Twelve-month clinical outcomes after coronary stenting with the Genous Bio-engineered R Stent in patients with a bifurcation lesion: from the e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) registry

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Background **The e-Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth (e-HEALING) registry was designed to capture clinical data on the use of the endothelial progenitor cell capture stent (ECS) in routine clinical practice. In this analysis, we investigated the 12-month clinical outcomes in patients treated with an ECS for a bifurcation lesion.**

Methods **The worldwide, prospective, nonrandomized e-HEALING registry aimed to enrol 5000 patients treated for coronary artery disease with one or more ECS between October 2005 and October 2007. Clinical follow-up was obtained at 1, 6, and 12 months. The primary endpoint was target vessel failure (TVF), defined as the composite of cardiac death, myocardial infarction, and target vessel revascularization at 12 months.**

Results **A total of 573 patients were treated for at least one bifurcation lesion and were assessed in the current analysis. Baseline characteristics showed a median age of 65 years; 21% were diabetic patients and 36% had unstable angina. A total of 63% of the bifurcation lesions were located in the left artery descending and the mean stent length was 20.7 ± 12.6 mm. At 12 months, TVF was 12.7% and target lesion revascularization was 7.5%. Definite or probable stent thrombosis occurred in 1.7% of the patients. Moreover, one or more stents per lesion [hazard ratio (HR): 2.79, 95% confidence interval (CI): 1.60–4.86, $P < 0.001$], predilatation (HR: 0.39, 95% CI: 0.17–0.87, $P = 0.023$), and lesions located in the right coronary artery (HR: 4.56, 95% CI: 1.07–19.5, $P = 0.041$) were independent predictors of TVF.**

Conclusion **In the e-HEALING registry, coronary bifurcation stenting with the ECS results in favorable clinical outcomes and low incidences of repeat revascularization and stent thrombosis.** *Coron Artery Dis* **23:201–207** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The endothelial progenitor cell capture stent (ECS) is a novel stent technology with a 'prohealing' approach. The stent struts are coated with a biocompatible matrix with murine, monoclonal, antihuman $CD34^+$ antibodies that are covalently attached. These antibodies specifically target the surface antigens present on circulating endothelial progenitor cells (EPC), thereby creating an immune affinity surface for preferentially capturing these circulating cells. After the EPCs are immobilized on the stent surface, it is hypothesized that these cells rapidly differentiate into a functional endothelial layer. This 'prohealing' technology may effectively inhibit stent-related thrombus formation and neointimal hyperplasia. The clinical safety and efficacy of the ECS was demonstrated in the Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth (HEALING) First-In-Man [1] and HEALING II study [2,3] in noncomplex, de-novo coronary lesions with only 1 month of dual antiplatelet therapy (DAPT) prescribed. At 1 year, both studies showed favorable clinical outcomes.

Several randomized studies evaluating different treatment strategies of bifurcation lesions have provided valuable insights. However, clinical outcomes after stenting of

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coronary bifurcation lesions in a real-world population are limited. The e-HEALING [4] registry is a multicenter, prospective, worldwide, postapproval registry that evaluated the ECS in 4996 patients. The e-HEALING registry included different types of patients and lesions with varying degrees of complexity. At the 1-year follow-up, the primary endpoint of target vessel failure (TVF), defined as the composite of cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR), was 8.4%. The target lesion revascularization (TLR) rate was 5.7%, and definite or probable stent thrombosis (ST) occurred in 1.1% of the patients.

In this study, we evaluated the 12-month clinical outcomes of patients enrolled in the e-HEALING registry who were treated with an ECS for a bifurcation lesion.

Materials and methods

Study design

The study design of the e-HEALING registry has been reported previously [4]. In brief, the design was a multicenter, prospective postmarketing surveillance registry including 4996 patients from 144 centers in Europe, Asia Pacific, Middle East, and Latin America between October 2005 and October 2007. Patients undergoing a nonurgent percutaneous coronary intervention (PCI) were eligible for inclusion if they had at least one de-novo or restenotic coronary artery lesion suitable for stenting. ECS of 2.75–4.00 mm in diameter and 9–33 mm in length were available. Per protocol, it was recommended that patients were at least on statin therapy for 2 weeks. This study was conducted according to the Declaration of Helsinki. The local medical ethics committees approved the study protocol at sites at which such approval was required. If determined necessary, written informed consent was obtained. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [5].

Endothelial progenitor cell capture stent

The ECS comprises a polysaccharide matrix coating with anti-CD34$^+$ antibodies covalently bonded to the surface of a 316l stainless-steel stent (Genous Bio-engineered R Stent; OrbusNeich Medical Technologies, Fort Lauderdale, Florida, USA). These anti-CD34$^+$ antibodies specifically target the circulating EPC population associated with neovascularization and arterial repair response.

Study population and procedure

For this substudy, we included all patients who underwent a nonurgent PCI for a bifurcation lesion treated with an ECS who were enrolled in the e-HEALING registry. A baseline angiogram was performed to assess angiographic inclusion and exclusion criteria. PCI was performed according to the local standard institutional practice. Predilatation and postdilatation were left to the discretion of the operator. The use of concomitant medication was left to the discretion of the operator and according to the local standard clinical practice. All patients were to receive aspirin indefinitely. Clopidogrel (75 mg once daily) was recommended for at least 1 month after nonurgent stenting and for 6 or 12 months in patients treated for an acute coronary syndrome or an ST-elevation MI according to local practice. When a patient was treated for multiple lesions, all lesions were preferably treated with an ECS but not mandatory per protocol.

Data collection and management

Baseline clinical, angiographic, and procedural characteristics were collected and stored in a central internet-based electronic data capture system (Eventa; KIKA Medical, Paris, France), with built-in queries to improve accuracy, and independently maintained by a contract research organization (Cardialysis, Rotterdam, the Netherlands). Angiographic variables were obtained by visual estimation.

All outcome events were assessed at discharge of initial hospitalization, at 30 days, at 6 months, and at 12 months. An independent Clinical Event Committee adjudicated the following events: death, MI, TVR, TLR, and ST. The Clinical Event Committee was managed independently by Cardialysis.

All site personnel were trained on the protocol, device, and internet-based database before the initiation of the registry at each respective center. Trained and qualified clinical research associates of Cardialysis monitored the registry throughout its duration by personal visits to the physicians' facilities, telephone contact with the physician or designee, and/or remotely through the internet-based database. A comprehensive, integrated data management plan, including on-line queries and remote data cleaning, was implemented to insure the integrity of the data. All changes to the database were tracked by an audit trail.

Clinical endpoints and definitions

The primary clinical endpoint of this substudy of the e-HEALING registry was TVF at the 12-month follow-up, defined as the composite of cardiac death, MI (unless unequivocally attributable to a nontarget vessel), and TVR by either PCI or bypass graft surgery. The secondary endpoints included the composite of cardiac death, MI, and clinically driven TLR, as well as the individual components of TVF, all-cause mortality, TLR, and ST. All deaths were considered cardiac death unless otherwise documented. A non-Q-wave MI was defined as an elevation in postprocedure creatinine kinase-myocardial band levels above two times the upper limit of normal in the absence of pathological Q waves. A Q-wave MI was defined as the development of new, pathological Q-waves in two or more continuous leads with an elevation of creatinine kinase-MB above the upper limit of normal.

TLR was defined as any repeat PCI of the bifurcation target lesion or bypass surgery of the target vessel performed for restenosis, wherein the bifurcation target lesion was defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent or the related side branch. A revascularization was indicated clinically if the stenosis of the treated lesion was at least 50% of the lumen diameter on the basis of quantitative coronary angiography with one of the following: a positive history of recurrent angina pectoris, objective signs of ischemia at rest (ECG changes) or a positive ischemia-detection test, or abnormal results of any invasive functional diagnostic test. A revascularization of a stenosis of at least 70% of the lumen diameter by angiographic assessment in the absence of the above-mentioned ischemic signs or symptoms was also considered a TLR. TVR was defined as the repeat revascularization of any segment of the index major coronary artery treated at the index procedure. ST was defined according to the definitions of the Academic Research Consortium criteria [6].

Statistical analysis

Categorical variables were reported with counts and percentages, and continuous variables were reported with the means and SDs or median and interquartile ranges. Cumulative event rates were estimated using the Kaplan–Meier method and compared with the log-rank test. Follow-up was censored at the last known date of follow-up or at 12 months, whichever came first. As a frame of reference, baseline and outcomes variables of patients included in the e-HEALING registry treated without bifurcation lesions are presented in the tables.

A Cox regression analysis was performed to identify independent predictors of the primary endpoint of TVF using all clinical and angiographic variables included in Tables 1 and 2. The continuous variables age, lesions per patient, baseline angiographic findings, stents per lesion, and the final angiographic findings were entered into the model as categorical variables as follows: age of less than 65 years, one or more lesion per patient, lesion length of more than 20 mm, reference vessel diameter of more than 3.0 mm, percentage diameter stenosis of more than 70%, and one or more stent per lesion, respectively. Statistical significance was accepted for a two-sided value of P less than 0.05. Statistical analyses were performed at the Academic Medical Center Amsterdam using the SPSS software package (version 17; SPSS Inc., Chicago, Illinois, USA).

Results

Baseline clinical, angiographic, and procedural characteristics

In the e-HEALING registry, a total of 4996 patients were included. Fifty-two patients were excluded because of missing procedure-related data ($n = 16$); no ECS was implanted or ECS placement was unknown ($n = 36$). Five patients were excluded due to missing follow-up data. Of the 4944 patients, 573 patients were treated for one or more bifurcation lesions. The baseline clinical characteristics are summarized in Table 1. The median age of the patients treated for one or more bifurcation lesions was 65 years; 78% were men and 21% were diabetic patients. The baseline angiographic and procedural characteristics are summarized in Table 2. On average, 1.6 lesions per patient were treated (bifurcation lesions and nonbifurcation lesions).

A total of 617 bifurcation lesions were treated. Sixty-three percent of the bifurcation lesions were located in the left artery descending and 56% of the bifurcation lesions were classified as a type B2 or C lesion. The mean lesion length was 16.8 ± 8.7 mm and the reference vessel diameter was 3.0 ± 0.4 mm by visual estimation. A mean of 1.2 stents per bifurcation lesion was used.

Outcomes in patients with bifurcation lesions

The 12-month clinical outcomes are summarized in Table 3. At the 12-month clinical follow-up, the cumulative rate of TVF was 12.7%. A Kaplan–Meier curve of TVF is shown

Table 1 Baseline clinical characteristics

Variable	Bifurcation lesion ($n=573$)	Nonbifurcation lesions ($n=4366$)
Demographics – number/total number (%)		
Age – median (IQR)	65 (55–73)	63 (54–72)
Male sex	477 (78)	3447 (79)
Diabetes		
Oral medication	120 (21)	843 (19)
Insulin dependent	31 (5.4)	242 (5.5)
Hypertension	381 (67)	2992 (69)
Hypercholesterolemia	411 (72)	3257 (75)
Current smoker	130 (23)	1099 (25)
Family history of MI	186 (33)	1195 (28)
History – number/total number (%)		
Prior MI	242 (42)	1575 (36)
Prior PCI	129 (23)	819 (19)
Prior CABG	35 (6.1)	269 (6.2)
Prior stroke	32 (5.6)	263 (6.1)
Ischemic status – number/total number (%)		
Unstable angina	206 (36)	1885 (43)
Stable angina	279 (49)	1859 (43)
Silent ischemia	88 (15)	622 (14)
Medication use – number/total number (%)		
Aspirin	486 (85)	3609 (83)
Clopidogrel	366 (64)	2560 (59)
Angiotensin II receptor blockers	69 (12)	461 (11)
Angiotensin-converting-enzyme inhibitors	244 (43)	1573 (36)
β-Blockers	385 (67)	2413 (55)
Calcium antagonists	104 (18)	645 (15)
Nitrates	213 (37)	1357 (31)
Statins	464 (81)	3495 (80)
Indication PCI – number/total number (%)		
Elective PCI	298 (52)	2084 (48)
Unstable angina	74 (13)	919 (21)
Non-STEMI	28 (4.9)	261 (6.0)
Post-STEMI	38 (6.6)	362 (8.3)
Post unstable angina	46 (8.0)	257 (5.9)
Post-non-STEMI	38 (6.6)	218 (5.0)
Others/unknown	51 (8.9)	272 (6.2)

CABG, coronary artery bypass grafting; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 2 Baseline angiographic and procedural characteristics

Variable	Bifurcation lesion ($n=573$)	Nonbifurcation lesions ($n=4366$)
Patient characteristics		
Multivessel PCI	246 (42%)	589 (13%)
Lesions per patient – mean (SD)	1.6 (0.8)	1.3 (0.6)
Lesion characteristics of the bifurcation lesion	($L=617$)	($L=5947$)
Lesion type – number (%)		
De novo	600 (97)	5812 (98)
Restenotic	17 (3)	135 (2.3)
Location of bifurcation – number (%)		
Left main/LAD/RCx	25 (4)	58 (1.0)
LAD territory	387 (63)	2495 (42)
RCx territory	149 (24)	1283 (21)
RCA territory	53 (9)	2084 (35)
Bypass graft	3 (1)	72 (1)
ACC/AHA lesion classification – number (%)		
A	17 (3)	993 (17)
B1	174 (28)	2158 (36)
B2	276 (45)	1670 (28)
C	150 (24)	1126 (19)
Calcification – number (%)	196 (32)	1696 (29)
Baseline angiographic findings – mean (SD)		
Lesion length main branch (mm)	16.8 (8.7)	16.8 (8.6)
Percentage diameter stenosis – main branch	85 (12)	85 (12)
Predilatation performed – number (%)	468 (76)	3614 (61)
Preprocedure thrombus – number (%)	70 (11)	657 (11)
Stent length – mm (in the main branch) – mean (SD)	20.7 (12.6)	19.3 (10.5)
Stent diameter – mm (in main branch) – mean (SD)	3.1 (0.4)	3.1 (0.4)
Stent use		
Stents per lesion – mean (SD)	1.2 (0.5)	1.1 (0.4)
Postdilatation – number (%)	299 (49)	2227 (37)
Final angiographic findings – mean (SD)		
Percentage diameter stenosis – main branch	5 (16)	4 (14)
Final TIMI flow grade – number (%)		
0	5 (1)	195 (3.3)
1	2 (1)	36 (0.6)
2	17 (3)	194 (3.3)
3	593 (96)	5522 (93)

Angiographic variables were obtained by visual estimation.
ACC, American College of Cardiology; AHA, American Heart Association; LAD, left artery descending; PCI, percutaneous coronary intervention; RCA, right coronary artery; RCx, ramus circumflex; TIMI, thrombolysis in myocardial infarction.

in Fig. 1. The cumulative event rate for the composite of cardiac death, MI, and TLR at 12 months was 11.7%.

At 12 months, 2.3% of the patients died from a cardiac cause and 3.8% had an MI. Clinically indicated TLR occurred in 7.9% and TVR occurred in 9.6% of the patients. The occurrence of ST is summarized in Table 4. Acute-definite or acute-probable ST, according to the Academic Research Consortium criteria, occurred in two patients (0.3%). Subacute or late definite or probable ST occurred in seven patients (1.0%) and one (0.2%) patient, respectively. Patients (83%) were on DAPT at the 30-day follow-up, 59% at 6 months, and 46% at 12 months, respectively.

Independent predictors of target vessel revascularization

Multivariate analysis using the Cox regression analysis revealed that one or more stents per lesion [hazard ratio (HR): 2.79, 95% confidence interval (CI): 1.60–4.86, $P<0.001$], no predilatation performed (HR: 0.39, 95% CI: 0.17–0.87, $P=0.023$), and lesions located in the right coronary artery (HR: 4.56, 95% CI: 1.07–19.5, $P=0.041$) were independent predictors of TVF.

Table 3 Twelve-month clinical outcomes

Outcome	Number (%)[b]	
	Bifurcation lesion ($n=573$)	Nonbifurcation lesions ($n=4366$)
Main composite outcome		
TVF[a]	73 (12.7)	328 (7.5)
Composite outcomes		
Cardiac death, MI, TLR	67 (11.7)	312 (7.1)
Cardiac death or MI	33 (5.8)	128 (2.9)
Individual outcomes		
Death	16 (2.8)	95 (2.2)
Cardiac death	13 (2.3)	67 (1.5)
Myocardial infarction	22 (3.8)	71 (1.6)
Q-wave MI	3 (0.5)	14 (0.3)
Non-Q-wave MI	20 (3.5)	57 (1.3)
Clinically indicated TLR	45 (7.9)	221 (5.1)
PCI	38 (6.6)	207 (4.7)
CABG	10 (1.7)	20 (0.5)
TVF	55 (9.6)	249 (5.7)
PCI	46 (8.9)	226 (5.2)
CABG	12 (2.1)	30 (0.7)

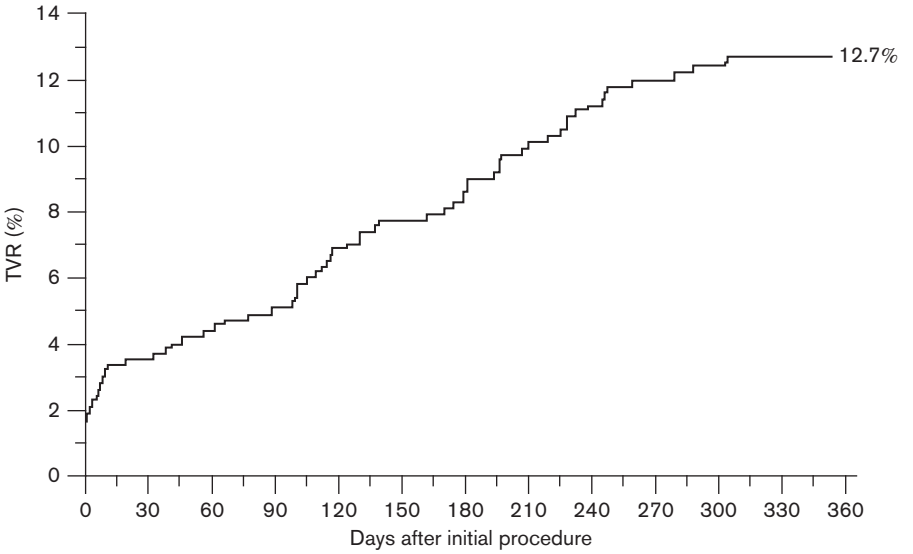
CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TVF, target vessel failure.
[a]TVF: composite of death or MI attributable to target vessel or TVR.
[b]Kaplan–Meier estimates.

Discussion

From a large, multicenter registry encompassing real-world data, we reported the clinical outcomes of patients undergoing nonurgent PCI with the ECS for a bifurcation lesion. At 12 months, the cumulative rate of TVF was 12.7% and the TLR rate was 7.5%. The occurrence of ST was low at 1.7% definite or probable, with only 0.2% late ST. Independent predictors of TVF were stents per lesion, no predilatation performed, and lesions located in the right coronary artery. Our findings confirm and extend our previous findings in which we analyzed a single-center patient population treated for a bifurcation lesion with an ECS [7]. In this study, we evaluated 178 patients who underwent nonurgent PCI. Of all patients, 16% were patients with diabetes, 62% had stable angina, and 98% were treated with a single-stent technique. Of all lesions, 83% were 'true bifurcation' lesions and the mean stent length in the main branch was 23.6 mm. At 12 months, the composite of cardiac death, MI, and TVR was 14.0% and TLR was 10.7%. In the multicenter, worldwide e-HEALING registry, patients treated for a bifurcation lesion were older and had more risk factors for coronary artery disease but fewer patients were treated for a chronic total occlusion. Yet, the clinical results were similar between both patient populations.

Data available on real-world bifurcation stenting are limited. The Italian Multicenter Registry on Bifurcations [8] enrolled 4314 unselected patients with bifurcation lesions treated

Fig. 1



Kaplan–Meier curve of target vessel failure. TVR, target vessel revascularization.

Table 4 Stent thrombosis according to the Academic Research Consortium definition

	Number (%)[d]	
Outcome	Bifurcation lesion ($n=573$)	Nonbifurcation lesions ($n=4366$)
Definite stent thrombosis	6 (1.0)	25 (0.6)
Acute[a]	1 (0.2)	5 (0.1)
Subacute[b]	4 (0.7)	13 (0.3)
Late[c]	1 (0.2)	7 (0.2)
Probable stent thrombosis	3 (0.5)	20 (0.5)
Acute	1 (0.2)	3 (0.1)
Subacute	2 (0.3)	14 (0.3)
Late	0 (–)	3 (0.1)
Possible stent thrombosis	10 (1.7)	35 (0.8)
Acute	0 (–)	0 (–)
Subacute	0 (–)	0 (–)
Late	10 (1.7)	35 (0.8)
Definite or probable stent thrombosis	9 (1.6)	45 (1.0)
Acute	2 (0.3)	8 (0.2)
Subacute	6 (1.0)	27 (0.6)
Late	1 (0.2)	10 (0.2)

[a]Acute stent thrombosis is defined as occurring within 24 h after stent implantation.
[b]Acute stent thrombosis is defined as occurring subacute from 24 h to 30 days.
[c]Acute stent thrombosis is defined as occurring late from 30 days to 12 months.
[d]Kaplan–Meier estimates.

with a drug-eluting stent (DES) between January 2002 and December 2006. Of all patients, 25% were patients with diabetes, 52% presented with stable angina, 35% underwent multivessel PCI, 66% were treated with a single-stent technique, and the mean stent length in the main branch was 21.9 mm. At 12 months, the composite endpoint of cardiac death, MI, and TLR by either PCI or bypass surgery was 13.1%, TLR was 10.2% or definite ST was 1.1%. Moreover, the registry showed that a main-branch stenting-alone approach provided better outcomes than a complex stenting strategy. Furthermore, DES use and a double-stent strategy were not associated with an increased risk of ST. Finally, in bifurcation lesions treated with DES, the duration of DAPT of less than 6 months was associated with a worse 12-month outcome. In the Korean multicenter Coronary Bifurcation Stenting registry [9], 1668 unselected patients with a nonleft main bifurcation lesion were treated with DES between January 2004 and June 2006. A total of 31% of patients had diabetes, 41% had stable angina, 83% were treated with a single-stent technique, and the mean stent length in the main branch was 30.7 mm. At 12 months, the major adverse cardiac events rate, defined as the composite of cardiac death, MI, and TLR, was 4.5% and TLR was 3.4%, with no differences between the single-stent and the double-stent groups. Definite or probable ST was 0.7% at 1 year. Although the e-HEALING registry was designed to capture postmarketing clinical data on every patient receiving an ECS, a fair number of patients treated for a bifurcation lesion were included. The baseline characteristics of our registry are comparable to the patients enrolled in the Italian Multicenter Registry on Bifurcations registry and the 12-month clinical outcomes are fairly comparable. In contrast, the Coronary Bifurcation Stenting registry included more patients with diabetes and stent length was longer but a remarkably low TLR rate was observed during the 12-month follow-up. This may partly be explained by the fact that 32% of the patients underwent IVUS guidance following stent placement. Whether the ECS will perform equally well to DES in bifurcation lesions needs to be evaluated in a randomized study.

Establishment of a functional endothelium and thereby restoring the cellular vascular integrity and homeostasis

may also prevent platelet aggregation and in-stent thrombus formation [10]. In bifurcation lesions, ST might jeopardize a large myocardial area and treatment of bifurcation lesions was shown to be a risk factor for ST. DES-related ST was reported to have an incidence from 0 to 2.2% after a one-stent technique and 0–6.9% after a two-stent technique [11–20]. In this registry, the occurrence of definite or probable ST was 1.7%.

The optimal stent strategy that maintains both main-branch and side-branch patency remains to be established. Although a double-stent strategy assures the best angiographic results, multiple randomized studies have demonstrated that a provisional main-branch stenting strategy is as efficacious as a double-stent strategy [12,13,18,21–23]. The conventional stenting techniques for bifurcation lesions are limited by the inability of complete scaffolding of the side-branch ostium, distortion of the main-branch stent following side-branch dilatation, difficulty in maintaining access to the side branch throughout the procedure, failure to wire the side branch through the main-branch stent, and side-branch jailing [24]. In the e-HEALING registry, no specific data were captured on the technique for stenting bifurcation lesions [i.e. (provisional) T-stenting, crush or culotte stenting, kissing balloons technique, etc.)]; a second stent was used in only a minority of the bifurcation lesions. The design of the ECS has a modular structure, with the center zone consisting of a dual helix lattice, thereby providing omnidirectional flexibility and radial strength. The ECS offers cells that act independently, minimizing the distortional effects of the contra-lateral section of the stent when side-branch dilatation through a strut is performed. Moreover, the cells can be expanded up to 4.5 mm in diameter to enable excellent side branch access, providing the interventional cardiologist with the opportunity to perform side-branch stenting when necessary.

The potential underreporting of adverse events is an important limitation of all large registries, although the present registry was organized with a comprehensive data management plan that included frequent monitoring of all participating sites and full event verification. Moreover, no specific data were captured on the technique for stenting bifurcation lesions.

Data taken from the e-HEALING registry showed that coronary bifurcation stenting with the ECS resulted in favorable 12-month clinical outcomes and low incidences of repeat revascularizations and ST.

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Conflicts of interest

The Academic Medical Center received unrestricted research grant support from OrbusNeich Medical BV. All other authors declare that they have no conflict of interest.

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