

## Angiographic and Optical Coherence Tomography Insights Into Bioresorbable Scaffold Thrombosis Single-Center Experience

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**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 center. 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. (*Circ Cardiovasc Interv.* 2015;8:e002369. DOI: 10.1161/CIRCINTERVENTIONS.114.002369.)

**Key Words:** bioabsorbable implants ■ coronary artery disease ■ drug-eluting stents ■ tomography, optical coherence

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.<sup>1-3</sup> Bioresorbable vascular scaffolds (BVSs) are a new treatment for coronary artery disease that could potentially alleviate such problems.<sup>4,5</sup> To date, bioresorbable scaffolds have been evaluated in first-in-man or highly selected study cohorts with simple lesions in low-risk patient populations,<sup>4-7</sup> 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.<sup>8-10</sup>

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 thrombosis<sup>11,12</sup> or delayed healing and neoatherosclerosis for late thrombosis.<sup>1,2</sup> 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 center since 2006.<sup>4-7</sup> Since

Received September 24, 2014; accepted April 13, 2015.

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The Data Supplement is available at <http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.114.002369/-/DC1>.

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*Circ Cardiovasc Interv* is available at <http://circinterventions.ahajournals.org>

DOI: 10.1161/CIRCINTERVENTIONS.114.002369

### WHAT IS KNOWN

- Bioresorbable scaffolds are a new treatment for coronary artery disease with a favorable long-term healing response that could potentially alleviate long-term complications of metallic stents such as neoatherosclerosis and incomplete healing.
- Several real-world registries have demonstrated relatively high rates of scaffold thrombosis, driven mainly by increased rates of acute and subacute scaffold thrombosis.

### WHAT THE STUDY ADDS

- The main pathomechanisms for both early and late bioresorbable scaffold thrombosis are similar to those of metallic stents and consist of suboptimal implantation with underexpansion, malapposition, and incomplete lesion coverage.
- Addition to suboptimal implantation and similar to metallic stents, the absence of appropriate antiplatelet therapy administration is also an important contributor to bioresorbable scaffold thrombosis.

September 2012, Absorb BVS was approved for commercial use in Netherlands and has been used in our center 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.<sup>13,14</sup> Up to June 1, 2014, a total of 733 everolimus-eluting BVS had been implanted in 469 patients in our center.

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.<sup>15</sup> 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 intraprocedural 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.<sup>16</sup> Angiographic analysis at the event included assessment of thrombolysis in myocardial infarction flow grade, thrombus burden,<sup>17</sup> 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.<sup>4,14</sup>

### 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.<sup>17,14</sup> 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 center without obvious connection to other surrounding struts,<sup>7,18</sup> 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 $\pm$ SD, median [interquartile 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 discontinuation  $<1$  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 suspected in 2, whereas 4 patients with very late thrombosis after 1 year were only receiving aspirin.

**Table 1. Clinical and Demographic Characteristics**

	BVS (n=14)	Metal (n=15)	P Value
Age, y	60.2±10.5	64.2±11.6	0.35
Male, n (%)	14 (100)	10 (66.7)	0.042
Type, n (%)			0.70
Acute	4 (28.6)	2 (13.3)	
Subacute	2 (14.3)	4 (26.7)	
Late	5 (35.7)	5 (33.3)	
Very late	3 (21.4)	4 (26.7)	
Time to event, d	152.6±210.1	232.0±237.9	0.35
Clinical syndrome (baseline)			0.79
Stable angina, n (%)	5 (35.7)	3 (20.0)	
Unstable angina, n (%)	1 (7.1)	2 (13.3)	
NSTEMI, n (%)	3 (21.4)	4 (26.7)	
STEMI, n (%)	5 (35.7)	6 (40.0)	...
Clinical syndrome (scaffold/stent thrombosis)			0.48
UA, n (%)	0 (0)	1 (6.7)	
NSTEMI, n (%)	7 (50.0)	5 (33.3)	
STEMI, n (%)	7 (50.0)	9 (60.0)	
Antiplatelet therapy at scaffold/stent thrombosis*			
Aspirin, n (%)	11 (78.6)	12 (92.3)	0.99
P2Y12 inhibitor, n (%)			0.58
Clopidogrel	3 (21.4)	5 (38.5)	
Prasugrel	5 (35.7)	3 (23.1)	
Ticagrelor	1 (7.1)	0 (0)	
Oral anticoagulation, n (%)	3 (21.4)	1 (6.7)	0.33
CAD risk factors			
Hypertension, n (%)	9 (64.3)	5 (35.7)	0.26
Dyslipidemia, n (%)	6 (42.9)	7 (50.0)	0.99
Diabetes mellitus, n (%)	1 (7.1)	6 (42.9)	0.08
Smoking, n (%)	6 (42.9)	2 (14.3)	0.21
Family history of CAD, n (%)	5 (35.7)	5 (35.7)	0.99
Comorbidities			
Prior cerebrovascular accident, n (%)	3 (21.4)	2 (13.3)	0.60
Peripheral vascular disease, n (%)	1 (7.1)	0 (0)	0.99
Kidney disease, n (%)	0 (0.0)	2 (14.3)	0.48
Prior MI, n (%)	2 (14.3)	5 (35.7)	0.39
Prior PCI, n (%)	2 (14.3)	4 (28.6)	0.65
Prior CABG, n (%)	0 (0.0)	0 (0)	...
COPD, n (%)	1 (7.1)	1 (7.1)	0.99

Values are presented as mean±SD or n (%). BVS indicates bioresorbable vascular scaffold; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; and UA, unstable angina.

\*For 2 patients in the metallic stent group, poor compliance was suspected but not confirmed.

**Angiographic and Procedural Characteristics**

Angiographic and procedural characteristics of baseline and repeat procedure are reported in Tables 2 and 3, respectively. Pre- and postdilation was used more frequently in

**Table 2. Angiographic and Procedural Characteristics at Baseline Implantation**

Angiographic Characteristics	BVS (n=14)	Metal (n=15)	P Value
Vessel, n (%)			0.37
LAD	9 (64.3)	6 (40.0)	
LCx	3 (21.4)	4 (26.7)	
RCA	2 (14.3)	5 (33.3)	
Bifurcation	3 (21.4)	4 (26.7)	0.99
Ostial LAD/LCx lesion	6 (42.9)	5 (33.3)	0.71
AHA/ACC classification			0.17
A/B1	4 (28.6)	1 (6.7)	
B2/C	10 (71.4)	14 (93.3)	
Preprocedure			
TIMI flow grade, n (%)			0.57
0	5 (35.7)	5 (33.3)	
1	0 (0)	2 (13.3)	
2	1 (7.1)	1 (6.7)	
3	8 (57.1)	7 (46.7)	
Total occlusion (n=10)			0.30
RVD, mm	2.98±0.22	2.66±0.59	
Non-total occlusion (n=19)			
RVD, mm	2.61±0.35	2.60±0.66	0.95
Minimal lumen diameter, mm	0.94±0.26	0.96±0.29	0.89
Diameter stenosis, %	64.1±9.8	61.8±10.9	0.64
Lesion length, mm	19.38±9.04	24.16±10.72	0.25
Postprocedure			
TIMI flow grade, n (%)			0.99
0	0 (0)	0 (0)	
1	0 (0)	0 (0)	
2	0 (0)	1 (7.1)	
3	14 (100)	13 (92.9)	
RVD, mm	2.62±0.33	2.56±0.59	0.71
Minimal lumen diameter, mm	2.32±0.22	2.23±0.36	0.44
Diameter stenosis, %	10.9±9.5	11.7±10.5	0.82
Acute gain, mm	1.29±0.38	1.45±0.35	0.35
Dissection, n (%)	2 (14.3)	3 (21.4)	0.99
Side-branch occlusion	1 (7.1)	1 (7.1)	0.99
Procedural data			
Predilation, n (%)	13 (92.9)	7 (50.0)	0.033
Postdilation, n (%)	7 (50.0)	0 (0)	0.006
Thrombus aspiration, n (%)	4 (28.6)	5 (35.7)	0.99
OCT guidance, n (%)	5 (35.7)	0 (0)	0.041
Overlap, n (%)	3 (21.4)	4 (26.7)	0.99
Bifurcation intervention, n (%)			0.99
T-stenting	1 (7.1)	1 (6.7)	
Balloon dilation of side-branch ostium	1 (7.1)	1 (6.7)	
Mean scaffolds/stents per patient, n	1.4±0.6	1.4±0.5	0.84
Total scaffold/stent length per patient, mm	28.57±14.56	30.29±15.91	0.77
Mean scaffold/stent diameter per patient, mm	3.18±0.27	2.90±0.47	0.06

All values presented as n (%) or mean±SD. ACC indicates American College of Cardiology; AHA, American Heart Association; BVS, bioresorbable vascular scaffold; LAD, left anterior descending artery; LCx, left circumflex artery; OCT, optical coherence tomography; RCA, right coronary artery; RVD, reference vessel diameter; and TIMI, thrombolysis in myocardial infarction.

**Table 3. Angiographic Characteristics at Thrombosis**

Angiographic Characteristics	BVS (n=14)	Metal (n=15)	P Value
TIMI flow grade, n (%)			0.47
0	9 (64.3)	10 (66.7)	
1	2 (14.3)	3 (20.0)	
2	2 (14.3)	0 (0)	
3	1 (7.1)	2 (13.3)	
Thrombus burden index, n (%)			0.47
0	0 (0)	0 (0)	
1	0 (0)	0 (0)	
2	2 (14.3)	1 (6.7)	
3	3 (21.4)	2 (13.3)	
4	0 (0)	2 (13.3)	
5	9 (64.3)	10 (66.7)	
Total occlusion (n=19)			
RVD, mm	2.93±0.32	2.37±0.69	0.042
Non-total occlusion (n=10)			
RVD, mm	2.42±0.66	2.61±0.36	0.59
Minimal lumen diameter, mm	0.90±0.17	0.94±0.97	0.93
Diameter stenosis, %	60.0±15.0	66.0±33.5	0.73

All values presented as n (%) or mean±SD. BVS indicates bioresorbable vascular scaffold; RVD, reference vessel diameter; and TIMI, thrombolysis in myocardial infarction.

BVS compared with metallic stents (predilation: 92.9% versus 50.0%;  $P=0.033$  and postdilation: 50.0% versus 0%;  $P=0.006$ ), with a trend for higher scaffold diameter in BVS (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.

### 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 mm<sup>2</sup> [2.61–6.08 mm<sup>2</sup>] versus 5.84 mm<sup>2</sup> [4.11–7.58 mm<sup>2</sup>];  $P<0.001$ ) and scaffold area (7.63 mm<sup>2</sup> [6.32–8.95 mm<sup>2</sup>] versus 8.14 mm<sup>2</sup> [6.83–9.46 mm<sup>2</sup>];  $P<0.001$ ) compared 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 mm<sup>2</sup> [0–3.44 mm<sup>2</sup>] versus 0.44 mm<sup>2</sup> [0.00–6.70 mm<sup>2</sup>];  $P=0.18$ ).

**Table 4. OCT Findings at Thrombosis**

	BVS (n=9)	Metal (n=5)	P Value
Baseline characteristics in OCT subgroup			
Age, y	60.3 [53.1–67.3]	64.0 [59.0–73.0]	0.44
Male, n (%)	9 (100)	3 (60.0)	0.11
Type, n (%)			0.40
Acute	1 (11.1)	0 (0)	
Subacute	1 (11.1)	2 (40.0)	
Late	5 (55.6)	3 (60.0)	
Very late	2 (22.2)	0 (0)	
Time to event, d	129.0 [24.5–319.5]	139.0 [6.5–227.5]	0.99
OCT variables			
Analyzed struts, n	222 [76.5–310.5]	202 [81.5–514.5]	0.80
Minimum lumen area, mm <sup>2</sup>	1.87 [0.92–3.23]	1.42 [0.98–3.25]	0.90
Mean lumen area, mm <sup>2</sup>	4.77 [3.72–6.83]	5.33 [3.87–5.72]	0.90
Minimum scaffold/stent area, mm <sup>2</sup>	6.88 [5.10–7.24]	4.87 [2.97–5.72]	0.07
Mean scaffold/stent area, mm <sup>2</sup>	7.59 [6.86–8.95]	6.49 [5.10–7.23]	0.11
Ratio of minimum scaffold/stent area to reference area	0.93 [0.73–1.12]	0.82 [0.52–1.36]	0.54
Ratio of minimum scaffold/stent diameter to nominal diameter	0.87 [0.84–0.89]	0.83 [0.66–0.89]	0.53
Malapposition area, mm <sup>2</sup>	0.13 [0.04–0.26]	0.05 [0–0.31]	0.86
Mean neointimal/attached thrombus area, mm <sup>2</sup>	1.70 [1.28–2.63]	1.48 [0.93–2.19]	0.34
Malapposed struts, %	2.50±3.27	4.63±4.70	0.48*
Malapposition distance, μm	293±257	287±271	0.36*
Scaffolds/stents with any malapposed strut, n (%)	5 (55.6)	4 (80.0)	0.58
Scaffolds/stents with >5% malapposed struts, n (%)	2 (22.2)	1 (20.0)	0.99
Thrombus, n (%)	8 (88.8)	5 (100)	0.99
Scaffold discontinuity, n (%)	2 (22.2)		

Values presented as n (%), median [IQR], or mean±SD. BVS indicates bioresorbable vascular scaffold; IQR, interquartile range; and OCT, optical coherence tomography.

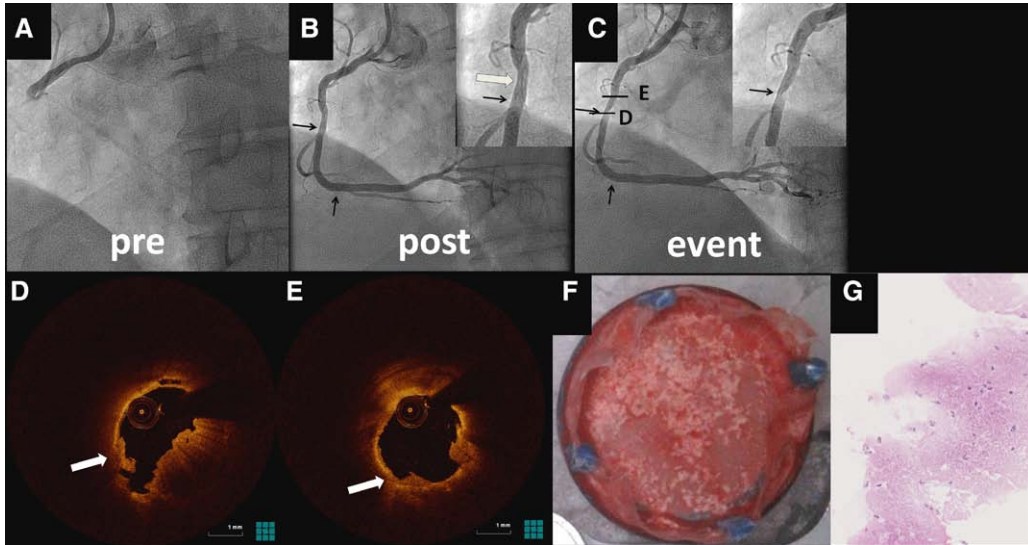
\* $P$  values calculated with multilevel regression using within-patient and within-frame intercepts as random effects.

### 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 predilated 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



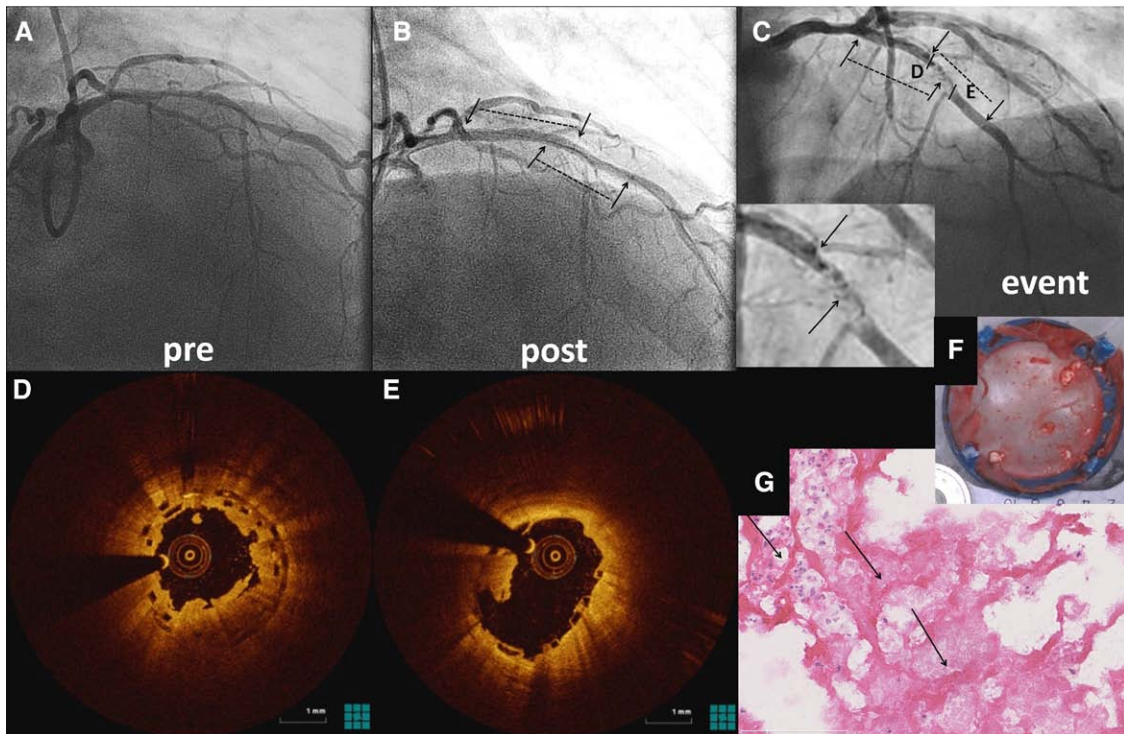
**Figure 1.** Acute thrombosis because of incomplete lesion coverage. **A**, Preprocedural and **(B)** postprocedural angiogram after bioresorbable vascular scaffold implantation in a ST-segment–elevation myocardial infarction patient undergoing primary percutaneous coronary intervention. Mild haziness 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.

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 mm<sup>2</sup>). In 1 case,

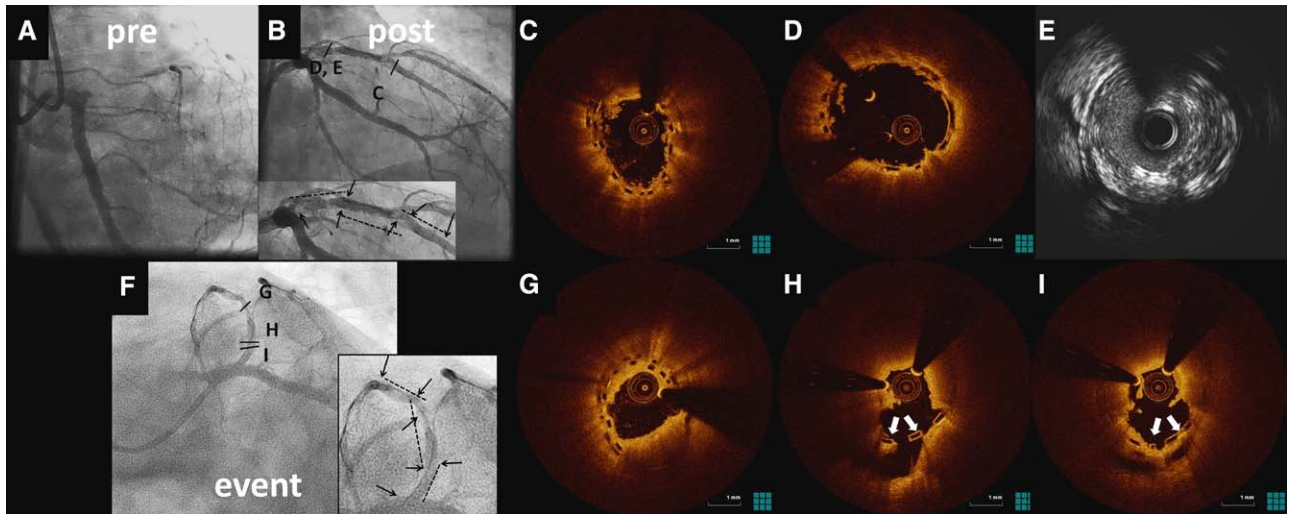
there were no findings suggesting suboptimal implantation, but there was suspicion of poor compliance with DAPT.

*(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



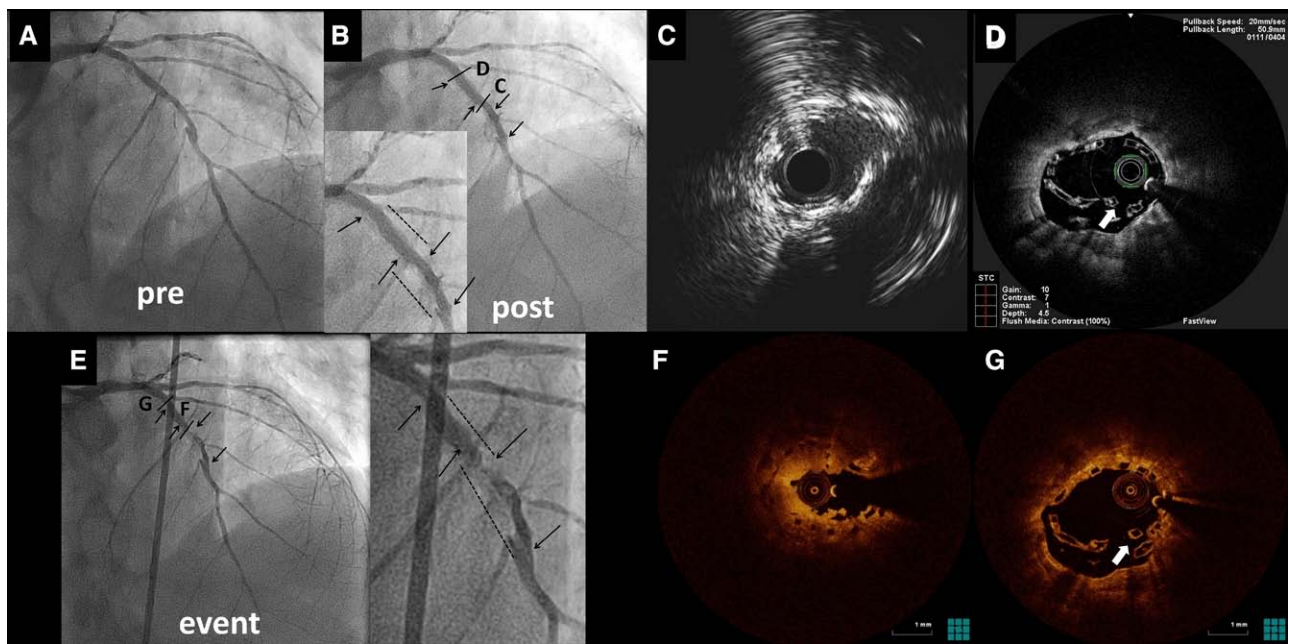
**Figure 2.** Subacute bioresorbable vascular scaffold thrombosis in extensive strut overlap. **A**, Preprocedural and **(B)** postprocedural angiogram at baseline. **C**, Angiogram at event showing contrast deficit in the scaffolded segment. **D and E**, Optical coherence tomography demonstrates thrombus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



**Figure 3.** Late bioresorbable vascular scaffold (BVS) thrombosis and malapposition. BVS implantation in a total left anterior descending artery occlusion with postdilation (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). Postdilation 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).

II in the Data Supplement). In most patients, (very) late BVS thrombosis was 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,<sup>19</sup> possibly

resulting from balloon dilation of the scaffolded segment after the index 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 underexpanded 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



**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 mm<sup>2</sup>; F), whereas the fracture site remains free of thrombus (G).

malapposition (8.6% malapposed struts) and intrascaffold 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 very late metallic stent thrombosis, baseline or follow-up angiography did not suggest any mechanical issues, while intravascular imaging was not performed.

### 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 favorable BVS long-term healing response<sup>4,7</sup> and clinical results comparable with metallic DES,<sup>5,6</sup> 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,<sup>8,9</sup> 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 thrombosis<sup>12</sup> 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 coverage 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.<sup>20–22</sup> 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  $\mu\text{m}$ ) and bench observations of increased thrombogenicity of thick-strut stents which is more pronounced at overlap sites,<sup>21</sup> together with histological observations of Zahn-lines in the aspirates, indicate a potential involvement of flow disturbances induced by long overlap and make a case for minimizing overlap 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.<sup>23</sup> It is important however to note that imaging guidance during the procedure might drive the operator to excessive postdilation, 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.<sup>3,12</sup> 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<sup>24</sup>; however, there is high prevalence in patients with events,<sup>1</sup> and late malapposition in first-generation DES has been identified as predictor of very long-term adverse outcome.<sup>25</sup> In our series, malapposition in (very) late BVS thrombosis (1.9 $\pm$ 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.<sup>26</sup> Likewise, malapposition distance (486 $\pm$ 225  $\mu\text{m}$ ) was similar to metallic stents (265 $\pm$ 151  $\mu\text{m}$ ) and at the range of previously reported values in metallic DES thrombosis (mean: 350  $\mu\text{m}$ ).<sup>1</sup> 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.<sup>19</sup> Whether small

discontinuities, resulting from normal scaffold resorption, are associated with thrombosis is unclear. Notwithstanding this poorly documented association of discontinuity with thrombosis,<sup>18</sup> precautionary measures such as respecting the postdilatation 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.<sup>27</sup> 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.<sup>28</sup> 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 withdrawn in patients receiving chronic oral anticoagulation, as in 3 patients in our BVS series. Therefore, considering our observations 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,<sup>29</sup> and optimal BVS sizing and postdilating, thus avoiding underexpansion<sup>23</sup> or scaffold fracture. Moreover, similar to metallic DES, proper DAPT administration must be emphasized.<sup>27</sup> 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-center 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 center, leading to possible underestimation. As OCT was not systematically performed, it was only available for 9 of 14 patients. Routine 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.<sup>1,7</sup> 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.

### Acknowledgments

Dr Karanasos acknowledges the funding support of St Jude Medical.

### Sources of Funding

Thoraxcenter receives unrestricted grants from the Abbott Vascular and St. Jude Medical.

### Disclosures

None.

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