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Two-year clinical outcomes of the "Italian diffuse/multivessel disease absorb prospective registry" (IT-DISAPPEARS)☆

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ABSTRACT

Background: Large prospective studies on the use of bioresorbable vascular scaffolds (BVS) for diffuse coronary artery disease are lacking. IT DISAPPEARS is a large multicentre prospective registry investigating the short and long-term outcomes of everolimus-eluting BVS in patients with long coronary lesions and/or multivessel coronary artery disease (ClinicalTrials.gov: NCT02004730). We hereby report the 2-year outcomes of the registry.
Methods: We enrolled 1002 patients with complex lesions undergoing implantation of 2040 BVS with a prespecified technique including predilation, correct sizing, and postdilation with non-compliant balloons. The primary endpoint was the rate of device-oriented composite endpoint (DOCE), consisting of cardiac death, target vessel-related myocardial infarction (MI), and ischaemia-driven target lesion revascularization (TLR). Secondary endpoints included: 1) patient-oriented composite endpoint (POCE), consisting of all-cause mortality, all infarctions and all revascularisations; 2) definite/probable scaffold thrombosis.
Results: Clinical presentation was an acute coronary syndrome in 59.8% of patients. Total BVS length implanted was 47 ± 22 mm. Postdilation of all scaffolds per patient was performed in 96.8%, while optimal implantation as per study guidelines was applied in 71.4%. Through 2-year follow-up, DOCE occurred in 9.5% of patients (cardiac death 0.6%, target vessel-related MI 5.3%, TLR 6.6%). The rate of POCE was 16.6% and of scaffold thrombosis 1.1%. Female gender, total length of coronary lesions, treatment of bifurcation lesions and use of 2.5 mm scaffolds were independent predictors of DOCE.
Conclusions: The 2-year results of IT-DISAPPEARS show that BVS may yield acceptable clinical outcomes in patients with complex coronary lesions when the implantation technique is appropriate.

1. Introduction

In recent years, excessively high rates of target lesion failure (TLF) and scaffold thrombosis with bioresorbable vascular scaffolds (BVS) were initially reported [1–3], and then confirmed up to 3 years of follow-up in randomized trials [4,5], prospective registries [6,7] and meta-analyses [8,9], leading to the fall in BVS use. We designed the

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"Italian diffuse/multivessel disease ABSORB prospective registry" (IT-DISAPPEARS) to investigate the long-term results of the implantation of the everolimus-eluting Absorb™ BVS (Abbott Vascular, Santa Clara, CA, USA) in the setting of diffuse coronary artery disease (CAD), where the potential advantages of BVS are theoretically maximised. Importantly, in this registry we mandated the use of a careful implantation technique [10], consisting of lesion predilation and high-pressure postdilation. In 2017, our registry was the first to report good 1-year clinical outcomes with BVS in patients with diffuse CAD [11]. Most recently, the ABSORB IV trial, the first randomized trial to recommend a careful scaffold implantation technique, reported non-inferior 1-year outcomes with BVS as compared to drug-eluting stents (DES) [12].

We hereby investigate at 2-year follow-up whether our accurate implantation technique allows preventing the high rates of scaffold thrombosis and TLF observed at medium-term follow-up in previous studies [4–7].

2. Methods

2.1. Patient selection and procedural features

This prospective registry was promoted by the Italian Society of Interventional Cardiology and was conducted at 38 centers (ClinicalTrials.gov number, NCT02004730). The study design was previously reported [11,13]. Briefly, between November 2014 and January 2016, consecutive patients with diffuse disease of one coronary vessel (lesion length > 24 mm) and/or disease of at least two different coronary vessels undergoing percutaneous coronary intervention with BVS were eligible for enrolment. Only de novo lesions of native coronary vessels (excluding left main trunk) with a reference diameter between 2.5 and 3.75 mm could be treated with scaffolds.

A pre-specified, careful implantation technique was recommended: (1) define reference vessel diameter (RVD) with quantitative coronary angiography and implant appropriate size scaffolds in vessels with RVD ≥2.5 mm and ≤ 3.8 mm; (2) predilate with a balloon ≤0.5 mm smaller than the RVD; (3) postdilate at high-pressure with a non-compliant balloon with a balloon:scaffold ratio of ≈1:1, up to 0.5 mm larger than the nominal scaffold diameter [10]. For a technique to be considered optimal in a patient with multiple BVS-treated lesions, it had to be applied in all lesions. In each patient, we defined "optimal technique" the presence of optimal predilation, sizing and postdilation in all BVS-treated lesions, according to the study design. Use of metallic stents was strongly discouraged in vessels treated with BVS, but allowed elsewhere. Patients with acute coronary syndromes, including ST-segment elevation myocardial infarction (MI), were included. Dual antiplatelet therapy (DAPT) was recommended for 1 year in all patients, while prolonged DAPT was left at operator's discretion. Aspirin (≥100 mg daily) was continued indefinitely.

2.2. Follow-up and endpoints

Independent study monitors remotely verified all case report forms, while an independent clinical events committee adjudicated all major adverse events. Follow-up is ongoing annually through 5 years, and is currently complete through 2 years.

The primary endpoint was the device-oriented composite endpoint (DOCE) of cardiac death, target vessel-related myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR) at 1 year [11]. By definition, DOCE corresponds to the combined endpoint of TLF used in most BVS trials. The secondary endpoints included the patient-oriented composite endpoint (POCE) (composite of all-cause mortality, all MI and all revascularizations) and scaffold thrombosis. Myocardial infarction was always considered target vessel-related, unless angiography proved that it was not related to the vessel (s) treated with BVS. Periprocedural MI was defined according to the Third Universal Definition of MI.

2.3. Statistical analysis

Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Continuous variables are described as mean ± SD and were compared by *t*-test or Mann-Whitney test, as appropriate. Patients who were lost to follow-up and in whom no known event had occurred were not included in the denominator for calculation of binary endpoints. Kaplan-Meier estimates were used to construct survival curves for the time-to-event variables, which were compared by the log-rank test. The independent predictors of DOCE and POCE were assessed by Cox proportional hazards regression analysis; variable selection for the multivariate model was performed entering all baseline and procedural characteristics in a subset selection multiple regression with hierarchical forward selection with switching. A 2-sided p value < 0.05 was used for all statistical tests to define significance. All statistical analyses were performed using NCSS 11 software (NCSS LLC, Kaysville, UT, USA).

3. Results

Baseline demographics and procedural characteristics were previously reported [11], and are summarized in Table 1 (complete data are reported in Data-In-Brief Tables 1 and 2); clinical outcomes up to 1 year are summarized in Table 2.

3.1. Clinical outcomes through 2 years

Data regarding 2-year follow-up were complete for 926 patients (92.4%). Forty-nine out of 76 patients lost at follow-up were clustered in 10 centres enrolling a total of 117 patients; of these, 7 centres enrolled <10 patients each. At 2-year follow-up, 23.1% of patients were still on DAPT. Cumulative event rates from index procedure through 2 years are shown in Table 2. Kaplan-Meier estimates of time-to-event variables are reported in Fig. 1 (estimates slightly may differ from crude incidences because of repeated events occurring in the same patients). The Kaplan-Meier estimate of the primary endpoint of DOCE was 9.4% at 2 years (Fig. 1A), while the estimate of POCE was 16.5% (Fig. 1B). Death occurred in 2.1% of patients, with 0.6% being due to cardiac causes. Target vessel-related MI occurred in 5.3% of patients and was mainly represented by periprocedural MI (2.8%); only 5 target vessel-related MI occurred between 1 and 2 years, resulting in a rather flat hazard curve (Fig. 1C). The clinical presentation was STEMI in 1 patient with definite scaffold thrombosis (3 months after DAPT cessation), requiring primary angioplasty with DES implantation, and NSTEMI in 4 patients with scaffold restenosis. Of these, 3 were treated with TLR with DES implantation (all were still on DAPT), and one with medical therapy (1 month after DAPT cessation). A few non-target vessel-related MI also occurred, with an overall 2-year MI rate of 6.2%. The 2-year estimate rate of TLR was 6.2% (Fig. 1D); the rate of non-TLR was 8.4%, for a total 12.5%

Table 1
Baseline profile and procedural characteristics.

	$N = 1002$
Age	60.0 ± 10.4
Male gender	853 (85.1%)
Chronic renal failure (eGFR <60 ml/min)	90 (9.3%)
Prior myocardial infarction	208 (20.8%)
Prior revascularization	258 (5.8%)
Acute coronary syndrome	599 (59.8%)
ST-segment elevation myocardial infarction	218 (21.8%)
Multivessel disease	572 (57.1%)
Left anterior descending artery disease	801 (80.0%)
Total lesion length, mm	40 ± 19
Vessels treated with BVS: 1	806 (80.4%)
2	176 (17.6%)
3	20 (2.0%)
Reference vessel diameter, mm	3.0 ± 0.4
Number of BVS implanted	2.0 ± 1.0
Total BVS length, mm	47 ± 22
Full plastic jacket (overlapping BVS >56 mm in a single vessel)	145 (14.4%)
Any BVS-treated bifurcation	278 (27.7%)
Any BVS-treated moderately/severely calcific lesion	140 (14.0%)
Implantation of ≥1 BVS 2.5 mm diameter	353 (35.2%)
Scaffold:Reference vessel diameter ratio	1.01 ± 0.07
Use of overlapping BVS	483 (48.2%)
Predilation	991 (98.9%)
Predilation with non-compliant balloon	343 (34.2%)
Postdilation	970 (96.8%)
Postdilation with non-compliant balloon	847 (84.5%)
IT DISAPPEARS implantation recommendations:	
Optimal predilation [balloon ≥ (RVD-0.5 mm)]	860 (85.8%)
Optimal sizing	1002 (100%)
Optimal postdilation [BVS ≤ balloon ≤ (BVS + 0.5 mm)]	818 (81.6%)
Optimal IT DISAPPEARS technique	715 (71.4%)
Anatomically complete revascularization	712 (71.1%)
Functionally complete revascularization	831 (82.9%)

Values are mean ± SD, or n (%).
BVS: bioresorbable vascular scaffold; eGFR: estimated glomerular filtration rate; PSP: predilation, sizing, postdilation; RVD: reference vessel diameter.

Table 2
Cumulative incidence of adverse events through follow-up.

	0–1 year ($N = 956$)	0–2 years ($N = 926$)
Myocardial infarction	52 (5.4%)	57 (6.2%)
Target vessel-related	45 (4.7%)	49 (5.3%)
Target vessel-related (excluding type 4a)	17 (1.8%)	21 (2.3%)
Non target vessel-related	7 (0.7%)	8 (0.9%)
Target lesion revascularization	45 (4.7%)	61 (6.6%)
Non-target lesion revascularization	60 (6.2%)	78 (8.4%)
Any revascularization	91 (9.5%)	116 (12.5%)
Stroke	2 (0.2%)	3 (0.3%)
Scaffold thrombosis	9 (0.9%)	10 (1.1%)
Definite	8 (0.8%)	9 (1.0%)
Probable	1 (0.1%)	1 (0.1%)
All-cause death	12 (1.2%)	19 (2.1%)
Cardiac death	5 (0.5%)	6 (0.6%)
DOCE	95 (9.9%)	119 (12.9%)
POCE	169 (17.6%)	210 (22.7%)
DOCE (hierarchical)	69 (7.2%)	88 (9.5%)
POCE (hierarchical)	122 (12.8%)	154 (16.6%)

Values are n (%).
DOCE: device-oriented composite endpoint; POCE: patient-oriented composite endpoint.

rate of any revascularization. Scaffold thrombosis was observed in 10 patients (1.1%), being definite in 9 and probable in 1 case. Of note, between 1 and 2 years only 1 scaffold thrombosis occurred in a diabetic patient presenting with STEMI; after recanalization, severe in-scaffold restenosis with neoatherosclerosis was documented with optical coherence tomography. Details on scaffold thromboses in the first year (all of them on DAPT) were previously reported [11]. In order to assess the potential impact of incomplete follow-up on study endpoints, we repeated the analysis on the 885 patients enrolled in the 28 centers with follow-up completeness ≥96% (858 patients followed-up; follow-up completeness 96.9%), obtaining superimposable Kaplan-Meier estimates of DOCE, POCE, target vessel-related MI and TLR at 2 years (9.5%, 15.8%, 5.0% and 6.1%, respectively) and scaffold thrombosis rate (1.1%, 9 patients).

3.2. Predictors of clinical outcomes

The variables selected by multiple regression analysis to enter Cox analysis to identify predictors of DOCE were: female gender, multivessel disease, disease of the left anterior descending artery, total lesion length, total BVS length, treatment of a long lesion, treatment of bifurcations, implantation of a 2.5 mm-diameter scaffold, and overlapping scaffolds. By multivariable analysis, female gender (HR 1.73; 95% CI 1.03–2.91; $p = 0.040$), total lesion length (by 10-mm increments) (HR 1.12; 95% CI 1.02–1.22; $p = 0.013$), implantation of at least one 2.5 mm-diameter BVS (HR 1.69; 95% CI 1.09–2.62; $p = 0.020$) and treatment of at least one bifurcation lesion (HR 1.67; 95% CI 1.08–2.59; $p = 0.022$) were independent predictors of DOCE through 2-year follow-up. Kaplan-Meier curves of DOCE stratified by presence/absence of independent predictors are depicted in Fig. 2. Clinical and procedural characteristics of the 926 patients who were followed-up through 2 years,

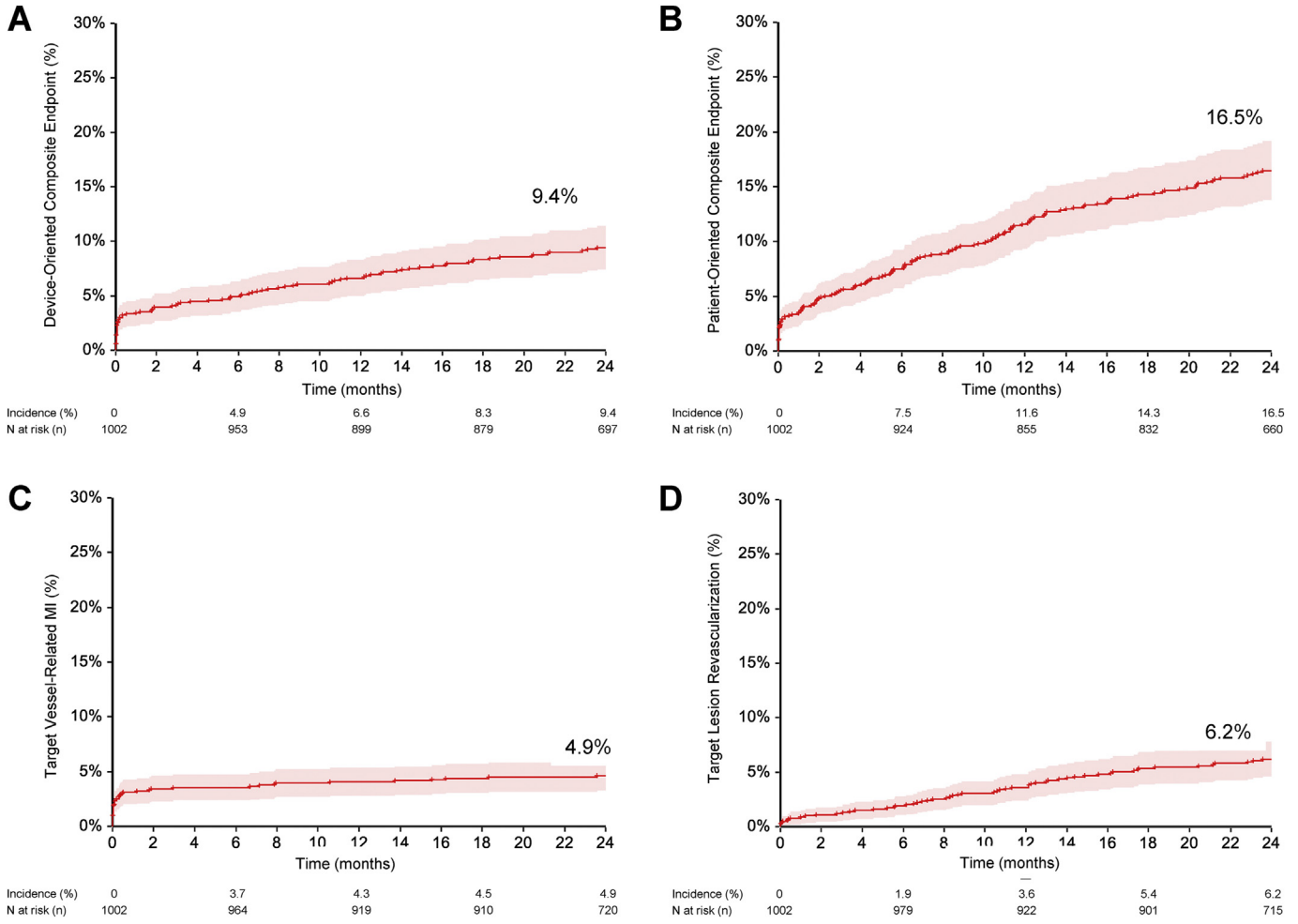

Fig. 1. Kaplan-Meier survival estimates through 2 years for the occurrence of: A) device-oriented composite endpoint; B) patient-oriented composite endpoint; C) target vessel-related myocardial infarction (MI); D) target lesion revascularization.

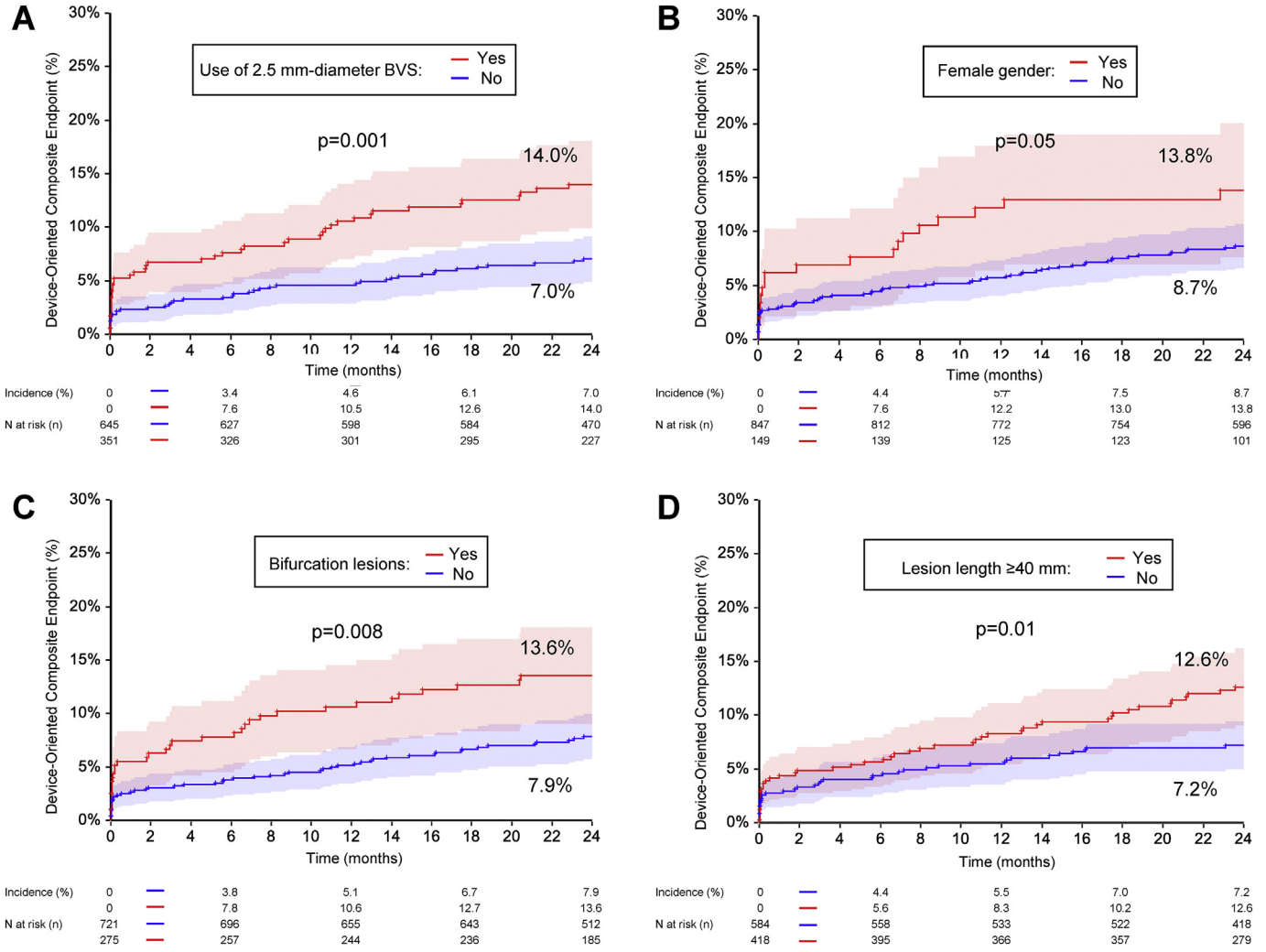

Fig. 2. Kaplan-Meier survival estimates through 2 years for the occurrence of Device-Oriented Composite Endpoint stratified by: A) implantation of 2.5 mm-diameter scaffold; B) gender; C) treatment of bifurcation lesions; D) total lesion length ≥ 40 mm.

grouped according to the occurrence of DOCE through 2-year follow-up are reported in Data-In-Brief Tables 3 and 4.

The variables selected by multiple regression analysis to enter Cox analysis for POCE were: female gender, multivessel disease, disease of the left anterior descending artery, total lesion number, total lesion length, total number of BVS-treated lesions, treatment of bifurcations, implantation of a 2.5 mm-diameter scaffold, and functionally complete revascularization. Multivessel disease (HR 1.76; 95% CI 1.20–2.59; $p = 0.004$), treatment of a bifurcation lesion (HR 1.64; 95% CI 1.17–2.30; $p = 0.004$), implantation of at least one 2.5 mm-diameter BVS (HR 1.47; 95% CI 1.06–2.04; $p = 0.020$) and functionally complete revascularization (HR 0.62; 95% CI 0.43–0.90; $p = 0.012$) were independent predictors of POCE. Kaplan-Meier curves of POCE stratified by presence/absence of independent predictors are depicted in the accompanying Data-In-Brief Fig. 1. The results of multivariable analysis for both DOCE and POCE were substantially unvaried when restricting the analysis to the 885 patients enrolled in the centers with follow-up completeness ≥96% (Data-In-Brief Table 5).

None of the implantation technique components were associated with DOCE or POCE.

4. Discussion

IT-DISAPPEARS is the only prospective multicentre registry evaluating the use of BVS in patients with diffuse and/or multivessel disease with a predefined careful implantation technique. The main findings of our registry at 2 years are as follows:

- The 9.5% rate of DOCE through 2 years was acceptable, being lower than the 2-year TLF rate of 11.0% observed in ABSORB III, enrolling patients with less complex coronary disease;
- The rate of target vessel-related MI was acceptably low at 5.3%, consisting of 2.8% periprocedural MI and 2.5% MI between discharge and 2 years; in particular, only 4 target vessel-related MI occurred between 1 and 2 years;
- TLR showed a constant accrual of events through follow-up, reaching 6.6% at 2 years; overall revascularization rate was 12.5%, reflecting the contribution of disease progression in this diffuse CAD cohort;
- Scaffold thrombosis rate was acceptably low at 1.1%, with only 1 event occurring between 1 and 2 years of follow-up.
- Implantation of at least one 2.5 mm-diameter BVS and treatment of at least one bifurcation lesion were independent predictors of both DOCE and POCE through 2-year follow-up

The interest for the potential advantages of BVS was dramatically hampered by the finding of significantly higher rates of scaffold thrombosis and TLF, as compared with DES in randomized trials [4,5]. Early "real world" registries of BVS had reported acceptable outcomes, but also a disturbing signal regarding an unexpected high scaffold

thrombosis rate [1–3], possibly related to inadequate implantation technique [14]. In contrast, our registry mandated a predefined careful implantation technique [10], proven by the 97% postdilation rate, by far the highest among contemporary BVS registries (range 40% to 72%) [1,3,15,16]. The second element of originality of our study was the presence, as inclusion criterion, of complex coronary lesions and diffuse CAD. The first report on BVS for very long lesions described an alarmingly high 5.3% scaffold thrombosis rate at 1 year follow-up in 23 patients receiving >60 mm of overlapping BVS in a single vessel [17]. More recently, in another single-centre experience, complex lesions were associated with significantly higher rates of early scaffold thrombosis and of restenosis beyond 1 year of follow-up [7]. Importantly, the use of optimal implantation technique was associated with a dramatically lower rate of both scaffold thrombosis and restenosis. In the large all-comers RAI registry, treatment of very long lesions with a "full plastic jacket" (implantation of >56 mm of overlapping BVS) was associated with a two-fold increase in target vessel revascularization as compared with shorter lesions [18]. However "full plastic jacket" showed similar rates of DoCE, POCE, and definite scaffold thrombosis at a median follow-up of 22 months. The largest cohort of patients with long lesions treated with BVS belongs to the GHOST-EU registry [19]. Among 276 patients with lesions ranging from 30 to 60 mm, the 1-year TLF rate was 4.5%, target vessel-related MI 0.8% (periprocedural MI were not included), TLR 4.5% and scaffold thrombosis 1.1%; these results are comparable to those of our registry [11]. In IT-DISAPPEARS, both the extent of CAD (as assessed by total lesion length) and "full plastic jacket" were associated with 2-year DOCE at univariate analysis, with total lesion length being also an independent predictor of DOCE, confirming that BVS are no exception to the association between lesion length and risk of TLR.

Another element of anatomical complexity, i.e. the presence of bifurcation lesions, was also independently associated with 2-year DOCE in our registry. In GHOST-EU, the 1-year TLF and scaffold thrombosis rates of patients receiving BVS (mostly a single scaffold) in bifurcation lesions were rather high, 6.4% and 2.5%, respectively [20]. In a more recent retrospective series, an appropriate implantation technique allowed for a much lower scaffold thrombosis rate (0.7% at 2 years), although TLF rate was comparable (8.2% at 2 years) [21]. Our findings confirm that bifurcation lesions are associated with higher DOCE rates as compared to non-bifurcations, but clarify that, when implantation technique is appropriate, incremental DOCE are mostly periprocedural MI, without increase in scaffold thrombosis.

The 3-year results of the ABSORB III trial greatly contributed to the loss of interest in BVS technology; in fact, target vessel-related MI rate through 3 years was significantly increased with BVS (8.6% vs. 5.9%; $p = 0.03$), as was device thrombosis (2.3% vs. 0.7%; $p = 0.01$) [5]. However, most of the difference was related to early events, since the TLF rate between 1 and 3 years was similar between groups (7.0% vs. 6.0%, $p = 0.39$). Although ABSORB III enrolled patients with less extensive coronary disease as compared with IT-DISAPPEARS (total scaffold length 21 ± 7 mm vs 47 ± 22 mm), our 2-year target vessel-related MI and scaffold thrombosis rates (5.3% and 1.1%, respectively) are lower than those observed in ABSORB III (7.3% and 1.9%, respectively). In addition to the higher postdilation rate in IT-DISAPPEARS (97% vs 66%), the exclusion of vessels smaller than 2.5 mm in diameter was also key to the better outcomes. In fact, 18.8% of the ABSORB III population received a BVS in vessels with RVD < 2.25 mm and this was found to be an independent predictor of 3-year TLF and scaffold thrombosis. In IT-DISAPPEARS, only 28.6% of the BVS implanted were 2.5 mm in diameter [11], and use of at least one 2.5 mm-diameter BVS was found to be an independent predictor of 2-year DOCE and POCE. The smaller vessel and scaffold diameter observed in women may also underlie the role of female gender as independent predictor of DOCE in our registry.

The determinant role of vessel sizing and implantation technique was retrospectively demonstrated in various studies [7,14] and lead to the definition of the so-called "PSP technique", consisting of lesion Predilation, correct scaffold Sizing, and Postdilation [22]. The negative results of randomized trials such as ABSORB III [5] and AIDA [4] may be explained by the lack of an appropriate implantation technique, leading to the 3-fold increase in the risk of device thrombosis with BVS compared to DES, persisting beyond 1 year of follow-up in the most recent network meta-analysis [9]. In particular, very late scaffold thrombosis may be a consequence of initial scaffold malapposition, leading to late scaffold dismantling and increased risk of thrombosis following DAPT discontinuation. A wider use of intracoronary imaging during scaffold implantation is warranted for this reason.

In a recent pooled analysis of five ABSORB studies, an optimal implantation technique was retrospectively defined as: lesion predilation with a balloon to RVD ratio of ≥1:1; correct BVS sizing based on QCA; post-dilation with a noncompliant balloon at ≥18 atm and larger than the nominal scaffold diameter, but not by >0.5 mm larger [23]. In this analysis, aggressive predilation was found to be an independent predictor of scaffold thrombosis between 1 and 3 years, while optimal postdilation (balloon:scaffold ratio > 1:1) was an independent predictor of TLF. Our prospective definition of optimal implantation was less demanding, leading to less aggressive predilatation (balloon:RVD ratio of 1:1 in 43% of patients) and postdilatation (balloon:scaffold ratio > 1:1 in 30% of patients). In our experience, we did not find an impact of implantation technique on clinical outcomes, probably because of the high rate of patients (71.4%) receiving an optimal implantation (according to our recommendations) of all BVS deployed. In particular, an optimal postdilation of all scaffolds with a balloon:scaffold ratio of ≈1:1 was applied in 81.6% of our patients. Even using the more demanding definition proposed by Stone and coworkers [23], optimal postdilation was applied in 30% of our patients, as compared with 12.4% in ABSORB studies. Therefore, considering the clinical outcomes of the study, we can speculate that our recommended implantation technique was good enough to allow for an acceptably low risk of scaffold thrombosis. This hypothesis is confirmed by the recent publication of the 1-year results of the ABSORB IV trial, reporting a TLF rate non-inferior with BVS as compared to DES (7.8% vs. 6.4%; $p_{\text{non-inferiority}} = 0.0006$), and a scaffold thrombosis rate as low as 0.7% vs. 0.3% for DES ($p = 0.16$) [12]. The authors ascribe the improved outcomes in ABSORB IV to the optimised technique, namely the avoidance of very small vessels (3% vs. 19% of lesions had RVD < 2.25 mm) and high-pressure scaffold postdilation (84% vs. 66%). Importantly, in ABSORB IV the recommended scaffold implantation technique included predilatation of the target lesion and high-pressure scaffold postdilation with a non-compliant balloon sized up to 0.5 mm larger than the nominal scaffold diameter, exactly as in our registry. Therefore, based on the 1-year results of ABSORB IV and on the 2-year results of IT-DISAPPEARS, this simple implantation technique appears sufficient to avoid the high TLF rate previously reported.

4.1. Limitations

Our study has several limitations. Firstly, the consecutiveness of enrolment was not monitored, thus a certain degree of selection bias cannot be ruled out. Secondly, DES were implanted in 40% of patients, although in almost always in short coronary lesions in different vessels from the BVS. This bias was mitigated by the careful adjudication of adverse events. Finally, 2-year follow-up completeness was 92.4%; the clustering of patients lost at follow-up in a few centers limits the risk of systematically missing death events possibly related to the device. In fact, the rates of all adverse events were substantially unvaried when restricting the analysis to the 885 patients enrolled in centers with follow-up completeness ≥96%.

5. Conclusions

This is the first large study designed to investigate BVS results in patients with diffuse CAD and is unique in prospectively mandating a careful implantation technique. Our results demonstrate that first-

generation BVS technology yield acceptable freedom from DOCE and scaffold thrombosis at medium-term follow-up, if vessel sizing and operator technique are appropriate.

Conflict of interest

A.S.P., B.C., and F.B. report being members of the advisory board of Abbott Vascular and speakers' honoraria from Abbott Vascular; M.D.C. reports speakers' honoraria from Abbott Vascular; C.I. reports study grants and speakers' honoraria from Abbott Vascular. All other authors have no conflict of interest to disclose related to the present work.

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