Angiographic and optical coherence tomography insights into bioresorbable scaffold thrombosis: single-centre experience

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ABSTRACT

Background

As bioresorbable vascular scaffolds (BVSs) are being increasingly used in complex real-world lesions and populations, BVS thrombosis cases have been reported. We present angiographic and optical coherence tomography (OCT) findings in a series of patients treated in our center for definite bioresorbable scaffold thrombosis.

Methods and Results

Up to June 2014, 14 patients presented with definite BVS thrombosis in our centre. OCT was performed in 9 patients at the operator's discretion. Angiographic and OCT findings were compared with a control group comprising 15 patients with definite metallic stent thrombosis. In the BVS group, time interval from index procedure to scaffold thrombosis ranged from 0 to 675 days. Incomplete lesion coverage by angiography was identified in 4 of 14 cases, malapposition by OCT in 5 of 9 cases, strut discontinuity in 2 of 9 cases, and underexpansion in 2 of 9 cases. Five patients had discontinued dual antiplatelet therapy, and in 3 of them discontinued dual antiplatelet therapy discontinuation had occurred the week preceding the event. There were no significant differences in angiographic or OCT findings between BVS and metallic stent thrombosis.

Conclusions

Suboptimal implantation with incomplete lesion coverage, underexpansion, and malapposition comprises the main pathomechanism for both early and late BVS thrombosis, similar to metallic stent thrombosis. Dual antiplatelet therapy discontinuation seems to also be a secondary contributor in several late events. Our observations suggest that several potential triggers for BVS thrombosis could be avoided.

INTRODUCTION

Metallic drug-eluting stents (DESs) are the current standard for invasive treatment of coronary artery disease. However, metallic DES have been associated with late complications such as neoatherosclerosis and incomplete healing that can lead to failure even at long-term follow-up.1–3 Bioresorbable vascular scaffolds (BVSs) are a new treatment for coronary artery disease that could potentially alleviate such problems.4,5 To date, bioresorbable scaffolds have been evaluated in first-in-man or highly selected study cohorts with simple lesions in low-risk patient populations,4–7 whereas vascular response in lesions of real-world patients might differ. As BVSs are being increasingly used in more complex lesions, several cases of BVS thrombosis have been reported.8–10

In metallic DES, intravascular imaging has elucidated pathophysiologic mechanisms of stent thrombosis, underscoring the significance of procedural factors such as inadequate stent expansion and vascular trauma for acute thrombosis11, 12 or delayed healing and neoatherosclerosis for late thrombosis.1, 2 Whether BVS thrombosis is amenable to the same factors remains unknown.

We aimed to present angiographic and optical coherence tomography (OCT) findings in a series of patients with definite bioresorbable scaffold thrombosis treated in our catheterization laboratory and compare them with a control group of patients with definite metallic stent thrombosis.

METHODS

Study Population

The everolimus-eluting BVS (Absorb; Abbott Vascular, Santa Clara, CA) has been used in clinical trials in our centre since 2006.4–7 Since September 2012, Absorb BVS was approved for commercial use in the Netherlands and has been used in our centre also in more complex patients and lesions, while outcomes of these patients are recorded in the Expanded Clinical Use of Everolimus Eluting Bioresorbable Vascular Scaffolds for Treatment of Coronary Artery Disease (BVS- Expand) and Everolimus-Eluting Bioresorbable Vascular Scaffolds for Treatment of Patients Presenting With ST-Segment–Elevation Myocardial Infarction (BVS-STEMI) registries.13, 14 Up to June 1, 2014, a total of 733 everolimus-eluting BVS had been implanted in 469 patients in our centre.

Since 2006 and up to June 2014, 14 patients were admitted to our laboratory because of definite BVS thrombosis. Definite BVS thrombosis was identified using the Academic Research Consortium definition requiring both angiographic evidence of scaffold thrombosis (including 5-mm edge segments) and clinical evidence of acute coronary syndrome and were classified as acute, subacute, late, or very late.15 Treatment of BVS

thrombosis, including thrombus aspiration or invasive imaging, was performed at the operator's discretion. All patients have provided informed consent.

To understand potential differences and similarities between BVS and metallic stent thrombosis, we used consecutive patients with definite metallic stent thrombosis as control. Between September 1, 2012 and June 1, 2014, 55 patients presented with definite metallic stent thrombosis. We excluded patients with stent thrombosis in left main or in graft (n=4), as these typically large vessels are not suited for BVS with its currently limited diameter range, and patients with very late stent thrombosis >2 years since implantation (n=36), as the available follow-up period in BVS does not allow a meaningful comparison of very late thrombosis at that interval. Thus, 15 patients with definite metallic stent thrombosis were included as control (2 acute, 4 subacute, 5 late, and 4 very late between 1 and 2 years).

Angiographic Analysis

Angiographic analysis was performed for baseline implantation and for stent/scaffold thrombosis, including quantitative coronary angiography and assessment of intra-procedural complications. Incomplete lesion coverage (also called geographical miss) was defined as the longitudinal mismatch between implantation site and diseased coronary segment or coronary segment subjected to balloon dilatation, and its identification required a consensus characterization by 2 observers that reviewed the baseline angiography, applying established methodology.16 Angiographic analysis at the event included assessment of thrombolysis in myocardial infarction flow grade, thrombus burden,17 and quantitative coronary angiography measurements.

OCT Image Acquisition

OCT was performed at the operator's discretion, after thrombus aspiration, in 9 patients with BVS thrombosis and in 5 patients with metallic stent thrombosis. OCT acquisition was performed with the Lightlab/St Jude (C7XR/Illumien, St Jude/Lightlab, St Paul, MN) or the Terumo Lunawave (Terumo Corporation, Tokyo, Japan) frequency-domain imaging systems, as previously described.4, 14

OCT Image Analysis

OCT image analysis was performed offline in 1-mm intervals within the treated segment, including proximal and distal 5-mm long edge segments, after excluding frames with <75% lumen contour visibility, as previously described.1,7,14 Scaffold struts were defined malapposed in the absence of contact with the vessel wall, whereas metallic stent struts were malapposed when the distance of the adluminal strut reflection from the vessel wall exceeded the nominal strut thickness (metal backbone plus coating). These definitions do not include struts in front of side-branches or their ostium (polygon of

confluence), which are defined as side- branch–related struts. Intraluminal struts belonging to adjacent clusters of apposed struts in overlapping scaffolds were not considered malapposed. Thrombus was defined as irregular endoluminal or mural mass and scaffold discontinuity (in BVS) as struts overhanging each other at the same angular sector, with or without malapposition, or isolated struts at the luminal centre without obvious connection to other surrounding struts,7,18 further classified as fracture (present at baseline and follow-up) or late discontinuity (present only at follow-up). OCT findings in BVS thrombosis were compared between frames with and without thrombus.

Statistical Analysis

All analyses were performed with SPSS 20.0 (IBM, Chicago, IL). Continuous variables are presented as mean ± SD, median [inter- quartile range], or estimated means (95% confidence interval), whereas categorical variables are reported as count and percentages. Differences in continuous baseline or angiographic variables were assessed with *t* test, whereas in categorical variables with the $\chi 2$ or Fisher exact test. Differences in OCT variables were assessed with Mann–Whitney and paired comparisons with Wilcoxon, because of the small sample size and skewed nature of these variables. Frame- or strut-level analysis was performed with mixed linear or logistic regression, as struts are clustered within each frame within each patient. Strut-level malapposition was assessed by mixed logistic regression using within-frame and within-patient intercepts as random effects. Frame-level differences were assessed with mixed linear or logistic regression analysis using within-patient intercepts as random effect. All *P* values are 2-sided with a value <0.05 indicating significance.

RESULTS

Baseline Characteristics and Concomitant Therapy Baseline characteristics for BVS (n=14) and metallic stents (n=15) are reported in Table 1. There were no significant differences in baseline characteristics with the exception of a higher proportion of men in BVS (100% versus 67%; *P*=0.042).

At the time of BVS thrombosis, 5 patients were not receiving dual antiplatelet therapy (DAPT) (2 with premature dis- continuation <1 year and 3 with planned discontinuation >1 year). In three patients, DAPT discontinuation had occurred the week preceding the event. In metallic stents, complete DAPT discontinuation <1 year was confirmed in 1 patient and BVS compared with metallic stents (predilation: 92.9% versus 50.0%; *P*=0.033 and post-dilation: 50.0% versus 0%; *P*=0.006), with a trend for higher scaffold diameter in (3.18±0.27 versus 2.90±0.47; *P*=0.06). OCT post implantation had been performed in 5 of 14 patients in BVS and in none of the metallic stents. Incomplete lesion coverage was

observed in four BVS cases, and in one case with metallic stent. Two patients with BVS had an angiographically visible edge dissection (one proximal, one distal) after baseline implantation, left untreated.

Table 1. Clinical and demographic characteristics

	n=14
Age (years)	60.2±10.5
Male n(%)	14(100)
Clinical syndrome at baseline	
Stable angina n(%)	5(35.7)
Unstable angina n(%)	1(7.1)
NSTEMI n(%)	3(21.4)
STEMI n(%)	5(35.7)
Clinical syndrome at scaffold thrombosis	
NSTEMI n(%)	7(50.0)
STEMI n(%)	7(50.0)
Antiplatelet therapy at scaffold thrombosis	
Aspirin n(%)	11(78.6)
Clopidogrel n(%)	3(21.4)
Prasugrel n(%)	5(35.7)
Ticagrelor n(%)	1(7.1)
Oral anticoagulation n(%)	3(21.4)
CAD risk factors	
Hypertension n(%)	9(64.3)
Dyslipidemia n(%)	6(42.9)
Diabetes n(%)	1(7.1)
Smoking n(%)	6(42.9)
Family history of CAD n(%)	5(35.7)
Comorbidities	
Prior cerebrovascular accident n(%)	3(21.4)
Peripheral vascular disease n(%)	1(7.1)
Kidney disease n(%)	0(0.0)
Prior MI n(%)	2(14.3)
Prior PCI n(%)	2(14.3)
Prior CABG n(%)	0(0.0)
COPD n(%)	1(7.1)

Abbreviations: NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; CAD=coronary artery disease; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft; COPD=chronic obstructive pulmonary disease

OCT Findings

OCT at thrombosis was performed in 9 of 14 patients with BVS and in 5 of 15 patients with metallic stents. There was no significant difference in OCT findings between BVS and metallic stent thrombosis (Table 4). In (very) late thrombosis, the incidence of malapposed struts was 1.9%±2.2% for BVS versus 5.6%±6.2% for metallic stents (*P*=0.31), and malapposition distance 486±225 µm for BVS versus 265±151 µm for metallic stents (*P*=0.17).

In BVS thrombosis, frames with thrombus had lower lumen (4.35 mm2 [2.61–6.08 mm2] versus 5.84 mm2 [4.11–7.58 mm2]; *P*<0.001) and scaffold area (7.63 mm2 [6.32–8.95 mm2] versus 8.14 mm2 [6.83–9.46 mm2]; *P*<0.001) com- pared with frames without thrombus (Table I in the Data Supplement). No difference was found in frame-level malapposition incidence (*P*=0.75), whereas malapposition area was numerically higher in frames with thrombus, without reaching significance (1.54 mm2 [0–3.44 mm2] versus 0.44 mm2 [0.00–6.70 mm2]; *P*=0.18).

Patient-Specific Substrates of Thrombosis

Tables II and III in the Data Supplement present patient-specific clinical, procedural, angiographic and OCT characteristics in BVS thrombosis.

(Sub)acute Thrombosis

In (sub)acute scaffold thrombosis, suboptimal implantation was the main mechanism. Incomplete lesion coverage was observed in three patients (Figure I in the Data Supplement), either because of mismatch of the pre-dilated segment and the scaffolded segment or because of incomplete coverage of the thrombosed segment in ST-segment–elevation myocardial infarction (Figure 1). In 2 cases with BVS implantation in ostial left anterior descending artery, angiography demonstrated scaffold protrusion into left main suggesting malapposition, also with underexpansion in one. Finally, in 1 case, thrombus was observed in a long overlap segment (7 mm by OCT), together with compact fibrin and Zahn-lines in aspirate histology (Figure 2), despite good expansion and apposition. In metallic stents, (sub)acute thrombosis was attributed to edge dissections in 3 cases, strut protrusion into left main with associated malapposition in 1 case, and extensive under- expansion in 1 case (minimal stent area, 1.19 mm2). In 1 case, there were no findings suggesting suboptimal implantation, but there was suspicion of poor compliance with DAPT.

(Very) Late Thrombosis

In 1 case, despite meeting Academic Research Consortium criteria for definite thrombosis, OCT disclosed the absence of thrombus and occlusive edge restenosis as substrate (Figure II in the Data Supplement). In most patients, (very) late BVS thrombosis was

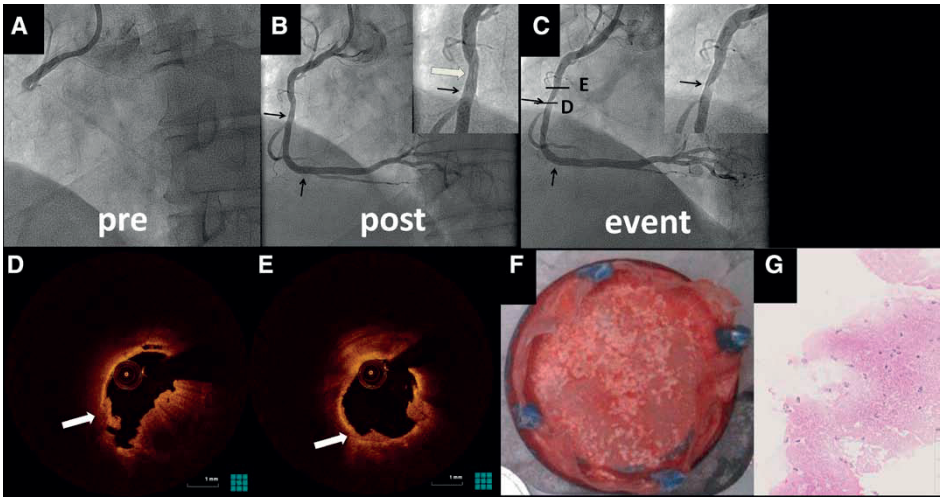

Figure 1 Acute thrombosis because of incomplete lesion coverage.
A, Preprocedural and (B) postprocedural angiogram after bioresorbable vascular scaffold implantation in a ST-segment–elevation myocardial infarction patient undergoing primary percutaneous coronary intervention. Mild haziness at the proximal edge postprocedure (arrow). C, Angiogram at event after thrombus aspiration. Red and white thrombus at the proximal scaffold segment (D) and proximal edge segment (E) extending >5 mm. The thrombus is overlying a thin-cap fibroatheroma, with possible rupture (arrow). Thrombus aspirate histology (F and G) demonstrates platelet-rich thrombus.

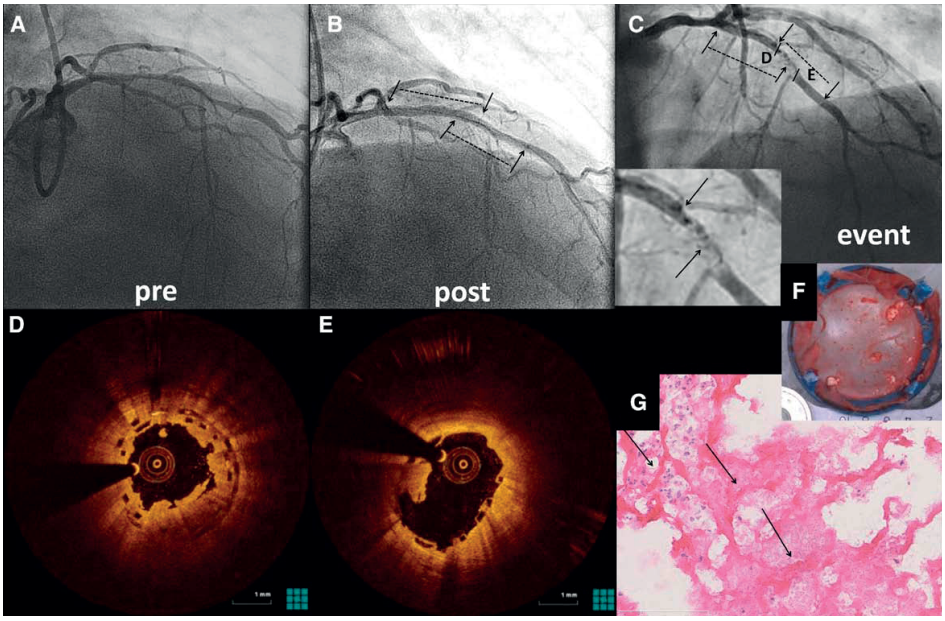

Figure 2 Subacute bioresorbable vascular scaffold thrombosis in extensive strut overlap.
A, Preprocedural and (B) postprocedural angiogram at baseline. C, Angiogram at event showing contrast deficit in the scaffolded segment. D and E, Optical coherence tomography demonstrates thrombus mainly at the overlap (D). F and G, Thrombus aspirate histology shows compact fibrin with Zahn-lines (arrows).

Table 2. Angiographic and procedural characteristics at baseline implantation

Angiographic characteristics	n=14
Vessel	
LAD n,(%)	9(64.3)
RCA n,(%)	2(14.3)
LCX n,(%)	3(21.4)
Bifurcation	3(21.4)
Ostial LAD/LCx lesion	6(42.9)
AHA/ACC classification	
A/B1	3(21.4)
B2/C	11(78.6)
Pre-procedure	
TIMI flow grade n,(%)	
0	5(35.7)
1	0(0)
2	1(7.1)
3	8(57.1)
Total occlusion (n=5)	
RVD, mm	2.98±0.22
Non-total occlusion (n=9)	
RVD, mm	2.61±0.35
Minimal lumen diameter, mm	0.94± 0.26
Diameter stenosis, %	64.1±9.8
Lesion length, mm	22.08±10.78
Post-procedure	
TIMI flow grade n,(%)	
0	0(0)
1	0(0)
2	0(0)
3	14(100)
RVD, mm	2.68± 0.33
Minimal lumen diameter, mm	2.32±0.26
Diameter stenosis, %	13.0±6.4
Dissection n,(%)	2(14.3)
Side-branch occlusion	1(7.1)
Procedural data	
Pre-dilatation n,(%)	13(92.9)
Post-dilatation n,(%)	7(50.0)
Thrombus aspiration n,(%)	4(28.6)
OCT guidance n,(%)	5(35.7)
Overlap n,(%)	3(21.4)

Table 2. Angiographic and procedural characteristics at baseline implantation (*continued*)

Angiographic characteristics	n=14
Bifurcation scaffolding	
T-stenting n,(%)	1(7.1)
Balloon dilation of side-branch ostium n,(%)	1(7.1)
Mean scaffolds per patient, n	1.36±0.63
Total scaffold length per patient, mm	28.57±14.56
Mean scaffold diameter per patient, mm	3.18±0.27

All values presented as n(%) or mean±SD. Abbreviations: RVD=reference vessel diameter; OCT=optical coherence tomography

Table 3. Angiographic characteristics at BVS thrombosis

Angiographic characteristics	n=14
TIMI flow grade, n,(%)	
0	10(71.4)
1	1(7.1)
2	2(14.3)
3	1(7.1)
Thrombus burden index, n,(%)	
0	0(0)
1	0(0)
2	1(7.1)
3	3(21.4)
4	0(0)
5	10(71.4)
Total occlusion (n=10)	
RVD, mm	2.94±0.30
Non-total occlusion (n=4)	
RVD, mm	2.23±0.65
Minimal lumen diameter, mm	0.86±0.18
Diameter stenosis, %	58.5±16.9

All values presented as n(%) or mean±SD. Abbreviations: RVD=reference vessel diameter

observed in the presence of regional suboptimal flow conditions, such as strut malapposition, scaffold fracture, and underexpansion. Four of 7 patients with (very) late BVS thrombosis undergoing OCT had malapposed struts. In 2 patients, malapposition was observed in the absence of scaffold discontinuity (Figure 3), also with underexpansion and restenosis in one of them. In the other 2 patients, malapposition was observed because of strut discontinuity: 1 with late discontinuity and intraluminal thrombus, 19 possibly resulting from balloon dilation of the scaffolded segment after the index

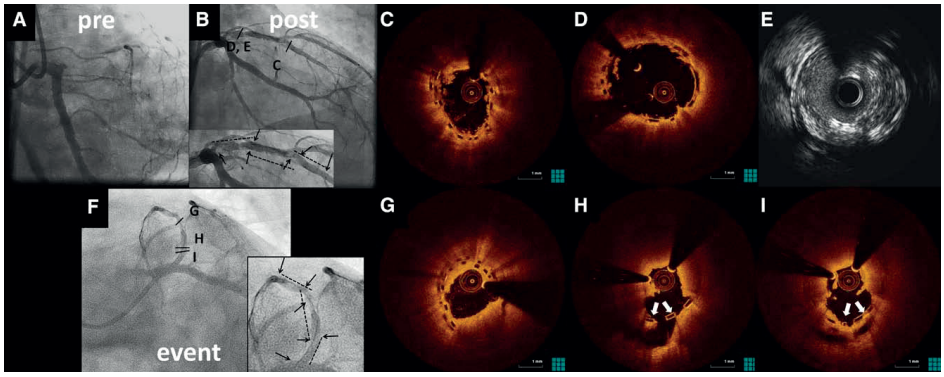

Figure 3 Late bioresorbable vascular scaffold (BVS) thrombosis and malapposition.
BVS implantation in a total left anterior descending artery occlusion with post-dilation (A), resulting in acceptable angiographic result with mild haziness (B), but residual thrombus by optical coherence tomography (OCT; C and D) and residual plaque burden by intravascular ultrasound (E). Post-dilation was not repeated, considering the risk of side-branch occlusion. F, Angiogram at event after thrombus aspiration. G through I, OCT shows massive red thrombus, and late malapposition (arrows).

procedure, whereas acute fracture had been detected in a second case. In this second case, late thrombosis occurred 2 days after both aspirin and clopidogrel discontinuation; however, there was no thrombus in the fracture site, but in an under expanded long overlap segment (Figure 4). In 3 cases, the substrate was not clearly identified: 1 very late thrombosis case where late discontinuity was suspected but not clearly identified because of thrombus (Figure III in the Data Supplement), 1 very late thrombosis case with extensive baseline malapposition (8.6% malapposed struts) and intra-scaffold dissections (no imaging at the event), and 1 late thrombosis case with T-stenting with BVS in a left anterior descending artery- diagonal bifurcation. The 2 latter patients were not receiving any antiplatelet agent at the time of late scaffold thrombosis. In metallic stents, late thrombosis was associated with malapposition in 2 cases and with strut protrusion into left main in another case. Complete DAPT discontinuation was confirmed in an additional patient and suspected in another with late thrombosis. In 4 patients with

Table 4. Optical coherence tomography findings in frames with and without thrombus

	Frames with thrombus (n=140)	Frames without thrombus (n=112)	p-value
Lumen area, mm^2	4.35(2.61-6.08)	5.84(4.11-7.58)	0.001
Scaffold area, mm^2	7.63(6.32-8.95)	8.14(6.83-9.46)	0.001
Malapposition area, mm^2 (n=16)	1.54(0-3.44)	0.44(0.00-6.70)	0.182
Frames with malapposition, %	7.6(0.0-16.2)	8.9(0.2-17.6)	0.752
Frames with overlap, %	8.3(1.5-15)	3.5(0.0-10.4)	0.196

All values presented as estimated marginal means (95% confidence intervals).

very late metallic stent thrombosis, baseline or follow-up angiography did not suggest any mechanical issues, while intravascular imaging was not performed.

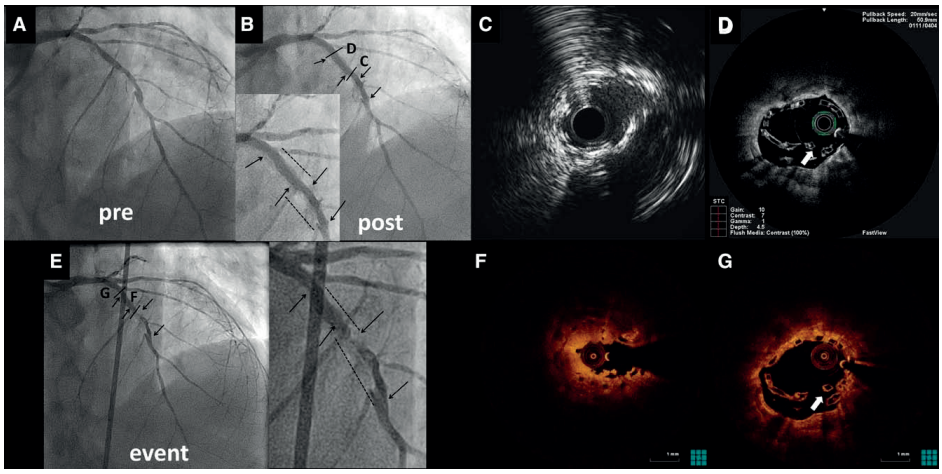

Figure 4. Late scaffold thrombosis after dual antiplatelet therapy discontinuation in overlapping bioresorbable vascular scaffold (BVS) with underexpansion. Overlapping BVS implantation in a diffuse calcified left anterior descending artery lesion (**A**), with acceptable angiographic result (**B**), but underexpansion by intravascular ultrasound (**C**), and scaffold fracture at the proximal edge by optical coherence tomography (OCT; **D**), possibly because of deep catheter intubation. The patient experienced late thrombosis 161 days post implantation (**E**), 2 days after aspirin and clopidogrel discontinuation. OCT shows thrombosis mainly at the overlap region, with low minimal scaffold area (4.21 mm2; **F**), whereas the fracture site remains free of thrombus (**G**).

DISCUSSION

This real-world case series provides unique insights in the mechanisms of BVS thrombosis. The main findings of our study are (1) device thrombosis remains an issue with BVS, with the timing of the event evenly distributed from acute to very late thrombosis; (2) similar to metallic stents, acute and subacute BVS thrombosis is predominantly associated with suboptimal implantation; and (3) late and very late scaffold thrombosis is frequently observed in the presence of regional suboptimal flow conditions, often in combination with cessation of DAPT.

Notwithstanding promising results from first-in-man studies showing favourable BVS long-term healing response 4, 7 and clinical results comparable with metallic DES, 5, 6 little is known about vascular healing after BVS implantation in complex lesions. Real-world registries have reported high 6-month BVS thrombosis rates, driven mainly by increased early thrombosis, 8, and 9 implying a possible role of suboptimal implantation. In our series, we report on 14 cases of definite BVS thrombosis at different intervals since implantation and compare the imaging findings with a control group of metallic

stents with definite stent thrombosis from the same time period, thus providing imaging insights into this complication. Importantly, suboptimal implantation was identified in both groups in a similar extent, suggesting that achieving an optimal implantation result might be more crucial than the type of implanted device in avoiding device thrombosis.

(Sub)acute BVS Thrombosis: Impact of Suboptimal Implantation

In acute and subacute BVS thrombosis, suboptimal implantation, comprising incomplete lesion coverage, malapposition, and underexpansion, was identified as the leading morphological substrate. This finding is in line with established substrates for metallic stent thrombosis12 and confirmed by observations in our control group. As the current BVS generation has a relatively high crossing profile, BVSs require rigorous lesion preparation, potentially translating to higher risk for incomplete coverage of the injured segment, compared with direct stenting often applied with metallic stents. Thus, our findings might urge the operator to specifically ensure complete cover- age of the lesion and injured segments, including angiographically apparent edge dissections.

Furthermore, the development of acute and subacute BVS thrombosis in 2 ST-segment–elevation myocardial infarction patients, after BVS implantation in ostial left anterior descending artery with scaffold protrusion into the left main, raises speculation that hemodynamic disturbances resulting from the protrusion and the associated malapposition could be a substrate for thrombosis.20–22 This was also documented by OCT in 2 metallic stent thrombosis cases, suggesting a similar contribution of this mechanism.

Finally, 1 case of subacute thrombosis occurred despite good expansion and apposition, in the presence of long strut overlap. The high strut thickness of Absorb BVS (150 μm) and bench observations of increased thrombogenicity of thick-strut stents which is more pronounced at overlap sites, 21 together with histological observations of Zahnlines in the aspirates, indicate a potential involvement of flow disturbances induced by long overlap and make a case for minimizing over- lap length in treatment of long lesions by BVS. Whether this increased strut thickness could translate to increased thrombogenicity in vivo in the presence of an optimal implantation result remains unknown.

These findings underscore the significance of a meticulous BVS implantation technique, potentially including invasive imaging guidance, which has proven advantages over angiography for achieving optimal lesion treatment, in terms of coverage and expansion.23 It is important however to note that imaging guidance during the procedure might drive the opera- tor to excessive post-dilation, potentially leading to scaffold fracture. Therefore, thorough lesion evaluation before implantation might help avoid situations with pronounced mismatch between scaffold and artery size.

Late and Very Late BVS Thrombosis: Prominent Role of Suboptimal Flow Conditions

(Very) late thrombosis events in our series were attributed to factors potentially affecting flow conditions. These include underexpansion and pronounced strut protrusion into the lumen as a result of malapposition, bifurcation intervention, or strut discontinuity. Underexpansion has been identified as an important predictor of metallic DES thrombosis.3, 12 the significance of optimal expansion in avoiding BVS thrombosis is underscored by the finding of lower scaffold area in sites with thrombus compared with sites without thrombus.

The role of malapposition in late metallic DES thrombosis is debated 24; however, there is high prevalence in patients with events,1 and late malapposition in first-generation DES has been identified as predictor of very long-term adverse outcome.25 In our series, malapposition in (very) late BVS thrombosis (1.9±2.2%) did not differ significantly from late metallic stent thrombosis and was higher than the range reported for follow-up of second-generation metallic DES.26 Likewise, malapposition distance (486 ± 225 μm) was similar to metallic stents (265 ± 151 μm) and at the range of previously reported values in metallic DES thrombosis (mean: 350 μm).1 Therefore, malapposition of such extent, either persistent or late-acquired, might contribute to (very) late scaffold thrombosis.

As opposed to metallic DES, extensive malapposition in BVS might also result from strut discontinuity, which was associated with extensive thrombosis in a very late event in our series, possibly triggered by DAPT cessation.19 Whether small discontinuities, resulting from normal scaffold resorption, are associated with thrombosis is unclear. Notwithstanding this poorly documented association of discontinuity with thrombosis,18 precautionary measures such as respecting the post-dilation limits and cautious catheter recrossing or reintervention at later time points should be considered.

Role of DAPT Discontinuation

In addition to suboptimal implantation, DAPT cessation seems to play a role in BVS thrombosis, as in metallic DES.27 In 3 cases, there was a close temporal association of DAPT cessation with clinical manifestation of BVS thrombosis, tracking with observations in first-generation metallic DES, where scheduled P2Y12 inhibitor withdrawal was associated with increased ischemic events.28 As we assume concomitant suboptimal flow conditions in these patients, caused by underexpansion or extensive malapposition, we speculate on a possible synergistic effect of these factors in scaffold thrombosis. Consequently, these observations might raise questions about the need for platelet reactivity testing in patients with complex procedures or where optimal expansion cannot be achieved. Furthermore, the impact of DAPT cessation could be more pronounced when both aspirin and P2Y12 inhibitor are with- drawn in patients receiving chronic oral anticoagulation, as in 3 patients in our BVS series. Therefore, considering our observa-

tions of ongoing thrombotic risk even beyond 1 year, BVS implantation in such patients should be accompanied by adequate antiplatelet therapy or avoided in case of high bleeding risk.

Clinical Implications

Collectively, our findings underscore the significance of an optimal implantation result for minimizing the incidence of BVS thrombosis. Intravascular imaging at baseline could allow for early recognition and treatment of incomplete lesion coverage, better procedural planning in ostial lesions, 29 and optimal BVS sizing and post-dilating, thus avoiding underexpansion 23 or scaffold fracture. Moreover, similar to metallic DES, proper DAPT administration must be emphasized.27 Therefore, future studies should focus on optimal DAPT duration in patients with BVS, whereas platelet reactivity testing might be considered in selected patients with suboptimal implantation or complex intervention. Finally, in patients concomitantly receiving anticoagulants, administration of at least 1 antiplatelet agent until resorption or for life should be considered, pending appropriate studies.

LIMITATIONS

This study is focusing on a mechanistic understanding of BVS thrombosis. The study design and its single-centre nature preclude firm estimations of BVS thrombosis incidence and predictors in real-world populations, considering the inclusion of patients treated for BVS thrombosis in our centre, leading to possible underestimation. As OCT was not systematically performed, it was only available for 9 of 14 patients. Rou- tine OCT use could have provided further insights into the pathomechanisms of BVS thrombosis, whereas the small number of patients undergoing OCT might be a limitation in the mixed model analysis of OCT variables. Moreover, the lack of a control group of BVS without thrombosis precludes assessment of morphological predictors of BVS thrombosis. Residual thrombus might have underestimated our results, hampering complete substrate visualization, while precluding coverage assessment, which is based on thickness measurements for BVS, that are inaccurate in the presence of attached thrombus, rather than on visual confirmation of overlying tissue as in metallic stents.1, 7 Therefore, a possible contribution of incomplete strut coverage could not be systematically evaluated. Finally, no platelet function tests were performed that could evaluate a possible contribution of increased platelet reactivity to BVS thrombosis.

CONCLUSIONS

Suboptimal implantation with underexpansion, malapposition, and incomplete lesion coverage comprised the main pathomechanisms for both early and late BVS thrombosis in our series, similar to metallic stent thrombosis. DAPT discontinuation seems to also be a secondary contributor in several late events. Our observations suggest that a number of potential triggers for BVS thrombosis could be avoided and might warrant prospective validation.

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Supplemental Material

METHODS

Quantitative coronary angiography

Quantitative coronary angiography was performed using CAAS 5.11 (Pie Medical Imaging, Maastricht, Netherlands) and included reference vessel diameter (RVD), diameter stenosis (DS%), and minimal lumen diameter (MLD).

Histopathological analysis of thrombus aspirates

Thirteen patients underwent thrombus aspiration. Aspiration samples were successfully retrieved in four (30.8%) and were collected after filtering (40µm cell strainer BD Biosciences), snap-frozen and stored at -80°C. Macroscopic characteristics such as color, size and number of particles were documented. The frozen samples were cryosectioned (5µm serial sections), fixed with buffered paraformaldehyde 4%, and stained with hematoxylin-eosin as a routine stain, rosorcin-fuchin as an elastin stain and alcian blue for proteoglycans. Polarized light was used to detect birefringence.

RESULTS

Histopathological findings of thrombus aspirates

Four thrombus specimens were submitted for histopathology analysis. One sample did not contain any thrombus. One case contained only micro-thrombi [mean length 36µm (25-52µm)] without cellular elements. Two cases contained overt thrombi: one being platelet-rich and one containing compact fibrin with Zahn-lines. Eosinophilic granulocytes were observed in both but comprised <10% of all granulocytes, reflecting normal distribution. There was no evidence of hypersensitivity towards scaffold material. Vessel wall components and atheroma were not observed. There was no birefringence indicative of polymeric scaffold material in the aspirates.

Treatment of BVS thrombosis

Seven of 14 patients were treated by implantation of a metallic DES. Two patients with acute thrombosis due to edge problems were treated by additional BVS implantation. Four patients were treated by combination of thrombectomy and balloon dilation, while in one patient the attempt for treatment of acute thrombosis failed. This patient developed a large myocardial infarction (CK_{peak}: 4358U/L), which led to poor left ventricular

Table 1. OCT findings at scaffold thrombosis

OCT findings	n=9
Analyzed struts, n	208±145
Minimum lumen area, mm^2	2.26±1.56
Mean lumen area, mm^2	5.00±2.21
Minimum scaffold area, mm^2	6.21±1.20
Mean scaffold area, mm^2	7.88±1.42
Ratio of minimum scaffold area to reference area	0.93±0.20
Ratio of minimum scaffold diameter to nominal diameter	0.87±0.06
Malapposition area, mm^2 (n=3)	0.184±0.181
Mean neointimal/attached thrombus area, mm^2	1.99±0.78
Mean non-attached thrombus area, mm^2	0.017±0.028
Malapposed struts, %	2.8(1.5-4.1)
Malapposition distance(μm)	348(214-482)
Scaffolds with at least 1 malapposed strut, n,(%)	5(55.5)
Scaffolds with >5% malapposed struts, n,(%)	2(22.2)
Thrombus n,(%)	8(88.8)
Scaffold discontinuity n,(%)	2(22.2)

Values presented as n(%) or mean±SD. Malapposed struts and distance presented as estimated marginal mean (95% confidence intervals). Abbreviations: OCT=optical coherence tomography

systolic function and implantation of an implantable cardioverter-defibrillator for non-sustained ventricular tachycardia. In all patients, antiplatelet therapy after thrombosis was recommended for at least one year, continued by aspirin alone, including patients concomitantly receiving oral anticoagulation.

Outcome after treatment of BVS thrombosis

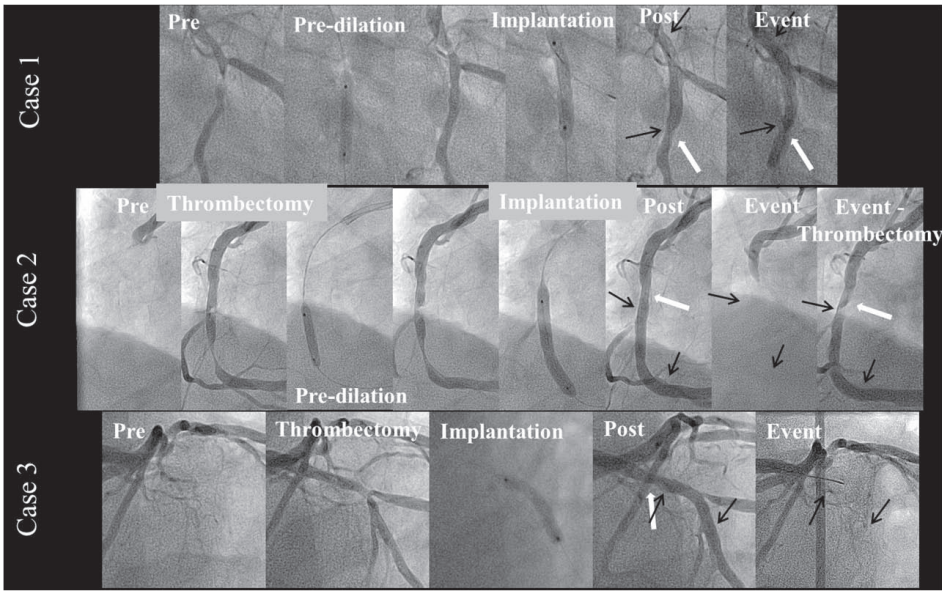
In 11 patients, follow-up was uneventful, while 3 patients suffered a recurrent event: One patient died of cardiac cause 4 days after the procedure. Another patient receiving a metallic DES for the treatment of BVS thrombosis, had an invasive follow-up 6 months after the thrombosis. OCT showed an overall good healing result with nevertheless sporadic clusters of uncovered struts. This patient suffered recurrent thrombosis, one year after the initial event, and 5 days after scheduled prasugrel discontinuation. Another patient had a repeat target vessel revascularization 4 months after thrombosis by coronary artery bypass graft (CABG), due to restenosis of the metal DES implanted for the treatment of BVS thrombosis.

Table 2. Patient-level characteristics

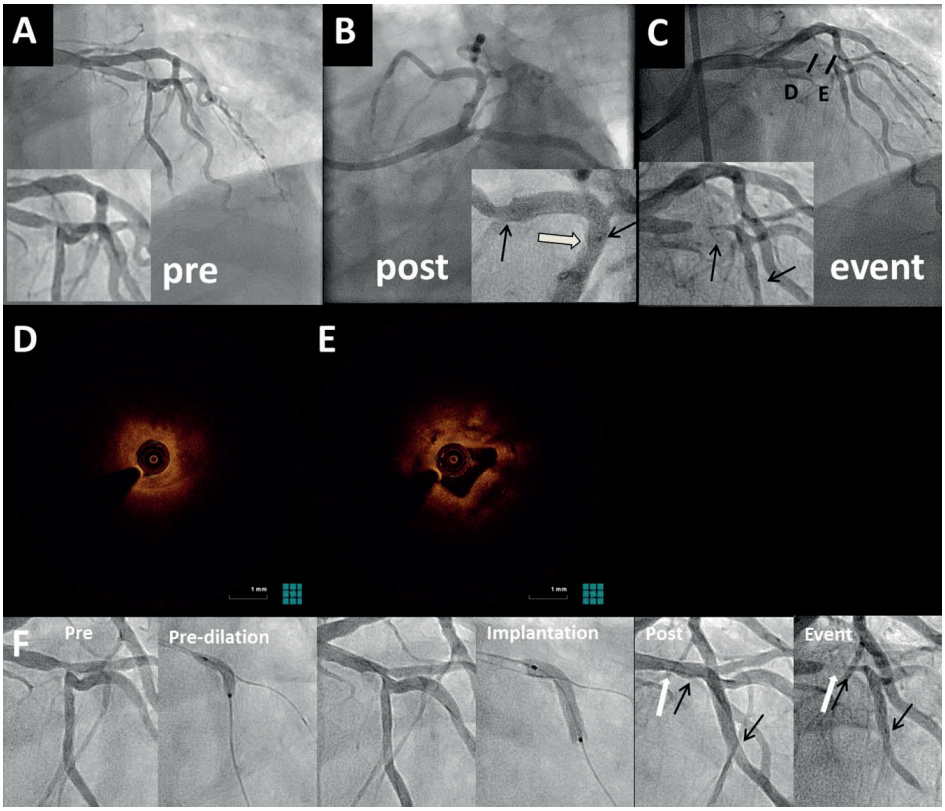
					Baseline and procedural characteristics								Scaffold thrombosis				
Case	Age	ACS	Prescribed P2Y12 inhibitor	Treated vessel	AHA/ ACC class	Bifur-cation	Ostial LAD/ LCx lesion	No of BVS	Total BVS length	OCT guided	Pre-dil	Post-dil	Type	Time (days)	ASA	P2Y12 inh	OAC
1	50	Yes	clopidogrel	LCX	C	-	-	1	18	-	+	-	Acute	0	+	+	-
2	51	Yes	ticagrelor	RCA	B1	-	-	1	28	-	+	-	Acute	0	+	+	-
3	59	Yes	prasugrel	LAD	C	-	-	1	18	-	-	-	Acute	1	+	+	-
4	62	Yes	prasugrel	LAD	B1	-	+	1	18	-	+	-	Acute	1	+	+	-
5	49	Yes	prasugrel	LAD	B2	-	+	1	18	-	+	+	Subacute	17	+	+	-
6	45	No	clopidogrel	LAD	B2	-	-	2	56	-	+	+	Subacute	2	+	+	-
7	65	Yes	prasugrel	LAD	B2	+	-	1	18	-	+	+	Late	142	+	+	-
8	69	Yes	clopidogrel	LAD	C	+	+	3	64	+	+	+	Late	47	+	+	-
9	59	No	prasugrel	LAD	C	-	+	1	28	-	+	+	Late	112	+	+	-
10	55	No	clopidogrel	LCX	A	-	+	1	18	+	+	-	Very late	675	+	-	-
11	71	No	clopidogrel	LAD	C	-	-	2	36	+	+	+	Late	161	-	-	+
12	62	Yes	prasugrel	RCA	C	-	-	1	28	+	+	-	Very late	478	+	-	-
13	86	Yes	clopidogrel	LCX	C	-	+	1	28	+	+	-	Very late	371	-	-	+
14	60	No	clopidogrel	LAD	C	+	-	2	24	-	+	+	Late	129	-	-	+

Table 3. Patient-level angiographic and OCT findings

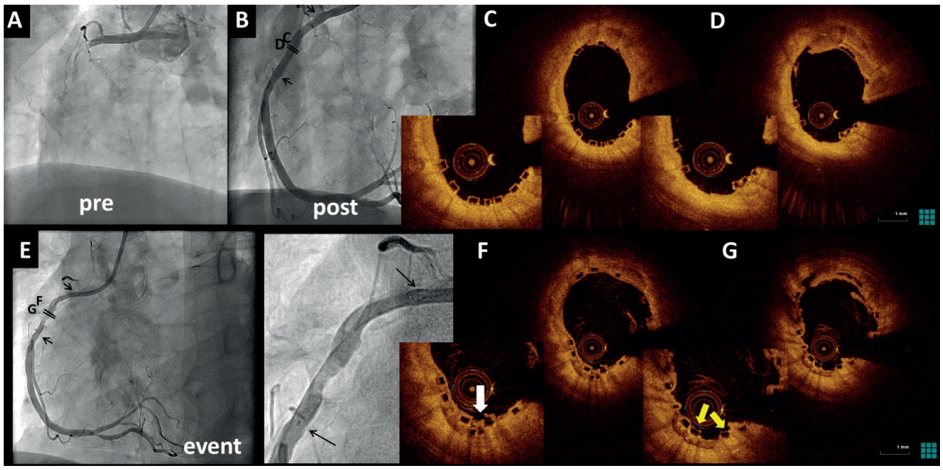
Case	Type	Time (days)	Incomplete lesion coverage	Malapposition	Re-stenosis	Discontinuity	Under-expansion	Other baseline findings	Other follow-up findings	Recent DAPT disconti-nuation	DAPT disconti-nuation <1y
1	Acute	0	+ (dissection)	N/A	-	-	-	-	-	-	-
2	Acute	0	+ (thrombosed segment)	Yes	-	-	-	-	-	-	-
3	Acute	1	+ (thrombosed segment)	N/A	-	-	-	-	-	-	-
4	Acute	1	-	Suspected (angio)	-	-	-	-	-	-	-
5	Subacute	17	-	Suspected (angio)	-	-	Suspected (angio)	-	-	-	-
6	Subacute	2	-	No	-	-	-	-	Thrombus overlying extensive overlap region (7mm)	-	-
7	Late	142	+ (dissection)	N/A	+ (edge)	-	-	-	Occlusive proximal edge restenosis- no thrombus	-	-
8	Late	47	-	Yes (late malapposition)	-	-	-	Residual plaque burden/ residual thrombus	-	-	-
9	Late	112	-	Yes	+	-	+	-	-	-	-
10	Very late	675	-	Yes (late malapposition)	-	Late discontinuity	-	-	-	+	-
11	Late	161	-	Yes (Fracture)	-	Fracture	+	-	Thrombus overlying underexpanded overlap region	+	+
12	Very late	478	-	Resolved	-	Possible late discontinuity	-	-	-	-	-
13	Very late	371	-	Yes (Baseline)	-	-	-	Extensive intra-scaffold dissections	-	+	-
14	Late	129	-	No	-	-	-	-	Uncovered struts protruding at the bifurcation	-	+



Supplementary Figure 1 Summary of the cases with acute thrombosis due to incomplete lesion coverage Black arrows indicate the scaffold markers and white arrows indicate the uncovered edge segment.



Supplementary Figure 2 Late stent thrombosis re-classified by OCT as edge restenosis resulting from incomplete lesion coverage.
A. Pre-procedural and B. post-procedural angiogram at baseline showing proximal edge dissection (white arrow). C. Angiogram at event (142 days) shows contrast deficit at the proximal edge, extending within the scaffold with TIMI I flow. OCT discloses occlusive edge restenosis (D) and restenosis within the scaffold with layered pattern (E), without luminal thrombus. F. Angiographic review demonstrating incomplete lesion coverage. Black arrows indicate the scaffold markers and white arrows the uncovered edge segment.



Supplementary Figure 3 Very late scaffold thrombosis without definite substrate.
BVS implantation in a proximal RCA lesion due to STEMI (A), with good post-procedural angiographic (B) and OCT (C-D) result. The patient suffered very late scaffold thrombosis 478 days post implantation, while only on aspirin (E). OCT shows suspected scaffold discontinuity (F; white arrow) and uncovered and possibly malapposed struts (G; yellow arrow) proximally to the thrombosed segment.