Prevalence, predictors, prognostic significance, and effect of techniques on outcomes of coronary lesion calcification following implantation of drug-eluting stents: a patient-level pooled analysis of stent-specific, multicenter, prospective IRIS-DES registries

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Aims **There is limited information on the clinical relevance and procedural impact of coronary artery calcification (CAC) in the contemporary percutaneous coronary intervention (PCI) setting. This study sought to determine the incidence and clinical significance of procedural techniques on the outcomes in 'real-world' patients with CAC undergoing PCI with drug-eluting stents (DESs).**

Methods and results **Using patient-level data from seven stent-specific, prospective DES registries, we evaluated 17 084 patients who underwent PCI with various DES types between July 2007 and July 2015. The primary outcome was target-vessel failure (TVF), defined as a composite of cardiac death, target-vessel myocardial infarction, or target-vessel revascularization. Outcomes through 3 years (and between 0–1 and 1–3 years) were assessed according to CAC status (none/mild vs. moderate/severe) and stenting technique (predilation or post-dilation). Among 17 084 patients with 22 739 lesions included in the pooled dataset, moderate to severe CAC was observed in 11.3% of patients (10.1% of lesions). Older age, lower BMI, diabetes, hypertension, family history of coronary artery disease, and renal failure were independent predictors of moderate/severe CAC. The presence of moderate/severe CAC was significantly associated with an adjusted risk of TVF at 3 years [hazard ratio, 1.37; 95% confidence interval (CI), 1.19–1.58; *P*<0.001]. For severe CAC, optimal lesion preparation with predilation was associated with a lower 3-year rate of TVF (no vs. yes, 22.3 vs. 12.8%), in which the effect of predilation was prominent at the late period of 1–3 years (hazard ratio, 0.28; 95% CI, 0.12–0.69; *P*=0.003) than at the early period through 1 year (hazard ratio, 1.16; 95% CI, 0.37–3.71; *P*=0.80). However, post-dilation (with a high-pressure noncompliant balloon) had no effect on the outcome.**

Conclusions **In this study, moderate/severe CAC was common (~10%) and strongly associated with TVF during 3 years of follow-up. For severe CAC, optimal lesion preparation with pre-balloon dilation has a significant effect on long-term outcomes, especially during the late period beyond 1 year. Clinical Trial Registration – URL: http://www.clinicaltrials.gov. Unique identifier: NCT01186133. *Coron Artery Dis* 32: 42–50**

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Introduction

Coronary artery calcification (CAC) is a risk factor for adverse outcomes in the general population and in patients with coronary artery disease (CAD) [1]. With increasing age of the population undergoing percutaneous coronary intervention (PCI), the prevalence of CAC is also steadily increasing; however, calcified lesions represent a challenging subset of complex high-risk lesions for PCI. Prior reports suggested a detrimental effect of CAC on procedural success and clinical outcomes after PCI with stent implantation [2–5].

Several studies have demonstrated that drug-eluting stents (DESs) are more effective than bare-metal stents for CAC treatment [1,6,7]. However, metallic DES and

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devices for plaque modification have only modestly improved outcomes in patients with CAC and the adverse event rates after PCI for calcified lesions remain high. Furthermore, data on the absolute efficacy and safety of DESs in patients with CAC are conflicting: some studies reported similar rates of angiographic and clinical outcomes in DES-treated calcified and noncalcified lesions [7,8], whereas other studies reported higher rates of efficacy and safety outcomes in DES-treated calcified lesions than in noncalcified lesions [9,10]. In addition, with regard to procedural characteristics, the presence of CAC may impair stent delivery and optimal expansion and possibly damage the polymer and drug coating, increasing the risk for future device-related outcomes. However, until recently, the impact of the procedural technique (optimal predilation or post-high-pressure-dilation) on clinical outcomes is still undermined after PCI with DES implantation for severe CAC.

By using individual patient-level data from several stent-specific registries, we therefore sought to investigate the prevalence, correlates, and impact of CAC on the clinical outcomes in patients undergoing PCI with DES implantation. Moreover, we performed a comprehensive analysis of the effect of procedural technique on early and late outcomes after PCI for severe CAC.

Methods

Study population

As a part of an ongoing academic project, individual patient-level data were pooled from the Interventional Cardiology Research Incorporation Society – Drug-Eluting Stents (IRIS-DES) registry (NCT01186133) between 15 July 2007 and 29 July 2015. The IRIS-DES registry has been described previously [11]. Briefly, the IRIS-DES involves prospective, multicenter recruitment of unrestricted patients undergoing PCI with DES in Korea, and consists of several different arms of second- and first-generation DES in contemporary PCI situations. The pooled dataset consisted of individual patient data from seven different DES registry cohorts. The key features of each DES registry are reported in online Table 1, Supplemental digital content 1, *http://links.lww.com/MCA/A353* and online Figure 1, Supplemental digital content 1, *http://links.lww.com/MCA/A353*. These registries were supported by the CardioVascular Research Foundation, Seoul, Korea, and there was no industry involvement in the design, conduct, or analysis of the study. The study protocol was approved by the ethics committee at each participating center, and all patients provided written, informed consent for participation in this prospective registry.

Qualitative and quantitative coronary angiographic analyses were performed in a dedicated angiographic core laboratory according to current standards. The angiographic analysts prospectively classified the CAC in analogy with previous studies [2,7,10]. At the time of the angiographic analysis, the reviewers were blinded to the patients' clinical characteristics, stent type, and outcomes. Angiographic CAC was identified as readily apparent radio-opacities or X-ray-absorbing masses, noted within the apparent vascular wall at the site of the target lesion before any contrast injection. The severity of CAC was classified as none or mild, moderate (radiopacities noted only during the cardiac cycle before contrast injection), or severe (radiopacities seen without cardiac motion before contrast injection, usually affecting both sides of the arterial lumen). For the present analysis, the study patients were categorized into patients with no or mild CAC versus those with moderate or severe CAC.

Percutaneous coronary intervention procedures and clinical follow-up

In the IRIS-DES registry, interventional procedures were performed according to standard techniques, routine clinical protocols, and current medical guidelines, which did not differ between stent-specific registries. This registry did not specify the types of DES according to clinical or anatomic features. Details of the intervention, such as lesion predilation, stent implantation, or stent post-dilation were left at the discretion of the treating physician. Periprocedural anticoagulant was administered according to standard regimens. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the operator. All patients undergoing PCI received a loading dose of aspirin and $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) before or during PCI. After the procedure, aspirin was continued indefinitely and $P2Y_{12}$ receptor inhibitors were prescribed for at least 12 months regardless of the DES type.

Clinical follow-up was conducted during hospitalization and at 30 days, 6 months, 12 months, and every 6 months thereafter. At each visit, information pertaining to patients' clinical status, all interventions, and outcome events were recorded. Baseline characteristics and outcome data were collected using a dedicated electronic case report form by specialized personnel at each participating center and were stored in a common database. The internet-based system provides each center with immediate and continuous feedback on the processes and quality-of-care measures. Monitoring and verification of registry data are periodically performed in the participating hospitals by members of the academic coordinating center (Clinical Research Center, CardioVascular Research Foundation, Asan Medical Center, Seoul, Korea) [11].

Study outcomes and definitions

The primary outcome of the study was target-vessel failure (TVF), which was defined as a composite of death of cardiac causes, target-vessel myocardial infarction (MI), or target-vessel revascularization (TVR). Various secondary outcomes were also assessed, including death (any causes or cardiac causes), target-vessel MI (periprocedural or

spontaneous), TVR, target-lesion revascularization, and stent thrombosis.

Death was considered to have a cardiac cause unless an unequivocal noncardiac cause could be established. The diagnosis of MI was based on clinically relevant MI according to the Society for Cardiovascular Angiography and Interventions definition [12]. TVR was defined as any type of percutaneous or surgical revascularization procedure involving the target vessel of the stented segment. TLR included repeat revascularization involving the stented segment.

Definite or probable stent thrombosis was assessed according to the Academic Research Consortium definition [13]. All endpoints as defined and adjudicated in each individual registry were utilized. All endpoints were confirmed using the source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee.

Statistical analysis

The baseline characteristics of the study population, including patient demographics, risk factors or comorbidities, clinical presentation, concomitant medications, and anatomic/procedural features, were examined using proportions for categorical variables and mean ± SD for continuous variables according to the severity of CAC. Categorical variables were assessed using chi-square tests and Fisher's exact tests, and continuous variables were assessed using Student's *t*-tests or Wilcoxon rank-sum tests, as appropriate. Independent predictors of the presence of moderate or severe CAC were entered into a multivariable logistic regression analysis including the following baseline covariates: age, sex, BMI, diabetes, hypertension, hyperlipidemia, smoking, family history of CAD, previous MI, previous heart failure, previous PCI, previous bypass surgery, renal failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, and clinical presentation. Generalized estimating equations were used to account for between-study heterogeneity and within-study clustering.

Observed event rates at 3 years and survival curves were generated using the Kaplan–Meier method and compared with the log-rank test. For primary and key secondary clinical outcomes, we prespecified examining the event rates between the time of treatment (time 0) and 3-year follow-up, and separately from 0 to 1 year and from 1 to 3 years (landmark analysis). In addition, unadjusted and adjusted Cox proportional hazard models were used to compare clinical events according to the severity of CAC. To determine the independent association of the presence of moderate or severe CAC on outcomes and to compensate for the nonrandomized design of observational studies, we used a propensity score method. We fitted weighted Cox proportional hazards models using the inverse probability of treatment weighting (IPTW) approach [14]. The propensity scores were estimated without regard to outcomes, with multiple logistic regression analysis. A full nonparsimonious model was developed that included covariates in Tables 1 and 2.

In addition, we determined the impact of procedural technique (predilation or post-highpressure-dilation) on the 3-year rate of TVF according to the severity of CAC (no/mild, moderate, or severe). A landmark analysis was also performed to examine whether the effect of a specific technique may vary in the early period after PCI (before 1 year) and in the late period after PCI (between 1 and 3 years). All reported *P* values were two-sided and have not been adjusted for multiple testing. All analyses were performed with SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA) and the R programming language.

Results

Characteristics of patients and predictors of coronary artery calcification

During July 2007 and July 2015, a total of 17 084 patients from seven stent-specific, prospective IRIS-DES registries were included for the current analysis. The distributions of CAC per patient and per lesion are shown in online Figure 2, Supplemental digital content 1, *http://*

Table 1 Baseline demographic and clinical characteristics according to the severity of coronary artery calcification

Characteristics	No or mild CAC (*n*=15 153)	Moderate or severe CAC (*n*=1931)	*P* value
Age (years)	63.4 ± 10.8	66.5 ± 10.2	<0.001
Men	10 615 (70.1)	1223 (63.3)	<0.001
BMI (kg/m^2)	24.7 ± 3.1	24.3 ± 3.4	<0.001
Diabetes mellitus	4934 (32.6)	774 (40.1)	<0.001
Hypertension	9139 (60.3)	1368 (70.8)	<0.001
Hyperlipidemia	5897 (38.9)	759 (39.3)	0.76
Current smoking	4463 (29.5)	482 (25.0)	<0.001
Family history of CAD	853 (5.6)	128 (6.6)	0.08
Previous MI	815 (5.4)	117 (6.1)	0.24
Previous CHF	320 (2.1)	66 (3.4)	<0.001
Previous PCI	1935 (12.8)	256 (13.3)	0.57
Previous CABG	271 (1.8)	52 (2.7)	0.008
Renal failure	469 (3.1)	116 (6.0)	<0.001
Cerebrovascular disease	1065 (7.0%)	186 (9.6)	<0.001
Peripheral vascular disease	268 (1.8)	56 (2.9)	0.001
Chronic lung disease	358 (2.4)	59 (3.1)	0.075
Ejection fraction (%)	58.9 ± 10.3	58.1 ± 11.6	0.002
Clinical presentation			<0.001
Stable angina	6276 (41.4)	801 (41.5)	
Unstable angina	4831 (31.9)	694 (35.9)	
NSTEMI	2119 (14.0)	239 (12.4)	
STEMI	1927 (12.7)	197 (10.2)	
Discharge medications			
Aspirin	14 931 (98.5)	1904 (98.6)	0.90
ADP receptor antagonist	14 856 (98.0)	1905 (98.7)	0.08
β-Blocker	8917 (58.8)	1165 (60.3)	0.22
Calcium channel blocker	5642 (37.2)	697 (36.1)	0.34
ACE inhibitor or ARB	7841 (51.7)	1103 (57.1)	<0.001
Statin	12 241 (80.8)	1518 (78.6)	0.03

Values are mean ± SD or *n* (%).

ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CABG, coronary-artery bypass grafting; CAC, coronary artery calcification; CAD, coronary artery disease; CHF, congestive heart failure; NSTEMI, non-ST-elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

links.lww.com/MCA/A353. In the overall population, 1931 (11.3%) patients had moderately or severely calcified coronary lesions. Patients with moderate or severe CAC were older, included more women than men, had a higher prevalence of risk factors (diabetes, hypertension, prior heart failure, prior bypass surgery, renal failure, and non-coronary atherosclerotic vascular disease), and had lower ejection fraction (Table 1). Patients with moderate or severe CAC less commonly presented with acute MI. With regard to anatomic and procedural characteristics, patients with moderate or severe CAC had a higher prevalence of left anterior descending involvement or total occlusion and had a larger number of stents implanted, longer total stent length, and smaller stent diameter (Table 2). Pre-balloon dilation was performed in approximately 90% of patients and post-high-pressure dilation (with a noncompliant balloon) was performed in approximately 46% of patients. Use of cutting balloon and rotational atherectomy was very rare. Multivariable logistic regression analysis was conducted to determine the independent predictors of the presence of moderate or severe CAC, and the results are shown in online Table 2, Supplemental digital content 1, *http://links.lww.com/MCA/A353*. In this model, older age, lower BMI, diabetes, hypertension, family history of CAD, and renal failure were independent correlates of moderate or severe CAC.

Table 2 Baseline lesion and procedural characteristics according to the severity of coronary artery calcification

Characteristics	No or mild CAC (n=20441)	Moderate or severe CAC (n=2298)	P value
Lesion location			
Left main	879 (4.3)	115 (5.0)	0.13
Left anterior descending	9687 (47.4)	1246 (54.2)	<0.001
Left circumflex	4205 (20.6)	364 (15.8)	<0.001
Right	5703 (27.9)	574 (25.0)	0.003
ACC-AHA lesion class			<0.001
A	999 (4.9)	27 (1.2)	
B1	4427 (21.7)	248 (10.8)	
B2	3551 (17.4)	458 (19.9)	
C	11464 (56.1)	1565 (68.1)	
Restenotic lesion	613 (3.0)	64 (2.8)	0.61
Bifurcation lesion	5244 (25.7)	592 (25.8)	0.93
Total occlusion	2294 (11.2)	300 (13.1)	0.01
Type of DES			0.02
Early-generation DES	4455 (21.8)	549 (23.9)	
New-generation DES	15986 (78.2)	1749 (76.1)	
No. of stents[a]	1.2±0.5	1.3±0.6	<0.001
Stent length (mm)[a]	29.2±15.4	33.1±17.1	<0.001
Stent diameter (mm)[a]	3.2±0.4	3.1±0.4	<0.001
Pre-balloon dilation	18351 (89.8)	2142 (93.2)	<0.001
Use of cutting balloon	288 (1.4)	39 (1.7)	0.31
Use of rotablator	7 (0.1)	33 (1.4)	<0.001
Post-high-pressure balloon dilation	9552 (46.7)	1052 (45.8)	0.39
Use of IVUS	9609 (47.0)	902 (39.3)	<0.001

Values are mean±SD or *n* (%).
[a]The number, length, and diameter of stents were calculated per lesion.
ACC-AHA, American College of Cardiology-American Heart Association; DES, drug-eluting stents; CAC, coronary artery calcification; IVUS, intravascular ultrasound.

Clinical impact of coronary artery calcification

The median duration of follow-up was 3.4 years (interquartile range, 2.6–4.2 years). The Kaplan–Meier estimates of primary and secondary outcomes at 3 years according to CAC severity are shown in Fig. 1 and Table 3. Patients with moderate or severe CAC had a higher 3-year rate of TVF than those with no or mild CAD (12.7 vs. 9.1%, $P<0.001$). The 3-year rates of death, MI, repeat revascularization, and stent thrombosis were also higher in patients with moderate or severe CAC.

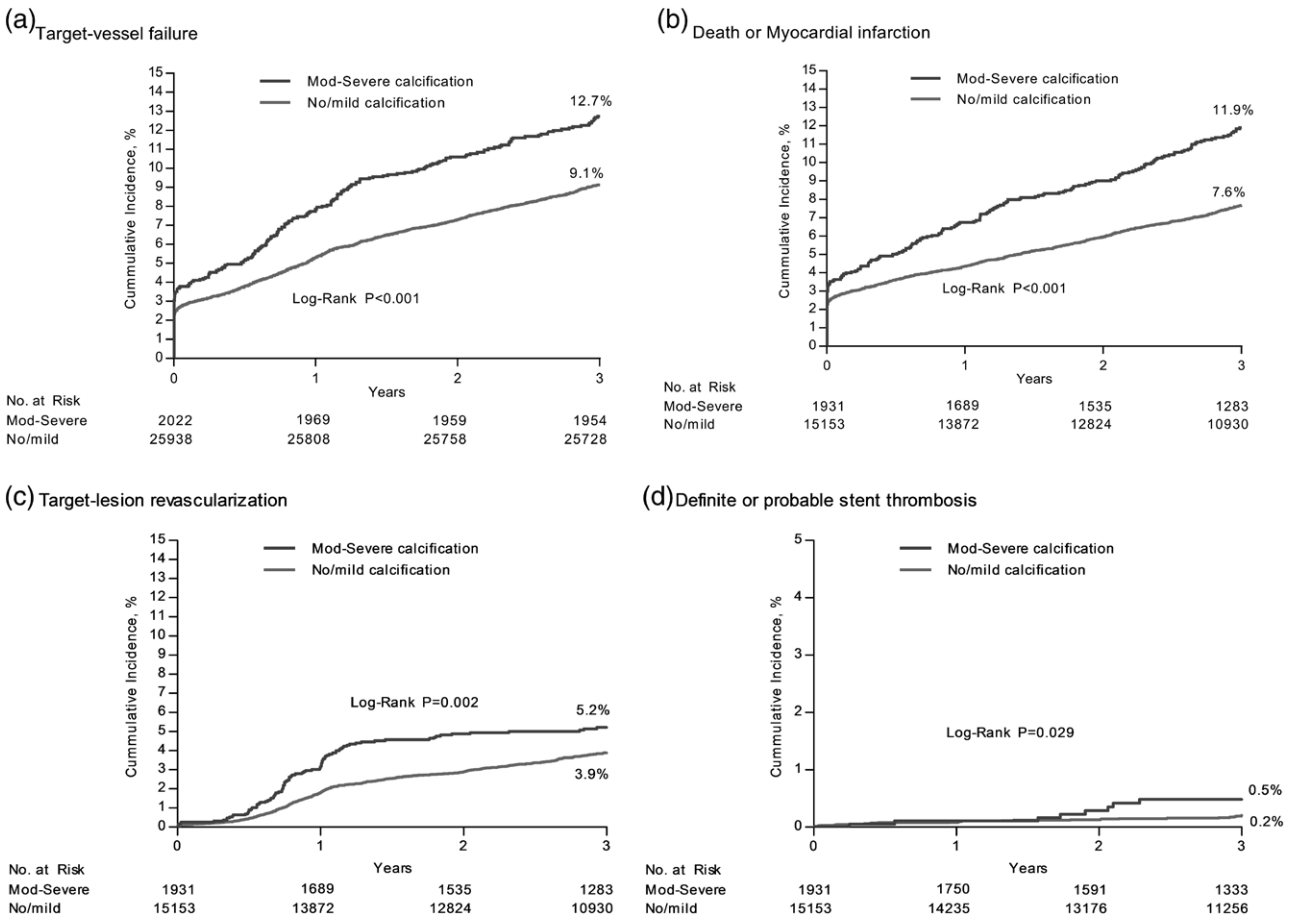
According to each category of CAC, the differential risk of TVR was separated into the none or mild versus moderate or severe category (online Figure 3, Supplemental digital content 1, *http://links.lww.com/MCA/A353*). In the landmark analysis, the presence of moderate or severe CAC was consistently associated with higher risks of TVF and death or MI in the early (<1 year) and late (1–3 years) period. However, the impact of moderate or severe CAC on target-lesion revascularization was more pronounced in the early period, whereas the impact on stent thrombosis was more pronounced in the late period (online Figure 4, Supplemental digital content 1, *http://links.lww.com/MCA/A353*). After IPTW adjustment for baseline covariates, the presence of moderate or severe

Table 3 Unadjusted and adjusted 3-year clinical outcomes according to the severity of coronary artery calcification

			Unadjusted		IPTW adjusted	
Characteristics	No or mild CAC (n=15153)	Moderate or severe CAC (n=1931)	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Primary outcome						
Target-vessel failure[a]	1306 (9.1)	229 (12.7)	1.43 (1.24–1.65)	<0.001	1.37 (1.19–1.58)	<0.001
Secondary outcomes						
Death						
From any causes	681 (4.9)	148 (8.4)	1.77 (1.48–2.12)	<0.001	1.38 (1.14–1.67)	0.001
From cardiac causes	439 (3.1)	94 (5.4)	1.74 (1.40–2.18)	<0.001	1.41 (1.11–1.78)	0.005
Target-vessel MI	465 (3.2)	82 (4.4)	1.40 (1.11–1.78)	0.005	1.46 (1.16–1.84)	0.001
Periprocedural	333 (2.2)	56 (2.9)	1.32 (1.00–1.76)	0.05	1.43 (1.09–1.88)	0.01
Spontaneous	136 (1.0)	27 (1.6)	1.62 (1.07–2.44)	0.02	1.54 (1.01–2.33)	0.04
Target-vessel revascularization	719 (5.2)	124 (7.1)	1.43 (1.18–1.73)	<0.001	1.32 (1.08–1.60)	0.006
Target-lesion revascularization	537 (3.9)	92 (5.2)	1.41 (1.13–1.76)	0.002	1.33 (1.06–1.67)	0.01
Definite or probable stent thrombosis	28 (0.20)	8 (0.50)	2.33 (1.06–5.11)	0.04	2.02 (0.88–4.61)	0.10

Values are number of events, percentages (Kaplan–Meier estimates), and hazard ratio (95% CI).
[a]Target-vessel failure was defined as a composite of death from cardiac causes, target-vessel MI, or target-vessel revascularization.
CAC, coronary artery calcification; CI, confidence interval; IPTW, inverse probability of treatment weighting; MI, myocardial infarction.

Fig. 1



Kaplan–Meier curves for 3-year primary and key secondary outcomes according to the severity of coronary artery calcification. In each figure, cumulative incidence curves are shown for TVF stratified by calcium severity (a); death or myocardial infarction (b); target-lesion revascularization (c); and definite or probable stent thrombosis (d). TVF was defined as a composite of death of cardiac causes, target-vessel myocardial infarction, or target-vessel revascularization. TVF, target-vessel failure.

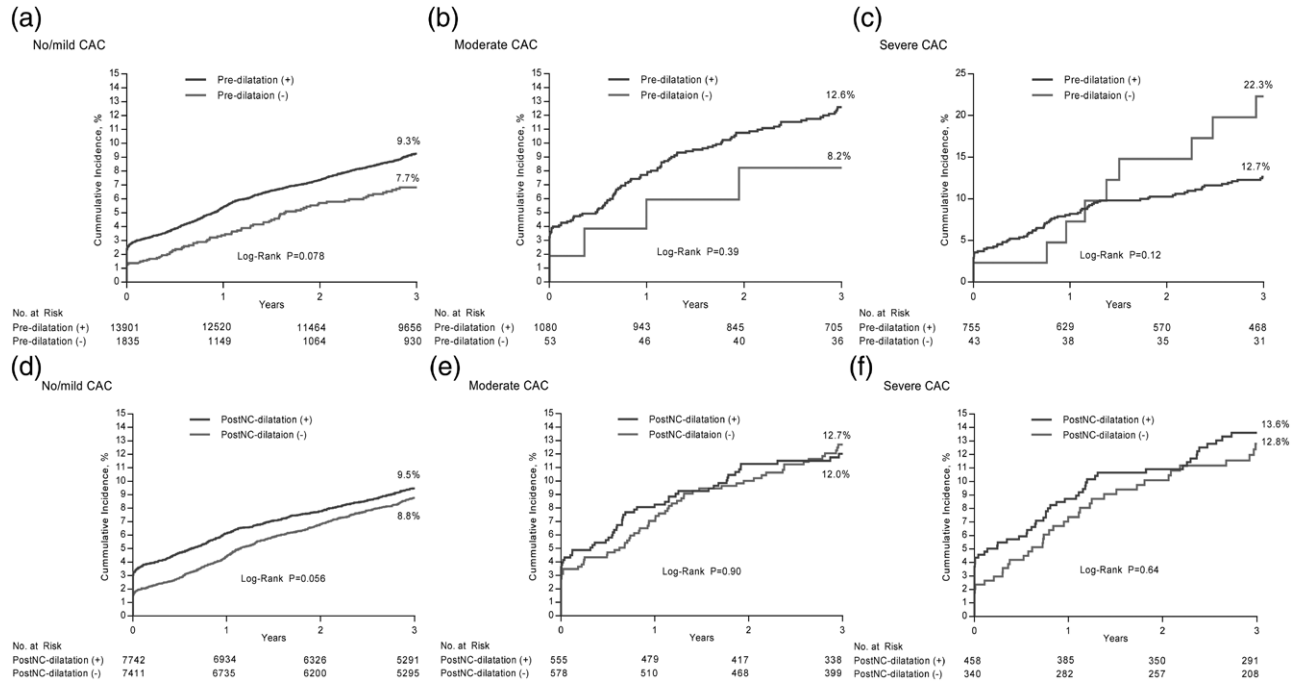
Table 4 Landmark analysis of target-vessel failure according to technique, stratified by the severity of coronary artery calcification

	Target-vessel failure through 1 year				Target-vessel failure during 1–3 years			
	Event rate (%)[a]				Event rate (%)			
Characteristics	Not done	Done	Hazard ratio (95% CI)	*P* value	Not done	Done	Hazard ratio (95% CI)	*P* value
No or mild CAC (*n*=15153)								
Pre-balloon dilation	4.3	5.4	1.27 (0.96–1.68)	0.098	3.6	4.1	1.13 (0.81–1.56)	0.45
Post-high-pressure balloon dilation	4.4	6.1	1.40 (1.21–1.62)	<0.001	4.5	3.5	0.78 (0.65–0.92)	0.003
Moderate CAC (*n*=1133)								
Pre-balloon dilation	5.9	7.7	1.34 (0.42–4.25)	0.42	2.5	5.3	2.17 (0.30–15.7)	0.44
Post-high-pressure balloon dilation	7.0	8.3	1.19 (0.77–1.82)	0.43	6.0	4.1	0.69 (0.38–1.23)	0.28
Severe CAC (*n*=798)								
Pre-balloon dilation	7.3	8.2	1.16 (0.37–3.71)	0.80	16.2	4.9	0.28 (0.12–0.69)	0.003
Post-high-pressure balloon dilation	7.4	8.7	1.22 (0.73–2.02)	0.45	5.9	5.3	0.92 (0.47–1.81)	0.81

[a]Event rates are based on the Kaplan–Meier estimates.
[b]Target-vessel failure was defined as a composite of death of cardiac causes, target-vessel MI, or target-vessel revascularization.
CAC, coronary artery calcification; CI, confidence interval; MI, myocardial infarction.

CAC was independently associated with increased risks of TVF, death, MI, or repeat revascularization and with a trend toward increasing risk of stent thrombosis (Table 4). The effect of moderate or severe CAC on the risk for the primary endpoint of TVF according to several key subgroups is illustrated in online Figure 5,

Fig. 2



Kaplan–Meier curves showing the relationship between technique and TVF, stratified by the severity of coronary artery calcification. TVF, target-vessel failure. In each figure, 3-year cumulative incidence curves are shown for target-vessel failure stratified by pre-noncompliant or post-noncompliant balloon dilation (a); death or myocardial infarction (b); target-lesion revascularization (c); and definite or probable stent thrombosis (d). Target-vessel failure was defined as a composite of death of cardiac causes, target-vessel myocardial infarction, or target-vessel revascularization.

Supplemental digital content 1, *http://links.lww.com/MCA/A353*. There was no significant heterogeneity in the risk for TVF according to types of DES.

Effect of technique on outcomes

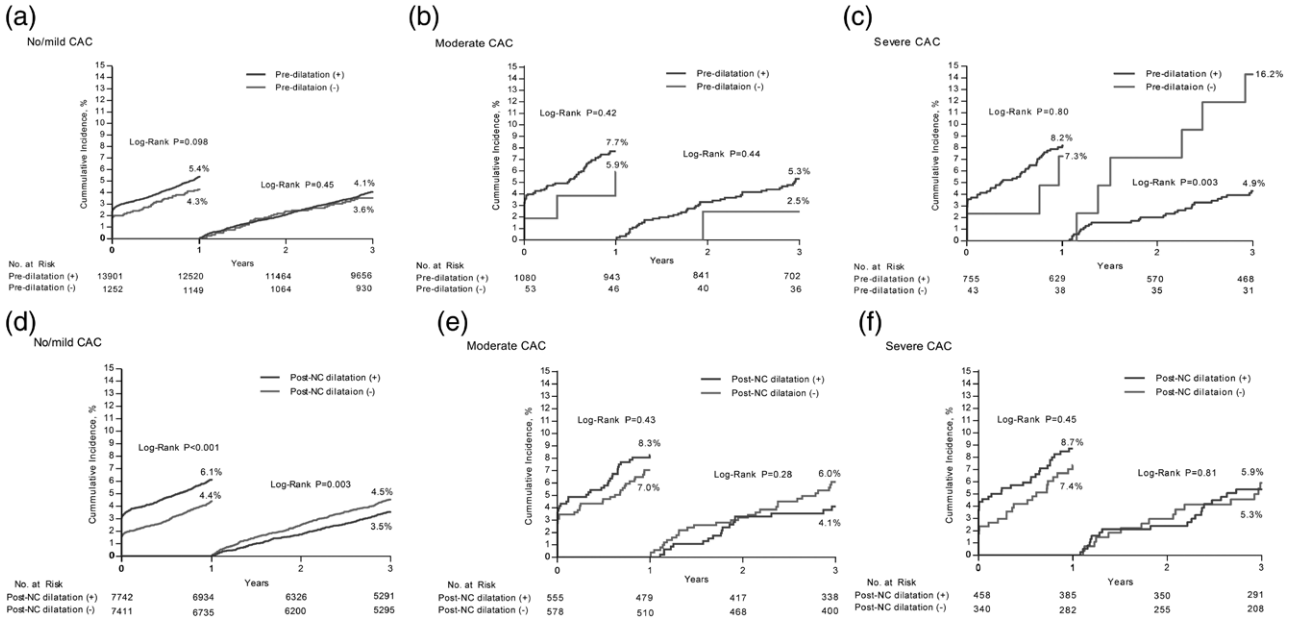
The impact of stenting technique (predilation or post-high-pressure dilation) is shown in Fig. 2 and online Table 3, Supplemental digital content 1, *http://links.lww.com/MCA/A353*. In each category of CAC, there was no statistically significant difference in the 3-year rate of TVF according to stenting technique. However, among patients with severe CAC, there was an indication of a slightly lower rate of TVF in the group without predilation than in the group with predilation at 1 year. However, during continued follow-up of 1–3 years, there was a substantially higher rate of TVF in the group without predilation. Accordingly, in the landmark analysis, the event rate of TVF was similar at 1 year between the group without predilation and the group with predilation (7.3 vs. 8.2%, $P=0.80$). Thereafter, there was a continuous separation of the curves, with a significantly higher rate of events in patients without predilation than in those with predilation (16.2 vs. 4.9%, $P=0.003$) (Fig. 3 and Table 4). By contrast, we did not find an effect of post-high-pressure dilation (with a noncompliant balloon) on the risk of TVF in the entire follow-up and also in the early or late period.

Discussion

The present study, based on a pooled analysis of 17 084 patients enrolled in seven stent-specific registries, is the largest report to date examining the prevalence and clinical relevance of CAC and the effect of technique on outcomes in the 'real-world' PCI setting with the use of contemporary DES. The major findings are that (1) the prevalence of moderate or severe CAC was approximately 10%, and several clinical covariates were associated with a higher likelihood of CAC; (2) the presence of moderate or severe CAD was significantly associated with increased risks of TVF, death, MI, repeat revascularization, and stent thrombosis; (3) there was no significant heterogeneity in the risk for TVF according to different types of DES; and (4) for severe CAC, predilation was not associated with the 1-year rate of TVF, but was significantly associated with a higher risk of TVF between 1 and 3 years. However, post-dilation with a high-pressure noncompliant balloon was not associated with the 3-year rate of TVF. Such findings emphasize the paramount importance of optimal lesion preparation with predilation for ensuring better long-term outcomes (especially for the late period >1 year) rather than post-dilation.

In our study, approximately 10% of patients had moderate to severe CAC; the prevalence of moderate or severe

Fig. 3



Landmark analysis of the effect of stenting technique on target-vessel failure, stratified by the severity of coronary artery calcification. In each figure, landmark analysis of 1-year and 1–3-year cumulative-incidence curves are shown for target-vessel failure stratified by pre-noncompliant or post-noncompliant balloon dilation (a) death or myocardial infarction (b); target-lesion revascularization (c); and definite or probable stent thrombosis (d). Target-vessel failure was defined as a composite of death of cardiac causes, target-vessel myocardial infarction, or target-vessel revascularization.

CAC was relatively lower than the reported rate from clinical studies involving Western populations [3,4,15]. Although a prior study showed that CAC is most frequent in Caucasians [16], the ethnic difference in the prevalence and impact of CAC is still unknown. Further studies might be required to determine whether this differential rate of CAC was due to an ethnic disparity or a measurement bias between studies. A number of risk factors contribute to the development of CAC [1]. Similar to previous reports, common risk factors (e.g. advanced age, diabetes, and chronic kidney disease) were found to be associated with the presence of moderate or severe CAC. Enhanced understanding of the risk factors or covariates that contribute to CAC is needed if more effective preventive or therapeutic strategies are to be developed.

The extent of CAC correlates with the degree of atherosclerotic plaque burden. Although prior PCI studies have shown a differential prognostic implication of CAC on clinical outcomes after DES implantation [3,4,7,9,15] most of the studies suggested a strong association of severe calcified lesions with a higher risk of major cardiovascular events including death, MI, repeat revascularization, and stent thrombosis. Our study also obtained consistent findings: patients with moderate or severe CAC have a higher clinical risk profile and remain at a higher risk for short-term and long-term adverse clinical events in the contemporary PCI setting with diverse types of DES. We also found that the adverse effect of CAC on outcomes seems to be uniform across clinical and angiographic subsets, including different types of newer-generation DES, as shown in recent studies [4,15,17]. The plausible reasons for such uniform prognostic impact of CAD, irrespective of different types of contemporary DES, might be explained by the fact that drug elution is unlikely to be uniform and effective enough for preventing neointimal hyperplasia in the case of calcific lesions, and also that damage to strut and polymer during the complex procedure may offset the benefit of DES [18]. In addition, stent underexpansion, asymmetric expansion, and malapposition are frequently observed in heavily calcified lesions.

In severely calcified lesions, sufficient lesion preparation with predilation of the target lesion is important for optimal implantation of DESs. Extensive calcification in severely obstructive lesions impedes device delivery and increases the risk of procedural failure. From a physician's point of view, if a lesion lumen is considered sufficient to deliver a device, it can be thought of as full expansion to a high-pressure noncompliant balloon instead of optimal predilation by fear of extensive dissection or perforation. But, in the procedural viewpoint, post-dilation with a high-pressure noncompliant balloon cannot guarantee full expansion and well apposition of deployed stents in severe CAC without optimal predilation. Our findings

strongly support a more important prognostic value of predilation than post-dilation for treating severe CAC; there were substantially different outcomes according to the presence or absence of pre-dilation, but not that of post-high-pressure dilation. In contemporary PCI practice, diverse nonatherectomy strategies (cutting or scoring balloons) and atherectomy strategies (rotational, orbital, or laser atherectomy) are available for treating severe CAC [19]. Unfortunately, owing to the extremely low rate of use of such devices in our registry, we cannot assess the therapeutic impact of these adjunctive methods to PCI in calcified lesions. This phenomenon may be due to the good performance of the DES, which may be due to the weakening of the lesion preparation concept over the past bare metal stent. Additional measures to mitigate ischemic risk and improve suboptimal device-oriented outcomes in this high-risk population are warranted and require further investigations.

Several limitations of our study should be considered. First, as this study is observational in nature, the overall findings should be considered hypothetical and hypotheses generating only. In addition, the information provided is limited because it is not a registry specific to calcific lesions. For example, information about the IVUS finding of calcific lesions or on the use of DAPT by time-point is not provided. Second, coronary angiography has limited sensitivity in detecting the presence of calcified plaques. The ambiguity of this definition has been pointed out as a limitation in many studies. However, coronary angiography has a high specificity for detecting severe CAC. Third, as compared with the PCI practice in other institutions and of other specialists [6], the use of rotational atherectomy was very low in our study, potentially limiting the reproducibility of these results in other settings. Finally, owing to the limited number of hard clinical endpoints (i.e. stent thrombosis and mortality), our study was underpowered to detect the differences of such clinically relevant outcomes according to the severity of CAD and stenting technique.

Conclusion

In contemporary clinical PCI practice with diverse types of DES, the presence of moderate or severe CAC was common. Patients with moderate or severe CAC had a higher risk of cardiovascular events during the long-term follow-up, and the detrimental effect of CAC on ischemic outcomes seems to be uniform irrespective of different types of DES. In severe coronary calcific lesions, optimal lesion preparation through pre-balloon dilation, rather than post-dilation, has a significant effect on the long-term outcome.

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Conflicts of interest

There are no conflicts of interest.

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