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REVIEW

Neoatherosclerosis
— Long-Term Assessment of Bioresorbable Vascular Scaffold —

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Although metallic stents improved the safety and efficacy of percutaneous coronary intervention (PCI), even the latest generation of drug-eluting stents (DES) is still limited by several factors. The limitations of DES are mainly related to the permanent metallic caging in vessel, chronic inflammatory response to the polymer and adverse effects of antiproliferative drug on endothelial tissue, leading to impaired physiological vasomotor response and late stent-related adverse events such as stent thrombosis and neoatherosclerosis. Bioresorbable vascular scaffold (Absorb BVS; Abbott Vascular) was designed to overcome these drawbacks of DES by disappearing from the vessel wall. Absorb BVS, however, was withdrawn from the world market because of increased incidence of scaffold thrombosis compared with DES. Importantly, only very limited long-term post-BVS implantation data are available, especially with regard to neoatherosclerosis, which can lead to very late adverse events even after resorption of the scaffold. Therefore, the goal of this review was to highlight the mid to long term clinical outcomes published to date, and to describe the features of the intimal healing process and neoatherosclerosis in the 5 years following Absorb BVS implantation, mainly based on our previous study. This may provide important information on the pathophysiology of the scaffolded vessel for clinicians, and promote identification of future bioresorbable materials for PCI that will minimize the stimulus for neoatherosclerosis.

Key Words: Bioresorbable vascular scaffold; Neoatherosclerosis; Percutaneous coronary intervention

Since the introduction of metallic stents into clinical use, these devices have substantially improved the quality of coronary revascularization and have continued evolving.[1] Drug-eluting stents (DES) led to a significant reduction in the incidence of restenosis in comparison with bare-metal stents, and improved the overall safety and efficacy of percutaneous coronary intervention (PCI).[2,3] Permanent metallic stents in a coronary artery, however, play a role in the occurrence of neoatherosclerosis, that is, a de novo atherosclerotic plaque overlying the stent, and could strongly contribute to late catch-up phenomenon and very late stent thrombosis.[4] Neoatherosclerosis is histologically characterized by an accumulation of lipid-laden foamy macrophages with or without necrotic core formation and/or calcification in the neointima and is also an accelerated process compared with atherosclerosis in native vessels.[5,6] For the purpose of overcoming these drawbacks of metallic DES, bioresorbable scaffolds (BRS) were introduced into clinical practice. They are antiproliferative DES-like devices that are designed to provide mechanical scaffolding during the first year following implantation, and are completely absorbed and disappear from the vessel after several years. The bioresorbable vascular scaffold (Absorb BVS Rev.1.1; Abbott Vascular) is the most comprehensively characterized, and was the only device available for clinical use in Japan. In 2017, the Absorb BVS was withdrawn from the world market because of unfavorable mid-term results, contrary to expectations. The concept of a resorbable stent, however, is still very attractive to cardiologists, especially PCI operators, and we have an obligation to learn from failed devices and to elucidate what will happen in the coronary artery after BVS implantation, in order to identify future bioresorbable materials and improve treatment for patients with atherosclerotic coronary artery disease. The goal of this review is therefore to summarize clinical data available for Absorb BVS to understand the characteristics of the pathophysiology of the scaffolded vessel, based mainly on our previous study,[7] including individual cases involving Absorb BVS from Shonan Kamakura General Hospital.

Absorb BVS Clinical Data

Absorb BVS was a drug-eluting BRS that consisted of 157-μm-thick struts with a poly-L-lactide backbone and a poly-D,L-lactide coating with the antiproliferative drug everolimus.[8] To date, the Absorb BVS is the most investigated BRS. Several multicenter, prospective, clinical trials compared the Absorb BVS with the Cobalt-chromium everolimus-eluting stent (CoCr-EES) Xience (Abbott

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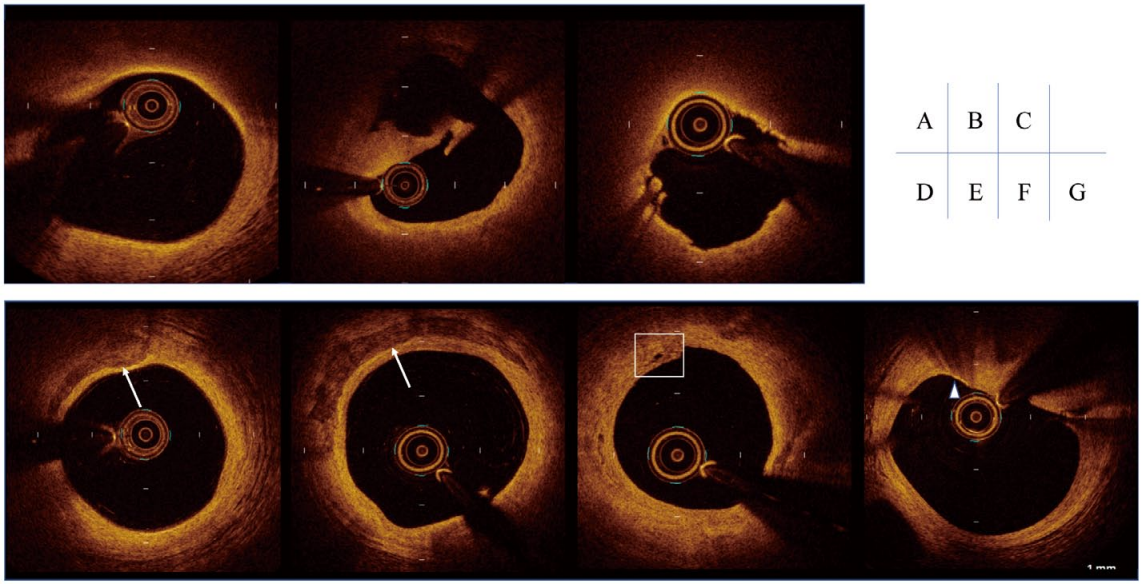

Figure 1. Typical optical coherence tomography findings of neoatherosclerosis at 5 years after Absorb bioresorbable vascular scaffold. (**A**) Lipid-laden intima is defined as a diffusely bordered, signal-poor region with overlying signal-rich bands in the intima. (**B**) Plaque rupture. (**C**) Thin-cap fibroatheroma-containing intima: fibrous cap thickness ≤65 μm at the thinnest segment and an angle of lipid tissue ≥180° with thrombus. (**D**,**E**) Calcification as a well-delineated, signal-poor region with sharp borders (white arrow). (**F**) Neovascularization as the presence of signal-poor holes or tubular structures with a diameter of 50–300 μm that are not connected to the vessel lumen (box). (**G**) Macrophage infiltration as a bright spot with a high signal variance from surrounding tissue (white arrowhead).

Vascular).[9–14] Although the rates of cardiac death and clinically driven target lesion revascularization (TLR) for the Absorb BVS were similar to those for the CoCr-EES during 1-year follow-up, a numerically higher incidence of definite or probable stent thrombosis was reported from the ABSORB trials, EVERBIO II and TROFI II trials.[10–14] In a meta-analysis of these trials, involving 3,738 patients, patients who received the Absorb BVS had a significantly higher risk of scaffold thrombosis than those with CoCr-EES (1.3% vs. 0.5%; P=0.05).[15] In addition, the AIDA trial noted a significantly higher rate of scaffold thrombosis (definite or probable) for the Absorb BVS than for the CoCr-EES through 2 years of follow-up (cumulative event rates, 3.5% vs. 0.9%; hazard ratio [HR], 3.87; 95% CI: 1.78–8.42, P<0.001).[16] Furthermore, in a larger-scale meta-analysis the incidence of device-oriented outcomes (cardiac death, target vessel-related myocardial infarction [MI] and ischemia-driven TLR) and of scaffold thrombosis were significantly higher for the Absorb BVS than for the CoCr-EES.[17,18] As a result, Absorb BVS was withdrawn from the world market in September 2017. Also, with regard to the long-term results, the ABSORB III trial confirmed increased rates of the composite of death, MI, or revascularization (HR, 1.21; 95% CI: 1.01–1.45), target vessel MI (HR, 1.41; 95% CI: 1.02–1.96) and of stent thrombosis (HR, 2.38; 95% CI: 1.05–5.39) through 5-year follow-up with Absorb BVS compared with CoCr-EES.[19]

Several studies have determined the potential risk factors of scaffold thrombosis using intra-coronary imaging, especially optical coherence tomography (OCT). In the early to mid-phase following Absorb BVS implantation, in other words, while the scaffold is still visible inside the treated coronary artery, scaffold thrombosis is mainly caused by problems during implantation, such as suboptimal vessel sizing to scaffold, over- or under-expansion and malapposition of Absorb BVS.[20–22] These factors have been reported as the risk factors for scaffold discontinuity, late malapposition and uncovered struts leading to late or very late scaffold thrombosis.[23] With the aim of overcoming early and late events deemed to be related to procedural issues, the concept of PSP (optimal pre-dilatation, vessel and device sizing, and aggressive post-dilatation) was advocated and has been evaluated.[19] To date, the results of PSP have been controversial.[16,21] Therefore, the question of whether technical features can have positive effects on BRS device outcomes remains inconclusive.

In contrast, long-term 5-year follow-up data on Absorb BVS are still scarce. Our group reported on the occurrence and progression of in-scaffold neoatherosclerosis with luminal narrowing in the 5 years after Absorb BVS 1.1 implantation.[7] Neoatherosclerosis, by its nature, can lead to very late adverse events and may affect late prognosis in patients who have undergone Absorb BVS implantation. Therefore, from the viewpoint of neoatherosclerosis, it is worth re-reviewing the Absorb BVS data at this stage.

Neoatherosclerosis of Absorb BVS

Neoatherosclerosis has recently been defined as a novel disease manifestation of atherosclerosis in the coronary artery in the neointima following stent implantation.[6] Histologically, neoatherosclerosis is characterized by an accumulation of lipid-laden foamy macrophages with or without necrotic core formation and/or calcification in the

Table. Reports of Neoatherosclerosis Following Absorb BVS Implantation

Study	Article type	No. patients	Event	Timing	Findings
Mangiameli et al[26]	Case report	n=1	VLST	15 months	Neointimal rupture with mural white thrombus
Bastante et al[27]	Case report	n=1	ISR	7 months	New lipid pools between the struts and recurrent ISR of BVS
Hiltrop et al[28]	Case report	n=1 (2 lesions)	VLST	16 months and 31 months	Heterogeneous neointima with high signal attenuation Accumulation of macrophages
Sato et al[29]	Case report	n=1	ISR	12 months	Diffusely bordered, signal-poor regions with lipid-rich plaque
Simsek et al[30]	Full article	n=1 out of 8	–	5 years	TCFA
Kang et al[31]	Case report	n=1	ISR	8 months	TCFA (appearing as intimal hyperplasia)
Yamaji et al[32]	Full article	n=36 (38 lesions)	VLST	12–43 months	Neoatherosclerosis was observed as a mechanism underlying VLST in 18.4% of lesions
Moriyama et al[7]	Full article	n=20	–	1 year and 5 years	Neoatherosclerosis proceeded with lumen narrowing ≤5 years Mainly involving lipid including TCFA, calcification and neovascularization

BVS, bioresorbable vascular scaffold; ISR, in-stent restenosis; TCFA, thin-cap fibroatheroma; VLST, very late stent thrombosis.

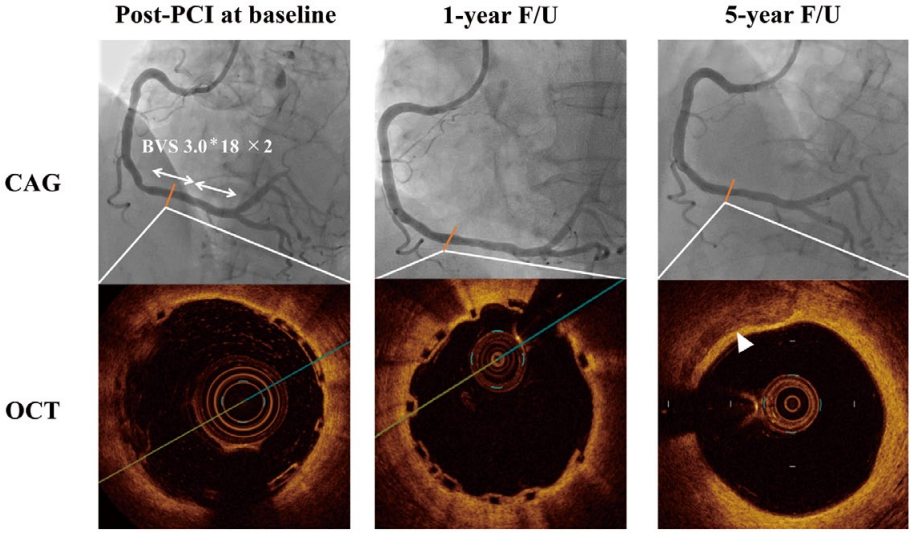

Figure 2. In-scaffold calcium growth at 5 years, in a 73-year-old woman with angina pectoris. Two Absorb bioresorbable vascular scaffolds rev.1.1 3.0×18mm were implanted at the distal right coronary artery with sufficient scaffold expansion. At 1-year follow-up, optical coherence tomography (OCT) showed good expansion of scaffold without any malapposition. At 5 years, scaffolds were not visible on OCT. Calcium growth (white arrowhead) was observed in neointimal tissue (≤200 μm from the end-luminal border). CAG, coronary angiography; F/U, follow-up; PCI, percutaneous coronary intervention.

neointima.[24] OCT enables the best characterization of neointimal tissue within stents due to its superior axial resolution (10–20 μm). For quantitative OCT analysis, neoatherosclerosis is defined as lipid-laden plaque including thin-cap fibroatheroma (TCFA) with or without intimal rupture and/or thrombus, and/or calcific plaque with or without neovascularization and/or macrophages.[25] Typical features of neoatherosclerosis at 5 years following Absorb BVS are shown in **Figure 1**. Data regarding neoatherosclerosis after Absorb BVS implantation are still very limited (**Table**).[7,26–32] To the best of our knowledge, our previous study first and comprehensively described the incidence of neoatherosclerosis at 5 years following Absorb BVS rev.1.1 implantation on serial imaging.[7] Neoatherosclerosis was more prevalent at 5 years than at 1 year (1 year vs. 5 years, calcification: 28% vs. 94%, P<0.01; lipid-laden plaque: 17% vs. 61%, P<0.01; TCFA: 0% vs. 22%, P<0.02, respectively) on OCT follow-up.[7] Here, we discuss each of the major findings of neoatherosclerosis and vasomotor response following Absorb BVS implantation.

Pathologically, calcification occurs during cell death or when localized to peri-strut regions involving fibrin, especially after DES implantation.[5,33] Progression of calcification is one of the main findings suggestive of neoatherosclerosis following metallic stent implantation. Morphological characteristics vary widely from microcalcification to fragmented or sheet calcification.[5] In our study, calcification was the most frequent component of neoatherosclerosis in the in-scaffold segment rather than in the out-scaffold segment 5 mm adjacent to the edge of the

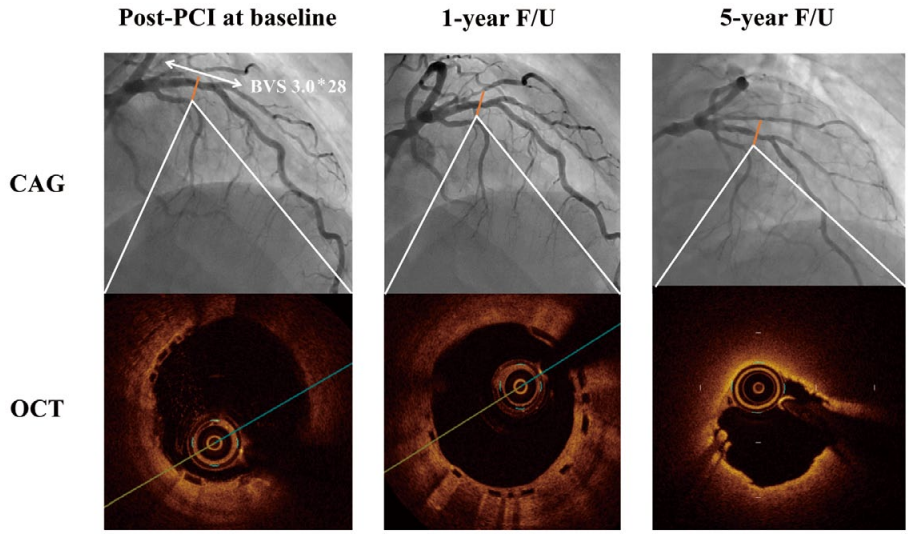

Figure 3. In-scaffold thin-cap fibroatheroma (TCFA) at 5 years, in a 65-year-old man with angina pectoris. Absorb bioresorbable vascular scaffold (BVS) rev.1.1 3.0×28 mm was implanted at the proximal left anterior descending coronary artery with sufficient expansion of scaffold. At 1-year follow-up, optical coherence tomography (OCT) showed sufficient expansion of BVS and intimalization over scaffold. At 5 years, although the scaffolds were completely absorbed, TCFA was identified with moderate luminal narrowing on OCT. CAG, coronary angiography; F/U, follow-up; PCI, percutaneous coronary intervention.

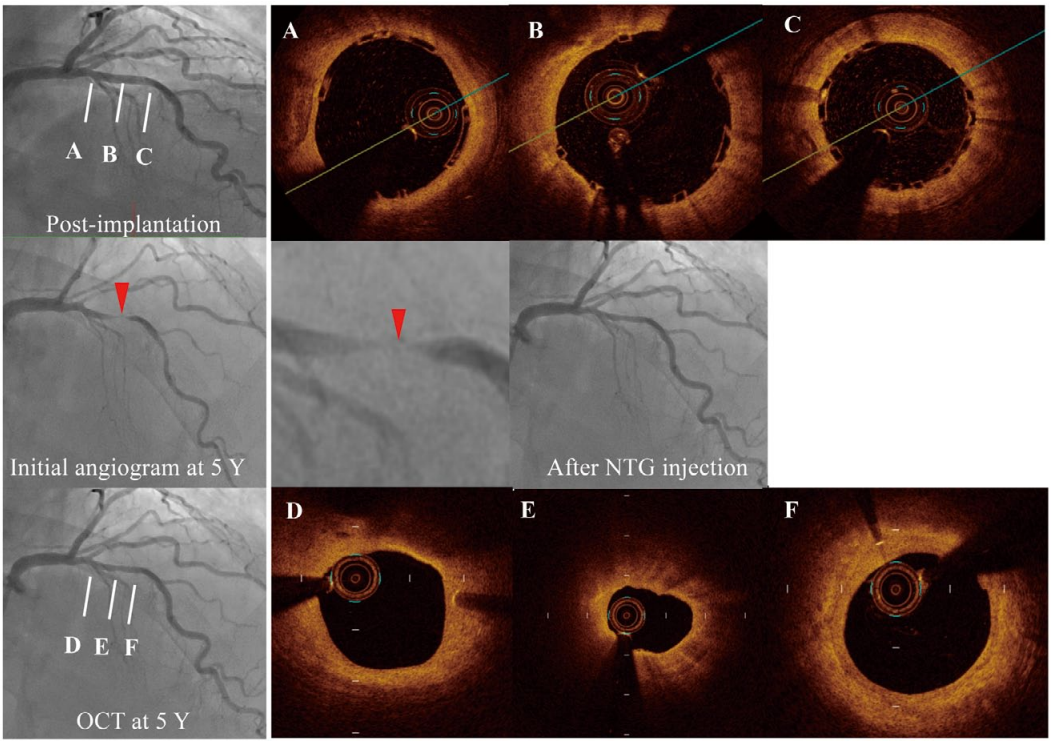

Figure 4. In-scaffold vasospastic angina at 5 years, in a 78-year-old man who had undergone percutaneous coronary intervention with bioresorbable vascular scaffold (BVS) 3.0×18 mm in significant organic stenosis of the proximal left anterior descending coronary artery. (**A**–**C**) Coronary angiography (CAG) and optical coherence tomography (OCT) showed excellent results. At 5 years after the index procedure, he was referred from the other hospital because of frequent atypical chest pressure. CAG indicated significant stenosis in the in-scaffold segment (red arrowhead). After nitroglycerine (NTG) injection, the lesion was fully expanded with resolution of symptoms. (**E**) On detailed observation, OCT confirmed neoatherosclerosis including lipid-plaque with luminal narrowing. (**D**,**F**) Proximal and distal edge of BVS. This patient was diagnosed with vasospastic angina, and an oral calcium channel blocker improved the chest symptom.

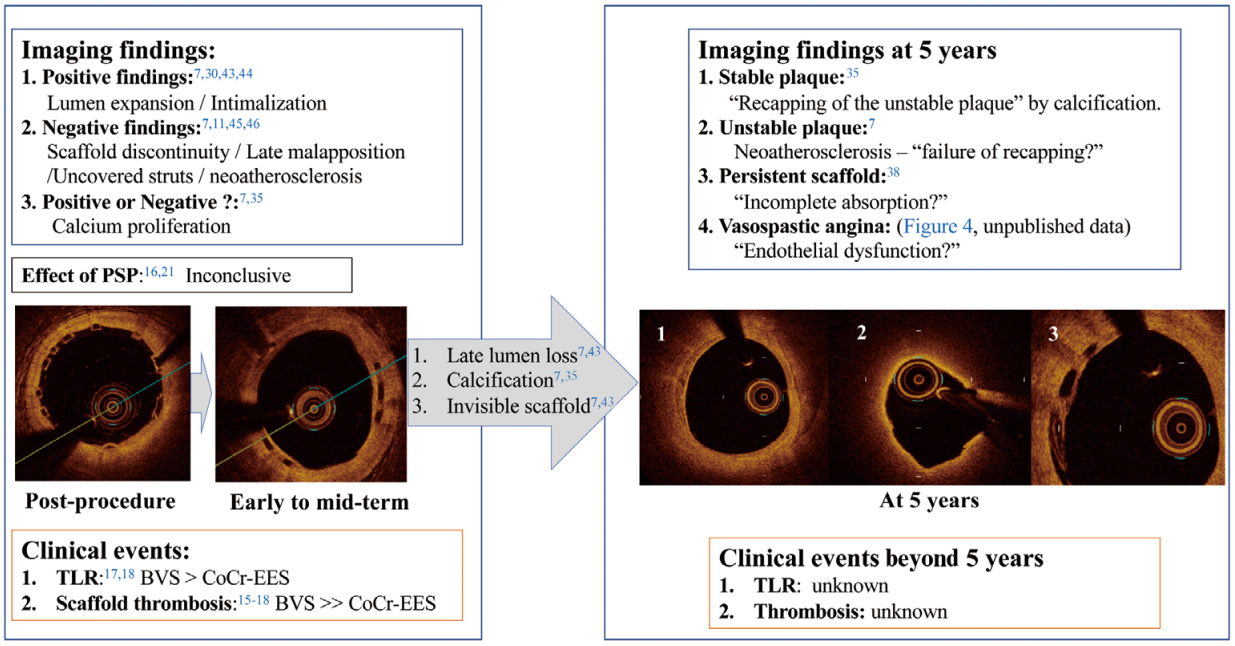

Figure 5. Summary of clinical and imaging data following Absorb bioresorbable vascular scaffold (BVS) implantation. CoCr-EES, Cobalt-chromium everolimus-eluting stent; PSP, pre-dilatation, sizing and post-dilatation; TLR, target lesion revascularization.

BVS.[7] On cross-sectional (CS) quantitative analysis (CS at 1 year, n=4,777; at 5 years, n=4,236), the proportion of calcification significantly increased from 0.4% (CS, n=16) at 1 year to 23.1% (CS, n=980) at 5 years (P<0.01) in the in-scaffold segments, along with a significant increase in its arc and area (arc, 42.2±15.6° vs. 68.4±29.5°, P<0.01; area, 0.24±0.18 mm^2 vs. 0.55±0.27 mm^2, P<0.01). A typical case of calcium proliferation at 5 years is presented in **Figure 2**. Moreover, serial coronary computed tomography analysis confirmed significant growth of calcification in the scaffolded vessel. The vasomotor response to nitroglycerine (NTG) in the in-scaffold segment was impaired compared with that in the out-scaffold segment,[7] indirectly supporting the existence of neoatherosclerosis, especially in advanced coronary calcification, as previously reported.[7] Histological studies have clearly shown growth of calcification in preclinical animal model from 3 months to 42 months after implantation of the Absorb BVS.[34] This could support the results of our reports.[7] In contrast, Zeng et al noted contradictory results, in which calcium growth was similar between the in- and out-scaffold segments from baseline to 5 years on intravascular ultrasound echogenicity analysis (Δcalcium area: in-scaffold, Δ=0.21 mm^2; out-scaffold, Δ=0.22 mm^2; P=0.881).[35] Also, they stated that new calcified plaque should not be confused with neoatherosclerosis.[35] Moreover, the phenomenon of "recapping of the underlying plaque" transforms the unstable plaque phenotype to a stable one. First, these articles by us and Zeng et al have limitations because of the technology used to assess calcification. This might explain the discrepancies between these reports. Second, we confirmed that calcification exists together with vulnerable plaque, such as lipid including TCFA and neovascularization. Hence, this finding may be associated with the failure to recap the underlying plaque after Absorb BVS rev.1.1 implantation.

On CS-quantitative analysis, the proportion of lipid-laden plaque significantly increased from 0.9% (CS, n=36 out of 4,777) at 1 year to 11.6% (CS, n=492 out of 4,236) at 5 years (P<0.01) in the in-scaffold segments, along with a significant increase in its arc and a decrease of cap thickness (arc, 38.7±16.8° vs. 129.1±58.4°, P<0.01; cap thickness, 172.1±24.1 μm vs. 91.8±46.9 μm, P<0.01; **Figure 3**).[7] A previous study reported on the time course of neoatherosclerosis after DES implantation.[36] At 48-month follow-up, 75% of all lesions with 50% diameter stenosis had lipid plaque and neovascularization.[36] In-stent lipid-laden neoatherosclerosis is frequently observed in patients with very late stent thrombosis (VLST) following revascularization using metallic stent. Especially, in-stent plaque rupture was identified as the dominant pathological mechanism causing VLST in 30% of patients.[36] In a previous analysis of patients with VLST who had undergone OCT, Taniwaki et al reported that neoatherosclerosis (observed in 27.6% of patients) was a causative factor in the occurrence of VLST following DES implantation.[25] In another OCT analysis, neoatherosclerosis was also found to be the most frequent cause of VLST (34.7%), followed by malapposition (33.7%) and uncovered strut (24.5%).[37] In terms of VLST following BVS implantation, Yamaji et al reported on the frequency of the underlying mechanism of VLST in the INVEST registry.[32] Neoatherosclerosis was observed as the underlying mechanism of VLST in 18.4% of lesions at 26.9±11.3 months after BVS implantation. In a median 4.7-year follow-up, scaffold discontinuity was the most common mechanism underlying VLST (42%), followed by strut malapposition (18%).[32] Theoretically, scaffold is completely absorbed by 5 years, with the exception of a rare case of persistent scaffold at >5 years.[38] Therefore,

after resorption of the scaffold, only neoatherosclerosis would be a potential mechanism of VLST after BVS. Further studies with longer follow-up are warranted to investigate this major concern.

After metallic stent implantation, vasomotor response at the stented segment is obviously absent. Absorb BVS was developed to overcome this absence of vasomotion at the stented segment. The ability of the artery to respond to vasodilator stimuli may play an important role in physiological recovery. Small studies of patients with Absorb BVS, however, have produced mixed results.[39,40] Gomez-Lara et al presented data on the 3-year coronary artery assessment of the infarcted-related artery vasomotion treated with Absorb BVS or CoCr-EES.[41] Vasomotion was assessed using acetylcholine (endothelium-dependent reaction) or NTG (endothelium-independent reaction) injection. At 3 years, 60% of patients had paradoxical vasoconstriction in response to acetylcholine, and this was significantly more often observed in the Absorb BVS group than in the CoCr-EES group (77.8% vs. 25.0%, P=0.008). NTG-mediated vasodilatation was either unchanged or preserved with the Absorb BVS.[41] This suggests that partial resorption of the scaffold could allow more artery motion with the Absorb BVS than with the metallic stent. In terms of 5-year assessment, two reports investigated vasomotor response after NTG injection.[7,40] Dudek et al confirmed a numerical increase in vasomotor response to NTG from 2 to 5 years after Absorb BVS on quantitative coronary angiography (QCA) according to mean lumen diameter (mean in-scaffold lumen diameter: 2 years, 0.03±0.09 mm; 3 years, 0.05±0.12 mm; 5 years, 0.07±0.08 mm, P=0.40). The degree of vasomotor response in the in-scaffold segment, however, was lower compared with the adjacent segments,[40] and our data also support this: we confirmed that a significantly smaller change was observed for the in-scaffold than for the out-scaffold segment after NTG injection at 5 years after Absorb BVS implantation on QCA according to mean lumen diameter (Δ in-scaffold, +0.009±0.012 mm vs. Δ out-scaffold, +0.14±0.14 mm, P<0.01), which could further support the existence of neoatherosclerosis.[7] Moreover, we encountered one case of in-scaffold vasospastic angina (VSA) deemed to be based on neoatherosclerosis at 5 year after BVS implantation (**Figure 4**; Shonan Kamakura General Hospital, N.M., K.S., Y.T., and S.S., unpublished data 2019). Although the pathogenesis of VSA has not been fully elucidated, endothelial dysfunction based on atherosclerosis has been proposed as one of the major mechanisms of VSA.[42] Hence, vasomotor response in the late phase after BVS implantation should be investigated as with neoatherosclerosis in the future study of BRS.

Here, we have summarized the clinical and imaging data for the Absorb BVS (**Figure 5**). We found that in-scaffold neoatherosclerosis mainly consists of lipid including TCFA, calcification, and neovascularization at 5 years after BVS resorption. The neointima of the BVS was involved in vulnerable plaque in the late phase.[7] The development of neoatherosclerosis is a conceptually unanticipated finding after BVS deployment. Further study is needed to identify biomaterial for PCI that will minimize the stimulus for neoatherosclerosis with advances in systemic pharmacotherapy to prevent atherosclerosis. Moreover, careful long-term follow-up beyond 5 years after BVS implantation is needed, and larger studies are warranted to assess the association between neoatherosclerosis and long-term clinical events after BVS implantation.

Disclosures

The authors declare no conflicts of interest.

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