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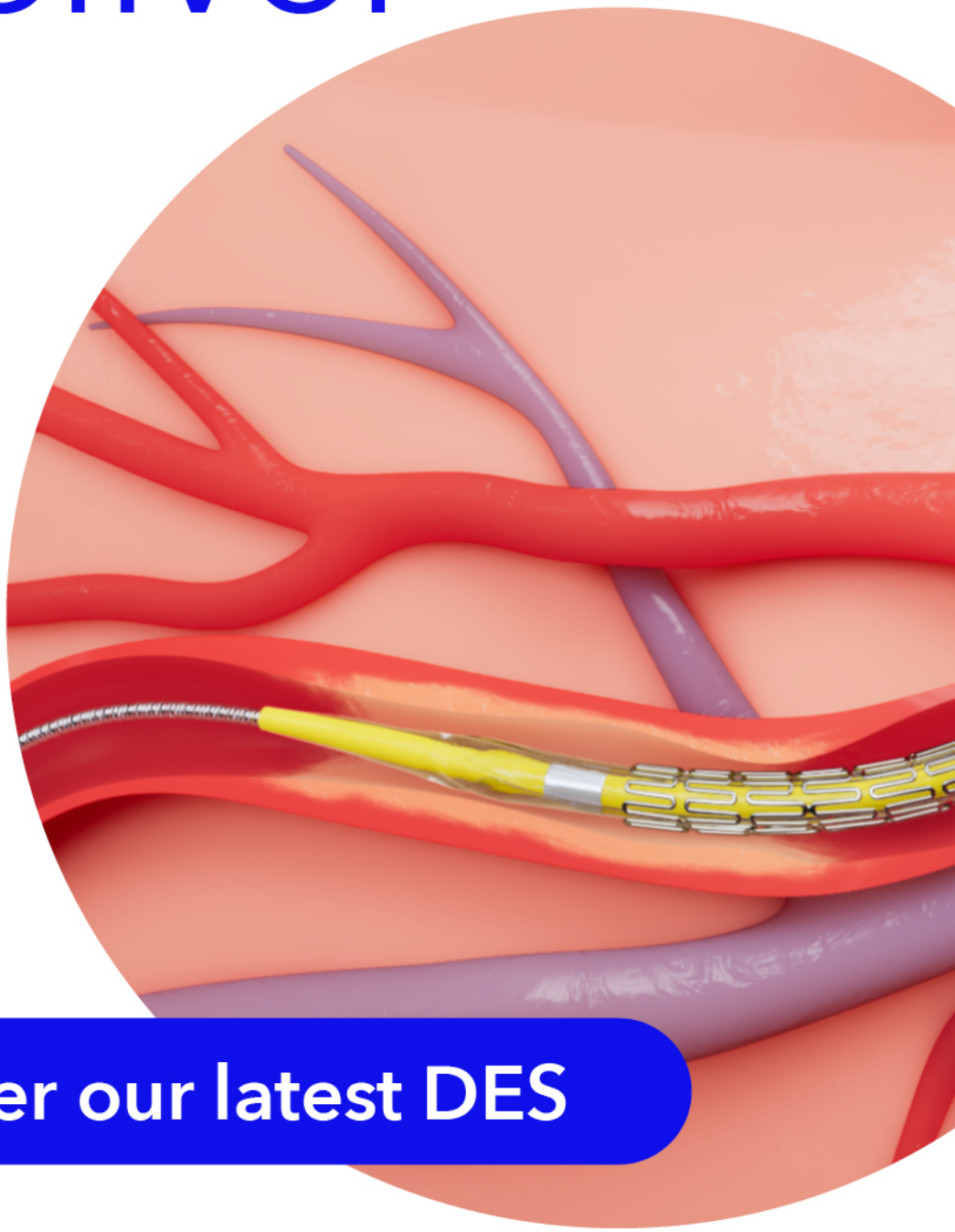

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Optical coherence tomography-derived predictors of stent expansion in calcified lesions

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Abstract

Background: Severe coronary artery calcification is associated with stent under-expansion and subsequent stent failure.

Aims: We aimed to identify optical coherence tomography (OCT)-derived predictors of absolute (minimal stent area [MSA]) and relative stent expansion in calcified lesions.

Methods: This retrospective cohort study included patients who underwent percutaneous coronary intervention (PCI) with OCT assessment before and after stent implantation between May 2008 and April 2022. Pre-PCI OCT was used to assess calcium burden and post-PCI OCT was used to assess absolute and relative stent expansion.

Results: A total of 361 lesions in 336 patients were analyzed. Target lesion calcification (defined as OCT-detected maximum calcium angle ≥ 30°) was present in 242 (67.0%) lesions. Following PCI, median MSA was 5.37 mm^2 in calcified lesions and 6.24 mm^2 in noncalcified lesions ($p < 0.001$). Median stent expansion was 78% in calcified lesions and 83% in noncalcified lesions ($p = 0.325$). In the subset of calcified lesions, average stent diameter, preprocedural minimal lumen area, and total calcium length were independent predictors of MSA in multivariable analysis (mean difference 2.69 mm^2/mm^2, 0.52 mm^2/mm, and −0.28 mm^2/5 mm, respectively, all $p < 0.001$). Total stent length was the only independent predictor of relative stent expansion (mean difference −0.465% per mm, $p < 0.001$). Calcium angle, thickness,

Abbreviations: AUC, area under the curve; BVS, bioresorbable vascular stent; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; EI, eccentricity index; IVL, intravascular lithotripsy; LAD, left anterior descending; LCX, left circumflex; LM, left main; MLA, minimal lumen area; MSA, minimal stent area; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RCA, right coronary artery; RLA, reference lumen area.

and the presence of nodular calcification were not significantly associated with MSA or stent expansion in multivariable analyses.

Conclusion: Calcium length appeared to be the most important OCT-derived predictor of MSA, whereas stent expansion was mainly determined by total stent length.

KEYWORDS

coronary artery calcification, minimal stent area, optical coherence tomography, percutaneous coronary interventions, stent expansion

1 | INTRODUCTION

Coronary artery calcification (CAC) is indicative of advanced atherosclerosis and has been associated with worse clinical outcomes following percutaneous coronary intervention (PCI).[1,2] The latter has been largely linked to a higher risk of stent underexpansion in calcified lesions and small minimal stent areas (MSAs),[3,4] which proved to be the most important predictor of stent failure.[5–8]

Multiple treatment options, including cutting and scoring balloons, rotational or orbital atherectomy, and intravascular lithotripsy (IVL), have been developed with the aim to modify target lesion calcification before stent implantation, and their use has been advocated in lesions with severe calcium, with arbitrary calcium burden thresholds for the respective technologies.[9] However, there is a lack of randomized data, linking the use of these technologies to improved stent expansion, and validated guidelines on the selection of specific lesion modification techniques before stent implantation.[10]

Unlike standard coronary angiography, optical coherence tomography (OCT) has a high sensitivity to detect the extent of coronary calcification.[11,12] Several small retrospective studies identified a variety of OCT-derived calcium characteristics as predictors of stent expansion. Multivariable analyses identified maximum calcium thickness and angle, as well as calcium volume and area as the most important classifiers of calcium burden, however, with limited consistency throughout the different studies.[3,13–15] In addition, a dedicated score combining calcium angle, thickness, and length was associated with percentage stent expansion. The score however failed to demonstrate a significant link to the final MSA, which proved to be a stronger predictor of stent failure as compared with stent underexpansion in more recent work.[14,16] Moreover, the score did not take the presence of calcified nodules or the effects of specific lesion modification techniques into account.

The current explorative study was designed to supplement and substantiate current treatment recommendations on how pre-PCI OCT assessment can be used to recognize calcified lesions that require more aggressive lesion preparation. The objective of this study is therefore to identify specific OCT-based predictors of absolute and relative stent expansion in calcified lesions.

2 | METHODS

2.1 | Patient population

In this single-center, retrospective, observational cohort study, we enrolled patients who underwent PCI with pre- and postprocedural OCT. All patients who underwent an OCT-guided PCI in the Erasmus Medical Center between November 2004 and March 2022 were screened for eligibility. Patients were included if pre- and post-PCI OCT pullbacks were available. Reasons for exclusion were as follows: (1) treatment of in-stent restenosis, (2) lesion modification performed before the first OCT, (3) the presence of thrombus precluding assessment of calcification, (3) inability to match the pre- and post-PCI OCT, and (4) inadequate quality of the OCT pullback. Multiple lesions per patient could be included. The Institutional Review Board of the Erasmus Medical University Center waived ethical approval for the present study due to the retrospective nature of the data used (MEC-2021-0894).

2.2 | Study procedures

Stent implantation was performed according to standard techniques. The use of intracoronary imaging and the use of predilatation, specialty balloons, atherectomy, IVL, and postdilatation, were at the discretion of the operator.

2.3 | OCT acquisition and analyses

OCT images were acquired with the Dragonfly Optis or Dragonfly Duo OCT Catheters (Abbott). The pullbacks were stored in a local database and were analyzed offline.

Pre- and post-PCI OCT analyses were performed with dedicated software (QCU-CMS, version 4.69, Leiden University Medical Center). In case multiple OCT pullbacks were available, only the first pre-PCI pullback and most final post-PCI pullbacks were analyzed.

Pre- and post-PCI OCT pullbacks were matched based on the stented segment in the post-pullback to identify the target segment to be analyzed on the pre-PCI pullback. On the pre-PCI pullback,

quantitative measurements of luminal areas, calcium angle, and calcium thickness were performed on 1 frame/mm within the identified target segment. Furthermore, the presence of calcified nodules was assessed visually and was defined as presence of calcium protruding into the lumen with strong signal attenuation and an irregular surface.[17]

Lesions were considered as calcified when the maximum calcium angle in the target segment was at least 30°.[15] In case multiple calcium angles were present in one frame, the maximum calcium angle was defined as the sum of the calcium angles. Furthermore, the maximum calcium thickness within the target segment was measured. The calcium length of the calcium deposit with the maximum calcium angle was measured, as well as the total calcium length in the target segment. The calcium score was calculated for each lesion according to the methodology described by Fujino et al.[14]

For the maximum calcium angle, exploratory cutoffs at 90°, 180°, 270°, and 360° were investigated. The variables calcium thickness and calcium length were dichotomized based on the median angle and thickness.

On the post-PCI pullback, quantitative measurements of luminal and stent areas were performed on one frame/mm, including the stented segment and 5 mm proximal and distal reference segments. Distal and proximal reference lumen areas (RLAs) were defined as the average lumen area in the 5 mm distal and proximal reference segments, respectively. Absolute stent expansion was defined as the MSA in the stented segment. Relative stent expansion was subsequently defined as (MSA/average of proximal and distal RLA) × 100% and as (MSA/distal RLA) × 100%. Stents were considered to be under-expanded if the relative stent expansion based on the average of the proximal and distal RLA was <80%.[18] In addition, the number of stents with stent expansion <70% of the average RLA was calculated to facilitate comparisons with the literature. The eccentricity index (EI) was defined as the minimal stent diameter at the cross-section of the MSA divided by the maximum stent diameter at the same cross-section. In addition, post-PCI pullbacks were inspected to identify presence of malapposition, tissue protrusion, and stent edge dissections. Malapposition was defined as presence of at least two malapposed struts with a malapposition distance of at least 0.2 mm. Tissue protrusion was defined as the presence of any tissue protruding through the stent struts.

2.4 | Study outcomes

The primary outcome of this study was absolute stent expansion based on the post-PCI OCT defined MSA. Secondary outcomes were relative stent expansion (%) and the presence of edge dissections, malapposition, and tissue protrusion.

2.5 | Statistical analysis

All continuous data are presented as median and first and third quartiles due to non-normal distributions. Categorical data are presented as numbers and percentages. Due to the non-normal bivariate distribution of the data, Spearman's correlation coefficients (r) were used to explore the associations of calcium angle, thickness and length with MSA and stent expansion.

To account for clustering of lesions within patients, mixed effect models with nested random intercepts were used for all between-group comparisons on lesion level. Linear regression was performed to identify predictors of MSA. For analysis of the secondary (binomial) outcomes, a generalized linear mixed model was used. In the multivariable analyses, a maximum of 1 variable per 10 observations for linear models or per 10 events for logistic models were estimated to avoid overfitting. In the multivariable model, total calcium length, maximum calcium arc, maximum calcium thickness, the presence of calcified nodules, lesion preparation techniques, and postdilatation were included. Additional variables were selected based on a $p < 0.15$ in univariable analysis.

All statistical tests were two-sided and p-values < 0.05 were considered statistically significant. Statistical analyses were conducted using SPSS (version 25.0, SPSS Inc.) and R (R Core Team 2021; version 4.1.1, packages: lme4, lmerTest, numDeriv).

3 | RESULTS

3.1 | Patient characteristics

Detailed information on patient inclusion and exclusion is presented in Supporting Information: Figure 1. A total of 336 patients were included in the present study. The median age was 64 years (25th–75th percentile 54–72) and 70% of patients were male. In 33.9% of patients, the indication for PCI was stable angina (Supporting Information: Table 1)

3.2 | Procedural characteristics and OCT findings

OCT analyses included 361 lesions analyzed pre- and post-PCI, out of which 242 (67.0%) lesions were calcified. Within the 242 calcified lesions, calcification with a maximum calcium arc ≥90° was present in 178 (73.6%) analyzed target lesions and 71 (29.3%) lesions had a maximum calcium angle of 180° or more.

Table 1 shows the procedural characteristics of calcified versus noncalcified lesions. In calcified lesions, a larger number of stents and longer total stent length was used, whereas a smaller average stent diameter was used ($p = 0.020$, $p < 0.001$, and $p = 0.004$, respectively). Lesion preparation and postdilatation were performed more often in calcified lesions ($p < 0.001$ and $p = 0.013$, respectively). The maximum inflation pressure used for postdilatation was significantly higher in calcified lesions as compared with noncalcified lesions (18.0 (25th–75th percentile 16.0–20.0) atm vs. 16.0 (25th–75th percentile 15.0–18.0) atm, $p = 0.008$), whereas no significant difference were found in maximum postdilatation balloon size or balloon-to-artery ratio.

TABLE 1 Procedural characteristics and pre-PCI OCT findings in calcified and noncalcified lesions.

Variable	Overall (361)	No calcium (119)	Calcium (242)	*p*
Vessel, *n* (%)				0.087
LAD	245 (67.9)	71 (59.7)	174 (71.9)	
LCX	55 (15.2)	20 (16.8)	35 (14.5)	
RCA	59 (16.3)	27 (22.7)	32 (13.2)	
LM	2 (0.6)	1 (0.8)	1 (0.4)	
Lesion type B2/C, *n* (%)	219/359 (61.0)	56 (47.1)	163 (67.4)	**<0.001**
Stent type BVS, *n* (%)	38/352 (10.8)	19/114 (16.7)	19/238 (8.0)	**0.020**
Number of stents, *n* (%)				**0.020**
Single stent	309 (85.6)	109 (91.6)	200 (82.6)	
Two stents	47 (13.0)	10 (8.4)	37 (15.3)	
Three stents	5 (1.4)		5 (2.1)	
Total stent length (mm), median (IQR)	23.0 (18.0–33.0)	18.0 (15.0–26.0)	26.0 (18.0–35.0)	**<0.001**
Average stent diameter (mm), median (IQR)	3.0 (3.0–3.5)	3.5 (3.0–3.5)	3.0 (3.0–3.5)	**0.004**
Maximum lesion preparation, *n* (%)				**<0.001**
No lesion preparation	204 (56.5)	86 (72.3)	118 (48.8)	
Predilatation	137 (38.0)	32 (26.9)	105 (43.4)	
Specialty balloon[a]	2 (0.5)		2 (0.8)	
Shockwave	9 (2.5)		9 (3.7)	
Atherectomy[b]	8 (2.2)		8 (3.3)	
Postdilatation before post-PCI OCT, *n* (%)	226/360 (62.8)	62/117 (53.0)	163 (67.4)	**0.013**
Maximum postdilatation balloon size (mm), median (IQR)	3.5 (3.0–4.0)	3.5 (3.0–4.0)	3.5 (3.0–4.0)	0.505
Maximum inflation pressure (atm), median (IQR)	18.0 (16.0–20.0)	16.0 (15.0–18.0)	18.0 (16.0–20.0)	**0.008**
Balloon-to-artery ratio, median (IQR)	1.17 (1.00–1.20)	1.14 (1.00–1.17)	1.17 (1.00–1.20)	0.464
Pre-PCI OCT assessment				
MLA (mm^2), median (IQR)	2.01 (1.42–2.75)	2.11 (1.47–3.07)	1.96 (1.41–2.66)	**0.023**
Maximum calcium angle (°), median (IQR)	–	–	130 (88–211)	–
Maximum calcium thickness (mm), median (IQR)	–	–	0.95 (0.78–1.15)	–
Total calcium length (mm), median (IQR)	–	–	8.5 (4.8–15.0)	–
Calcium length of deposit with maximum calcium arc (mm), median (IQR)	–	–	5.0 (3.0–8.30)	–
Presence of calcified nodule, *n* (%)	–	–	23 (9.5)	–

Note: Bold *p*-values are statistically significant.

Abbreviations: BVS, bioresorbable vascular stent; IQR, interquartile range; LAD, left anterior descending; LCX, left circumflex; LM, left main; MLA, minimal lumen area; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RCA, right coronary artery.

[a]Cutting or scoring balloons.

[b]Orbital or rotational atherectomy.

3.3 | Pre-PCI OCT findings

Within the subset of calcified lesions, the median maximum calcium angle was 130° (25th–75th percentile 88–211), median maximum calcium thickness was 0.95 mm (25th–75th percentile 0.78–1.15) and the median total calcium length was 8.5 mm (25th–75th percentile 4.8–15.0). Calcified nodules were observed in 9.5% of the calcified lesions (Table 1).

3.4 | Post-PCI OCT findings

Table 2 shows the post-PCI OCT findings for calcified and noncalcified lesions. Following PCI, median MSA was 5.37 mm^2 in calcified lesions and 6.24 mm^2 in noncalcified lesions ($p < 0.001$). In addition, calcified lesions had a median relative stent expansion of 78%, compared with a stent expansion of 83% in noncalcified lesions ($p = 0.325$). However, the relative stent expansion based on the distal

TABLE 2 Post-PCI OCT findings in calcified versus noncalcified lesions.

Variables	Overall (361)	No calcium (119)	Calcium (242)	*p*
MLA (mm^2), median (IQR)	5.81 (4.49–7.44)	6.42 (4.93–8.12)	5.37 (4.38–7.22)	**0.002**
MSA (mm^2), median (IQR)	5.78 (4.39–7.37)	6.24 (4.85–8.22)	5.37 (4.27–7.04)	**<0.001**
MSA < 4.5 mm^2, *n* (%)	95 (26.3)	24 (20.2)	71 (29.3)	0.066
MSA < 5 mm^2, *n* (%)	132 (36.6)	33 (27.7)	99 (40.7)	**0.016**
Stent expansion (%), median (IQR)				
% of average RLA	81 (67–93)	83 (70–93)	78 (67–92)	0.325
% of distal RLA only	102 (89–120)	100 (86–115)	102 (90–121)	**0.049**
Stent expansion < 80%, *n* (%)	176/354 (49.7)	51 (42.9)	125/235 (53.2)	0.067
Stent expansion < 70%, *n* (%)	103/354 (29.1)	30 (25.2)	73/235 (31.1)	0.253
RLA (mm^2), median (IQR)	7.25 (5.60–9.38)	7.64 (6.03–10.25)	7.05 (5.39–8.92)	**0.029**
Proximal RLA (mm^2)	8.68 (6.58–11.62)	9.11 (6.85–11.80)	8.50 (6.35–11.46)	0.710
Distal RLA (mm^2)	5.48 (4.17–7.26)	6.24 (4.65–8.62)	5.09 (4.06–6.83)	**<0.001**
EI	0.84 (0.79–0.89)	0.86 (0.81–0.89)	0.84 (0.78–0.89)	0.052
Submedial edge dissection (>3 mm), *n* (%)	20 (5.5)	5 (4.2)	15 (6.2)	0.438
Malapposition, *n* (%)	156 (43.2)	23 (19.3)	133 (55.0)	**<0.001**
Tissue protrusion, *n* (%)	193 (53.5)	59 (49.6)	134 (55.4)	0.338

Note: Bold *p*-values are statistically significant.

Abbreviations: EI, eccentricity index; MLA, minimal lumen area; MSA, minimal stent area; RLA, reference lumen area.

reference only was larger in calcified lesions as compared with noncalcified lesions (102% vs. 100%, $p = 0.049$), inherent to the significantly smaller distal RLA in calcified lesions (5.09 vs. 6.24 mm^2, $p < 0.001$). Malapposition was more frequent in stents implanted in calcified lesions (55.0% vs. 19.3%, $p < 0.001$).

Figure 1 displays post-PCI MSA, percentage stent expansion and occurrence of malapposition, and stent underexpansion by calcium angle, thickness, length, and the presence of calcified nodules. Overall, calcium angle, thickness or presence of calcified nodules did not significantly impact MSA, although in calcified lesions with a maximum calcium angle ≥90°, median MSA was significantly smaller as compared to lesions with <90° of calcification (5.22 mm^2 vs. 6.36 mm^2, $p = 0.034$, Supporting Information: Table 2). In addition, larger maximum calcium angles were associated with worse relative stent expansion (Figure 1, $p = 0.028$). We observed a smaller median MSA in stents implanted in lesions with a total calcium length ≥10 mm as compared with a length <10 mm (5.14 mm^2 vs. 6.05 mm^2, respectively, $p = 0.005$), as well as worse relative stent expansion (73.8% vs. 82.5%, respectively, $p < 0.001$) and a larger proportion of underexpanded stents (61.3% vs. 46.5%, respectively, $p = 0.028$) (Figure 1).

Furthermore, stents implanted in lesions with a larger calcium angle, thickness, and length were more often malapposed ($p < 0.001$), as well as stents inserted in lesions with calcified nodules ($p = 0.010$) (Figure 1 and Supporting Information: Table 3). When comparing lesions with a calcium score of 4 (calcium deposit with maximum calcium angle >180°, maximum thickness >0.5 mm, and length >5 mm) with those with a lower calcium score, we found a higher proportion of malapposition after stent implantation (84.0% vs. 47.4%, $p < 0.001$), whereas no significant differences in absolute or relative stent expansion were observed (Supporting Information: Table 4).

Repeating the analyses using only the maximum calcium angle instead of the sum of the calcium angles (in case of multiple calcium angles in one frame) did not lead to any important differences in the results.

3.5 | Correlation between calcium parameters, MSA, and stent expansion

Figure 2A–C shows the correlations between calcium parameters and MSA (panel A1, B1, and C1) and relative stent expansion (panel A2, B2, and C2). We observed weak but significant negative correlations between total calcium length and relative stent expansion ($r = -0.23$, $p < 0.001$) and maximum calcium angle and relative stent expansion ($r = -0.18$, $p = 0.006$).

3.6 | Effect of lesion modification

Results on the effect of calcium, presence of calcified nodules and calcium score on stent expansion remained consistent in sensitivity analyses excluding cases treated with specialty balloons, IVL, or

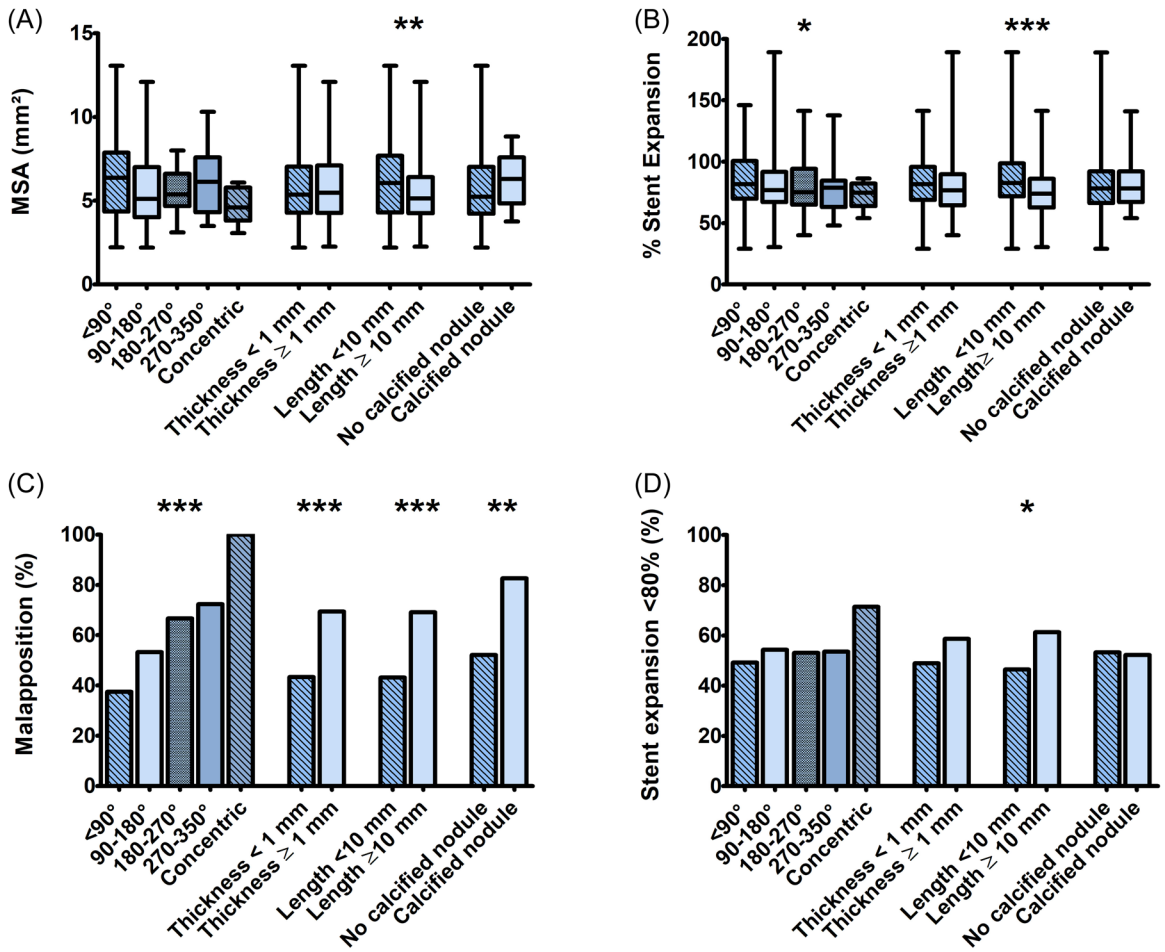

FIGURE 1 Impact of calcification characteristics on post-percutaneous coronary intervention (PCI) results. Boxplots and barcharts showing the impact of calcium angle, thickness, length, and calcified nodules on (A) minimal stent area (MSA), (B) percentage stent expansion, (C) malapposition, and (D) stent underexpansion. *p* values for between-group comparisons were obtained using (generalized) linear mixed models. For the effect of calcium angle, the *p* value obtained from the univariable models with calcium angle as a continuous predictor is presented. Boxes represent 25th–75th percentiles and whiskers represent the minimum and maximum values. ***$p \leq 0.001$; **$p \leq 0.01$; *$p \leq 0.05$. [Color figure can be viewed at wileyonlinelibrary.com]

atherectomy and, in addition, showed a small but significant difference in EI in calcified versus noncalcified lesions (0.84 vs. 0.86, $p = 0.050$), as well as in lesions with calcified nodules as compared to lesions without calcified nodules (0.78 vs. 0.84, $p = 0.005$). (Supporting Information: Tables 3–5).

When comparing lesions treated with predilatation only to those treated with specialty balloons, IVL, or atherectomy, both indices for absolute and relative stent expansion were numerically larger in lesions subject to speciality balloons, IVL, or atherectomy (Supporting Information: Table 6).

3.7 | Predictors of absolute and relative stent expansion

In multivariable analysis, larger average stent diameters and pre-PCI minimal lumen areas (MLAs) were associated with a larger MSA (mean difference 2.69 mm^2/mm and 0.52 mm^2/mm^2, both $p < 0.001$), whereas a larger total calcium length was associated with a smaller MSA (mean difference −0.28 mm^2/5 mm, $p = 0.001$) (Table 3). Total stent length was identified as the sole independent predictor (mean difference −0.465%/mm, $p = 0.001$) for relative stent expansion. Maximum calcium angle, calcium thickness, and presence of calcified nodules did not show significant associations with absolute or relative stent expansion. In addition, we could not identify a significant effect of lesion preparation with predilatation only or specialty balloons, IVL, or atherectomy on MSA or stent expansion (Figures 2).

A sensitivity analysis excluding cases treated with specialty balloons, IVL or atherectomy yielded similar results (Supporting Information: Table 8). Similarly, repeating the analysis using the maximum calcium angle only instead of the sum of the calcium angles in case of multiple angles in one frame did not lead to different results.

An additional sensitivity analysis excluding patients presenting with ST-elevation myocardial infarction revealed no major

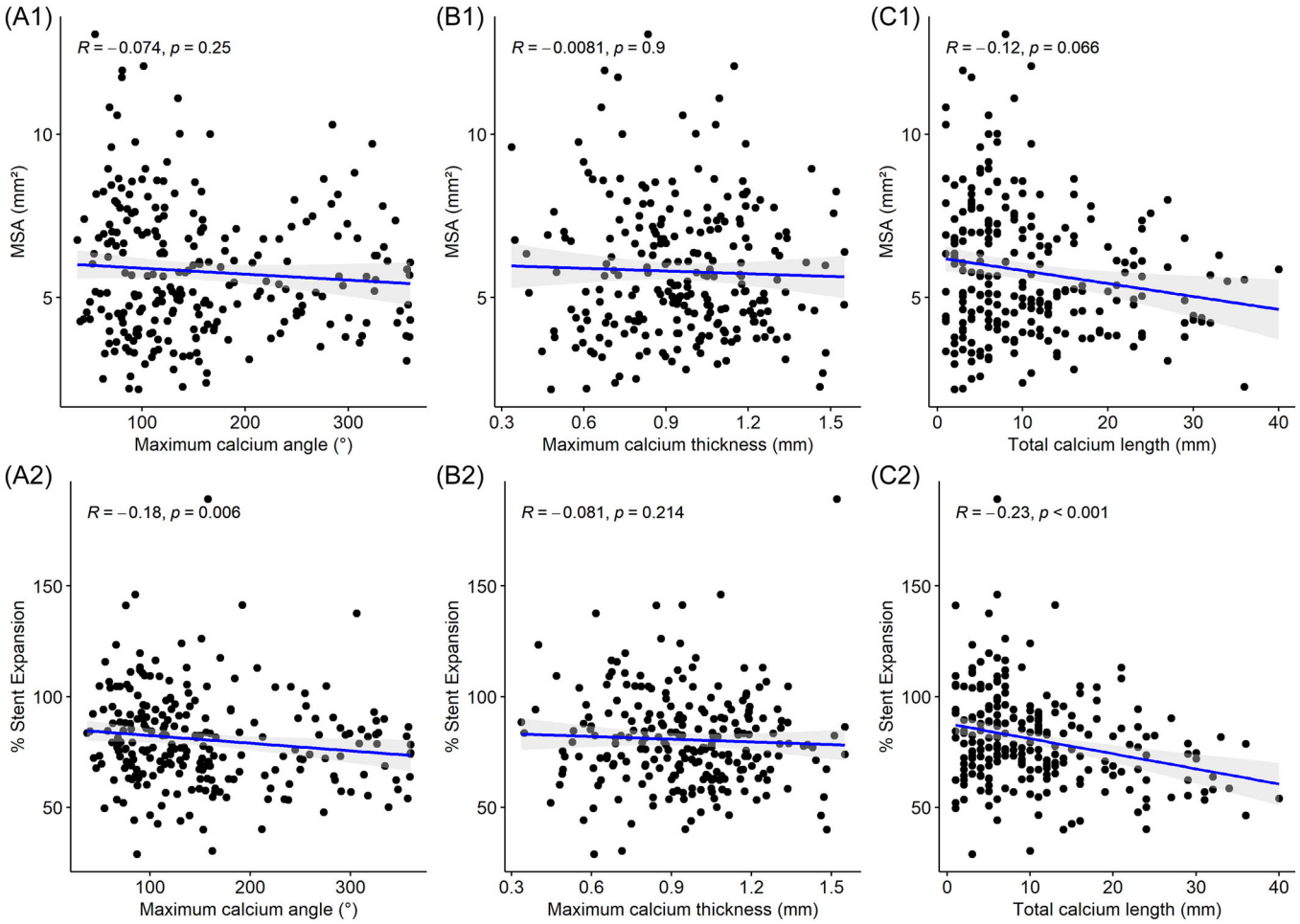

FIGURE 2 Correlation between calcium characteristics and absolute and relative stent expansion. Scatterplots show the correlation between calcium angle (A), thickness (B), and length (C) and minimal stent area (MSA) (A1–C1) and % stent expansion (A2–C2). Spearman's correlation coefficients are presented. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Predictors of MSA (mm^2) and stent expansion (%) in multivariable linear regression analysis.

Predictors of MSA (mm^2)	β (95% CI)	p	Predictors of % stent expansion	β (95% CI)	p
eGFR (per ml/min/1.73 m^2)	−0.006 (−0.015 to 0.003)	0.212	eGFR (per ml/min/1.73 m^2)	0.0006 (−0.147, 0.149)	0.993
Total stent length (per mm)	0.004 (−0.012 to 0.019)	0.648	Total stent length (per mm)	−0.465 (−0.721, −0.210)	**<0.001**
Average stent diameter (per mm)	2.693 (2.332 to 3.053)	**<0.001**	Average stent diameter (per mm)	3.771 (−2.422, 9.964)	0.235
Lesion preparation			Lesion preparation		
Predilatation	−0.239 (−0.549 to 0.072)	0.140	Predilatation	−0.199 (−5.508, 5.110)	0.942
Lesion modification	−0.026 (−0.659 to 0.607)	0.936	Lesion modification	6.592 (−3.508, 16.69)	0.202
MLA pre (per mm^2)	0.515 (0.347–0.683)	**<0.001**	MLA pre (per mm^2)	−0.122 (−2.722, 2.478)	0.927
Calcium maximum angle (per 90°)	0.161 (−0.048 to 0.370)	0.134	Calcium maximum angle (per 90°)	0.359 (−3.045, 3.764)	0.836
Calcium max thickness (per mm)	−0.035 (−0.768 to 0.698)	0.926	Calcium max thickness (per mm)	2.631 (−8.860, 14.12)	0.654
Total calcium length (per 5 mm)	−0.277 (−0.426 to −0.127)	**<0.001**	Total calcium length (per 5 mm)	−2.345 (−4.809, 0.118)	0.064
Calcified nodule	0.024 (−0.583 to 0.631)	0.939	Calcified nodule	5.240 (−3.991, 14.47)	0.267
Postdilatation	−0.317 (−0.657 to 0.023)	0.070	Postdilatation	−5.308 (−10.81, 0.190)	0.060

Note: Bold *p*-values are statistically significant.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; MLA, minimal lumen area; MSA, minimal stent area.

differences in our principal findings (Supporting Information: Table 6). However, in patients presenting with either stable angina pectoris or NSTE-ACS, total calcium length, which was already identified as a significant predictor for MSA now also appeared to be a predictor of relative stent expansion (mean difference −3.546%/5 mm, $p = 0.009$, Supporting Information: Table 10). Representative cases examples of the impact of target lesion calcification on post-PCI results are presented in Figure 3.

4 | DISCUSSION

The main findings of this OCT-based study can be summarized as follows: (1) calcified lesions are associated with worse absolute stent expansion as compared to non-calcified lesions; (2) among individual calcium characteristics, calcium length appeared to be the sole independent predictor of absolute stent expansion; and (3) stents implanted in calcified lesions were more frequently malapposed. The presence of malapposition was related to larger calcification angle, thickness, or length, as well as presence of calcified nodules.

The relationship between lesion calcification and absolute and relative stent expansion has been generally accepted.[3,4,14] As MSA is the most important predictor of stent failure,[5,6] several techniques to modify calcification before stent implantation have been developed with the aim to improve final MSA. Devices such as orbital or rotational atherectomy or IVL have been recommended for heavily calcified or noncrossable lesions. Nevertheless, randomized controlled trials confirming their superiority to plain old balloon angioplasty for lesion preparation along with dedicated guidelines on their use are lacking.[19]

Whereas our results confirm the association between calcification and stent expansion in general, we were not able to link previously proposed calcium quantification parameters such as the presence of calcific nodules, calcium thickness, and calcium arc >180° to absolute and relative stent (under)expansion. As such, we only observed weak correlations with stent expansion for calcium length and calcium angle, and no significant correlation for calcium thickness. Although we observed worse absolute (but not relative) stent expansion in lesions with a calcium arc >90°, the predictive value of calcium arc disappeared when correcting for calcium length, calcium thickness, preprocedural MLA, and lesion preparation. Using the previously proposed cutoff of 180° did not alter our findings.

In addition, and in contrast to previous studies,[13,14] we did not find an effect of calcium thickness on stent expansion. Conversely, we identified total calcium length as a significant and independent predictor of MSA and we found a trend toward significance for the effect of calcium length on relative stent expansion. Whereas the significant predictive value of calcium length might be a surrogate for longer lesion and stent lengths in general, the effect of calcium length on MSA remained significant after adjustment for total stent length. The total calcium length in a lesion thus appears to be reflective of the total calcium burden as well as the severity and diffuseness of coronary artery disease, thereby likely impacting stent expansion.

The apparent discrepancies between the results from our study and previous work, can at least in part be explained by differences in the study population. The present study population included more patients presenting with ACS, larger calcium angles and thicker calcium deposits.[14] As a result, stent underexpansion was more prevalent in our data and previously proposed calcium variables and scores appeared less discriminative. Moreover, we adjusted for additional factors and confounders, such as preprocedural MLA, lesion preparation, postdilatation and estimated glomerular filtration rate. Next to this, the aim of the present study was not to develop a score, but rather to provide more detailed insights into the association between calcium burden and stent expansion. We therefore deliberately refrained from dichotomization and combination of data based on receiver operating curve analyses. Finally, our results indicate that stent underexpansion is a multifactorial problem that can only partly be explained by type and quantity of calcium, or at least by the way calcium was quantified in the present study. The large variation in MSA and stent expansion in both calcified as well as non-calcified lesions in the present study, together with the lack of consistent calcium based stent expansion predictors among a series of previous studies, warrants further study.[3,13,14]

The inconsistency and limited discriminative ability of currently available calcium characteristics suggests that the individual effect of manually defined parameters as calcium length, thickness and angle do not suffice in classifying lesions into risk categories. Hence, a more comprehensive metric may be needed to identify lesions that may benefit from the use of more aggressive lesion preparation. Fujino et al.[14] aimed to achieve this by combining the calcium angle, thickness, and length into one score that demonstrated promising results in the validation set. Nevertheless, 70.1% of the lesions with a calcium score of four in their study achieved adequate stent expansion despite being classified as high-risk lesions and the area under the curve (AUC) for predicting stent underexpansion was not significantly better than that of angiography-detected calcification (0.86 vs. 0.84). In the present study, with a larger sample size and higher overall calcium burden, we were not able to confirm a significant predictive effect of this calcium score on either absolute or relative stent expansion.

Recently, Ma et al.[15] aimed to identify new predictors of stent underexpansion and found a good diagnostic performance for the total calcium volume in predicting stent underexpansion, with an AUC of 0.94. Although commercially available automated calcium quantification tools based on either intravascular ultrasound or OCT are currently lacking, promising developments in artificial intelligence may provide a better and clinical applicable solution in the near future.[20]

Whereas the impact of higher degrees of calcification on stent expansion was unconvincing, we found a strong association between the presence of calcium and final risk of malapposition. Larger maximum calcium angle, thickness, and length, as well as the presence of nodular calcifications were all associated with the occurrence of malapposition. The relevance and clinical impact of malapposition has long been topic of debate, with intracoronary imaging studies yielding varying results. Yet, a recent study by Kim

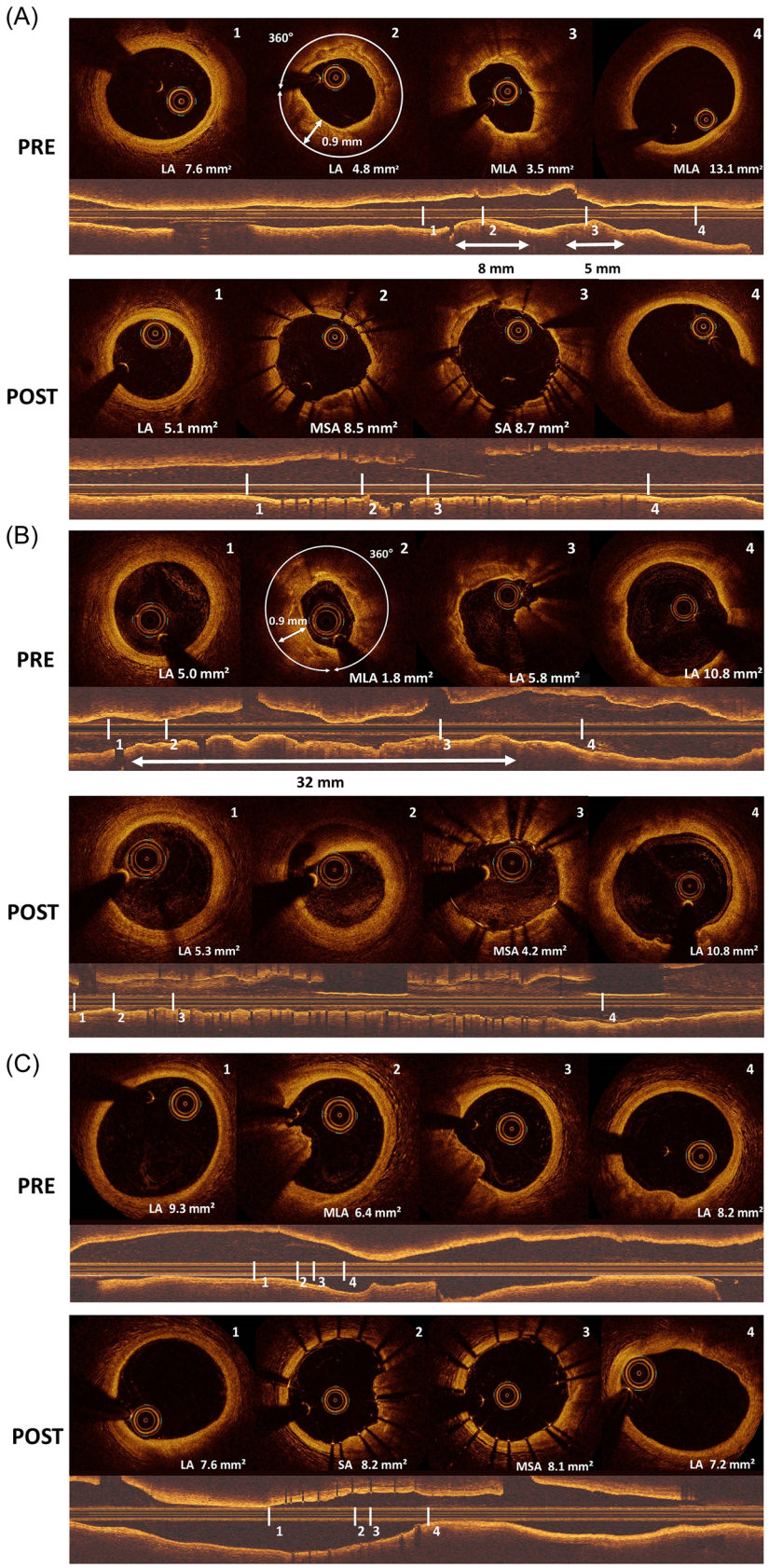

FIGURE 3 Case examples of the differential impact of target lesion calcification. (A) A case of concentric calcification with a thickness of 0.9 mm and a total calcium length of 13 mm. Despite the calcification, the post-percutaneous coronary intervention (PCI) pullback shows good stent expansion with an minimal stent area (MSA) of 8.5 mm^2 (stent expansion 90%) after stenting with a 4.0 × 26 mm DES and postdilatation. (B) A case with long (38 mm), concentric calcification, and a calcified nodule. Following predilatation, stenting with a 3.0 × 34 mm DES and postdilatation, the optical coherence tomography (OCT) shows an underexpanded stent with an MSA of 4.2 mm^2 (stent expansion 58%) and a distal submedial edge dissection. (C) A case with a protruding calcified nodule. After stenting with a 3.5 × 8 mm DES and postdilatation, the OCT shows adequate stent expansion (MSA 8.00, stent expansion 92%), but malapposition caused by the calcified nodule. [Color figure can be viewed at wileyonlinelibrary.com]

et al.[7] demonstrated a significant impact of malapposition volume on major safety events. Acknowledging the latter, the higher rate of malapposition in more severely calcified lesions may be an important additional mediator in the association between calcification and clinical outcomes that warrants further investigation.

Although the use of specialty devices has been advocated in severe calcified lesions, the recently presented EXIT-CALC trial could not demonstrate a significant difference in stent expansion between lesions treated with IVL as compared with conventional predilatation.[21] Moreover, in the COPS study no significant difference in MSA was observed between lesions treated with cutting balloons as compared with noncompliant balloons, although the trial did show a significant difference in MSA at the calcium site.[22] In line with the subanalysis on specialty devices in the present study, the small sample size of both studies should be acknowledged and a clear trend toward better stent expansion with more aggressive lesion preparation was consistently observed. Adequately powered randomized trials will be needed to demonstrate the potential superiority of these lesion preparation techniques as compared with routine noncompliant balloons.

4.1 | Limitations

A number of limitations of this study need to be addressed. First, this was a retrospective, observational cohort study in which patients were selected based on the availability of a pre- and post-PCI OCT. As the use of intracoronary imaging was at the discretion of the operator, the generalizability of our results may be limited. In severely calcified lesions, the OCT catheter pre-intervention may not have been able to cross and therefore patients with severely calcified lesions may have had a lower chance of being included in this study.

In addition, our sample contained only a limited number of cases in which atherectomy or IVL was used. Therefore, we could not provide effect estimates for the efficacy of these devices in different degrees and types of calcification. Moreover, due to the retrospective and observational nature of the data we could not prevent the influence of confounding by indication, which further hampered accurate identification of the effects of lesion preparation techniques and other procedural factors on post-PCI outcomes. Furthermore, there may be additional confounding by unmeasured factors that could not be accounted for due to the retrospective nature of this study. Finally, the limited sensitivity of OCT for the detection of deep calcium may have led to underestimation of the calcium burden in some cases.

5 | CONCLUSION

Stent underexpansion is a multifactorial problem, among which calcification is one of the factors associated with worse absolute stent expansion. Next to pre-PCI MLA and average stent diameter, total calcium length appeared to be the only independent predictor of absolute stent expansion (MSA) in calcified lesions. Larger prospective studies are needed to identify accurate predictors of stent underexpansion and to evaluate the effects of specific types of calcium modification.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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