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Clinical Outcome after Everolimus-Eluting Stent Implantation for Small Vessel Coronary Artery Disease: XIENCE Asia Small Vessel Study

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There are limited data on outcomes after implantation of everolimus-eluting stents (EES) in East Asian patients with small vessel coronary lesions. A total of 1,600 patients treated with XIENCE EES (Abbott Vascular, CA, USA) were divided into the small vessel group treated with one ≤2.5 mm stent (n=119) and the non-small vessel group treated with one ≥2.75 mm stent (n=933). The primary end point was a patient-oriented composite outcome (POCO), a composite of all-cause death, myocardial infarction (MI), and any repeat revascularization at 12 months. The key secondary end point was a device-oriented composite outcome (DOCO), a composite of cardiovascular death, target-vessel MI, and target lesion revascularization at 12 months. The small vessel group was more often female, hypertensive, less likely to present with ST-elevation MI, and more often treated for the left circumflex artery, whereas the non-small vessel group more often had type B2/C lesions, underwent intravascular ultrasound, and received unfractionated heparin. In the propensity matched cohort, the mean stent diameter was 2.5±0.0 mm and 3.1±0.4 mm in the small and non-small vessel groups, respectively. Propensity-adjusted POCO at 12 months was 6.0% in the small vessel group and 4.3% in the non-small vessel group (p=0.558). There was no significant difference in DOCO at 12 months (small vessel group: 4.3% and non-small vessel group: 1.7%, p=0.270). Outcomes of XIENCE EES for small vessel disease were comparable to those for non-small vessel disease at 12-month clinical follow-up in real-world Korean patients.

Key Words: *Coronary Artery Disease; Drug-Eluting Stents; Everolimus*

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INTRODUCTION

Small vessel coronary artery disease (CAD) is encountered in 30% to 50% of patients undergoing percutaneous coronary intervention (PCI) and has been associated with a higher risk of adverse clinical events including repeat revascularization and stent thrombosis (ST).[1,2] Compared to early-generation drug-eluting stents (DES), contemporary newer-generation DES have thinner struts with more biocompatible polymers, which may be advantageous in small target vessels because strut thickness and a smaller in-stent lumen diameter are known predictors of restenosis after stenting.[3] Currently, however, outcome data for

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after second-generation DES for small vessel lesions are scarce.[4-7]

XIENCE everolimus-eluting stent (EES) is a thin-strut cobalt-chromium alloy with a durable and biocompatible polymer that releases everolimus (100 μg/cm^2) over a 3- to 4-month period. The clinical safety and efficacy of the XIENCE V EES was previously demonstrated in Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System (SPIRIT) II, III and IV trials[8-10] and other investigator-sponsored studies.[11,12] The pooled analysis of SPIRIT II,[8] SPIRIT III,[9] SPIRIT IV[10] randomized trials demonstrated significantly lower rates of myocardial infarction (MI), target lesion revascularization (TLR), ST, and major adverse cardiac events (MACE) with EES compared with first-generation paclitaxel-eluting stents (PES).[4] A small vessel subgroup analysis from the XIENCE V USA study compared 1-year clinical outcomes between patients who received a single 2.5 mm stent (small vessel group, n=838) and those treated with a single >2.5 mm stent (non-small vessel group, n=2,015).[6] The 1-year clinical outcomes after XIENCE V EES were similar in both small and non-small vessel groups with regard to definite or probable ST (0.37% vs. 0.40%), cardiac death or MI (4.5% vs. 5.1%) and TLR (3.8% vs. 3.0%).

There is, however, a paucity of data on outcomes after EES in East Asian patients with small vessel coronary lesions. The present study aimed to investigate the 12-month clinical outcomes after XIENCE EES stent placement in real-world Korean patients with small vessel CAD.

MATERIALS AND METHODS

1. Patient selection and enrollment

The present XIENCE Asia Small Vessel Study is a prospective, multicenter, observational study. Patients were eligible for inclusion if they were ≥18 years of age and had lesions requiring interventions amendable for implantation of XIENCE EES (Abbott Vascular, CA, USA) during the index procedure. Patients were excluded if they had left main stem disease, previous intervention in the target vessel, graft vessel disease, left ventricular ejection fraction (LVEF) <30%, cardiogenic shock, major bleeding within 3 months or major surgery within 2 months, platelet count <120,000 cells/mm^3, Hgb <9 g/dL, serum creatinine ≥2.0 mg/dL or on dialysis, or serum aspartate or alanine aminotransferase level >3 times upper normal reference values.

A total of 1,600 patients were recruited from 9 teaching hospitals in Korea from 2013 to 2019. Patients were divided into the small vessel group (119 patients) who received one ≤2.5 mm stent and the non-small vessel group (933 patients) who were treated with one ≥2.75 mm stent (Fig. 1). The present study was conducted according to the Declaration of Helsinki. The institutional review board of all participating centers approved the study protocol. The approval number was CNUH-2012-136 of Chonnam National University Hospital. Written informed consent was obtained from all participating patients.

2. Device description and procedure

The XIENCE EES consists of a thin-strut (81 μm) L605 cobalt-chromium alloy that releases everolimus (100 μg/cm^2) over a 3- to 4-month period from a 7.6 μm-thick durable and biocompatible circumferential polymer (poly-n-butyl-methacrylate and copolymer of vinylidine fluoride and hexafluoro-propylene). The XIENCE EES used in the study were Xience Prime, Xience Xpedition, and Xience Alpine in diameters of 2.25 to 4.00 mm and in lengths of 8, 12, 15, 18, 23, 28, 33, and 38 mm.

3. Study procedure

All procedures were performed according to the standard guidelines.[13] Patients received loading doses of aspirin (300 mg) and a P2Y12 inhibitor (ticagrelor 180 mg, prasugrel 60 mg, or clopidogrel 300-600 mg) before PCI. Clopidogrel was routinely used in patients with stable angina pectoris. Patients with acute coronary syndrome received a potent P2Y12 inhibitor (prasugrel or ticagrelor) or clopidogrel based on individual bleeding and ischemic risk. The selection of vessels treated, devices used, and adjunctive drugs administered to support PCI was left to the discretion of the operator. After PCI, patients received maintenance doses of either clopidogrel (75 mg daily), ticagrelor (90 mg twice daily) or prasugrel (10 mg daily). Aspirin was given at a dose of 100 mg daily. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor were prescribed after PCI for at least 6 months for patients with stable angina pectoris and 12 months for patients with acute coronary syndrome unless they were at high risk of bleeding.[13,14]

4. Clinical endpoints and follow-up

The primary end point was a patient-oriented composite outcome (POCO) defined as a composite of all-cause death, MI, and any repeat revascularization at 12 months.[15] The key secondary end point was a device-oriented composite outcome (DOCO) defined as a composite of cardiovascular death, target-vessel MI, and TLR at 12 months.[15] Other secondary endpoints included target vessel failure defined as a composite of cardiovascular death, target-vessel MI, and target vessel revascularization (TVR); definite or probable

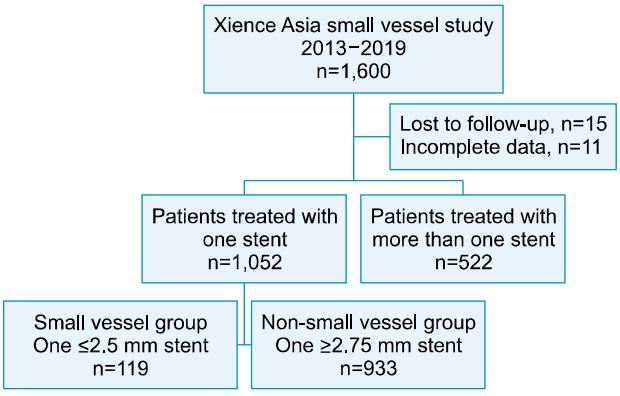

FIG. 1. Study population.

ST defined by the Academic Research Consortium;[15] and bleeding complications classified according to the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria[16] at 12 months. MI was defined as the recurrence of symptoms or the presence of electrocardiogram changes in association with a rise in cardiac biomarker levels above the upper limit of normal. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself. Procedural success was defined as post-procedure diameter stenosis $<30\%$, TIMI 3 flow in all target lesions as visually assessed by the treating physician. Clinical follow-up was scheduled at 1, 6, 9, 12 months after the index procedure by phone or preferably by outpatient clinic visit. Additionally, self-reported DAPT usage was also examined in both groups. There was no mandatory angiographic follow-up in this study and follow-up coronary angiography was performed on an ischemia-driven basis. TVR was considered to be ischemia driven if associated with a positive functional study, a target vessel diameter stenosis $\geq 50\%$ by core laboratory quantitative analysis with ischemic symptoms, or a target vessel diameter stenosis $\geq 70\%$ with or without documented ischemia.

5. Statistical analysis

Continuous variables were expressed as mean±standard deviation and were compared with the Student t test. Categorical variables were presented as numbers and percentages and were compared with the Chi-square test or Fisher's exact test. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated for outcome variables using Cox regression analysis. In order to adjust for potential confounders, propensity scores were used. The propensity scores were estimated for the likelihood of receiving treatment for the small vessel using a multiple logistic regression model that contained 23 covariates: age, sex, body mass index, smoking status, hypertension, diabetes mellitus, dyslipidemia, prior MI, chronic kidney disease, family history of CAD, prior heart failure, prior stroke, prior peripheral artery disease, prior PCI, prior coronary artery bypass graft surgery, clinical presentation, disease extent, American College of Cardiology/American Heart Association (ACC/AHA) lesion type B2/C, severe calcification, bifurcation, thrombotic lesion, treated vessel, and intravascular ultrasound (IVUS) use. The c-statistic for the propensity model was 0.80, indicating a good ability to discriminate treatment groups. The Hosmer-Lemeshow goodness-of-fit test p value was 0.13, confirming good calibration and fit of the multivariable model that estimated the propensity score. Matching was performed using a greedy matching protocol (1:1 nearest neighbor matching without replacement) with a caliper width of 0.2 of the standard deviation. A total of 117 patients in the small vessel group were matched to 117 patients in the non-small vessel group. After matching, none of the covariates showed a standardized difference exceeding 10%, suggesting that all of the measured covariates were well balanced between the matched groups.[17] The risks of clinical end points in the matched cohort were compared by using a Cox proportional hazards regression model stratified on matched pairs. All p values were 2 tailed, with statistical significance set at a level of <0.05. Statistical analyses were conducted using SPSS version 21 (SPSS Inc., Chicago, IL, USA) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Baseline clinical characteristics

Baseline clinical characteristics before and after propensity matching are shown in Table 1. In all patients, the small vessel group was more often female (37.0% vs. 25.5%, p=0.008), hypertensive (67.2% vs. 57.2%, p=0.037), and less likely to present with ST-elevation MI (4.2% vs. 10.6%, p=0.027), as compared to the non-small vessel group. No differences were observed between the two groups after propensity score matching (Table 1).

2. Lesion and procedural characteristics

The small vessel group more often received treatment for the left circumflex artery (50.4% vs. 14.4%, $p<0.001$), whereas the non-small vessel group more often had ACC/AHA type B2/C lesion (75.6% vs. 83.8%, p=0.026), treatment for the left anterior descending artery (33.6% vs. 59.4%, $p<0.001$) and the right coronary artery (14.3% vs. 25.8%, p=0.006), and more often received unfractionated heparin (27.7% vs. 41.9%, p=0.003) and IVUS (8.4% vs. 22.1%, $p<0.001$) (Table 2). After propensity matching, there were no differences between the two groups. In the propensity-matched cohort, the mean stent diameter was 2.5±0.0 mm in the small vessel group and 3.1±0.4 mm in the non-small vessel group. Procedural success rates were 100% in both groups (Table 2).

3. Antithrombotic medication

Antithrombotic medication at discharge and at 12 months is shown in Table 3. At discharge, in the propensity matched patients, the use of aspirin was 100% in both groups and of P2Y12 inhibitors was 100% and 99.1% in the small and non-small vessel groups, respectively (p=0.316). At 12 months, in the propensity matched cohort, there was no difference between the small and non-small vessel groups in the use of aspirin (91.5% vs. 88.9%, p=0.510) and P2Y12 inhibitors (92.3% vs. 91.5%, p=0.811). DAPT was used in 83.8% in the small vessel group and in 80.3% in the non-small vessel group (p=0.496).

4. Clinical outcomes

In-hospital and 12-month clinical outcomes are presented in Table 4. There was no death or ST in either group before and after propensity score matching with low rates

Table 1. Baseline clinical characteristics of enrolled patients

Variables	All patients			Propensity-matched patients		
	Small vessel group (n=119)	Non-small vessel group (n=933)	p value	Small vessel group (n=117)	Non-small vessel group (n=117)	p value
Age (yr)	64.5±10.6	62.6±10.7	0.060	64.4±10.6	63.8±11.1	0.679
Female	44 (37.0%)	238 (25.5%)	0.008	43 (36.8%)	46 (39.3%)	0.686
Body mass index (kg/m^2)	25.2±4.7	24.8±3.2	0.383	25.2±4.7	25.3±3.3	0.811
Current smoker	34 (28.6%)	285 (30.5%)	0.659	33 (28.2%)	34 (29.1%)	0.885
Hypertension	80 (67.2%)	534 (57.2%)	0.037	79 (67.5%)	81 (69.2%)	0.779
Diabetes mellitus	41 (34.5%)	265 (28.3%)	0.162	40 (34.2%)	42 (35.9%)	0.784
Dyslipidemia	58 (48.7%)	474 (50.8%)	0.671	56 (47.9%)	55 (47.0%)	0.896
Prior MI	5 (4.2%)	20 (2.1%)	0.165	5 (4.3%)	4 (3.4%)	0.734
Chronic kidney disease	1 (0.8%)	6 (0.6%)	0.803	1 (0.9%)	1 (0.9%)	1.000
Family history of CAD	2 (1.7%)	22 (2.4%)	0.641	2 (1.7%)	1 (0.9%)	0.561
Prior heart failure	3 (2.5%)	8 (0.9%)	0.093	2 (1.7%)	1 (0.9%)	0.561
Prior stroke	11 (9.2%)	49 (5.3%)	0.077	11 (9.4%)	9 (7.7%)	0.640
Prior peripheral artery disease	3 (2.5%)	11 (1.2%)	0.229	3 (2.6%)	4 (3.4%)	0.701
Prior PCI	14 (11.8%)	69 (7.4%)	0.096	13 (11.1%)	9 (7.7%)	0.370
Prior CABG	1 (0.8%)	6 (0.6%)	0.803	1 (0.9%)	0 (0.0%)	0.316
Clinical presentation						
Stable angina	25 (21.0%)	174 (18.3%)	0.479	25 (21.4%)	23 (19.7%)	0.746
Unstable angina	58 (48.7%)	458 (49.1%)	0.943	57 (48.7%)	58 (49.6%)	0.896
ST-segment elevation MI	5 (4.2%)	99 (10.6%)	0.027	5 (4.3%)	5 (4.3%)	1.000
Non-ST-segment elevation MI	31 (26.1%)	205 (22.0%)	0.315	30 (25.6%)	31 (26.5%)	0.882
LVEF (%)	62.3±9.3	61.6±9.2	0.460	62.3±9.4	62.1±7.9	0.808

Values are n (%), mean±SD. CABG: coronary artery bypass graft surgery, CAD: coronary artery disease, LVEF: left ventricular ejection fraction, MI: myocardial infarction, PCI: percutaneous coronary intervention.

Table 2. Angiographic and procedural characteristics

Variables	All patients			Propensity-matched patients		
	Small vessel group (n=119)	Non-small vessel group (n=933)	p value	Small vessel group (n=117)	Non-small vessel group (n=117)	p value
Disease extent						
1 vessel disease	87 (73.1%)	702 (75.2%)	0.613	86 (73.5%)	86 (73.5%)	1.000
2 vessel disease	25 (21.0%)	176 (18.9%)	0.575	24 (20.5%)	21 (17.9%)	0.619
3 vessel disease	7 (5.9%)	55 (5.9%)	0.996	7 (6.0%)	10 (8.5%)	0.450
Lesion complexity						
ACC/AHA lesion type B2/C	90 (75.6%)	782 (83.8%)	0.026	88 (75.2%)	91 (77.8%)	0.644
Severe calcification	1 (0.8%)	0 (0.0%)	0.113	0 (0.0%)	0 (0.0%)	-
Bifurcation	1 (0.8%)	9 (1.0%)	0.895	0 (0.0%)	0 (0.0%)	-
Thrombotic lesion	0 (0.0%)	7 (0.8%)	0.343	0 (0.0%)	0 (0.0%)	-
Treated vessel						
Left anterior descending artery	40 (33.6%)	554 (59.4%)	<0.001	39 (33.3%)	42 (35.9%)	0.680
Left circumflex artery	60 (50.4%)	135 (14.4%)	<0.001	60 (51.3%)	57 (48.7%)	0.695
Right coronary artery	17 (14.3%)	241 (25.8%)	0.006	17 (14.5%)	17 (14.5%)	1.000
Ramus intermedius artery	2 (1.7%)	3 (0.3%)	0.101	1 (0.9%)	1 (0.9%)	1.000
Intravascular ultrasound use	10 (8.4%)	206 (22.1%)	<0.001	10 (8.5%)	9 (7.7%)	0.811
Anticoagulation agent						
Unfractionated heparin	33 (27.7%)	391 (41.9%)	0.003	32 (27.4%)	32 (27.4%)	1.000
Low molecular weight heparin	48 (40.3%)	429 (46.0%)	0.244	46 (39.3%)	60 (51.3%)	0.066
Glycoprotein IIb/IIIa inhibitor	0 (0.0%)	17 (1.8%)	0.138	0 (0.0%)	1 (0.9%)	0.316
Stent diameter (mm)	2.5±0.0	3.2±0.4	<0.001	2.5±0.0	3.1±0.4	<0.001
Stent length (mm)	23.6±8.2	24.4±7.9	0.308	23.5±8.1	22.3±7.2	0.238
Procedural success	119 (100.0%)	933 (100.0%)	-	117 (100.0%)	117 (100.0%)	-

Values are n (%) or mean±SD. ACC/AHA: American College of Cardiology/American Heart Association, PCI: percutaneous coronary intervention, TIMI: thrombolysis in myocardial infarction.

TABLE 3. Antithrombotic medication at discharge and 12 months

Variables	All patients			Propensity-matched patients		
	Small vessel group (n=119)	Non-small vessel group (n=933)	p value	Small vessel group (n=117)	Non-small vessel group (n=117)	p value
At discharge						
Aspirin	119 (100.0%)	932 (99.9%)	0.887	117 (100.0%)	117 (100.0%)	-
P2Y12 inhibitor	119 (100.0%)	931 (99.8%)	0.786	117 (100.0%)	116 (99.1%)	0.316
Clopidogrel	90 (75.6%)	653 (70.1%)	0.215	89 (76.1%)	89 (76.7%)	0.906
Ticagrelor	21 (17.6%)	189 (20.1%)	0.530	20 (17.1%)	19 (16.4%)	0.884
Prasugrel	8 (6.7%)	91 (9.8%)	0.283	8 (6.8%)	8 (6.9%)	0.986
Warfarin	0 (0.0%)	9 (1.0%)	0.282	0 (0.0%)	1 (0.9%)	0.316
At 12 months						
Aspirin	108 (90.8%)	833 (89.3%)	0.622	107 (91.5%)	104 (88.9%)	0.510
P2Y12 inhibitor	110 (92.4%)	848 (90.9%)	0.577	108 (92.3%)	107 (91.5%)	0.811
Clopidogrel	93 (78.2%)	694 (74.4%)	0.373	91 (77.8%)	98 (83.8%)	0.246
Ticagrelor	12 (10.1%)	97 (10.4%)	0.916	12 (10.3%)	7 (6.0%)	0.231
Prasugrel	5 (4.2%)	57 (6.1%)	0.405	5 (4.3%)	2 (1.7%)	0.446
Warfarin	0 (0.0%)	9 (1.0%)	0.282	0 (0.0%)	1 (0.9%)	0.316
Dual antiplatelet therapy	99 (83.2%)	748 (80.2%)	0.433	98 (83.8%)	94 (80.3%)	0.496
Aspirin plus clopidogrel	84/99 (84.8%)	599/748 (80.1%)	0.259	83/98 (84.7%)	85/94 (90.4%)	0.230
Aspirin plus ticagrelor	10/99 (10.1%)	94/748 (12.6%)	0.482	10/98 (10.2%)	7/94 (7.4%)	0.501
Aspirin plus prasugrel	5/99 (5.1%)	55/748 (7.4%)	0.401	5/98 (5.1%)	2/94 (2.1%)	0.445
Single antiplatelet therapy	20 (16.8%)	185 (19.8%)	0.433	19 (16.2%)	23 (19.7%)	0.496
Aspirin monotherapy	9/20 (45.0%)	85/185 (45.9%)	0.936	9/19 (47.4%)	10/23 (43.5%)	0.801
P2Y12 inhibitor monotherapy	11/20 (55.0%)	100/185 (54.1%)	0.936	10/19 (52.6%)	13/23 (56.5%)	0.801
Clopidogrel	9/11 (81.8%)	95/100 (95.0%)	0.088	8/10 (80.0%)	13/13 (100.0%)	0.178
Ticagrelor	2/11 (18.2%)	3/100 (3.0%)	0.076	2/10 (20.0%)	0/13 (0.0%)	0.178
Prasugrel	0/11 (0.0%)	2/100 (2.0%)	0.811	0/10 (0.0%)	0/13 (0.0%)	-

Values are n (%).

of MI, repeat revascularization, stroke, or bleeding events. Propensity-adjusted POCO at 12 months was 6.0% in the small vessel group and 4.3% in the non-small vessel group (p=0.558) (Table 4 and Fig. 2A). There was also no significant difference in DOCO at 12 months (small vessel group: 4.3% and non-small vessel group: 1.7%, p=0.270) (Table 4 and Fig. 2B).

DISCUSSION

The major finding of the present study is that XIENCE EES implantation for patients with small vessel CAD showed clinical outcomes comparable to those with non-small vessel CAD at 12-month follow-up. In the propensity-adjusted cohort, 12-month event rates were low and not significantly different between the small and non-small vessel groups with regard to MI (2.6% vs. 2.6%), TLR (1.7% vs. 0.0%), POCO (6.0% vs. 4.3%), and DOCO (4.3% vs. 1.7%). There were no deaths or ST in either group with low rate MI, highlighting the safety of this stent. These results further support the therapeutic benefit of XIENCE EES platform to a real-world patient population with small vessel disease in Korea.

In daily clinical practice, the treatment of small vessel CAD remains a challenge due to an increased risk of repeat revascularization and/or ST after PCI.[1] Apart from the higher risk caused by restenosis, patients with small vessel lesions are known to differ in baseline characteristics from those with lesions in larger vessels. Patients with small vessel CAD are often female[18] and diabetic[4,19] and treated for longer lesions[20] or multiple vessels.[21]

Small vessel lesions were associated with a higher risk of repeat revascularization and ST after PCI with early-generation DES which have thick struts and less biocompatible polymers.[1,2] Similarly, in a substudy of the Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary Revascularization (LEADERS) trial,[22] in which 1,707 patients were treated with either a second-generation thick-strut biolimus-eluting stent (BES) or first-generation sirolimus-eluting stent (SES). There were significantly higher rates of TLR (9.6% vs. 2.6%, p=0.001) and MACE (12.1% vs. 7.1%, p=0.041) in patients treated in small vessels ($\leq$2.75 mm). There was no difference in outcome between BES and SES.

Contemporary newer-generation DES have thinner struts with more biocompatible polymers, which may be advantageous in small target vessels. The pooled analysis of randomized trials of SPIRIT II,[8] SPIRIT III,[9] SPIRIT IV,[10] which enrolled relatively non-complex patient pop-

TABLE 4. Clinical outcomes during hospitalization and at 12 months

Variables	All patients				Propensity-matched patients			
	Small vessel group (n=119)	Non-small vessel group (n=933)	HR (95% CI)	p value	Small vessel group (n = 117)	Non-small vessel group (n=117)	HR (95% CI)	p value
In-hospital outcome								
Death from any cause	0 (0%)	0 (0.0%)	-	-	0 (0%)	0 (0.0%)	-	-
MI	3 (2.5%)	28 (3.0%)	0.82 (0.25-2.71)	0.750	3 (2.6%)	2 (1.7%)	1.47 (0.25-8.81)	0.672
Target vessel MI	3 (2.5%)	25 (2.7%)	0.93 (0.28-3.08)	0.905	3 (2.6%)	2 (1.7%)	1.47 (0.25-8.81)	0.672
Repeat revascularization	0 (0.0%)	2 (0.2%)	-	0.786	0 (0%)	0 (0.0%)	-	-
TLR	0 (0.0%)	1 (0.1%)	-	0.887	0 (0%)	0 (0.0%)	-	-
TVR	0 (0.0%)	2 (0.2%)	-	0.786	0 (0%)	0 (0.0%)	-	-
Non-TVR	0 (0.0%)	1 (0.1%)	-	0.887	0 (0%)	0 (0.0%)	-	-
Stroke	0 (0.0%)	1 (0.1%)	-	0.887	0 (0%)	0 (0.0%)	-	-
Ischemic stroke	0 (0.0%)	1 (0.1%)	-	0.887	0 (0%)	0 (0.0%)	-	-
Stent thrombosis	0 (0.0%)	0 (0.0%)	-	-	0 (0%)	0 (0.0%)	-	-
TIMI major/minor bleeding	1 (0.8%)	6 (0.6%)	1.32 (0.16-11.12)	0.798	1 (0.9%)	0 (0.0%)	-	0.316
TIMI major bleeding	0 (0.0%)	0 (0.0%)	-	-	0 (0%)	0 (0.0%)	-	-
Outcome at 12 months								
Death from any cause	0 (0.0%)	0 (0.0%)	-	-	0 (0%)	0 (0.0%)	-	-
MI	3 (2.5%)	30 (3.2%)	0.78 (0.24-2.57)	0.688	3 (2.6%)	3 (2.6%)	1.00 (0.20-4.98)	0.996
Target vessel MI	3 (2.5%)	25 (2.7%)	0.94 (0.28-3.12)	0.921	3 (2.6%)	2 (1.7%)	1.51 (0.25-9.01)	0.654
Repeat revascularization	4 (3.4%)	24 (2.6%)	1.32 (0.46-3.81)	0.606	4 (3.4%)	2 (1.7%)	2.01 (0.37-10.95)	0.422
TLR	2 (1.7%)	2 (0.2%)	7.85 (1.11-55.70)	0.039	2 (1.7%)	0 (0.0%)	-	0.498
TVR	3 (2.5%)	10 (1.1%)	2.37 (0.65-8.60)	0.191	3 (2.6%)	1 (0.9%)	3.01 (0.31-28.91)	0.340
Non-TVR	1 (0.8%)	15 (1.6%)	0.53 (0.07-4.01)	0.537	1 (0.9%)	1 (0.9%)	1.00 (0.06-16.06)	0.998
Stroke	0 (0.0%)	5 (0.5%)	-	0.548	0 (0.01%)	1 (0.9%)	-	0.316
Ischemic stroke	0 (0.0%)	5 (0.5%)	-	0.548	0 (0.01%)	1 (0.9%)	-	0.316
Stent thrombosis	0 (0.0%)	0 (0.0%)	-	-	0 (0%)	0 (0.0%)	-	-
TIMI major/minor bleeding	1 (0.8%)	18 (1.9%)	0.43 (0.06-3.24)	0.414	1 (0.9%)	3 (2.6%)	0.34 (0.04-3.24)	0.346
TIMI major bleeding	0 (0.0%)	5 (0.5%)	-	0.548	0 (0.0%)	1 (0.9%)	-	0.316
POCO	7 (5.9%)	52 (5.6%)	1.06 (0.48-2.33)	0.890	7 (6.0%)	5 (4.3%)	1.41 (0.45-4.44)	0.558
DOCO	5 (4.2%)	27 (2.9%)	1.45 (0.56-3.77)	0.444	5 (4.3%)	2 (1.7%)	2.52 (0.49-12.98)	0.270
Target vessel failure	6 (5.0%)	35 (3.8%)	1.35 (0.57-3.20)	0.501	6 (5.1%)	3 (2.6%)	2.01 (0.50-8.05)	0.322

Values are n (%). CI: confidence interval, DOCO: device-oriented composite outcome, HR: hazard ratio, MI: myocardial infarction, Non-TVR: non-target vessel revascularization, POCO: patient-oriented composite outcome, TIMI: thrombolysis in myocardial infarction, TLR: target lesion revascularization, TVR: target vessel revascularization.

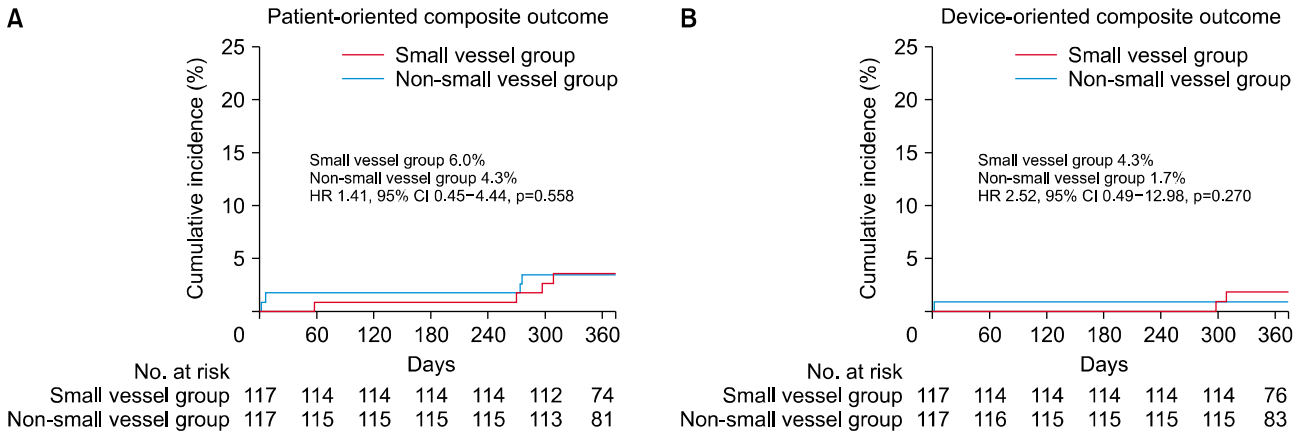

FIG. 2. Propensity-adjusted clinical outcomes at 12 months. (A) Patient-oriented composite outcome. (B) Device-oriented composite outcome. CI: confidence interval, HR: hazard ratio.

ulations and COMPARE[11] which included an unselected cohort of consecutive patients demonstrated significantly lower rates of MI, TLR, ST, and MACE with XIENCE V EES compared with first-generation PES.[4] Similarly, an analysis from the prospective, single-arm PLATINUM small vessel and long lesion studies reported significantly lower 1-year target lesion failure (TLF) with platinum chromium EES compared to a prespecified performance goal based on historical results with the first-generation PES in the TAXUS V[23] trial (2.4% vs. 21.1%, $p < 0.001$).[5] In a subgroup analysis from the XIENCE V USA study on 2,853 patients with XIENCE V EES, there was no significant difference between small vessels (2.5 mm stent) and non-small vessels ($>$2.5 mm stent) in terms of ST (0.37% vs. 0.40%), cardiac death or MI (4.5% vs. 5.1%), and TLR (3.8% vs. 3.0%) at 1 year.[6] In addition, an analysis of pooled data from the RESOLUTE global clinical program demonstrated comparable 2-year clinical outcomes between small vessels defined as a reference vessel diameter (RVD) $\leq$2.5 mm and non-small vessels (RVD $>$2.5 mm) with Resolute zotarolimus eluting stents (ZES).[7] There was no significant difference in TLF (small vessels 10.1% vs. non-small vessels 8.7%) at 2 years. In contrast, a substudy of the Durable Polymer-based Stent Challenge of Promus Element Versus Resolute Integrity in an All Comers Population (DUTCH PEERS) randomized trial, the 2-year clinical outcomes of all-comer patients treated with second-generation ZES or platinum-chromium EES for lesions in at least one small coronary vessel ($<$2.5 mm, n=798) were worse than those of patients with target lesions in larger vessels ($\geq$2.5 mm, n=1,013).[24] The rates of TLF (9.5% vs. 5.4%, p=0.001) and target vessel MI (3.1% vs. 1.3%, p=0.006) and TLR (4.8% vs. 2.8%, p=0.02) were higher in patients treated in at least one small vessel. However, the results of this post hoc analysis should be interpreted taking into account some limitations arising from the fact that patients with lesions treated in larger vessels ($\geq$2.5 mm) were included in the definition of the small vessel group and discrepancies in the baseline and lesion characteristics might have contributed to the less favorable outcomes in the small vessel group. More recently, a subgroup analysis in 259 patients with small target vessels ($\leq$2.75 mm) from 5-year follow-up data of the Study of the Orsiro Drug Eluting Stent System (BIOFLOW-II) trial[25] revealed comparable outcomes between the ultrathin strut SES and XIENCE EES in terms of TLR (8.7% vs. 8.9%, respectively) and TLF (11.1% vs. 15.5%, respectively). Similar findings in favor of newer-generation DES in small vessel CAD were observed in clinical studies conducted in East Asian populations. A 2-year clinical study from 509 Japanese patients supported the better outcomes of EES over the first-generation PES in small vessels ($<$2.5 mm)[26] with lower rates of TVR (8.0% vs. 13.9%, p=0.03) and MACE (8.7% vs. 14.3%, p=0.05). An observational study that enrolled 1,132 Japanese patients and compared thin-strut EES (XIENCE V or platinum-chromium EES) with thick-strut BES in small vessels treated with 2.5 mm stents revealed comparable results at 2 years with regard to TLR (8.4% vs. 8.3%) and MACE (11.8% vs. 12.1%, respectively).[27] A recent observational study from the Korea Acute Myocardial Infarction Registry showed comparable 1-year outcome of second-generation DES (Endeavor-ZES vs. Xience V or platinum-chromium EES) for small vessel CAD (stent diameter $\leq$2.75 mm) in 1,565 Korean patients with acute MI.[28] There were no significant difference in TLR (1.2% vs. 1.4%), TLF (4.9% vs. 6.9%) or MACE (9.4% vs. 9.8%) at 1 year in the propensity score matched population.[28]

The findings of the present study compare favorably with the similarly designed XIENCE V USA small vessel study[6] conducted in broad real-world populations. In fact, the overall event rates for the small vessel group were lower in our study than in XIENCE V USA substudy:[6] TLR (1.7% vs. 3.8%), ST (0% vs. 0.37%), and TLF (4.3% vs. 5.7%). This may have possibly resulted from the use of contemporary PCI practice in our study including more frequent use of potent P2Y12 inhibitors, high-intensity statins, and IVUS given the enrollment period from 2013 to 2019 of this study compared to from July 2008 to December 2008 of XIENCE V USA. One-year follow-up results demonstrated safety and effectiveness of XIENCE EES in the treatment of patients with small vessel CAD despite gender difference with higher proportion of women, higher prevalence of hypertension and less use of IVUS in the small vessel group. The results from this study reflect real-world clinical outcomes of XIENCE EES in small vessel treatment with contemporary clinical practice in the East Asian population.

1. Limitations

There are some limitations to the present study. Firstly, this was an observational, single-arm study lacking head-to-head comparison with other DES. Owing to the nature of the present analysis, the results should be considered hypothesis generating. Secondly, the sample size was relatively small, and the study may have been too underpowered to detect differences in clinical endpoints. Event rates were numerically higher in the small vessel group compared to the non-small vessel group even though there were no significant statistical differences between the groups, which may be due to the relatively small number of patients in the small vessel group. Thirdly, follow-up was done for 12 months only. Longer-term follow-up would be desirable given that in newer-generation DES, a considerable proportion of TLR occur beyond 1 year after PCI.[29] Finally, in the present study, a small vessel was defined as a coronary artery treated with a stent diameter of 2.5 mm or less, with the majority of cases not determined by quantitative coronary angiography or intravascular imaging studies. As the angiographic lumen area can be misleading and the true lumen diameter is often underestimated in the small vessels,[30] the use of intracoronary imaging is recommended to quantitatively assess the true vessel size and to reduce variability and potential bias. Furthermore, information on the use of adjunctive non-compliant balloons

was not available including whether they were used or not; and if they were used, details on their diameters, lengths, and maximal pressures applied, which could enable, in some cases, treatment of lesions larger than 2.5 mm in diameter.

In conclusion, this prospective, real-world study showed that 12-month clinical outcomes of XIENCE EES in small vessels were comparable to those in non-small vessels in real-world Korean patients. A comparative study between different types of DES for small vessel disease with longer-term follow-up is warranted.

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CONFLICT OF INTEREST STATEMENT

None declared.

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