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Original Article

Long-term outcome of patients with very small coronary artery disease: A comparison of drug-eluting and bare metal stents

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Abstract

Background: Among patients with very small vessel disease and chronic kidney disease (CKD), the comparative efficacy of bare metal stents (BMSs) versus drug-eluting stents (DESs) is not frequently addressed. This study aimed to evaluate the long-term outcomes of patients with very small vessel disease managed with percutaneous coronary intervention.

Methods: Our study included 158 consecutive patients undergoing percutaneous coronary intervention from January 2003 to December 2013. The primary end points were cardiovascular death and target vessel failure, which consisted of cardiovascular death, target vessel-related myocardial infarction, and ischemia-driven target vessel revascularization.

Results: BMSs were used in 37 patients, while DESs were utilized in 121 patients. During the mean follow-up period of 2.7 ± 2.2 years (median 2.1 years; interquartile range, 1.3−4.2 years), the target vessel failure rate was 48.6% versus 28.1% (BMS vs. DES, $p = 0.020$) and the cardiovascular death rate was 27% versus 18.2% (BMS vs. DES, $p = 0.241$). The use of a DES (hazard ratio: 0.44, 95% confidence interval: 0.24−0.79, $p = 0.006$) remained the most significant predictor of target vessel failure after multivariate analysis. In CKD subgroup analysis, the benefit of a 2.25 mm DES was evident only in the subgroup with CKD, but such a benefit disappeared in those without CKD.

Conclusion: Compared with BMSs, implantation of DESs in a patient population with very small vessel disease effectively reduced target vessel failure. However, the beneficial effects of DESs appeared to be evident only in the subgroup with CKD.

Keywords: Bare-metal stent; Chronic kidney disease; Coronary artery disease; Drug-eluting stent; Percutaneous coronary intervention

1. Introduction

Previous studies have shown that patients with small vessels are at a higher risk of restenosis and adverse outcomes after percutaneous coronary intervention (PCI).[1−4] The use of drug-eluting stents (DESs) has been demonstrated to be effective in reducing not only the risk of restenosis, but also the incidence of repeated revascularization, compared with bare metal stents (BMSs).[5−15] Ardissino et al[16] reported that

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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the use of a sirolimus-eluting stent (SES) might reduce restenosis and major adverse cardiac events (MACEs) in small vessels with a diameter of $\leq$ 2.75 mm when compared with a BMS. Furthermore, an SES is associated with a lower rate of clinical and angiographic restenosis when compared with a paclitaxel-eluting stent, although the rates of death, myocardial infarction (MI), and stent thrombosis were similar for both stents,[17–19] and such a benefit was also observed in the non-diabetes mellitus subgroup.[20] By contrast, patients with very small coronary vessel (2.25 mm) disease are less frequently included in these clinical trials, and the long-term prognosis (> 1 year) of stenting with a DES or BMS remains unclear. Therefore, the aim of our study was to evaluate the long-term clinical outcomes of patients with very small vessel disease who were treated with 2.25 mm stents.

2. Methods

This study included 158 consecutive patients undergoing PCI with stenting for very small vessels ($\leq$ 2.25 mm) in Taipei Veterans General Hospital, Taipei, Taiwan from January 2003 to December 2013. The vessel size was determined by quantitative coronary analysis in the catheterization laboratory.

2.1. Interventional procedure

We performed PCI and ventriculography using the standard procedure, after obtaining signed informed consent from all patients. Unfractionated heparin (10,000 IU bolus) was administered prior to the procedure to achieve an activated clotting time of > 300 seconds. After predilatation, we deployed the stent with high-pressure balloon dilatation to achieve optimal stent apposition. Debulking by means of rotablator was used only in highly calcified lesions, and the use of intravascular ultrasound and glycoprotein IIb/IIIa receptor antagonist was at the operators' discretion. Coronary stenting was considered angiographically successful if residual stenosis < 30% with coronary thrombolysis in myocardial infarction Grade 3 flow was obtained at the end of the procedure. After stent implantation, all patients received aspirin (100 mg/d) indefinitely and clopidogrel (300 mg loading dose, then 75 mg/d) or ticlopidine (500 mg loading dose, then 250 mg twice a day) for at least 1 month (BMS) or at least 12 months (DES). Medications for the treatment of angina pectoris (calcium channel blockers, beta-blockers, and nitrates) were continued.

2.2. Angiographic analysis

Coronary angiograms were obtained after intracoronary injection of nitroglycerin. Quantitative coronary angiographic end points included reference vessel diameter, minimum lumen diameter (MLD), percent diameter stenosis (% DS), acute gain, and late lumen loss. Acute gain was defined as the difference between the MLD immediately after the placement of the stent and the MLD before the procedure. Late lumen loss was defined as the difference between the MLD immediately after the procedure and the MLD at follow-up. Reference vessel diameter, MLD, and % DS were measured before the procedure and at follow-up.

2.3. Follow-up

The clinical follow-up data were collected by scheduled monthly clinic evaluations or through direct telephone contact. All patients were followed up completely, without any noted case loss during follow-up.

2.4. Primary end point

The primary end point of the study included cardiovascular death and target vessel failure (TVF), which included cardiovascular death, target-vessel-related MI, and ischemia-driven target vessel revascularization. Cardiovascular death was defined as death related to a cardiovascular diagnosis, complications of procedure, or unexplained (unexpected) causes. MI was defined as the presence of significant new Q waves in at least two electrocardiographic leads or symptoms compatible with MI associated with an increase in creatine kinase-MB fraction more than three times the upper limit of the reference range. Target lesion revascularization was defined as any repeated percutaneous intervention of the target lesion performed for > 50% angiographic renarrowing of the treated lesion from 5 mm proximal to 5 mm distal to the stent, or repeat bypass surgery. Stent thrombosis occurrence was classified as definite, probable, or possible according to the Academic Research Consortium criteria,[21] and was considered as acute (within 24 hours), subacute (within 30 days), late (after 30 days and within 12 months), and very late (after 1 year). As chronic kidney disease (CKD) might be associated with clinical outcomes of these patients with small stents, we calculated the estimated glomerular filtration rate according to the simplified version of the Modification of Diet in Renal Disease Study prediction equation formula, modified by Ma et al[22] for Chinese patients [estimated glomerular filtration rate = $175 \times \text{plasma creatinine}^{-1.234} \times \text{age}^{-0.179} \times 0.79$ (if female)]. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for $\geq$ 3 months . The study protocol was approved by the Institutional Review Board at Taipei Veterans General Hospital, and informed written consent was obtained from each participant.

2.5. Statistical analysis

Continuous data are presented as the mean ± standard deviation or with a confidence interval (CI) of 95%. Categorical variables were compared by Chi-square test or Fisher's exact test. Continuous variables are presented as mean ± standard deviation and were compared by Student *t* test. Baseline characteristics and clinical outcomes were compared between patients treated with BMSs versus those treated with DESs in each group. The long-term actuarial event-free survival curve of patients undergoing PCI was estimated by the use of the Kaplan–Meier method. Cox regression analysis was performed to determine independent predictors of primary end

point, TVF, and cardiovascular death, with those variables with $p < 0.10$ in the univariate analysis being included in the stepwise multivariate model. The hazard ratio (HR) and 95% CI were calculated. A p value < 0.05 was considered to be statistically significant. The software package SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

3. Results

3.1. Patient characteristics

The baseline characteristics of the 158 patients are summarized in Table 1. The mean age of the population was 72.6 ± 11.9 years, with male (73.4%) predominance. About one-third of the patients presented with acute coronary syndrome (53 patients, 33%). In particular, 93 (58.8%) patients and 78 (49.4%) patients suffered from diabetes and CKD, respectively, suggesting that our patients belonged to the high-risk population. All patients were successfully treated with PCI, with 121 patients (76.4%) receiving DESs and 37 receiving BMSs (23.6%). In the DES group, first-generation stents (SESs and paclitaxel-eluting stents) were used in 25 patients, and new-generation DESs, including everolimus-eluting and zotarolimus-eluting stents, were used in 92 patients. There were no significant differences in procedure characteristics between the two groups except that the stent length was significantly longer in the DES group (21.9 ± 5.1 mm in the BMS group, 25.1 ± 5.8 mm in the DES group, $p = 0.006$). Of note, the use of small stents in the chronic total occlusion lesion was similar in both groups [10 (27%) in the BMS group, and 47 (38.8%) in the DES group, $p = 0.190$]. Furthermore, the use of rotablation and intravascular ultrasound was also similar in both groups [1 (2.7%) patient and 5 (13.5%) patients in the BMS group, 13 (10.7%) patients and 23 (19%) patients in the DES group, $p = 0.132$ and $p = 0.444$, respectively].

Table 1
Baseline patient characteristics of patients with different type of stent (BMS and DES).

Baseline demographics	BMS ($n = 37$)		DES ($n = 121$)		p
	N	%	*N*	%	
Age (y)	72.7 ± 10.8		72.5 ± 12.2		0.255
Gender (%)					0.228
Male	30	81.1	86	71.1	
Female	7	18.9	35	28.9	
Lab data					
Creatinine	2.1 ± 2.3		1.9 ± 2.1		0.989
eGFR	52.3 ± 26.3		58.0 ± 29.5		0.293
LVEF	45.5 ± 14.6		47.8 ± 12.1		0.107
Procedure characteristics (%)					
Stent length (mm)	21.9 ± 5.1		25.1 ± 5.8		0.006
Calcification	16	43.2	56	46.3	0.745
Bifurcation	0	0	4	3.3	0.263
CTO	18	48.6	50	41.3	0.431
IVUS	5	13.5	23	19	0.444
Rotablation	2	5.4	13	10.7	0.326
IABP	4	10.8	10	8.3	0.633
ECMO	2	5.4	3	2.5	0.374
Cardiogenic shock	5	13.5	9	7.4	0.255
PCI due to ACS	16	43.2	42	34.7	0.346
Unstable angina	3	8.1	11	9.1	0.854
STEMI	5	13.5	6	5.0	0.074
NSTEMI	9	24.3	23	19.0	0.481
VT/Vf	1	2.7	11	9.1	0.199
IIb/IIIa	4	10.8	17	14	0.612
Treated vessel (%)					
RCA	6	16.2	18	14.9	0.842
LAD	16	43.2	61	50.4	0.445
LCX	14	37.8	40	33.1	0.592
RI	1	2.7	2	1.7	0.682
Comorbidities (%)					
CHF	14	37.8	33	27.3	0.219
Previous CABG	2	5.4	15	12.4	0.230
Previous PCI	12	32.4	46	38.0	0.537
Previous MI	4	10.8	21	17.4	0.340
Previous CVA	8	21.6	12	9.9	0.061
PAOD	6	16.2	11	9.1	0.221
Hypertension	35	94.6	107	88.4	0.277
Diabetes mellitus	20	54.1	73	60.3	0.497
CKD	21	56.8	57	47.1	0.304
Hyperlipidemia	26	70.6	81	66.9	0.705
Smoking	13	35.1	35	28.9	0.472
Multivessel	33	89.2	114	94.2	0.293

Data are presented as mean ± standard deviation or *n* (%).
ACS = acute coronary syndrome; BMS = bare metal stent; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; CKD = chronic kidney disease; CTO = chronic total occlusion; CVA = cerebral vascular accident; DES = drug-eluting stent; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; IABP = intra-aortic balloon pumping; IVUS = intravascular ultrasound; LAD = left anterior descending artery; LCX = left circumflex artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction; PAOD = peripheral arterial occlusive disease; PCI = percutaneous coronary intervention; RCA = right coronary artery; RI = ramus intermediate; STEMI = ST segment elevation myocardial infarction; Vf = ventricular fibrillation; VT = ventricular tachycardia.

3.2. Angiographic results

Acute and follow-up angiographic results were comparable between the DES and BMS groups, as shown in Table 2. Compared with the BMS group, the reference vessel diameter and lesion length before procedure were, respectively, smaller and longer in the DES group (1.96 ± 0.31 mm vs. 2.07 ± 0.19 mm, $p = 0.013$ and 24.73 ± 5.90 mm vs. 22.45 ± 5.02, $p = 0.049$, respectively). At follow-up, the use of DESs was associated with significantly less % DS and less late loss (% DS: 10.01 ± 22.39 vs. 47.64 ± 41.17, $p = 0.005$; late loss: 0.24 ± 0.51 vs. 1.14 ± 0.96, $p = 0.004$).

3.3. Outcomes

The mean follow-up period was 2.7 ± 2.2 years (median, 2.1 years; interquartile range, 1.3–4.2 years). The adverse events during the follow-up period are summarized in Table 3, and there were 32 cardiovascular deaths [10 (27%) in the BMS group, 22 (18.2%) in the DES group, $p = 0.241$] and 52 TVF [18 (48.6%) in the BMS group, 34 (28.1%) in the DES group, $p = 0.02$]. One case of subacute stent thrombosis was noted in the BMS group 24 days after index procedure, which resulted

Table 2
Quantitative coronary angiography results.

QCA in-stent lesion characteristics	BMS ($n = 37$)	DES ($n = 121$)	p
Before intervention			
RVD (mm)	2.07 ± 0.19	1.96 ± 0.31	0.013
MLD (mm)	0.11 ± 0.15	0.12 ± 0.16	0.748
% DS	94.62 ± 7.19	93.58 ± 9.23	0.559
Lesion length (mm)	22.45 ± 5.02	24.73 ± 5.90	0.049
After intervention			
Acute gain (mm)[a]	2.20 ± 0.16	2.15 ± 0.18	0.204
Follow-up			
RVD (mm)	2.15 ± 0.32	2.24 ± 0.14	0.211
MLD (mm)	1.16 ± 0.98	2.05 ± 0.53	0.004
% DS	47.64 ± 41.17	10.01 ± 22.39	0.005
Late lumen loss (mm)[b]	1.14 ± 0.96	0.24 ± 0.51	0.004

Data are presented as means ± standard deviation.
BMS = bare metal stent; DES = drug-eluting stent; DS = diameter stenosis; MLD = minimal luminal diameter; QCA = quantitative coronary angiography; RVD = reference vessel diameter.
[a] Acute gain was defined as the difference between the minimal luminal diameter immediately after and before the placement of the stent.
[b] Late lumen loss was defined as the difference between the minimal luminal diameter immediately after the procedure and the minimal luminal diameter during follow-up.

in nonfatal MI. There were no cases with acute, late, or very late stent thrombosis. Fig. 1 shows the cumulative incidence curves of TVF obtained by the use of the Kaplan–Meier method between the BMS and DES groups, and also shows that the use of a DES was associated with a lower risk of TVF ($p < 0.001$). In multivariate Cox regression analysis, the use of DES (HR: 0.44, 95% CI: 0.24–0.79, $p = 0.006$), clinical presentation as acute coronary syndrome (HR: 2.48, 95% CI: 1.41–4.37, $p = 0.002$), and left ventricular ejection fraction (HR: 0.94, 95% CI: 0.93–0.96, $p < 0.001$) were identified as independent predictors of TVF. By contrast, creatinine upon admission (HR: 1.18, 95% CI: 1.06–1.32, $p = 0.002$), disease presented as acute coronary syndrome (HR: 3.23, 95% CI: 1.52–6.87, $p = 0.002$), and left ventricular ejection fraction (HR: 0.95, 95% CI: 0.92–0.97, $p < 0.001$) were independent predictors of cardiovascular death (Table 4). Moreover, subgroup analysis showed that the use of DESs was associated with a lower risk of TVF than BMSs only in patients with

Table 3
Outcomes of patients with different types of stents (BMSs and DESs).

Outcomes	BMS ($n = 37$)		DES ($n = 121$)		p
	N	%	N	%	
MACCE	18	48.6	35	28.9	0.026
MI	3	8.0	3	2.5	0.117
Stroke	3	8.0	3	2.5	0.117
All-cause mortality	13	35.1	30	24.8	0.216
TLR	8	21.6	11	9.1	0.040
TVF	18	48.6	34	28.1	0.020
CV death	10	27.0	22	18.2	0.241

BMS = bare metal stent; CV = cardiovascular; DES = drug-eluting stent; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction; TLR = target lesion revascularization; TVF = target vessel failure.

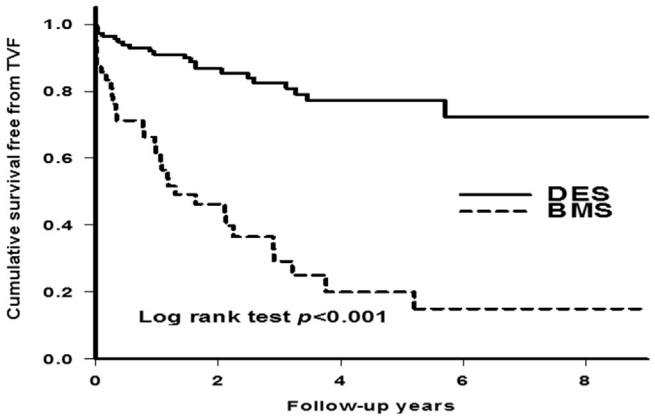

Fig. 1. Kaplan–Meier analysis for the probability of cumulative survival free from target vessel failure according to the use of BMSs and DESs. BMS = bare metal stent; DES = drug-eluting stent; TVF = target vessel failure.

CKD ($p \leq 0.01$), but not in patients without CKD ($p = 0.61$; Fig. 2). There was a significant interaction between the predictive power of the use of DESs/BMSs for TVF risk and CKD (interaction $p = 0.01$). By contrast, the use of first- or new-generation DESs in patients with or without diabetes did not appear to be associated with the risk of long-term TVF or cardiovascular death.

As a 2.25 mm stent might be used either alone or in connection with a larger stent for full-metal jacket stenting, we compared the results of the 2.25 mm stent alone ($n = 117$) or as a part of long stenting ($n = 41$), and found that there were no significant differences in TVF and cardiovascular death between these two groups ($p = 0.564$ and $p = 0.052$, respectively).

4. Discussion

The results of this study showed that in a high-risk cohort undergoing coronary stenting for very small coronary artery, the use of DESs was associated with fewer incidents of TVF compared with the use of BMSs. In particular, the beneficial effect of 2.25 mm DESs appeared to be evident only in patients with CKD, but not in those without CKD.

Few studies have compared the clinical safety and efficacy of DESs and BMSs for the treatment of very small vessel (< 2.5 mm) disease. The *post hoc* subanalysis of TAXUS V trial

Table 4
Analyses of risk factors for target vessel failure (cardiovascular death, target vessel-related myocardial infarction, target vessel revascularization) and cardiovascular death in all groups (BMS and DES).

Predictive variables	Target vessel failure		Cardiovascular death	
	HR (95% CI)	p	HR (95% CI)	p
Cr when admission	—	—	1.18 (1.06–1.32)	0.002
ACS	2.48 (1.41–4.37)	0.002	3.23 (1.52–6.87)	0.002
LVEF	0.94 (0.93–0.96)	<0.001	0.95 (0.92–0.97)	<0.001
Drug-eluting stent	0.44 (0.24–0.79)	0.006	—	—

ACS = acute coronary syndrome; BMS = bare metal stent; CI = confidence interval; Cr = creatinine; DES = drug-eluting stent; HR = hazard ratio; LVEF = left ventricular ejection fraction.

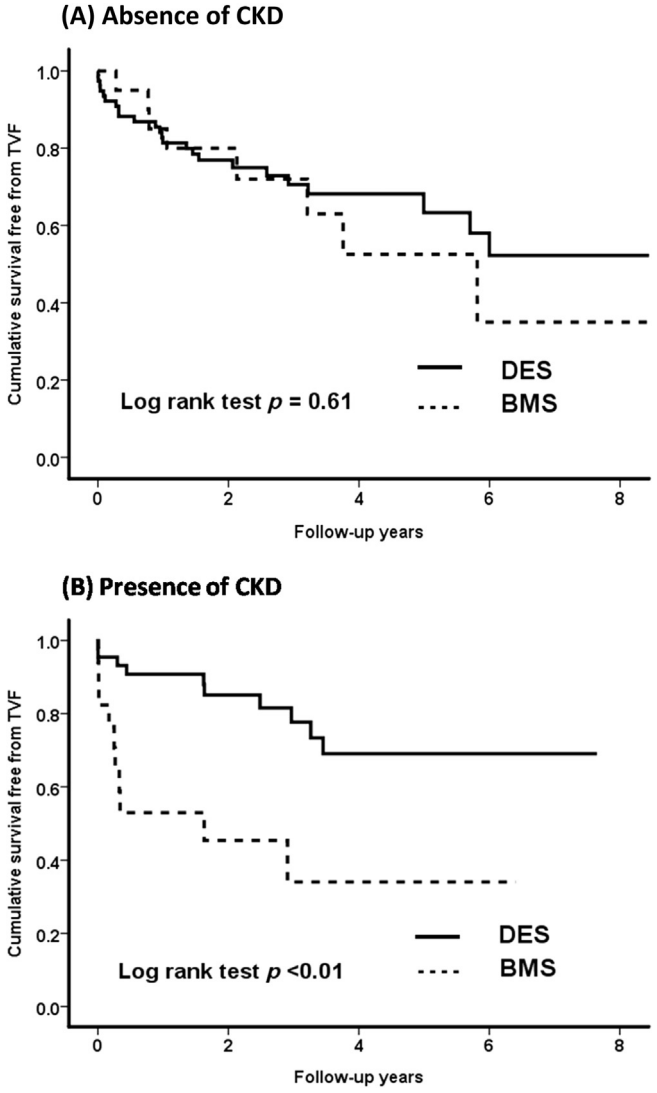

Fig. 2. Kaplan−Meier analysis for the probability of cumulative survival free from target vessel failure according to the (A) absence or (B) presence of CKD. BMS = bare metal stent; CKD = chronic kidney disease; DES = drug-eluting stent; TVF = target vessel failure.

analyzed the clinical results of patients with a mean luminal diameter of 2.08 mm treated with 2.25 mm paclitaxel-eluting stents. This showed that restenosis rates were reduced significantly when compared with BMSs, although angiographic binary restenosis and target lesion revascularization still occurred in approximately 20% and 10% of patients, respectively, using DESs. Furthermore, in this subanalysis, there were no significant differences in the rates of death, MI, and stent thrombosis at 1 month and 9 months between the paclitaxel-eluting stent and BMS groups.[23] Another subgroup analysis from the RESEARCH Registry by Lemos et al[24] compared the performance of 2.25 mm SESs with that of SESs of $\geq$ 2.5 mm diameter in the same procedure. At the 1-year follow-up, the binary restenosis rate and target lesion revascularization were 10.7% and 5.5%, respectively.[25] Our study also showed similar results that the use of DESs was associated with lower risk of TVF and cardiac vascular death. However, the rate of TVF was much higher in our study, which may be related to more comorbidities in our population. Further studies for very small vessel stenting in a lower-risk cohort are recommended.

Few trials have examined the association between stent efficacy and clinical outcomes in patients with CKD arising from concerns of higher MACE rates, mortality, higher prevalence of diabetes mellitus,[26] lower procedure success rate, coronary lesion calcification and lesion complexity,[27−32] greater thrombogenicity,[33,34] increased platelet dysfunction, and risk of restenosis.[35,36] Previous reports had compared first-generation DESs with BMSs, and revealed that the use of DESs may decrease the risk of target vessel revascularization; however, DES use was not effective in reducing mortality risk in CKD patients.[24,37,38] Ishio et al[39] also reported that SESs, compared with BMSs, reduced in-stent restenosis but not in-segment restenosis or target lesion revascularization in patients on dialysis (mean stent diameter, 3.03 $\pm$ 0.36 mm). Furthermore, Toutouzas et al[40] found that second-generation DESs (mean stent diameter, 2.92 $\pm$ 0.32 mm) had increased efficacy and were safe in reducing the rates of target lesion revascularization and stent thrombosis compared with those in non-CKD patients, although no significant differences regarding MACEs or nonfatal MI were found.

When first- and second-generation DESs were compared, Chan et al[41] reported that in patients with creatinine clearance < 60 mL/min, the use of first- and second-generation DESs showed a similar rate of nonfatal MI, target vessel revascularization, and all-cause mortality, with the only noted superiority for second-generation DESs over BMSs being 4-year MACEs.[42−44] Thereafter, patients with CKD appear to be at high risk for long-term MACE compared with patients without CKD. The use of DESs in patients with CKD may reduce the risk of instent restenosis (ISR) and target vessel revascularization. However, the very small vessel disease in the CKD subgroup had never been investigated. Our result supported the proposition that superiority of 2.25 mm DESs over BMSs is evident only in patients with CKD.

4.1. Limitations

Several limitations of the present study should be acknowledged, which included its small sample size, non-randomized nature, and different stenting times because treatment strategies to address very small vessel disease have evolved over time. Moreover, being a single-center observational retrospective analysis, there is an inherent selection bias, an under-reporting bias, and confounding factors related to unmeasured variables; these results should be confirmed in a prospective randomized manner. Third, only about two-thirds of our patients received follow-up coronary angiography by clinical indications (102 patients, 64.5%), and incomplete angiographic follow-up-related potential bias might have a substantial impact on the analytic results.

In conclusion, DESs were associated with a lower risk of TVF when compared with BMSs in patients treated for very small vessel (< 2.25 mm) disease. However, these beneficial

effects of DESs appeared to be evident only in the subgroup with CKD.

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