Potentially increased incidence of scaffold thrombosis in patients treated with Absorb BVS who terminated DAPT before 18 months

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Eurointervention. 2017 Jun 2

ABSTRACT

Aims

To investigate the impact of dual antiplatelet therapy (DAPT) termination on late and very late scaffold thrombosis (ScT) in patients treated with Absorb bioresorbable vascular scaffold (BVS).

Methods and Results

Data of registries of 3 centers were pooled (808 patients). To investigate the effect of DAPT termination on ScT after a minimum of 6 months, we selected a subgroup ('DAPT study cohort' with 685 patients) with known DAPT status > 6 months and excluded the use of oral anticoagulants and early ScT. In this cohort, definite/ probable ScT incidence for the period on DAPT was compared to ScT incidence after DAPT termination. ScT incidence was 0.83 ScT/ 100 py with 95% confidence interval (CI): 0.34-1.98. After DAPT termination, the incidence was higher (1.77/ 100 py; 95% CI: 0.66-4.72), compared to the incidence on DAPT (0.26/ 100 py, 95% CI: 0.04-1.86; p=0.12) and increased within the month after DAPT termination (6.57/ 100 py, 95% CI 2.12-20.38; p=0.01). No very late ScT occurred in patients who continued on DAPT for a minimum of 18 months.

Conclusion

Incidence of late and very late definite/ probable ScT was acceptable. Incidence was low while on DAPT but potentially higher when DAPT was terminated before 18 months.

INTRODUCTION

Bioresorbable scaffolds are the new treatment option for coronary interventions with the aim to overcome some of the limitations of metal drug-eluting stents (DES), such as very late stent thromboses (ST) and reinterventions due to polymer reactions, strut fracture, neoatherosclerosis and inflammation.

The Absorb bioresorbable vascular scaffold (BVS, Abbott Vascular, Santa Clara, California, USA) has been most intensively studied. Multiple meta-analyses, showed comparable one-year outcomes for target lesion failure (TLF) of BVS versus cobalt-chromium based everolimus eluting Xience metal stent (CoCr-EES; Abbott Vascular, Santa Clara, CA, USA) in selected patients. Numbers of scaffold thrombosis (ScT) and target vessel MI tended to be higher in BVS group. [1-3]_ENREF_2 In populations reflecting real-world patients [4-8], ScT occurs more frequent. More recently, concerns were expressed about the occurrence of very late (> 1 year) scaffold thrombosis (VLScT). [9, 10] In randomized controlled trials (RCT's), VLScT up to 2 years were low on one (1.6%) but higher in another (2.0%) at 3 years. [11, 12]

Dual antiplatelet therapy (DAPT) reduces the risk of local thrombotic events related to stent implantation, systemic thrombotic events, and cardiovascular mortality. In the current ESC and AHA/ ACC guidelines, a minimum DAPT duration of 6 months after DES implantation is recommended, with prolonged treatment in patients with an increased risk for thrombotic events and low bleeding risks. For BVS, the optimal DAPT duration is not yet clearly defined. [13, 14] The early studies investigating BVS applied a minimum DAPT duration of 6 months. In the more recent RCT's, a minimum duration of 12 months was implemented. [11, 15]

To summarize, data on long-term ScT outcomes after BVS implantation in real-world patients is lacking and information on optimal DAPT duration missing. To fill the gap, we describe the incidence of ScT and investigated the impact of DAPT termination on late and very late ScT in regular clinical practice.

METHODS

Population

Patients were pooled from registries of 3 Dutch centers where the Absorb BVS was used as part of daily clinical practice. The decision to treat a patient with BVS was made at the discretion of the interventional cardiologist.

The patients of the Erasmus Medical Center were derived from two investigator-initiated, single-center, single-arm registries (BVS Expand and BVS STEMI). In- and exclusion criteria have been described elsewhere. [5, 6] Patients included in the two other hospital

registries were part of local all-comers registries initiated for the control of quality of standard care following introduction of a new CE approved device.

Between September 2012 and April 2015, 808 patients treated with at least one BVS were included in this study (total cohort). To investigate specifically the association between DAPT and late events without interference of oral anticoagulants, the DAPT cohort was selected by including patients with a known DAPT status and with duration of at least 6 months, without the occurrence of early ScT and without usage of (new) oral anticoagulants ((N)OAC).

Ethics

This is an observational study, performed based on international regulations, including the declaration of Helsinki. Data were collected in an encrypted database with the approval of the local ethics committee. The Absorb BVS received the CE mark and the BVS can be currently used routinely in Europe in different settings without a specific written informed.

Procedure

PCI was performed according to current clinical practice standards. The radial or femoral approach using 6 or 7 French catheters were the principal route of vascular access. All patients were treated with unfractionated heparin (at a dose of 70-100 UI/ kg). According to the guidelines, patients with stable angina were preloaded with 300 mg of aspirin and 600 mg of clopidogrel. Patients presenting with ACS were preloaded with 300 mg of aspirin and 60 mg of prasugrel or 180 mg of ticagrelor. Previous guidelines for DES and per hospital policies were used to prescribe DAPT and this was also based on the operator's instructions.

Follow-up

Survival status was obtained from municipal civil registries. Follow-up information specific for hospitalization and major cardiovascular events was obtained through questionnaires that were mailed individual patients at 1, 6, 12 and 18 months after procedure. In case of an absent response after reminder mail, patients were called thereafter or information was gathered from general practitioners or hospitals. Information on DAPT status and the stopping date of P2Y12 inhibitor were collected. When an exact stopping date was available (through questionnaires, pharmacies, general practitioners or hospital letters), the date was used to compute the duration of DAPT. When patients did not exactly recall the precise stopping date but instead noted that he or she used DAPT for a period of one year, duration of DAPT was recorded as 365 days. In case of a patient writing that he/ she had visited the hospital, aditional medical records and discharge letters were consulted to check if any event had occurred.

Definitions

ScT was classified as ST according to the Academic Research Consortium (ARC). [16] ScT were reported reported as either acute (≤24 hours), subacute (1-30 days), late (30-365 days) and very late (>365 days). DAPT termination was described as the date on which one of the two components of DAPT (aspirin or P2Y12 inhibitor) had been terminated.

Endpoints

The primary endpoint in the DAPT study cohort was the incidence rate of definite or probable ScT beyond 6 months while the patient was either using DAPT or had terminated DAPT. This time period (6 – 18 months) was chosen because we assumed that, based on the healing process, the pathophysiology of scaffold thrombosis in the period between 6 and 18 months was similar. To investigate the time relation with DAPT more in detail, an additional analysis was performed for the first month after DAPT termination compared to the incidence rate while on DAPT.

Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation or median (25^{th}-75^{th} percentile). For each time period, the ScT incidence was calculated as the number of events divided by the sum of the follow-up times for each individual. The variable 'on DAPT' was computed as the stopping date of DAPT minus the date of the index procedure. In case of a ScT while the patient was using DAPT, 'on DAPT' was reported as days until the event. 'Off DAPT' was calculated as 18 months post-procedure (or the latest available follow-up date) minus the time period until termination of the P2Y12 inhibitor. In case of ScT while DAPT was terminated, days off DAPT were computed as follows: date of ScT minus date of DAPT termination. The cumulative incidence of study endpoints was estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All statistical tests were patient-based, two-sided and the P value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 21 (IL, US).

RESULTS

Between September 2012 and January 2015, 808 patients were included in the pooled database. The DAPT study cohort consisted of 685 patients (figure 1). Survival status in this group was known in 100% and median follow-up duration was 730 (interquartile range [IQR]: 531.8 – 923.3) days. Median duration of DAPT was 367 (IQR: 365 – 398) days and with a range from 180 to 1237 days. Hundred and thirty (19%) had a DAPT duration

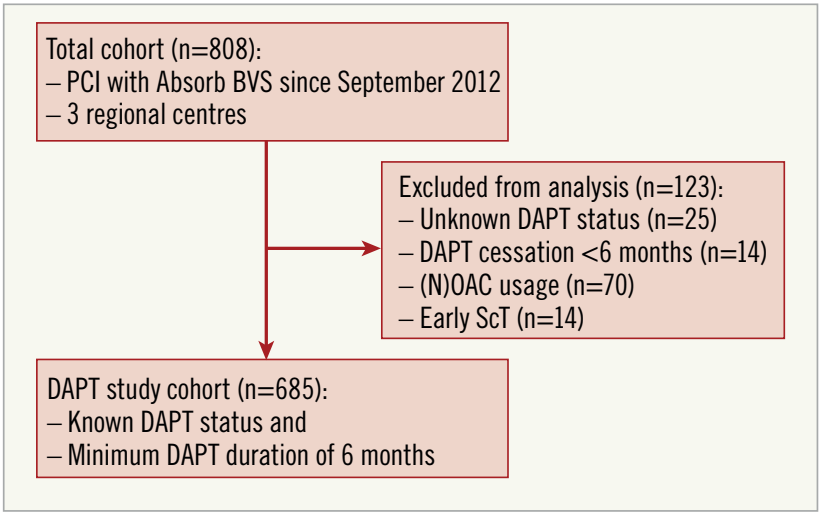

Figure 1 Study flow chart

ranging between 6 months and 1 year and 81% had a DAPT duration of at least 365 days. Eighty-nine patients (12.9%) continued DAPT until the last follow-up. Figure 3A displays the individual duration of DAPT for the patients.

Baseline characteristics

Baseline characteristics of both the full cohort and the DAPT study cohort are presented in table 1. In the DAPT study cohort, mean age was 57.9 (±10.6) years, 73.9% were male, 14.3% were diabetic, and 12.4 % had a history of myocardial infarction. Most patients (70.3%) presented with ACS. The largest part of the patients used a more potent P2Y12 inhibitor such as prasugrel or ticagrelor (76.6%). Mean number of lesions/ patients was 1.19 (±0.45). Moderate or severe lesion calcification, as assessed by angiography, was present in 32.9% and bifurcation in 21.3%. AHA/ ACC lesion classification type B2/ C was present in 45.7%.

Procedural details

Procedural details are described in table 2. In the DAPT study cohort, a total of 964 BVS were implanted. Pre-dilatation was performed in 88.3% of the patients, post-dilatation in 56.7 % and intravascular imaging (OCT or IVUS) in 31.3%. A 2.5 mm BVS was used in 21.8%. Mean scaffold diameter and mean scaffold length were 3.1 (± 0.4) mm 20.9 (± 5.8) mm. Device success and procedural success were achieved in 98.3% and 98.0%, respectively.

Table 1. Patient and lesion characteristics

	Total cohort N=808, L=949	DAPT study cohort N=685, L=813
Median follow-up in days (IQR)	729 (516 – 899.75)	730 (531.8 – 923.3)
Gender (%)		
Men	73.9	73.9
Women	26.1	26.1
Mean age in years (±SD)	58.46 (10.91)	57.9 (10.6)
Smoking (%)	50.8	51.5
Hypertension (%)	47.9	45.0
Dyslipidemia (%)	45.9	45.4
Diabetes Mellitus (%)	14.2	14.3
Family history of CAD (%)	48.8	49.5
Prior MI (%)	12.8	12.4
Prior PCI/ CABG (%)	13.7	13.4
Presentation with multivessel disease (%)	30.8	30.3
Indication for PCI (%)		
Stable angina	26.6	26.1
Unstable angina	10.1	10.0
NSTEMI	30.7	31.2
STEMI	28.6	29.1
Silent ischemia	3.9	3.6
Periphery artery disease (%)	3.8	3.2
Heart failure (%)	4.0	2.5
Renal insufficiency (%)	3.3	2.5
ASA + P2Y12 inhibitor (%)		
clopidogrel	39.8	38.3
prasugrel	38.2	38.3
ticagrelor	22.0	23.4
Median duration of DAPT in days (IQR) Min and max DAPT duration in days		367 (365 – 398) 180 - 1237
Number of lesions per patient (±SD)	1.17 (0.44)	1.19 (0.45)
Left anterior descending artery (%)	54.4	54.2
Left circumflex artery (%)	20.9	21.4
Right coronary artery (%)	24.7	24.4
Bifurcation (%)	23.0	21.3
Calcification (moderate or severe) (%)	33.7	32.9
CTO (%)	3.1	3.2

Table 1. Patient and lesion characteristics (*continued*)

	Total cohort N=808, L=949	DAPT study cohort N=685, L=813
ACC/ AHA lesion classification (%)		
A	10.3	10.3
B1	43.5	44.0
B2	28.4	27.3
C	17.8	18.4

ASA: Aspirin; CABG: coronary artery bypass grafting ; CAD: coronary artery disease; CTO: chronic total occlusion; DAPT: dual antiplatelet therapy; IQR: interquartile range; L:lesions; MI: myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; P: patients; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction

Table 2. Procedural characteristics

		Total cohort P=808, L=949	DAPT study cohort P=685, L=813
Pre-dilatation (%)		88.4	88.3
Invasive imaging at baseline (%)		30.8	31.3
Total number of scaffolds implanted		1119	964
	2.5 mm BVS (%)	22.7	21.8
	3.0 mm BVS (%)	39.2	40.7
	3.5 mm BVS (%)	38.1	37.4
Mean scaffold diameter, mm (±SD)		3.08 (0.38)	3.08 (0.38)
Mean scaffold length, mm (±SD)		20.90 (5.83)	20.94 (5.83)
Mean total scaffold length per patient, mm (±SD)		32.48 (20.99)	33.14 (21.60)
Overlap (%)		29.7	30.6
Post-dilatation (%)		55.4	56.7
Clinical device success (%)		98.0	98.3
Clinical procedure success (%)		97.2	98.0

Clinical outcomes

In the total cohort of 808 patients, 26 definite or probable ScT occurred with a cumulative event rate, described as Kaplan-Meier estimate, of 3.3% (95% CI: 2.1 – 4.5) at 18 months (figure 2). The majority (1.7%) were early ScT: acute ScT rate was 0.2% (95% CI: -0.2 – 0.6) and subacute ScT rate was 1.5% (95% CI: 0.7 – 2.3). Late and very late ScT were less frequent: 1.0% (95% CI: 0.2 – 2.0) and 0.6% (95% CI: 0.02 – 1.2) respectively. In the DAPT study cohort Kaplan-Meier estimates for late and very late ScT were similar (0.9% and 0.7% respectively).

Figure 3B shows the duration in days while off DAPT and the association with very late ScT in the DAPT study cohort. Four cases of very late definite/ probable ScT occurred: at 379 days (10 days after DAPT termination), at 416 days (35 days after DAPT termina-

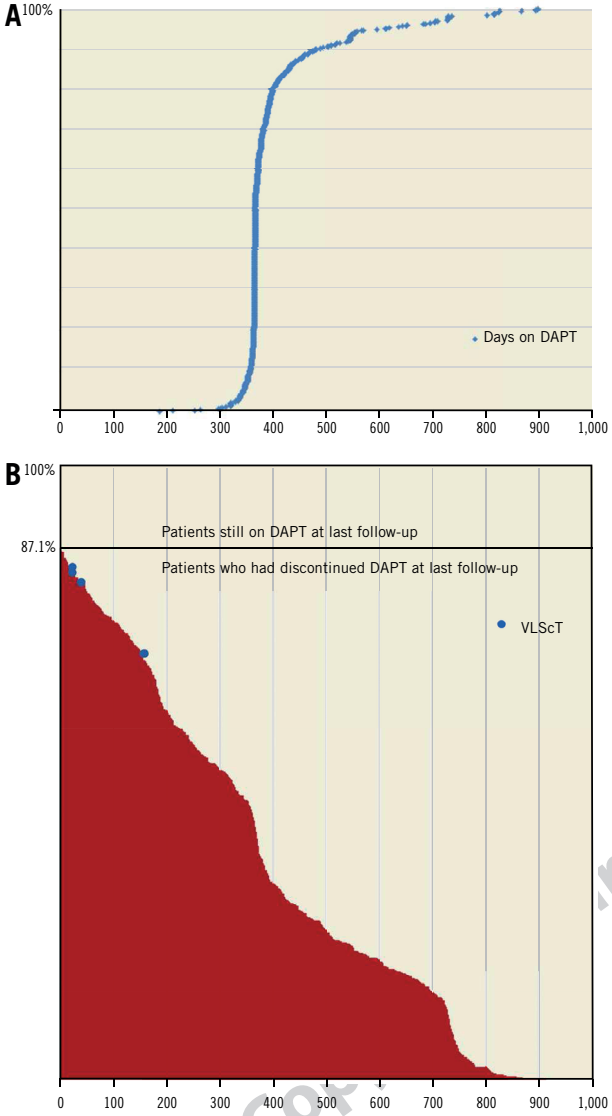

Figure 2 DAPT duration for all individual patients
A) Days on DAPT in the DAPT study cohort. B) Days off DAPT in the DAPT study cohort. Blue dots indicate the ScT timing in relation to the number of days off DAPT. VLScT: very late scaffold thrombosis.

tion) at 429 days (20 days after DAPT termination) and 526 (149 after DAPT termination). Cases have been described elsewhere. [17] These four patients were using aspirin but had terminated P2Y12 inhibitor. Their duration of DAPT was a little over 365 days. However, this was not based on a specific reason such as an increased ischemic risk. Rate of definite/ probable ScT in this particular time frame was 0.7%.

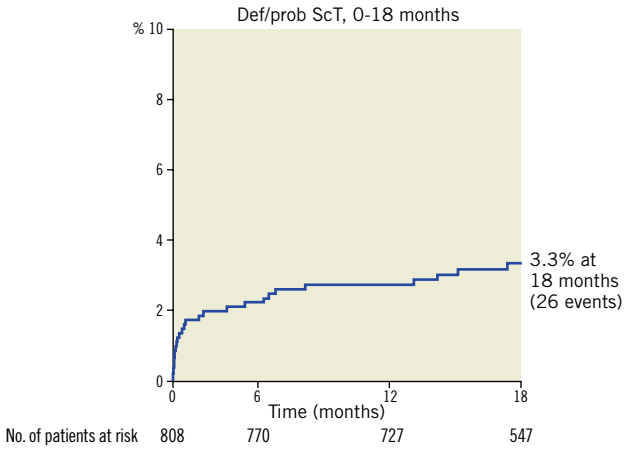

Figure 3 Cumulative ScT rate in the total cohort from the index procedure up to 18 months post procedure.
ScT: scaffold thrombosis

For reasons of comparability with current literature, incidences per 100 patient-years (py) were computed in the DAPT study cohort (figure 4, table 3). For calculating the incidence of ScT in the time period 6 - 18 months, 607.52 py were available and 5 events occurred (one late ScT and 4 very late ScT) with an incidence of 0.83/ 100 py (95% CI: 0.34 – 1.98).

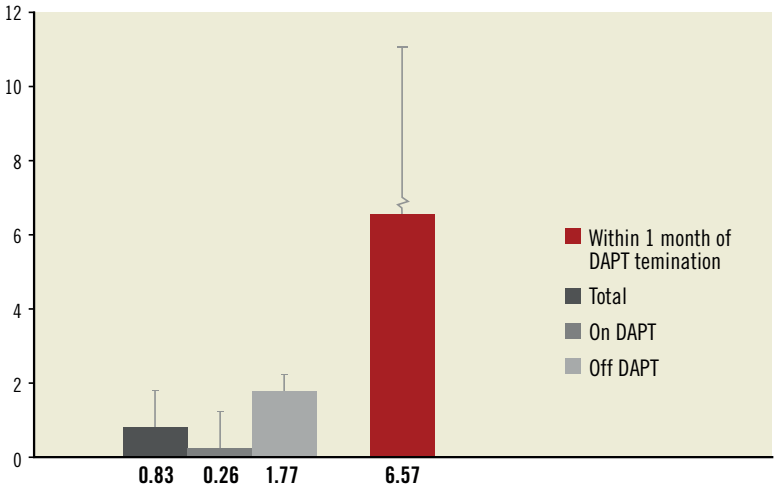

Figure 4 Incidence densities for the whole DAPT study cohort, in patients on and off DAPT and within the first month of termination in the DAPT study cohort.
DAPT: dual antiplatelet therapy.

Table 3. Incidences of definite/ probable ScT per 100 patient-years

	Incidence rates per 100 patient-years (95% CI) 6 – 18 months
Total	0.83 (0.34 - 1.98)
On DAPT period	0.26 (0.04 – 1.86)
Off DAPT period	1.77 (0.66 – 4.72)
Within 1 month of DAPT termination	6.57 (2.12 – 20.38)

DAPT: dual antiplatelet therapy; py: patient-years; ScT: scaffold thrombosis

For the period on DAPT, 381.90 py were available and 1 event occurred (at day 208). This resulted in an incidence of 0.26/ 100 py (95% CI: 0.04 – 1.86). For the period after DAPT termination, 225.62 py and 4 events were reported with ScT incidence of 1.77/ 100 py (95% CI: 0.66 – 4.72), numerically 6.8 times higher than the incidence on DAPT but not statistically significant (p=0.12).

For the incidence of ScT in the first month of DAPT termination, 45.64 py were available and 3 events occurred, which subsequently provided an incidence of 6.57/ 100 py (95% CI: 2.12 – 20.38). This was statistically significant when compared to the incidence in the on DAPT period (p=0.01). The incidence of ScT during the last month of DAPT usage was 0.

DISCUSSION

To our knowledge this is the first study that reports on the impact of DAPT termination on the occurrence of definite/ probable ScT in Absorb BVS in a clearly defined study cohort, reflecting real-world patients. The main findings of our study are as follows: 1) Incidence of definite or probable late and very late ScT in patients that are on DAPT is low; 2) All cases of very late ScT at 18 months were not using DAPT at time of the event; 3) Incidence of ScT in patients off DAPT is potentially increased within the first 18 months post-implantation, with the highest incidence within one month after termination of DAPT.

Overall incidence of late and very late ScT

Overall, late and very late scaffold thrombosis rate in this multi-center, real-world registry was acceptable and comparable to the rates in selected populations as included in approval studies for different countries. [11, 12, 15] In this study and regardless of DAPT status, the overall incidence density of late and very late def/ prob ScT were 1.0 and 1.44 per 100 patient-years respectively. A large all-comer observational cohort study, investigating ST in metal DES during 4-year follow-up, reported a late ST incidence density of

0.4 def/ prob ST per 100 patient-years in patients treated with newer-generation EES. For SES and PES, incidence densities were higher for both late (SES: 0.7/ 100 patient-years and PES: 1.5 per 100 patient-years) and very late ST (SES: 2.8/ 100 patient-years and PES: 4.0/ 100 patient-years). In this regard, late and very late ScT incidence in BVS patients seems comparable to first generation metal DES.[18]

DAPT and late events

At 18 months, there were 4 patients with VLScT, all while not using DAPT during the event. Three out of four cases appeared to be associated with DAPT termination. The incidence density was 1.79/ 100 patient-years in patients who were not continually on DAPT. Importantly, incidence of ScT within one month of DAPT termination was even higher. In the Absorb Extend study, 50% of the ScT cases were related to either premature DAPT termination or resistance to clopidogrel. [19] The ABSORB Japan trial reported two years follow-up. Two out of four patients with VLScT were not using DAPT at time of the event. In the recently published ABSORB II RCT , three-year results revealed 6 cases of VLScT. Of note, all cases of late and very late ScT occurred in patients off DAPT. Moreover, in patients who did not terminate DAPT up to 3 years, no ScT were described. [12] In our series, the relationship between the moment of DAPT termination and occurrence of VLScT was notable, with 3 out of 4 cases within 35 days of DAPT termination, a finding not so clear in the ABSORB II and ABSORB Japan trials. Thus, as reported in multiple studies, DAPT termination seems to play an important role in the occurrence of VLScT.

Possible causes late ScT

Other factors besides DAPT termination, that were associated with ScT were suboptimal implantation technique, late discontinuities, uncovered struts, neoatherosclerosis, high maximum footprint, small minimal lumen diameter, small vessels, higher % diameter stenosis, overlap, ostial lesions and decreased LVEF. [11, 20-25] Late and very late ScT while DAPT was terminated, might be explained by the high volume of implanted material with special attention the increased strut thickness, which could cause laminar flow disturbance and subsequently the triggering of platelet deposition. [26] This might be a special problem in small vessels or when full dilatation was not achieved without high pressure post-dilatation using non-compliant balloons. In early BVS-registries, there was a higher risk of malapposition, often induced by undersizing, which occurs regularly. [5] During the first large studies in BVS patients, high pressure post-dilatation with non-compliant balloons was not mandatory as result of a case where strut fractures were observed. Nowadays, a different implantation tactic for BVS is used after an optimal implantation strategy, started in January 2014, was associated with a large reduction in ScT incidence. [20, 27] Also, thinner strut BVS are currently being developed, which will mitigate the risk of ScT.

STUDY LIMITATIONS

This was a retrospective and registry data – pooled study. As the sample size is limited and numbers of this low-frequence event are small, these results should be interpreted with caution and considered hypothesis generating. More data and dedicated studies are needed to confirm our suggestion to prolong DAPT in BVS treated patients. Lastly, quantitative coronary analysis (QCA) was not available in all patients.

CONCLUSION

The incidence of probable/ definite late and very late ScT in BVS patients who are on DAPT in our study is low. However, the incidence of early ScT and also the occurrence of very late ScT are not negligible. Between 6 and 18 months, incidence of ScT in patients who terminated DAPT is potentially increased.

Impact on daily practice

As long as studies with an optimal implantation strategy haven't revealed data on safe DAPT termination before 18 months, it would be reasonable to consider extension of DAPT. Prolonging DAPT even up to three years could be a possible solution in patients with an increased risk of ischemic events and low bleeding risk (the DAPT score can be used for risk assessment [28]), as the resorption process of Absorb BVS is completed in 3 years and until that time, the polymer is still present and the risk of very late ScT is lurking. The decision whether or not to continue DAPT beyond a certain time point cannot be made by a 'one size fits all' principle and should be individual-based.

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Epilogue