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CORONARY ARTERY DISEASE

Twelve-month Outcomes After Coronary Stenting With the Genous™ Bio-Engineered R Stent™ in Diabetic Patients from the e-HEALING Registry

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Objectives: *We compared 12-month outcomes, regarding ischemic events, repeat intervention, and ST, between diabetic and nondiabetic patients treated with the Genous™ EPC capturing R stent™ during routine nonurgent percutaneous coronary intervention (PCI) using data from the multicenter, prospective worldwide e-HEALING registry.*

Background: *Diabetic patients have an increased risk for restenosis and stent thrombosis (ST).*

Methods: *In the 4,996 patient e-HEALING registry, 273 were insulin requiring diabetics (IRD), 963 were non-IRD (NIRD), and 3,703 were nondiabetics. The 12-month primary outcome was target vessel failure (TVF), defined as target vessel–related cardiac death or myocardial infarction (MI) and target vessel revascularization. Secondary outcomes were the composite of cardiac death, MI or target lesion revascularization (TLR), and individual outcomes including ST. Cumulative event rates were estimated with the Kaplan–Meier method and compared with a log-rank test.*

Results: *TVF rates were respectively 13.4% in IRD, 9.0% in NIRD, and 7.9% in nondiabetics ($P < 0.01$). This was mainly driven by a higher mortality hazard in IRD ($P < 0.001$) and NIRD ($P = 0.07$), compared with nondiabetics. TLR rates were comparable in NIRD and nondiabetics, but significantly higher in IRD ($P = 0.04$). No difference was observed in ST.*

Conclusion: *The 1-year results of the Genous stent in a real-world population of diabetics show higher TVF rates in diabetics compared with nondiabetics, mainly driven by a higher mortality hazard. IRD is associated with a significant higher TLR hazard. Definite or probable ST in all diabetic patients was comparable with nondiabetics.*
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Introduction

Diabetic patients are at an increased risk of angiographic or clinical restenosis after percutaneous coronary intervention (PCI) with stent placement.[1] This is mainly due to exaggerated intimal hyperplasia associated with diabetes mellitus.[2] Compared with bare metal

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stenting, drug-eluting stents (DES) have been shown to reduce the incidence of in-stent restenosis by inhibiting or delaying neo-endothelialization, both in diabetic and nondiabetic patients.[3,4] However, their use is hampered by the occurrence of late and very late stent thrombosis (ST).[5] Moreover, diabetics constitute a high-risk subgroup for developing ST within DES-treated patients.[6] The use of a stent technology that promotes endothelialization and inhibits intimal hyperplasia may reduce the overshadowing risk of restenosis and ST in diabetic patients. Recently, a novel stent technology with a "pro-healing" approach, the bio-engineered Genous™ endothelial progenitor cell (EPC) capturing stent™, has been shown to be associated with a low incidence of repeat revascularization and ST.[7] These captured EPCs can differentiate into a functional endothelial layer covering the stent struts and may thereby reduce the risk of intimal hyperplasia and ST. We investigated the 12-month outcomes, regarding ischemic events, repeat intervention, and ST, in insulin and noninsulin requiring diabetic (NIRD) patients treated with the Genous stent during routine nonurgent PCI using data from the multicenter, prospective worldwide e-HEALING registry.

Methods

Study Design. The current analysis is a post hoc analysis of the e-HEALING registry. The study design, data collection and management, quality control, and list of sites/investigators have been published previously.[7] e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) was a worldwide, multicenter postmarketing registry. Approximately 5,000 patients were included between October 2005 and October 2007 from 144 centers in Europe, Asia/Pacific, Middle East, Africa, and Latin America. The local medical ethics committees approved the study protocol, and written informed consent was obtained.

Device Description. The Genous stent comprises 316L stainless steel stent platform to which a monoclonal anti-CD34+ antibody is coupled to the stent surface through a covalently coupled polysaccharide matrix coating (Genous™ Bio-engineered R stent™, OrbusNeich Medical Technologies, Fort Lauderdale, FL, USA).

Study Population and Procedures. Patients who underwent a nonurgent PCI with at least 1 lesion stented with a Genous stent (diameter 2.50–4.00 mm, length 9–33 mm) in accordance with the Instructions for Use were eligible for the e-HEALING registry. The indication for PCI was left at the discretion of the operator. Patients were recommended to receive at least 2 weeks of statin therapy prior to PCI. Dual antiplatelet therapy was recommended for at least 1 month postprocedure and aspirin indefinitely. The use of concomitant medication was left at the discretion of each treating physician.

Definition of Diabetes Mellitus. The presence of diabetes mellitus was defined as a prior established diagnosis of diabetes mellitus and/or the use of medication to control blood glucose. Patients taking insulin were considered insulin requiring, patients not taking insulin were considered noninsulin requiring. Information was entered into the electronic case report form by the local investigator; no blood glucose measurements were performed.

Outcomes. The main outcome of the e-HEALING registry was target vessel failure (TVF) at 12-month follow-up, defined as the composite of cardiac death or myocardial infarction (MI) unless unequivocally attributable to a nontarget vessel and target vessel revascularization (TVR). Secondary outcomes were the composite of cardiac death, MI, and clinically indicated target lesion revascularization (TLR), the individual outcomes all-cause death, cardiac death, MI (non-Q wave or Q wave), TLR, TVR, ST according to the definitions of the Academic Research Consortium (ARC),[8] major and minor bleeding, and stroke. A non-Q wave MI was defined as an elevation of postprocedure creatine kinase (CK) levels above two times the upper limit of normal (ULN) in the absence of pathological Q waves. A Q wave MI was defined as the development of new, pathological Q waves in 2 or more continuous leads with an elevation of CK-MB above the ULN. TLR was defined as any repeat-PCI of the target lesion or coronary artery bypass grafting (CABG) of the target vessel. A revascularization was clinically indicated if the stenosis of the treated lesion was at least 50% of the lumen diameter based on 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 in the absence of the above-mentioned ischemic signs or symptoms was also considered a

clinically indicated TLR. TVR was defined as the repeat revascularization of any segment of the major coronary artery treated at the index procedure. Finally, bleeding was considered major when it led to death or permanent disability, suspected or proven intracranial, produced a fall in hemoglobin >3 mmol/L, led to transfusion of 2 or more units of whole blood of packed cells, or led to peripheral vascular surgery. All other bleeding was considered as minor.

Data Collection and Management. 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 maintained by a contract research organization (CRO) (Cardialysis, Rotterdam, The Netherlands). Angiographic variables were obtained by visual estimation. All outcome events were assessed at discharge of initial hospitalization, at 30 days, 6 months. and 12 months. The following events were adjudicated by an independent Clinical Event Committee (CEC) whose members did not participate in the study: death, MI, TVR, TLR, and ST. Trained and qualified Clinical Research Associates monitored the registry throughout its duration remotely through the internet-based database. Ten percent of the sites were selected randomly for on-site monitoring including full source data verification.

Statistical Analysis. Our current analyses focus on diabetic patients, with attention to insulin and noninsulin requiring diabetes mellitus. Categorical variables were reported with counts and percentages, and continuous variables were reported with the means and standard deviations (SD) or median and interquartile ranges (IQR). 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. Hazard ratios were calculated in Cox proportional-hazards models. For the outcome TLR, 3 sets of models were used: unadjusted using univariable analyses, adjusted multivariable with forced entry of established prognostic factors for in-stent-restenosis (lesion length, stent length, vessel diameter, post-treatment lumen diameter[9]), and adjusted multivariable using independent predictors identified by backward selection of baseline and procedural variables. A $P < 0.1$ by the Likelihood Ratio test was deemed significant. For the main outcome TVF, we performed unadjusted univariable analyses and adjusted multivariable using identified independent predictors for TVF. Statistical analyses were performed at the Academic Medical Center, University of Amsterdam.

Results

Patients. Of the 4,996 patients entered in the e-HEALING registry, 52 patients were excluded because of missing procedure-related data (n = 16), no Genous stent was placed or Genous placement was unknown (n = 36). Five patients were excluded because of missing follow-up data. Of the remaining 4,939 patients, 1,236 (25%) were diabetics. The median age of the diabetic patients was 64 years, 73% were male, and the mean body mass index was 28.3. IRD constitute 22% of the diabetes group, 78% were noninsulin requiring. The baseline characteristics of the insulin requiring (IRD), NIRD, and nondiabetics are shown in Table 1. Generally, diabetics had a higher burden of risk factors, a more extended history of cardiovascular disease, and a higher medication use. The median time of follow-up of the total population was 365 days (IQR 358–365 days). The completeness of follow-up for clinical events was 98.9% at 30 days (±1 week), 97.1% at 6 months (±2 weeks), and 92.3% at 12 months (±4 weeks).

Angiographic and Procedural Characteristics. In diabetics, an average of 1.4 lesions per patient was treated with an average 1.1 stents per lesion. Ninety-seven percent of the lesions treated were de novo, 3% were restenotic lesions. Of all lesions, 10% were bifurcation lesions. A total of 48% of the treated lesions were ACC/AHA type B2 or C, mean lesion length was 16.8 ± 8.4 mm, and the reference vessel diameter was 3.0 ± 0.4 mm. Detailed angiographic and procedural characteristics of the IRD, NIRD, and nondiabetics are shown in Table 2.

Adherence to Dual Antiplatelet Therapy. Adherence to dual antiplatelet therapy in the IRD at 30-day, 6-month, and 12-month follow-up was, respectively, 82.2%, 49.8%, and 26.7%. The adherence was, respectively, 78.4%, 59.2%, and 31.8% in NIRD and 81.4%, 59.7%, and 35.5% in nondiabetics (30-day $P = 0.09$, 6-month $P < 0.001$, 12-month $P < 0.001$).

Outcomes. The main 12-month outcome of TVF was significantly higher in diabetics compared with nondiabetics (10.0% vs. 7.9%, $P = 0.03$). This was mainly due to a higher event rate in IRD, compared

Table 1. Baseline Characteristics of the Study Patients

Characteristic	Insulin Requiring Diabetics (n = 273)		Noninsulin Requiring Diabetics (n = 963)		Nondiabetic Patients (n = 3,703)		P value*
Demographics—no./total no. (%)							
Age—median (IQR)	66	(56–73)	64	(57–71)	62	(53–72)	<0.001
Male gender	185/273	(67.8%)	721/963	(74.9%)	2,988/3,702	(80.7%)	<0.001
BMI—mean (SD)	28.5	(5.3)	28.2	(6.5)	26.9	(4.0)	<0.001
Hypertension	217/273	(79.5%)	754/961	(78.5%)	2,402/3,696	(65.0%)	<0.001
Hypercholesterolemia	199/273	(72.9%)	769/960	(80.1%)	2,700/3,691	(73.2%)	<0.001
Current smoker	49/273	(17.9%)	182/963	(18.9%)	998/3,703	(27.0%)	<0.001
Family history of MI	71/272	(26.1%)	238/958	(24.8%)	1,072/3,693	(29.0%)	0.11
Congestive heart failure	31/271	(11.4%)	37/959	(3.9%)	108/3,683	(2.9%)	<0.001
History—no./total no. (%)							
MI	116/273	(42.5%)	356/963	(37.0%)	1,345/3,703	(36.3%)	0.12
Percutaneous coronary intervention	65/273	(23.8%)	211/963	(21.9%)	672/3,703	(18.1%)	<0.01
CABG	37/273	(13.6%)	70/963	(7.3%)	197/3,703	(5.3%)	<0.001
Prior stroke	25/270	(9.3%)	55/960	(5.7%)	215/3,690	(5.8%)	0.07
Indication for PCI—no./total no. (%)							0.02
Elective	116/273	(42.5%)	492/963	(51.1%)	1,683/3,703	(45.4%)	
Acute coronary syndrome	134/273	(49.1%)	402/963	(41.7%)	1,700/3,703	(45.9%)	
Other/unknown	23/273	(8.4%)	69/963	(7.2%)	320/3,703	(8.6%)	
Medication use—no./total no. (%)							
Aspirin	233/273	(85.3%)	816/963	(84.7%)	3,046/3,703	(82.3%)	0.10
Clopidogrel	164/273	(60.1%)	628/963	(65.2%)	2,134/3,703	(57.6%)	<0.001
Angiotensin II receptor blockers	40/273	(14.7%)	133/963	(13.8%)	357/3,703	(9.6%)	<0.001
ACE inhibitors	139/273	(50.9%)	411/963	(42.7%)	1,267/3,703	(34.2%)	<0.001
Beta blockers	169/273	(61.9%)	590/963	(61.3%)	2,039/3,703	(55.1%)	<0.001
Calcium antagonists	59/273	(21.6%)	186/963	(19.3%)	504/3,703	(13.6%)	<0.001
Nitrates	93/273	(34.1%)	316/963	(32.8%)	1,161/3,703	(31.4%)	0.49
Statins	214/273	(78.4%)	802/963	(83.3%)	2,943/3,703	(79.5%)	0.02

BMI = body mass index; CABG = coronary artery bypass grafting; IQR = interquartile range; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.
*Overall comparison of the 3 groups.

with nondiabetics (13.4% vs. 7.9%, P < 0.01). There was no significant difference in NIRD and nondiabetics (9.0% vs. 7.9%, P = 0.31). Kaplan–Meier curves of the main outcome are shown in Figure 1. There was a trend, at the margin of statistical significance, to a higher composite event rate of death, MI or TLR (9.3% vs. 7.5%, P = 0.054) in the diabetic population. This was mainly due to higher mortality among diabetics (3.8% compared with 1.8% in nondiabetics, P < 0.001). Although the event rates of the individual outcome MI were numerically higher in diabetics, we did not observe a significant difference (P = 0.67). TLR rates were 6.4% in diabetics versus 5.4% in nondiabetics (P = 0.23). The individual outcome TLR occurred significantly more often in IRD compared with nondiabetics (P = 0.04), while no difference was observed between NIRD and nondiabetics (P = 0.66). Definite or probable ST occurred in 1.1% of the diabetics, compared with 1.1% in the nondiabetics (P = 0.87). The clinical outcomes, according to (non-)insulin requiring diabetes mellitus, are shown in detail in Table 3.

Cox Proportional-Hazards Models. In univariable analysis, the presence of IRD was associated with a higher TLR hazard (HR 1.59, 95% CI: 1.01–2.49, P = 0.045) compared with nondiabetics, while NIRD was associated with a comparable hazard (HR 1.07, 95% CI: 0.79–1.45, P = 0.66). These hazard ratios were not materially affected by adjustment for the established risk factors for TLR. In our dataset, the following variables were identified as significant predictors for TLR: current smoking, history of congestive heart failure, indication for PCI, mean reference vessel diameter, ≥1 lesion classified as ACC/AHA B2 or C, ≥1 restenotic lesion treated, or ≥1 bifurcation treated (P < 0.05 for all). Adjustment for these identified predictors did not materially alter the hazard ratios as well. The unadjusted and adjusted models are shown in Table 4.

Table 2. Baseline Angiographic and Procedural Characteristics

Characteristic	Insulin Requiring Diabetics		Noninsulin Requiring Diabetics		Nondiabetic Patients		P value**
Patient characteristics	273		963		3,703		
Target lesion coronary artery							
Multivessel PCI	54/271	(19.9%)	187/960	(19.5%)	594/3,695	(16.1%)	0.02
Bypass graft	5/271	(1.8%)	15/960	(1.6%)	26/3,695	(0.7%)	0.01
Left main	4/271	(1.5%)	15/960	(1.6%)	70/3,695	(1.9%)	0.72
Lesions per patient—mean (SD)	1.4	(0.8)	1.4	(0.6)	1.3	(0.6)	0.03
Lesion characteristics	389		1,310		4,914		
Lesion type—no./total no. (%)							
De novo	378/389	(97.2%)	1,273/1,310	(97.2%)	4,809/4,914	(97.9%)	0.27
Restenotic	11/389	(2.8%)	37/1310	(2.8%)	105/4,914	(2.1%)	
Bifurcation lesion	35/389	(9.0%)	139/1310	(10..6%)	492/4,914	(10.0%)	0.63
Lesion classification—no./total no. (%)							<0.01
A	43/389	(11.1%)	201/1,310	(15.3%)	769/4,914	(15.6%)	
B1	159/389	(40.9%)	489/1,310	(37.3%)	1,694/4,914	(34.5%)	
B2	133/389	(34.2%)	355/1,310	(27.1%)	1,480/4,914	(30.1%)	
C	54/389	(13.9%)	265/1,310	(20.2%)	971/4,914	(19.8%)	
Baseline angiographic findings—mean (SD)*							
Lesion length—mm	16.2	(8.2)	17.0	(8.5)	16.8	(8.7)	0.32
Reference-vessel diameter (mm)	3.0	(0.4)	3.0	(0.4)	3.0	(0.4)	<0.01
Stenosis—% of vessel diameter	84.9	(12.5)	83.9	(12.4)	85.1	(12.0)	0.01
Baseline TIMI flow grade—no./total no. (%)							<0.001
Grade 0	26/389	(6.7%)	108/1,310	(8.2%)	521/4,914	(10.6%)	
Grade 1	26/389	(6.7%)	131/1,310	(10.0%)	516/4,914	(10.5%)	
Grade 2	55/389	(14.1%)	242/1,310	(18.5%)	886/4,914	(18.0%)	
Grade 3	282/389	(72.5%)	829/1,310	(63.3%)	2,991/4,914	(60.9%)	
Stent use							
Stents per lesion—mean (SD)	1.1	(0.4)	1.1	(0.5)	1.1	(0.4)	0.53
Type of stent placed							<0.001
Genous only	318/389	(81.7%)	1,082/1,310	(82.6%)	4,247/4,914	(86.4%)	
Genous and/or other	60/389	(15.4%)	201/1,310	(15.3%)	573/4,914	(11.7%)	
No or unknown	11/389	(2.8%)	27/1,310	(2.1)	94/4,914	(1.9%)	
Direct stenting attempted	153/389	(39.3%)	842/1,310	(35.7%)	1,871/4,914	(38.1%)	0.23
Final angiographic findings—mean (SD)*							
Reference-vessel diameter (mm)	3.0	(0.5)	3.0	(0.5)	3.1	(0.4)	0.001
Stenosis—% of vessel diameter	5.0	(13.8)	4.3	(13.6)	4.5	(14.5)	0.72
Final TIMI flow grade—no./total no. (%)							<0.001
Grade 0	2/389	(0.5%)	25/1,310	(1.9%)	173/4,914	(3.5%)	
Grade 1	2/389	(0.5%)	2/1,310	(0.2%)	34/4,914	(0.7%)	
Grade 2	7/389	(1.8%)	38/1,310	(2.9%)	166/4,914	(3.4%)	
Grade 3	378/389	(97.2%)	1,245/1,310	(95.0%)	4,541/4,914	(92.4%)	

*Assessed by visual estimation.
*Overall comparison the three groups.
SD = standard deviation; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.

After adjustment for identified risk factors (age, previous PCI, history of stroke, indication for PCI, mean reference vessel diameter, mean lesion length, minimal 1 restenosis or B2/C lesion or bifurcation, minimal 1 lesion with postprocedure TIMI 0–2 flow) for the main outcome TVF, the presence of IRD was associated with a significantly higher TVF hazard (HR 1.53, 95% CI: 1.06–2.19. P = 0.02) and NIRD with a comparable TVF hazard (HR 1.05, 95%CI: 0.82–1.35, P = 0.70) using nondiabetics as the reference group. The adjusted HR when comparing diabetics with nondiabetics was 1.16 (95% CI: 0.93–1.44, P = 0.19).

Discussion

Our present analysis provides insight in clinical outcomes of diabetic patients undergoing nonurgent PCI

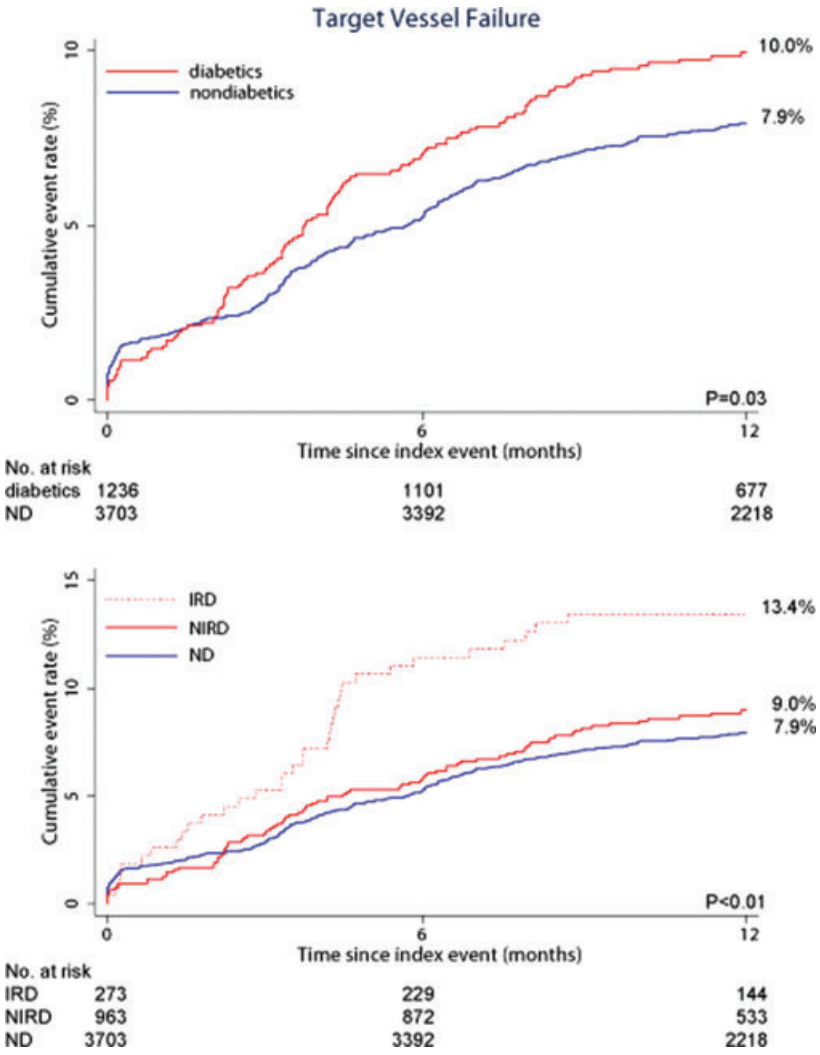

Figure 1. Kaplan–Meier curves of TVF according to diabetes mellitus. Shown is the outcome TVF, according to diabetes in the upper panel and according to insulin dependence in the lower panel. P value calculated with the log-rank test; IRD = insulin requiring diabetics, NIRD = noninsulin requiring diabetics; ND = nondiabetics.

with the Genous stent. We found that the 12-month incidence of TVF and the composite of cardiac death, MI or TLR were higher among diabetics compared with nondiabetics. This was mainly driven by an increased mortality in the IRD and NIRD compared with nondiabetics. While the TLR rates were comparable in NIRD and nondiabetics, IRD identified a subgroup with a significantly higher TLR rate. Importantly, there was no difference in definite or probable ST in patients with diabetes compared with nondiabetic patients treated with the Genous stent in the presence of a recommendation of 1 month of dual antiplatelet therapy.

Previous Studies. In the diabetic subpopulation of the ARRIVE program evaluating a paclitaxel-eluting stent, a TLR rate of 4.9% was reported at 1-year follow-up, which is comparable with the TLR rate of 6.4% in our current analysis.[10] Further comparisons with other diabetic subpopulations from registries are hampered by shorter follow-up times which is important because of the late luminal loss associated with DES,[11,12] TLR were not separately reported,[13] because all included patients underwent multivessel PCI,[14] or because the clinical outcome was influenced by routine angiographic follow-up which is associated with an increased revascularization rate due to the "oculostenotic reflex".[15] We therefore emphasize the importance of comparing the Genous stent directly with different DES types, as there seem to be significant differences in restenosis rates among DES types in diabetics and nondiabetics.[16]

While we did not observe a difference in NIRD and nondiabetics regarding adjusted hazard for TLR,

Table 3. Twelve-Month Outcomes by Diabetic Status

Outcome - No. (%)†	Insulin Requiring Diabetics (n = 273)		Noninsulin Requiring Diabetics (n = 963)		Nondiabetic Patients (n = 3,703)		P value‡ IRD vs. ND	P value‡ NIRD vs. ND
Main composite outcome								
TVF*	35	(13.4%)	83	(9.0%)	283	(7.9%)	<0.01	0.31
Individual outcomes								
Death	19	(7.3%)	26	(2.8%)	66	(1.8%)	<0.001	0.07
Cardiac death	15	(5.8%)	21	(2.3%)	44	(1.2%)	<0.001	0.02
MI	10	(3.8%)	15	(1.6%)	68	(1.9%)	0.03	0.56
Q wave MI	2	(0.8%)	4	(0.4%)	11	(0.3%)		
Non-Q wave MI	8	(3.0%)	11	(1.2%)	58	(1.6%)		
TLR	21	(8.3%)	53	(5.8%)	192	(5.4%)	0.04	0.66
Percutaneous coronary intervention	20	(7.9%)	48	(5.3%)	177	(5.0%)		
CABG	2	(0.8%)	8	(0.9%)	20	(0.6%)		
Target vessel revascularization	23	(9.1%)	62	(6.8%)	219	(6.2%)	0.06	0.51
Percutaneous coronary intervention	21	(8.3%)	55	(6.0%)	196	(5.5%)		
CABG	3	(1.2%)	11	(1.2%)	28	(0.8%)		
Composite outcomes								
Device oriented : cardiac death, target vessel MI, TLR	35	(13.4%)	75	(8.1%)	261	(7.3%)	<0.001	0.43
Patient oriented : death, MI, any revascularization	48	(18.3%)	114	(12.2%)	412	(11.5%)	<0.01	0.53
Cardiac death, MI, TLR	35	(13.4%)	75	(8.1%)	269	(7.5%)	<0.001	0.58
Death or MI	23	(8.8%)	39	(4.2%)	128	(3.5%)	<0.001	0.38
Cardiac death or MI	19	(7.2%)	34	(3.6%)	108	(3.0%)	<0.001	0.33
Other events								
Bleeding	5	(1.9%)	8	(0.8%)	53	(1.5%)	0.57	0.15
Major bleeding	4	(1.6%)	2	(0.2%)	20	(0.6%)		
Minor bleeding	1	(0.4%)	6	(0.6%)	33	(0.9%)		
CVA	2	(0.2%)	0	(0.0%)	14	(0.4%)	0.32	0.43
ST according to ARC definition§								
Definite or probable ST	5	(1.9%)	9	(1.0%)	40	(1.1%)	0.25	0.70
Acute	0	(0.0%)	2	(0.2%)	8	(0.2%)		
Subacute	4	(1.5%)	3	(0.3%)	26	(0.7%)		
Late	1	(0.4%)	4	(0.4%)	6	(0.2%)		
Definite ST	3	(1.1%)	5	(0.5%)	23	(0.6%)	0.93	0.72
Acute	0	(0.0%)	2	(0.2%)	4	(0.1%)		
Subacute	2	(0.7%)	0	(0.0%)	15	(0.4%)		
Late	1	(0.4%)	3	(0.3%)	4	(0.1%)		

*TVF: composite of cardiac death or MI attributable to target vessel, or TVR.
†Kaplan–Meier estimates.
‡Pairwise log-rank test.
§Acute ST is defined as occurring within 24 hours after stent implantation, subacute from 24 hours to 30 days, and late from 30 days to 12 months.
IRD = insulin requiring diabetics; NIRD = noninsulin requiring diabetics; ND = nondiabetics. MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; TLR = target lesion revascularization.

there was a significantly higher hazard in the IRD. Higher TLR percentages have been reported in IRD in a subreport of the randomized SIRIUS trial.[17] However, a direct comparison with NIRD or nondiabetics was not performed. Restenosis is mediated through different cellular proliferation cascades, both insulin- or non-insulin-stimulated, potentially explaining the difference between IRD and NIRD.[18] Despite the higher TLR or TVR rate in IRD, the TVR rate (9.1%) was comparable to those observed in a registry from Washington after serolimus-eluting (10.3%) or paclitaxel-eluting (12.1%) stent placement.[19]

Although the presence of diabetes is associated with an increased risk of developing ST, comparable

Table 4. Unadjusted and Adjusted Hazard Ratios for TLR

	TLR		
Variable	HR	(95% CI)	P value
Unadjusted analysis			
Diabetic status			
Nondiabetics	–	Referent	–
Insulin requiring diabetics	1.59	(1.01–2.49)	0.045
Noninsulin requiring diabetics	1.07	(0.79–1.45)	0.66
Adjusted for established predictors			
Diabetic status			
Nondiabetics	–	Referent	–
Insulin requiring diabetics	1.54	(0.98–2.42)	0.06
Noninsulin requiring diabetics	1.05	(0.78–1.43)	0.75
Mean reference vessel diameter (mm)	0.57	(0.41–0.80)	<0.01
Mean stent length (mm)	1.01	(0.98–1.04)	0.51
Mean lesion length (mm)	1.01	(0.99–1.03)	0.44
Mean diameter stenosis post procedure (%)	1.00	(1.00–1.01)	0.42
Adjusted for identified predictors			
Diabetic status			
Nondiabetics	–	Referent	–
Insulin requiring diabetics	1.57	(1.00–2.47)	0.05
Noninsulin requiring diabetics	1.03	(0.76–1.39)	0.87
Current smoker	0.67	(0.49–0.92)	0.01
History of congestive heart failure	0.29	(0.09–0.91)	0.03
Indication for PCI			
Elective	–	Referent	–
ACS	1.11	(0.87–1.42)	0.42
Other/unknown	0.47	(0.24–0.89)	0.02
Mean reference vessel diameter (mm)	0.59	(0.43–0.83)	<0.01
Minimal 1 B2 or C lesion treated	1.45	(1.13–1.87)	<0.01
Minimal 1 restenosis treated	2.15	(1.02–3.52)	<0.01
Minimal 1 bifurcation treated	1.43	(1.03–1.98)	0.03
Adjusted for identified predictors			
Diabetics versus nondiabetics	1.14	(0.87–1.49)	0.35

ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.

definite or probable ST was observed in diabetics and nondiabetics. On a greater scale, the incidence of 1.2% of definite or probable ST in our diabetic subpopulation is comparable or lower than those reported in all patients from the e-Cypher,[20] EVENT,[14] e-Five,[21] and ARRIVE 1[22] registries. This is a promising finding in this subpopulation, keeping in mind the theoretical higher risk for developing ST and the fact that DAPT use was generally lower in the diabetic patients.

Insulin-Requiring Diabetics. Besides the higher TLR hazard in the IRD, we also observed significantly higher cardiac death and MI rates. This can partly be explained by the higher baseline risk profile as indicated by more advanced macrovascular disease (higher frequency of congestive heart failure, prior PCI, or CABG) and a more frequent presentation with ACS. We did not have information about microvascular disease, including renal dysfunction. Second, the adherence to DAPT was lower in the IRD. Although this did not result in higher ST rates, it could be a possible explanation for non-ST-related cardiac death or MI. Numerically higher death or MI rates have been observed previously in patients treated with bare metal stents (BMS) or DES.[23]

Endothelial Progenitor Cells. It has been postulated that in patients with cardiovascular risk factors, including diabetes, the number of circulating EPCs is reduced because of direct influence on the mobilization and half-life of the EPCs or possible depletion of EPCs due to continuous endothelial damage or dysfunction.[24] We did not assess EPC numbers in the present study. Yet, if we extrapolate these findings to

our current results, the comparable TLR rates in NIRD and nondiabetics may be explained by the effectiveness of the EPC capturing technology. Furthermore, there was a significantly higher statin use in NIRD prior to the index procedure, with the pleiotrophic effect of statin therapy potentially enhancing circulating EPC levels.[25]

Clinical Implications. Current clinical data indicate the superior performance of DES over BMS; however, conflicting results have been shown regarding safety after DES placement.[26] Further research on efficacy should focus on randomized comparisons between Genous versus DES or BMS, while longer follow-up is needed to assess the safety of the various stents regarding ST. The current results show a good safety at 1-year after Genous stenting in a high-risk population for ST.

Limitations. Our findings should be interpreted in the light of the following limitations. First, despite extensive adjustments for established and identified variables for TLR, unknown sources of bias could have affected our analyses. Second, underreporting of outcomes associated with registries could have occurred despite the comprehensive data-management plan of the e-HEALING registry. Finally, 12-month outcomes may be too short to investigate the occurrence of late ST.

Conclusion

The 1-year results of the Genous stent in a real-world population of diabetics show higher TVF rates in diabetics compared with nondiabetics, mainly driven by a higher mortality hazard. IRD is associated with a significant higher TLR hazard. Definite or probable ST in all diabetic patients was comparable with nondiabetics.

Disclosure

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