JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 12, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.03.029

Long-Term Clinical Outcomes of Patients Treated With Everolimus-Eluting Bioresorbable Stents in Routine Practice

2-Year Results of the ISAR-ABSORB Registry

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ABSTRACT

OBJECTIVES The aim of this study was to report clinical outcomes in patients treated in routine practice 2 years after everolimus-eluting bioresorbable stent (BRS) implantation.

BACKGROUND Long-term results in patients undergoing BRS implantation in routine clinical practice are sparse, and existing evidence from randomized trials considers mostly selected patients.

METHODS The ISAR-ABSORB registry enrolled consecutive patients undergoing BRS implantation in routine clinical practice at 2 high-volume centers in Germany. Angiographic follow-up was scheduled after 6 to 8 months and clinical follow-up to 24 months. The primary endpoint was the composite of death, myocardial infarction, or target lesion revascularization, and secondary endpoints included individual components of the primary endpoint and definite stent thrombosis. Event rates were calculated using the Kaplan-Meier method.

RESULTS A total of 419 patients were included. The mean age was 66.6 ± 10.9 years, 31.5% had diabetes, and 39.0% presented with acute coronary syndrome. Forty-nine percent of lesions were considered complex (American College of Cardiology/American Heart Association type B2 or C), and 13.1% were bifurcation lesions. The mean reference vessel diameter was 2.89 ± 0.46 mm. At 2 years, the primary endpoint had occurred in 21.6% of patients: death in 6.3%, myocardial infarction in 3.9%, target lesion revascularization in 16.0%, and definite stent thrombosis in 3.8%.

CONCLUSIONS Long-term follow-up of patients treated with BRS in routine practice showed higher event rates than expected. Future studies are required to determine the impact of changes in implantation technique and to define the optimal duration of dual antiplatelet therapy in these patients. (J Am Coll Cardiol Intv 2017;10:1222–9)

Bioresorbable stents (BRS) are a novel alternative to metallic drug-eluting stents (DES) for percutaneous coronary intervention, which aim to reduce the incidence of late stent failure by removing the nidus for direct adverse events related to the stent backbone (1). Additional hypothesized benefits include late luminal enlargement and restoration of arterial vasomotion (2), though neither of these advantages could be demonstrated in a recently reported randomized clinical trial (3).

A meta-analysis that included data from 6 randomized trials comparing BRS with metallic everolimus-eluting stents reported comparable efficacy at 1 year but raised concerns with BRS related to a 2-fold

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Manuscript received January 5, 2017; revised manuscript received March 10, 2017, accepted March 23, 2017.

increased risk for stent thrombosis in BRS-treated patients (4). Moreover, although long-term clinical outcomes of patients enrolled in randomized trials have been reported (3,5–7), these studies were limited by the inclusion of only patients in clinically stable condition with noncomplex lesions, thus limiting the generalizability of their findings. Although outcomes of BRS implantation in more complex patient populations have been reported from "all comers" registries, the duration of reported follow-up is limited to 6 to 12 months (8–11).

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Against this background, the aim of the present study was to evaluate long-term clinical outcomes among patients with a broad range of clinical and lesion characteristics undergoing BRS implantation in a real-world setting.

METHODS

PATIENT SELECTION. The study was performed at 2 centers in Munich, Germany. Consecutive patients with de novo lesions undergoing single-vessel or multivessel percutaneous coronary intervention with everolimus-eluting BRS between September 2012 and June 2014 were included. Patients were considered eligible for treatment in case of: 1) a stenosis of at least 50% diameter stenosis; and 2) angina symptoms and/or pathological functional testing. The study details have previously been described (12).

PROCEDURE AND FOLLOW-UP. The investigated BRS consists of a backbone composed of poly-L-lactic acid, coated with a mixture of poly-D-L-lactic acid and the antirestenotic drug everolimus. The strut thickness is 150 μm. Pre-dilatation was mandatory, advised maximum balloon pressure at implantation was within the burst rate limits, and the decision to perform post-dilatation was at the discretion of the operator. Procedural success was defined as residual stenosis of <30% with TIMI (Thrombolysis In Myocardial Infarction) flow grade 3. During the procedure, all patients received unfractionated heparin or bivalirudin. All patients received a loading dose of aspirin and an adenosine diphosphate receptor antagonist according to the clinical presentation and guidelines, followed by aspirin indefinitely and 12 months of the selected adenosine diphosphate receptor antagonist (13). Daily electrocardiographic recordings and laboratory testing of cardiac biomarkers were performed daily until discharge. Clinical follow-up was conducted by telephone or office visit at 1, 12, and 24 months, and routine angiographic follow-up was scheduled for all patients at 6 to 8 months. Relevant data were collected and entered into a computer database by specialized personnel of the clinical data management center (ISAResearch Center, Munich, Germany). In case a death was reported, documents were requested from the family practitioner or last treating physician. The primary endpoint was a clinical composite of death, myocardial infarction, and ischemia-driven target lesion revascularization (TLR). Secondary endpoints included the individual components of the primary endpoint in addition to stent thrombosis defined by Academic Research Consortium criteria.

QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS. Quantitative coronary angiographic analysis of the index procedure and the follow-up angiogram was performed off-line with an automated edge detection system (CMS version 7.1, Medis Medical Imaging Systems, Leiden, the Netherlands). Bifurcation lesions were defined as lesions occurring at or adjacent to a significant branch of a major coronary artery (subjectively defined as a side branch the operator would not wish to lose). Measurements included percentage diameter stenosis, in-segment binary restenosis, and in-stent late luminal loss, defined as the difference between minimal luminal diameter post-implantation and minimal luminal diameter at angiographic follow-up. Further details of the quantitative coronary angiographic protocol have been published previously (12).

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or as median (interquartile range), and categorical variables are expressed as percentages and counts. Event rates were calculated according to the Kaplan-Meier method. For statistical analysis, the R statistical package version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used. Variable selection for the multivariate model was performed using the least absolute shrinkage and selection operator regression method provided in the R package glmnet after entering all baseline and procedural characteristics as candidates. A Cox proportional model was applied after also entering a cluster term to account for the frequent presence of multiple treated lesions in the same patient. A p value <0.05 was considered to indicate statistical significance.

RESULTS

A total of 419 patients were included in the analysis. The mean age at the time of the index procedure was

ABBREVIATIONS AND ACRONYMS

BRS = bioresorbable stent(s)

DES = drug-eluting stent(s)

TLR = target lesion revascularization

TABLE 1 Baseline Clinical Characteristics (n = 419)

Age (yrs)	66.6 ± 10.9
Male	321 (76.6)
Diabetes	132 (31.5)
Insulin treated	43 (10.3)
Hypertension	361 (86.2)
Hypercholesterolemia	281 (67.1)
Current smoker	90 (21.5)
Glomerular filtration rate <60 mL/min	98 (23.8)
Body mass index (kg/m^2)	27.8 ± 4.8
Left ventricular ejection fraction (%)	55.2 ± 9.4
Previous myocardial infarction	109 (26.0)
History of coronary artery bypass surgery	18 (4.3)
Multivessel disease	319 (76.1)
Clinical presentation	
Stable coronary artery disease	256 (61.1)
Unstable angina	48 (11.5)
Non-ST-segment elevation myocardial infarction	80 (19.1)
ST-segment elevation myocardial infarction	35 (8.4)

Values are mean ± SD or n (%).

TABLE 2 Lesion and Procedural Characteristics (n = 527 Lesions)

Baseline lesion characteristics	
Target vessel	
Left anterior descending coronary artery	237 (45.0)
Left circumflex coronary artery	110 (20.9)
Right coronary artery	176 (33.4)
Venous bypass graft	4 (0.8)
Complex lesion morphology*	258 (49.0)
Bifurcation lesion	69 (13.1)
Chronic occlusion	7 (1.3)
Reference vessel diameter (mm)	2.89 ± 0.46
Minimal luminal diameter (mm)	0.91 ± 0.47
Diameter stenosis (%)	68.6 ± 15.3
Lesion length (mm)	15.8 ± 9.5
Lesions per patient	1.3 ± 0.5
1 lesion treated	327 (78.0)
2 lesions treated	79 (18.9)
3 lesions treated	10 (2.4)
4 lesions treated	3 (0.7)
Procedural characteristics	
Pre-dilatation	515 (97.7)
Nominal balloon size (mm)	3.24 ± 0.46
Maximum balloon pressure (atm)	15.0 ± 3.9
Maximum stent diameter (mm)	3.12 ± 0.38
Stents per lesion	1.2 ± 0.4
Total stent length (mm)	26.9 ± 13.2
Patients with stent overlap	75 (17.9)
Patients treated with at least one 2.5-mm BRS	101 (24.1)
Post-dilatation	377 (71.5)
Lesion characteristics post-intervention	
Minimal luminal diameter (mm)	2.60 ± 0.41
Diameter stenosis (%)	13.7 ± 6.5
Post-procedural medication†	
Aspirin	400 (95.5)
ADP receptor antagonist	419 (100.0)
Clopidogrel	311 (74.4)
Ticagrelor	52 (12.4)
Prasugrel	56 (13.7)
Oral anticoagulation	59 (14.1)
Vitamin K antagonist	48 (11.5)
Rivaroxaban	7 (1.7)
Dabigatran	4 (1.0)
Statins	390 (93.1)

Values are n (%) or mean ± SD. *Complex lesion morphology was defined as lesion types B2 and C according to the American College of Cardiology/American Heart Association grading system. †Per patient (n = 419).
ADP = adenosine diphosphate; BRS = bioresorbable stent.

66.6 ± 10.9 years, 76.6% were men, and 31.5% had diabetes. Acute coronary syndrome was present in 38.9% of patients. Baseline characteristics are displayed in Table 1. Forty-nine percent of lesions were considered complex, defined as American College of Cardiology/American Heart Association type B2 or C lesion morphology. The mean reference vessel diameter was 2.89 ± 0.46 mm, and the mean lesion length was 15.8 ± 9.5 mm. Pre-dilatation and post-dilatation were performed in 97.7% and 71.5% of cases, respectively. Optical coherence tomography was used in 3.6%. Angiographic success was achieved in 510 lesions (96.8%). Procedural details are shown in Table 2. At discharge, 95.5% of patients received aspirin, and all patients received adenosine diphosphate receptor antagonists. In addition, 14.7% were on oral anticoagulation.

OUTCOMES. Angiographic follow-up was available for 71.0% (374 of 527) of the lesions. Quantitative coronary angiographic analysis demonstrated a mean in-stent late luminal loss of 0.27 ± 0.51 mm and a mean in-segment diameter stenosis of 27.7 ± 16.1% at 6- to 8-month angiographic follow-up. Angiographic findings at follow-up are provided in Table 3. The median clinical follow-up duration was 24.0 months (interquartile range: 20.5 to 24.0 months). At 2 years, the incidence of the primary endpoint was 21.6%: 6.3% of patients died, 3.9% had myocardial infarctions, and 16.0% required TLR. Definite stent thrombosis occurred in 3.8% of patients. Clinical outcomes are shown in Table 4, and event rates by Kaplan-Meier estimates are shown in Figures 1 and 2. Details of patients who experienced definite stent thrombosis are presented in Table 5.

The least absolute shrinkage and selection operator method was used to select the variables from Tables 1 and 2 to be entered into the multivariate Cox proportional model for assessing the independent predictors of the primary endpoint and TLR at 2 years.

TABLE 3 Angiographic Outcomes at 6 to 9 Months (n = 374 Lesions)

Reference vessel diameter (mm)	2.95 ± 0.46
Angiographic characteristics (in-stent)	
Minimal luminal diameter (mm)	2.33 ± 0.63
Diameter stenosis (%)	21.2 ± 17.4
Late luminal loss (mm)	0.27 ± 0.51
Angiographic characteristics (in-segment)	
Minimal luminal diameter (mm)	2.14 ± 0.59
Diameter stenosis (%)	27.7 ± 16.1
Late luminal loss (mm)	0.21 ± 0.50
Restenosis rate	30 (8.0)

Values are mean ± SD or n (%).

No independent predictor of the composite endpoint was identified, and the only independent predictor of TLR was implanted BRS size (−0.5 mm) (Table 6).

DISCUSSION

The main finding of this study was that in a real-world, all-comers population undergoing percutaneous coronary intervention, BRS offer reasonable long-term clinical results, but rates of adverse events were higher than expected, driven mainly by TLR, though also due in part to a high rate of stent thrombosis. Moreover, no independent predictor of the primary endpoint was identified, and the only independent predictor of TLR was the maximum BRS diameter.

Short- to medium-term clinical outcomes from a number of all-comers registries have been reported, but the duration of follow-up reported in published research has generally not exceeded 12 months. Moreover, in randomized trials of BRS, clinical primary endpoints were assessed at 1 year after implantation. However, given that resorption of the Absorb BRS has been shown to take up to 2 to 4 years (14), it is intuitive that potential advantages may not become apparent until a later juncture, either during degradation or after complete resorption of the device. Indeed, in single-arm studies, late luminal enlargement between 6 months and 2 years has been observed on serial imaging (15), and restoration of vessel vasomotion has been shown in response to acetylcholine and nitroglycerin at 12 and 24 months, respectively (16). However, neither of these advantages could be demonstrated in a recently reported randomized clinical trial with primary assessment at 3-year follow-up (3).

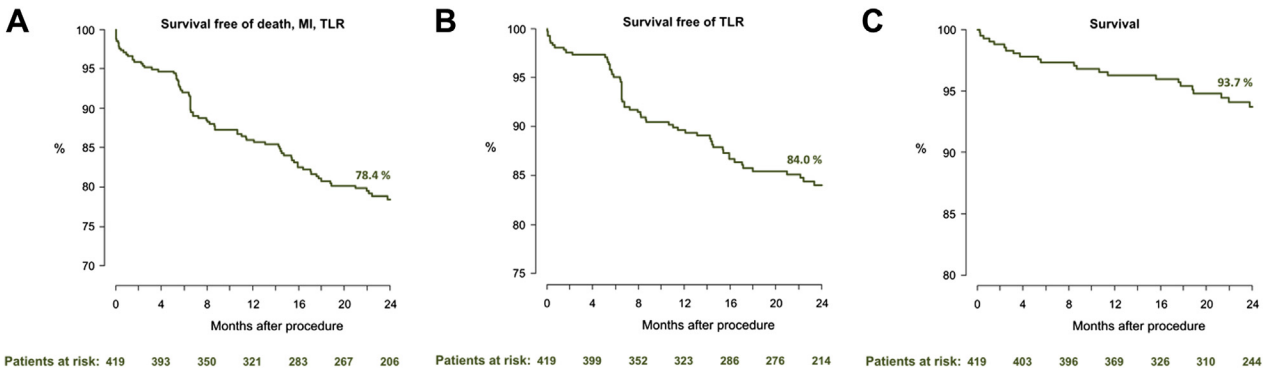
TABLE 4 Clinical Outcomes at 2 Years (n = 419)

	1 Year	2 Years
Death	3.7	6.3
Cardiac death	2.2	3.1
Myocardial infarction	2.7	3.9
Death or myocardial infarction	5.8	9.3
Definite stent thrombosis	2.5	3.8
Definite or probable stent thrombosis	2.9	4.2
Target lesion revascularization	10.6	16.0
Composite of death, myocardial infarction, and target lesion revascularization	14.3	21.6

Values are % by Kaplan-Meier estimates.

Clinical outcomes at 2- to 3-year follow-up have been reported in a number of randomized trials comparing outcomes of patients treated with the Absorb BRS versus conventional DES. The 501-patient ABSORB II trial showed a higher rate of target lesion failure (TLF) (a composite of cardiac death, target vessel myocardial infarction, and TLR) in the BRS group, occurring in 10% of patients in the BRS group (vs. 5% in the DES group; p = 0.0425), and a numerically higher rate of definite stent thrombosis in 3% (vs. 0.0%, respectively; p = 0.06) (3). Furthermore, the study failed to demonstrate noninferiority of the BRS with regard to late luminal loss after 3 years and superiority regarding vasomotion testing (3). The 2-year results of the ABSORB Japan trial were consistent, again showing numerically higher event rates in the BRS group but no statistically relevant differences between treatment arms (6). TLF (which differed from the definition used in ABSORB II by the inclusion of target vessel myocardial infarction rather than all myocardial infarction and all TLR rather than just ischemia-driven TLR) occurred in 7.3% in the BRS group (vs. 3.8% in the DES group, p = 0.18) and definite stent thrombosis in 3.1% (vs. 0.8% for DES, p = 0.28) (6). More recently 2-year data from the pivotal ABSORB-III trial was presented showing that at 2 years the rate of TLF was now higher with BRS compared with DES (11.0% vs. 7.9%; p = 0.03) (17). Subsequently, the large-scale AIDA (Amsterdam Investigator-initiateD Absorb strategy all-comers) trial reported comparable rates of TLF between BRS and DES at median follow-up of 707 days (11.7% vs. 10.7%; p = 0.43), but a significantly higher rate of definite/probable stent thrombosis with BRS (3.5% vs. 0.9%; p < 0.001) (18). Thus, there is a considerable degree of variation in event rates even among randomized trials. Nonetheless, despite a high rate of pre-dilatation (97.7%), a rate of post-dilatation comparable with or higher than those in randomized trials, and good acute procedural results, rates of adverse events are numerically higher in our report (primary endpoint of death myocardial infarction and

FIGURE 1 Clinical Outcomes at 24 Months in Patients Treated With Bioresorbable Stents

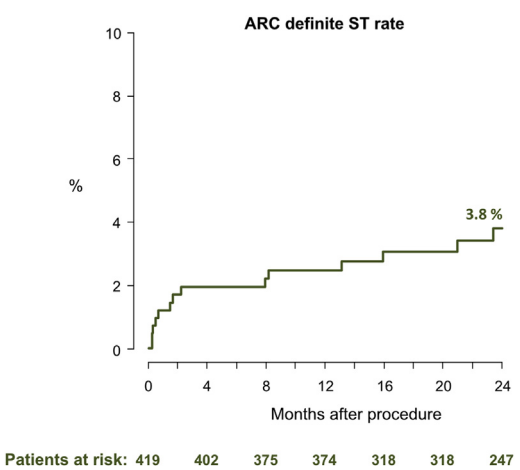


(A) Composite of death, myocardial infarction (MI), or target lesion revascularization (TLR). **(B)** TLR. **(C)** Death.

TLR 21.6%, stent thrombosis 3.8%). TLF was driven mainly by TLR in the present registry (16.0%) compared with rates ranging from 2.1% to 5.7% in the aforementioned trials.

There are a number of potential explanations for this discrepancy in event rates. First and foremost, patients enrolled in randomized trials were highly selected, whereas the ISAR-ABSORB registry was broadly inclusive, resulting in an older patient population, with a generally less favorable cardiac risk factor profile. Moreover, patients with acute myocardial infarction were excluded from most of these trials, whereas this accounted for clinical presentation in more than a quarter of patients in the ISAR-ABSORB registry, with non-ST-segment elevation myocardial infarction accounting for the majority. With respect to lesion complexity, bifurcation lesions with side branches >2 mm in diameter and chronic total occlusions were excluded from many randomized studies (19,20) but were included in the current registry, with bifurcations accounting for 13% of lesions, for example. Furthermore, lesions treated in our registry were longer than those treated in randomized trials.

FIGURE 2 Definite Stent Thrombosis at 24 Months in Patients Treated With Bioresorbable Stents



ARC = Academic Research Consortium; ST = stent thrombosis.

In terms of stent thrombosis specifically, the rate of 2.5% in our registry at 1 year was higher than rates in the randomized studies, which ranged from 0% to 1.5% at 1 year. Between 1 and 2 years, however, rates of stent thrombosis in the BRS group doubled in the cases of the ABSORB Japan and TROFI II trials and increased by a factor of 5 in the case of ABSORB II trial between 1 and 3 years (from 0.6% to 3.0%). In the ABSORB Japan trial, optical coherence tomography showed malapposition and uncovered struts as possible reasons in patients with stent thrombosis between 1 and 2 years, although no flow disturbances were seen during angiographic follow-up (6). Although overall rates were higher in the ISAR-ABSORB registry, the increase during the corresponding interval was not as dramatic.

The only independent predictor of TLR was a smaller BRS diameter. Although no influence of the BRS diameter on the primary endpoint and only a trend toward a higher TLR rate (11.7% vs. 8.3%; $p = 0.42$) was observed after 1 year (21), poor outcomes for patients with small-vessel disease has been described in the ABSORB III trial (22). It is not surprising that a smaller BRS diameter is a predictor of outcomes, because the

TABLE 5 Details of Definite Stent Thrombosis

Case #	Time (days)	Diabetes	ACC/AHA Classification	Minimum BRS Diameter (mm)	Post-Dilatation	Maximum Balloon Pressure (atm)	ADP Antagonist	On DAPT
1	245	Insulin	B1	3.0	No	17	Clopidogrel	Yes
2	7	No	B2	2.5	No	12	Ticagrelor	Yes
3	8	No	B1	3.5	No	18	Prasugrel	Yes
4	14	Oral	B2	3.5	No	10	Clopidogrel	Yes
5	20	No	B1	3.0	Yes	15	Clopidogrel	Yes
6	49	No	B2	3.5	No	12	Clopidogrel	No
7	393	No	B1	3.0	No	15	Clopidogrel	Yes
8	66	Oral	B1	3.0	No	14	Clopidogrel	Yes
9	44	Diet	B2	3.5	Yes	17	Clopidogrel	Yes
10	237	Insulin	B2	3.0	No	16	Clopidogrel	Yes
11	8	No	B2	3.5	Yes	12	Clopidogrel	Yes
12	478	No	B2	3.5	No	12	Clopidogrel	No
13	629	Insulin	B1	3.5	No	18	Clopidogrel	No
14	702	No	B2	3.0	Yes	14	Clopidogrel	No

ACC = American College of Cardiology; AHA = American Heart Association; DAPT = dual antiplatelet therapy; other abbreviations as in Table 2.

probability of restenosis is higher because of a lower threshold for ischemia when considering the same proportion of tissue growth than in larger vessels and the BRS strut thickness of 160 μm.

Finally, the ISAR-ABSORB registry included patients treated in the very early days of clinical experience with BRS. Over time, the implantation technique has evolved. Indeed, the impact of a learning curve on adverse clinical outcomes with BRS has been described, with 1 study showing a considerably higher rate of TLF (cardiac death, target vessel myocardial infarction, and TLR) at 6-month follow-up between the first 100 consecutive patients and the second 100 consecutive patients in an all-comers registry (10.1% vs. 1.1%; $p < 0.01$), driven by target vessel revascularization (23). Another study including 1,300 patients, of whom 42 experienced stent thrombosis, demonstrated a decrease in the rate of stent thrombosis after the implementation of a protocol-mandated implantation technique (24). In addition, an analysis of data from the GHOST-EU registry showed that the presence of lesion predilatation, accurate sizing, and scaffold postdilatation was an independent predictor of 1-year adverse events (hazard ratio: 0.75; 95% confidence interval: 0.61 to 0.93; $p = 0.007$) (25). Taking these findings into account, careful selection of low-risk patients in addition to a dedicated treatment strategy may have the potential to improve clinical outcomes going forward.

STUDY LIMITATIONS. This was a single-arm observational study, so outcomes were not compared with those with current-generation DES. Patients were enrolled at 2 centers, a factor that may influence the generalizability of the results to the broader interventional cardiology community. The number of patients might have been too small to accurately identify predictors of the primary endpoint or TLR. There was no routine intravascular imaging at baseline or follow-up angiography, performance of which may have allowed the identification of additional predictors of BRS failure. Finally, although in accordance with institutional practice, all patients treated with BRS were invited for angiographic follow-up, only approximately 70% attended for follow-up. In a prior analysis of this dataset, a sensitivity analysis showed

TABLE 6 Multivariate Analysis of Predictors of the Primary Endpoint and TLR

	Composite of Death, MI, and TLR		TLR	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (yrs)	1.21 (0.91–1.60)	0.19	1.21 (0.83–1.78)	0.33
Sex	0.66 (0.35–1.25)	0.20	0.52 (0.24–1.16)	0.11
Hypercholesterolemia	1.40 (0.78–2.52)	0.26	–	–
Current smoker	0.61 (0.32–1.17)	0.14	0.48 (0.21–1.11)	0.09
Body mass index	–	–	1.04 (0.76–1.43)	0.81
Ejection fraction (−10%)	1.21 (1.53–0.96)	0.11	1.27 (1.61–1.00)	0.05
Glomerular filtration rate (−30 ml/min)	–	–	0.82 (1.15–0.58)	0.25
Multivessel disease	1.39 (0.71–2.73)	0.34	–	–
Number of lesions	1.23 (0.87–1.76)	0.25	–	–
Complex lesion morphology*	1.09 (0.66–1.79)	0.74	1.31 (0.74–2.31)	0.35
Bifurcation lesion	1.54 (0.88–2.68)	0.13	1.48 (0.76–2.87)	0.25
Post-dilatation	1.24 (0.76–2.01)	0.39	–	–
Stent overlap	1.25 (0.75–2.09)	0.40	1.47 (0.82–2.64)	0.20
Maximum stent diameter (−0.5 mm)	–	–	1.39 (1.90–1.02)	0.04
Total stent length	1.06 (0.95–1.18)	0.33	1.08 (0.96–1.21)	0.19

*Complex lesion morphology was defined as lesion types B2 and C according to the American College of Cardiology/American Heart Association grading system.

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; TLR = target lesion revascularization.

that the rates of death and the composite of death and myocardial infarction were significantly higher in patients without angiographic follow-up compared with those with follow-up (12). This should be borne in mind when interpreting angiographic follow-up data.

CONCLUSIONS

The present study is the first report of long-term clinical outcomes among patients undergoing BRS implantation during routine clinical practice. Event rates were higher than expected, possibly explained in part by a less favorable cardiovascular risk profile and lesion characteristics, in addition to the effect of very early clinical experience with the device. Randomized studies with less restrictive inclusion criteria and longer clinical follow-up are required.

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PERSPECTIVES

WHAT IS KNOWN? BRS have entered clinical practice, and evidence from randomized trials is available, demonstrating reasonable results for selected patients.

WHAT IS NEW? The present analysis is the first to report long-term follow-up of all comers undergoing BRS implantation during routine clinical practice. The event rates were higher than expected, with the implanted stent size being identified as an independent predictor of poor outcomes.

WHAT IS NEXT? Further long-term data, as well as randomized studies with minimal inclusion criteria, is necessary. Information from intravascular imaging studies will be needed to better understand reasons for BRS failure.

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KEY WORDS bioresorbable stent(s), clinical outcomes, percutaneous coronary intervention