Korean Circ J. 2025 Jan;55(1):5-16
https://doi.org/10.4070/kcj.2024.0172
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Original Research

Check for updates

Sex Differences in Procedural Characteristics and Clinical Outcomes Among Patients Undergoing Bifurcation PCI

OPEN ACCESS

Received: May 25, 2024
Revised: Jul 28, 2024
Accepted: Aug 27, 2024
Published online: Oct 11, 2024

Correspondence to
Bon-Kwon Koo, MD, PhD
Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: bkkoo@snu.ac.kr

ORCID iDs
Hyun Jin Ahn
https://orcid.org/0000-0001-5920-1585
Francesco Bruno
https://orcid.org/0000-0003-0019-0273
Jeehoon Kang
https://orcid.org/0000-0002-9078-2231
Doyeon Hwang
https://orcid.org/0000-0002-0215-5319
Han-Mo Yang
https://orcid.org/0000-0002-1548-2351
Jung-Kyu Han
https://orcid.org/0000-0002-0016-0747
Leonardo De Luca
https://orcid.org/0000-0002-8552-1272
Ovidio de Filippo
https://orcid.org/0000-0002-4915-9501

Hyun Jin Ahn, MD[1], Francesco Bruno, MD[2], Jeehoon Kang, MD[1], Doyeon Hwang, MD[1], Han-Mo Yang, MD[1], Jung-Kyu Han, MD[1], Leonardo De Luca, MD[3], Ovidio de Filippo, MD[2], Alessio Mattesini, MD[4], Kyung Woo Park, MD[1], Alessandra Truffa, MD[5], Wojciech Wanha, MD[6], Young Bin Song, MD[7], Sebastiano Gili, MD[8], Woo Jung Chun, MD[9], Gerard Helft, MD[10], Seung-Ho Hur, MD[11], Bernardo Cortese, MD[12], Seung Hwan Han, MD[13], Javier Escaned, MD[14], Alaide Chieffo, MD[15], Ki Hong Choi, MD[7], Guglielmo Gallone, MD[2], Joon-Hyung Doh, MD[16], Gaetano De Ferrari, MD[2], Soon-Jun Hong, MD[17], Giorgio Quadri, MD[18], Chang-Wook Nam, MD[11], Hyeon-Cheol Gwon, MD[7], Hyo-Soo Kim, MD[1], Fabrizio D'Ascenzo, MD[2], and Bon-Kwon Koo, MD, PhD[1]

[1]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea
[2]Department of Internal Medicine, Città della Salute e della Scienza, Turin, Italy
[3]Department of Cardiosciences, San Camillo-Forlanini Hospital, Roma, Italy
[4]Cardiologia Interventistica AOU Careggi, Florence, Italy
[5]Division of Cardiology, Cardinal Massaia Hospital, Asti, Italy
[6]Department of Cardiology, Medical University of Silesia, Katowice, Poland
[7]Department of Cardiology Sungkyunkwan University, Samsung Medical Center, Seoul, Korea
[8]Division of Cardiology, Ospedale Monzino, Milan, Italy
[9]Department of Internal Medicine, Samsung Changwon Hospital, Changwon, Korea
[10]Pierre and Marie Curie University, Paris, France
[11]Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea
[12]Scientific Committee Fondazione Ricerca e Innovazione Cardiovascolare and DCB Academy, Milano, Italy
[13]Department of Internal Medicine, Gachon University Gil Hospital, Incheon, Korea
[14]Hospital Clínico San Carlos, IDISSC, and Universidad Complutense de Madrid, Madrid, Spain
[15]Division of Cardiology, Ospedale San Raffaele, Milan, Italy
[16]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea
[17]Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Seoul, Korea
[18]Division of Cardiology, Ospedale di Rivoli, Rivoli, Italy

AUTHOR'S SUMMARY

The between-sex differences in coronary artery disease are well known; however, the impact of sex on outcomes after percutaneous coronary intervention (PCI) is controversial. Moreover, sex differences in bifurcation lesions and the effect of sex after bifurcation PCI have not yet been discussed. In this study, women undergoing bifurcation PCI showed anatomical characteristics similar to those of their male counterparts. In addition, when they underwent equal procedural strategies, the long-term outcomes were comparable.

Alessio Mattesini
https://orcid.org/0000-0001-8697-2692
Kyung Woo Park
https://orcid.org/0000-0003-2432-4432
Alessandra Truffa
https://orcid.org/0000-0002-1197-7162
Wojciech Wanha
https://orcid.org/0000-0003-1220-9496
Young Bin Song
https://orcid.org/0000-0003-3986-9152
Sebastiano Gili
https://orcid.org/0000-0002-0542-0448
Woo Jung Chun
https://orcid.org/0000-0002-4053-0474
Gerard Helft
https://orcid.org/0000-0003-0389-9122
Seung-Ho Hur
https://orcid.org/0000-0002-3895-1915
Bernardo Cortese
https://orcid.org/0000-0002-5808-7810
Seung Hwan Han
https://orcid.org/0000-0002-7315-7557
Javier Escaned
https://orcid.org/0000-0003-4932-0112
Alaide Chieffo
https://orcid.org/0000-0002-3505-9112
Ki Hong Choi
https://orcid.org/0000-0001-7511-9581
Guglielmo Gallone
https://orcid.org/0000-0001-8011-6844
Joon-Hyung Doh
https://orcid.org/0000-0001-7966-9564
Gaetano De Ferrari
https://orcid.org/0000-0003-4940-0876
Soon-Jun Hong
https://orcid.org/0000-0003-4832-6678
Giorgio Quadri
https://orcid.org/0000-0003-4164-2758
Chang-Wook Nam
https://orcid.org/0000-0002-3370-5774
Hyeon-Cheol Gwon
https://orcid.org/0000-0002-4902-5634
Hyo-Soo Kim
https://orcid.org/0000-0003-0847-5329
Fabrizio D'Ascenzo
https://orcid.org/0000-0002-6646-9317
Bon-Kwon Koo
https://orcid.org/0000-0002-8188-3348

Trial Registration
ClinicalTrials.gov Identifier: NCT03068494

Funding
This study was supported by grants HI19C0481 and HC19C0305 from the Patient-Centered Clinical Research Coordinating Center funded by the Ministry of Health & Welfare and by grant RS-2023-00215667 from the Ministry of

ABSTRACT

Background and Objectives: The risk profiles, procedural characteristics, and clinical outcomes for women undergoing bifurcation percutaneous coronary intervention (PCI) are not well defined compared to those in men.
Methods: COronary BIfurcation Stenting III (COBIS III) is a multicenter, real-world registry of 2,648 patients with bifurcation lesions treated with second-generation drug-eluting stents. We compared the angiographic and procedural characteristics and clinical outcomes based on sex. The primary outcome was 5-year target lesion failure (TLF), a composite of cardiac death, myocardial infarction, and target lesion revascularization.
Results: Women (n=635, 24%) were older, had hypertension and diabetes more often, and had smaller main vessel and side branch reference diameters than men. The pre- and post-PCI angiographic percentage diameter stenoses of the main vessel and side branch were comparable between women and men. There were no differences in procedural characteristics between the sexes. Women and men had a similar risk of TLF (6.3% vs. 7.1%, p=0.63) as well as its individual components and sex was not an independent predictor of TLF. This finding was consistent in the left main and 2 stenting subgroups.
Conclusions: In patients undergoing bifurcation PCI, sex was not an independent predictor of adverse outcome.

Trial Registration: ClinicalTrials.gov Identifier: NCT03068494

Keywords: Sex difference; Percutaneous coronary intervention; Coronary artery disease; Coronary vessels; Drug-eluting stents

INTRODUCTION

Cardiovascular disease is a leading cause of death in women[1]; it is well known that women differ from men in not only coronary anatomy but also pathophysiology, presentation, and prognosis.[2] Women have smaller coronary arteries, thinner myocardial walls, and higher resting coronary blood flow.[3][4] Plaque characteristics are different in women as well, resulting in a higher incidence of nonobstructive coronary artery disease (CAD); moreover, plaque erosion is considered the leading cause of thrombus formation compared to plaque rupture in men.[5] These findings strongly suggest the need for sex-specific diagnostic and therapeutic approach to CAD.[6] However, the impact of sex on clinical outcomes after percutaneous coronary intervention (PCI) remains controversial.[7]

Coronary bifurcation lesions represent a challenging subset of lesions in the field of coronary intervention.[8] However, sex-based differences after bifurcation PCI are not well defined, and a thorough investigation of baseline and procedural characteristics of bifurcation PCI based on sex and their prognostic long-term impact has not yet been conducted.[9][10] Therefore, we aimed to evaluate the sex differences in bifurcation lesion characteristics, procedures, and outcomes after bifurcation PCI using second-generation drug-eluting stents (DES).

Food and Drug Safety, Republic of Korea. The funding agency had no role in study design, analysis, interpretation of data, the writing of the manuscript or in the decision to submit the article for publication.

Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Ahn HJ, Koo BK; Data curation: Bruno F, Kang J, Hwang D, Yang HM, Han JK, De Luca L, De Filippo O, Mattesini A, Park KW, Truffa A, Wanha W, Song YB, Gili S, Chun WJ, Helft G, Hur SH, Cortese B, Han SH, Escaned J, Chieffo A, Choi KH, Gallone G, Doh JH, De Ferrari G, Hong SJ, Quadri G, Nam CW, Gwon HC, Kim HS, D'Ascenzo F, Koo BK; Formal analysis: Ahn HJ, Koo BK; Funding acquisition: Koo BK; Investigation: Koo BK; Methodology: Ahn HJ, Bruno F, Kang J, Hwang D, Yang HM, Han JK, De Luca L, De Filippo O, Mattesini A, Park KW, Truffa A, Wanha W, Song YB, Gili S, Chun WJ, Helft G, Hur SH, Cortese B, Han SH, Escaned J, Chieffo A, Choi KH, Gallone G, Doh JH, De Ferrari G, Hong SJ, Quadri G, Nam CW, Gwon HC, Kim HS, D'Ascenzo F, Koo BK; Supervision: Koo BK; Visualization: Ahn HJ; Writing - original draft: Ahn HJ; Writing - review & editing: Ahn HJ, Koo BK.

METHODS

Ethical statement

This study was performed according to Declaration of Helsinki (2013) and the Institutional Review Board (IRB) of each center approved the study protocol (Seoul National University Hospital IRB No. 1702-099-832). The requirement for written informed consent was waived due to the retrospective nature of the study.

Study population

The study population was derived from the COronary BIfurcation Stent III (COBIS III) registry (ClinicalTrials.gov, NCT03068494), which is a retrospective, multicenter, observational, and real-world registry of patients with bifurcation lesions treated with second-generation DES. Between January 2010 and December 2014, 2,648 patients with bifurcation lesions from 21 medical centers in South Korea were enrolled in the registry. The inclusion criteria for the registry were: 1) Patients who were at least 19 years old and had any type of coronary bifurcation lesion in the major epicardial artery treated solely with second generation DES; and 2) Main vessel (MV) diameter ≥2.5 mm, and side branch (SB) diameter ≥2.3 mm as determined using core laboratory quantitative coronary angiography (QCA) analysis. The major exclusion criteria were: 1) Cardiogenic shock or cardiopulmonary resuscitation during hospitalization; 2) Protected left main (LM) disease; and 3) Severe left ventricular systolic dysfunction (ejection fraction <30%). Coronary interventional procedures were performed according to relevant standard guidelines. Treatment strategies for stenting, including DES type, use of one or two stents, use of intravascular imaging, and access site, were chosen at the interventionist's discretion.

Data collection and quantitative coronary angiography analysis

The data collection, coronary angiography, and PCI methods for the COBIS III registry have been described previously.[11] Briefly, all baseline and procedural coronary angiograms were reviewed and quantitatively analyzed at an angiographic core laboratory (Heart Vascular Stroke Institute, Samsung Medical Center, Seoul, Republic of Korea) using a validated automated edge-detection system (Centricity CA 1000; GE HealthCare, Waukesha, WI, USA). Bifurcation lesions were classified according to the Medina classification, and true bifurcation lesions were defined as Medina classification type 1.1.1, 1.0.1, and 0.1.1. The pre- and post-procedure minimum lumen diameter, reference diameter, and percent diameter stenosis were assessed for both the MV and SB.

Study definition and outcomes

The primary outcome of this study was the occurrence of target lesion failure (TLF), defined as a composite of cardiac death, spontaneous myocardial infarction (MI), and target lesion revascularization (TLR). Secondary outcomes included individual components of the primary endpoint, target vessel revascularization (TVR), and all-cause death. All the clinical events were verified by an independent committee. Sex was defined as the assigned sex at birth that was registered with the National Health Insurance Service.

Statistical analysis

Categorical data were expressed as numbers and frequencies (percentages) and continuous data as mean ± standard deviations. Categorical variables were compared between groups using the χ^2 test or Fisher's exact test, as appropriate, and continuous variables were compared using Student's t-test. Kaplan-Meier curves were used to demonstrate the cumulative incidence of clinical events according to sex, and the significance level was assessed using a log-rank test.

https://doi.org/10.4070/kcj.2024.0172

Patients were censored at 5 years or when events occurred. To compare outcomes according to sex, multivariable Cox proportional hazard regression analysis was performed, adjusting for variables that were statistically significant in the univariable analysis or clinically relevant. The following variables were included in the adjustment: age, body mass index (BMI), hypertension, diabetes, current smoking status, clinical diagnosis, true bifurcation, and baseline MV reference diameter. The results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). All probability values were 2-sided, and p values <0.05 were considered statistically significant. Statistical analyses were performed using R Statistical Software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

Subgroup and sensitivity analysis

The relative impact of sex on the primary outcome following covariate adjustment was further tested in subgroups according to age (≤65 vs. >65 years), hypertension, diabetes, chronic kidney disease (CKD), current smoking, clinical presentation, left ventricular ejection fraction (LVEF) (<50% vs. ≥50%), true bifurcation and vessel size (<3 vs. ≥3 mm). As the COBIS III registry solely consists of a single ethnic group (Korean patients), we performed a sensitivity analysis using the veRy Thin Stents for Patients with Left mAIn or bifurcatioN in Real life (RAIN) registry, which is a real-world registry of 2,889 patients who underwent bifurcation PCI enrolled from 15 centers in Italy from May 2015 to December 2017.[12]

RESULTS

Baseline patient characteristics

A total of 2,648 patients with bifurcation lesions were enrolled in the COBIS III registry, including 635 (24.0%) women and 2,013 (76.0%) men. The baseline characteristics according to sex are presented in **Table 1**. In comparison with men, women were older (68.8±10.0 vs. 62.1±10.8 years, p<0.001), and had higher prevalence of hypertension and diabetes (66.9% vs. 53.6%, p<0.001; 39.7% vs. 32.4%, p=0.001, respectively).

Angiographic findings and procedural characteristics

The lesions and procedural characteristics are presented in **Table 2**. The vessel reference diameters were smaller in women than in men for both the MV and SB. However, there was no difference in the angiographic percent diameter stenosis between the 2 groups before

Table 1. Baseline clinical characteristics

Baseline characteristics	Women (n=635)	Men (n=2,013)	p value
Age (years)	68.8±10.0	62.1±10.8	<0.001
BMI (kg/m^2)	24.2±3.4	24.6±2.0	0.03
Hypertension	425 (66.9)	1,079 (53.6)	<0.001
Diabetes	252 (39.7)	653 (32.4)	0.001
Dyslipidemia	247 (38.9)	762 (37.9)	0.67
Current smoker	33 (5.2)	765 (38.0)	<0.001
Previous MI	20 (3.1)	93 (4.6)	0.14
Previous PCI	71 (11.2)	252 (12.5)	0.41
LVEF (%)	59.3±10.6	58.4±9.6	0.06
Diagnosis			0.08
Stable coronary syndrome	228 (35.9)	801 (39.8)	
ACS	407 (64.1)	1,212 (60.2)	

Categorical data were expressed as numbers and frequencies (percentages) and continuous data as mean ± standard deviations.
ACS = acute coronary syndrome; BMI = body mass index; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

https://doi.org/10.4070/kcj.2024.0172

Table 2. Angiographic findings and procedural results

Variables	Women (n=635)	Men (n=2,013)	p value
Lesion characteristics			
Multivessel disease	375 (59.1)	1,272 (63.2)	0.07
Bifurcation location			0.98
LM	224 (35.3)	711 (35.3)	
LAD	291 (45.8)	917 (45.6)	
LCX	85 (13.3)	265 (13.2)	
RCA	35 (5.5)	120 (6.0)	
True bifurcation	305 (48.0)	950 (47.2)	0.75
Medina classification			0.67
1,1,1	208 (32.8)	631 (31.3)	
1,0,1	35 (5.5)	133 (6.6)	
0,1,1	62 (9.8)	186 (9.2)	
1,0,0	62 (9.8)	234 (11.6)	
1,1,0	100 (15.7)	327 (16.2)	
0,1,0	141 (22.2)	434 (21.6)	
0,0,1	27 (4.3)	68 (3.4)	
Quantitative coronary angiography			
Bifurcation angle (degrees)	70.9±21.4	71.5±22.1	0.59
Before procedure			
MV reference diameter (mm)	3.2±0.5	3.3±0.5	<0.001
SB reference diameter (mm)	2.6±0.5	2.6±0.4	0.007
MV diameter stenosis (%)	72.8±14.5	73.9±14.9	0.10
SB diameter stenosis (%)	44.6±27.5	44.1±27.1	0.70
After procedure			
MV residual diameter stenosis (%)	15.4±10.4	15.7±9.8	0.61
SB residual diameter stenosis (%)	35.6±26.8	36.3±26.0	0.56
Procedural characteristics			
Radial access	337 (53.1)	1,170 (58.1)	0.03
IVUS guidance	237 (37.3)	817 (40.6)	0.16
Bifurcation PCI technique			0.47
Simple crossover	403 (63.5)	1,282 (63.7)	
One stent with SB balloon	109 (17.2)	400 (19.9)	
Two stenting technique	123 (10.4)	331 (16.4)	
Number of stents per patient	1.8±1.0	1.8±1.0	0.69
MV maximal stent diameter (mm)	3.0±0.6	3.2±0.7	<0.001
MV stent length (mm)	28.6±13.1	29.1±14.0	0.45

Categorical data were expressed as numbers and frequencies (percentages) and continuous data as mean ± standard deviations.
IVUS = intravascular ultrasound; LAD = left anterior descending; LCX = left circumflex; LM = left main; MV = main vessel; PCI = percutaneous coronary intervention; RCA = right coronary artery; SB = side branch.

and after bifurcation PCI (**Figure 1**). LM bifurcation lesions accounted for 35.3% in both women and men, while true bifurcation lesions accounted for 48.0% in women and 47.2% in men (p=0.75). Women received radial approach less than men; however, the intravascular ultrasound (IVUS)-guided PCI rates were comparable (37.3% vs. 40.6%, p=0.16). There were no differences in the bifurcation PCI techniques between the two sexes, with the simple crossover technique being the most common (63.5% vs. 63.7%, p=0.96) (**Figure 2**). MV stent diameter was smaller in women (3.0±0.6 vs. 3.2±0.7 mm, p<0.001) but there was no difference in stent length.

Clinical outcomes

The median clinical follow-up was 4.2 years. During hospitalization, MI or cardiogenic shock occurred at a similar rate in women and men; however, access site bleeding occurred more frequently in women (1.1% vs. 0.3%, p=0.03) (**Supplementary Table 1**). The 5 year-observed primary outcomes were not different between the sexes (women vs. men, 6.3% vs. 7.1%, adjusted HR, 0.82; 95% CI, 0.56–1.20; p=0.30), and the individual components of the

https://doi.org/10.4070/kcj.2024.0172

primary outcome were also comparable (**Table 3**, **Figure 3**). TLF rate was also comparable for patients undergoing LM (8.9% vs. 10.8%, adjusted HR, 0.83; 95% CI, 0.49–1.38; p=0.47)

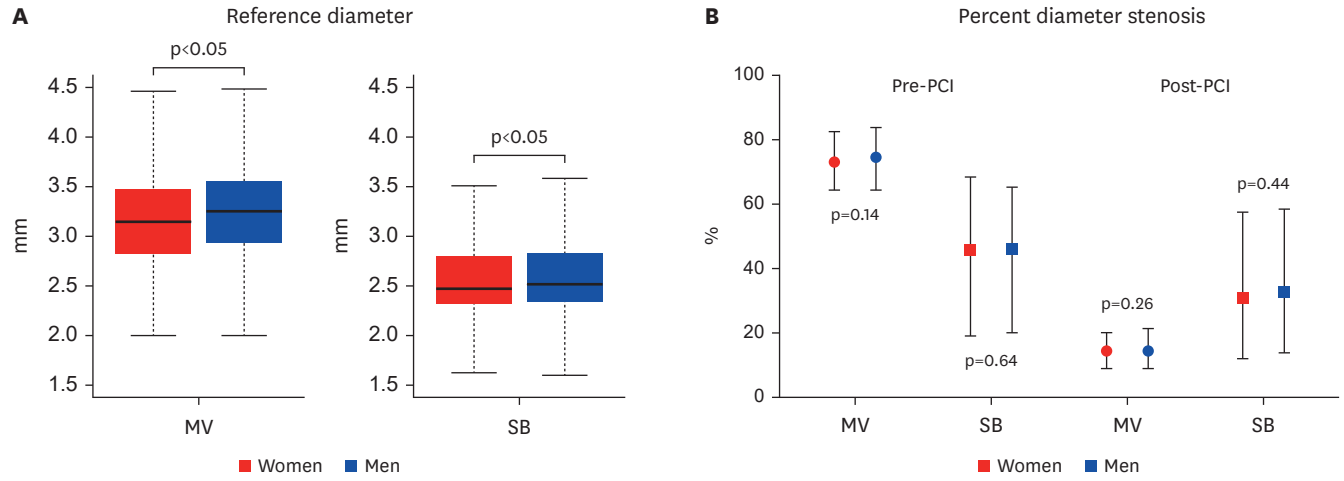


Figure 1. Sex difference in reference diameter and percent diameter stenosis.
Reference diameter was smaller in women than men for both the MV and SB. However, percent diameter stenoses of the MV and SB were comparable in women and men before and after bifurcation PCI. (A) Maximum, minimum and median is expressed in horizontal lines and interquartile range in colors. (B) Median value is expressed in circle (MV) or square (SB) and interquartile range in error bars.
MV = main vessel; PCI = percutaneous coronary intervention; SB = side branch.

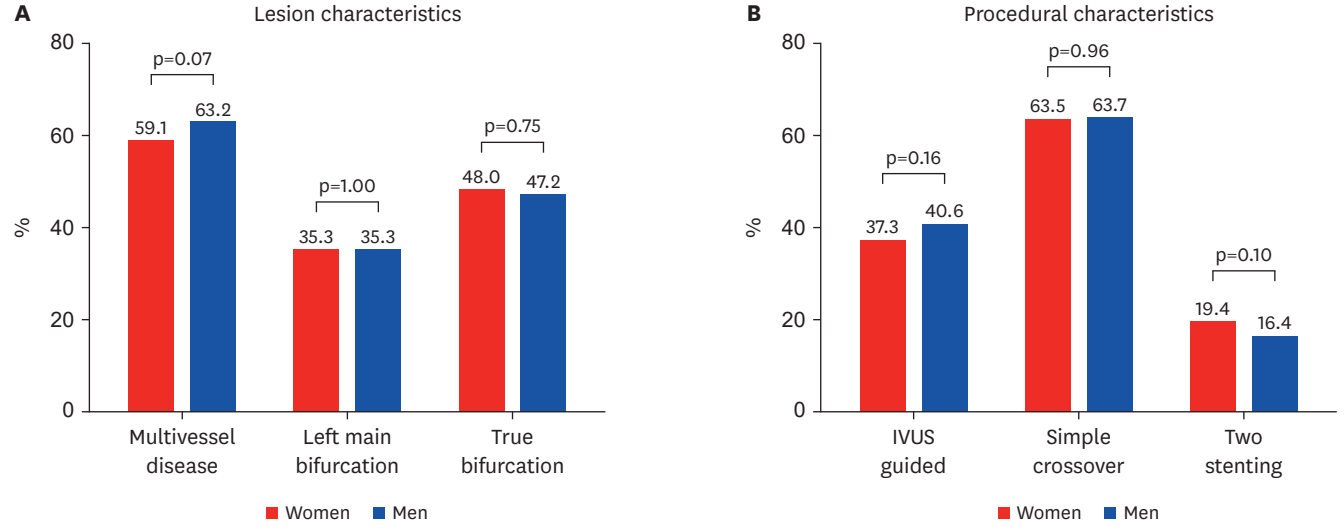


Figure 2. Sex differences in lesion and procedural characteristics in bifurcation PCI.
There were no differences in lesion and procedural characteristics between women and men.
IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

Table 3. Clinical outcomes according to sex

Clinical events	Incidence		Univariable analysis		Multivariable analysis	
	Women (n=635)	Men (n=2,013)	Unadjusted HR (95% CI)	p value	Adjusted HR* (95% CI)	p value
TLF	40 (6.3%)	143 (7.1%)	0.92 (0.65–1.30)	0.63	0.82 (0.56–1.20)	0.30
Cardiac death	13 (2.0%)	49 (2.4%)	0.87 (0.47–1.60)	0.66	0.55 (0.29–1.09)	0.07
MI	9 (1.4%)	31 (1.5%)	0.95 (0.45–1.99)	0.89	0.83 (0.37–1.84)	0.64
TLR	24 (3.8%)	81 (4.0%)	0.97 (0.62–1.53)	0.90	1.14 (0.69–1.86)	0.61
TVR	31 (4.9%)	133 (6.6%)	0.76 (0.51–1.12)	0.16	0.84 (0.55–1.28)	0.42
All-cause death	28 (4.4%)	86 (4.3%)	1.07 (0.70–1.64)	0.75	0.70 (0.45–1.11)	0.13

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; TLF = target lesion failure; TLR = target lesion revascularization; TVR = target vessel revascularization.
*Adjusted for age, body mass index, current smoking, hypertension, diabetes, clinical diagnosis, true bifurcation and baseline main vessel reference diameter.

https://doi.org/10.4070/kcj.2024.0172

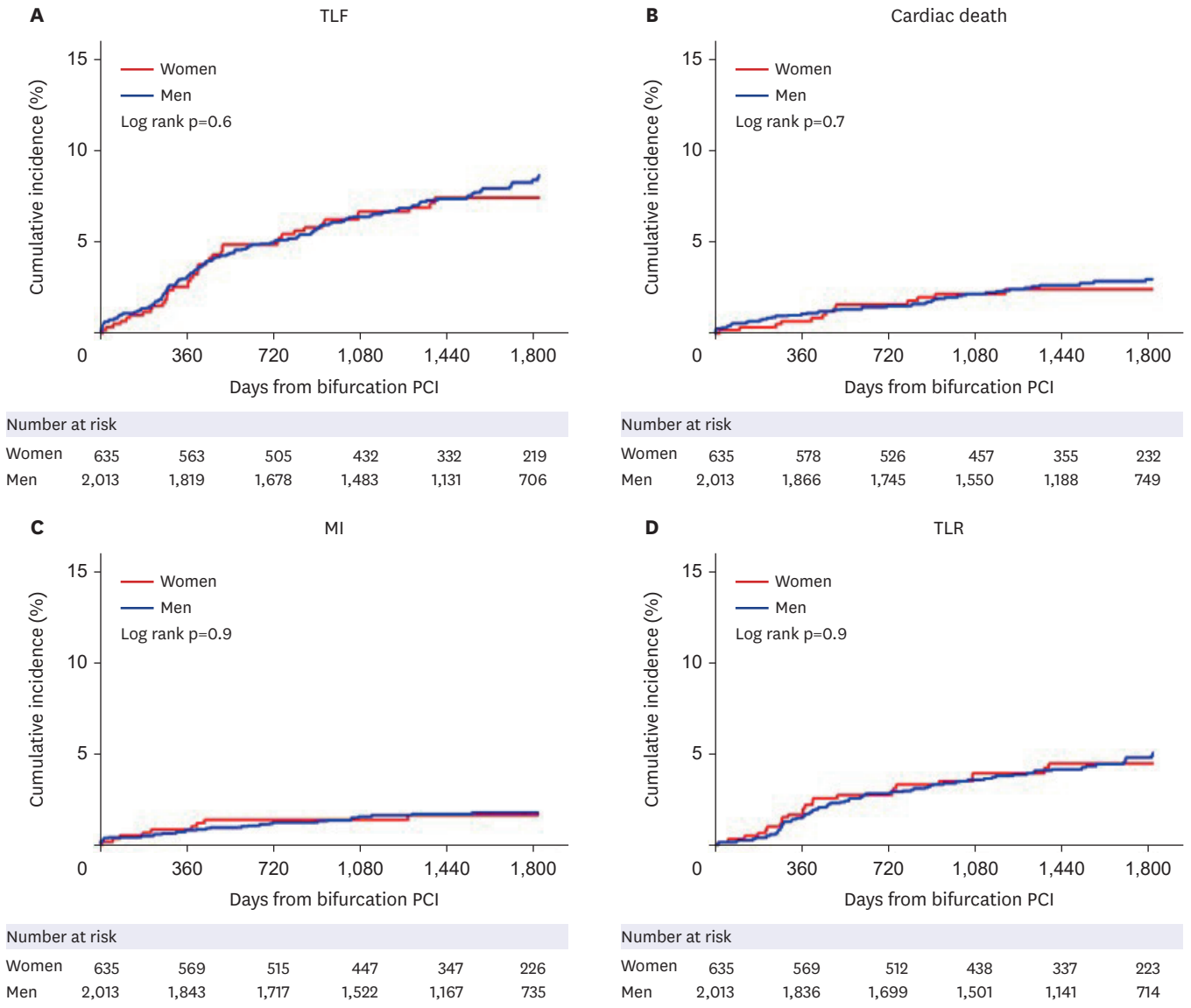


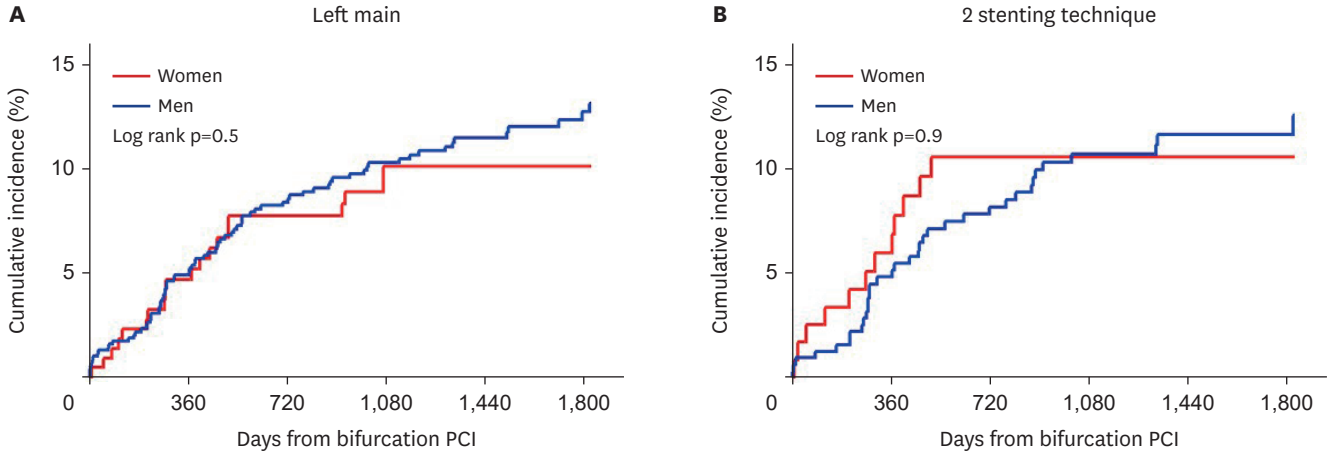
Figure 3. Five year time-to-event curves for the primary outcome and its individual components by sex.
Women showed comparable outcomes to men for the primary outcome (TLF) and its individual components.
MI = myocardial infarction; TLF = target lesion failure; TLR = target lesion revascularization.

or two stenting PCI (9.8% vs. 10.6%, adjusted HR, 1.07; 95% CI, 0.53–2.14; p=0.86) (**Supplementary Table 2**, **Figure 4**). There were no differences in sex-based outcomes in patients who received IVUS guidance and those who did not (**Supplementary Figure 1**).

Subgroup and sensitivity analysis

In the subgroup analysis for the primary outcome, there was a significant interaction between age and sex, where younger age was associated with a higher risk of adverse outcome in women compared with men (≤65 years, adjusted HR, 1.87; 95% CI, 1.06–3.27; p=0.03; p for interaction 0.003). Moreover, interaction p value was significant for diabetes mellitus (DM) and sex where women had higher risk than men in patients with DM (adjusted HR, 1.23; 95% CI, 0.74–2.04; p=0.43; p for interaction 0.03) (**Supplementary Figure 2**).

https://doi.org/10.4070/kcj.2024.0172



Number at risk						
Women	224	193	170	143	112	74
Men	711	613	557	488	372	229

Number at risk						
Women	123	104	89	74	52	34
Men	331	289	264	226	165	98

Figure 4. Primary outcome according to sex in left main, 2 stenting groups.
Patients undergoing left main PCI or 2 stenting techniques also showed similar outcomes between sexes.
PCI = percutaneous coronary intervention.

The RAIN registry consists of 674 women (23.3%) and 2,215 men (76.7%). Women were older and had more comorbidities than men. The clinical diagnoses were similar (p=0.09), and there were no differences in LM bifurcation (22.6% vs. 25.3%, p=0.17), true bifurcation (49.3% vs. 47.8%, p=0.53), or the two stenting strategies (17.1% vs. 18.4%, p=0.46) between the 2 groups (**Supplementary Table 3**). There was no significant difference in the 2-year outcomes between women and men (**Supplementary Table 4**, **Supplementary Figure 3**).

DISCUSSION

The present study investigated sex differences on baseline, procedural characteristics, and clinical outcomes in patients undergoing bifurcation PCI and the principal findings of this study are summarized as follows: 1) Despite the fact that women undergoing bifurcation PCI presented with more cardiovascular risk factors and smaller vessel size, angiography data showed that there was no significant difference in bifurcation location including LM, and in procedural techniques such as IVUS use or bifurcation PCI strategy between women and men; 2) Women receiving bifurcation PCI equal to that as their men counterparts experienced a comparable risk of TLF, including patients receiving LM and 2 stenting techniques; 3) In adjusted analysis, there was notable interaction between sex and age, DM; and 4) Sensitivity analysis revealed comparable PCI outcomes between sex in Italian patients as well.

In our study, women comprised only 24% of the total study population. Since this is a registry study that enrolled patients who underwent PCI with the same inclusion criteria for both sexes (MV diameter ≥2.5 mm, and SB diameter ≥2.3 mm), it could be hypothesized that women were less likely to be included because they have smaller vessel sizes. However, as many sex-specific studies from post hoc analysis of randomized controlled trials or registries have shown,[13-15] among patients who undergo PCI, women generally constitute about 25%, implying that this percentage is not limited to this study. Women were older than men and had more comorbidities, which is consistent with the results of previous studies.[13)16)] Meanwhile,

https://doi.org/10.4070/kcj.2024.0172

although the angiographic complexity and techniques used for bifurcation stenting can significantly affect outcomes and could vary between women and men, few studies have explicitly elaborated on sex-specific differences in the anatomic and procedural characteristics of bifurcation lesions.[7] Using core laboratory-assessed angiographic characteristics that are typically not discussed in most meta-analyses or registry-based studies, the women in our study showed similar anatomical complexity of bifurcation lesions, including bifurcation angle or percent diameter stenosis in the MV and SB, despite the smaller vessel size.

A natural trait of bifurcation lesions is that relying solely on angiography for guidance can lead to ambiguous visualization of these specific lesions, which could have a critical impact on stent implantation.[17] Intracoronary imaging devices can assist in assessing the geometry of bifurcation lesions, including the carina, and precisely measuring vessel and stent dimensions,[18] with the latest research such as the OCTOBER trial[19] suggesting favorable outcomes with use of imaging in bifurcation lesions. Furthermore, a recent study reported sex differences in assessing stenosis severity between visual angiographic assessment and QCA, raising the concern that women could be subject to overestimation of the severity of diameter stenosis compared to men when evaluated only through angiography.[20] Therefore, adjunctive intravascular imaging could be essential, especially in women. In our study, both women and men showed comparable rates of IVUS-guided PCI, leading to judicious selection of the bifurcation technique, stent size, and stent length without disparity between sexes.

Compared with men, women undergoing bifurcation PCI showed higher rates of access site bleeding, which is in line with the results of previous studies.[13][21] However, there was no significant difference in in-hospital cardiac death or MI between sexes. In our study, women had similar long term clinical outcomes after bifurcation PCI as men, despite worse clinical risk profiles. In a sex substudy of the IRIS-MAIN registry,[14] women also showed similar rates of primary outcomes in both the LM ostium/shaft and LM bifurcation subgroups. In the IRIS-MAIN study, the repeat revascularization rate of target vessels or lesions was higher in women, which could be attributed to more 1st generation DES use in women than in men. In a single-center study in Israel,[22] female sex was reported to be an independent risk factor for all-cause death (HR, 1.867; 95% CI, 1.044–3.340; p=0.035). However, women underwent more LM PCI and PCI with 1st-generation DES were partially included in this study. In contrast to the aforementioned studies, our registry data showed comparable percentage of LM bifurcation PCI between sex, and since our study exclusively enrolled patients who received 2nd-generation DES, there was also no sex difference in DES generation. This may in part, explain the contrary results of our study compared to the previous studies that showed worse outcomes in women after PCI. Our study suggests that implementing thorough assessments and performing PCI procedures based on those results is more crucial than sex itself on long term clinical outcomes.

Younger age has been reported to be an important factor in sex-based outcomes, where disparities in PCI outcomes are markedly worse in younger women[23] as consistent with the results of our study. In a previous study that focused on sex-based outcomes according to age, women aged <50 years had less severe angiographic CAD than young men but had a higher risk of repeat revascularization. This disproportionate risk for adverse events could be explained by a more aggressive phenotype of early onset CAD in young women, the effect of estrogen across the menopause transition, and the tendency of women to report more post-PCI angina, leading to repeat catheterization and revascularization.[24] Regarding the interaction between DM and sex, it is hypothesized that greater endothelial dysfunction

and impairment of the coagulation profile in women with DM compared to men lead to a favorable environment for the development of ischemic heart disease.[25] However, the sex-specific impact of diabetes on outcomes after PCI is controversial, with some studies emphasizing special attention on diabetic women[26] while others report no difference in outcomes between sexes in diabetic patients.[27] Although no study has compared Western and Asian patients in terms of the impact of sex on PCI outcomes, analyses conducted in Western countries tend to report worse long-term outcomes in women, whereas studies conducted in Asian countries tend to show no sex-related differences.[28] Using the RAIN registry, we investigated the racial differences in sex-related outcomes after bifurcation PCI. Italian women had worse cardiovascular risk factors than men, but both sexes underwent similar rates of LM bifurcation PCI, true bifurcation PCI, and the 2 stenting strategies. Consequently, the outcome was comparable between the sexes in the Italian cohort.

There were several limitations in this study. First, because this study was based on an observational analysis of a retrospective registry, other confounding factors may have influenced the results. Second, non-invasive or invasive tests to assess the functional status of the epicardial coronary arteries were not performed, which is a crucial element underscored when discussing sex difference in CAD.[29] Third, the choice of stent type, treatment strategy, and medications were decided at the operating physician's discretion. Fourth, the inclusion of patients who underwent bifurcation PCI more than 10 years ago in the COBIS III registry could raise concern about the generalizability of the analysis to the modern era. However, high use of IVUS and mandatory 2nd-generation DES provides some confidence that these data are applicable to contemporary populations. Fifth, there is the possibility of selection bias since women's coronary arteries are usually smaller than men's but the vessel size criteria of the registry did not differ between sexes. Finally, because of the inherent limitation of the study design and lack of statistical power, the results must be interpreted as descriptive and hypothesis generating only.

In conclusion, our study showed that although women with bifurcation lesions are prone to have worse clinical risk factors, employing suitable treatment strategies could result in comparable outcomes to men, even in patients undergoing LM or 2-stent bifurcation PCI. Sex itself was not found to be a factor influencing outcomes. Instead, strategies tailored to individual patient characteristics, regardless of sex, appear to be crucial in bifurcation PCI.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
In hospital complications

Supplementary Table 2
Primary outcome according to sex in LM, non-LM, 2 stent, 1 stent groups

Supplementary Table 3
Baseline characteristics according to sex in the RAIN registry

Supplementary Table 4
Clinical outcomes according to sex in the RAIN registry

https://doi.org/10.4070/kcj.2024.0172

Supplementary Figure 1

Primary outcome according to sex in IVUS, non-IVUS use groups. There were no differences in sex-based outcomes between patients in those who received IVUS guidance and also those who did not.

Supplementary Figure 2

Subgroup analysis. There was a significant interaction with age, diabetes and sex for the primary outcome. Adjusted for age, BMI, current smoking, HTN, diabetes, clinical diagnosis, true bifurcation, and baseline main vessel reference diameter.

Supplementary Figure 3

Clinical outcomes according to sex in the RAIN registry. There were no significant differences in the 2-year outcomes between women and men in the RAIN registry.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation* 2020;141:e139-596. PUBMED | CROSSREF
2. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation* 2016;133:916-47. PUBMED | CROSSREF
3. Mericli M, Nádasy GL, Szekeres M, et al. Estrogen replacement therapy reverses changes in intramural coronary resistance arteries caused by female sex hormone depletion. *Cardiovasc Res* 2004;61:317-24. PUBMED | CROSSREF
4. Taqueti VR. Sex differences in the coronary system. *Adv Exp Med Biol* 2018;1065:257-78. PUBMED | CROSSREF
5. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006;47:S21-9. PUBMED | CROSSREF
6. Rodriguez Lozano PF, Rrapo Kaso E, Bourque JM, et al. Cardiovascular imaging for ischemic heart disease in women: time for a paradigm shift. *JACC Cardiovasc Imaging* 2022;15:1488-501. PUBMED | CROSSREF
7. Thandra A, Jhand A, Guddeti R, et al. Sex differences in clinical outcomes following percutaneous coronary intervention of unprotected left main coronary artery: a systematic review and meta-analysis. *Cardiovasc Revasc Med* 2021;28:25-31. PUBMED | CROSSREF
8. Sawaya FJ, Lefèvre T, Chevalier B, et al. Contemporary approach to coronary bifurcation lesion treatment. *JACC Cardiovasc Interv* 2016;9:1861-78. PUBMED | CROSSREF
9. Osman M, Ghaffar YA, Osman K, et al. Gender-based outcomes of coronary bifurcation stenting: a report from the National Readmission Database. *Catheter Cardiovasc Interv* 2022;99:433-9. PUBMED | CROSSREF
10. Doolub G, Iannaccone M, Rab T, et al. Sex-based treatment and outcomes for coronary bifurcation stenting: a report from the e-ULTIMASTER registry. *Catheter Cardiovasc Interv* 2023;102:430-9. PUBMED | CROSSREF
11. Choi KH, Song YB, Lee JM, et al. Prognostic effects of treatment strategies for left main versus non-left main bifurcation percutaneous coronary intervention with current-generation drug-eluting stent. *Circ Cardiovasc Interv* 2020;13:e008543. PUBMED | CROSSREF
12. Kang J, Bruno F, Rhee TM, et al. Impact of clinical and lesion features on outcomes after percutaneous coronary intervention in bifurcation lesions. *JACC Asia* 2022;2:607-18. PUBMED | CROSSREF
13. Serruys PW, Cavalcante R, Collet C, et al. Outcomes after coronary stenting or bypass surgery for men and women with unprotected left main disease: the EXCEL trial. *JACC Cardiovasc Interv* 2018;11:1234-43. PUBMED | CROSSREF
14. Shin ES, Lee CW, Ahn JM, et al. Sex differences in left main coronary artery stenting: different characteristics but similar outcomes for women compared with men. *Int J Cardiol* 2018;253:50-4. PUBMED | CROSSREF
15. Hara H, Takahashi K, van Klaveren D, et al. Sex differences in all-cause mortality in the decade following complex coronary revascularization. *J Am Coll Cardiol* 2020;76:889-99. PUBMED | CROSSREF

16. Kim HS, Tonino PA, De Bruyne B, et al. The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy. *JACC Cardiovasc Interv* 2012;5:1037-42. PUBMED | CROSSREF
17. Baumgart D, Haude M, Birgelen Cv C, Ge J, Görge G, Erbel R. Assessment of ambiguous coronary lesions by intravascular ultrasound. *Int J Cardiovasc Intervent* 1999;2:3-12. PUBMED | CROSSREF
18. Costa RA, Costa MA, Moussa ID. Bifurcation lesion morphology and intravascular ultrasound assessment. *Int J Cardiovasc Imaging* 2011;27:189-96. PUBMED | CROSSREF
19. Holm NR, Andreasen LN, Neghabat O, et al. OCT or angiography guidance for PCI in complex bifurcation lesions. *N Engl J Med* 2023;389:1477-87. PUBMED | CROSSREF
20. Xu X, Fam JM, Low AF, et al. Sex differences in assessing stenosis severity between physician visual assessment and quantitative coronary angiography. *Int J Cardiol* 2022;348:9-14. PUBMED | CROSSREF
21. Nicolas J, Claessen BE, Cao D, et al. A sex paradox in clinical outcomes following complex percutaneous coronary intervention. *Int J Cardiol* 2021;329:67-73. PUBMED | CROSSREF
22. Schamroth Pravda N, Perl L, Greenberg G, et al. Impact of sex on outcomes of bifurcation lesion percutaneous coronary intervention: results from a single-centre prospective registry. *Coron Artery Dis* 2022;31:31-6. PUBMED | CROSSREF
23. Kosmidou I, Leon MB, Zhang Y, et al. Long-term outcomes in women and men following percutaneous coronary intervention. *J Am Coll Cardiol* 2020;75:1631-40. PUBMED | CROSSREF
24. Epps KC, Holper EM, Selzer F, et al. Sex differences in outcomes following percutaneous coronary intervention according to age. *Circ Cardiovasc Qual Outcomes* 2016;9:S16-25. PUBMED | CROSSREF
25. Fourny N, Beauloye C, Bernard M, Horman S, Desrois M, Bertrand L. Sex differences of the diabetic heart. *Front Physiol* 2021;12:661297. PUBMED | CROSSREF
26. Maier B, Thimme W, Kallischnigg G, et al. Does diabetes mellitus explain the higher hospital mortality of women with acute myocardial infarction? Results from the Berlin Myocardial Infarction Registry. *J Investig Med* 2006;54:143-51. PUBMED | CROSSREF
27. Ogita M, Miyauchi K, Dohi T, et al. Gender-based outcomes among patients with diabetes mellitus after percutaneous coronary intervention in the drug-eluting stent era. *Int Heart J* 2011;52:348-52. PUBMED | CROSSREF
28. Trabattoni D, Teruzzi G, Montorsi P, et al. Comparison of the effectiveness of percutaneous intervention of the left-main coronary artery with everolimus-eluting stents in women -vs- men. *Am J Cardiol* 2019;124:1357-62. PUBMED | CROSSREF
29. Zhang J, Jiang J, Hu X, et al. Sex differences in fractional flow reserve- or intravascular ultrasound-guided percutaneous coronary intervention. *JACC Cardiovasc Interv* 2023;16:2426-35. PUBMED | CROSSREF