Long-Term Clinical Outcomes After Bioresorbable Vascular Scaffold Implantation for the Treatment of Coronary In-Stent Restenosis

A Multicenter Italian Experience

Elisabetta Moscarella, MD*; Alfonso Ielasi, MD*; Francesco Granata, MD; Sebastian Coscarelli, MD; Eugenio Stabile, MD, PhD; Azeem Latib, MD; Bernardo Cortese, MD; Maurizio Tespili, MD; Akihito Tanaka, MD; Claudia Capozzolo, MD; Luigi Caliendo, MD, PhD; Antonio Colombo, MD; Attilio Varricchio, MD, PhD

Background—Treatment of in-stent restenosis (ISR) is still challenging. In this setting, the use of bioresorbable vascular scaffold (BVS) seems attractive because it allows drug delivery combined with transient vessel scaffolding. We aimed to investigate the long-term results after BVS use in ISR lesions.

Methods and Results—A prospective analysis was performed on all patients who underwent percutaneous coronary intervention with BVS implantation for ISR at 7 Italian Centers. Primary end point was the device-oriented composite end point (cardiac death, target vessel myocardial infarction, and ischemia-driven target lesion revascularization) at the longest follow-up available. From April 2012 to June 2014, 116 patients (127 lesions) underwent percutaneous coronary intervention for ISR with BVS implantation. Among the ISR lesions, the majority were drug-eluting stent ISR (78, 61.6%), de novo ISR (92, 72.4%), and diffuse ISR (81, 63.8%). Procedural success was achieved for all (100%) patients. No in-hospital death, myocardial infarction, or revascularization occurred. At 15 months of follow-up, the incidence of the device-oriented composite end point estimated with the Kaplan–Meier method was 9.1%. No significant differences were reported between drug-eluting stent and bare-metal stent ISR groups in terms of device-oriented composite end point (10.9% versus 6.4%; hazard ratio, 1.7; 95% confidence interval, 0.5–6.5; P=0.425) and its singular components (cardiac death: 2.8% versus 2.0%, hazard ratio, 1.3; 95% confidence interval, 0.1–14.1, P=0.843; target vessel myocardial infarction: 1.5% versus 0%, P=0.421; ischemia-driven target lesion revascularization: 9.6% versus 4.4%, hazard ratio, 2.3; 95% confidence interval, 0.5–10.8, P=0.309).

Conclusions—Our registry suggests that the use of BVS implantation for the treatment of complex drug-eluting stent and bare-metal stent ISR lesions might be associated with acceptable long-term clinical outcomes. **(*Circ Cardiovasc Interv*. 2016;9:e003148. DOI: 10.1161/CIRCINTERVENTIONS.115.003148.)**

Key Words: coronary restenosis ■ drug-eluting stent ■ myocardial infarction ■ percutaneous coronary intervention ■ stent

Treatment of in-stent restenosis (ISR) is still a technical challenge for interventional cardiologists. Several studies have demonstrated that treating drug-eluting stent (DES) ISR is even more challenging because of the unfavorable substrate of DES ISR because of the presence of resistant stent underexpansion or neoatherosclerosis that have been shown to be associated with poorer clinical and angiographic outcomes than treating bare-metal stent (BMS) ISR.[1–4] Despite this, current recommended options for ISR treatment are DES or drug-eluting balloon (DEB), regardless of the type of ISR lesion (within BMS or DES).[5] However, both these technologies present some drawbacks and recently the bioresorbable vascular scaffold (BVS, ABSORB; Abbott Vascular, Santa Clara, CA) has emerged as an attractive alternative strategy for ISR.[6,7] BVS

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From the Department of Cardio-Thoracic Science, Second University of Naples, Presidio Ospedaliero "Monaldi", Azienda Ospedaliera Dei Colli, Napoli, Italy (E.M.); Cardiology Division, Azienda Ospedaliera Bolognini Seriate, Bergamo, Italy (A.I., M.T.); Laboratory of Invasive Cardiology, Santa Maria della Pietà Hospital, Nola, Napoli, Italy (F.G., L.C., A.V.); Cardiovascular Intervention Unit, San Martino Hospital, Belluno, Italy (S.C.); Laboratory of Invasive Cardiology, Dipartimento di Scienze Biomediche Avanzate, Università degli Studi "Federico II", Napoli, Italy (E.S.); Interventional Cardiology Unit, EMO-GVM Centro Cuore Columbus ed Ospedale San Raffaele, Milano, Italy (A.L., A.T., A.C.); Laboratory of Invasive Cardiology, Azienda Ospedaliera Fatebenefratelli, Milano, Italy (B.C.); and Laboratory of Invasive Cardiology, Department of Cardiology, Presidio Ospedaliero "Monaldi", Azienda Ospedaliera Dei Colli, Napoli, Italy (C.C.).

*Drs Moscarella and Ielasi contributed equally to this work and are joint first authors.

Correspondence to Elisabetta Moscarella, MD, Department of Cardiothoracic Sciences, Second University of Naples, Napoli, Italy. E-mail elisabetta.moscarella@gmail.com

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WHAT IS KNOWN

- Treating in-stent restenosis remains challenging. Current options include drug-eluting stents or drug-eluting balloons; however, both of these strategies have limitations.
- Recently, bioabsorbable vascular scaffolds have been proposed as an option to treat restenosis lesions.

WHAT THE STUDY ADDS

- This is the largest registry with the longest follow-up available on bioabsorbable vascular scaffold use for in-stent restenosis treatment.
- Our results suggest that bioabsorbable vascular scaffold to treat in-stent restenosis is associated with acceptable long-term results and may be considered as an alternative to treat in-stent restenosis.

allows drug-delivery combined with transient vessel scaffolding, thus obviating the limitations of DES or DEB.[8] Indeed, compared with DEB, BVS achieves excellent acute gain, prevent acute recoil and stabilize dissections, whereas compared with DES it avoids the addition of a further permanent metallic layer. So, BVS could theoretically reduce the occurrence of long-term clinical events compared with both DCB and DES. However, the use of BVS in this setting may be limited by the BVS struts thickness, especially in small vessels with multiple stent layers already implanted, and by the need of long dual antiplatelet therapy. Moreover, the presence of the previous implanted stent may nullify the advantages associated with BVS use (restoring vasomotion and positive remodeling). A recent study has shown that BVS use for ISR is feasible and is associated with favorable early and midterm clinical outcomes.[7] However as of today, there is no data on the long-term (>12 months) behavior of BVS in the ISR lesion subset. The aim of our study was to investigate the long-term clinical outcome after BVS implantation in DES and BMS–ISR.

Methods

Population, Data Collection, and Procedures

Although BVS implantation for the treatment of ISR is outside the instruction for use given by the manufacturer, a prospective, not protocol driven, cohort analysis was performed on all consecutive patients who underwent percutaneous coronary intervention with BVS 1.1 implantation for ISR in 7 Italian centers.

The study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from all study patients treated with BVS for ISR. The main characteristics of the BVS 1.1 were already described elsewhere.[8]

In the analysis, all consecutive patients treated with BVS with either DES or BMS ISR lesions (defined as a luminal diameter stenosis >50% within the stent or within 5 mm of the stent edges) were included, occurring both in a native coronary artery and in a coronary artery bypass graft. The decision to treat the ISR lesion with a BVS rather than a new generation DES or a DEB was left to the operator's discretion but conditioned by the presence of suitable anatomy (absence of tortuosity or severe calcification proximal to the target lesion), lesion (reference vessel diameter [RVD] visually assessed at the target lesion site ≥2.3 mm and ≤3.7 mm without large thrombus burden in the target vessel), and clinical characteristics (absence of severe comorbidities known at the time of hospital admission, contraindications, or high-likelihood of noncompliance to 12 months of dual antiplatelet therapy). Available lengths for BVS during the study period were 12, 18, and 28 mm.

Procedures

ISR lesions were classified according to Mehran classification.[9] The BVS were implanted after mandatory predilatation, whereas the use of cutting/scoring balloon was left at operator's decision. BVS implantation was performed to cover 2 to 5 mm of nondiseased tissue on either side of the target lesion. Postdilatation with noncompliant balloon (with a maximum diameter 0.5 mm higher than the BVS diameter) and intracoronary imaging with optical coherence tomography (Ilumien Optis, St. Jude Medical, St.Paul, MN), and intravascular ultrasound pre- and post-BVS implantation were not mandatory. The BVS overlap strategy (marker-to-marker or marker over marker) was left to the operator's discretion as well as arterial access (radial or femoral), and periprocedural antithrombotics (ie, glycoprotein IIb/IIIa inhibitors and heparin or bivalirudin).

Even if there is no evidence for need of a longer dual antiplatelet therapy after BVS implantation, in accordance to other authors and with the current standard practice, all patients were required to receive >75 mg of aspirin daily lifelong in association with clopidogrel (75 mg daily) or ticagrelor (90 mg twice a day) or prasugrel (10 mg daily) for a minimum of 12 months.

Patient Follow-Up

Clinical data were collected during hospital visit or by telephone contact at 30 days, 1 year, and 2 years. Angiographic follow-up was not scheduled but performed only in case of symptom recurrence or noninvasive demonstration of inducible myocardial ischemia. Clinical events were defined according to the Academic Research Consortium definitions.[10]

Study End Points

Primary end point was a device-oriented composite end point (DOCE), including cardiac death, target vessel myocardial infarction, ischemia-driven target lesion revascularization. Secondary end point was a patient-oriented composite end point (POCE), including all-cause death, any reinfarction, and any revascularization (target vessel revascularization). Furthermore, we evaluated the single components of DOCE, POCE, and the incidence of definite/probable BVS–in-stent thrombosis. Procedural success was defined as a final residual stenosis at the restenotic site <30% without in-hospital POCE.

Angiographic Analysis

Quantitative coronary angiographic analysis was performed offline by an expert analyst using automated edge-detection algorithms. In each lesion, the coronary segment including the stent and 5-mm proximal and distal to the stent edge were analyzed. The following quantitative coronary angiographic parameters were measured: RVD, minimal lumen diameter, and percent diameter stenosis, acute percent recoil defined as the difference between the mean diameter of the stent delivery balloon (or if used, mean diameter of postdilatation balloon) at the highest pressure and the mean lumen diameter of the stented segment after balloon deflation, expressed as percentage. Binary restenosis was defined as stenosis >50% of the luminal diameter in the target lesion.[11]

Statistical Analysis

The Kolmogorov–Smirnov test was used to determine normality in data distribution. Continuous variables were expressed as mean±SD. Comparisons of clinical, echocardiographic, angiographic, or procedure-related characteristics of patients were performed by means of Student *t* test or Wilcoxon rank-sum test (continuous variables), or χ^2 (categorical) and on the basis of the distribution according to the lesion types (BMS or DES ISR). In survival analysis, patients were

censored if they had not experienced the end point of interest at the end of the follow-up. To account for possible nonindependence of multiple observations from 1 patient, cluster robust SEs were used in all Cox Regression analyses. Hazard ratio and 95% confidence interval were calculated considering BMS ISR group as reference. If there were zero events in 1 group, hazard ratio was not calculated and the 2 groups were compared using event rate and its time-specific SD.

All analyses were conducted using SPSS software (IL) version 20.0 and all reported *P* values are 2-sided. The *P* values were considered significant if <0.05.

Results

From April 2012 to June 2014, a total of 116 consecutive patients (127 lesions) underwent percutaneous coronary intervention for ISR with BVS implantation. Baseline clinical and demographic characteristics of the population according to the ISR stent type (BMS or DES) are depicted in Table 1. Angiographic characteristics of the ISR lesions treated are shown in Table 2.

Among the ISR lesions treated with BVS, the majority were DES-ISR (78, 61.6%), and 35 (27.7%) were recurrent (previously treated with DES and DEB or both at different times). According to Mehran classification, the angiographic ISR pattern was defined as diffuse in 81 (63.8%) and focal in 46 (36.2%) lesions, respectively.

Quantitative coronary angiographic analysis was available for all lesions. Target lesion length was 28.18±15.44 mm requiring the use of 1.4±0.6 BVS per lesion, with a mean BVS length of 34.9±18.4 mm per lesion. No differences were reported in quantitative coronary angiographic data between the DES-ISR versus BMS-ISR groups. BVS overlap was needed in 50 (39.4%) of the lesions. BVS overlap with DES, or DEB was needed in 3 (2.4%) and 1 (0.8%) of the lesions, respectively, and

Table 1. Baseline Patient Characteristics

	Overall	Restenosis Type		*P* Value
		BMS	DES	
No. of patients	116	47	69	
Demographic characteristics				
Age, y, mean±SD	66.04±10.02	68.6±8.9	63.6±10.7	0.2
Male sex, n (%)	98 (84.5)	40 (85.1)	59 (84.1)	0.7
Body mass index, kg/m^2, mean±SD	25.54±8.22	23.87±9.35	26.34±7.25	0.1
Cardiovascular risk factors, n (%)				
Hypertension	81 (69.8)	33 (70.2)	48 (69.6)	0.9
Hypercholesterolemia	80 (69.0)	31 (66.0)	49 (71.0)	0.5
Diabetes mellitus	34 (29.3)	14 (29.8)	21 (30.4)	0.9
IDDM	14 (12.1)	5 (10.6)	9 (13.0)	0.7
Smoking history	59 (50.9)	18 (38.3)	41 (59.4)	0.3
Cardiac history, n (%)				
Previous myocardial infarction	71 (61.2)	29 (61.7)	42 (60.9)	0.9
Previous bypass surgery	13 (11.2)	5 (10.6)	8 (11.6)	0.7
Clinical characteristics				
Peripheral artery disease, n (%)	17 (14.7)	6 (12.8)	11 (15.9)	0.6
LV ejection fraction, mean±SD	49.92±10.59	51.2±9.07	49.27±10.9	0.4
Chronic kidney disease (eGFR<60 mL/min), n (%)	17 (14.7)	5 (10.6)	12 (17.4)	0.3
Previous stroke, n (%)	3 (2.6)	1 (2.1)	2 (2.9)	0.8
COPD, n (%)	11 (9.5)	4 (8.5)	7 (10.1)	0.8
Clinical presentation, n (%)				
UA	24 (20.7)	9 (19.1)	16 (23.2)	0.6
NSTEMI	20 (17.2)	6 (12.8)	14 (20.3)	0.3
STEMI	7 (6.0)	3 (6.4)	4 (5.8)	0.9
Stable CAD	65 (56.0)	29 (61.7)	35 (50.7)	0.3

Data are mean±SD or n (%). BMS indicates bare-metal stent(s); CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DES, drug-eluting stent(s); eGFR, estimated glomerular filtration rate; IDDM, insulin-dependent diabetes mellitus; ISR, in-stent restenosis; LV, left ventricle; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.

Table 2. Angiographic Characteristics

	Overall	Restenosis Type		*P* Value
		BMS	DES	
No. of lesions	n=127	49 (38.5)	78 (61.6)	
Target vessel, n (%)				
Left anterior descending artery	66 (52.0)	25 (51.0)	41 (52.6)	0.9
Left circumflex artery	24 (18.9)	9 (18.4)	15 (19.2)	0.9
Right coronary artery	35 (27.6)	15 (30.6)	20 (25.6)	0.5
Saphenous vein graft	2 (1.6)	0 (0)	2 (2.6)	0.3
No. of diseased vessels, n (%)				
One vessel	69 (54.3)	25 (51.0)	44 (56.4)	0.5
Two vessels	33 (26.0)	15 (30.6)	18 (23.0)	0.3
Three vessels	24 (19.7)	9 (18.3)	16 (20.5)	0.8
Recurrent restenosis, n (%)	35 (27.6)	11 (22.4)	23 (29.5)	0.4
Stent type, n (%)				
ISR after BMS	49 (38.5)	49 (100)	0 (0)	
ISR after DES	78 (61.5)	0 (0)	78 (100)	
First generation DES	51 (40.2)	0 (0)	51 (65.4)	
Second-generation DES	27 (21.3)	0 (0)	24 (34.6)	
Pattern of restenosis, n (%)*				
Focal	46 (36.2)	18 (36.7)	28 (35.9)	0.9
Type IA	2 (4.3)	1 (5.6)	1 (3.6)	0.7
Type IB	15 (32.6)	5 (27.8)	10 (35.7)	0.6
Type IC	20 (43.5)	8 (44.4)	12 (42.8)	0.9
Type ID	9 (19.6)	4 (22.2)	5 (17.9)	0.7
Diffuse	81 (63.8)	31 (63.3)	50 (64.1)	0.6
Pattern II (intrastent)	43 (53.1)	18 (58.1)	24 (48.0)	0.5
Pattern III (proliferative)	33 (40.7)	12 (38.7)	22 (44.0)	0.6
Pattern IV (total occlusive)	5 (6.2)	1 (3.2)	4 (8.0)	0.4
QCA analysis				
Lesion length, mm	28.18±15.44	29.5±16.1	26.9±14.9	0.6
RVD, mm	3.06±0.38	2.9±4.3	3.0±0.5	0.08
No. of stents/lesion	1.4±0.6	1.4±0.6	1.4±0.6	0.8
Diameter of stent, mm	3.0±0.39	2.9±0.4	3.0±0.4	0.3
Mean BVS length, mm	34.92±18.38	36.16±18.4	35.04±18.8	0.9
Maximum pressure of stent, atm	14.88±4.3	14.6±4.3	14.6±4.5	0.9
MLD preprocedure, mm	0.83±0.38	0.78±0.4	0.83±0.4	0.3
MLD postprocedure, mm	2.81±0.64	2.8±0.6	2.7±0.6	0.8
Acute gain, mm†	2.0±0.85	2.0±0.7	2.0±0.9	0.9
Mean diameter of largest balloon, mm	3.26±0.47	3.2±0.5	3.3±0.5	0.2
Mean diameter of stent immediately after balloon inflation, mm	3.12±0.47	3.0±4.8	3.2±0.5	0.5
Acute absolute recoil, mm	0.13±0,13	0.12±0.13	0.12±0.14	0.5
Acute percent recoil, %	3.92±4.09	3.71±3.95	3.77±4.3	0.5
Stenosis preprocedure, %	60.95±33.36	58.4±34.4	56.7±32.7	0.7
Stenosis postprocedure, %	7.33±11.04	7.41±11.8	7.64±10.23	0.9

Data are mean±SD or n (%). BMS indicates bare-metal stent(s); BVS, bioresorbable vascular scaffold; DES, drug-eluting stent(s); ISR, in-stent restenosis; MLD, minimum lumen diameter; QCA, quantitative coronary angiography; and RVD, reference vessel diameter.

*According to Mehran criteria.

†Defined as difference MLD postprocedure–MLD preprocedure.

it was mainly because of vessel size not suitable for BVS use. The acute recoil in the total population was on the average of 0.13±0.13 mm (3.92±4.09%) and similar to that observed when BVS are used for the treatment of native coronary lesions.[12] Procedural characteristics are shown in Table 3.

Procedural success was achieved in all patients. In 1 patient, a bailout DES implantation was needed because of proximal BVS edge dissection occurrence not suitable for a second BVS implantation. No in-hospital POCE occurred. The incidences of the clinical end points at 6 and 15 months (Kaplan–Meier estimates) are depicted in Table 4. Clinical follow-up information was obtained at 6 months in 116 eligible patients (100%), at 12 months in 110 eligible patients (94.8%), at 15 months in 106 eligible patients (91.4%).

At 6 months of follow-up, 3 DOCE and 5 POCE occurred. Two ischemia-driven target lesion revascularization (1.7% per patient and 1.6% per lesion) were reported. DOCE rate was 2.0% in BMS ISR group and 2.6% in DES ISR group. At 12 months, the annual incidence rate of DOCE was 9.1%. DOCE rate was 6.4% in BMS ISR group and 10.9% in DES ISR group.

At 15 months of follow-up, no significant differences were reported between DES and BMS ISR groups in terms of DOCE rate (10.9% versus 6.4%; hazard ratio, 1.7; 95% confidence interval, 0.5–6.5; P=0.425) and its singular components (Table 4).

BVS–ISR was the cause of TLR in 8 cases (2 presented as non–Q-wave myocardial infarction and the others as effort angina), of those 5 were successfully managed by re-percutaneous coronary intervention with DEB, whereas in 3 cases a DES was implanted (Table 5). Definite BVS–in-stent thrombosis occurred in 1 case, 11 months after the index procedure in a patient on DAT, and was successfully treated with BVS implantation.

Four patients (3.4%) died. Among these, 1 patient with severe left ventricular dysfunction (ejection fraction 30%) died of cardiogenic shock 15 days after the index procedure (probable BVS–in-stent thrombosis). Two patients died for unknown reasons (cardiac death caused by possible BVS–in-stent thrombosis)

Table 3. Procedural Characteristics

	Overall	Restenosis Type		*P* Value
		BMS	DES	
No. of lesions	n=127	49 (38.5)	78 (61.6)	
Predilation, n (%)	127 (100)	49 (100)	78 (100)	
Predilation scoring balloon, n (%)	13 (10.2)	7 (14.3)	6 (7.7)	0.2
Thrombectomy devices use, n (%)	2 (1.6)	0 (0)	2 (2.6)	0.3
Postdilation, n (%)	110 (88)	43 (87.8)	68 (87.2)	0.9
Overlap, n (%)				
BVS–BVS	50 (39.4)	20 (40.8)	30 (38.5)	0.8
BVS–DES	3 (2.4)	2 (4.1)	1 (1.3)	0.3
BVS–DEB	1 (0.7)	1 (2.0)	0 (0)	0.2
Procedural success, n (%)	126 (99.2)			
Bailout stenting, n (%)	1 (0.8)	0 (0)	1 (1.3)	0.4
TIMI flow pre-PCI, n (%)				
TIMI 0	5 (3.9)	1 (2.0)	4 (5.1)	0.4
TIMI 1	7 (5.5)	1 (2.0)	6 (7.7)	0.2
TIMI 2	16 (12.6)	6 (12.2)	10 (12.8)	0.9
TIMI 3	99 (78.0)	41 (83.7)	58 (74.4)	0.2
TIMI flow grade 3 after procedure, n (%)	127 (100)	49 (100)	78 (100)	
Intracoronary imaging pre-PCI, n (%)				
OCT	27 (21.3)	9 (18.8)	18 (23.1)	0.6
IVUS	1 (0.8)	0 (0)	1 (1.3)	0.4
Intracoronary imaging post-PCI, n (%)				
OCT	29 (22.8)	10 (22.2)	19 (26.0)	0.6
IVUS	1 (0.8)	0 (0)	1 (1.3)	0.4
GP IIb/IIIa Inhibitors, n (%)	5 (3.9)	2 (4.1)	3 (3.8)	0.9
Bivalirudine use, n (%)	4 (3.1)	2 (4.1)	2 (2.6)	0.6

Data are mean±SD or n (%). BMS indicates bare-metal stent(s); BVS, bioresorbable vascular scaffold; DEB, drug-eluting balloon; DES, drug-eluting stent(s); GP, glycoprotein; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; and TIMI, thrombolysis in myocardial infarction.

Table 4. Rate of the Clinical End Points at Follow-Up (Kaplan–Meier Estimates)

	Overall	Restenosis Type		HR (CI 95%)	*P* Value
		BMS	DES		
No. of patients	116	47	69		
No. of lesions	127	49	78		
	n (%*)	n (%*)	n (%*)		
Events at 6 mo					
DOCE	3 (2.4)	1 (2.0)	2 (2.6)		
Cardiac death	2 (1.6)	1 (2.0)	1 (1.3)		
Target vessel MI	0	0	0		
ID-TLR	2 (1.6)	0	2 (2.6)		
POCE	5 (4.0)	2 (4.1)	3 (3.9)		
All-cause death	3 (2.4)	1 (2.0)	2 (2.6)		
Any reinfarction	0	0	0		
TVR	3 (2.4)	1 (2.1)	2 (2.6)		
Definite/Probable BVS in-stent thrombosis	1 (0.8)	0	1 (1.3)		
Events at 12 mo					
DOCE	11 (9.1)	3 (6.4)	8 (10.9)		
Cardiac death	3 (2.5)	1 (2.0)	2 (2.8)		
Target vessel MI†	1 (0.9)	0	1 (1.5)		
ID-TLR	9 (7.6)	2 (4.4)	7 (9.6)		
POCE	13 (10.6)	4 (8.3)	9 (12.1)		
All-cause death	4 (3.3)	1 (2.0)	3 (4.0)		
Any reinfarction	3 (2.7)	0	3 (4.4)		
TVR	10 (8.4)	3 (6.4)	7 (9.6)		
Definite/Probable BVS in-stent thrombosis	2 (1.7)	0	2 (2.8)		
Events at 15 mo					
DOCE	11 (9.1)	3 (6.4)	8 (10.9)	1.7 (0.5–6.5)	0.425
Cardiac death	3 (2.5)	1 (2.0)	2 (2.8)	1.3 (0.1–14.1)	0.843
Target vessel MI	1 (0.9)	0	1 (1.5)	…	0.421
ID-TLR	9 (7.6)	2 (4.4)	7 (9.6)	2.3 (0.5–10.8)	0.309
POCE	14 (12.3)	4 (8.3)	10 (14.9)	1.6 (0.5–5.2)	0.427
All-cause death	4 (3.3)	1 (2.0)	3 (4.0)	1.9 (0.2–18.5)	0.577
Any reinfarction	3 (2.7)	0	3 (4.4)	…	0.162
TVR	11 (10.1)	3 (6.4)	8 (12.4)	1.7 (0.5–6.6)	0.426
Definite/Probable BVS in-stent thrombosis†	2 (1.7)	0	2 (2.8)	…	0.153

BMS indicates bare-metal stent(s); BVS, bioresorbable vascular scaffold; CI, confidence interval; DES, drug-eluting stent(s); DOCE, device-oriented composite end point; HR, hazard ratio; ID-TLR, ischemia-driven target lesion revascularization; MI, myocardial infarction; POCE, patient-oriented composite end point; and TVR, target vessel revascularization.

*Event rate (%); calculated by Cox Regression with cluster robust SEs taking in account t for possible nonindependence of multiple observations from 1 patient, considering BMS ISR group as reference.

†HR was not estimated because of zero events in 1 group, *P* value was calculated using event rate and its time-specific SD.

at 2 and 11 months, respectively, whereas another one died for noncardiac reason. Figure shows the Kaplan–Meier curve reporting the incidence of the primary end point (DOCE) at 15 months of follow-up.

Discussion

Our registry demonstrates that the use of BVS for ISR lesion treatment is associated with favorable long-term clinical results for both DES and BMS ISR.

Table 5. Ischemia-Driven Target Lesion Revascularizations

	Age, y	Sex	Diabetes Mellitus	ISR Stent Type	ISR Pattern	ISR Type	BVS	Clinical Presentation	Months From IP	BVS ISR	DAPT	Treatment
Pt 1	62	Male	Yes	DES	Diffuse	Recurrent	3.5/28	STEMI	11	Diffuse	Yes	BVS
Pt 2	53	Male	No	DES	Diffuse	De Novo	3.5/28+3.0/28	SCAD	2	Focal	Yes	DEB
Pt 3	59	Male	No	DES	Diffuse	Recurrent	3.0/28	SCAD	6	Focal	Yes	DES
Pt 4	71	Female	Yes	DES	Focal	De Novo	2.5/28+2.5/18	NSTEMI	15	Diffuse	No	DES
Pt 5	75	Male	No	DES	Diffuse	Recurrent	3.5/12+3.0/28	SCAD	9	Focal	Yes	DES
Pt 6	51	Female	No	DES	Focal	Recurrent	3.0/18	NSTEMI	10	Focal	Yes	DEB
Pt 7	76	Male	No	BMS	Diffuse	De Novo	2.5/28	SCAD	8	Focal	Yes	DEB
Pt 8	45	Female	No	DES	Focal	De Novo	3.5/12	SCAD	11	Focal	Yes	DEB
Pt 9	81	Male	No	BMS	Diffuse	De Novo	2.5/28	SCAD	12	Focal	No	DEB

BMS indicates bare-metal stent; BVS, bioresorbable vascular scaffold; DAPT, dual antiplatelet therapy; DEB, drug-eluting balloon; De Novo, first restenosis occurrence; DES, drug-eluting stent; IP, index procedure; ISR, in-stent restenosis; NSTEMI, non–ST-segment–elevation myocardial infarction; SCAD, stable chronic artery disease; and STEMI, ST-segment–elevation myocardial infarction.

Although DES has significantly reduced the ISR rate compared with BMS, this phenomenon continues to exist and it is not benign.[13] Treating ISR lesions remains a technical challenge, and outcomes are even poorer for patients with DES compared with those presenting with BMS-ISR.[3] Indeed, patients presenting with DES-ISR have already failed the best currently available antirestenosis treatment; thus making it more difficult to achieve an acceptable long-term result.

Current recommended treatment options for ISR are DES and DEB, irrespective of the stent type (within BMS or DES).[5] Second-generation DES has shown good results for both BMS and DES ISR, but the use of DES is limited by the addition of a further permanent metallic layer into the arterial wall, especially in patients already presenting with multiple stent layers as a consequence of recurrent-resistant DES-ISR.[14]

Therefore, the use of DEB has been widely encouraged as ISR therapy.[15–18] However, DEB is associated with poorer clinical and angiographic outcomes when compared with second-generation DES for the treatment of ISR.[19] First, as ISR is mainly characterized by large volume of hyperplastic tissue, DEB may not be able to achieve acute luminal gain to the same extent as another stent that can compress this tissue,[20] and may be complicated by acute recoil or dissection requiring a bailout stenting. Second, all currently available DEB are coated with paclitaxel that has now been superseded by sirolimus because of its superiority as antiproliferative drug. Furthermore, on the long-term follow-up the use of DEB for DES-ISR is less efficacious than for BMS-ISR.[21]

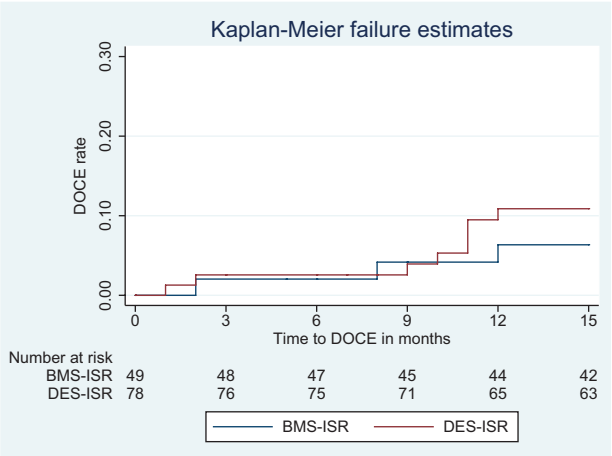

Figure. Kaplan–Meier curves showing the incidence of the primary end point (DOCE) at 15 months follow-up. BMS indicates bare-metal stent; DES, drug-eluting stent; and ISR, in-stent restenosis.

In this contest, despite currently representing an off-label indication, the BVS has emerged as an attractive alternative therapy for ISR.[6,7] Thanks to its characteristics, BVS can potentially overcome the limitations associated with the use of DES or DEB for ISR treatment. Indeed BVS allows everolimus drug-delivery combined with transient vessel scaffolding. Thus, compared with DES it avoids the addition of a further permanent metallic layer into the arterial wall. Whereas compared with DEB it may achieve greater acute gain, prevent acute recoil, and stabilize dissections. Furthermore, BVS allows a more prolonged drug-delivery, which is comparable with that obtained after DES implantation,[22] and it delivers everolimus, which is known to be a superior antiproliferative drug compared with paclitaxel.[23] However, the BVS struts thickness (150 μm) associated with a higher BVS/vessel ratio compared with what observed for conventional metallic DES (26% versus 12%)[24] may represent an important limitation to its use particularly in small restenotic vessels (RVD ≤2.8 mm). However, the biggest available BVS diameters of 3.5 mm may limit its use in larger (RVD >3.7 mm) restenotic vessels. Thus, in patients with diffuse ISR with a small (RVD <2.8 mm) or a large segment (RVD >3.7 mm) involved, a hybrid approach with the use of BVS and DEB distally or BVS and DES proximally may be required, as it occurred in 4 of our patients.

Currently, there is an increasing use of BVS in an unselected population including patients with acute coronary syndrome and complex coronary anatomy,[25] and some registries have reported the feasibility of BVS use for ISR treatment.[6,7] What does our study add to the topic? First, we report the largest multicenter study with the longest follow-up available. Second, our registry deals with high-risk patients

(44% presenting with acute coronary syndrome and 61% had previous myocardial infarction) with complex lesions (27% recurrent ISR, 64% diffuse ISR pattern of whom 6.1% occlusive, with mean lesion length of 28±15 mm, and 62% DES-ISR), whereas lesions included in the Restenosis Intrastent of Bare Metal Stents (RIBS) V and IV trials, were not of high complexity and those at greatest risk of recurrence (lesions >30 mm, in-stent total occlusion) were excluded.[19,20] Despite the complex ISR lesions treated in the present registry, the rate of ischemia-driven target lesion revascularization at follow-up was promisingly low (7.8%) and similar to those observed when DEB or DES are used in simpler ISR lesions (13% and 4.5%, respectively. in the RIBS IV trial; 6% and 1%, respectively, in the RIBS V trial). The systematic ISR lesion predilation and the high rate of postdilation (88% compared with 68.4% reported in other studies not involving ISR[26]) might both explain these favorable results. Particularly, the predilatation is crucial to evaluate the feasibility of BVS–in-stent implantation on the basis of the balloon crossability homogeneous predilatation noncompliant or scoring balloon expansion while the postdilation results are important to obtain an optimal BVS–in-stent expansion and apposition. Finally, although the long-term follow-up of DEB is less efficacious for DES-ISR than for BMS-ISR,[21] we did not find any differences in terms of long-term clinical outcomes between DES and BMS ISR groups. However, this finding requires to be tested in studies adequately powered for clinical end points.

To date, there is no standardized strategy for scaffold failure treatment. When BVS restenosis occurs after 6 months or later, the biodegradation phase has already started and the scaffold has lost its properties, so simple dilatation has unknown outcomes.[27] In our registry, operators decided to treat scaffold restenosis with DEB rather than with DES, in case of focal restenosis pattern, irrespective of the presentation time, to avoid a further stent implantation in a vessel already treated with ≥1 stent and the BVS that has not completed the absorption.

Even if the best treatment strategy of a true BVS thrombosis remains to be defined, the use of another BVS in this setting may be considered hazardous. In our specific case, after BVS recanalization the angiography (intravascular imaging was unfortunately not performed) showed a residual stenosis at the proximal edge of the BVS that the operator felt confident to treat with the implantation of another BVS.

Limitations

The main limitations of the study were its observational nature, based on a single-arm, multicenter registry, and the lack of a direct comparison with the actual standard treatment (current generation DES or DEB). Furthermore, this is a registry of consecutive ISR lesions treated with BVS and not a collection of consecutive all-comers ISR lesions. Indeed, the use of BVS instead of DES or DEB was left to the operator's decision in the presence of suitable patient and lesion characteristics. Of course, this aspect could have influenced our results. In addition, source verification and queries generation from the coordinating center to the participating sites were undertaken to account partly for the unavoidable bias of site-reported events adjudication Moreover, our registry lacks of systematic angiographic follow-up, which may be helpful in evaluating BVS performance, even if the occurrence of angiographically evident but clinically silent restenosis is not a frequent phenomenon. However, this behavior reflects the everyday patient management in different Italian hospitals.

Conclusions

Our registry suggests that the use of BVS implantation for the treatment of complex BMS and DES ISR lesions might be associated with acceptable long-term clinical outcomes.

Larger randomized trials of head-to-head comparison versus contemporary standard of care are strongly needed to fully assess the potential clinical benefit of BVS in ISR lesion treatment.

Disclosures

None.

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Long-Term Clinical Outcomes After Bioresorbable Vascular Scaffold Implantation for the Treatment of Coronary In-Stent Restenosis: A Multicenter Italian Experience

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