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Sex-Related Outcomes of Successful Drug-Coated Balloon Treatment in De Novo Coronary Artery Disease

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Purpose: Although drug-coated balloon (DCB) treatment is known to be effective for de novo lesions, the influence of sex on angiographic and clinical outcomes remains unknown. This study aimed to investigate the angiographic and clinical impact of DCB treatment in patients with de novo coronary lesions according to sex.

Materials and Methods: A total of 227 patients successfully treated with DCB were retrospectively enrolled and divided into two groups according to sex. The primary endpoint was late lumen loss (LLL) at 6-month angiography, and the secondary endpoint was target vessel failure (TVF), which included cardiac death, target vessel myocardial infarction, target lesion revascularization, and target vessel thrombosis.

Results: The study enrolled 60 women (26.4%) and 167 men (73.6%). Compared to men, women had a smaller vessel size, larger DCB to reference vessel ratio, and more dissections after DCB treatment (55.0% vs. 37.1%, p=0.016). Women also had a significantly higher LLL compared to men (0.12±0.26 mm vs. 0.02±0.22 mm, p=0.012) at the 6-month follow-up angiography. During a median follow-up of 3.4 years (range 12.7–28.9 months), TVF was similar (women 6.7% vs. men 7.8%, p=0.944). In multivariable analysis, women were independently associated with a higher LLL.

Conclusion: LLL was higher in women, but there was no difference in TVF between women and men. Based on multivariable analysis, the women sex was an independent predictor of higher LLL (Impact of Drug-coated Balloon Treatment in de Novo Coronary Lesion; NCT04619277).

Key Words: Drug-coated balloon, balloon angioplasty, coronary artery disease, sex difference, clinical outcome

INTRODUCTION

Although the mortality from coronary artery disease (CAD) has decreased due to improved prevention and treatment strategies, it remains one of the leading causes of morbidity and mortality in both sexes worldwide. Previous studies have suggested that gender differences have diminished, possibly through the evolution of percutaneous coronary intervention (PCI)-related treatments.[1,2] Unfortunately, in other studies, women have been shown to have an increased risk of adverse events following PCI, including an increased risk of bleeding.[3,4] The women sex is an independent predictor of bleeding but not of ischemic

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events after adjusting for differences in dual antiplatelet therapy (DAPT) duration, baseline characteristics, and treatment characteristics.[5] Even after normalization for left ventricular mass, women subjects tend to have smaller diameter coronary arteries compared to men.[6] Although drug-eluting stents (DES) are the preferred treatment for PCI in CAD,[7] their efficacy is relatively poor in small coronary arteries.[8] The neointimal proliferation and local inflammation that follow PCI result in higher rates of in-stent restenosis and recurrent ischemic events in small vessels.[9,10] Compared to men, small vessel disease is more common in women; and given their increased risk of bleeding with DAPT after stenting, lesions in women are more difficult to treat adequately.

Drug-coated balloons (DCB) have comparable efficacy to DES for the treatment of small vessel disease.[11,12] An added advantage of using DCB over DES is the short duration of DAPT required, especially in patients with high bleeding risk or those with contraindications to its long-term use.[13,14] Nevertheless, to date, there have been no studies on the sex-related differences in the efficacy of DCB treatment for de novo coronary lesions. Therefore, we aimed to examine the sex-related differences in angiographic and long-term clinical outcomes after DCB treatment of de novo coronary lesions.

MATERIALS AND METHODS

Patient population

This retrospective study enrolled patients from Peking University Shougang Hospital and Ulsan Medical Center between July 2014 and August 2018 who had successful PCI performed with DCB for de novo coronary lesions (Impact of Drug-coated Balloon Treatment in de Novo Coronary Lesion; NCT04619277). Patients were excluded for any of the following circumstances: if there was any use of DCB for in-stent restenosis; if they presented with ST-segment elevation myocardial infarction; if they were hemodynamically unstable at presentation, or had a life expectancy of <1 year. The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating center (IRB no: Ulsan Medical Center, USH-20-004; Peking University Shougang Hospital, IRBW2021-09-01). The study was conducted in accordance with the Declaration of Helsinki (2013).

Procedure

All patients were pretreated with 200 mg of aspirin and 300–600 mg of clopidogrel as loading doses, and 100 U/kg of unfractionated heparin was injected intravenously to maintain an activated clotting time of ≥250 s during the procedure. Intracoronary nitroglycerin (200 μg) was administered routinely before diagnostic coronary angiography. Intervention was performed according to the international and the Asia-Pacific consensus recommendations on DCB treatment.[15-17] Specifically, predilation with a plain balloon, including a scoring balloon, was mandatory (the recommended balloon-to-vessel ratio was 0.8 to 1.0). In cases of flow-limiting dissection after predilation, PCI using a DES was recommended without using a DCB. The practice at both institutions was not to stent type A to C coronary dissections [National Heart, Lung, and Blood Institute (NHBLI) classification system for intimal tears by the Coronary Angioplasty Registry] in the absence of symptoms, ECG changes, hemodynamic disturbances, or the persistence of a Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. Stenting was performed for type D or higher coronary dissections and/or impaired distal flow after predilation. All patients who had either no dissection or type A to C dissections following predilation went on to undergo treatment with DCB, and were included in the study. The DCB was inflated for 30 s to 60 s at nominal pressure. After using DCB, the final assessment was undertaken at least 5 min after administering a bolus of intracoronary vasodilator to catch any acute vessel closure. In these cases, bailout stent implantation was considered. The use of glycoprotein IIb/IIIa receptor inhibitors was allowed in cases of high thrombus burden. Dual antiplatelet treatment was prescribed for 1 to 3 months, after which the patients were prescribed aspirin monotherapy.

Definitions and endpoints

Angiographic success was defined as evidence of final residual stenosis by visual estimate ≤30%, with TIMI flow grade 3. Procedural success was defined as angiographic success without the occurrence of in-hospital adverse cardiac events [defined as any occurrence of cardiac death, myocardial infarction, target vessel revascularization (TVR), or target vessel thrombosis]. The primary endpoint was late lumen loss (LLL), and the secondary endpoint was target vessel failure (TVF, composed of cardiac death, target vessel myocardial infarction, TVR, and target vessel thrombosis).

Follow-up

All patients underwent clinical follow-up after the index procedure, with 90.8% having scheduled angiographic follow-up with quantitative coronary assessment at the 6-month mark. All measurements were performed on angiograms recorded after 200 μg of intracoronary nitroglycerin administration. Identical projections were used for each comparison. Quantitative analysis of angiographic data was analyzed offline by a single independent expert using the CAAS system (5.10, Pie Medical Imaging B.V., Maastricht, The Netherlands). The following parameters were analyzed: reference vessel diameter (RVD), minimal lumen diameter (MLD), percent diameter stenosis, acute lumen gain (defined as the difference between MLD after index PCI and MLD at baseline), net lumen gain (defined as the difference between MLD at follow-up and MLD at baseline), LLL (defined as the difference between MLD after index PCI and MLD at follow-up), lesion length, binary reste-

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Table 1. Patient Clinical Characteristics

	Total (n=227)	Women (n=60)	Men (n=167)	*p* value
Age, yr	59.4±9.7	61.6±11.0	58.5±9.1	0.034
Hypertension	146 (64.3)	47 (78.3)	99 (59.3)	0.008
Hypercholesterolemia	161 (70.9)	41 (68.3)	120 (71.9)	0.606
Diabetes mellitus	89 (39.2)	25 (41.7)	64 (38.3)	0.649
Current smoker	80 (35.2)	5 (8.3)	75 (44.9)	<0.001
Prior MI	18 (7.9)	5 (8.3)	13 (7.8)	0.893
Prior PCI	52 (22.9)	15 (25.0)	37 (22.2)	0.653
Prior stroke	37 (16.3)	9 (15.0)	28 (16.8)	0.751
Clinical presentation				
Stable CAD	193 (85.0)	51 (85.0)	142 (85.0)	0.754
Acute coronary syndrome	34 (15.0)	9 (15.0)	25 (15.0)	0.254

MI, myocardial infarction; PCI, percutaneous coronary intervention; CAD, coronary artery disease.
Values are mean±SD or n (%).

nosis, and dissection persistence (NHBLI classification). Late lumen enlargement was defined as an increase in the luminal diameter of the lesion from the immediate postprocedural measurement to follow-up measurements. This was frequently observed after DCB angioplasty for de novo CAD. Measurements included the whole segment, which was treated 5 mm proximally and distally. Binary restenosis was defined as stenosis of at least 50% of the luminal diameter as determined at the angiographic follow-up.

Statistical analysis

The independent expert analyzing the angiographic data was blinded to the gender and clinical data of patients. Categorical variables are presented as counts and percentages, and they were compared using Pearson's chi-square or Fisher's exact tests. Continuous variables are presented as mean±standard deviation or median [interquartile range (IQR)] according to a normal distribution as confirmed by the Kolmogorov-Smirnov test. The correlations between parameters were tested using the Spearman correlation coefficient. The cumulative incidence of clinical events was compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were analyzed using the Cox proportional hazard model. For multivariable analysis, adjustments were made for age, sex, hypertension, diabetes mellitus, current smoking, clinical presentation, prior PCI, multivessel disease, scoring balloon use, DCB to reference vessel ratio, dissection presence, RVD, lesion length, and MLD. Linear regression analysis was used to estimate the correlation coefficient between quantitative variables. All probability values were two-sided. *p* values<0.05 were considered statistically significant. Statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study population consisted of 227 consecutive patients treated with paclitaxel-coated balloons (SeQuent Please, B. Braun Melsungen AG, Berlin, Germany) for de novo CAD, who were retrospectively entered into the database and categorized by sex. The population consisted of 60 women (26.4%) and 167 men (73.6%). Angiographic and procedural success was achieved in all patients. None of the patients required administration of glycoprotein IIb/IIIa inhibitor or bailout stenting during the hospitalization period. Baseline clinical characteristics of the study population are shown in Table 1. Women were older and more women had hypertension, whereas men were more frequent smokers (8.3% vs. 44.9%, $p<0.001$).

Baseline angiographic and procedural characteristics are shown in Table 2. Of note, compared to men, women had smaller RVD (2.2, IQR: 2.0–2.5 mm vs. 2.5, IQR: 2.1–2.8 mm, $p<0.001$), smaller DCB diameters (2.5, IQR: 2.0–2.8 mm vs. 2.5, IQR: 2.5–3.0 mm, $p=0.008$), larger DCB to reference vessel ratios (1.14±0.20 vs. 1.09±0.15, $p=0.033$), and more dissections after DCB use (55.0% vs. 37.1%, $p=0.016$). In women, the predilation balloon to reference vessel ratio was higher than that in men (1.14±0.20 vs. 1.07±0.17, $p=0.010$). The DCB to predilation balloon ratio was similar in both sexes (1.02±0.16 in women vs. 1.03±0.14 in men, $p=0.745$). Acute lumen gain was also similar (1.40±0.47 mm in women vs. 1.51±0.51 mm in men, $p=0.143$).

Angiographic follow-up data of the 206 patients (90.8% of total patients, 88% of women, and 92% of men) returning for scheduled angiography at 6 months (IQR: 5 to 9-month) after treatment are shown in Table 2. The primary endpoint, LLL, was significantly higher in women (0.12±0.26 mm vs. 0.02±0.22 mm, $p=0.012$) (Fig. 1). Women also had a significantly lower net lumen gain (1.26±0.43 mm vs. 1.47±0.54 mm, $p=0.011$). The distribution of LLL was similar in both sexes (Fig. 2). Of the 206 lesions, 66 (32.0%) developed late lumen enlargement (24.5% in women and 34.6% in men) during the follow-up period. Dissection immediately after DCB treatment was more common

Table 2. Angiographic and Procedural Characteristics

	Total (n=227)	Women (n=60)	Men (n=167)	*p* value
Culprit vessel				
Left anterior descending artery	81 (35.7)	26 (43.3)	55 (32.9)	0.149
Left circumflex artery	90 (39.6)	22 (36.7)	68 (40.7)	0.582
Right coronary artery	56 (24.7)	12 (20.0)	44 (26.3)	0.328
Multivessel disease	143 (63.0)	35 (58.3)	108 (64.7)	0.436
Scoring balloon in predilation	22 (9.7)	3 (5.0)	19 (11.4)	0.205
Predilation balloon diameter, mm	2.5 (2.0–3.0)	2.5 (2.0–3.0)	2.5 (2.5–3.0)	0.103
Predilation balloon to reference vessel ratio	1.08±0.18	1.14±0.20	1.07±0.17	0.010
DCB diameter, mm	2.5 (2.5–3.0)	2.5 (2.0–2.8)	2.5 (2.5–3.0)	0.008
DCB diameter ≥3 mm	70 (30.8)	50 (23.4)	20 (33.6)	0.625
DCB to reference vessel ratio	1.10±0.17	1.14±0.20	1.09±0.15	0.033
DCB to predilation balloon ratio	1.03±0.15	1.02±0.16	1.03±0.14	0.745
DCB length, mm	20 (17–20)	20 (17–20)	20 (17–26)	0.276
DCB maximal pressure, atm	8 (7–9)	8 (7–10)	8 (7–9)	0.518
DCB inflation duration, second	60 (45–60)	60 (41–60)	55 (45–60)	0.892
Quantitative coronary angiography				
Pre-procedure	n=227	n=60	n=167	
Reference vessel diameter, mm	2.5 (2.1–2.8)	2.2 (2.0–2.5)	2.5 (2.1–2.8)	<0.001
Lesion length, mm	15.2 (9.8–20.0)	14.4 (9.9–18.8)	15.5 (9.7–20.5)	0.213
Minimal lumen diameter, mm	0.8 (0.4–1.1)	0.7 (0.4–1.0)	0.9 (0.5–1.1)	0.035
Diameter stenosis, %	66.2±16.5	66.7±16.8	66.0±16.5	0.783
Post-procedure	n=227	n=60	n=167	
Minimal lumen diameter, mm	2.3 (1.9–2.7)	2.1 (1.9–2.5)	2.4 (2.1–2.7)	<0.001
Diameter stenosis, %	9.6±11.2	9.8±10.0	9.6±11.6	0.865
Acute lumen gain, mm	1.48±0.50	1.40±0.47	1.51±0.51	0.143
Follow-up	n=206	n=53	n=153	
Minimal lumen diameter, mm	2.3 (2.0–2.6)	2.0 (1.8–2.3)	2.4 (2.0–2.7)	<0.001
Diameter stenosis, %	9.8±12.0	12.1±13.6	9.0±11.3	0.101
Net lumen gain, mm	1.42±0.52	1.26±0.43	1.47±0.54	0.011
Late lumen loss, mm	0.05±0.24	0.12±0.26	0.02±0.22	0.012
Late lumen enlargement	66 (32.0)	13 (24.5)	53 (34.6)	0.174
Binary restenosis	2 (1.0)	1 (1.9)	1 (0.7)	0.449
Dissection right after predilation	n=227	n=60	n=167	<0.001
None	133 (58.6)	27 (45.0)	106 (63.5)	
A	59 (26.0)	13 (21.7)	46 (27.5)	
B	22 (9.7)	15 (25.0)	7 (4.2)	
C	13 (5.7)	5 (8.3)	8 (4.8)	
Dissection after DCB treatment	n=227	n=60	n=167	<0.001
None	132 (58.1)	27 (45.0)	105 (62.9)	
A	58 (25.6)	12 (20.0)	46 (27.5)	
B	24 (10.6)	16 (26.7)	8 (4.8)	
C	13 (5.7)	5 (8.3)	8 (4.8)	
Dissection at follow-up	n=206	n=53	n=153	0.123
None	201 (97.6)	50 (94.3)	151 (98.7)	
A	4 (1.9)	2 (3.8)	2 (1.3)	
B	1 (0.5)	1 (1.9)	0	
C	0	0	0	

DCB, drug-coated balloon.
Values are mean±SD, median (interquartile ranges, 25th–75th), or n (%).

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in women. However, most of these disappeared angiographically during follow-up (no dissection: 94.3% in women and 98.7% in men) (Fig. 3). Moreover, no new dissections or no worse dissections were observed at follow-up in either sex. The presence of dissection and its severity were not associated with LLL in either sex (Fig. 4). The cumulative frequency of MLD, diameter stenosis, and LLL are shown in Fig. 5.

The clinical outcomes are presented in Table 3. During a median follow-up of 3.4 years (IQR: 25–53 months), the TVF was comparable, with a rate of 6.7% in women and 7.8% in men (p=0.922), and driven mainly by TVR in both groups. There was no cardiac death, and only one target vessel myocardial infarction, which occurred in men at 22-month, and was related to target lesion revascularization. In the multivariable analysis, the women sex was the only independent risk factor for LLL (Table 4).

In the multivariable analysis, women, stable CAD, higher DCB to reference vessel ratio, and longer lesion length were independently associated with a higher risk of dissection. Women had more dissections after DCB treatment; and dissections were significantly associated with women [odds ratio (OR)=2.69, p=0.009], stable CAD (OR=5.17, 95% CI: 1.82–17.34, p=0.004), DCB to reference vessel ratio (OR=1.36, 95% CI: 1.06–1.79, p=

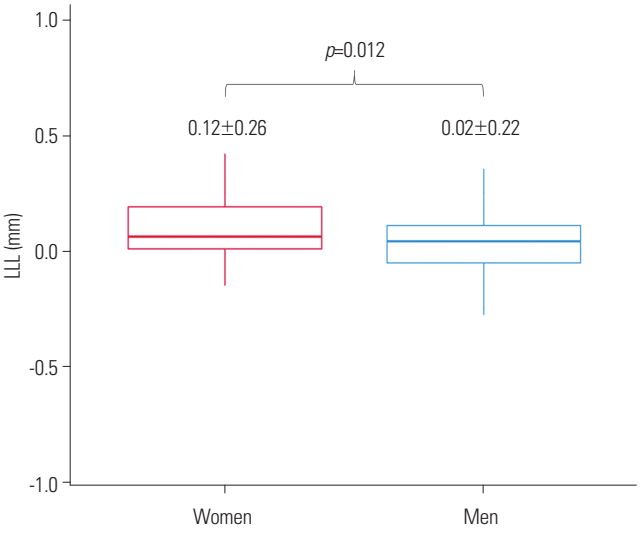

Fig. 1. Sex difference in late lumen loss (LLL).

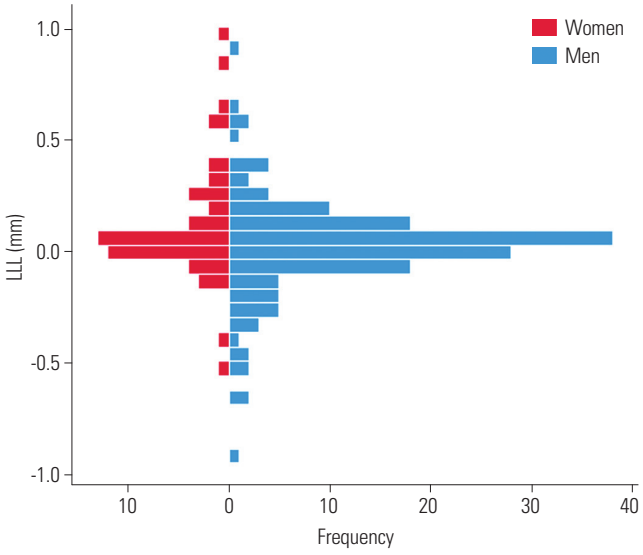

Fig. 2. Comparison of late lumen loss (LLL) frequency according to sex.

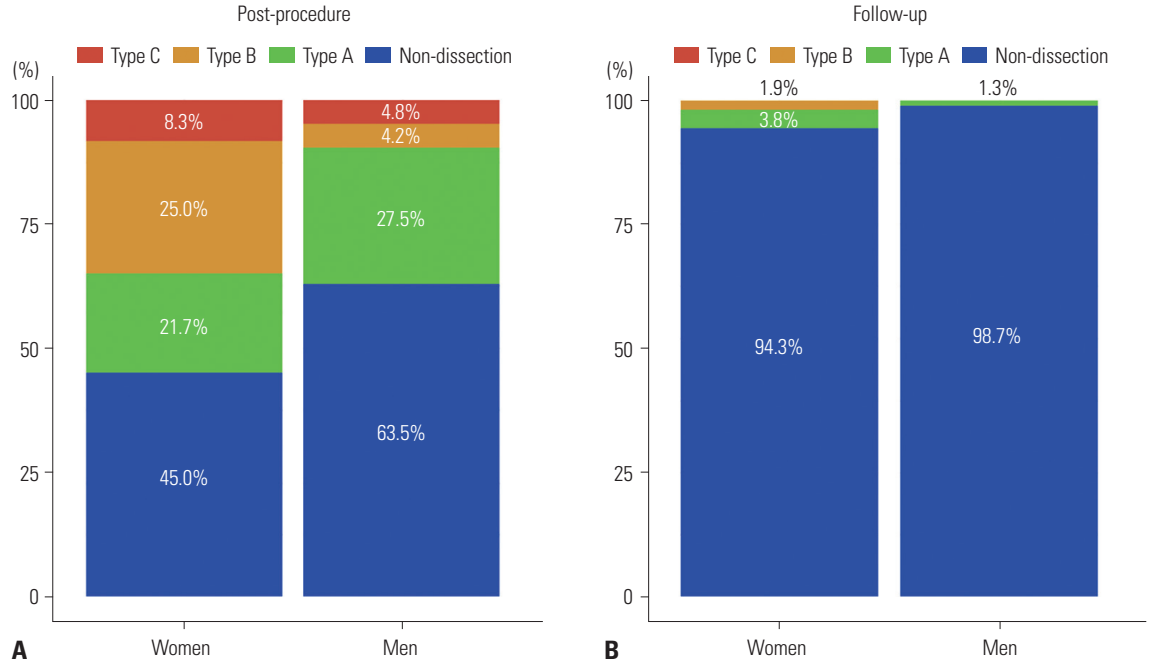

Fig. 3. Comparison of the prevalence of dissection by type after the procedure (A) and at follow-up (B) according to sex.

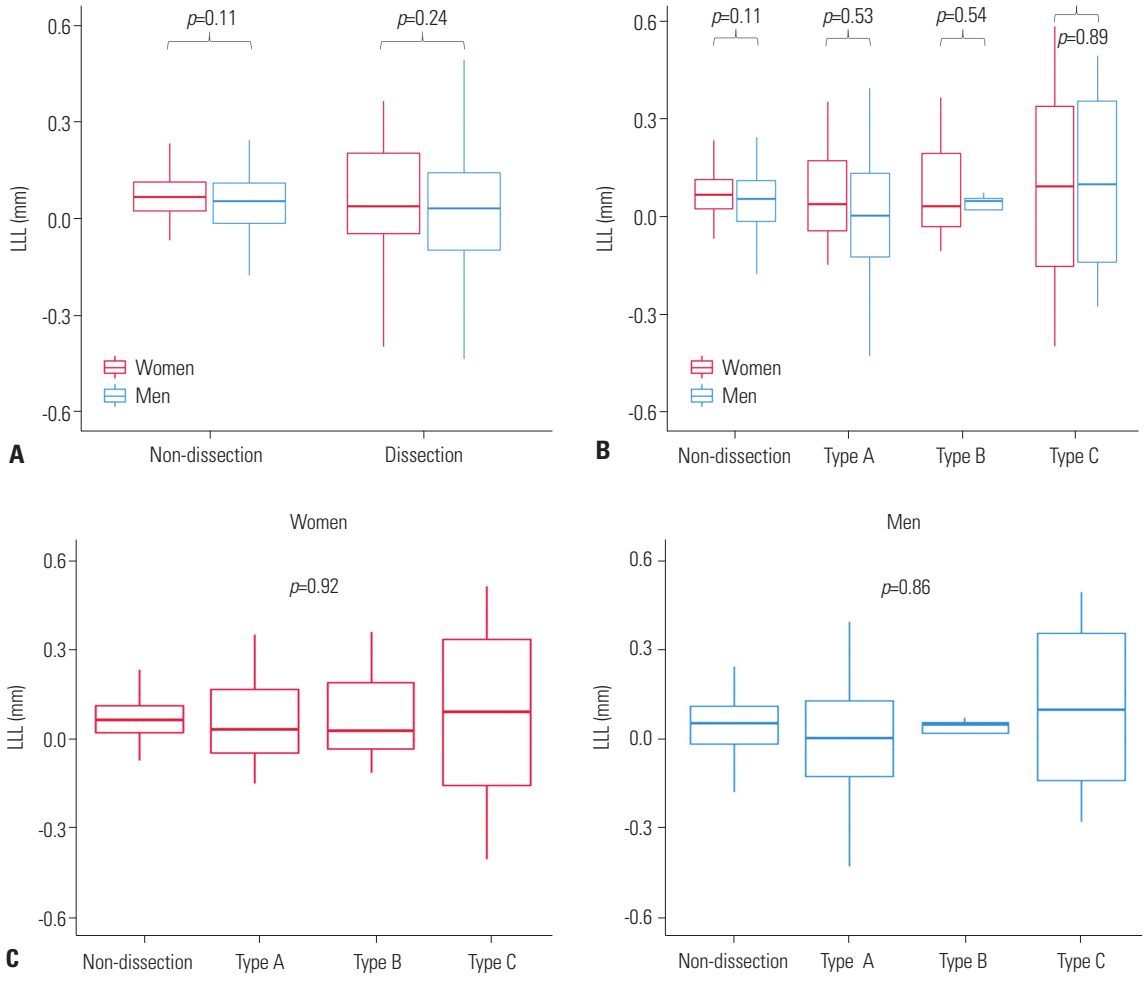

Fig. 4. Sex difference in LLL according to the presence of dissection (A) and comparison of LLL according to the dissection severity (B). LLL according to the severity of dissection in both sexes (C). LLL, late lumen loss.

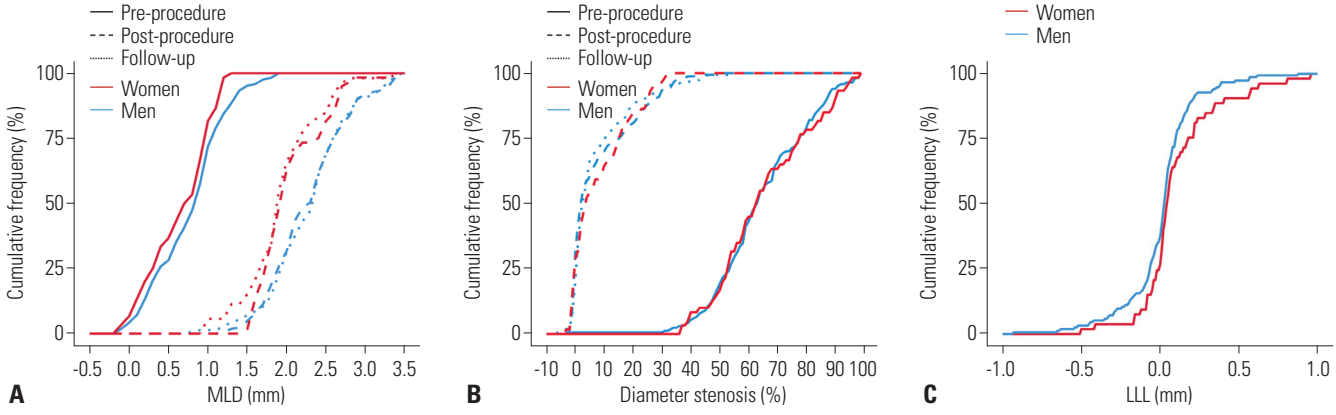

Fig. 5. Cumulative frequency distribution curves of MLD (A) and percent diameter stenosis (B) pre-procedure, post-procedure, and at follow-up. Cumulative frequency distribution curves of LLL according to sex (C). MLD, minimal lumen diameter; LLL, late lumen loss.

0.020), and lesion length (OR=1.11, 95% CI: 1.04–1.18, *p*=0.001), even after adjusting for clinical, angiographic, and procedural characteristics (Supplementary Table 1, only online).

DISCUSSION

The main findings of our study on the angiographic and clinical outcomes of DCB treatment for de novo coronary lesions according to sex were as follows: 1) women had a smaller

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Table 3. Comparison of Clinical Outcomes according to Sex

	Total (n=227)	Women (n=60)	Men (n=167)	*p* value*
Cardiac death	0	0	0	-
Target vessel myocardial infarction	1 (0.4)	0	1 (0.6)	0.573
Target lesion revascularization	6 (2.6)	2 (3.3)	4 (2.4)	0.528
Target vessel revascularization	17 (7.5)	4 (6.7)	13 (7.8)	0.944
Target vessel thrombosis	0	0	0	-
Target vessel failure	17 (7.5)	4 (6.7)	13 (7.8)	0.944

Event rates are presented as the proportion of patients with events in groups during a median follow-up duration of 3.4 years (range 12.7–28.9 months). Target vessel failure included cardiac death, target vessel myocardial infarction, target vessel revascularization, and target vessel thrombosis.
Values are n (%).
*p value is from the log-rank test.

Table 4. Independent Predictors of Late Lumen Loss

	Multivariable analysis		
	Beta	95% CI	*p* value
Women	0.091	0.006–0.176	0.036
Age	-0.002	-0.006–0.001	0.188
Hypertension	-0.026	-0.098–0.045	0.464
Diabetes	0.040	-0.029–0.110	0.256
Prior PCI	0.061	-0.021–0.143	0.143
Stable CAD	0.054	-0.039–0.147	0.256
DCB to reference vessel ratio	-0.118	-0.389–0.152	0.388
Scoring balloon use	-0.081	-0.200–0.037	0.177
Presence of dissection	-0.029	-0.106–0.048	0.455
Reference vessel diameter	-0.020	-0.107–0.067	0.648
Lesion length	0.004	-0.003–0.010	0.261
Minimal lumen diameter	-0.005	-0.097–0.088	0.920

PCI, percutaneous coronary intervention; CAD, coronary artery disease; DCB, drug-coated balloon.

vessel size (despite this, a larger DCB compared to RVD was used and women had more dissections after DCB treatment), 2) women had higher LLL compared to men, and 3) the women sex was an independent predictor of higher LLL.

Women coronary arteries are naturally smaller than men coronary arteries. This is independent of the body size and persists even after normalization for left ventricular mass.[6,18] In this study, women had a smaller RVD compared to men, which was consistent with previous studies.[19,20] The predilation balloon to reference vessel ratio was larger in women as the selected predilation balloon diameter did not differ between men and women. This finding can help explain why dissections occurred more frequently in women after predilation. The DCB diameter was relatively smaller in women, but the DCB to reference vessel ratio was larger. The DCB to the predilation balloon ratio was similar in men and women. Dissections after DCB treatment were not statistically significant compared to dissections observed after predilation. In women, predilation balloons and DCBs were larger than the RVD compared to men, which is believed to have resulted in more dissections in women. Therefore, in women, operators should be careful not to overestimate the size when choosing the predilation balloon and DCB.

Immediately after DCB treatment, there was no difference in acute lumen gain between the sexes, but the net lumen gain on follow-up angiography was greater in men. The primary endpoint, LLL, was higher in women (0.12±0.26 mm vs. 0.02±0.22 mm, p=0.012). However, the presence of dissection and higher LLL, which occurred in many women, were not related (Fig. 4A). Moreover, LLL did not differ according to the type of dissection in either sex (Fig. 4B and C). Reassuringly, in both men and women, dissections were rarely seen on follow-up angiography. Even the non-flow-limiting dissections that occurred after DCB treatment had mostly healed by the 6-month follow-up, and they did not result in restenosis or impact the outcomes. This phenomenon was different from the era of plain old balloon angioplasty, where in-hospital death rates were higher in women (0.3%) than in men (0.09%).[18] In contemporary practice, unlike in the angioplasty era, DES, dual antiplatelets, and anticoagulants are available to help manage complications after balloon angioplasty. The present study excluded cases of severe or flow-limiting dissections after balloon angioplasty and only evaluated angiography and clinical follow-up of those who successfully received DCB treatment. However, our findings did confirm that balloon angioplasty can now be used safely with the knowledge that optimal medical support and that new-generation DES are available to manage flow-limiting dissections or acute vessel closures, thereby enabling DCB treatment to achieve DES-like clinical results.[12,13,21,22] This effect may be one of the reasons women have had positive results after DCB treatment. In a previous study regarding the sex differences in angiographic outcomes after PCI, the 2-year follow-up angiography showed no difference in terms of in-stent LLL (0.18±0.54 mm vs. 0.20±0.99 mm, p=0.76) and in-segment binary restenosis (8.5% vs. 8.5%, p=0.76) after DES implantation between women and men, respectively.[23] In the current study, LLL was higher in women than in men (0.12±0.26 mm vs. 0.02±0.22 mm, p=0.012). Considering that the mechanism by which DES and DCB inhibit intimal hyperplasia is through antiproliferative drugs, it is difficult to assess the higher levels of LLL in women than in men in this study. This result may be due to the small number of samples; therefore, studies with a larger sample size may be needed in the future. Our study had sever-

al limitations. First, this study was a retrospective analysis of a relatively small number of patients. Second, the study population was limited as they came from two centers with expertise in this type of PCI. Consequently, the low incidence of TVF made it difficult to show the impact of sex on TVF. However, this was consistent with other studies on DCB treatment in de novo lesions.[12,13,21,22] Third, there was no information on medications, such as statins or antithrombotics, that could affect LLL in this study. Fourth, the present study did not target all patients, and focused only on those who successfully received DCB treatment. In this study, it was not possible to determine the proportion of patients who received DES implantation in both groups since lesion preparation was not appropriate after predilation. Therefore, the results of this study should be interpreted carefully. Large-scale prospective studies are needed to clarify the mechanisms responsible for TVF in men and women after DCB treatment.

In conclusion, women had worse LLL, while there was no difference in TVF between women and men. Based on the multivariable analysis, the women sex was an independent predictor of higher LLL and the presence of dissection.

AUTHOR CONTRIBUTIONS

Conceptualization: Eun-Seok Shin and Tang Qiang. Data curation: Eun-Seok Shin, Tang Qiang, and Liu Kun. Formal analysis: Eun-Seok Shin, Tang Qiang, Liu Kun, Eun Jung Jun, and Youngjune Bhak. Investigation: Eun-Seok Shin, Tang Qiang, Liu Kun, and Eun Jung Jun. Methodology: Eun-Seok Shin, Tang Qiang, and Liu Kun. Project administration: Eun-Seok Shin and Tang Qiang. Resources: Eun-Seok Shin and Tang Qiang. Software: Eun Jung Jun and Youngjune Bhak. Supervision: Eun-Seok Shin and Tang Qiang. Validation: Eun Jung Jun and Youngjune Bhak. Visualization: Eun Jung Jun and Youngjune Bhak. Writing—original draft: Eun-Seok Shin and Liu Kun. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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