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Percutaneous Coronary Intervention

Long-Term Clinical Outcomes of New-Generation Drug-Eluting Stents in Coronary Artery Disease: A Real-World Observational Study

Hsun-Hao Chang,[1,2,3] Chi-Feng Hung,[3,4] I-Chih Chen,[1] Po-Ching Wu,[1] Li-Wei Liu[1] and Ching-Chang Fang[1]

Background: Treating vessels with a very small reference vessel diameter (RVD) in coronary artery disease is challenging.

Objective: Long-term evaluation of new-generation drug-eluting stents (DESs) for the treatment of coronary lesions with different RVDs.

Methods: From April 2009 to March 2019, 780 patients who underwent single coronary stenting were divided into ≤ 2.25 (very small), 2.5-3.0 (small), and ≥ 3.5 mm (large) DES groups after 1:2:2 propensity score matching. The primary endpoint was target lesion failure (TLF), and the secondary endpoints were major adverse cardiac events (MACEs) and stent thrombosis (ST).

Results: During 3 years after new-generation DES implantation, TLF and MACE rates were significantly lower in the very small DES group. The risk of TLF was significantly lower in the very small DES group compared to the small DES group [very small vs. small: TLF, adjusted hazard ratio (HR) = 0.282, p = 0.040]. The risks of MACEs and all-cause mortality were significantly lower in the very small DES group compared to the small DES group (very small vs. small: MACEs, adjusted HR = 0.215, p = 0.001; all-cause mortality, adjusted HR = 0.181, p = 0.005). The cumulative incidence rates of TLF-free (log-rank test p = 0.001) and MACE-free (log-rank test p < 0.001) survival were significantly different among the groups, and the very small DES group had a high event-free survival rate. No cases of ST occurred in any group.

Conclusions: Our results indicate that the use of new-generation DESs for treating coronary lesions in very small vessels is safe and effective.

Key Words: Major adverse cardiac events • New-generation drug-eluting stent • Stent thrombosis • Target lesion failure • Very small coronary artery disease

INTRODUCTION

Percutaneous coronary intervention (PCI) in small caliber vessels accounts for approximately 30%-40% of all intervention procedures.[1] These procedures represent a challenge for interventional cardiologists,[2] mainly because of high rates of restenosis and stent thrombosis (ST).[3] Additionally, the DUTCH PEERS randomized trial reported that patients with small vessel coronary artery disease (CAD) (diameter, < 2.5 mm) who were treated with PCI had higher adverse event and target lesion failure (TLF) rates than their counterparts with large vessel CAD.[4]

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[1]Department of Cardiology, Tainan Municipal Hospital (Managed by Show Chwan Medical Care Corporation), Tainan; [2]Department of Chemistry; [3]Graduate Institute of Biomedical and Pharmaceutical Science; [4]School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan.
Corresponding author: Dr. Ching-Chang Fang, Department of Cardiology, Tainan Municipal Hospital (Managed by Show Chwan Medical Care Corporation), No. 670, Chongde Road, East District, Tainan City 701033, Taiwan. Tel: 886-6-336-4950; Fax: 886-6-290-2148; E-mail: fcc0215@yahoo.com.tw

PCI for the treatment of CAD traditionally includes plain old balloon angioplasty, bare-metal stent (BMS) and drug-eluting stent (DES) implantation, and, more recently, drug-coated balloon (DCB) angioplasty. PCI with DES implantation is an established treatment strategy for large coronary vessels (diameter, > 3 mm)[5] because it reduces the risk of restenosis and the incidence of repeated revascularization procedures compared with BMSs.[6] A 3-year analysis of the BASKET study reported that the major adverse cardiac event (MACE) rate was significantly higher for BMS placement than for DES placement in patients with small vessel disease (diameter, < 3.0 mm).[7] The PEPCAD I study reported that DCB angioplasty was an alternative to first-generation DES implantation for the treatment of small vessel disease (diameter, 2.25-2.8 mm).[8]

It is known that obstructive lesions in very small vessels (diameter, ≤ 2.25 mm) are frequently encountered, and such lesions can be symptomatic.[9] However, no optimal recommendations regarding the intervention of choice for very small vessel disease have been postulated. In recent years, continued concern about ST has led to improvements in stent design.[10] New-generation DESs are associated with improved clinical outcomes and reduced risks of restenosis and ST compared with the results for first-generation DESs.[11] New-generation DESs have been introduced in recent years, and their efficacy and safety in patients with small vessel disease appear to match those in patients with large vessel disease.[12] For very small vessel CAD, new-generation DES implantation could effectively reduce the TLF rate compared with BMS implantation[13] and provide better outcomes than first-generation DESs.[14]

Nonetheless, small vessel disease remains a powerful predictor of restenosis and adverse clinical events even with the advent of new-generation DESs.[15] However, patients with very small vessel disease (diameter, ≤ 2.25 mm) are less frequently included in clinical trials, and the long-term prognosis of new-generation DES implantation remains unclear. Therefore, we conducted this retrospective study of real-world cases to compare the rates of TLF, MACEs, and ST during 3 years after new-generation DES implantation in patients with various vessel diameters, including very small (≤ 2.25 mm), small (2.5-3.0 mm), and large (≥ 3.5 mm) vessels at a single center in Taiwan.

METHODS

Study population

In this retrospective cohort study, all data were obtained from patient medical records at Tainan Municipal Hospital, Taiwan, ROC. The study period was from April 2009 to March 2019 (Figure 1). Patients aged ≥ 20 years with ischemic heart disease attributable to native coronary artery stenosis with de novo lesions were considered eligible for inclusion in the study. Patients were initially excluded if they had received multiple different-sized stents in the index procedure.

Different definitions of "small coronary vessel" have been used in previous studies, such as a reference vessel diameter (RVD) of < 2.8-3.0 mm[16] or RVD of < 2.5 mm.[4] Another study defined small coronary vessels based on a stent diameter of ≤ 2.5 mm.[17] In addition, stents with diameters of 2.0 and 2.25 mm have become available as technology advances, and thus PCI using 2.0- and 2.25-mm devices has been defined as treatment for "very small caliber CAD."[18]

In this study, small and large coronary vessels were defined as target vessels with RVDs of 2.5-3 mm and ≥ 3.5 mm, respectively. These lesions were treated using new-generation DESs with the same respective diameters. Very small coronary vessels were defined when the target vessel had an RVD of ≤ 2.25 mm, and the lesion was treated using one new-generation DES of 2.0 or 2.25 mm in diameter. These very small stents included the 2.0-mm diameter Resolute Onyx (15 lesions), 2.25-mm Resolute Onyx (zotarolimus-eluting stent, 18 lesions), Resolute Integrity (zotarolimus-eluting stent, 29 lesions), ENDEAVOR Resolute (zotarolimus-eluting stent, 28 lesions), Synergy (everolimus-eluting stent, 27 lesions), Promus Premier (everolimus-eluting stent, 22 lesions), UltiMaster (sirolimus-eluting stent, 9 lesions), XIENCE Xpedition (everolimus-eluting stent, 5 lesions), BioFreedom (biolimus-eluting stent, 2 lesions), and BioMatrix (biolimus-eluting stent, 1 lesion).

The patients were followed up for at least 6 months during 3 years following the new DES implantation. The key exclusion criteria were evidence of cardiogenic shock or a history of malignant neoplasm.

Procedure

Unfractionated heparin was administered to main-

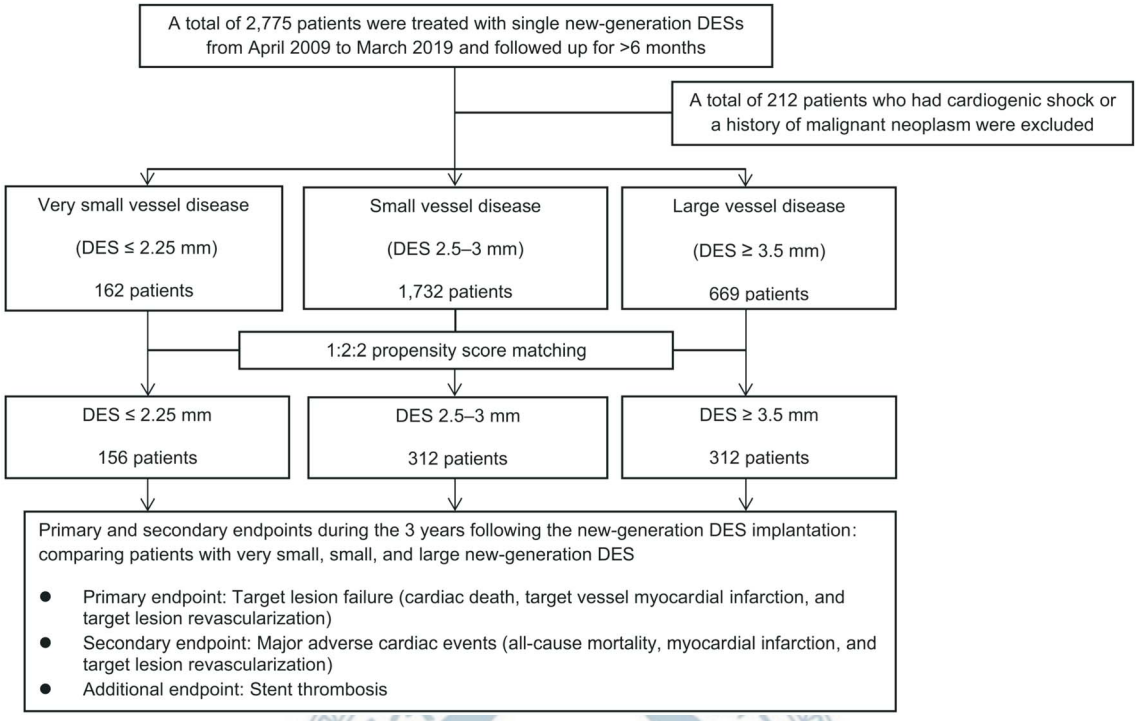

Figure 1. *Patient selection scheme for very small, small, and large vessel disease in patients undergoing percutaneous coronary intervention using new-generation drug-eluting stents. DES, drug-eluting stent.*

tain an activated clotting time of 250-350 s during PCI. We deployed the stents according to standard procedures at each lesion to achieve optimal stent apposition. The use of high-pressure noncompliant balloon post-dilatation and intravascular ultrasound (IVUS) was at the discretion of the operator. All patients received dual antiplatelet therapy comprising aspirin (100 mg/day) and ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300 mg loading dose followed by 75 mg once daily) for 6-12 months after stenting.

At our hospital, the date of first use of the new-generation 2.25-mm DES (ENDEAVOR Resolute: zotarolimus-eluting stent) was December 17, 2010, and that of the 2.0-mm diameter DES (Resolute Onyx: zotarolimus-eluting stent) was September 20, 2017.

We compared the adverse clinical event rates during 3 years following DES implantation between the patients treated for lesions in one very small coronary vessel (≤ 2.25 mm) and those treated for lesions in small (2.5-3.0 mm) or large (≥ 3.5 mm) vessels.

Clinical outcomes

Patients underwent clinical follow-up during the 3 years after the initial PCI procedure; the primary endpoint was the risk of TLF, which was defined as a composite of cardiac mortality, target vessel-related myocardial infarction (MI), and clinically driven target lesion revascularization (TLR). Cardiac mortality was defined as death due to a cardiac cause, such as MI, fatal arrhythmia, or heart failure.

TLF was the key parameter for efficacy and safety, and it reflected any device- and lesion-associated adverse events that occurred during follow-up. TLF due to death was attributed to a cardiac cause unless an unequivocal noncardiac cause was established. Target vessel-related MI was attributedto the target vessel or cases of MI that could not be clearly attributed to a nontarget vessel. Clinically driven TLR was defined as any need of repeated revascularization in the segment originally treated with a new-generation DES after the documentation of recurrent clinical ischemic symptoms and signs following the initial procedure.

The secondary clinical endpoint was the risk of MACEs, which was defined as a composite of all-cause mortality, MI, and clinically driven TLR. The third endpoint was ST, including acute (within 24 h), subacute (within 30 days),

late (30 days to 12 months), and very late (after 12 months) ST, after the initial procedure. The endpoint and timing of ST were defined according to the definitions of the Academic Research Consortium.[19]

Considering that the risks of MACEs and acute thrombosis are high in patients with acute coronary syndrome (ACS: unstable angina, ST-segment elevation MI, or non-ST-segment elevation MI), we compared the clinical endpoints among the three groups in which the patients with ACS were separated from those without ACS (non-ACS).

Statistical analysis

Each patient with a very small (≤ 2.25 mm) DES was matched to two patients with small (2.5-3.0 mm) DESs and two patients with large (≥ 3.5 mm) DESs using nearest neighbor full matching within calipers determined by the propensity score.

To control for selection bias and the potential confounders in this study, a caliper width of "0" of the propensity score was used for matching age, sex, hypertension, hyperlipidemia, diabetes mellitus (DM), and tobacco smoking to perform full matching on all supplied covariates (Figure 1).

Data are presented as frequencies (percentages) for categorical variables and as the mean ± standard deviation for normally distributed continuous variables.

Subgroup comparisons were performed using chi-square test for categorical variables and one-way ANOVA test for continuous variables. We used multivariate Cox proportional hazard regression modeling to estimate adjusted the hazard ratios (HRs) and 95% confidence interval (CI) of clinical adverse events (TLF and MACEs) between patients treated with very small, small, or large new-generation DESs after adjustment for age, sex, tobacco smoking, medication use (statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers), and comorbidities (DM, hypertension, and hyperlipidemia).

Kaplan-Meier analysis was used to calculate the cumulative incidence of clinical endpoint-free survival, and the log-rank test was used to compare between-group differences. Data analysis was performed using SPSS (IBM Corp., Released 2013, IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

RESULTS

Baseline, lesion, and procedural characteristics of the study population

The study flowchart is shown in Figure 1. After 1:2:2 propensity score matching, there were 156, 312, and 312 patients in the very small, small, and large vessel groups, respectively. These groups were treated with ≤ 2.25, 2.5-3.0, and ≥ 3.5 mm DESs, respectively.

Table 1 presents the baseline characteristics of the patients by the size of the implanted stent. No patient was aged 20-30 years before propensity score matching. After propensity score matching, age, sex, hypertension, hyperlipidemia, DM, and tobacco smoking were similar among the three groups. There were no significant differences in baseline characteristics among the three groups, apart from higher proportions of patients with insulin-treated DM ($p = 0.034$) and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 in the small DES group.

The baseline characteristics of the lesions and procedures are shown in Table 2. There were no significant differences in the incidence of multivessel disease ($p = 0.121$) among the three groups, however longer lesion length ($p < 0.001$) and final stent length ($p < 0.001$) were noted in the small DES group.

The treated vessels were significantly different among the three groups. We subdivided the location of the stenotic lesions in the treated vessels into proximal, middle, and distal and branch segments of the coronary artery (Supplementary Table 1), and significant differences were noted among the three groups. More stenotic lesions were located in the proximal segments and fewer stenotic lesions were located in the distal and branch segments in the small and large DES groups than those in the very small DES group.

Regarding lesion type, the very small DES group had fewer type B lesions ($p = 0.002$) but more type C ($p = 0.002$) and chronic total occlusion ($p < 0.001$) lesions. However, there was no significant difference in bifurcation lesions among the three groups ($p = 0.569$). In the large DES group, high-pressure noncompliant balloon post-dilatation ($p < 0.001$) and IVUS ($p < 0.001$) were used more frequently. Meanwhile, there was no significant differences in the diameter of stenosis before ($p = 0.490$) and after ($p = 0.616$) PCI among the three groups.

Table 1. Baseline characteristics of patients

Baseline patient characteristics	Drug-eluting stent diameter			p value
	≤ 2.25 mm	2.5-3.0 mm	≥ 3.5 mm	
Number of patients	156	312	312	
Age (years)				
31-50 (years)	6 (4)	12 (4)	12 (4)	1.000
51-70 (years)	86 (55)	172 (55)	172 (55)	1.000
≥ 71 (years)	64 (41)	128 (41)	128 (41)	1.000
Male	112 (71.8)	224 (71.8)	224 (71.8)	1.000
Hypertension	125 (80.1)	250 (80.1)	250 (80.1)	1.000
Hyperlipidemia	110 (70.5)	220 (70.5)	220 (70.5)	1.000
DM	83 (53.2)	166 (53.2)	166 (53.2)	1.000
Insulin-treated DM	12 (7.7)	38 (12.2)	20 (6.4)	0.034
Tobacco smoking	37 (23.7)	74 (23.7)	74 (23.7)	1.000
Unstable angina	84 (53.8)	136 (43.6)	143 (45.8)	0.105
AMI				
STEMI	5 (3.2)	26 (8.3)	18 (5.8)	0.087
NSTEMI	15 (9.6)	34 (10.9)	32 (10.3)	0.908
Baseline LVEF (%)	60 ± 11	62 ± 12	61 ± 11	0.752
eGFR < 60 mL/min/1.73 m^2	46 (29.5)	106 (34)	73 (23.4)	0.014
In-hospital medication				
Statin	137 (87.8)	274 (87.8)	279 (89.4)	0.790
ACEI/ARB	52 (33.3)	114 (36.5)	100 (32.1)	0.485

Baseline LVEF (%) data are expressed as mean ± standard deviation and other data are expressed as n (%).
ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricle ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Table 2. Baseline characteristics of lesions and procedures

	Drug-eluting stent diameter			p value
	≤ 2.25 mm	2.5-3.0 mm	≥ 3.5 mm	
Number of lesions	156	312	312	
Lesion length (mm)	25.89 ± 14.76	27.32 ± 15.43	24.45 ± 14.81	< 0.001
RVD (mm)	2.22 ± 0.12	2.76 ± 0.26	3.56 ± 0.26	< 0.001
Multivessel disease	136 (87.2)	261 (83.7)	249 (79.8)	0.121
Treated vessel				
Left main	0	2 (0.6)	50 (16)	< 0.001
Left anterior descending	55 (35.3)	146 (46.8)	105 (33.7)	0.002
Left circumflex	66 (42.3)	81 (26)	16 (5.1)	< 0.001
Right coronary artery	35 (22.4)	83 (26.6)	141 (45.2)	< 0.001
AHA/ACC lesion type				
A	0	0	0	-
B	63 (40.4)	170 (54.5)	180 (57.7)	0.002
C	93 (59.6)	142 (45.5)	132 (42.3)	0.002
Chronic total occlusion	22 (14.1)	20 (6.4)	13 (4.2)	< 0.001
Bifurcation	24 (15.4)	57 (18.3)	48 (15.4)	0.569
Final stent length (mm)	30.49 ± 15.73	34.18 ± 18.44	29.33 ± 17.9	< 0.001
High-pressure post-dilatation	53 (32.7)	364 (55.7)	262 (72.8)	< 0.001
IVUS	49 (31.4)	82 (26.3)	180 (57.7)	< 0.001
MLD (mm)				
Pre-PCI	0.29 ± 0.23	0.46 ± 0.31	0.68 ± 0.39	< 0.001
Post-PCI	2.16 ± 0.16	2.72 ± 0.77	3.38 ± 0.26	0.006
Diameter stenosis (%)				
Pre-PCI	86.76 ± 10.56	83.37 ± 10.94	81.18 ± 10.57	0.490
Post-PCI	2.57 ± 6.52	1.51 ± 23.35	4.90 ± 6.71	0.616

Data are expressed as mean ± standard deviation or as n (%).
AHA/ACC, American Heart Association/American College of Cardiology; IVUS, intravascular ultrasound; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; RVD, reference vessel diameter.

Clinical endpoints

Table 3 shows the primary (TLF) and secondary (MACEs) clinical outcomes during the 3 years following new-generation DES implantation among the three groups. The TLF and MACE rates were significantly lower in the very small DES group. TLF occurred in 1.9% of very small DESs, 7.4% of small DESs, and 1.9% of large DESs (p = 0.001); MACEs occurred in 3.2% of very small DESs, 15.7% of small DESs, and 7.1% of large DESs (p < 0.001). No cases of ST occurred in the three DES groups at 3 years.

We found a significantly lower risk of TLF in the very small group compared to the small DES group (TLF: very small vs. small, adjusted HR = 0.282, 95% CI = 0.084-0.942, p = 0.040; Table 4). There was no significant difference in the risk of TLF in the very small group compared to the risk in the large DES group (TLF: very small vs. large, adjusted HR = 0.912, 95% CI = 0.212-3.918, p = 0.901; Table 4).

We also found significantly lower risks of MACEs and all-cause mortality in the very small DES group compared to the small DES group (very small vs. small: MACEs, adjusted HR = 0.215, 95% CI = 0.086-0.542, p = 0.001; all-cause mortality, adjusted HR = 0.181, 95% CI = 0.055-0.592, p = 0.005; Table 5). In addition, a significantly lower risk of all-cause mortality was observed in the very small DES group compared to the large DES group (very small vs. large: all-cause mortality, adjusted HR = 0.287, 95% CI = 0.085-0.976, p = 0.044; Table 5).

Because patients with ACS are at a higher risk of MACEs,[20] we divided the patients into ACS and non-ACS groups for further analysis, as shown in Supplementary Tables 2 and 3, respectively. In the patients with ACS (Supplementary Table 2), the TLF (p = 0.001) and MACE (p < 0.001) rates were significantly lower in the very small DES group during the 3 years of follow-up. In the non-ACS patients (Supplementary Table 3), the TLF (p = 0.480) and MACE (p = 0.183) rates were not significantly different among the three groups.

The 3-year cumulative free survival rates of TLF and

Table 3. Three-year clinical outcomes of patients treated with very small, small, and large new-generation DESs

	Very small (N = 156) N (%)	Small (N = 312) N (%)	Large (N = 312) N (%)	p value
TLF	3 (1.9)	23 (7.4)	6 (1.9)	0.001
MACE	5 (3.2)	49 (15.7)	22 (7.1)	< 0.001
All-cause mortality	3 (1.9)	35 (11.2)	22 (7.1)	0.002
Cardiac	1 (0.6)	11 (3.5)	6 (1.9)	0.124
Noncardiac	2 (1.3)	24 (7.7)	16 (5.1)	0.015
MI	0	3 (1.0)	0	0.104
Culprit (target vessel MI)	0	1 (0.3)	0	0.472
Nonculprit	0	2 (0.6)	0	0.222
Clinically driven TLR	2 (1.3)	11 (3.5)	0	0.002
Stent thrombosis	0	0	0	-

DES, drug-eluting stent; MACE, major adverse cardiac event; MI, myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization.

Table 4. Three-year TLF rate in patients treated with very small, small, and large new-generation DESs

Primary endpoint	Very small (N = 156) vs. small (N = 312)		Very small (N = 156) vs. large (N = 312)		Small (N = 312) vs. large (N = 312)	
	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
TLF	0.282 (0.084–0.942)	0.040	0.912 (0.212–3.918)	0.901	3.897 (1.583–9.595)	0.003
Cardiac mortality	0.189 (0.024–1.475)	0.112	0.194 (0.012–3.100)	0.246	1.947 (0.710–5.336)	0.195
Target vessel MI	0.030 (0.000–> 10)	0.731	NA	NA	> 10 (0.019–> 10)	0.909
Clinically driven TLR	0.382 (0.084–1.731)	0.212	> 10 (0.000–> 10)	0.958	> 10 (0.000–> 10)	0.929

CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; MI; myocardial infarction; NA, not available; TLF, target lesion failure; TLR, target lesion revascularization.

Table 5. Three-year MACE rate in patients treated with very small, small, and large new-generation DESs

Secondary endpoint	Very small (N = 156) vs. small (N = 312)		Very small (N = 156) vs. large (N = 312)		Small (N = 312) vs. large (N = 312)	
	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
MACE	0.215 (0.086–0.542)	0.001	0.478 (0.180–1.269)	0.138	2.232 (1.345–3.704)	0.002
All-cause mortality	0.181 (0.055–0.592)	0.005	0.287 (0.085–0.976)	0.044	1.534 (0.894–2.631)	0.120
MI	0.000 (0.000–> 10)	0.976	NA	NA	> 10 (0.000–> 10)	0.963
Clinically driven TLR	0.382 (0.084–1.731)	0.212	> 10 (0.000–> 10)	0.958	> 10 (0.000–> 10)	0.929

CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; MACE, major adverse cardiac event; MI; myocardial infarction; NA, not available; TLR, target lesion revascularization.

MACEs were derived using the Kaplan-Meier method. As shown in Figure 2, there were significant differences in TLF-free survival (Figure 2A: log-rank test, p = 0.001) and MACE-free survival (Figure 2B: log-rank test, p < 0.001) rates among the three groups. The time-to-event-free curves revealed that new-generation very small DESs had higher event-free survival rates, indicating that new-generation very small DESs were safe and effective during the 3 years following DES implantation.

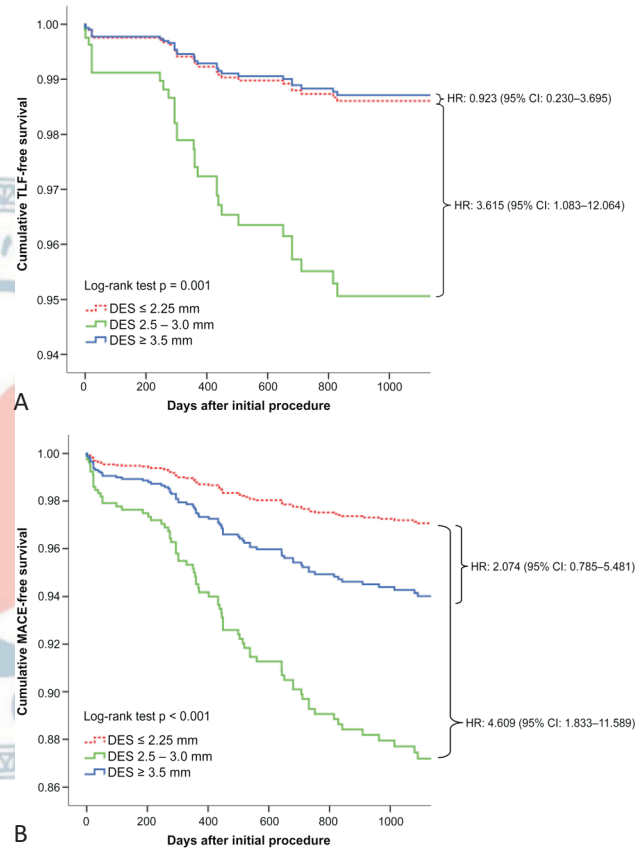

Figure 2. *The Kaplan-Meier curves of cumulative incidence of (A) TLF-free and (B) MACE-free survival rates among the three DES groups up to 3 years after implantation of new-generation DESs. CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; MACE, major adverse cardiac event; TLF, target lesion failure.*

DISCUSSION

Significant CAD in small vessels (typically defined as a reference diameter of < 2.8 mm) is a common finding during cardiac catheterization, and it accounts for approximately one-third of PCI procedures.[21] Asian patients are physically smaller than those in Western populations; therefore, the vessels treated in Asian patients are often narrower than those in Western patients.[22] Therefore, operators who treat Asian patients must develop expertise in treating very small vessels (diameter, ≤ 2.25 mm) CAD. Therefore, it is essential to verify the clinical outcomes associated with the use of very small coronary stents. PCI for lesions in very small coronary vessels (≤ 2.25 mm) is associated with an increased risk of adverse clinical outcomes,[23] and percutaneously treating these vessels is particularly challenging. The size of the coronary vessels to be treated is an important determinant of the clinical outcome following PCI.[24] The long-term outcomes of BMSs are disappointing in small vessels.

DESs, and especially new-generation DESs,[25] have revolutionized the concept of small vessel stenting with improved clinical outcomes. New-generation DESs have been shown to significantly reduce the risks of MI, ST,[14] and TLF,[26] which may cause first-generation DESs to disappear. Accordingly, carefully tracking and studying the clinical outcomes and adverse events of PCI using new-generation DESs in patients with very small vessel CAD is important.

A recent substudy of the LEADERS trial, in which 1,707 patients were treated with either a biolimus-eluting stent or sirolimus-eluting stent, revealed significantly higher risks of MACEs (12.1% vs. 7.1%, HR = 1.720, p = 0.04) and TLR (9.6% vs. 2.6%, HR = 3.724, p = 0.001) after the treatment of small vessels (≤ 2.75 mm) than after the treatment of large vessels (> 2.75 mm) in the biolimus-eluting stent arm of the trial.[27] The results of the Resolute Japan Small Vessel Study (R-Japan SVS: vessel diameter, 2.25 mm) revealed a TLF rate of 7.9% (5/63) and MACE rate of 14.3% (9/63) 3 years after DES placement.[28] Beyond that, although some studies have reported that DCB angioplasty was not inferior to new-generation DES placement in patients with small vessel disease (RVD = 2.25-2.75 mm),[3] another study reported a high rate of TLR among patients with very small vessel CAD (vessel size ≤ 2.0 mm, 10.3%; vessel size > 2.0 mm, 3.5%) who underwent DCB angioplasty because the lesions were unsuitable for stent implantation.[29]

The first report of a DES (Resolute Onyx 2.0-mm zotarolimus-eluting stent)[9] specially designed for very small vessel disease (RVD = 2.0-2.25 mm) reported lower TLF (5%, 5/100) and MACE (5%, 5/100) rates after 13 months of follow-up. Our study is one of the few reports to compare the incidence of adverse cardiovascular events (TLF and MACEs) 3 years after new-generation DES placement in patients with CAD involving very small (≤ 2.25 mm), small (2.5-3.0 mm), and large (≥ 3.5 mm) vessels at a single center. Our results showed that the clinical outcomes of the very small DES group were not inferior to those of the small and large DES groups in this propensity score matched study. In the DUTCH PEERS randomized trial,[4] patients with small vessel lesions (< 2.5 mm) treated with novel DESs had a higher TLF rate than those without small vessel treatment.[4]

Furthermore, despite a wide range of results in each vascular territory, stronger associations have been observed between large vessel disease, tobacco smoking, and hyperlipidemia, whereas DM has been shown to be more specific for small vessel disease.[30] Therefore, to minimize potential bias, we adjusted our results for multiple confounders, including age, sex, hypertension, hyperlipidemia, DM, and tobacco smoking.

In our study, the TLF and MACE rates were significantly lower in the very small DES group during the 3 years following DES implantation. We compared the risks of TLF and MACEs by vessel size after adjusting for potential cofounders, and the results revealed that the risks of TLF and MACEs were significantly lower in the very small DES group compared to the small DES group. In addition, there were no significant differences in the risks of TLF and MACEs between the very small and large DES groups. A possible explanation for the lower risks of TLF and MACEs in the very small DES group may be due to the location of stenotic lesions [large (proximal) versus small (distal) coronary artery], because we found that there were more stenotic lesions located in the proximal segments in the small and large DES groups than in the very small DES group. The proximal segments of the coronary artery had higher rates of atherosclerotic lesions and more soft and unstable plaques than the distal segments; therefore, the thrombotic occlusion rate was higher in the proximal segments of the coronary arteries than in the distal ones. Large vessel lesions in one territory have also been shown to be more frequently associated with concomitant lesions in other territories.[30]

In addition to plaque ruptures related to atherosclerosis, stenotic lesions are more progressive when they are located proximal to and/or appear in a large lumen. The progression rate is correlated with the clinical outcomes,[31] because the progression of coronary disease is more likely to cause clinical symptoms in large (proximal) segments than that in small (distal) segments. In addition, one advantage of small vessel CAD is the small portion of myocardium supplied by small coronary arteries; thus, the clinical risk may be lower when performing PCI for artery occlusion.[32]

The calcium score could be another explanation for our findings, because the ACCURACY Trial revealed that coronary arteries with larger vessel diameters were more likely to have high calcium scores,[33] and the calcium density of coronary arteries is significantly associated with a high risk of MACEs.[34] Notwithstanding, the results show that even when new-generation DESs are used, treatment for very small CAD is still a challenge, depending on the patients' and lesion-specific characteristics.

A previous study demonstrated that patients with ACS are at higher risks of MACEs and acute thrombosis.[20] In our study, lower TLF and MACE rates were found in the very small DES group compared to the other two DES groups at 3 years in the patients with ACS. There-

fore, new-generation very small DESs appear to be safe and effective, especially for patients with ACS.

Finally, significantly higher 3-year cumulative TLF-free and MACE-free survival rates were observed in the very small DES group. In contrast, Hsieh et al. reported a lower event-free survival rate for very small vessel than for small and large vessels.[35] The main reason for the different clinical outcomes between our study and Hsieh et al.'s study may be because Hsieh et al. used Palmaz-Schatz and other BMSs in the very small vessel group, whereas we used new-generation DESs, which are associated with a lower risk of adverse events than BMSs.[13] The CENTURY JSV study also reported that 2.25-mm diameter new-generation DESs were safe and effective for treating very small CAD through 2 years after stent implantation.[22] The long-term benefits of new-generation DESs may be related to the technology of the polymer, which provides anti-proliferative benefits and can reduce the incidence of adverse cardiac events. Thus, new-generation DESs represent a viable treatment option for very small vessel CAD.

Stent length has been shown to be an independent predictor of ST after DES implantation, with a higher ST if the stented segment is $\geq$ 31.5 mm long.[36] However, no ST was noted in the three DES groups after 3 years of follow-up in the present study, which is in agreement with the observations of the Resolute Japan SVS study.[28] The Bello study also identified no cases of definite or probable ST in patients with very small vessel CAD.[37]

Inadequate stent expansion has been associated with ST, and optimal stent expansion can be evaluated via IVUS.[38] Adjuvant high-pressure noncompliant balloons post-dilatation after stent implantation under IVUS guidance can improve stent expansion and decrease the risks of ST and restenosis.[39] In addition to IVUS-guided PCI and adjuvant high-pressure noncompliant balloon post-dilatation, an longer total stent length can predict adverse events after PCI.[40] Yano et al. also demonstrated that IVUS-guided long (24-32 mm) and ultra-long (> 32 mm) new-generation DESs were associated with favorable clinical outcomes at 2 years after PCI.[41] However, we found that new-generation DESs may be effective and safe for the treatment of very small CAD despite the fact that the average final stent length of the very small DES group (30.49 $\pm$ 15.73 mm) was not especially short, and there was less usage of high-pressure noncompliant balloon post-dilatation and IVUS in the very small DES group. Thus, we believe that regardless of the rates of TLF, MACEs or ST, new-generation DESs play an important role because more advanced technology may allow for the use of thinner struts with more biocompatible polymers. This could then result in greater flexibility and deliverability, reduce vascular injury and inflammation, accelerate endothelialization, decrease neointimal proliferation,[42] and provide sufficient arterial repair after stenting.[43]

Study limitations

Several limitations of this study must be addressed. (1) We did not consider some confounders, such as chronic total occlusion, bifurcation lesions, calcification, and complexity of the diseased coronary arteries. Regarding the complexity of lesions, very small vessels exhibit complex lesions more frequently than large vessels.[35] Therefore, lesion complexity can affect the clinical outcome.[44] (2) We did not consider the effects of patient medications, especially antiplatelet (ticagrelor and clopidogrel) medications. However, treatment with ticagrelor versus clopidogrel improved clinical outcomes in the PLATO study.[45] (3) Biochemistry profiles should be considered because their values could influence the clinical outcomes. In particular, both elevated fasting glucose and total cholesterol levels are associated with an increased risk of noncardiac mortality among patients with CAD.[46] (4) In this study, some lesions were not assessed using IVUS, which could have caused underestimation of the true lumen diameter of coronary vessels and mislabeling of large vessels as small vessels.[35] (5) High-pressure noncompliant balloon post-dilatation significantly reduced the in-stent restenosis rate; unfortunately, not all operators used it routinely for every lesion. (6) We should consider the influence of complete revascularization because incomplete revascularization is also an independent risk factor for MACEs in patients with CAD treated with PCI.[47]

CONCLUSIONS

This single-center 3-year follow-up study demonstrated that patients with very small vessel ($\leq$ 2.25 mm) CAD who were treated with new-generation DESs had

lower TLF and MACE rates. Therefore, the use of new-generation DESs represents a safe and feasible approach for the treatment of very small vessel CAD.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Subdivision of stenotic lesion locations in treated vessels as per the stent size

	Very small (N = 156) N (%)	Small (N = 312) N (%)	Large (N = 312) N (%)	p value
Left main	0	2 (0.6)	50 (16)	< 0.001
Left anterior descending				
LAD-P	0	38 (12.2)	74 (23.7)	< 0.001
LAD-M	6 (3.8)	70 (22.4)	30 (9.6)	< 0.001
LAD-D	31 (19.9)	30 (9.6)	1 (0.3)	< 0.001
LAD-D1	14 (9.0)	6 (1.9)	0	< 0.001
LAD-D2	4 (2.6)	2 (0.6)	0	0.011
Left circumflex				
LCx-P	8 (5.1)	26 (8.3)	13 (4.2)	0.080
LCx-D	47 (30.1)	43 (13.8)	3 (1.0)	< 0.001
LCx-OM	11 (7.1)	12 (3.8)	0	< 0.001
Right coronary artery				
RCA-P	2 (1.3)	18 (5.8)	58 (18.6)	< 0.001
RCA-M	3 (1.9)	20 (6.4)	60 (19.2)	< 0.001
RCA-D	10 (6.4)	39 (12.5)	21 (6.7)	0.019
RCA-PDA	14 (9.0)	3 (1.0)	0	< 0.001
RCA-PL	6 (3.8)	3 (1.0)	2 (0.6)	0.015

Data are expressed as N (%).
D, distal; D1, first diagonal branch; D2, second diagonal branch; LAD, left anterior descending; LCx, left circumflex; M, middle; OM, obtuse marginal branch; P, proximal; PDA, posterior descending artery; PL, posterolateral branch; RCA, right coronary artery.

Supplementary Table 2. Three-year clinical outcomes of patients with ACS treated with very small, small, and large new-generation DESs

	Very small (N = 102) N (%)	Small (N = 189) N (%)	Large (N = 186) N (%)	p value
TLF	3 (2.9)	22 (11.6)	6 (3.2)	0.001
MACE	4 (3.9)	38 (20.1)	15 (8.1)	< 0.001
All-cause mortality	2 (2.0)	25 (13.2)	15 (8.1)	0.005
Cardiac	1 (1.0)	11 (5.8)	6 (3.2)	0.104
Noncardiac	1 (1.0)	14 (7.4)	9 (4.8)	0.056
MI	0	3 (1.6)	0	0.100
Culprit (target vessel MI)	0	1 (0.5)	0	0.466
Non-culprit	0	2 (1.1)	0	0.216
Clinically driven TLR	2 (2.0)	10 (5.3)	0	0.004
Stent thrombosis	0	0	0	-

ACS, acute coronary syndrome; DES, drug-eluting stent; MACE, major adverse cardiac event; MI, myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization.

Supplementary Table 3. Three-year clinical outcomes of non-ACS patients treated with very small, small, and large new-generation DESs

	Very small (N = 54) N (%)	Small (N = 123) N (%)	Large (N = 126) N (%)	p value
TLF	0	1 (0.8)	0	0.480
MACE	1 (1.9)	11 (8.9)	7 (5.6)	0.183
All-cause mortality	1 (1.9)	10 (8.1)	7 (5.6)	0.259
Cardiac	0	0	0	-
Noncardiac	1 (1.9)	10 (8.1)	7 (5.6)	0.259
MI	0	0	0	-
Clinically driven TLR	0	1 (0.5)	0	0.480
Stent thrombosis	0	0	0	-

DES, drug-eluting stent; MACE, major adverse cardiac event; MI, myocardial infarction; non-ACS, non-acute coronary syndrome; TLF, target lesion failure; TLR, target lesion revascularization.