Heart Vessels (2012) 27:360–369
DOI 10.1007/s00380-011-0167-8

ORIGINAL ARTICLE

Applying the National Institute for Clinical Excellence criteria to patients treated with the Genous™ Bio-engineered R stent™: a sub-study of the e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) worldwide registry

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Received: 22 February 2011 / Accepted: 3 June 2011 / Published online: 2 July 2011

Abstract The National Institute for Clinical Excellence (NICE) guidelines recommend the use of bare-metal stents (BMS) in non-complex lesions with a low risk of restenosis (diameter $\geq$3 mm and lesion length $\leq$15 mm) and the use of drug-eluting stents (DES) in more complex lesions with a high risk of restenosis (diameter <3.0 mm or lesion length >15 mm). However, the guidelines were created based on studies evaluating BMS and DES only. We performed an analysis of patients undergoing non-urgent percutaneous coronary intervention with the novel endothelial cell capturing stent (ECS). The ECS is coated with $CD34^+$ antibodies that attract circulating endothelial progenitor cells to the stent surface, thereby accelerating the endothelialization of the stented area. We analyzed all patients enrolled in the worldwide e-HEALING registry that met the NICE criteria for either low-risk or high-risk lesions and were treated with $\geq$1 ECS. The main study outcome was target vessel failure (TVF) at 12-month follow-up, defined as the composite of cardiac death or MI and target vessel revascularization (TVR). A total of 4,241 patients were assessed in the current analysis. At 12-month follow-up, TVF occurred in 7.0% of the patients with low-risk lesions and in 8.8% of the patients with high-risk lesions ($p = 0.045$). When evaluating the diabetic patients versus the non-diabetic patients per risk group, no significant differences were found in TVF, MI or TVR in either risk group. The ECS shows good clinical outcomes in lesions carrying either a high or a low risk of restenosis according to the NICE guidelines with comparable rates of cardiac death, myocardial infarction, and stent thrombosis. The TVF rate with ECS was slightly higher in patients with high-risk lesions, driven by higher clinically driven TLR. The risk of restenosis with ECS in patients carrying high-risk lesions needs to be carefully considered relative to other risks associated with DES. Furthermore, the presence of diabetes mellitus did not influence the incidence of TVF in either risk group.

Keywords Percutaneous coronary intervention · National Institute for Clinical Excellence · Endothelial progenitor cells · Restenosis

On behalf of the e-HEALING investigators.

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Abbreviations

DES	Drug-eluting stent
BMS	Bare metal stent
ST	Stent thrombosis
DAPT	Dual anti-platelet therapy
PCI	Percutaneous coronary intervention
NICE	National Institute for Clinical Excellence
ECS	Endothelial progenitor cell capturing stent
EPC	Endothelial progenitor cells
HEALING	Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth registry
MI	Myocardial infarction
TVF	Target vessel failure
TVR	Target vessel revascularization
TLR	Target lesion revascularization
CEC	Clinical Event Committee
IRD	Insulin requiring diabetic
NIRD	Non-insulin requiring diabetic
CABG	Coronary artery bypass grafting
PES	Paclitaxel-eluting stent
SES	Sirolimus-eluting stent

Introduction

The introduction of drug-eluting stents (DES) has decreased the rates of in-stent restenosis compared with bare metal stents (BMS) [1–5]. As a result, DESs are being used in all types of patients and lesions with varying degrees of complexity. However, there is continued concern about the safety of DES regarding the delayed functional endothelialization of the stent struts associated with vasomotor dysfunction and the occurrence of (very) late stent-related thrombosis (ST) [6–9]. To reduce the incidence of ST, prolonged dual anti-platelet therapy (DAPT) is recommended. Yet, there is uncertainty about the duration of DAPT, the additional costs, and the associated risk of bleeding [10–13]. In addition, early observational studies demonstrated that treatment with BMS showed good results regarding restenosis in target lesions located in large vessels and in short lesions [14–16].

At present, the European Society of Cardiology guidelines for percutaneous coronary intervention (PCI) refer to the National Institute for Clinical Excellence (NICE) guidance indicating that DESs are only recommended over BMS for patients with symptomatic coronary artery disease in whom the target coronary artery is <3 mm in caliber or the lesion length is >15 mm [17, 18]. The NICE guidelines comprise recommendations for cost-effective application of new technologies such as drug-eluting stents into clinical practice. The NICE guidelines do not include a recommendation concerning a novel type of stent, the endothelial progenitor cell capturing stent (ECS). The ECS is coated with a polysaccharide matrix and covalently coupled antihuman $CD34^+$ antibodies. These antibodies are able to capture bone marrow-derived circulating endothelial progenitor cells (EPCs) from circulating blood flow, and in animal models it was shown that these EPCs rapidly differentiate into a functional endothelial layer after immobilization [19–21]. In humans, the first clinical studies evaluating the ECS showed promising results in patients carrying simple coronary artery lesions [22–24]. Hereafter, several studies have been carried out reporting on the performance of the ECS in more complex patients and lesions [25–28]. In our current analysis, we evaluate the 1-year clinical outcomes of patients enrolled in the worldwide e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) registry undergoing non-urgent PCI with the ECS using the NICE criteria.

Methods

Source population

The current analysis is a retrospective analysis of the worldwide e-HEALING registry evaluating the ECS. The study design, data collection and management, quality control and list of sites/investigators have been described previously [29]. In short, nearly 5,000 patients that received at least one ECS were enrolled between October 2005 and October 2007 in 144 centers in Europe, Asia/Pacific, the Middle East, Africa and Latin America. The e-HEALING registry complied with the principles of the Declaration of Helsinki regarding investigation in humans and was approved by the local institutional review board at each participating center if required. If determined necessary, written informed consent was obtained.

Device description

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

Study population and procedures

For the current analysis we included all patients from the e-HEALING registry in whom the NICE criteria would apply, that is patients that underwent a non-urgent PCI with

at least one lesion stented with an ECS (diameter 2.50–4.00 mm, length 9–33 mm) in accordance with the Instructions for Use. Patients were excluded form the current analyses if a myocardial infarction (MI) had occurred in the preceding 24 h and if there was angiographic evidence of thrombus in the target artery. Dual anti-platelet therapy was recommended for at least 1 month post-procedure and aspirin indefinitely. The use of concomitant medication was left at the discretion of each treating physician.

NICE guidelines

The NICE guidelines on the use of coronary artery stents recommend the use of DES when the target artery has a reference diameter of <3.0 mm or the lesion has a length of >15 mm as these lesions are considered to carry a higher risk of restenosis. In contrast, a target artery with a reference diameter of ≥3.0 mm and a lesion length of ≤15 can be treated with a BMS as these lesions are considered at low risk of restenosis. These criteria do not apply to ST elevation myocardial infarction patients or patients in whom there is angiographic evidence of thrombus in the target artery. In this manuscript, the NICE guidance was used to evaluate the clinical outcome at 1-year follow-up in patients with lesions carrying a low risk versus a high risk of restenosis determined at the index procedure. Lesions at low risk of restenosis were defined as shorter than or equal to 15 mm, with a reference vessel diameter equal to or larger than 3 mm. All other lesions were considered to be at high risk of restenosis. Both lesion length and reference vessel diameter were a visual estimate by the treating physician.

Outcomes and data management

The main study outcome of our post-hoc analysis was target vessel failure (TVF) at 12-month follow-up, defined as the composite of cardiac death or MI, unless unequivocally attributable to a non-target vessel, and target vessel revascularization (TVR). Secondary outcomes were the composite of cardiac death, MI and clinically indicated target lesion revascularization (TLR), and the individual outcomes: all-cause death, cardiac death, MI (non-Q-wave or Q-wave), TLR, TVR and ST according to the definitions of the Academic Research Consortium [30]. The outcome definitions have been described previously [29].

All outcome events were assessed at discharge of the initial hospitalization, at 30 days, at 6 months and at 12 months. Baseline patient and lesion, procedure-related and angiographic 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 (CRO) (Cardialysis Rotterdam, The Netherlands). Ten percent of the sites were selected randomly for on-site monitoring including full source data verification. An independent Clinical Event Committee (CEC) adjudicated the following events: death, MI, TVR, TLR and ST. The CEC was managed by Cardialysis.

Statistical analysis

Categorical variables were reported with counts and percentages, and continuous variables were reported with the means and standard deviations. 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. The effect of the NICE criteria on TLR was assessed with an unadjusted Cox proportional-hazards model. The statistical analysis was performed at the Academic Medical Center-University of Amsterdam with the Statistical Package for Social Sciences software version (version 16, SPSS Inc., Chicago, IL, USA).

Results

Of the 4,996 patients entered in the e-HEALING registry, 755 were excluded from the current analysis. For 16 patients procedure-related data were missing. In 36 patients no ECS was placed or ECS placement was unknown. Five patients were excluded because of missing follow-up data, and in 698 patients angiographic evidence was found of thrombus in the target artery. Therefore, a total of 4,241 patients were eligible for our analysis. The baseline characteristics of the study population are depicted in Table 1. The average age of patients with lesions carrying a low risk of restenosis was 63.7 years and in patients with lesions carrying a high risk of restenosis, 62.5 years ($p < 0.01$). Seventy-six percent were male in the population carrying low-risk lesions and 80% in the population carrying high-risk lesions ($p = 0.10$). Furthermore, diabetes mellitus was present in 22% of the patients with low-risk lesions versus 27% in the patients with high-risk lesions ($p < 0.01$). Of all other cardiovascular risk factors, only the occurrence of hypercholesterolemia was statistically significant between both populations ($p < 0.01$). Patients with a high risk of restenosis less often had a history of PCI ($p = 0.03$).

Over 85% of all patients were on aspirin. Clopidogrel was administered in 58% of the population with low-risk lesions versus 64% in the population with high-risk lesions before the PCI procedure ($p < 0.01$). Furthermore,

Table 1 Baseline clinical characteristics and medication use

	Low risk $N = 1,292$	High risk $N = 2,949$	p-value
Demographics			
Age (years)	63.7 ± 11.0	62.5 ± 11.6	<0.01
Male gender	984 (76%)	2,352 (80%)	0.10
Body mass index (kg/m^2)	27.4 ± 4.3	27.2 ± 5.0	0.20
Diabetes	280 (22%)	805 (27%)	<0.01
Non-insulin dependent	220 (79%)	623 (77%)	
Insulin dependent	60 (21%)	182 (23%)	
Hypertension	878 (68%)	2,081 (71%)	0.08
Hypercholesterolemia	950 (74%)	2,278 (77%)	<0.01
Current smoker	280 (22%)	649 (22%)	0.81
Family history of coronary artery disease	368 (28%)	815 (28%)	0.24
History			
History of MI	433 (34%)	1,006 (34%)	0.70
History of PCI	288 (22%)	573 (19%)	0.03
History of CABG	89 (7%)	199 (7%)	0.87
Ischemic status			
Silent ischemia	169 (13%)	508 (17%)	<0.01
Stable angina pectoris	629 (49%)	1,429 (48%)	
Unstable angina pectoris	494 (38%)	1,012 (34%)	
Medication use			
Aspirin	1,102 (85%)	2,583 (88%)	0.04
Clopidogrel	750 (58%)	1,890 (64%)	<0.01
Angiotensin II receptor blockers	142 (11%)	342 (12%)	0.57
Angiotensin-converting enzyme inhibitors	510 (39%)	1,086 (37%)	0.10
Beta-blockers	775 (60%)	1,731 (59%)	0.43
Calcium antagonists	225 (17%)	461 (16%)	0.15
Nitrates	473 (37%)	928 (31%)	<0.01
Statins	1,070 (83%)	2,526 (86%)	0.02
Indication PCI			
Non-STEMI, ongoing instability	71 (5%)	131 (4%)	0.14
Unstable angina pectoris, ongoing instability	256 (20%)	552 (19%)	0.40
Post-STEMI	77 (6%)	205 (7%)	0.23
Post-non STEMI	74 (6%)	147 (5%)	0.32
Post-unstable angina pectoris	97 (8%)	171 (6%)	0.04
Elective PCI	648 (50%)	1,592 (54%)	0.02
Others/unknown	69 (5%)	151 (5%)	0.46
Multivessel PCI	141 (11%)	1,016 (34%)	<0.01
Coronary artery bypass graft	12 (1%)	24 (1%)	0.70
Left main	21 (2%)	61 (2%)	0.34
Lesions per patient	1.1 ± 0.4	1.5 ± 0.7	<0.01

Values are n (%) or mean ± SD

MI myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *STEMI* ST-segment elevation myocardial infarction

multi-vessel PCI was performed in 11 and 34% of the patients, respectively ($p < 0.01$).

Table 2 shows the baseline angiographic characteristics. Almost all treated lesions were de novo lesions (as per e-HEALING protocol), and approximately 10% were bifurcation lesions. Average lesion length of the treated patients with low-risk lesions was 11.6 ± 2.8 and 19.6 ± 9.5 mm in patients with high-risk lesions ($p < 0.01$). Reference vessel diameter was 3.3 ± 0.3 and 2.9 ± 0.4 mm, respectively ($p < 0.01$). The occurrence of type B2/C lesions was 35 versus 52% ($p < 0.01$) with a mean stent use of 1.05 ± 0.28 versus 1.16 ± 0.51 stents per lesion

Table 2 Baseline angiographic and procedural characteristics (NICE criteria per lesion)

	Low risk $L = 1{,}995$	High risk $L = 3{,}723$	p-value
De novo lesion	1,961 (98%)	3,635 (98%)	0.10
Restenotic lesion	34 (2%)	88 (2%)	
Bifurcation	202 (10%)	373 (10%)	0.90
Lesion length (mm)	11.6 ± 2.8	19.6 ± 9.5	<0.01
Reference vessel diameter (mm)	3.3 ± 0.3	2.9 ± 0.4	<0.01
Stenosis pre-procedure (% of vessel diameter)	82.9 ± 11.5	84.1 ± 12.0	<0.01
ACC/AHA lesion classification			<0.01
A	356 (18%)	613 (16%)	
B1	945 (47%)	1,195 (32%)	
B2	537 (27%)	1,075 (29%)	
C	157 (8%)	840 (23%)	
Pre-procedure TIMI flow			<0.01
Grade 0	56 (3%)	257 (7%)	
Grade 1	129 (6%)	432 (12%)	
Grade 2	329 (16%)	696 (19%)	
Grade 3	1,481 (74%)	2,338 (63%)	
Stent use			
Stents per lesion	1.05 ± 0.28	1.16 ± 0.51	<0.01
Direct stenting attempted	961 (48%)	1,227 (33%)	<0.01
Post-procedure TIMI flow			<0.01
Grade 0	42 (2%)	153 (4%)	
Grade 1	8 (0%)	25 (1%)	
Grade 2	43 (2%)	138 (4%)	
Grade 3	1,902 (95%)	3,407 (92%)	
Stenosis post procedure (% of vessel diameter)	3.7 ± 12.1	5.3 ± 16.5	<0.01

Values are n (%) or mean ± SD

TIMI thrombolysis in myocardial infarction

($p < 0.01$), and direct stenting occurred in 48% of the low-risk lesions and in 33% of the high-risk lesions ($p < 0.01$).

The clinical outcomes are summarized in Table 3. At 12-month follow-up, the primary endpoint of TVF, defined as the composite of cardiac death, MI and TVR, occurred in 7.0% of the patients carrying low-risk lesions and in 8.8% of the patients carrying high-risk lesions ($p = 0.045$). The cumulative event rate of TVF for both treatment arms is shown in Fig. 1. The TVR rates were 5.1 and 6.9% ($p = 0.02$), target lesion-related MI rates were 1.5 and 2.0% ($p = 0.30$), and cardiac death occurred in 1.4 and 1.6% ($p = 0.51$) of the patients, respectively. TLR rates were 4.5 and 6.0% ($p = 0.04$). Furthermore, definite ST was present in 0.5 and 0.6% of the patients ($p = 0.79$).

In univariable analysis with an unadjusted Cox proportional-hazards model, the presence of high-risk lesions was associated with a higher TLR hazard (HR 1.38, 95% CI: 1.02–1.86, $p = 0.04$) compared with patients carrying low-risk lesions.

Table 4 outlines the populations carrying low- and high-risk lesions stratified by the presence of diabetes. When evaluating the diabetic patients versus the non-diabetic patients in patients carrying a low risk of restenosis, no significant differences were found in TVF, MI or TVR between both groups; 9.2 versus 6.5% ($p = 0.15$). Cardiac death occurred more frequently in diabetic patients, with a low risk of restenosis ($p = 0.04$). In the population with high-risk lesions, the presence of diabetes also did not influence the TVF, MI or TVR rates. In the patients with high-risk lesions, cardiac death occurred more frequently in the diabetics ($p < 0.01$). Figure 2 represents the cumulative incidence of TVF in all four sub-groups. When further sub-dividing diabetic patients into insulin-requiring (IRD) and non-insulin requiring (NIRD), TVF occurred in 12.2% of the IRD with low-risk lesions versus 14.3% of the IRD patients with high-risk lesions ($p = 0.62$; in 8.4% of the NIRD with low-risk lesions versus 9.4% of the NIRD patients with high-risk lesions, $p = 0.58$). Within the population carrying low-risk lesions, no significant difference was found between the IRD and non-diabetic patients ($p = 0.09$).

Discussion

The current analysis is the first study to implement the NICE guidelines that were created using clinical data on

Table 3 One-year clinical outcomes

	Low risk $N = 1,292$		High risk $N = 2,949$		Relative risk (95% CI)	Log rank p-value
	No.	Rate (%)[†]	No.	Rate (%)[†]		
Primary efficacy endpoint						
Target vessel failure*	87	7.0	253	8.8	1.25 (1.05–1.56)	0.045
Individual outcomes						
Death	24	2.0	65	2.3	1.16 (0.75–1.80)	0.48
Cardiac death	17	1.4	47	1.6	1.19 (0.71–2.01)	0.51
MI	19	1.5	57	2.0	1.68 (0.99–2.83)	0.30
Q-wave MI	2	0.2	10	0.3	2.16 (0.49–9.52)	0.30
Non-Q-wave MI	17	1.3	47	1.6	1.20 (0.71–2.02)	0.50
Clinically indicated TLR	55	4.5	172	6.0	1.35 (1.02–1.77)	0.04
Percutaneous	49	4.0	162	5.7	1.42 (1.07–1.90)	0.02
Surgical	10	0.8	15	0.5	0.65 (0.24–1.77)	0.29
TVR	62	5.1	196	6.9	1.36 (1.05–1.76)	0.02
Percutaneous	53	4.3	182	6.4	1.48 (1.12–1.95)	<0.01
Surgical	13	1.1	20	0.7	0.67 (0.28–1.58)	0.26
Stent thrombosis						
Definite	7	0.5	18	0.6	1.14 (0.49–2.62)	0.79
Probable	1	0.1	14	0.5	6.15 (0.24–154.82)	0.045
Possible	11	0.9	29	1.0	1.15 (0.59–2.22)	0.70
Composite end points						
Device oriented: cardiac death, target vessel MI, TLR	80	6.5	234	8.1	1.26 (1.00–1.59)	0.05
Patient oriented: death, MI, any revascularization	134	10.8	351	12.2	1.13 (0.95–1.36)	0.16
Cardiac death, MI, TLR	81	6.5	240	8.4	1.28 (2.02–1.60)	0.04
Death or MI	41	3.3	111	3.8	1.17 (0.83–1.63)	0.35
Cardiac death or MI	34	2.7	95	3.3	1.21 (0.84–1.74)	0.31

[†] The event rate was determined with the use of Kaplan-Meier curves

* Target vessel failure is defined as the composite of cardiac death, MI attributable to the target lesion and clinically driven target vessel revascularization

MI myocardial infarction, *TLR* target lesion revascularization, *TVR* target vessel revascularization

DES and BMS in a worldwide post-marketing registry studying a novel device—the ECS. In the patients classified as carrying a high risk of restenosis, the average age was lower, more diabetes mellitus and hypertension were reported, and more lesions per patient were treated. When comparing the angiographic baseline characteristics between both populations, the patients with high-risk lesions carried lesions with more frequent type B2/C lesions and TIMI 0 or 1 flow. The primary endpoint of TVF, defined as the composite of cardiac death, MI and TVR, occurred in 7.0% of the patients with low-risk lesions and in 8.8% of the patients with high-risk lesions ($p = 0.045$). The difference in TVF was mainly driven by a higher rate of repeat revascularizations in the patients with high-risk lesions; no statistically significant differences were found regarding (cardiac) death, MI and ST.

To date, two studies have been carried out evaluating the ECS in patients with non-complex coronary artery lesions. In the HEALING-First-in-Man study enrolling 16 patients, the composite of cardiac death, stroke, MI and TVR was 6.3%, and no cases of stent thrombosis were reported at 9-month follow-up [22]. In the non-randomized HEALING II study, a total of 63 patients were enrolled, and the composite endpoint of cardiac death, MI and TLR at 18 months was 7.9%, mainly attributed to a relatively low clinically driven TLR rate of 6.3% [23, 24]. No ST was observed. These results compare nicely with the 7.0% TVF of patients with low-risk lesions in our analysis.

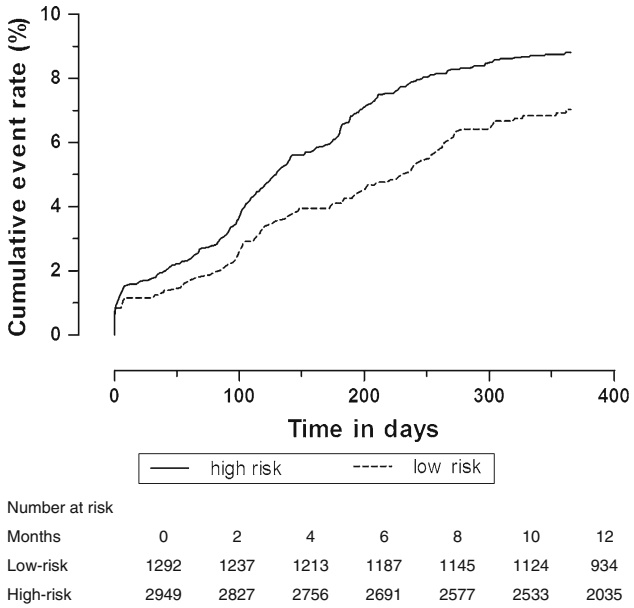


Fig. 1 Time to event curve for the primary endpoint of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization stratified by the risk of restenosis

Thus far, several studies have evaluated ECS-treated patients with a high risk of restenosis. In the single center, non-randomized study by Miglionico et al. [28], 80 patients carrying complex coronary lesions were treated with an ECS. The composite of cardiac death, MI and TVR was 16%, and the TLR rate was 13% at 14 months' follow-up. No ST was observed. Furthermore, our single-center ECS experience evaluated 405 all-comer patients that were treated with ≥1 ECS [27]. Average lesion length was 19.8 ± 9.8 mm, and 75% were type B2/C lesions. At 12-month follow-up, the primary endpoint defined as the composite of cardiac death, MI and TLR was 13.3%, mainly attributable to TLR, which was 10.9%. In the single center, randomized TRIAS Pilot study, the ECS was compared with the paclitaxel-eluting stent (PES) [26]. The baseline characteristics of the ECS-treated patients versus the PES-treated patients showed 92 and 84% type B2/C lesions and 83 and 80% lesions with a lesion length ≥23 mm. At 1-year follow-up, TVF was 17.3% and TLR was 12.2% in the ECS-treated patients, and 10.5% and 8.4% in the PES-treated patients, respectively. In addition, in the early terminated, international, multicenter, randomized TRIAS HR trial, the ECS was compared with conventional DES. Baseline characteristics showed 46 and 47% diabetic patients, and 65 and 66% type B2/C lesions with an average lesion length of 21.61 ± 12.8 and 21.88 ± 12.84 mm, respectively. The composite endpoints of cardiac death, MI and TLR at 12 months were 17.4 and 7.0% ($p = 0.98$ for non-inferiority) [31]. Compared to the 8.8% TVF and 6.0% TLR in our patients carrying lesions with a high risk of restenosis according to the NICE guidelines, the above-mentioned studies had worse clinical outcomes. This contrast can be explained by the difference in complexity of lesions carried by the enrolled patients. The NICE guidelines define high-risk lesions as being longer than 15 mm or smaller than 3.0 mm in diameter, while the above-mentioned studies utilized stricter criteria defining complex lesions as shown in the baseline angiographic characteristics of these studies. Moreover, the occurrence of a planned repeat angiography before the primary endpoint was reached in the above-mentioned studies might have caused angiography-driven repeat revascularizations, influencing the TVF rate, whereas no repeat angiography was planned in the e-HEALING registry.

Several studies have shown that diabetic patients are at considerably higher risk of restenosis and adverse clinical events after PCI compared to non-diabetic patients [32–35]. Interestingly, we found no significant difference between diabetic and non-diabetic patients in both patients with low-risk and high-risk lesions regarding the occurrence of TVF, MI or TVR, though numerically the diabetics showed slightly worse outcomes. Moreover, when subdividing the diabetic patients into IRD and NIRD, no significant difference was found in TVF in either risk group. Only cardiac death occurred more often in diabetic patients in both NICE groups. Diabetic patients with lesions of varying complexity within the NICE criteria have good clinical outcomes compared to non-diabetics when treated with an ECS.

While the NICE guidelines recommend BMS over DES for simple coronary lesions, there are several studies demonstrating a significantly lower event rate after DES compared to BMS. The SIRIUS trial evaluating sirolimus-eluting stents (SES) versus BMS in non-complex lesions with an average lesion length of 14.4 mm shows a TLR rate of 16.6% in BMS-treated patients versus 4.1% in DES-treated patients ($p < 0.01$) [4]. Furthermore, in the TAXUS IV trial PESs were randomized against BMSs in patients with simple coronary lesions with an average lesion length of 13.4 mm [5]. TLR was 15.1% in patients receiving a BMS and 4.4% in patients receiving a PES. However, it should be noted that although these studies were carried out in simple coronary lesions, it is not warranted that TLR only occurred in the restenotic lesions that had a diameter of >3.0 mm and a length of <15 mm at baseline. Therefore, comparing these results with the TLR rate of 4.5% in our registries' patients carrying simple lesions may create a bias. A randomized trial between ECS and BMS is pivotal to investigate whether ECS could be an attractive alternative to BMS. The

Table 4 One-year clinical outcomes in diabetic versus non-diabetic patients stratified by their risk of restenosis

	Low risk					High risk				
	Diabetics $N = 280$		Non-diabetics $N = 1{,}012$		Log rank p-value	Diabetics $N = 805$		Non-diabetics $N = 2{,}144$		Log rank p-value
	No.	Rate (%)†	No.	Rate (%)†		No.	Rate (%)†	No.	Rate (%)†	
Primary efficacy endpoint										
Target vessel failure*	24	9.2	63	6.5	0.15	82	10.5	171	8.2	0.05
Individual outcomes										
Death	9	3.4	15	1.6	0.05	30	3.9	35	1.7	<0.01
Cardiac death	7	2.7	10	1.0	0.04	24	3.1	23	1.1	<0.01
MI	6	2.3	13	1.3	0.28	19	2.4	38	1.8	0.30
Q-wave MI	2	0.8	0	0.0	<0.01	4	0.5	6	0.3	0.36
Non-Q-Wave MI	4	1.5	13	1.3	0.84	15	1.9	32	1.5	0.47
Clinically indicated TLR	14	5.5	41	4.2	0.43	51	6.6	121	5.8	0.41
Percutaneous	12	4.7	37	3.8	0.57	48	6.2	114	5.5	0.43
Surgical	3	1.2	7	0.7	0.49	6	0.8	9	0.4	0.26
TVR	17	6.7	45	4.6	0.22	59	7.7	137	6.6	0.30
Percutaneous	13	5.1	40	4.1	0.55	55	7.1	127	6.1	0.31
Surgical	5	1.9	8	0.8	0.13	8	1.0	12	0.6	0.19
Stent thrombosis										
Definite	2	0.7	5	0.5	0.65	6	0.8	12	0.6	0.56
Probable	1	0.4	0	0.0	0.06	3	0.3	11	0.5	0.63
Possible	5	1.9	6	0.6	0.05	18	2.4	11	0.5	<0.01
Composite end points										
Device oriented: cardiac death, target vessel MI, TLR	22	8.4	58	5.9	0.17	76	9.7	158	7.6	0.06
Patient oriented: death, MI, any revascularization	36	13.6	98	10.0	0.11	109	13.9	242	11.6	0.08
Cardiac death, MI, TLR	22	8.4	59	6.0	0.19	76	9.7	164	7.8	0.10
Death or MI	14	5.2	27	2.8	0.04	42	5.4	69	3.3	0.01
Cardiac death or MI	12	4.5	22	2.2	0.05	36	4.6	59	2.8	0.02

† The event rate was determined with the use of Kaplan-Meier curves

* Target vessel failure is defined as the composite of cardiac death, MI attributable to the target lesion and clinically driven target vessel revascularization

MI myocardial infarction, *TLR* target lesion revascularization, *TVR* target vessel revascularization

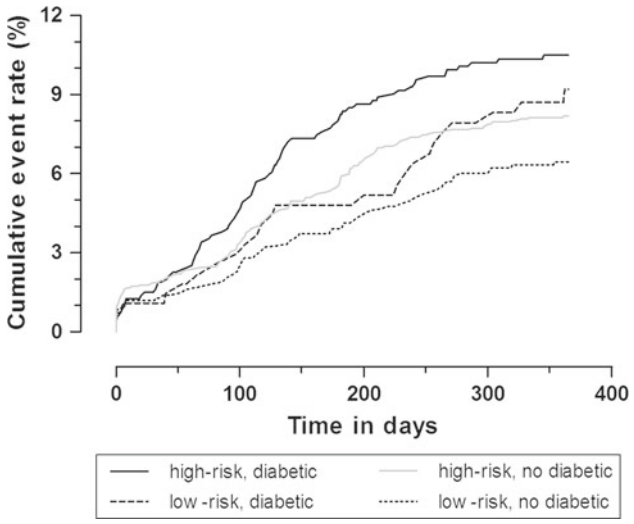
ongoing TRIAS Low Risk trial is designed to demonstrate the superiority of ECS relative to BMS in the occurrence of TLF at 12-month follow-up. The design of the trial has been published previously, and enrollment is ongoing [36].

Conclusions

The ECS shows good clinical outcomes in lesions carrying either a high or a low risk of restenosis according to the NICE guidelines with similar rates of cardiac death, myocardial infarction and stent thrombosis. The TVF rate with ECS was slightly higher in patients with high-risk lesions, driven by higher clinically driven TLR. The risk of restenosis with ECS in patients with high-risk lesions needs to be carefully considered relative to other risks associated with DES. Furthermore, the presence of diabetes mellitus did not influence the incidence of TVF in either group stratified by the NICE criteria.

Limitations

Some limitations deserve to be mentioned. First, the underreporting of adverse events is a potential important limitation of all large registries, even though the e-HEALING registry was organized with a comprehensive data-management plan that included monitoring of all sites



Number at risk

Months	0	2	4	6	8	10	12
Low-risk, no diabetic	1012	974	958	939	906	890	760
Low-risk, diabetic	280	265	257	250	242	236	195
High-risk, no diabetic	2144	2059	2017	1977	1888	1861	1529
High-risk, diabetic	805	770	742	717	691	675	535

Fig. 2 Time to event curve for the primary endpoint of cardiac death, myocardial infarction and clinically indicated target vessel revascularization stratified by the patients' risk of restenosis and the presence of diabetes mellitus

and full event verification. Second, angiographic variables were obtained by visual estimation.

Acknowledgments We thank all centers and investigators participating in the e-HEALING registry. Most importantly, we thank all participating patients.

Conflict of interest The Academic Medical Center received unrestricted research grant support from OrbusNeich Medical BV. The e-HEALING Registry was funded by OrbusNeich Medical BV, The Netherlands.

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