which the significant mortality benefit of CABG observed in women at 5 years disappeared at 10 years.[16] Similarly, our study showed that treatment effect could be different over a long-term period after PCI or CABG, according to sex. Especially in women, the risks of mortality and serious composite outcomes were different during

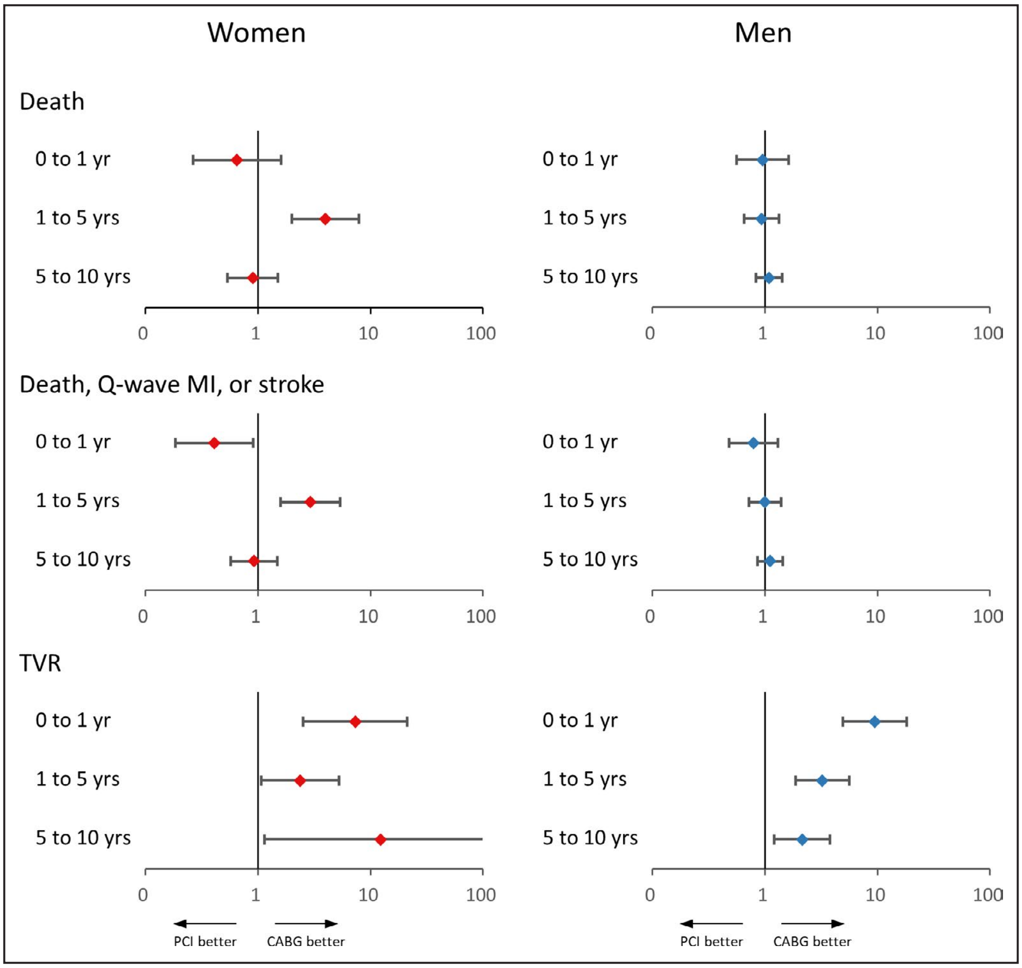

Figure 3. Impact of sex on the relative risks for clinical outcomes after percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).
MI indicates myocardial infarction; and TVR, target vessel revascularization.

early and midterm periods, with favorable outcomes in PCI during the early period but favoring CABG over PCI during the midterm period. The main mechanism of this observed finding is unclear. In women undergoing CABG who were older and had lower ejection fraction and more extensive coronary disease, the beneficial effect of CABG over PCI has been gradually manifested during the late follow-up period, which was not evident in the early period.[34] Although the reasons for some discordant observations between SYNTAXES and this study are not fully understood, differences in genetic and hormonal factors, and the sizes of coronary arteries, as well as the differences in patient profiles, and procedural and operative characteristics, have been mentioned as possible explanations.[5,35] In addition, a recent meta-analysis suggested the presence of the heterogeneous sex–treatment interaction in trials across Asian and Western regions.[12] Moreover, another possible difference is that we only accounted Q-wave MI during the periprocedural or long-term follow-up period for the serious composite end points. This is a strict definition of MI compared with that in other observational and randomized studies. This could be a reason for the differences in the result of our study and other clinical trials.

Limitations

There are several limitations in our study. First, although the present analysis was prespecified in the protocol, all observed findings should be interpreted as hypothesis generating only because of the inherent limitations of subgroup analyses without adjustment of multiple testing. Second, because this was a nonrandomized observational study, there might be inherent limitations and bias in treatment selection. Although IPTW analysis was used to adjust potential selection bias, unmeasured confounders that have affected the results cannot be excluded. Third, the MAIN-COMPARE registry was conducted between 2000 and 2006, with mixture of bare-metal stents and predominant use of first-generation drug-eluting stents for treatment with PCI, which might limit the generalizability of our findings to the contemporary clinical practice. In addition, because the study was performed in Korea, the direct application of observed findings to other ethnic groups or countries might be limited. Fourth, unfortunately, medical treatment data during the follow-up period were not exactly assessed. Concurrent clinical practice guidelines, such as target blood pressure, lipid profile, and other optimal medical therapy, have changed over time and could affect the observed outcomes in this study. Finally, considering the relatively small number of patients and clinical events and the inherent nature of the observational registry, the relative treatment effect differences of CABG or PCI by sex should be further investigated in large-sized clinical trials and meta-analyses of individual patient-level data.

CONCLUSIONS

In this extended follow-up of patients who underwent PCI or CABG for LMCA disease, differential treatment effect was observed between women and men. The adjusted 10-year mortality rates and serious composite outcomes were similar without time-dependent changes between the CABG and PCI arms in men. In contrast, CABG was more beneficial than PCI in women with regard to a reduction of mortality rates and composite outcomes, especially in the late period (beyond at least 1 year) of long-term follow-up. Because the study was observational and vulnerable to selection bias, the results should be considered only hypothesis generating, highlighting the need for further large-sized research.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S3
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Clinical Characteristics, Stratified by Sex.

Characteristics	Women (N=631)	Men (N=1,609)	p Value
Wave			0.745
BMS era (Jan 2003 – May 2006)	212 (33.6)	554 (34.4)	
DES era (May 2007 – June 2006)	419 (66.4)	1055 (65.6)	
Age, yr	61.6 ± 11.7	62.3 ± 10.1	0.179
Diabetes	200 (31.7)	522 (32.4)	0.772
Hypertension	345 (54.7)	763 (47.4)	0.002
Dyslipidemia	219 (34.7)	467 (29.0)	0.010
Current smoker	37 (5.9)	584 (36.3)	<0.001
Previous PCI	85 (13.5)	240 (14.9)	0.420
Previous MI	41 (6.5)	180 (11.2)	0.001
Previous CHF	16 (2.5)	49 (3.0)	0.612
Chronic lung disease	8 (1.3)	37 (2.3)	0.162
Cerebrovascular disease	34 (5.4)	127 (7.9)	0.048
Peripheral arterial disease	12 (1.9)	66 (4.1)	0.015
Renal failure	16 (2.5)	48 (3.0)	0.666
Ejection fraction	60.9 ± 10.3	58.4 ± 11.8	<0.001
Clinical indication			0.039
Silent ischemia	9 (1.4)	49 (3.0)	
Chronic stable angina	160 (25.4)	419 (26.0)	
Unstable angina	410 (65.0)	973 (60.5)	
NSTEMI	52 (8.2)	168 (10.4)	
Left main disease location			<0.001
Ostium or shaft	348 (55.2)	735 (45.7)	
Distal bifurcation	283 (44.8)	874 (54.3)	
Extent of diseased vessel			0.001
Left main only	129 (20.4)	220 (13.7)	
Left main plus 1-vessel	102 (16.2)	281 (17.5)	

disease			
Left main plus 2-vessel disease	148 (23.5)	438 (27.2)	
Left main plus 3-vessel disease	252 (39.9)	670 (41.6)	
Restenotic lesion	19 (3.0)	27 (1.7)	0.066

Values are n (%) or mean ± SD.

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CHF = congestive heart failure; DES = drug-eluting stent; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

Table S2. Procedural or Operative Characteristics, Stratified by Sex.

Characteristics	Women (N=631)	Men (N=1,609)	p Value
PCI Procedures	**(N=323)**	**(N=779)**	
Total stent number in LMCA	1.2 ± 0.4	1.2 ± 0.5	0.269
Total stent length in LMCA	25.4 ± 20.0	29.1 ± 20.9	0.006
Total stent number per patient	1.9 ± 1.2	2.0 ± 1.1	0.198
Average stent diameter in LMCA, mm	3.5 ± 0.5	3.5 ± 0.4	0.584
Type of stent			0.850
BMS	95 (29.4)	223 (28.6)	
DES	228 (70.6)	556 (71.4)	
Sirolimus-eluting stents	177 (54.8)	436 (56.0)	
Paclitaxel-eluting stents	51 (15.8)	120 (15.4)	
Intravascular ultrasound-guided PCI	245 (75.9)	574 (73.7)	0.500
Bifurcation treatment			0.152
Single-stent technique	271 (83.9)	623 (80.0)	
Two-stent technique	52 (16.1)	156 (20.0)	
CABG Procedures	**(N=308)**	**(N=830)**	
Number of grafts per patient	2.7 ± 0.9	2.9 ± 1.0	0.004
Number of arterial grafts	2.1 ± 0.9	2.2 ± 0.9	0.006
Number of vein graft	0.7 ± 0.8	0.7 ± 0.8	0.802
Use of left internal mammary artery	294 (95.5)	815 (98.2)	0.017
Off-pump surgery	126 (40.9)	352 (42.4)	0.698

CABG, coronary-artery bypass grafting; LMCA, left main coronary artery; PCI percutaneous coronary intervention.

Table S3. Crude and Adjusted Risks for 10-Year Outcomes, Stratified by Sex.

	Unadjusted Outcomes				Adjusted Outcomes with the Use of IPTW			
	Crude event rates at 10 years, n (%)				Adjusted event rates at 10 years, %			
	Women	Men	HR (95% CI)*	P	Women	Men	HR (95% CI)*	P
Death	119 (18.9)	378 (23.8)	0.78 (0.64-0.96)	0.019	20.8	24.4	0.85 (0.7-1.04)	0.111
Death, Q-wave MI, or stroke	139 (22.1)	422 (26.5)	0.82 (0.68-0.99)	0.042	23.5	26.7	0.88 (0.73-1.06)	0.186
TVR	75 (12.6)	207 (14.0)	0.91 (0.7-1.18)	0.475	12.4	14.4	0.87 (0.67-1.14)	0.314

*HR is the risk of different outcomes for women compared with men. †P value for interaction between sex (women vs. men) and revascularization strategy (PCI vs. CABG).

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio, IPTW = Inverse-Probability Treatment Weighting, MI = myocardial infarction; PCI = percutaneous coronary intervention; TVR = target-vessel revascularization; other abbreviations as in Table 1.

Figure S1. Crude 10-Year Kaplan-Meier Curves for Clinical Events, stratified by sex.

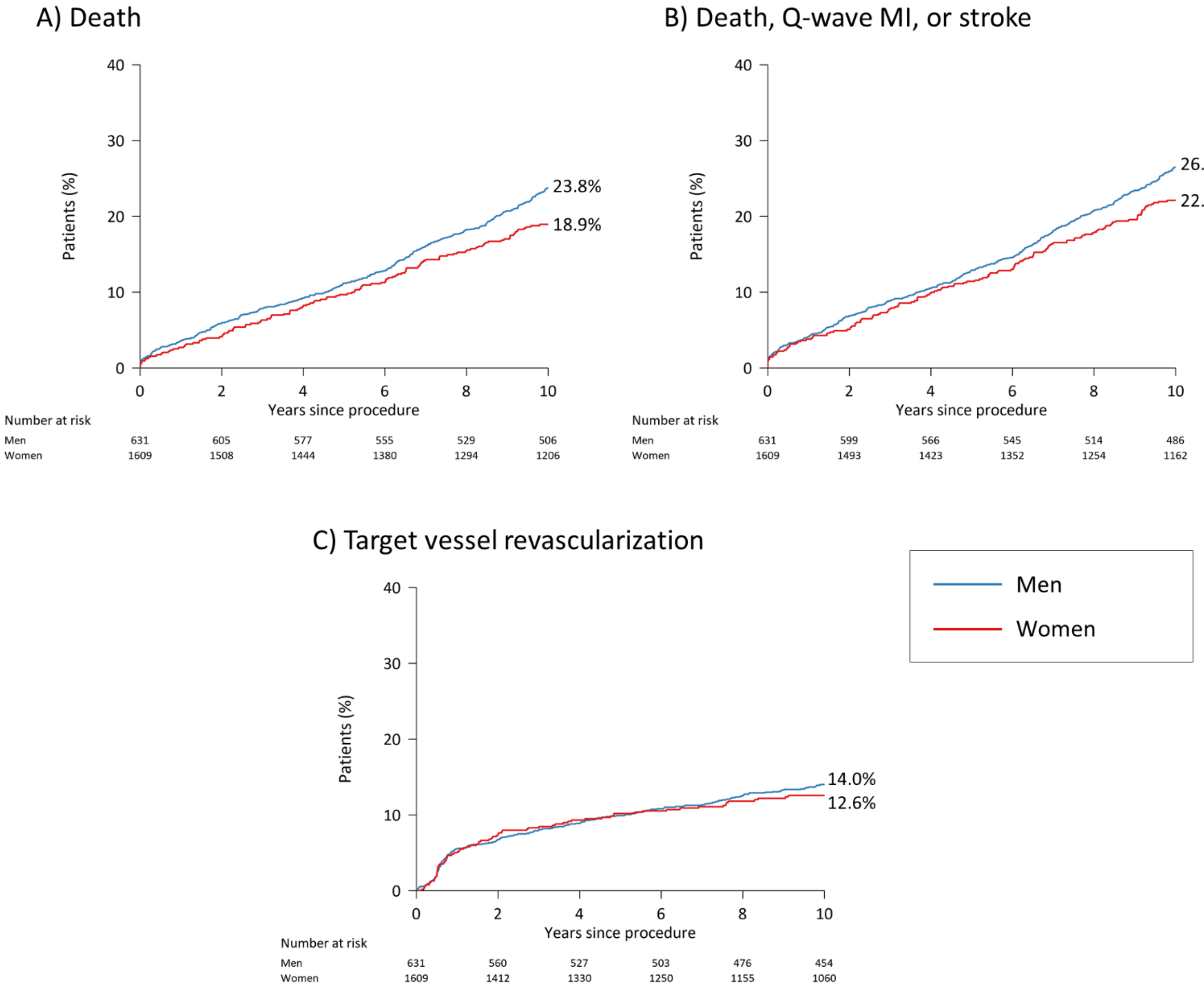

Figure S2. Adjusted 10-Year Kaplan-Meier Curves for Clinical Events, stratified by sex.