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Sex differences in left main coronary artery stenting: Different characteristics but similar outcomes for women compared with men

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ABSTRACT

Background: The clinical outcomes for women compared with men undergoing left main PCI were sparse. We compared the characteristics and long-term outcomes in women versus men after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) for unprotected left main CAD.
Methods: We identified 2328 patients (545 women; 1783 men) with unprotected left main CAD who received PCI with DES between January 2007 and December 2013 in the Interventional Cardiology Research In-cooperation Society-left MAIN revascularization (IRIS-MAIN) registry. The primary outcome was a composite of death from any cause, myocardial infarction, or stroke.
Results: The median follow-up time was 2.9 years (interquartile range: 1.0–4.1 years). Women were older, had a higher incidence of insulin-requiring diabetes mellitus and hypertension, and more commonly presented with acute coronary syndrome than men. Left main ostial lesion was more common in women, whereas left main bifurcation lesion with more extensive CAD was more common in men. The incidence of primary outcome was similar between the two groups (10.8% vs. 10.8%, respectively, log-rank $p = 0.587$). The results were similar after adjustment for baseline variables and consistent across major subgroups. The need for target lesion revascularization was significantly higher in women than in men (8.8% vs. 5.7%, respectively, $p < 0.05$) but the sex bias was not confirmed after adjusting for confounders.
Conclusions: Women, as compared to men, had different clinical and lesion characteristics but similar long-term outcomes after PCI with DES for left main CAD.

1. Introduction

Coronary artery bypass grafting (CABG) has been considered as the standard of care for left main coronary artery disease (CAD) [1–5]. Several randomized trials demonstrated that percutaneous coronary intervention (PCI) with drug-eluting stents (DES) showed favorable and similar long-term clinical outcomes compared with concurrent CABG [2,5]. Despite the safety and efficacy of left main PCI, however, only 24% of patients enrolled in each trial were women, and thereby data for women undergoing left main PCI were sparse [2,5]. It has been shown that women had different risk factors, presentations, atherosclerotic involvement, and outcomes compared with men in coronary artery disease [6–8]. However, little is known about sex differences in left main PCI.

In the present study, we investigated the sex differences in risk profile and long-term prognosis among patients with left main PCI with DES using the Interventional Research Incorporation Society-Left MAIN Revascularization (IRIS-MAIN) registry.

2. Methods

The study patients were recruited from the IRIS-MAIN registry (ClinicalTrials.gov number, NCT01341327). The registry was designed to evaluate the real-world outcomes of left main CAD and register all consecutive patients with left main CAD, defined as diameter stenosis >50% on coronary angiogram, between January 2007 and December 2013 from 50 academic and community hospitals in Asian countries (China, India, Indonesia, Japan, Malaysia, South Korea, Taiwan, and Thailand). All women and men undergoing PCI with DES were enrolled in the current analysis. The study protocol was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all patients before entering the study.

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PCI for left main CAD and other coronary artery diseases was performed according to the standard practical guidelines, as previously described [1,9]. The application of predilation, intravascular ultrasound, and intra-aortic balloon pumps, and the selection of a specific type of implanted stent, were at the discretion of the operator. Periprocedural anticoagulation was administered according to standard regimens. All patients undergoing PCI received a loading dose of aspirin and adenosine diphosphate (ADP) receptor antagonists before or during the intervention. After the procedure, aspirin was continued indefinitely and ADP receptor antagonists were prescribed for at least 12 months.

The primary outcome was a composite of death from any cause, myocardial infarction (MI), or stroke. Death was classified as either cardiac or non-cardiac death, with all death considered cardiac unless an unequivocal non-cardiac cause could be established. MI was defined as follows: 1) if occurring within 48 h after the index treatment, an increase in the creatine kinase–myocardial band (CK-MB) concentration of >5 times the upper reference limit with any of the followings: new pathological Q waves or new bundle branch block, new graft or new native coronary occlusion documented on angiography, and new regional wall motion abnormality or loss of viable myocardium on imaging studies [10]; 2) if occurring 48 h after the index treatment, an increase in the CK–MB concentration above the upper reference limit with ischemic symptoms or signs [11]. Stroke, as indicated by neurological deficits, was confirmed by a neurologist on the basis of imaging modalities. e. Stent thrombosis was evaluated according to the Academic Research Consortium definitions [12]. Repeat revascularization included any type of percutaneous or surgical revascularization procedures, regardless of whether the procedure was performed on a target lesion, a non-target lesion or a new lesion. All events were based on clinical diagnoses assigned by the patient's physician and were centrally adjudicated by an independent group of clinicians.

Baseline variables and outcome data were collected by a specialized personnel using a dedicated electronic case report form (e-CRF) at each center. Monitoring and verification of registry data were periodically performed in participating hospitals by the staff of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea). Clinical follow-up was conducted during hospitalization and at 30 days, 6 months, and 12 months and every 6 months thereafter. At each visit, data pertaining to the patient's clinical status, all interventions, and adverse events were recorded.

Continuous variables were expressed as means ± one standard deviation; categorical variables were presented as counts and percentages. Continuous variables were compared using Student's *t*-test; categorical variables were compared using χ^2 statistics or Fisher's exact test, as appropriate. Cumulative probabilities for the outcomes were estimated by the Kaplan-Meier method, and the Kaplan-Meier curves of women and men groups were compared using the log-rank test. Multivariable Cox proportional hazard analysis was performed to appraise the sex differences simultaneously adjusting for all variables with significant ($p < 0.05$) or borderline significant ($p \leq 0.10$) association with sex at univariate analysis and including, by default, diabetic status as well as disease location(s) in the left main CAD. The results of these analyses were reported as hazard ratios (HRs) with 95% confidence intervals (CI). All computation was performed using SPSS 11.0 (SPSS, Chicago, IL, USA).

3. Results

We identified 2328 patients with left main CAD (women: $n = 545$, men: $n = 1783$) among 5134 patients with PCI with DES enrolled in the IRIS-MAIN registry. In the comparison with men, women were older and had more hypertension insulin-requiring diabetes mellitus and more frequently women presented with acute coronary syndrome (ACS). By contrast, women were less likely to be ever-smokers or to have history of previous MI, peripheral vascular disease, and chronic pulmonary disease. In addition, left main ostial lesion was more common in women, whereas left main bifurcation lesion with more extensive CAD (left main plus 3 vessel disease) was more common in men. Therefore, the left main stent only strategy was more common in women and more complex 2-stent technique in men. The total number of stents used was higher in men and total stent length was longer in men. In both groups, IVUS-guided PCI was as high as 80%. Patients were well treated with optimal medication without between-group differences (Tables 1 and 2).

During the median follow-up time of 2.9 years (interquartile range: 1.0–4.1 years), there were 199 deaths from any cause (8.1% in women vs. 8.7% in men, $p = 0.651$), 45 MIs (2.0% in women vs. 1.9% in men, $p = 0.869$), and 38 strokes (1.8% in women vs. 1.6% in men, $p = 0.670$). The incidence of primary outcome was 10.8% in women, and 10.8% in men ($p = 0.970$). After multivariate adjustment for the baseline differences between the two groups, the risk of the primary outcome was also similar. Subgroup analysis revealed similar rates of primary outcome between the two groups according to the extent and severity of left main CAD and the extent of CAD (Fig. 2). Individual

Table 1
Baseline clinical characteristics.

Variables	Women ($n = 545$)	Men ($n = 1783$)	*p*-Value
Age, years	64.7 ± 11.8	63.3 ± 10.5	0.016
Body mass index, kg/m^2	24.7 ± 3.6	24.4 ± 2.8	0.054
Atrial fibrillation	9 (1.7)	52 (2.9)	0.090
Hypertension	376 (69.0)	1073 (60.2)	<0.001
Diabetes	185 (33.9)	602 (33.8)	0.937
Insulin treated diabetes	41 (7.5)	91 (5.1)	0.033
Dyslipidemia	269 (49.4)	862 (48.3)	0.679
Current smoking	25 (4.6)	541 (30.3)	<0.001
Previous myocardial infarction	27 (5.0)	144 (8.1)	0.014
Previous coronary intervention	98 (18.0)	290 (16.3)	0.347
Previous stroke	43 (7.9)	152 (8.5)	0.640
Previous heart failure	15 (2.8)	36 (2.0)	0.306
Family history of coronary artery disease	49 (9.0)	182 (10.2)	0.406
Peripheral vascular disease	13 (2.4)	88 (4.9)	0.011
Chronic pulmonary disease	3 (0.6)	54 (3.0)	0.001
Chronic renal failure	23 (4.2)	69 (3.9)	0.713
Shock at presentation	3 (0.6)	10 (0.6)	>0.99
Clinical diagnosis			
Stable angina or silent ischemia	215 (39.4)	808 (45.3)	0.016
Acute coronary syndrome	330 (60.6)	975 (54.7)	0.016
Lesion location			
Ostium	211 (38.7)	427 (23.9)	<0.001
Shaft	130 (23.9)	473 (26.5)	0.212
Bifurcation	319 (58.5)	1202 (67.4)	<0.001
Disease extent			
Left main only	90 (16.5)	175 (9.8)	<0.001
Left main plus 1 vessel disease	116 (21.3)	456 (25.6)	0.042
Left main plus 2 vessel disease	202 (37.1)	623 (34.9)	0.364
Left main plus 3 vessel disease	137 (25.1)	529 (29.7)	0.041
Left ventricular ejection fraction, %	60.8 ± 9.1	59.2 ± 9.7	0.004
Medication at discharge			
Aspirin	537 (98.7)	1737 (97.6)	0.127
Thienopyridines	527 (96.9)	1698 (95.4)	0.134
Cilostazole	171 (31.5)	546 (30.8)	0.751
Beta blocker	291 (54.7)	974 (55.5)	0.736
Calcium channel blocker	255 (48.4)	786 (45.5)	0.238
ACEi or ARB	198 (37.1)	658 (37.9)	0.728
Statin	239 (57.2)	718 (55.2)	0.476

Categorical variables: Chi-square test or Fisher's exact test.
Continuous variables: *t*-test.
Data are mean ± SD or number (percentage).
ACEi = angiotensin-converting enzyme inhibitor; ADP = adenosine diphosphate; ARB = angiotensin II receptor blocker.

Table 2
Procedural characteristics.

Variables	Women ($n = 545$)	Men ($n = 1783$)	*p* value
Use of intravascular ultrasound	438 (80.4)	1423 (79.8)	0.776
Stent technique			
Left main stent only	142 (26.1)	303 (17.0)	<0.001
Simple cross over technique	295 (54.1)	1048 (58.8)	0.055
2-stent technique	108 (19.8)	432 (24.2)	0.033
Total number of treated lesion	1.6 ± 0.8	1.7 ± 0.9	0.114
Total stent number per patient	2.1 ± 1.2	2.3 ± 1.3	0.004
Total stent length per patient, mm	49.8 ± 33.8	55.3 ± 35.5	0.001
Stent diameter, mm	3.4 ± 0.4	3.5 ± 0.3	0.004
Maximal stent pressure, mm Hg	15.9 ± 4.2	16.2 ± 4.6	0.264
Maximal stent diameter, mm	3.8 ± 0.5	3.9 ± 0.5	0.001
Final kissing balloon	163 (29.9)	609 (34.2)	0.065
Complete revascularization	388 (71.2)	1257 (70.5)	0.756
Hemodynamic support[a]	24 (4.4)	91 (5.1)	0.509
Stent type			
1st generation drug-eluting stent	156 (28.8)	441 (24.9)	0.067
2nd generation drug-eluting stent	385 (71.2)	1330 (75.1)	0.067

Categorical variables: Chi-square test or Fisher's exact test.
Continuous variables: *t*-test.
Data are mean ± SD or number (percentage).
[a] Insertion of intra-aortic balloon pump or extracorporeal membrane oxygenation.

Table 3
Clinical events at follow-up.

	Incidence			Univariate analysis			Multivariable analysis		
	Women ($N = 545$)	Men ($N = 1783$)	p value	Unadjusted HR	95% CI	p value	Adjusted HR[b]	95% CI	p value
Primary outcome[a]	59 (10.8)	192 (10.8)	0.970	0.922	0.689–1.235	0.587	0.837	0.578–1.211	0.344
Death from any cause	44 (8.1)	155 (8.7)	0.651	0.843	0.603–1.179	0.318	0.808	0.528–1.235	0.324
Cardiac death	36 (6.6)	122 (6.8)	0.847	0.875	0.603–1.270	0.483	0.805	0.496–1.308	0.381
Myocardial infarction	11 (2.0)	34 (1.9)	0.869	0.974	0.493–1.923	0.938	0.788	0.343–1.811	0.575
Stroke	10 (1.8)	28 (1.6)	0.670	1.094	0.531–2.253	0.808	0.482	0.167–1.390	0.177
Definite/probable ST	2 (0.4)	17 (1.0)	0.276	0.352	0.081–1.525	0.163	0.335	0.037–3.033	0.330
Any repeat revascularization	61 (11.2)	149 (8.4)	0.043	1.247	0.936–1.663	0.132	1.155	0.802–1.662	0.439
Target lesion	48 (8.8)	102 (5.7)	0.010	1.457	1.045–2.032	0.026	1.310	0.864–1.986	0.203
Target vessel	52 (9.5)	123 (6.9)	0.041	1.277	0.933–1.747	0.127	1.189	0.802–1.763	0.389
New lesion	13 (2.4)	46 (2.6)	0.800	0.888	0.491–1.607	0.695	0.746	0.330–1.684	0.480

Univariate and multivariable analysis: Cox proportional hazards model.
CI = confidence interval; HR = hazard ratio; ST = stent thrombosis.
[a] Composite of death from any cause, myocardial infarction, or stroke.
[b] Adjusting for age, body mass index, current smoking, hypertension, previous myocardial infarction, insulin treated diabetes, peripheral vascular disease, chronic pulmonary disease, clinical diagnosis, lesion location, disease extent, left ventricular ejection fraction, stent technique, total stent number per patient, total stent length per patient, stent diameter on average, final kissing balloon, and stent type.

components of the primary outcome were not significantly different between the two groups (Table 3 and Fig. 1). However, women more frequently needed target lesion and target vessel revascularization ($p < 0.05$) (Table 3).

4. Discussion

In this all-comer large, international, multicenter registry, women, as compared to men, had different clinical and lesion characteristics.

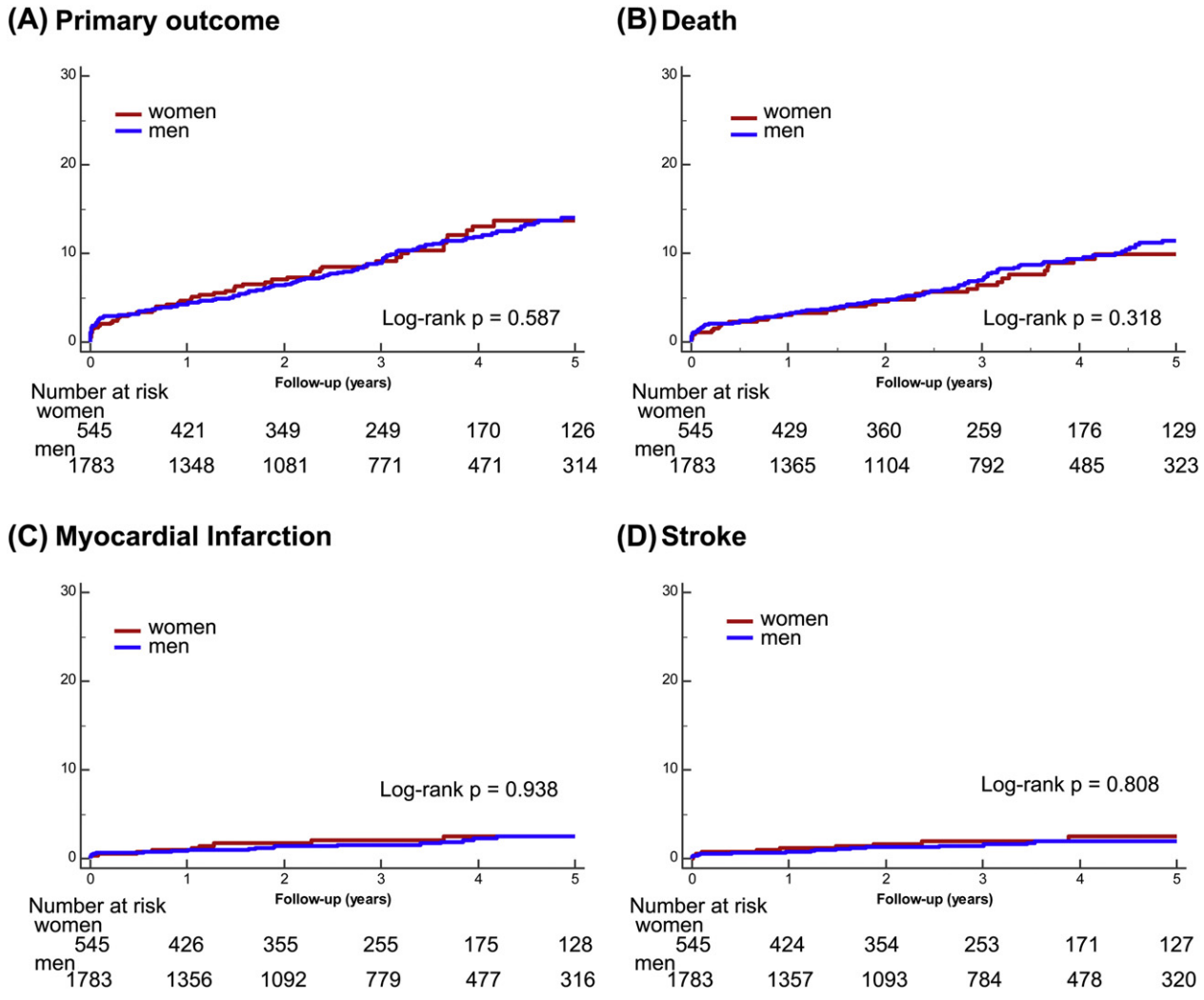

Fig. 1. Kaplan-Meier curves for each end point comparing women and men with percutaneous coronary intervention with drug-eluting stent for left main coronary artery disease. (A) Primary outcome, (B) death from any causes, (C) myocardial infarction, and (D) stroke. The p values were calculated using the log-rank test for all available follow-up data.

Women had more ostial lesions, less bifurcation lesions, and less extent of multivessel CAD. Therefore, a single stent cross-over technique was more frequently used in women with fewer numbers of DES. Despite differences in clinical profiles, anatomic complexity of CAD, and stenting techniques, women undergoing stenting for left main CAD showed similar rates of a composite of death, MI or stroke compared with men during follow-up.

Women have been linked to a poorer prognosis after coronary revascularization with higher risk of death and MI attributed to older age, a greater prevalence of comorbid conditions, and a higher CAD risk profile [13,14]. In a recent trial, women undergoing PCI for left main CAD more often presented with worse risk factors (older age, diabetes mellitus, hypertension, ACS, and consequently higher EuroSCORE), but these sex biases were not confirmed after adjusting for confounders [15]. A recent sub-study of the SYNTAX trial has shown that female gender was an independent correlate of 4-year mortality in the PCI arm even though adjustments for risk factors, including age and the SYNTAX score [16]. The main difference being that women in the SYNTAX trial had more complex baseline coronary disease - all three-vessel or left main CAD - compared with 25% of left main plus three-vessel disease in women from this trial [5]. In the Milan and New-Tokyo (MITO) Registry (1026 consecutive patients with de novo left main disease undergoing PCI using DES), women treated for left main disease had greater comorbidity and more complex lesions than men, and this resulted in a higher incidence of TLR, MI and cardiac death observed in women [17]. However, these results were not supported after adjustment for the propensity score. Both of these studies showed more severe clinical risk and lesion severity compared to this trial. The difference in baseline is thought to be the difference in outcome between men and women. Nonetheless, there was no difference after adjustments for risk factors and lesion severity. In the severe subset of left main CAD, even if several recent prospective multicenter randomized studies confirmed CABG to be the standard of care, no analyses were ever conducted focusing on sex differences especially with DES-based PCI on left main CAD [2,5]. Actually, women are usually older and have more comorbidities when they present with coronary artery disease. Moreover, they usually experience a delay in the clinical diagnosis, which may be readily translated into increased procedural morbidity and mortality even after coronary revascularization is eventually performed [18]. In this trial, the need for any repeat revascularization including target lesion and target vessel revascularization was significantly higher in women than in men (8.8% vs. 5.7%, $p = 0.010$ and 9.5% vs. 6.9%, $p = 0.041$, respectively). In women, 1st generation DES tended to be used more often than men, and this could contribute to more target lesion and target vessel revascularization in women. However, the rate of 1st DES and 2nd DES use was not different between women and men with TLR (1st DES: 43.8% vs. 50.0%, $p = 0.475$, respectively) and TVR (1st DES: 44.2% vs. 48.0%, $p = 0.651$, respectively). Furthermore, these sex biases were not confirmed after adjusting for confounders.

This study supports that a sex bias does not exist when underlying confounding factors (i.e., differences in baseline and procedural risk

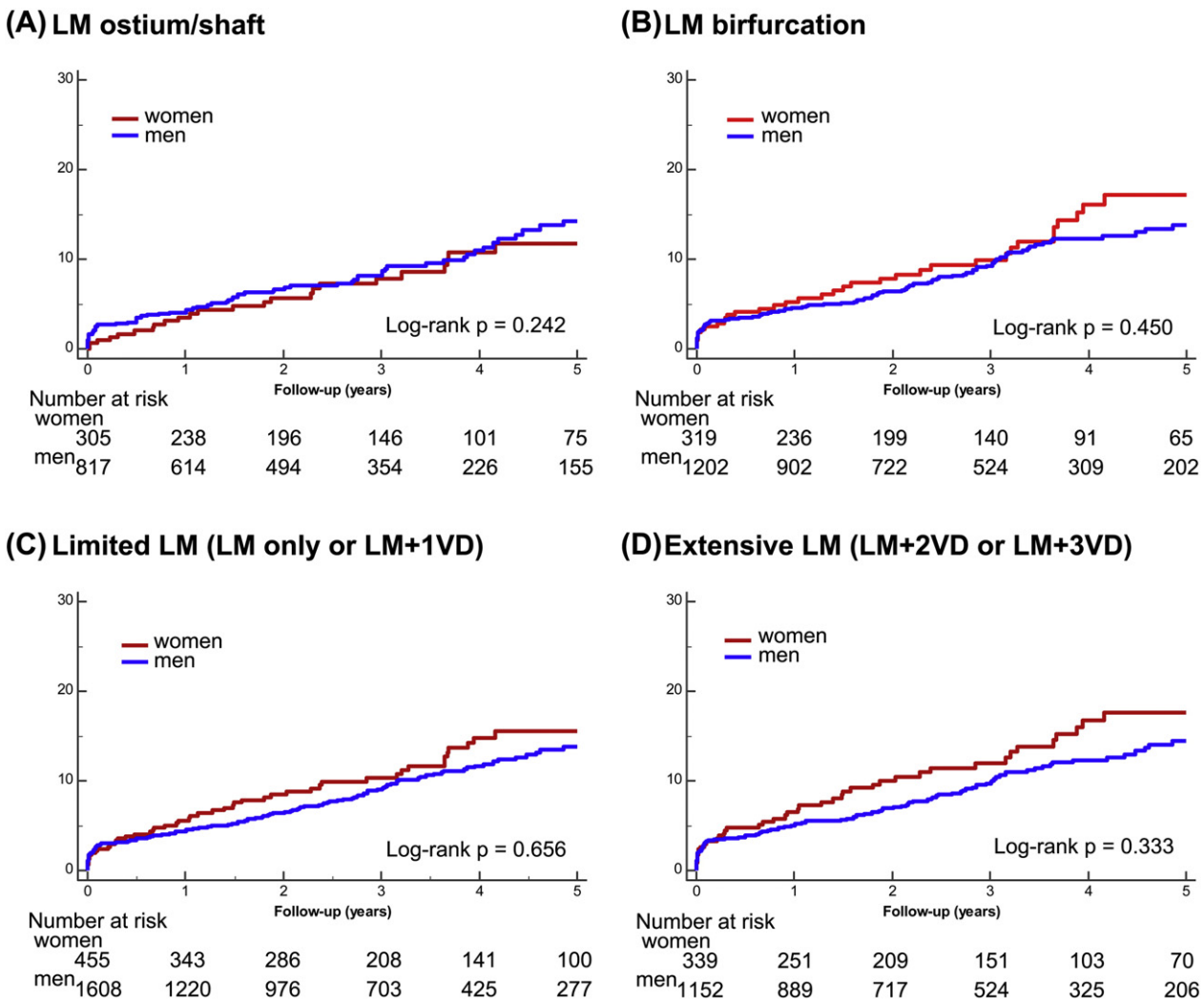

Fig. 2. Primary outcome according to subgroups. (A) Left main ostium or shaft, (B) left main bifurcation, (C) left main only or with 1-vessel disease (limited LM disease), and (D) left main only or with 2-vessel disease or 3-vessel disease (extensive LM disease). The *p* values were calculated using the log-rank test for all available follow-up data.

factors) are considered. No significant difference in long-term outcomes emerged among sex after multivariable adjustment. This international multicenter study reflects a current practice in the percutaneous management for all-comers with left main CAD as all high-volume interventional cardiology centers participated in data collection.

In subgroup analysis of this study, we compared the primary outcome according to the severity of left main CAD lesion between women and men. There was no difference in the primary outcome between patients with left main CAD ostium or shaft versus left main bifurcation. Also similar results were found in patients with different severity of combined multivessel disease (Fig. 2). These results showed that women undergoing PCI with DES for left main CAD have not worse outcome compared to men even though the combined lesion severity was severe.

An interesting finding in this study was that CAD severity in women was lower than in men although women were older and had a higher CAD risk profile including hypertension, insulin dependent diabetes mellitus, and ACS presentations. However, it was not clear whether this could explain that the primary outcome in women was not higher than in men. In a large PCI registry study published recently, women had fewer numbers of diseased vessels and left main disease although they had greater body mass index, higher prevalence of diabetes mellitus as well as hypertension, and more ACS presentations [19]. When patients aged 50 and over were followed up for 5 years in a study, there was no difference in major adverse outcomes (death, MI, and revascularization) between men and women [19]. Once CAD has developed, the prevalence of all risk factors except smoking is typically greater among women than among age-matched men, given that women with a cluster of risk factors are more prone to CAD [20]. Because women show a delayed onset of CAD and less extent of epicardial atherosclerosis compared to men, sex differences are likely to be reflected in early presentation of CAD, as well as comorbidities, diagnosis, management, and treatment. The causes of this difference are worth further investigation. In apparent contrast with the delayed average onset of CAD and lesser extent of epicardial atherosclerosis in women, sex differences are likely to be reflected on early presentation, as well as in the mechanisms, comorbidities, diagnosis, management, and response to treatment. The causes of this difference deserve further investigation.

Our study has several limitations that are inherent to its observational design. First, owing to the nature of the study design, we cannot account for a bias in patient selection for the index PCI and for subsequent repeat angiography and intervention. However, a nonselected, nonclinical trial-based population was enrolled in the IRIS-MAIN Registry, which was reflective of real-world cardiovascular treatment. Second, lack of information on medical compliance after hospital discharge could affect the results. Third, it was not possible to obtain data on patients undergoing CABG because of failed PCI, as this study population included only those actually undergoing PCI with DES. Finally, because Asian patients were included in this study, the results could not be applied to non-Asian people.

5. Conclusions

Among patients undergoing PCI for left main CAD, women had different clinical and lesion characteristics compared with men. However, women undergoing PCI for left main CAD showed similarly favorable long-term outcomes as in men. Thus, despite the important role of a different baseline risk profile in prognosis and the severity of angiographic diseases among sex, DES-based PCI for left main CAD brings favorable long-term clinical consequences in women as well as in men.

Disclosures

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