Genous™ endothelial progenitor cell capturing stent vs. the Taxus Liberté stent in patients with de novo coronary lesions with a high-risk of coronary restenosis: a randomized, single-centre, pilot study

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Aims

The purpose of this study was to evaluate the Genous™ endothelial progenitor cell capturing stent vs. the Taxus Liberté paclitaxel-eluting stent in patients with de novo coronary lesions with a high-risk of coronary restenosis.

Methods and results

We randomly assigned 193 patients with lesions carrying a high risk of restenosis to have the Genous stent or the Taxus stent implanted. Lesions were considered high risk of restenosis if one of the following applied: chronic total occlusion, lesion length >23 mm, vessel diameter <2.8 mm, or any lesion in a diabetic patient. At 1-year, the rate of the primary end point, target vessel failure (TVF), was 17.3% in the Genous stent group when compared with 10.5% in the Taxus stent group [risk difference (RD) 6.8%, 95% CI –3.1 to 16.7%], a difference predominantly due to a higher incidence of repeat revascularization in patients treated with the Genous stent. In contrast, no stent thrombosis was observed in the Genous stent group compared to 4 stent thromboses in the Taxus stent group (RD –4.2%; 95% CI –10.3 to 0.3%). Repeat angiography between 6 and 12 months in a subgroup of patients showed a significantly higher late loss in the Genous stent compared with the Taxus stent (1.14 ± 0.64 and 0.55 ± 0.61 mm).

Conclusion

In patients with lesions carrying a high risk of restenosis, the Genous stent resulted in a non-significant higher rate of TVF compared with the Taxus stent mainly due to more repeat revascularizations in the Genous stent group. There were four stent thromboses with Taxus stent, none with the Genous stent.

Keywords

Stent • Genous • Taxus • Restenosis • Percutaneous coronary intervention

Introduction

Drug-eluting stents (DES) have demonstrated a marked reduction in in-stent restenosis compared with bare metal stents (BMS) in the treatment of coronary artery disease.1–5 In order to reduce neointimal hyperplasia after DES placement, the antiproliferative drug induces a cytostatic or cytotoxic effect on the neointimal vascular tissue. However, this also impedes the natural healing response by delaying the formation of a functional endothelial layer covering the stent.6,7 In DES, a prolonged absence of

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re-endothelialization was observed, which was associated with the occurrence of late and very late stent thrombosis, and currently, long-term dual antiplatelet therapy is recommended.7

Rather than locally intervene with cytotoxic or cytostatic drugs, accelerated vascular healing with rapid establishment of a functional endothelial layer after vascular injury has been shown to assist in the prevention of neointimal proliferation and thrombus formation after stent placement.8,9 The Genous™ endothelial progenitor cell (EPC) capturing stent is coated with anti-human CD34+ antibodies that bind circulating EPCs from the peripheral blood to the stent surface. In the animal model, scanning electron microscopic images have demonstrated a complete re-endothelialization of the stent struts and vessel segments within only a few hours following Genous stent placement.10 It is hypothesized that these ‘captured’ EPCs can rapidly differentiate into a functional endothelial layer on the stent surface. The safety and feasibility of the Genous stent was evaluated in the non-randomized HEALING FIM registry11 and HEALING II study12,13 in patients with de novo coronary artery disease. Preliminary results of the world-wide e-HEALING registry have shown low repeat revascularization and low incidence of stent thrombosis.14 Thus far, randomized data of the attractiveness of the Genous stent in terms of rapid endothelialization to prevent repeat revascularization are lacking. This is the first randomized, single-centre study that compares the Genous™ EPC capturing stent with the Taxus Liberté paclitaxel-eluting stent, evaluating the efficacy and feasibility of the treatment of coronary artery lesions in patients with a high risk of restenosis.

Methods

Study design and patient population

The investigator-initiated single-centre TRI-stent Adjudication Study (TRIAS) study was a prospective, randomized, single-blind study performed in a high-volume centre with on-site cardiac surgery. The study complied with the principles of the Declaration of Helsinki regarding investigation in humans and was approved by the local institutional review board. The study was conducted from February 2006 to April 2007. The duration of follow-up is 5 years and here we report the 1 year outcome.

For the purpose of this study, coronary lesions were marked as carrying a high risk for restenosis if at least one of the following applied: (i) a chronic coronary artery occlusion; (ii) a coronary artery stenosis with a length of more than 23 mm; (iii) a lesion in a coronary artery with a diameter of less than 2.8 mm by visual estimation; (iv) any lesion in a diabetic patient. All other lesions were considered to be low-risk lesions. Patients accepted to undergo a non-urgent stent placement for de novo coronary artery stenosis with a high risk for restenosis were eligible for inclusion. All patients had either stable angina despite medical therapy, unstable angina pectoris or a non-ST-segment elevation myocardial infarction (MI). All patients were on statin therapy for at least 7 days prior to procedure, regardless of the type or dose of statins. Major exclusion criteria were recent ST-segment elevation MI (within the previous 72 h); unstable ventricular arrhythmia; severe renal (serum creatinin > 200 μg/L) or liver insufficiency; severe hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure over 100 mmHg after treatment); current therapy of immune-suppression, chemotherapy or radiotherapy, known immunosuppressive or autoimmune disease; previous administration of murine therapeutic antibodies or exhibited sensitization through the production of human anti-murine antibodies; contraindication to aspirin, heparin, clopidogrel, or any other drug related to this study; planned surgery within the first 6 months after the procedure that will require discontinuation of either aspirin or clopidogrel.

Study procedure

Written informed consent was obtained after the patient had been accepted for elective and non-urgent PCI. The angiographic in- and exclusion criteria were reassessed after initial angiography at the start of the procedure. All high-risk lesions were identified and recorded as such. After at least one high-risk lesion was identified, patients were randomly assigned in a single-blinded manner for treatment with a Genous stent or a Taxus stent in a 1:1 ratio. Randomization was performed using a sealed and signed envelope which was blinded to all study personnel. Randomization blocks were created with randomly chosen block sizes of one, two, three, or four. Low-risk lesions could be treated during the same procedure according to the treatment assignment or with a BMS.

Lesions were treated in accordance with standard PCI guidelines. Pre- and post-dilatation were left at the discretion of the operator. At the start of the procedure patients received heparin 5000 IU. The use of intravenous platelet glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. Patients were treated with aspirin 100 mg indefinitely. Clopidogrel was administered in a loading dose 300 mg directly before or after the procedure and was recommended (75 mg/day) for at least 1 month after Genous stent and at least 6 months after a Taxus stent implantation.

Genous™ endothelial progenitor cell capturing stent

The Genous stent comprises a covalently coupled polysaccharide matrix coating with monoclonal murine anti-human CD34+ antibodies on the adluminal stent surface, attached to a 316L stainless steel stent (Genous Bio-engineered R stent™, OrbusNeich Medical Technologies, Fort Lauderdale, FL, USA). These anti-CD34+ antibodies specifically target the circulating EPC population associated with post-natal neoangiogenesis and arterial repair response. The Genous stent received CE mark on 11 August 2005.

Taxus Liberté paclitaxel-eluting stent

The Taxus Liberté™-SR Paclitaxel-Eluting Coronary Stent (Boston Scientific, MA, USA) is a 316L stainless steel stent coated with a drug/polymer formulation consisting of paclitaxel and Translute™ Polymer Carrier. The polymer is mixed with the drug paclitaxel and then applied to the stents. There is no primer or topcoat layer. The drug/polymer coating is adhered to the entire surface (i.e. luminal and abluminal) of the stent.

Follow-up

Patients were scheduled for a hospital visit at 30 days, 6 months and 1 year. At the patient’s request, the hospital visit could be replaced by a telephone call. Patients were asked specific questions about the interim development of angina according to the Canadian Cardiovascular Society Classification of stable angina and Braunwald Classification of unstable angina. They were also monitored for major adverse cardiac events and the need for additional revascularizations of the index target lesions. If a major adverse cardiac event was reported, we reviewed hospital and chart records and contacted the
referring cardiologists and/or the patient’s general practitioner to complete information. All patients were invited for repeat coronary angiography between 6 and 12 months; however, participation of angiographic follow-up was not mandatory for inclusion in the study.

**Quantitative coronary analysis**

Coronary angiograms were obtained pre-procedural, post-procedural, and at follow-up (between 6 and 12 months) in at least two orthogonal projections after intracoronary injection of nitroglycerin. Off-line quantitative coronary analyses (QCAs) were performed by an independent core laboratory (Angiographic Core Laboratories, Cardiovascular Research Foundation, NY, USA) with observers blinded to the allocated stent. Images were analyzed using MEDIS QCA software version 6.0 (MEDIS, Leiden, The Netherlands). The tip of a 6 or 7 French catheter filled with contrast was used for calibration. The minimal lumen diameter (MLD) was measured at the narrowest point of the lesion or within the stent. Late lumen loss was defined as the difference between MLD after the procedure and at follow-up.

**Endpoints and definitions**

The primary endpoint was target vessel failure (TVF) defined as the composite of cardiac death, MI (unless documented to arise from the non-treated coronary artery), and target vessel revascularization (TVR) within 1 year. All deaths were considered cardiac death unless otherwise documented. Peri-procedural MI was defined as a rise in the creatine kinase-MB level or troponin T level of more than three times the upper limit of normal. Myocardial infarction (spontaneous) was defined as any rise in the creatine kinase-MB level or troponin T level above the upper reference limit. Target vessel revascularization was defined as any repeat revascularization of a target vessel by repeat percutaneous intervention or coronary artery bypass grafting (CABG). All events unequivocally not related to randomized (high-risk) lesions were excluded from the primary endpoint.

Secondary endpoints included non-cardiac death, target lesion revascularization (TLR), non-TVR, and stent thrombosis within 1 year after the index procedure. All endpoint definitions used are in accordance with the Academic Research Consortium.15 The primary endpoints were adjudicated by an independent clinical event committee, with members blinded to the assigned stent.

**Statistical analysis**

Originally, the study was designed as a non-inferiority study. Based on the results of the TAXUS IV trial (TVF rate of 10% at 1-year follow-up in the Taxus stent group) and the preliminary results of the e-HEALING registry, the assumed incidence of the primary endpoint was 10% at 1 year with an upper limit of non-inferiority of 16% in the Genous stent group. For this purpose, 620 patients would have been needed to provide the study with 80% power with a one-sided α of 5%. The enrolment in the study was discontinued after 193 patients had been included. At that time, the decision had been made to venture into a large, international, multicentre study with a similar study design (TRIAS HR trial: ISRCTN 74297220). Thus, the original power calculation does not apply to the current pilot study of 193 patients.

For the primary and secondary endpoints, no formal hypothesis testing was performed. Henceforth, for all endpoints, the cumulative risk differences (RDs) and the 95% confidence intervals (CIs) are presented for descriptive purposes only. For baseline characteristics, continuous variables with normal distributions were expressed as means ± SD and were compared with the use of an unpaired Student’s t-test. Categorical variables were compared with the use of the χ² test or Fisher’s exact test, where appropriate. The occurrence of the primary endpoint, TVF, over time is presented using the Kaplan–Meier method. Because no formal test was performed on the Kaplan–Meier curves, we present the 1-year cumulative RD and 95% CI. The percentage of patients on dual antiplatelet therapy was presented using the Kaplan–Meier method. The difference in the use of dual antiplatelet therapy between the groups was tested using the log-rank test, thus giving equal weight to the group differences observed at each time point. Only clinical events confirmed by the Clinical Event Committee were taken into account for the analysis of primary endpoint. For all statistical analyses, we used the SPSS software package (version 15, SPSS Inc., Chicago, IL, USA).

### Results

#### Baseline patient and lesion characteristics

Between February 2006 and April 2007, 193 patients were randomized to either a Genous stent (n = 98) or a Taxus stent (n = 95). As shown in Table 1, the two groups were similar with respect to all variables examined with the exception of diabetic

| Table 1 | Baseline characteristics of patients | Randomized to | P-value |
|---------|-------------------------------------|---------------|---------|
|         | Genous (n = 98) | Taxus Liberté (n = 95) |
| Age (years) | 62 ± 10 | 63 ± 11 | 0.657 |
| Male | 72 (73%) | 70 (74%) | 0.973 |
| Diabetes | 14 (14%) | 26 (27%) | 0.025 |
| NIDDM | 11 (11%) | 18 (19%) | 0.715 |
| IDDM | 3 (3%) | 8 (8%) | |
| Hypertension | 45 (46%) | 53 (56%) | 0.17 |
| Hyperlipidaemia | 62 (63%) | 50 (53%) | 0.135 |
| Family history of CAD | 52 (53%) | 61 (64%) | 0.116 |
| Current smoker | 32 (33%) | 30 (32%) | 0.244 |
| Prior myocardial infarction | 37 (38%) | 39 (41%) | 0.639 |
| Prior percutaneous intervention | 25 (26%) | 25 (26%) | 0.898 |
| Prior CABG | 3 (3%) | 3 (3%) | 0.969 |
| Angina pectoris | Stable | 80 (82%) | 81 (85%) | 0.498 |
| Unstable | 18 (18%) | 14 (15%) | |
| Statin therapy | Number of high-risk lesions treated | 98 (100%) | 93 (98%) | 0.241 |
| 1 | 78 (80%) | 71 (75%) | 0.519 |
| 2 | 17 (17%) | 18 (19%) | |
| 3 | 3 (3%) | 6 (6%) | |

Values are n (%) or mean ± SD.

(N)IDDM (non)-insulin-dependent diabetes mellitus; CAD, coronary artery disease; CABG, coronary artery bypass grafting.
mellitus. Angiographic characteristics of the high-risk lesions are shown in Table 2 and were well matched except for the percentage of vessels <2.8 mm treated which was higher in the Taxus stent-treated group. Overall, more than 80% of the randomized lesions were longer than 23 mm and nearly 30% of the lesions were chronic total occlusions. As a result of lesion and patient selection, a total of 89% of the randomized lesions were class B2 or C type lesions according to the American College of Cardiology–American Heart Association classification.

**Procedural characteristics**

All randomized high-risk lesions were treated according to the randomized assignment. The number of stents implanted per patient, the mean total stent length and post-procedural lesion diameter, and other deployment and implantation variables were similar in the two groups (Table 2). Peri-procedural administration of glycoprotein IIb/IIIa inhibitors did not differ between both groups (11% Genous stent vs. 16% Taxus stent; P = NS). In the Genous stent group, 5 out of 18 low-risk lesions were treated with a BMS and in the Taxus stent group 8 out of 17.

**Clinical outcomes**

Clinical follow-up was complete for all patients and events are listed in Table 3. The rate of the primary endpoint, TVF at 1 year, was 17.3% in the Genous stent group when compared with 10.5% in the Taxus stent group (RD 6.8%, 95% CI –3.1 to 16.7%). A Kaplan–Meier curve of event-free survival of TVF is shown in Figure 1. The cumulative rate of cardiac death or MI at 1 year was 3.1% in the Genous stent group when compared with 5.3% in the Taxus stent group (RD –2.2%, 95% CI –4.9 to 14.4%). During 1-year follow-up, no cases of cardiac death were observed in each treatment arm. Three patients (3.1%) in the Genous stent group and two patients (2.1%) in the Taxus stent group had a peri-procedural MI. In the Genous stent group, one patient had an occlusive dissection and one patient had a side branch occlusion. The third patient had recurrence of angina and underwent repeat angiography which showed a patent stent in the proximal RCx with TIMI 2 flow. This patient was treated with platelet glycoprotein IIb/IIIa inhibitor and heparin. In the Taxus stent group, both patients had an occlusive dissection. A total of three Taxus stent-treated patients had a spontaneous MI attributable to a stent thrombosis and one patient had a definite stent thrombosis which did not result in an MI. All patients who had a definite stent thrombosis were on dual antiplatelet therapy at the time of the event. No definite stent thrombosis was observed in the Genous stents, resulting in a numerical difference as compared to the Taxus stent (RD –4.2%; 95% CI –10.3 to 0.3%). The characteristics of patients with a definite stent thrombosis are summarized in Table 4. noteworthy, as a result of the recommendations, the percentage of patients on dual antiplatelet therapy was significantly lower in the Genous stent group when compared with the Taxus stent group and is shown in Figure 2 as a Kaplan–Meier curve.

Target lesion revascularization by PCI was performed in 12 patients (12.2%) treated with a Genous stent and in 8 patients (8.4%) with a Taxus stent (RD 3.8%, 95% CI –4.7 to 12.4%). In each treatment arm, one patient underwent a TLR by CABG. In the Genous stent group, two patients whom underwent CABG had patent stents as assessed by a pre-operative coronary angiogram and were considered as a non-TVR. The 1-year cumulative rate of cardiac death, MI or TLR was 15.3% in the Genous stent group when compared with 10.5% in the Taxus stent group (RD 4.8%, 95% CI –9.0 to 4.1%).

In the Genous stent group, one patient died from a sepsis 323 days after the index procedure. Two patients died in the Taxus stent group, the first from a pancreatic carcinoma 243 days after the index procedure and the second from a liver carcinoma at 338 days. The 1-year rate of non-TVR was 8.2% in the Genous stent group and 14.7% in the Taxus stent group (RD –6.5%, 95% CI –15.5 to 2.4%). In both groups, a non-TVR associated definite sub acute stent thrombosis occurred. No repeat revascularizations were performed in low-risk lesions in either group.

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**Table 2  Baseline angiographic and procedural characteristics of high-risk lesions**

| Characteristic                                | Genous (L = 121) | Taxus Liberté (L = 125) | P-value |
|-----------------------------------------------|------------------|-------------------------|---------|
| Type of lesion <sup>a</sup>                   |                  |                         |         |
| A                                             | 0 (0%)           | 2 (2%)                  | 0.295   |
| B1                                            | 10 (8%)          | 15 (12%)                |         |
| B2                                            | 54 (45%)         | 52 (42%)                |         |
| C                                             | 57 (47%)         | 56 (45%)                |         |
| Chronic total occlusion                       | 39 (32%)         | 30 (24%)                | 0.151   |
| Lesion length > 23 mm                         | 101 (83%)        | 100 (80%)               | 0.481   |
| Vessel diameter < 2.8 mm                      | 9 (7%)           | 25 (20%)                | 0.004   |
| Bifurcated lesions                            | 21 (17%)         | 23 (18%)                | 0.831   |
| Target coronary artery                        |                  |                         |         |
| Left main                                     | 1 (1%)           | 1 (1%)                  | 0.86    |
| Left anterior descending                      | 48 (40%)         | 46 (37%)                |         |
| Left circumflex                               | 31 (26%)         | 29 (23%)                |         |
| Right coronary artery                         | 41 (34%)         | 49 (39%)                |         |
| Pre-dilatation performed                      | 108 (89%)        | 111 (89%)               | 0.909   |
| Stent length (mm)                             | 31.7 ± 14.3      | 30.7 ± 12.0             | 0.561   |
| Stent diameter (mm)                           | 3.3 ± 0.4        | 3.2 ± 0.5               | 0.438   |
| Stents per lesion                             | 1.2 ± 0.5        | 1.2 ± 0.5               | 0.826   |
| Post-dilatation performed                     | 88 (73%)         | 88 (70%)                | 0.686   |
| Procedural success                            | 119 (98%)        | 124 (99%)               | 0.617   |

Values are n (%) or mean ± SD; L, number of lesions.

<sup>a</sup>According to ACC-AHA classification.
Angiographic follow-up was available in 90 patients (47%) and the median time of angiographic follow-up was 8 months (5–13 months). In the Genous stent group, angiographic follow-up was available for 53 patients: 37 patients (70%) had 1 lesion, 15 patients (28%) had 2 lesions and 1 patient (2%) had 3 lesions, amounting to a total of 70 high-risk lesions. In the Taxus stent group, angiographic follow-up was available for 37 patients: 24 patients (65%) had 1 lesion, 10 patients (27%) had 2 lesions, 3 patients (8%) had 3 lesions, amounting to a total of 53 high-risk lesions. The per-lesion QCA results of the high-risk lesions of all patients with angiographic follow-up are summarized in the left panel of Table 5.

In the MLD, pre- and post-procedure was comparable between the Genous stent arm and the Taxus stent arm. At follow-up, mean MLD was significantly smaller in the Genous stent arm compared with the Taxus stent arm, 1.48 ± 0.73 vs. 2.06 ± 0.69 mm, respectively (P < 0.0001).

### Table 3  One-year clinical follow-up

| Primary endpoint | Randomized to | Risk difference | 95% CI |
|------------------|---------------|-----------------|--------|
| TVF (composite of cardiac death, MI, or TVR) | Genous (n = 98) | 17 (17.3%) | 10 (10.5%) | 6.8% | −3.1 to 16.7% |
|                  | Taxus Liberté (n = 95) |                  |        |        |        |
| Other composite endpoints |                  | 15 (15.3%) | 10 (10.5%) | 4.8% | −9.0 to 4.1% |
| Cardiac death, MI, or TLR |                  | 3 (3.1%) | 5 (5.3%) | −2.2% | −4.9 to 14.4% |

Other events

- **Non-cardiac death**
  - Genous (n = 98): 1 (1.0%)
  - Taxus Liberté (n = 95): 2 (2.1%)
  - Risk difference: −1.1% (95% CI: −4.6 to 2.4%)

- **MI not related to a target lesion**
  - Genous (n = 98): 1 (1.0%)
  - Taxus Liberté (n = 95): 1 (1.1%)
  - Risk difference: −0.1% (95% CI: −2.9 to 2.8%)

- **Non-TVR**
  - Percutaneous
    - Genous (n = 98): 8 (8.2%)
    - Taxus Liberté (n = 95): 14 (14.7%)
    - Risk difference: −6.5% (95% CI: −15.5 to 2.4%)
  - Surgical
    - Genous (n = 98): 0
    - Taxus Liberté (n = 95): 0
    - Risk difference: 0.0% (95% CI: 0.8 to 2.1%)

- **Stent thrombosis not related to a target lesion**
  - Genous (n = 98): 1 (1.0%)
  - Taxus Liberté (n = 95): 1 (1.1%)
  - Risk difference: 1.1% (95% CI: 2.9 to 2.8%)

### Quantitative coronary analyses

Angiographic follow-up was available in 90 patients (47%) and the median time of angiographic follow-up was 8 months (5–13 months). In the Genous stent group, angiographic follow-up was available for 53 patients: 37 patients (70%) had 1 lesion, 15 patients (28%) had 2 lesions and 1 patient (2%) had 3 lesions, amounting to a total of 70 high-risk lesions. In the Taxus stent group, angiographic follow-up was available for 37 patients: 24 patients (65%) had 1 lesion, 10 patients (27%) had 2 lesions, 3 patients (8%) had 3 lesions, amounting to a total of 53 high-risk lesions. The per-lesion QCA results of the high-risk lesions of all patients with angiographic follow-up are summarized in the left panel of Table 5. In the MLD, pre- and post-procedure was comparable between the Genous stent arm and the Taxus stent arm. At follow-up, mean MLD was significantly smaller in the Genous stent arm compared with the Taxus stent arm, 1.48 ± 0.73 vs. 2.06 ± 0.69 mm, respectively (P < 0.0001).
As a result, late loss was significantly higher for the Genous stent arm compared with the Taxus stent arm, 1.14 ± 0.64 vs. 0.55 ± 0.61 mm, respectively (P < 0.0001). Figure 3 shows the cumulative distribution frequency curve of percentage diameter stenosis at pre-, post-procedure, and at follow-up for each of the treatment arm. The results of a per-patient QCA analysis using the mixed model were virtually the same as the results of the per lesion analysis (see Supplementary material online, Table S6).

The middle and right panels of Table 5 show the per-lesion QCA analyses when restricted to patients with clinically driven repeat coronary angiography (middle panel) and patients with non-clinically driven repeat angiography (right panel). In patients with clinically driven repeat coronary angiography, late loss was significantly higher in the Genous stent arm compared with the Taxus stent arm (1.40 ± 0.65 vs. 0.60 ± 0.54 mm; P = 0.002). Similar findings were found in patients with non-clinically driven angiography (late loss Genous stent 1.03 ± 0.60 vs. late loss Taxus stent 0.54 ± 0.62 mm; P < 0.0001).

Patients with angiographic follow-up were younger (60 ± 10 vs. 64 ± 11, P = 0.01), had more often two high-risk lesions treated (28 vs. 10%, P = 0.01), had less often a lesion length >23 mm at baseline (76 vs. 88%, P = 0.01), and had a different distribution of the target coronary artery (see Supplementary material online, Tables S7 and S8).

**Discussion**

In this single-centre, randomized pilot study, the Genous stent was compared with a second-generation Taxus stent for treatment of coronary artery lesions with a high risk of restenosis. The main findings of this study were that at 1 year, a non-significant trend towards a higher rate of TVF was observed in the Genous stent group compared to the Taxus stent group. In contrast, with only 1 month of dual antiplatelet therapy recommended, no definite stent thrombosis was observed in the Genous stent group compared with four cases in the Taxus stent group. This is the first randomized study comparing the outcome of the Genous stent with the Taxus stent.

The use of DES in complex lesions was evaluated in the TAXUS VI study in which 446 patients with long, complex lesions were randomized to treatment with either a Taxus stent or an equivalent BMS. Of all lesions, 56% were classified as complex lesions and mean lesion length was 20.6 mm, with a mean stent length of 33.4 mm. In the Taxus stent group, the 1-year rate of TVF was 16.4% and TLR was 8.3%. We included fewer diabetic patients but more type B2 and type C complex lesions compared with the TAXUS VI study. The 1-year TVF rate of the Genous stent group was comparable to the Taxus stent group of the TAXUS VI study. However, in our Taxus stent group, a lower rate of TVF was observed. This difference may be partly explained by the high incidence of MI in the Taxus stent group of the TAXUS IV. Furthermore, repeat angiography was performed in all Taxus stent patients in TAXUS VI which could have increased the rate of TVR due to angiography-driven revascularizations (occulo-stenotic reflex). Recently, the Genous stent was evaluated in a small, non-randomized registry including 80 consecutive patients who had two or more of the following high-risk features: diabetes mellitus, unstable coronary syndromes, left ventricular dysfunction, multi-interventions, or B2/C lesions. At 14 months follow-up TLR was 13%, but ischaemia-driven TLR was 5%, whereas the remaining 8% was treated for severity of angiographic restenosis and not because of recurrence of symptoms. The rate of TVF was 16% and, of interest, no cases of definite stent thromboses were observed. In general, patient characteristics were...
|                  | All patients with angiographic follow-up |                      | Patients with clinically driven angiography |                      | Patients with non-clinically driven angiography |                      |
|------------------|----------------------------------------|----------------------|---------------------------------------------|----------------------|-----------------------------------------------|----------------------|
|                  | Genouos (n = 53, L = 70)               | Taxus Liberté (n = 37, L = 53) | P-value                                      | Genouos (n = 18, L = 22) | Taxus Liberté (n = 7, L = 11) | P-value |
| Pre-procedure    |                                        |                      |                                             |                      |                                |                     |
| Reference vessel diameter | 2.74 ± 0.5                             | 2.69 ± 0.47          | 0.623                                       | 2.81 ± 0.49          | 2.67 ± 0.6                         | 0.477               |
| Minimal lumen diameter | 0.54 ± 0.41                            | 0.61 ± 0.41          | 0.325                                       | 0.53 ± 0.43          | 0.85 ± 0.37                        | 0.044               |
| Percentage diameter stenosis | 79 ± 15                                | 76 ± 15              | 0.220                                       | 80 ± 16              | 65 ± 17                           | 0.019               |
| Post-procedure   |                                        |                      |                                             |                      |                                |                     |
| Reference vessel diameter | 2.82 ± 0.46                            | 2.78 ± 0.46          | 0.620                                       | 2.88 ± 0.44          | 2.71 ± 0.61                        | 0.376               |
| Minimal lumen diameter | 2.63 ± 0.34                            | 2.61 ± 0.50          | 0.889                                       | 2.64 ± 0.39          | 2.52 ± 0.55                        | 0.428               |
| Percentage diameter stenosis | 7 ± 5                                  | 8 ± 7                | 0.676                                       | 10 ± 6               | 7 ± 7                            | 0.301               |
| At follow-up     |                                        |                      |                                             |                      |                                |                     |
| Reference vessel diameter | 2.48 ± 0.48                            | 2.71 ± 0.48          | 0.011                                       | 2.44 ± 0.62          | 2.56 ± 0.54                        | 0.597               |
| Minimal lumen diameter | 1.48 ± 0.73                            | 2.06 ± 0.69          | <0.0001                                     | 1.24 ± 0.75          | 1.92 ± 0.69                        | 0.022               |
| Percentage diameter stenosis | 41 ± 25                                | 24 ± 21              | <0.0001                                     | 49 ± 23              | 26 ± 19                           | 0.006               |
| Late loss        | 1.14 ± 0.64                            | 0.55 ± 0.61          | <0.0001                                     | 1.40 ± 0.65          | 0.60 ± 0.54                        | 0.002               |

n, number of patients; L, number of lesions.
Drug-eluting stents are associated with excessive inhibition of vascular cell proliferation which may lead to rare but serious complications such as late incomplete stent apposition, aneurysm formation, and late or very late stent thrombosis due to impaired re-endothelialization. A ‘pro-healing’ approach for prevention of in-stent restenosis is intuitively favoured over the use of cytotoxic or cytostatic drugs released from a DES. Circulating EPCs are able to differentiate into endothelial cells and contribute to postnatal neorevascularization. Moreover, EPCs have the ability to migrate to areas of vascular injury and initiate the arterial repair response, thereby improving tissue recovery and blood flow. Low baseline levels of circulating EPCs appear to correlate with angiographically documented CAD, in-stent restenosis, abnormal endothelial function, and prospectively predict an increase in cardiovascular mortality. Furthermore, studies have shown that patients with cardiovascular risk factors such as hyperlipidaemia, hypertension, diabetes mellitus, smoking, male gender, and advanced age have decreased quantity and quality of circulating EPCs. The main triggers of EPC mobilization are ischemia and vascular injury. HMG-CoA reductase inhibitors (statins) can mobilize and improve the function of EPCs in patient with stable CAD. Low levels of circulating EPCs in the peripheral blood were associated with worse angiographic outcome at 6 months compared with patients with normal EPC levels. Interestingly, patients who were on statin therapy had a two-fold higher level of circulating EPCs and showed a better clinical outcome up to 18 months of follow-up. Therefore, patients included in our study were required to be on statin therapy for at least 1 week prior to the index procedure. Importantly, the Genous technology is dependent on the number and functionality of the EPCs in the circulation, although we did not measure EPCs in our study.

The present study is a single-centre study and lacks the obvious advantages of a multicentre, international randomized study. Owing to small patient numbers, our study was not powered for robust clinical outcomes assessment. Moreover, no systematic angiographic follow-up was performed and therefore angiographic data have to be interpreted with caution. In addition, for the QCA results presented in the paper, we have assumed that all lesions were statistically independent. Since the vast majority of the patients had only one lesion, we considered this a reasonable assumption. However, the online supplement (see Supplementary material online, Table S6) contains results that have been adjusted for the clustering of lesions within patient. Although these results do not differ qualitatively from the results presented in the printed form of the paper, the adjusted analyses provide a better approximation of the between group variation so the adjusted estimates should be considered if these data are used for study planning purposes.

To increase patient recruitment and without awaiting the 1 year clinical results, the single-centre study was transformed into a multicentre, international study. In the two-armed TRIAS Program,
1260 patients with lesions carrying a high risk of restenosis will be randomized between a Genous stent and a DES (TRIAS HR trial). Similarly, 1300 patients with lesions carrying a low risk of restenosis will be randomized between a Genous stent and a BMS (TRIAS LR trial).

In conclusion, this first randomized, single-centre study showed no-significant heterogeneity rate of repeat revascularization in the Genous stent compared with the Taxus stent in patients treated for a coronary artery stenosis carrying a high risk of restenosis. In contrast, more stent thromboses occurred in the Taxus stent group. The balance between the occurrence of clinical restenosis vs. the risk of late and very late stent thrombosis and the impact on short and long-term patient outcome will be investigated in a larger setting.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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