Original Contribution

Safety and Effectiveness of the Genous Endothelial Progenitor Cell-Capture Stent: Follow-Up to 5 Years

Tiago Pereira-da-Silva, MD, Luís Bernardes, MD, Duarte Cacela, MD, António Fiarresga, MD, Lídia Sousa, MD, Lino Patrício, MD, Rui Cruz Ferreira, MD

ABSTRACT: Aims. To evaluate the long-term clinical outcomes following percutaneous coronary intervention (PCI) with the Genous stent in an unselected population. **Methods.** All patients admitted to a single center who underwent PCI using the GS exclusively, between May 2006 and May 2012, were enrolled, and a clinical follow-up of up to 60 months was carried out. The primary endpoint of major adverse cardiac event (MACE) rate was defined as the composite of cardiac death, acute myocardial infarction (AMI), and target lesion revascularization (TLR). **Results.** Of the 450 patients included (75.1% male; 65.5 ± 11.7 years), 28.4% were diabetic and acute coronary syndrome was the reason for PCI in 76.4%. Angioplasty was performed in 524 lesions using 597 Genous stents, with angiographic success in 97.1%. At a median of 36 months of follow-up (range, 1-75 months), MACE, AMI, TLR, stent restenosis (SR), and stent thrombosis (ST) rates were 15.6%, 8.4%, 4.4%, 3.8%, and 2.2%, respectively. Between 12 and 24 months, the TLR, SR, and ST rates practically stabilized, up to 60 months. Bifurcation lesions were independently associated with MACE, TLR, and SR. **Conclusion.** This is the first study reporting clinical results with the Genous stent up to 60 months. The Genous stent was safe and effective in the long-term, in an unselected population.

J INVASIVE CARDIOL 2013;25(12):666-669

Key words: endothelial progenitor cell, stent, percutaneous coronary intervention

The Genous bioengineered R stent (GS; OrbusNeich) is covered by monoclonal CD34+ antibodies that selectively capture circulating endothelial progenitor cells, thus accelerating healing of the stented lesion.[1,2]

Many studies have been published on the safety and effectiveness of the GS, but the studies with the longest follow-up reported the clinical outcomes at 36 months following percutaneous coronary intervention (PCI) with the GS[3,4] and one study included only ST-elevation myocardial infarction patients.[4] We aimed to evaluate the clinical outcomes up to 60 months following PCI with the GS in an unselected population.

Methods

Patients and data collection. We conducted a cohort study of all patients admitted to our center treated with PCI exclusively using the GS, between May 2006 and May 2012. The study protocol was approved by the hospital ethics committee and all patients signed informed consent forms before PCI.

Based on the clinical files, the following data were recorded: demographic and clinical data, including cardiovascular risk factors, previous cardiovascular events, and other comorbidities; angiographic and PCI procedural data; and in-hospital clinical and angiographic complications.

Based on phone enquiry or clinic visits, a clinical follow-up at 1, 12, 36, and 60 months after discharge was carried out. The study was concluded 1 month after the last patient was enrolled and at the end of the study all patients or their representatives (in case of death) were contacted. The following data were accounted for and verified by hospital records: death, acute myocardial infarction (AMI), target vessel revascularization (TVR), target lesion revascularization (TLR), clinical stent restenosis, stent thrombosis, angina or anginal equivalent, and dual-antiplatelet therapy discontinuation.

Patients who received a stent other than the GS, either in the same PCI where the GS was implanted or in a staged PCI, were excluded.

Endpoint. The primary endpoint of *major adverse cardiac event (MACE) rate* was defined as the composite of cardiac death, AMI, and TLR. Clinical stent restenosis and stent thrombosis incidence were also determined.

Definitions. All deaths were considered cardiac deaths unless otherwise documented. *AMI* was defined in accordance with the Academic Research Consortium (ARC)[5] as elevation of cardiac enzymes 3 times the upper limit of normal. *TVR* was defined as repeat revascularization of the previously treated vessel, and TLR as repeat revascularization within 5 mm to stent edges (in-segment). *Clinical stent restenosis* was defined as the presence of angina or anginal equivalent, associated with >50% stenosis in the segment covered by the stent or the adjacent 5 mm. Stent thrombosis was classified according to ARC definitions,[5] in which *definite stent thrombosis* is defined as angiographic or pathologic confirmation of acute stent thrombosis in patients with acute coronary syndromes; and *probable stent thrombosis* as any unexplained death in the 30 days following stent implantation or as target vessel myocardial infarction without angiographic confirmation of stent thrombosis or other identified culprit lesion. Stent thrombosis was classified as acute (first 24 hours), subacute (between 24 hours and 30 days), and late (after 30 days). Angiographic success was defined as residual stenosis of less than 10% and Thrombolysis in Myocardial Infarction (TIMI) flow score 3.

From the Cardiology Department, Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, Lisbon, Portugal.

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

Manuscript submitted July 1, 2013, provisional acceptance given July 29, 2013, final version accepted August 19, 2013.

Address for correspondence: Dr Tiago Pereira-da-Silva, Cardiology Department, Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, Rua de Santa Marta, nº 50, 1169-024, Lisbon, Portugal. Email: tiagopsilva@sapo.pt

Table 1. Demographic and clinical data.

Characteristic	n = 450
Male	338 (75.1%)
Hypertension	335 (74.4%)
Dyslipidemia	304 (67.6%)
Smoking history	159 (35.3%)
Diabetes mellitus	128 (28.4%)
Obesity	103 (22.9%)
Previous AMI	28 (6.2%)
Previous percutaneous coronary intervention	57 (12.7%)
Previous coronary artery bypass grafting	9 (2.0%)
Predischarge depressed LVEF (<55%)	181 (40.2%)
Cardiogenic shock	8 (1.8%)
Reason for performing PCI	
AMI without ST elevation	161 (35.8%)
AMI with ST elevation	151 (33.6%)
Stable coronary artery disease	106 (23.6%)
Unstable angina	32 (7.1%)

Data given as n (%). LVEF = left ventricular ejection fraction; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention.

Table 2. Angiographic data.

Characteristic	n = 450
Multivessel disease	202 (44.9%)
Lesions treated per patient	
1	364 (80.9%)
>1	86 (19.1%)
Intervened vessel	**n = 524**
Left anterior descending artery	226 (43.1%)
Right coronary artery	178 (34.0%)
Circumflex artery	114 (21.8%)
Left main artery	4 (0.8%)
Venous bypass graft	2 (0.4%)
Lesion risk profile	**n = 524**
Lesion type B2/C	254 (48.5%)
Long lesion	133 (25.4%)
Bifurcation lesion	53 (10.1%)
Calcified lesion	64 (12.2%)
Eccentric lesion	315 (60.1%)
Thrombotic lesion	111 (21.2%)
Restenosis (previous angioplasty with another stent)	7 (1.3%)

Table 3. Procedural data.

		Pre Intervention		Post Intervention	
TIMI flow score	N	n	(%)	n	(%)
0	524 lesions	135	(25.8%)	1	(0.2%)
1		37	(7.1%)	1	(0.2%)
2		22	(4.2%)	6	(1.1%)
3		330	(63.0%)	516	(98.5%)
	N	**n**		**(%)**	
Number of stents per patient	450 patients				
1		314		(69.8%)	
>1		136		(30.2%)	
Stent implantation					
Diameter of the stent (mm)	597 stents	3.00 (2.50-4.00)			
Length of the stent (mm)		15 (9-33)			
Pressure of inflation (atm)		18 (10-24)			
Duration of inflation (s)		20 (10-50)			
Post dilatation					
Diameter of the balloon (mm)	524 lesions with 50 post dilatations (9.5%)	3.00 (2.50-4.00)			
Length of the balloon (mm)		12 (6-28)			
Pressure of insufflation (atm)		16 (10-20)			
Duration of inflation (s)		20 (10-60)			
Kissing balloon	53 bifurcation lesions	10		(18.9%)	
Glycoprotein IIb/IIIa inhibitor (abciximab or tirofiban)	450 patients	132		(29.3%)	
Thrombus aspiration	450 patients	28		(6.2%)	

Discrete data given as n (%) and continuous variables as median (minimum-maximum). TIMI = Thrombolysis in Myocardial Infarction.

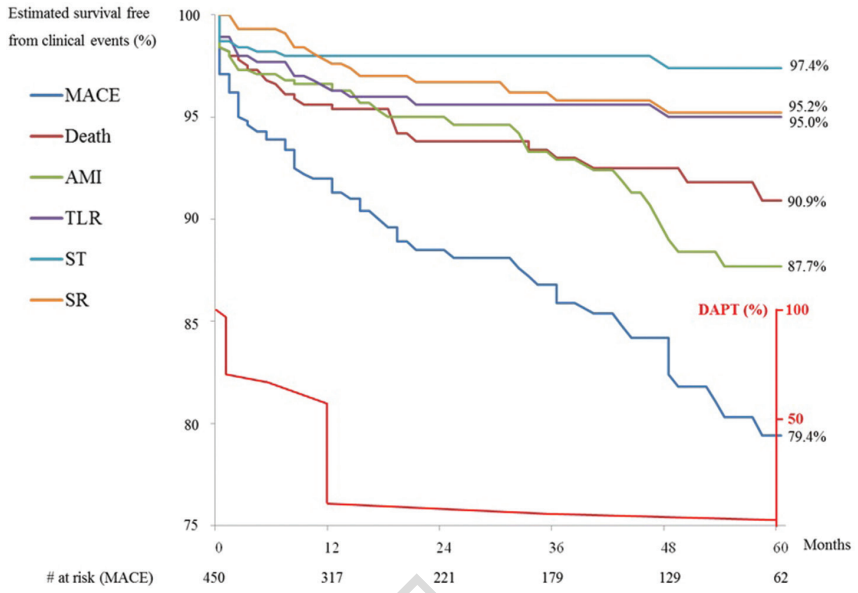

Figure 1. *Estimated survival free from clinical events (above) and continuous rate of dual-antiplatelet therapy (below). AMI = acute myocardial infarction; DAPT = dual-antiplatelet therapy; death = cardiac death; MACE = major adverse cardiac events; SR = clinical stent restenosis; ST = stent thrombosis; TLR = target lesion revascularization; # at risk (MACE) = number of patients at risk of major adverse cardiac events.*

Statistical analysis. Discrete data are presented as frequency (percentage), whereas continuous variables are presented as mean ± standard deviation or as median (range), when appropriate. Cumulative survival rates were estimated using the Kaplan-Meier method. A Cox proportional hazard multivariate analysis was used to identify independent predictors of MACE, TLR, and clinical stent restenosis by backward selection of all demographic, clinical, angiographic and procedural data. The estimated survival free from MACE, TLR, and clinical stent restenosis were compared between patients with and without bifurcation lesions using a log-rank test (*post hoc* analysis). A *P*-value of less than .05 was considered statistically significant. Data were analyzed using the software Statistical Package for the Social Science for Windows, version 16.0 (SPSS, Inc).

Results

PCI using the GS was performed in 468 patients and 18 were excluded since they received another type of stent in addition to the GS. In our cohort of 450 patients, a total of 338 (75.1%) were male and the mean age was 65.5 ±11.7 years. Demographic and clinical data are presented in Table 1. A total of 128 patients (28.4%) had diabetes mellitus on medication. Acute coronary syndrome was the most frequent reason for performing PCI (76.4%).

Angiographic data are presented in Table 2. Angioplasty was performed in 524 lesions, of which 226 (43.1%) were located in the left anterior descending artery and 254 (48.5%) were classified as type B2/C.[6] Fifty-three lesions (10.1%) were bifurcations (bifurcation type I in 31 patients, type II in 11 patients, and type III in 11 patients).[7] Mean stenosis of the intervened lesions was 91.1 ± 10.9%.

Procedural data is presented in Table 3. Angiographic success was achieved in 509 angioplasties (97.1%), and complete revascularization in 314 patients (69.8%). A total of 597 Genous stents were used (1.1/lesion). The median diameter of the stent implanted was 3.00 mm (2.50-4.00 mm) and the median length was 15 mm (9-33 mm).

Follow-up. Follow-up data were obtained from all patients. Median follow-up period was 36 months (1-75 months), since the last included patients had not completed 60 months after discharge at the end of the study. The clinical events that occurred during this period are presented in Table 4 and cumulative survival free from clinical events up to 60 months is presented in Figure 1. MACE, cardiac death, and AMI rates continued to increase up to 60 months. Conversely, TLR, clinical stent restenosis, and stent thrombosis rates stabilized between 12 and 24 months post PCI and maintained relatively stable up to 60 months (Figure 1).

Eight definite stent thromboses occurred (Table 4): 1 acute, 4 subacute (on days 2, 10, 11, and 21) and 3 late (months 2, 4, and 48). One subacute stent thrombosis was probably due to relative antiplatelet underdosing (100 mg acetylsalicylic acid plus 75 mg clopidogrel/day, despite a body weight of 141 kg). In another subacute stent thrombosis, the patient had previously discontinued antiplatelet therapy, against medical advice. No apparent stent abnormalities were found in the subsequent angiographies. PCI was performed with success in 7 patients; 1 patient underwent coronary artery bypass grafting since the left main artery was involved; all 8 patients survived. There were 2 probable stent thromboses: a sudden unexplained death 9 days after PCI (in ambulatory), and a death caused by AMI in a patient that was not catheterized and whose autopsy revealed a target-vessel AMI.

At 1 month and 12 months of follow-up, 95.3% and 57.6% of the patients were on dual-antiplatelet therapy, respectively.

Multivariate predictors of MACE, TLR, and clinical stent restenosis are presented in Table 5. Bifurcation lesion was the most important predictor of MACE and clinical stent restenosis and was the only predictor of TLR. At 60 months, estimated survival free from events was significantly lower for patients with bifurcation lesions in comparison with patients without bifurcation lesions, regarding MACE (log-rank test, *P*<.001), TLR (log-rank test, *P*=.01), and clinical stent restenosis (log-rank test, *P*=.01).

Discussion

This single-center study evaluated the long-term safety and effectiveness of the GS in an unselected population. The GS evidenced a good performance following PCI, probably related to the rapid endothelialization.[8] The rates of MACE, cardiac death, TVR, TLR, clinical stent restenosis, and stent thrombosis were low.

Few studies reported the clinical outcomes beyond 36 months after PCI with stent placement in all-comer populations,[9] and the longest follow-up study after PCI with the GS had a duration of 36 months.[3] In this study on 405 unselected patients, the

Table 4. Clinical events during follow-up: median follow up, 36 months (range 1-75 months).

Patients	N = 450
Major adverse cardiac events	70 (15.6%)
Death	57 (12.7%)
Cardiac	29 (6.4%)
Non-cardiac	28 (6.2%)
Acute myocardial infarction	38 (8.4%)
Target vessel revascularization	25 (5.6%)
Target lesion revascularization	20 (4.4%)
Coronary artery bypass grafting	4 (0.9%)
Percutaneous coronary intervention	16 (3.6%)
Clinical stent restenosis	17 (3.8%)
Stent thrombosis	10 (2.2%)
Definite	8 (1.8%)
Acute	1 (0.2%)
Subacute	4 (0.9%)
Late	3 (0.7%)
Probable	2 (0.4%)

primary endpoint of target lesion failure, defined as the composite of cardiac death, AMI, and TLR, was 18.3% and the need for TLR was 14.2%; definite and probable stent thrombosis occurred in 0.5% and 1.0%, respectively, and no cases of definite late or very late stent thrombosis were reported. In another study on 100 ST-elevation AMI patients who also received a GS, the rate of MACE, defined as cardiac death, AMI, and TLR, was 15.8% at a mean follow-up of 34 months and there were no cases of definite stent thrombosis.[4] Our data compare well with these studies on the long-term outcomes after PCI with the GS.

In our cohort, although MACE, cardiac death, and AMI continued to increase up to 60 months, the need for TLR, clinical stent restenosis, and stent thrombosis rates practically stabilized from 12 to 24 months, up to 60 months. This suggests that "GS failure" did not account for the sustained increase in MACE, death, or AMI. The deflecting TLR curve after the first year of PCI with the GS has been reported by Klomp et al.[3] Duckers et al[8] demonstrated late intimal tissue regression, with a luminal loss reduction of 24.4% between the 6- and 18-month of angiographic follow-up. In contrast, the risk of TLR after the first year of stent implantation may be higher and ongoing in patients treated with a drug-eluting stent.[10]

In our patients, bifurcation lesion was independently associated with MACE, TLR, and stent restenosis. In the study by Beijk el at,[11] where 573 patients were treated for at least 1 bifurcation lesion with the GS, the TLR rate was 12.7% at 12 months. These data suggest that bifurcation lesions may predict worse outcomes with the GS in comparison with non-bifurcation lesions.

Study limitations. This study has the limitation of reflecting the experience of a single center. In addition, the stent type was selected at the discretion of the operators and patients with higher thrombotic risk or lower dual antiplatelet therapy compliance might have been preferentially selected to receive the GS.

Table 5. Multivariate predictors of major adverse cardiac events, target lesion revascularization and clinical stent restenosis.

Major adverse cardiac events	HR	95% CI	*P*-Value
Bifurcation lesion	2.868	1.575-5.220	.01
Diabetes mellitus	2.054	1.238-3.408	.01
Depressed LVEF (<55%)	1.973	1.192-3.263	.01
Higher TIMI score (post intervention)	0.325	0.129-0.815	.02
Target lesion revascularization			
Bifurcation lesion	4.406	1.559-10.811	.01
Clinical stent restenosis			
Bifurcation lesion	4.705	1.602-13.814	.01
Higher residual stenosis (post intervention)	1.070	1.024-1.118	.01

TIMI = Thrombolysis in Myocardial Infarction; LVEF = left ventricular ejection fraction.

Nevertheless, this possible bias would worsen the endpoint rates, which have been low in this cohort.

Conclusion

The GS had a long-term favorable profile in a "real-world" unselected population. The TLR, stent restenosis, and stent thrombosis rates stabilized between 12 and 24 months, up to 60 months following PCI. Except in bifurcation lesions, the GS was safe and effective and may be a good option, considering the long-term clinical results.

References

1. Kutryk MJ, Kuliszewski MA. In vivo endothelial progenitor cell seeding for the accelerated endothelialization of endovascular devices. *Am J Cardiol.* 2003;92(Suppl 6A):94L-95L.
2. Kong D, Melo LG, Gnecchi M, et al. Cytokine-induced mobilization of circulating endothelial progenitor cells enhances repair of injured arteries. *Circulation.* 2004;110(14):2039-2046.
3. Klomp M, Beijk MA, Damman P, et al. Three-year clinical follow-up of an unselected patient population treated with the genous endothelial progenitor cell capturing stent. *J Interv Cardiol.* 2011;24(5):442-449.
4. Low AF, Lee CH, Teo SG, et al. Effectiveness and safety of the genous endothelial progenitor cell-capture stent in acute ST-elevation myocardial infarction. *Am J Cardiol.* 2011;108(2):202-205.
5. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115(17):2344-2351.
6. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. *Circulation.* 1990;82(4):1193-1202.
7. Safian RD. Bifurcation lesions. In: Safian RD, Freed M, eds. *Manual of Interventional Cardiology.* Royal Oak: Physicians' Press; 2001:221-236.
8. Duckers HJ, Soullié T, den Heijer P, et al. Accelerated vascular repair following percutaneous coronary intervention by capture of endothelial progenitor cells promotes regression of neointimal growth at long term follow-up: final results of the Healing II trial using an endothelial progenitor cell capturing stent (Genous R stent). *EuroIntervention.* 2007;3(3):350-358.
9. Hanna NN, Gaglia MA Jr, Torguson R, et al. Three year outcomes following sirolimus- versus paclitaxel-eluting stent implantation in an unselected population with coronary artery disease (from the REWARDS registry). *Am J Cardiol.* 2010;106(4):504-510.
10. Morice MC, Serruys PW, Barragan P, et al. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. *J Am Coll Cardiol.* 2007;50(14):1299-1304.
11. Beijk MA, Damman P, Klomp M, et al. 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. *Coron Artery Dis.* 2012;23(3):201-207.