Initial experience with everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with acute myocardial infarction

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Eurointervention. 2016 May 17

ABSTRACT

Background

Very limited data are currently available on mid-term outcomes after implantation of everolimus eluting bioresorbable scaffolds (BVS) for treatment of acute myocardial infarction.

Methods and Results

Patients presenting with STEMI and undergoing primary percutaneous coronary intervention, with BVS were evaluated and compared with patients treated with everolimus-eluting metal stents (EES) by applying propensity matching. Quantitative coronary angiography analysis and 18-month clinical follow-up were reported.

A total of 302 patients were analysed, 151 with BVS and 151 with EES. Baseline clinical characteristics were similar between groups. Final TIMI 3 flow was 87.4% vs 86.1% p= 0.296. At 18-month follow-up, all-cause mortality was 2.8 vs 3.0 in the BVS and EES group respectively p=0.99, MACE rate was higher in the BVS group 9.8% vs 3.6% p=0.02. Target lesion revascularizations was 5.7% vs 1.3% p=0.05. The 30-day MACE rate in BVS patients without post-dilatation was 6.8% in patients with post-dilatation was 3.6%. Scaffold thrombosis (ST) occurred primarily in the acute phase (acute ST 2.1% vs 0.7%, p=0.29; subacute 0.7% vs 0.7%, p=0.99; late 0.0% vs 0.0%; very late1.5% vs 0.0%, p=0.18). The majority of the cases with acute ST had no post-dilatation at the index procedure (3/4 cases)

Conclusions

Patients implanted with BVS showed an overall higher rate of clinical events compared with metal stents. The majority of clinical events occurred in the early phase after implantation and mainly in cases without post-dilatation. Optimisation of the implantation technique could be relevant also in acute patients.

INTRODUCTION

Bioresorbable vascular scaffolds (BVS) have been recently introduced as a novel approach for treatment of coronary artery disease, providing transient vascular support and drug delivery potentially restoring the vascular physiology after device bioresorption.[1-4]

The theoretical advantages of this novel technology such as late lumen enlargement restoration of coronary vasomotion and plaque sealing could suggest this device as particularly appealing for in patients with thrombotic soft plaques._ENREF_5 [5-7] Bioresorbable vascular scaffolds have been hypothesized to be particularly suitable for acute thrombotic lesion, which are frequently soft necrotic core rich plaques with a ruptured thin fibrotic cap.[8] Vessels with such lesions, could benefit the most from a treatment with bioresorbable devices leading to the so-called restoration therapy, represented by late lumen enlargement and re-acquisition of coronary vasomotion.[9, 10] Due to vasoconstriction and presence of thrombus, the treatment of acute lesions is often associated with device under-sizing and the occurrence of malapposition after thrombus dissolution. Theoretically, the complete bioresorption of the device would avoid the presence of long-term malapposed struts. In addition the BVS wider struts have been hypothesized to play a role in thrombotic material entrapment with a possible impact on distal embolization. In addition, polymer bioresorption and concomitant formation of a neointimal layer given by connective tissue and smooth muscle cells could stabilize the plaque creating a neo-thick fibrous cap, without the long term permanence of metallic material in the vessel wall. [5]

Initial small cohort studies with short follow-up and relatively selected populations reported encouraging results after BVS implantation in acute patients; however, at the current state of the art limited data are available on the mid-term performance of this novel device in patients presenting with acute myocardial infarction.[11-13] Given this background, we analyzed patients presenting with ST-elevation myocardial infarction treated with BVS and we compared angiographic and 18-month clinical results with a matched population implanted with everolimus- eluting stents (EES).

METHODS

Patients presenting with ST-segment elevation myocardial infarction and treated with BVS at the Thoraxcenter, Erasmus MC in Rotterdam between 1 November 2012 and 31 December 2014, were evaluated for the present analysis. Subjects included were patients ≥18-years old admitted with ST-segment elevation myocardial infarction (STEMI). Culprit lesions were located in vessels within the upper limit of 3.8 mm and the lower limit of 2.0 mm by online quantitative coronary angiography (QCA). The BVS

was implanted according to the manufacturer's indication for target-vessel diameter ranges and BVS diameters to be used. The BVS with a nominal diameter of 2.5 mm was implanted in vessels ≥2.0 and ≤3.0 mm by online QCA; the 3.0 mm BVS was implanted in vessels ≥2.5 and ≤3.3 mm by online QCA; the 3.5 mm BVS was implanted in vessels ≥3.0 and ≤3.8 mm. For each nominal diameter a further expansion of 0.5 mm was allowed. All patients were treated with unfractionated heparin at the dose of 70–100 UI/kg and dual antiplatelet therapy after treatment was planned to have a duration of 12 months. Exclusion criteria comprised pregnancy, known intolerance to contrast medium, uncertain neurological outcome after cardiopulmonary resuscitation, previous percutaneous coronary intervention with the implantation of a metal stent, left main (LM) disease, previous coronary artery bypass grafting (CABG), and participation in another investigational drug or device study before reaching the primary endpoints.

Propensity score was applied to match each STEMI patient treated with BVS to a comparable patient treated with everolimus-eluting stent (EES) at the same institution.

Baseline and post-scaffold/stent implantation quantitative coronary angiographic analysis, optical coherence tomography (when available) analyses at post- scaffold/stent implantation were performed. Clinical outcomes at the 18-month follow-up were evaluated. (Figure 1)

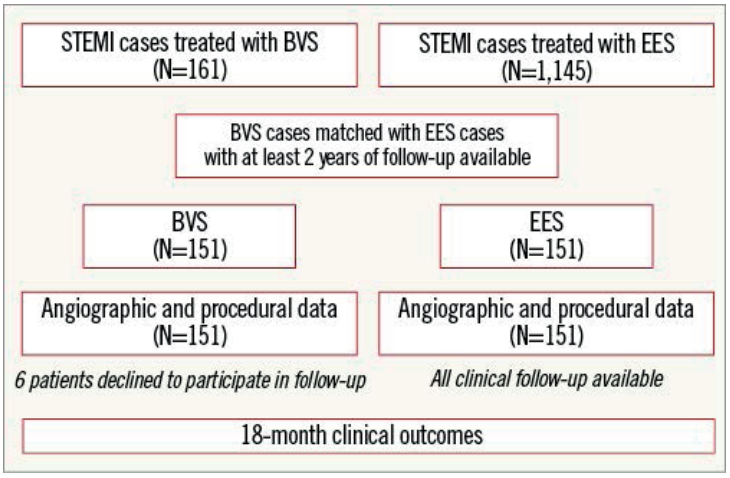

Figure 1 Flow chart of the study.

Study device

The second-generation BVS (Absorb BVS, Abbott Vascular, Santa Clara, CA) is a balloon-expandable scaffold consisting of a polymer backbone of poly-L-lactide (PLLA) coated with a thin layer of a 1:1mixture of an amorphous matrix of poly- D, L-lactide (PDLLA) polymer and 100 μg/cm^2 of the antiproliferative drug everolimus. Two platinum mark-

ers located at each BVS edge allow for accurate visualization of the radiolucent BVS during angiography or other imaging modalities. The PDLLA controls the release of everolimus, 80% of the drug is eluted within the first 30 days. Both PLLA and PDLLA are fully bioresorbable. The polymers are degraded via hydrolysis of the ester bonds, and the resulting lactate and its oligomers are transformed to pyruvate and metabolized in the Krebs cycle. Small particles, less than 2 µm in diameter, have also been shown to be phagocytized and degraded by macrophages. According to preclinical studies, [14] complete bioresorption of the polymer backbone occurs from is 2 to 3 years after implantation.[15]

Control device

The everolimus eluting coronary stent system is a balloon-expandable metallic platform stent manufactured from a flexible cobalt chromium alloy with a multicellular design and coated with a thin non-adhesive, durable, biocompatible acrylic, and fluorinated everolimus-releasing copolymer.

Quantitative coronary angiographic analysis

Angiographic views with minimal foreshortening of the lesion and limited overlap with other vessels were used whenever possible for all phases of the treatment. Comparison between pre and post treatment, were performed in matched angiographic views. In case of thrombotic total occlusion, pre-procedure quantitative coronary angiographic analysis was performed as proximally as possible from the occlusion (in case of a side branch distally to the most proximal take off of the side branch), as already reported.[11] Intracoronary thrombus was angiographically identified and scored in five grades as previously described.[16, 17] Thrombus grade was assessed before procedure and after thombectomy. The two-dimensional angiograms were analysed with the CASS 5.10 analysis system (Pie Medical BV, Maastricht, the Netherlands). In each patient, the treated region and the peri-treated regions (defined as 5 mm proximal and distal to the device edge) were analysed. The QCA measurements included reference vessel diameter (RVD), percentage diameter stenosis, minimal lumen diameter (MLD), and maximal lumen diameter (Dmax). Acute gain was defined as post-procedural MLD minus pre-procedural MLD (MLD value equal to zero was applied when culprit vessel was occluded pre-procedurally).

Procedural-Clinical outcomes and definitions

Device success was defined as successful delivery and deployment of the device with the attainment of <30% final residual stenosis, by angiographic visual estimation. Procedure success was defined as device success and no major peri-procedural complications (Emergent CABG, coronary perforation requiring pericardial drainage, residual dissection

impairing vessel flow—TIMI-flow II or less). All deaths were considered cardiac unless an undisputed non-cardiac cause was identified. Target-lesion revascularization (TLR) was defined as clinically driven if at repeat angiography the diameter stenosis was 70%, or if a diameter stenosis 50% was present in association with (i) presence of recurrent angina pectoris, related to the target vessel; (ii) objective signs of ischaemia at rest (ECG changes) or during exercise test, related to the target vessel; and (iii) abnormal results of any functional diagnostic test. Scaffold/stent thrombosis was defined according to the Academic Research Consortium definition.[18]

In BVS patients, first permission to participate in registry was obtained. A questionnaire was sent to all living patients with specific queries on re-hospitalization and cardiovascular events. For patients who suffered an adverse event at another centre, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary.

Statistical analysis

A propensity score matching was performed using a proprietary macro developed and tested for SPSS version 22.0 (SPSS Inc., Chicago, Illinois). First, the program performed a logistic regression to score all patients according to the treatment (BVS vs. EES), using as covariates clinical and procedural parameters: age (years), sex (male/female), cardiogenic shock (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), smoking (yes/no), diabetes mellitus (yes/no), pre-procedure TIMI-flow, culprit vessel. Second, the macro searched and selected the best match case of the EES group for every BVS case according to the absolute value of the difference between the propensity score of BVS and EES cases under consideration. Patients in the 2 groups were matched through a Greedy algorithm based on local optimization.[19] The control selected for a particular case was the one closest to the case in terms of distance. Analyses were then performed on the 2 matched groups (BVS vs. EES), stratified by pairs to account for propensity score matching. For the study, individual data were pooled on a patient-level basis. Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation. The student's t test and the chi square test (or Fishers' exact test) were used for comparison of means and percentages. The cumulative incidence of adverse events 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. Kaplan-Meier estimates were compared by means of the log-rank test. For the endpoint MACE, a landmark survival analysis was performed with the landmark time point of 30 days. All statistical tests were two-sided and the P value of < 0.05 was considered statistically significant.

RESULTS

A total of 1306 patients presenting with acute ST-segment elevation myocardial infarction were evaluated for the present analysis (161 patients implanted with BVS and 1145 patients implanted with EES with at least 2-year follow-up available). After matching, 302 patients treated with either BVS or EES (151 patients treated with BVS matched with 151 patients treated with EES) were analysed. Six patients (3.9%) in the BVS group declined to participate in follow-up.

Baseline clinical characteristics were balanced between groups as shown in Table 1.

Table 1 Baseline clinical characteristics

	BVS (N=151)	EES (N=151)	P value
Age, years	56.31 ±10.22	54.90 ±11.52	0.263
Male	109/151 (72.2)	113/151 (74.8)	0.696
Active smoker	71/151 (41.0)	89/151 (58.9)	0.050
Diabetes mellitus	17/151 (11.3)	15/151 (9.9)	0.852
Dyslipidaemia	43/151 (28.4)	41/151 (27.1)	0.226
Hypertension	60/151 (39.7)	56/151 (37.1)	0.723
Family History	51/151 (33.8)	52/151 (34.4)	1.000
Target vessel			0.520
LAD	64/151 (42.4)	62/151 (41.1)	
LCX	32/151 (21.2)	40/151 (26.5)	
RCA	51/151 (33.8)	46/151 (30.5)	
Diagonal	2/151 (1.3)	3/151 (2.0)	
Ramus Intermedius	2/151 (1.3)	0	
Left Main	0	0	
SVG	0	0	

Data are expressed as count and proportion (%) or mean ± standard deviation

A total of 403 devices (193 BVS) were deployed, aspiration thrombectomy was equally performed in the two groups (BVS 76.7% vs 76.8% EES, p=1.000). Pre-dilatation was performed two times more frequently in the BVS group (54.1% vs 28.4%, p<0.001) with a higher balloon / artery ratio (1.02 ± 0.24 vs 0.88 ± 0.21, p=0.002). Post-dilatation was also performed more frequently in the BVS group (and 39.7% vs 21.8%, p<0.001 respectively) but with a balloon / scaffold-stent ratio higher in EES group (1.07 ± 0.09 vs 1.12 ± 0.12, p= 0.031). The rate of post-dilatation increased over time, in the first 75 patients the rate of post-dilatation was 25.3% in the remaining 76 patients was 53.9%. Device success was similar between groups (98.7% vs 99.3%, p=1.000). (Table 2)

Table 2 Procedural characteristics

	BVS (N=151)	EES (N=151)	P value
Aspiration thrombectomy	115/151 (76.7)	116/151 (76.8)	1.000
Pre-dilatation performed	80/151 (54.1)	42/151 (28.4)	<0.001
Pre-dilatation balloon / artery ratio	1.02 ± 0.24	0.88 ± 0.21	0.002
Maximal diameter balloon pre-dilatation, mm	2.54 ± 0.47	2.40 ± 0.48	0.111
Supportive wire used	18/151 (12.2)	3/151 (2.0)	<0.001
Device failure	2/151 (1.5)	1/151 (0.7)	1.000
Device success	149/151 (98.7)	150/151 (99.3)	1.000
Procedure success	148/151 (98.0)	150/151 (99.3)	0.622
Mean scaffold diameter, mm	3.21 ±0.33	3.20 ± 0.46	0.827
Mean total nominal scaffold length, mm	26.32 ± 13.27	27.76 ± 14.81	0.378
Number of scaffolds deployed per treated vessel	1.28 ± 0.61	1.39 ± 0.73	0.148
0	2 (1.3)	0	0.398
1	115 (76.2)	108 (71.5)	
2	25 (16.6)	32 (21.2)	
3	8 (5.3)	7 (4.6)	
4	1 (0.7)	3 (2.0)	
5	0	1(0.7)	
Procedures with overlapping scaffolds, n (%)	31/151 (20.7)	39/151 (25.8)	0.340
Post-dilatation performed	60/151 (39.7)	33/151 (21.8)	<0.001
Post-dilatation balloon / scaffold or stent ratio	1.07 ± 0.09	1.12 ± 0.12	0.031
Maximal post-dilatation balloon diameter, mm	3.45 ± 0.41	3.54 ± 0.59	0.435
Complications occurring anytime during the procedure			
Any dissection	10/151 (6.7)	8/151 (5.3)	0.809
Thrombosis	0	0	
Perforation	1/151 (0.7)	0	

Data are expressed as count and proportion (%)or mean ± standard deviation

Baseline culprit vessels, vessel dimensions, percentage of stenosis, TIMI flow and thrombotic burden were similar between patients treated with BVS and those treated with EES. (Table 3)

At the end of the procedure, there were no cases of TIMI flow 0, and final TIMI 3 flow was achieved in 87.4% and 86.1% of BVS and EES group respectively (p= 0.296) with similar minimal lumen diameter and percentage stenosis.

6-month clinical outcomes Cardiac death was observed in 1.9 vs 2.0, p=0.97; the rate of any myocardial infarction was 5.5% in the BVS group and 1.3% in EES group, p=0.05. Target lesion revascularisation rate was 3.5% and 1.3% respectively, p=0.23. Acute scaffold thrombosis occurred in 2.1% of BVS implanted patients and 0.7% of EES implanted

Table 3 Angiographic characteristics

	BVS (N=151)	EES (N=151)	P value
Pre-procedure			
TIMI flow			0.213
0	80/151 (53.0)	85/151 (56.3)	
1	16/151 (10.6)	12/151 (7.9)	
2	31/151 (20.5)	40/151 (26.5)	
3	24/151 (15.9)	14/151 (9.3)	
Thrombus burden			0.551
1	24/148 (16.2)	20/150 (13.3)	
2	21/148 (14.2)	16/150 (10.7)	
3	12/148 (8.1)	9/150 (6.0)	
4	12/148 (8.1)	18/150 (12.0)	
5	79/148 (53.4)	87/150 (58.0)	
Total thrombotic occlusion			
RVD (mm)	2.76 ± 0.72	2.71 ± 0.47	0.608
Non-total thrombotic occlusion			
RVD (mm)	2.60 ± 0.52	2.72 ± 0.54	0.179
MLD (mm)	0.82 ± 0.46	0.91 ± 0.66	0.335
Diameter stenosis (%)	68.07 ± 15.08	66.27 ± 21.57	0.571
Post-procedure			
TIMI flow			0.296
0	0	0	
1	2/151 (1.3)	0/151	
2	17/151 (11.3)	21/151 (13.9)	
3	132/151 (87.4)	130/151 (86.1)	
RVD (mm)	2.63 ± 0.54	2.98 ± 1.76	0.023
MLD (mm)	2.11 ± 0.50	2.22 ± 0.54	0.067
Diameter stenosis (%)	20.64 ± 11.02	22.28 ± 9.92	0.181
Acute lumen gain	1.98 ± 0.67	2.06 ± 0.73	0.398

Data are expressed as count and percentages or mean ± standard deviation

patients, p=0.29. In both groups Subacute ST rate was 0.7%, p=0.99. Three out of 4 scaffold thromboses occurred in patients without post-dilatation performed at the index procedure. The overall MACE rate 7.6% vs 2.7%, p=0.06. A landmark analysis showed that the 30-day MACE rate in BVS patients without post-dilatation was 6.8% while in patients with post-dilatation was 3.6%.

12-month clinical outcomes From 6 to 12-month follow-up only a target lesion revascularization and one non-target vessel revascularization occurred in the group treated with bioresorbable vascular scaffold.

Table 4 Clinical outcomes

	6-month follow-up			12-month follow-up			18-month follow-up		
	BVS (n = 145)	EES (n = 151)	P value	BVS (n = 145)	EES (n = 151)	P value	BVS (n = 145)	EES (n = 151)	P value
All-cause death (%)	2.1 (3)	2.0 (3)	0.97	2.8 (4)	2.0 (3)	0.68	2.8 (4)	3.0 (4)	0.99
Cardiac	2.1 (3)	1.3 (2)	0.97	2.1 (3)	1.3 (2)	0.63	2.1 (3)	1.3 (2)	0.63
MACE (n.) %	7.6 (11)	2.7 (4)	0.06	8.1 (12)	2.7 (4)	0.03	9.8 (14)	3.6 (5)	0.03
MI (n.) %	5.5 (8)	1.3 (2)	0.05	5.5 (8)	1.3 (2)	0.05	6.3 (9)	2.3 (3)	0.07
TLR (n.) %	3.5 (5)	1.3 (2)	0.23	4.2 (6)	1.3 (2)	0.14	5.7 (8)	1.3 (2)	0.05
Non-TVR (n.) %	2.1 (3)	2.0 (3)	0.97	2.8 (4)	2.0 (3)	0.67	3.6 (5)	4.0 (5)	0.95
Definite ST (n.) %	2.8 (4)	1.3 (2)	0.38	2.8 (4)	1.3 (2)	0.38	4.3 (6)	1.3 (2)	0.15
Acute	2.1 (3)	0.7 (1)	0.29	2.1 (3)	0.7 (1)	0.29	2.1 (3)	0.7 (1)	0.29
Subacute	0.7 (1)	0.7 (1)	0.99	0.7 (1)	0.7 (1)	0.99	0.7 (1)	0.7 (1)	0.99
Late	-	-	-	-	-	-	0.0 (0)	0.0 (0)	-
Very late	-	-	-	-	-	-	1.5 (2)	0.0 (0)	0.18

18-month clinical outcomes From 12 to 18 month 2 very late scaffold thrombosis were observed in the BVS group, at 416 and 449 days after implantation, in both cases the dual antiplatelet therapy was interrupted at the moment of the event. In both cases the review of intravascular imaging showed scaffold malapposition. In the EES group 2 additional non TVR were reported one of them associated with a myocardial infarction.

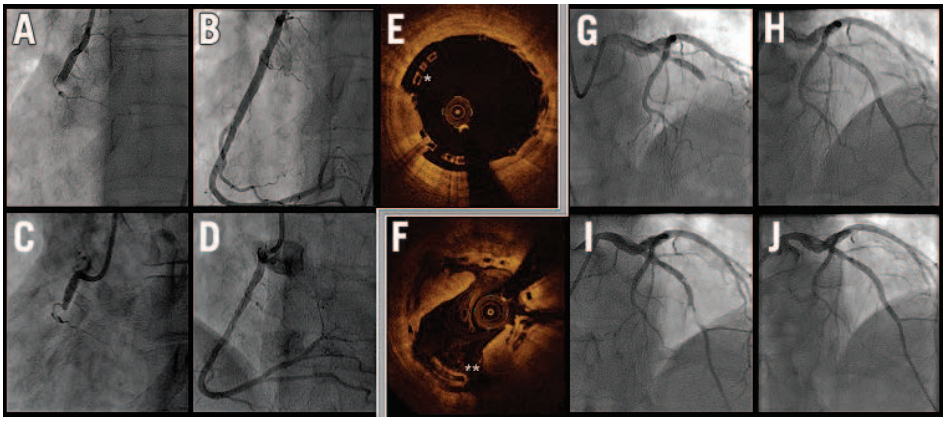

Figure 2 Cases of very late scaffold thrombosis
Both cases were performed with satisfactory final angiographic results. Case 1 (panels A-E): A) baseline; B) final result of the index procedure; C) thrombosis; D) final result of the event treatment. Post-dilatation was performed during the index intervention, but at the end of the procedure intravascular imaging (E) highlighted the remaining malapposition (*). Case 2 (panels F-J): G) baseline; H) final result of the index procedure; I) thrombosis; J) final result of the event treatment. At the time of the event, intravascular imaging (F) showed persistent malapposition (**).

DISCUSSION

The feasibility of BVS implantation in patients presenting with acute myocardial infarction has been recently reported with preliminary information on short-term clinical outcomes.[11-13] However, data comparing the mid-term performance of the bioresorbable technology with the current generation metal DES in this specific subset are limited. The present study represents an early investigation evaluating the use of the second-generation BVS for the treatment of patients presenting with STEMI in comparison with everolimus-eluting metal stents in terms of acute angiographic results and 18-month clinical outcomes.

The majority of the treated patients presented with a TIMI 0 or 1 and more than 60% of the lesions showed a large thrombus burden (4 or 5) in the culprit vessel, in line with what observed in recent large trials on myocardial infarction with minimal exclusion criteria.[20, 21] Such data suggest a patient's population with coronary lesions probably resembling the daily clinical practice in acute myocardial infarction.

Procedural and angiographic data showed an overall comparable device success rate between the two groups, with similar incidence of intra-procedural complication. At the end of the procedure the restoration of TIMI 3 flow was achieved in a high number of patients and similarly in both groups with comparable acute lumen gain, percentage diameter stenosis and minimal lumen diameter.

On the other hand, when analysing the clinical outcomes in the BVS group was observed a higher rate of events at 18-month follow-up with a larger number of TLR and MI an overall higher MACE rate. Although a difference became statistically significant at mid-term follow-up the larger component of such difference is due to events occurred in the very early phase after implantation. In particular three scaffolds thrombosis occurred on day one after implantation.

It should be highlighted that the devices analysed in the present study were used in a period when the post-dilation was not regarded as a key point during the device implantation especially in the acute subset. Studies reporting pooled data from different European registries performed in the same time period of our, showed similar rates of scaffold thrombosis at 30 days.[13]

Our group recognized the relevance of additional high-pressure post-dilation when implanting bioresorbable scaffolds[22] and this translated into a gradual increase in the use of this technique during the inclusion in the present study up the point that the rate of post-dilation was double in the second half of the enrolment compared to the first half.

This concept has been embraced by the scientific community and the current recommendations for BVS implantation suggest the high pressure post-dilatation as an

important action to improve scaffold deployment with a possible beneficial effect on clinical outcomes.[22]

In a later randomized trial, the TROFI II, evaluating short-term imaging results in either BVS or EES in acute myocardial infarction, the rate of subacute scaffold thrombosis was 1.1%. In this study the implantation technique was slightly different from ours, thrombus aspiration was mandatory in every patient with a post-dilation performed in a slightly higher number of cases.[23]

As a matter of fact in our investigation patients without post-dilatation had a higher MACE rate in the first month and both the very late scaffold thrombosis was associated with relevant malapposition. Given this background a possible role of the implantation technique in the occurrence of events cannot be excluded.

The acute myocardial infarction has been classically a field where operators attempted to re-establish the TIMI 3 flow in the culprit vessel reducing at the minimum the amount of manoeuvres, including aggressive post-dilatation, at the lesion site, to minimize the risk of distal embolization. However, a possible association between post-dilation and no-reflow or slow-flow phenomenon currently remains to be clarified[24, 25] and the seminal observation reported in the present study could support a more frequent use of the post-dilatation to optimize scaffold expansion even in acute patients. Large randomized trials currently under preparation may add in further understand on the real performance of bioresorbable technologies in the acute setting.

LIMITATIONS

The number of subject evaluated in the present study is limited and data on clinical outcomes should be considered descriptive and hypothesis generating.

The two study groups were not randomized, despite the use of propensity matching, unadjusted confounders might remain, possibly having an impact on results

Larger patient population and longer follow-up would be needed to adequately compare this novel technology with current generation metal DES.

CONCLUSION

The present study investigated the angiographic and mid-term clinical outcomes in patients treated with either BVS or EES. Implantation of bioresorbable vascular scaffold showed a higher rate of events. Procedural factors might have had a role in these findings and an optimal implantation technique including high pressure post-dilatation should be considered also in the acute setting when using bioresorbable scaffolds.

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