Vascular responses to coronary calcification following implantation of newer-generation drug-eluting stents in humans: impact on healing

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Aims

Vascular calcification is routinely encountered in percutaneous coronary intervention (PCI) and severe coronary calcification is a known predictor of in-stent restenosis and stent thrombosis. However, the histopathologic mechanisms behind such events have not been systematically described.

Methods and results

From our registry of 1211 stents, a total of 134 newer-generation drug-eluting stents (DES) (Xience, Resolute-Integrity, PROMUS-Element, and Synergy) with duration of implant ≥ 30 days were histologically analysed. The extent of calcification of the stented lesions was evaluated radiographically and divided into severe (SC, $n = 46$) and non-severely calcified lesions (NC, $n = 88$). The percent-uncovered struts per section {SC vs. NC; median 2.4 [interquartile range (IQR) 0.0–19.0] % vs. 0.0 (IQR 0.0–4.6) %, $P = 0.02$ } and the presence of severe medial tears (MTs) (59% vs. 44%, respectively, $P = 0.03$) were greater in SC than NC. In addition, SC had a higher prevalence of ≥ 3 consecutive struts lying directly in contact with surface calcified area (3SC) (52% vs. 8%, respectively, $P < 0.0001$). Multivariate analysis demonstrated that sections with duration of implantation ≤ 6 months [odds ratio (OR): 7.7, $P < 0.0001$], 3SC (OR: 6.5, $P < 0.0001$), strut malapposition (OR: 5.0, $P < 0.0001$), and lack of MTs (OR: 2.5, $P = 0.0005$) were independent predictors of uncovered struts. Prevalence of neoatherosclerosis was significantly lower in SC than that of NC (24% vs. 44%, $P = 0.02$).

Conclusion

Severe calcification, especially surface calcified area is an independent predictor of uncovered struts and delayed healing after newer-generation DES implantation. These data expand of knowledge of the vascular responses of stenting of calcified arteries and suggests further understand of how best to deal with calcification in patients undergoing PCI.

Keywords

Coronary artery calcification • Drug-eluting stents • Stent thrombosis • Dual antiplatelet therapy • Uncovered strut • Percutaneous coronary intervention

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Introduction

Coronary calcification is ubiquitously encountered during percutaneous coronary interventions (PCIs).^{1–3} In sudden coronary death victims, there is a progressive increase in coronary calcification as percent stenosis increases.⁴ While severe lesion calcification is an independent risk factor for complications after PCI,^{1,2} at the histopathologic levels, our understanding of the underlying causes of this excess risk are not well understood.

Newer-generation drug-eluting stents (DES) have shown superior clinical outcomes with lower rates of target lesion revascularization (TLR) and stent thrombosis (ST) compared to 1st generation DES.^{5,6} Uncovered struts following 1st generation DES implantation have been shown to be the best predictor of late ST.⁷ A large registry of patients with ST who underwent intracoronary imaging with optical coherence tomography (OCT) demonstrated that uncovered struts were the most common cause of acute, sub-acute and late ST.⁸ Studies suggest that one of the main causes of the lower rate of ST in the newer-generation DES compared to 1st generation DES is due to faster strut coverage from thinner strut dimensions; these findings have been validated in preclinical,⁹ clinical,¹⁰ and pathological¹¹ studies.

Lower risk of ST in newer-generation DES has led to a major paradigm-shift in the duration of dual antiplatelet therapy (DAPT) following PCI with DES. Although extending DAPT is the best strategy to prevent ST after DES implantation,^{12,13} long-term DAPT is reported to be associated with higher risk of bleeding with a higher mortality.¹⁴ The latest clinical guideline recommends 3-month DAPT in patients with high bleeding risk (HBR) following PCI for stable coronary artery disease (Class IIa B).¹³ Furthermore, more than 10 randomized controlled trials (RCTs) are currently evaluating the safety of <3 months DAPT in HBR patients.¹⁵ Common inclusion criteria to label a patient with HBR,¹⁶ include older age (≥ 75 years old), history of bleeding, renal failure, or stroke.

In clinical trials, such as these lesions-specific characteristics besides anatomic location or clinical presentation (e.g. acute coronary syndrome) are rarely used as exclusion criteria. Several clinical studies have also demonstrated that severe calcification of the stented lesion is a known independent predictor of poor clinical outcomes such as TLR and ST.^{17,18} However, detailed understanding of the histopathologic outcomes of stenting severely calcified lesions, such as speed of strut coverage and prevalence of neoatherosclerosis, have never been systematically studied. Therefore, the vascular response to stenting such lesions and a detailed understanding of how this might impact clinical outcomes remains unknown.

We hypothesized that severely calcified lesions may influence the speed of strut coverage especially when struts are in direct contact with luminal surface calcified areas. In the current study, we investigated pathologic response of healing in severely calcified lesions in patients implanted with newer-generation DES of ≥ 30 days duration.

Methods

Study population

Between July 1998 to August 2018, CVPath stent autopsy registry had received a total of 1211 stented lesions in 714 individuals. From this

registry, we collected lesions with newer-generation DES, which include Xience everolimus-eluting stent (Xience-EES, Abbott Vascular, Santa Clara, CA, USA), Resolute Integrity zotarolimus-eluting stent (Resolute-ZES, Medtronic, Medtronic, Minneapolis, MN, USA), PROMUS Element EES (Element-EES, Boston Scientific, Marlborough, MA, USA), and Synergy EES (Synergy-EES, Boston Scientific). Lesions with duration of implant <30 days, stents in bypass grafts, and lesions with more than three types of stents implanted at a single site were excluded from the analysis (Figure 1). The reason for excluding the lesions with more than three types of stents implanted at a single site was all the lesions with three types of stents were after PCI for recurrent in-stent restenosis lesions of 1st generation DES and the cause of restenosis of these lesions is more like hypersensitivity reaction, and degree of calcification seems less relevant. A total of 134 newer-generation DES from 104 autopsy cases (85 Xience-EES lesions and 29 Resolute-ZES lesions, 17 Element-EES lesions, and three Synergy-EES lesions) were identified (Figure 1). Sixty-six lesions from Xience-EES^{11,19} and two lesions from Element-EES²⁰ have been previously reported and were included in the present study. In hearts with multiple stents in one coronary artery, overlapped stents were considered as one lesion, whereas stents with >5-mm gaps were counted as separate lesions as previously described.⁷ Clinical records of each case including risk factors, duration, and indication of stent implantation were reviewed. Cause of death was categorized as stent-related death, non-stent-related cardiac death, and non-cardiac death, as previously described.⁷ An institutional review board at CVPath institute approved this study.

Histologic preparation

Coronary arteries were perfusion fixed in 10% formalin, removed from the heart and were radiographed. When calcification of the stented lesion was observed, the lesions were mildly decalcified in EDTA to keep a boundary of calcification as it was first detected by radiography. Stented lesions were dehydrated and submitted for plastic embedding in methyl-methacrylate. The entire stent was sequentially cut at 2–3 mm intervals. Histologic sections were cut on a rotary microtome at 6 μ m, mounted on charged slides, and stained with haematoxylin and eosin (H&E) stain with Movat pentachrome stain, as previously described.⁷

Assessment of stent fracture and pathologic sections

Stent fracture was assessed by radiograph as previously described.²¹ Morphometric analysis and histologic assessment of coronary sections were performed as previously described.^{11,19} In brief, Morphometric measurements were performed with image-analysis software after digital scanning (Zen2, Zeiss, Oberkochen, Germany). External elastic lamina, stent, and lumen areas, as well as neointimal thickness above each strut, were measured. Uncovered struts were identified by the presence of platelet and/or fibrin thrombus or bare struts with absence of neointima (Figure 2), and the ratio of uncovered-to-total stent struts per section was calculated and expressed as percent.⁷ Presence of malapposition of struts was diagnosed when axial distance between the strut's surface to the underlying luminal surface was greater than the strut thickness including polymer.²² The other pathological factors, including severity of inflammation, percentage of struts with fibrin were also evaluated.⁷ ST was defined as a thrombus occupying >30% of the cross-sectional area of the lumen while stent restenosis was defined as $\geq 75\%$ cross-sectional area narrowing by neointimal formation within the stented area, with or without atherosclerosis as previously described.⁷

Underlying atherosclerotic plaques were classified into stable and unstable lesions using our modified AHA classification.²³ Unstable lesions were defined as the stented segments with presence of a necrotic core

Figure 1 A flowchart showing inclusion and exclusion criteria, and classification of the extent of calcification in the stented lesions. From CVPath human autopsy registry, 134 stented lesions in 104 individuals were selected and categorized into non-severely calcified, i.e. none or mild (calcification barely seen or focally localized, <25% of stented segment), or moderate (multiple sites of calcification), and severely calcified stented segment, i.e. highly visible diffuse calcification, (>70% stented segment). DES, drug-eluting stents; LIMA, left internal mammary artery; SVG, saphenous vein graft.

and a ruptured fibrous cap with intra-plaque haemorrhage,²³ or the stented segments with presence of nodular calcification. Prevalence and type of neoatherosclerosis, which is defined as newly formed atherosclerotic changes within the stented segment, were also evaluated as previously described.¹¹

Severity of calcification

The severity of calcification in the stented lesion was assessed by radiographs as previously described: none, mild (calcification barely seen or focally localized; <25% stented segment), moderate (multiple site of calcification), and severe (highly visible diffuse calcification; >70% stented segment),²¹ and classified into two groups; severely calcified (SC) lesion and non-severely calcified (NC) lesion the latter included none, mild, and moderately calcified lesions (Figure 1).

Depth and circumference of calcification were assessed with histologic sections. Surface calcified area was defined as luminal calcification with the stent strut located directly over the calcified area without any intervening fibrous tissue between the abluminal side of stent strut and calcium. When lesions with ≥ 3 consecutive stent struts resting on surface area of calcification (Figure 2C) were observed, these were evaluated separately to determine the effect on strut coverage.

Statistical analysis

Continuous variables with normal distribution were expressed as means $\pm$ standard deviation after normality of distribution was confirmed by the Shapiro–Wilk test. Variables with non-normal distribution were expressed as median and interquartile range (IQR). Categorical data were analysed by the Fisher's exact tests or the χ^2 test. In continuous variables with normal distribution, the Student's *t*-test was used to define the significance of differences, Kruskal–Wallis test was used for comparisons of variables with non-parametric distribution. For lesion-level analysis, the

generalized estimating equation (GEE) method was used. Continuous variables were tested by the GEE method with γ with the log-link or Poisson model, as appropriate. Categorical data were tested by the GEE method with an ordinal logistic model or tubular Fisher's exact test, as appropriate. For factors assessed for lesion characteristic and pathologic features were selected for univariate analysis to predict delayed strut coverage; presenting with duration of implantation ≤ 6 months, more than three consecutive struts on surface calcified area, strut malapposition, lack of severe medial tear (MT), overlapping stent section, section with minimal stent area and Xience usage (vs. the other three types of DES). Variables with $P < 0.10$ in univariate analysis were entered into a multivariate analysis. Goodness of fit was evaluated with Hosmer–Lemeshow test. A P value of < 0.05 was considered statistically significant. JMP software (version 13.0, Cary, NC, USA), STATA software (version 14, StataCorp LLC, College Station, TX, USA), and SPSS software (version 19, IBM Corporation, Armonk, NY, USA) were used for statistical analyses.

Results

Patient/lesion characteristics and outcomes of drug-eluting stents

Clinical characteristics including age, sex, and cause of death were similar between SC and NC lesions, however, prevalence of diabetes mellitus, chronic kidney disease (CKD) were significantly higher in SC compared to NC (Table 1). The duration of implant was similar, and lesion characteristics including lesion location, number of stent implanted, prevalence of overlapping stents, bifurcation stenting, and stent length were similar except that SC had less prevalence of

Figure 2 Representative photomicrographs of covered (A and B) and uncovered (C–G) strut. Strut is considered as covered when the strut is fully covered by a surface layer of endothelial cells, irrespective of other underlying tissue characteristics (A, smooth muscle cell-rich neointima, and B, foamy macrophage rich neointima). Other images (C–G) show uncovered strut when the luminal strut surface remains bare (D) or shows presence of giant cells (arrows in C) and/or other inflammatory cells or is covered with fibrin/platelets (E–G). Ca^{2+} , calcification.

unstable lesions compared to NC (SC vs. NC; 11% vs. 34%, $P = 0.01$) (Table 1). The prevalence of stent fracture was similar in both groups.

The prevalence of ST was significantly higher in SC compared to NC [four cases (9%) vs. zero cases (0%), respectively, $P = 0.01$]. The prevalence of restenosis was also numerically higher in SC compared to NC which was borderline significant [8 cases (17%) vs. 6 cases (7%), respectively, $P = 0.054$].

Morphometric and pathologic analysis

Morphologic and morphometric analysis involved 11 706 struts from 920 cross-sections of stented arteries (Table 2). External elastic lamina area and stent area were similar in the two groups; however, underlying plaque area was significantly greater in SC as compared to NC [median 5.9 (IQR 4.9–8.8) mm^2 vs. 4.4 (IQR 3.1–6.3) mm^2 , respectively, $P < 0.0001$]. The percentage of uncovered strut per lesion was higher in SC [2.4 (IQR 0.0–19.0) %] as compared to NC [0.0 (IQR 0.0–4.6) %, $P = 0.02$]. Percent struts with fibrin deposition were similar between the two groups. Inflammation score was numerically less in SC compared to NC but failed to reach statistical significance

($P = 0.07$). When inflammation score was further compared based on presence or absence of restenosis, inflammation score was higher in lesions with restenosis irrespective of underlying calcification (Figure 3).

The prevalence of malapposed struts was significantly higher in SC (48%) vs. NC (27%, $P = 0.006$). Severe MT was observed more frequently in SC (59%) compared to NC (44%, $P = 0.03$). Prevalence of sections with ≥ 3 consecutive struts in direct contact with surface calcified area per lesion was also significantly higher in SC compared to NC (52% vs. 8%, respectively, $P < 0.0001$).

Impact of surface calcified area and medial tear in strut coverage and restenosis

To investigate the impact of ≥ 3 consecutive struts on surface calcified area (3SC) and MT on strut coverage and restenosis, lesions were stratified into four groups: (i) lesions without 3SC with MT (3SC-MT+); (ii) lesions without 3SC and no MT (3SC-MT-); (iii) lesions with 3SC and with MT (3SC+MT+); and (iv) lesions with

Table 1 Patient and lesion characteristics and outcomes of newer-generation drug-eluting stents

	Severe calcification (SC)	Non-severe calcification (NC)	P-value
Patient characteristics	<i>n</i> = 35	<i>n</i> = 69	
Age (years)	65 ± 12	61 ± 14	0.2
Male gender	23/35 (66%)	47/69 (68%)	0.8
Hypertension	31/32 (97%)	44/56 (79%)	0.02
Diabetes mellitus	25/32 (78%)	21/56 (38%)	<0.001
Hyperlipidaemia	20/32 (63%)	32/56 (57%)	0.7
Smoking	11/32 (34%)	19/54 (35%)	0.9
Chronic kidney disease	14/32 (44%)	6/54 (11%)	<0.001
Previous MI	20/34 (59%)	36/57 (63%)	0.7
Previous CABG	10/36 (28%)	14/69 (21%)	0.5
Cause of death			0.6
Stent-related	5 (14%)	6 (9%)	
Non-stent-related cardiac	19 (23%)	38 (55%)	
Non-cardiac	12 (33%)	24 (35%)	
Explant due to heart transplant	0 (0%)	1 (1%)	
Lesion characteristics	<i>n</i> = 46	<i>n</i> = 88	
Duration of implant (days)	360 (158–720)	365 (150–720)	0.6
Indications for stent implantation			
Stable CAD/ACS	41 (89%)/5 (11%)	58 (66%)/30 (34%)	0.01
Lesion location			
LM/LAD/LCX/RCA, <i>n</i>	4/20/10/12	4/29/30/25	0.3
Stent type			
Xience/Resolute/Promus/Synergy, <i>n</i>	27/13/5/1	58/16/12/2	0.6
Stent length (mm)	18.0 (12.0–28.0)	23.0 (16.0–31.8)	0.2
Overlapping stents	13 (28%)	29 (33%)	0.6
Bifurcation stenting	2 (4%)	7 (10%)	0.3
Number of stents per lesion	1.2 ± 0.6	1.3 ± 0.6	0.6
Underlying plaque morphology			
Acute thrombotic lesion/FA/FC/PIT/others, <i>n</i>	6/7/33/0/0	21/26/36/4/1	<0.001
Stent fracture	7 (15%)	9 (10%)	0.4
Pathological stent failure	12 (26%)	6 (7%)	<0.001
Stent thrombosis	4 (9%)	0 (0%)	0.01
Restenosis	8 (17%)	6 (7%)	0.054

ACS, acute coronary syndromes; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CTO, chronic total occlusion; DES, drug-eluting stents; FA, fibroatheroma; FC, fibrocalcific plaque; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main trunk; MI, myocardial infarction; PIT, pathological intimal thickening; RCA, right coronary artery.

3SC and no MT (3SC+MT-). These four groups were further compared based on stratification of duration of implant into two groups (1 to <6 months and ≥6 months). All four groups showed a gradual decrease in the percent-uncovered strut per lesion and a progressive increase in the maximum percent stenosis as the duration of implantation increased (Figures 4 and 5). The percent-uncovered strut per lesion was the highest in 3SC+MT- followed by 3SC-MT-, 3SC+MT+, and 3SC-MT+ at both 1 to <6 months and ≥6 months. In contrast, the maximum percent stenosis was the lowest in 3SC+MT- at both 1 to <6 months and ≥6 months.

Univariate analysis to identify predictors of delayed strut coverage is shown in Table 3. Duration of implant ≤6 months, more than three consecutive struts on surface calcified area, strut malapposition, and lack of severe MT were predictors of delayed strut coverage. Multivariate analysis demonstrated that sections with duration of

implantation ≤6 months [odds ratio (OR): 7.7, $P < 0.0001$], ≥3 consecutive struts on surface calcified area (OR: 6.5, $P < 0.0001$), strut malapposition (OR: 5.0, $P < 0.0001$), and lack of severe MT (OR: 2.5, $P = 0.0005$) were independent predictors of delayed strut coverage (Table 3). Goodness of fit was 0.1472, and C-statistic was 0.86904.

Prevalence and characteristics of neoatherosclerosis

The overall prevalence of neoatherosclerosis in SC groups was 24%, which was significantly lower than that of NC group (44%, $P = 0.02$). Calcification of the neointima was a common characteristic of neoatherosclerosis in SC (42%), whereas presence of foamy macrophage in the neointima was the most common in NC (61%) (Table 2).

Table 2 Morphometric analysis and neoatherosclerosis assessment

	Severe calcification (n = 46 lesions)	Non-severe calcification (n = 88 lesions)	P-value
Number of histologic sections evaluated	314	606	
Number of stent struts evaluated	4036	7670	
Morphometric analysis			
External elastic lamina area (mm ²)	13.7 (11.2–17.6)	12.8 (8.9–16.4)	0.1
Stent area (mm ²)	5.8 (4.3–7.5)	5.9 (4.3–7.2)	0.9
Lumen area (mm ²)	4.3 (2.8–6.3)	4.4 (3.3–5.6)	0.8
Underlying plaque area (mm ²)	5.9 (4.9–8.8)	4.4 (3.1–6.3)	<0.001
Mean neointimal thickness (mm)	0.14 (0.05–0.28)	0.16 (0.08–0.25)	0.8
Maximum percent stenosis (%)	33.2 (19.7–61.6)	34.1 (24.0–51.6)	0.3
Uncovered struts per lesion (%)	2.4 (0.0–19.0)	0.0 (0.0–4.6)	0.02
Sections with 30% uncovered struts	13 (28%)	14 (16%)	0.01
Pathologic analysis			
Struts with fibrin (%)	14.2 (4.0–29.0)	15.1 (4.8–34.8)	0.5
Inflammation score	0.6 (0.2–1.0)	0.8 (0.3–1.2)	0.07
Maximum injury score per lesion	3.0 (2.0–3.0)	2.0 (1.0–3.9)	0.03
Prevalence of malapposition	22 (48%)	24 (27%)	0.01
Severe medial tear	27 (59%)	39 (44%)	0.03
Prevalence of sections with >3 consecutive struts on surface calcified area per lesion	24 (52%)	7 (8%)	<0.001
Prevalence of neoatherosclerosis	11 (24%)	39 (44%)	0.02
Foamy macrophage/PIT	4 (9%)	23 (26%)	0.02
Fibroatheroma	3 (7%)	10 (11%)	0.4
Calcification	4 (9%)	5 (6%)	0.6
TCFA/in-stent plaque rupture	0 (0%)	1 (1%)	0.5

PIT, pathological intimal thickening; TCFA, thin cap fibroatheroma.

When the prevalence of neoatherosclerosis in SC vs. NC was further compared based on duration of implant (<1 year, and ≥1 year) (Figure 6), both groups demonstrated progressive increase in prevalence of neoatherosclerosis with greater duration of implant. Prevalence of neoatherosclerosis in SC was consistently lower than that in NC at both <1 year, and ≥1 year, but the differences were significant only for <1-year duration of implant ($P = 0.02$).

Discussion

Severe coronary calcification has been reported as an independent predictor of ST and TLR in patients treated with BMS and DES presenting with ACS in two large RCTs.¹⁷ Other studies have also shown a higher prevalence of TLR in severely calcified stable patients.¹⁸ Despite the fact that calcification is commonly encountered during PCI, to the best of our knowledge, the current study is the first histological study to investigate the outcome of patients, with and without severe calcification treated with newer-generation DES. Our results show delayed strut coverage, which has been reported to be one of the main causes of ST, was more frequent in severely

Figure 3 Box plots showing inflammation score stratified by presence or absence of severe calcification and presence or absence of in-stent restenosis. Red lines represent median values; the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively.

Figure 4 Representative photomicrographs showing delayed healing (A–C), well-covered struts (D–F), and in-stent restenosis (G–K) lesions. (A–C). A 79-year-old woman with past medical history of hypertension, chronic renal failure, and coronary artery disease with PROMUS Element everolimus-eluting stent implanted in the left anterior descending artery 92 days before death; patient died 7 days after transcatheter aortic valve replacement. Low power photomicrographs of the stented cross-sections stained with haematoxylin and eosin demonstrating circumferentially distribution of stent strut in a highly calcified surface area (A and B, the area of calcification is filled with yellow colour). In C, an uncovered stent strut is shown with underlying highly calcified surface area (high power view of the blue-boxed area in B). (D–F). A 60-year-old man with past medical history of diabetes with Xience everolimus-eluting stent implantation 90 days before death on a non-severely calcified lesion. In D, a low-power images of the stented section is shown; E shows the area of calcification (yellow); and F is high-power image of boxed area from E showing fully covered strut with neointima and surface endothelialization (haematoxylin and eosin). (G–L). A 69-year-old man with past medical history of hypertension, diabetes, and coronary artery disease with Resolute Integrity zotarolimus-eluting stent implantation 1 year prior to death. Low power images of stented sections (G, I, and K are haematoxylin and eosin stained, while H, J, and L are Movat pentachrome stained) demonstrating in-stent restenosis with massive neointimal overgrowth with a large medial tear in a severely calcified artery. Note highly calcified underlying surface area (I and J) outlined and filled with yellow colour, whereas the IEL and EEL regions are shown in orange and red lines, respectively. Note extensive medial tear with increased inter-strut distance (red double arrow in H) and severe restenosis. High-power images of the blue boxed areas in I and J are shown in K (haematoxylin and eosin), and L (Movat pentachrome stain).

Figure 5 Box plots showing percent-uncovered struts (A) and maximum percent stenosis (B) stratified by duration of implantation (1 to <6 months and ≥ 6 months) and by presence or absence of severe surface calcification and presence or absence of medial tear [four groups: (i) lesions without 3SC with MT (3SC-MT+); (ii) lesions without 3SC and MT (3SC-MT-); (iii) lesions with 3 SC and MT (3SC+MT+); and (iv) lesions with 3 SC without MT (3SC+MT-)]. Long lines represent median values; the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively.

calcified lesions.⁷ Not only is severe calcification of stented arteries associated with uncovered struts, but uncovered struts were more common in lesions where struts were in direct contact with calcified areas. This was further confirmed if more than three consecutive struts were in direct contact with an area of luminal calcification. On the other hand, percent stenosis was the highest in arteries with MTs in the presence of surface calcification, irrespective of duration of implantation (1–6 months and > 6 months). These data might explain possible reasons for two conflicting clinical outcomes in severely calcified lesions (i.e. delayed strut coverage due to surface calcification and excessive neointimal growth due to severe MT). In-stent neoatherosclerosis was also less in severely than non-severely calcified arteries and the prevalence of neoatherosclerosis was significantly greater when the duration of implant was < 1 year. The type of in-stent neoatherosclerosis was more frequently foamy macrophage type in non-severely vs. severely calcified arteries.

In the current study, MT was associated with increasing neointima growth, which is consistent with the previously published autopsy

studies.^{24,25} Farb et al.²⁴ reported that arterial MT was associated with a 29% increase in neointimal thickness compared with arteries with an intact media in BMS. Also, neointimal thickness, degree of inflammation, and neovascularization were greater when struts were in contact with a torn media/intima compared with struts on an intact fibrous cap. The ideal solution to balance the goals of reducing MTs with encouraging strut coverage in heavily calcified lesions may lie to making atherectomy devices which are able to fracture calcium while not causing excessive injury to the arterial wall. Newer devices such as a lithotripsy may be promising in this regards but their advantages need still to be proved against more traditional atherectomy devices.

Strut coverage begins with platelet aggregation and fibrin deposition, with inflammatory cell infiltration which consists acutely of neutrophils and monocytes, followed by macrophage infiltration and release of growth factors that attract both endothelial and smooth muscle cells.¹¹ The luminal surface of the stent struts and inter-strut areas get endothelialized and at the same time, there is matrix

Table 3 Univariate and multivariate analyses of predictors for delayed strut coverage in newer-generation drug-eluting stents

	Univariate				Multivariate			
	OR	Lower (95% CI)	Upper (95% CI)	P-value	OR	Lower (95% CI)	Upper (95% CI)	P-value
Duration of implantation ≤6 months	10.9	7.68	15.47	<0.001	7.7	5.18	11.5	<0.001
More than three consecutive struts on surface calcified area	5.6	3.47	9.16	<0.001	6.5	3.55	12.04	<0.001
Strut malapposition	9.6	6.63	13.84	<0.001	5.0	3.34	7.57	<0.001
Lack of severe medial tear	2.7	1.77	4.13	<0.001	2.5	1.53	4.34	0.001
Overlapping stent section	0.6	0.25	1.48	0.6				
Section with minimal stent area	1.5	0.8	2.69	0.2				
Xience usage (vs. the other three types of DES)	1.1	0.78	1.45	0.7				

DES, drug-eluting stents.

Figure 6 Prevalence of in-stent neoatherosclerosis stratified by duration of implant (<1 year and ≥1 year). Note higher prevalence of in-stent neoatherosclerosis in non-severely calcified lesion compared to severely calcified lesion. Stents implanted for <1 year with non-severe calcification show significantly greater neoatherosclerosis than severely calcified lesions.

deposition by the proliferating SMCs.¹¹ The main reason for lack of strut coverage on severely calcified luminal surface areas is likely due to lack of SMCs and loss of endothelial cells from destruction during the process of ballooning and stenting and the difficulty of these areas becoming recovered with cells given the lack of cellular scaffolding. SMCs have to migrate from a nearby region rich in SMCs, whereas endothelial cells require laying down of protein layer to allow anchoring. Nevertheless, further studies are needed to confirm or refute the proposed mechanism of strut coverage by endothelial and SMCs on highly calcified surfaces.

Because of delayed healing of severely calcified stented arteries, we believe longer duration DAPT treatment may be needed following newer-generation DES implantation. Patients with HBR are generally old (>75 years old) with history of CKD, which is a known risk factor for extensive coronary artery calcification.^{16,26} From our study it may be prudent to exclude the patients with severely calcified lesions from short-duration DAPT trials. Several preclinical studies have demonstrated less thrombogenicity of newer-generation DES,

due to thinner struts²⁷ as well as anti-thrombogenicity of the polymer coatings.^{28,29} In addition, recently published RCTs demonstrated similar rates of ST between shorter DAPT vs. 12-month DAPT in patients at low to middle bleeding risk.^{30,31} These results suggest that the impact of uncovered struts on risk of ST would be less in newer-generation DES vs. 1st generation DES which may be due to the presence of more biocompatible and thromboresistant polymers.^{30,31} However, uncovered struts at 1 or 3 months after stent implantation might induce ST especially after discontinuation of DAPT. Further clinical studies are needed to validate the importance of severe lesion calcification on DAPT duration.

Clinical studies using OCT demonstrated that the mean value of percent strut coverage up to 6 months after newer-generation DES implantation was 73–98%,^{32–34} higher than what is reported in our study (Figure 5A). There might be several reasons for this discrepancy. First, baseline patient characteristics are different. Second, there may be a discrepancy between ‘histologically defined’ and ‘OCT defined’ strut coverage because OCT is likely to over-diagnose strut coverage

Take home figure Effect of surface calcification on both uncoverage and excessive neointimal growth after stenting. Surface calcification and medial tear might cause adverse events, such as stent thrombosis and restenosis, after DES implantation. ST, stent thrombosis; TLR, target lesion revascularization.

as OCT cannot differentiate between early neointimal tissue and fibrin (Figure 2). Also, large amount of contrast injection is needed to acquire OCT images and, therefore, patients with CKD were excluded from clinical OCT studies.^{32–34} CKD is a known risk factor for coronary artery calcification,²⁶ and exclusion of these patients may result in lower prevalence of severely calcified lesions. Nevertheless, OCT is the best imaging modality to evaluate degree of calcification *in vivo*, therefore, longer DAPT duration might be considered when severe surface calcification is detected at the culprit lesion before stent implantation. The other imaging modalities, such as computed tomography (CT), angiography, and IVUS, are also reported to be feasible to assess severity of coronary arterial calcification.³⁵ As we have shown that ‘radiographically assessed severe calcification’ is associated with higher prevalence of surface calcification compared to ‘radiographically assessed non-severe calcification’ in the current study, longer DAPT duration might be considered when there is diffuse calcification that is appreciated before the intervention either by angiography or by intravascular imaging.

In the current study, we also demonstrated lower prevalence of neoatherosclerosis in severely calcified lesions vs. non-severely calcified lesions. The morphology of neoatherosclerosis was also different, neoatherosclerotic calcification was more common in SC lesions, whereas foamy macrophages were more frequent in NC lesions. Slower neointimal coverage of stent struts is the likely mechanism of lower prevalence of neoatherosclerosis. In addition, the different underlying morphologies of the plaque in severely calcified lesions as compared to non-severely calcified lesions with fewer SMCs with surrounding dense collagen and lack of inflammation in the former could also be a factor in determining differential vascular responses to stenting. Further studies are needed to better understand the different characteristics of neoatherosclerosis in severely calcified and non-severely calcified lesions.

Study limitations

The current study involved autopsy cases and not living patients, therefore, our finding may not be applicable in living patients treated with newer-generation of DES. Although we have included all the newer-generation DES from our autopsy registry, the number of the stents evaluated was relatively small, especially for a subgroup analyses. Thus such findings should always be considered hypothesis-generating rather than definitive. Also, there could be a selection bias as the individuals included may have a greater prevalence of adverse events compared to living patients. In addition, detailed patient information (i.e. patient history including detailed procedural information including use of atherectomy devices such as rotablator), as well as baseline lesion characteristics, were not available in some cases. Although there may be a risk for cutting artefacts or stent fractures during the processing, all stents underwent radiography prior to processing which allowed us to be sure that all fractures occurred prior to processing and thus were not simply an artefact. Pathologic responses after biodegradable polymer DES were not evaluated as almost all the DES in the present study had durable polymers. Although slower strut coverage in severely calcified lesions was consistently demonstrated, further clinical studies are needed to confirm the impact of severely calcified lesions for the prevalence of ST and restenosis. Nevertheless, the current autopsy study provides important information that cannot be easily obtained in clinical studies.

Conclusions

Severe calcification of stented arteries causes delayed healing of the stented lesion and luminal surface calcified area in direct contact with stent strut is an independent predictor of delayed strut coverage in

the newer-generation DES. Our data significantly enhance our understanding the effects of arterial calcification on vascular responses to stenting and suggests poor clinical outcomes in severely calcified lesions may in part be due to delayed healing.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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