Accelerating endothelialization of coronary stents by capturing circulating endothelial progenitor cells

Drug-eluting stents (DES) have become the standard of care for the treatment of coronary artery disease. However, late stent thrombosis has emerged as a major concern, especially in ‘off-label’ use. Pathologic studies of patients dying from late DES thrombosis demonstrate delayed arterial healing, characterized by persistent fibrin deposition and poor endothelialization. In recent years, a novel prohealing device was developed that captures circulating endothelial progenitor cells (EPCs) by immobilized antihuman-CD34 antibody as a surface coating. EPCs have the ability to migrate to areas of vascular injury and aid in the regeneration of damaged and dysfunctional endothelium. Preclinical results of the EPC-capture stent have shown promise in accelerating endothelialization as compared with bare metal and DES. Clinically, the safety and efficacy of the EPC-capture stent has been proven in numerous clinical trials with low incidence of late stent thrombosis. In this article, we discuss the relevance of the EPC-capture technology and the significance of current preclinical and clinical studies.

KEYWORDS: coronary stent • endothelial progenitor cell • endothelialization • late stent thrombosis

Over the past few decades, percutaneous interventions have emerged as the preferred treatment of choice for coronary artery disease. In the USA alone, more than one million percutaneous interventions are performed annually and more than 80% involve the use of coronary stents. Although coronary bare metal stent (BMS) had a dramatic impact on reducing restenosis rates, restenosis still occurred in up to 30% of cases [1,2]. The restenotic process consists predominantly of smooth muscle cells (SMCs) in a proteoglycan and type III collagenous matrix. The limitations of BMS led to the development of drug-eluting stents (DES), a more promising technique for the treatment of coronary artery disease.

First-generation DES (Cypher™, Cordis Corp., FL, USA and Taxus™, Boston Scientific, MA, USA) showed a significant reduction in restenosis rates as compared to BMS and became the standard of care for the treatment of coronary artery disease [3,4]. Antiproliferative drugs, cytostatic or cytotoxic, eluted from first-generation DES successfully inhibited SMC proliferation, resulting in suppression of neointimal growth. However, these drugs are not selective in their suppression of SMCs and also inhibit endothelial cell (EC) proliferation. Therefore, it is not surprising that late stent thrombosis (LST), a rare but life-threatening complication, has emerged as a major safety concern [5,6]. In addition to antiproliferative drugs, polymers used to coat DES, along with stent malaposition, may also play a role in LST [7]. The physiopathology of LST varies with the type of DES used and the underlying target lesion being treated. Nevertheless, there is a universal finding in all DES of delayed arterial healing, which is characterized by persistent fibrin deposition, sparse SMC coverage and incomplete re-endothelialization [7,8]. Our autopsy studies demonstrate that the most powerful predictor of stent thrombosis is endothelial coverage [9].

Because antiproliferative drugs deployed on DES do not specifically target SMCs, these drugs adversely impact endothelial proliferation, migration and function [10,11]. ECs, which line the arterial lumen, play a major role in the maintenance of vascular homeostasis including, the transportation of plasma molecules, regulation of vascular tone and synthesis of a large variety of antithrombotic factors. The adverse impact of antiproliferative drugs used on DES has been demonstrated by our group in preclinical models at 14 and 28 days to inhibit the regrowth of ECs and decrease the expression of platelet endothelial cell adhesion molecule (PECAM-1) and thrombomodulin. There was also an upregulation of mRNA and a decrease in VEGF production as compared to bare metal controls [11]. Similar findings have been confirmed in autopsy samples, in other...
words, the lack of endothelial coverage in DES even beyond 18 months in first-generation DES which led to the development of thinner stent struts in second-generation DES (Endevor™, Medtronic Vascular, CA, USA and Xience™ V, Abbott Vascular, CA, USA), with less or rapid drug release, and more biocompatible polymers that allow faster healing and accelerated endothelialization [12,13]. These changes have, in general, resulted in a reduction of LST, however the antiproliferative drugs are likely to remain in the diseased tissues especially in ‘off-label’ use for some time and are a concern for the continued potential of LST.

Another approach is to bypass antiproliferative drugs and instead accelerate the healing process (i.e., to restore the endothelium early after injury). During stenting, the endothelium is denuded and leads to focal fibrin and platelet aggregation, especially in the peri-strut regions where it is accompanied by inflammation, which is also dependent on the severity of injury [24]. Adherent platelets and leukocytes of nonendothelialized surfaces can release growth factors and cytokines, which initiate SMC proliferation and migration [15]. It has been demonstrated that proliferating SMCs accumulate in areas that are not fully re-endothelialized [16]. ECs produce a significant number of factors that regulate SMC differentiation and proliferation, like the cytokine TGF, angiotensin II and others similar to prostacyclin and nitric oxide that prevent platelet aggregation and SMC proliferation [17,18]. Therefore, ECs may themselves maintain the mitogenic quiescence of SMCs by growth-inhibitory factors [19].

**The Genous™ stent**

Besides the vessel wall cells, circulating progenitor cells have also been implicated to play a role in vascular healing following injury [20]. It has long been hypothesized that blood and ECs may share a common progenitor, known as the hemangioblast [21]. A single-cell-resolution fate map demonstrated that these cells in the early zebrafish experiments were capable of giving rise to both hematopoietic cells and ECs [22]. Asahara et al. first described endothelial progenitor cells (EPCs) and showed that circulating bone marrow-derived cells are capable of migrating to areas of vascular injury and aid in the regeneration of damaged and dysfunctional endothelium [20]. Therefore it is not surprising that biomedical engineers have thought of using circulating progenitor cells to accelerate the healing of the vessel wall.

The Genous™ stent, a bioengineered EPC-capturing stent (Genous Bioengineered R stent™; OrbusNeich Medical Technologies Inc., FL, USA) is a novel ‘prohealing’ stent design that aids in recruiting circulating EPCs. The R stent has unique dual helix designed specifically for flexibility, radial strength and natural conformability. The R stent is made from medical grade 316 stainless steel with a strut thickness of 0.0040 inches (102 µm). The R stent is coated using an immobilized antihuman-CD34 monoclonal antibody designed to capture circulating EPCs (Figure 1). The design of the Genous stent is therefore to accelerate endothelialization by early and continued recruitment of EPCs. The Genous stent was introduced in 2005 in the European market for use in patients eligible for stent placement with symptomatic ischemic heart disease due to de novo and/or restenotic coronary artery lesions.

Recently, a second generation of the Genous stent (Genous Bio-engineered Cobalt Chromium stent) was introduced to the market (CE mark in April 2010). The stent platform is made from the L605 cobalt–chromium alloy with strut thickness of 0.0032 inches (81 µm), a 20% reduction in strut thickness as compared with the original Genous stainless steel design, with greater stent flexibility and reduced stent profile. As in the previous design, the surface of the Genous Bio-engineered Cobalt Chromium stent is comprised of a polysaccharide matrix with CD34+ antibodies.

**Bench-top & preclinical assessment of the Genous stent**

The efficacy of immobilized CD34+ antibody-treated stainless steel surfaces was first tested by Kutryk et al. demonstrating rapid enhancement of bound ECs with the antibody substrate after 5 min with confluence being reached at 60 min [23]. The biological activity was evaluated using fluorescently labeled KG1a cells (immature hematopoietic cell line that express the CD34 antigen) and demonstrated uniform distribution of adherent CD34+ cells after incubation for 1 h. Recently, a similar in vitro assessment of the specificity of the immobilized CD34 antibody was tested using human peripheral CD34+ cells [24]. In the in vitro capture system, Genous and BMS were deployed in silicone tubing and were exposed to a cell mixture of PKH26 red fluorescent-labeled human monocytes (1 × 10^6 cells/ml) and PKH2 green fluorescent-labeled human CD34+ cells (2 × 10^5 cells/ml), under a constant rotation speed of 0.3 revolutions per min.
Confocal microscopy assessment of the stent struts showed that a significantly greater number of CD34+ cells adhere to the Genous stent as compared to the BMS (500 ± 158 vs 17 ± 8 cells/cm²; p < 0.001; Figure 2), whereas monocyte adherence was not significantly different between the two stents (79 ± 44 vs 58 ± 39 cells/cm²; p = 0.07), although a trend was observed for less monocytes on the Genous stent. Overall specificity of the Genous stent to capture CD34+ cells was significantly higher when compared with the BMS, with 86% of the attached cells being CD34+ compared with only 26% on the BMS.

Recent in vivo studies have also demonstrated enhanced endothelialization of the Genous stent, having an immobilized antihuman CD34 antibody coating. In the study by Larsen et al., acute (7 day) endothelialization rates were compared between the Genous stent and the BMS in a rabbit aorta and ilio-femoral injury model [24]. Scanning electron microscope (SEM) analysis revealed greater cell coverage between and above struts in the Genous stent versus the BMS (p < 0.01). Moreover, quantitative PCR showed increased levels of endothelial markers on the Genous stent for Tie-2 (p = 0.02) and P-selectin (p = 0.05) as compared with BMS, whereas for CD34 (p = 0.08) and CD31 (p = 0.07) levels there was a trend towards significance, thus indicating that the Genous stent promotes endothelialization.

van Beusekom et al. compared the performance of the Genous EPC capture stent to a BMS in a normal swine coronary stent model for early endothelialization (2 and 5 days) and neointimal thickness at 28 and 90 days [25]. Endothelialization by light microscopy and SEM confirmed higher rates of strut coverage in the EPC capture stent as compared with the BMS (2 days: 68 ± 29 vs 53 ± 36%; p = 0.028). At 5 days, both stent groups showed similar endothelialization rates (>95%). Longer durations (28 and 90 days) showed no differences between the groups in terms of neointimal thickness.

Genous stent performance has also been compared to sirolimus-eluting stents (SES) in a swine coronary model, with the results showing significantly greater endothelial coverage at 14 days by SEM analysis on the Genous
rate of endothelial coverage above the strut in the Genous + Genous group (95 ± 6%) and the Genous + SES group (79 ± 5%) compared with SES + SES group (36 ± 14%; p = 0.007) (Figure 3). The nonoverlapping proximal and distal segments from all three combinations showed higher endothelialization rates above the Genous segments (98 ± 3 and 100 ± 0% in Genous + Genous) as compared with the Genous + SES or SES + SES segments (62 ± 33% in Genous; 46 ± 20% in SES; p = 0.0003). Thus confirming that the Genous stent irrespective of whether it was overlapped with SES or not, always showed greater endothelialization versus SES.

**Genous clinical results**

- **First-in-man**

  The HEALING First-In-Man (HEALING-FIM) registry investigated the safety and feasibility of the Genous stent in a single-center, prospective, nonrandomized study [28]. A total of 16 stable or unstable angina or silent ischemia patients were enrolled. Patients received dual antiplatelet therapy (DAPT) for 1 month after stent deployment. At 6 months angiographic follow-up, Genous stent showed a 0.63 ± 0.52 mm late lumen loss and in-stent restenosis of 27.2 ± 20.9% as determined by intravascular ultrasound (IVUS). The 9 month composite major adverse cardiac event (MACE) rate (included cardiac death, stroke, myocardial infarction [MI] and target vessel revascularization) was 6.3% with no evidence of stent thrombosis.

- **Genous clinical trials in stable patients**

  Duckers et al. further evaluated the safety and efficacy of the Genous EPC capture stent in a multicenter, prospective nonrandomized registry study (HEALING II) [29]. Sixty three patients with single de novo native coronary artery lesions were enrolled. The composite MACE (death, MI, emergency coronary artery bypass graft and clinically driven target lesion revascularization [TLR]) rate was 6.3% at 9 months and 7.9% at 18 months, and the clinically driven TLR was 6.3% at both 9 and 18 months. Patients received DAPT for 1 month, similar to BMS, and showed no incidence of acute or subacute thrombosis. A significant late regression of neointimal hyperplasia was also observed between 6 and 18 months on quantitative coronary angiography (late lumen loss: 6 months = 0.78 ± 0.39 mm vs 18 months = 0.59 ± 0.31 mm; p = 0.001; 24.4% reduction) (Figure 4) and by IVUS (in-stent volume...
obstruction: 6 months = 22.94 ± 13.65% vs 18 months = 20.29 ± 14.34%; 11.4% reduction). The authors also correlated neointimal lumen loss to circulating levels of EPCs and showed that patients with normal EPC titers (>6.5/100 μl) at 6 months follow-up had low lumen loss (0.53 ± 0.06 mm, n = 25) as opposed to patients with low EPC titers (late lumen loss = 1.01 ± 0.07 mm, n = 24) [30]. In addition, statin therapy was associated with a 1.9-fold increase in EPC numbers (10.5 ± 1.12 vs 5.4 ± 0.94; p = 0.001) and improved angiographic outcome (late lumen loss: 0.50 ± 0.05 vs 0.65 ± 0.05 mm; p < 0.001).

The beneficial outcome of statin therapy in the HEALING II study lead to the design of the HEALING IIB study that aimed to assess the safety and efficacy of the Genous stent in conjunction with optimal statin therapy to stimulate EPC recruitment in 100 elective patients with de novo native coronary artery lesion [31]. Within 2 weeks after initiation of high-dose atorvastatin (80 mg once daily) pharmacotherapy, relative EPC levels increased by 5.6-fold and maintained elevated levels during a 30 day follow-up. Despite effective EPC recruitment, angiographic follow-up of late lumen loss data demonstrated no significant differences as compared to HEALING II at 6 months (0.76 ± 0.50 vs 0.78 ± 0.39 mm). Remarkably, comparable with the HEALING II study, angiographic late lumen loss was shown to be significantly reduced from 6 to 18 months (late lumen loss: 0.76 ± 0.50 vs 0.67 ± 0.54 mm; 11.8% reduction; p = 0.001).

The largest study completed to date to test the safety and efficacy of the Genous stent is the eHEALING registry, a worldwide, multicenter prospective study [32]. Approximately 5000 patients were included between October 2005 and 2007 from 144 centers in Europe, Asia/Pacific, Middle East, Africa and Latin America. The objective of the eHEALING registry was to assess the clinical outcome up to 12 months after placement of the Genous stent in a ‘real world’ population with a nonurgent percutaneous coronary intervention (PCI). Patients undergoing PCI with at least one lesion suitable for stenting with the Genous stent (diameter: 2.5–4.00 mm, length 9–33 mm) were enrolled. DAPT was administered to 83% of patients for 30 days, 59% at 6 months and 34% at 12 months. The cumulative event rate of cardiac death, MI and TLR, was 7.9% at 12 months. Target vessel failure (TVF) was 1.7, 5.7 and 8.4% at 30 days, 6 months and 12 months follow-up, respectively. Definite stent thrombosis was 0.6%, with the majority of cases having subacute (n = 17, 0.3%), followed by late (n = 8, 0.2%) and acute (6, 0.1%) stent thrombosis. In a post hoc analysis of the eHEALING study, patients who continued DAPT from 30 days through 6 months (n = 2654) were compared with patients on DAPT for only 30 days (n = 4249) and showed a similar incidence of cumulative event rate (6.5 vs 6.3%, p = 0.89). Definite or probable stent thrombosis increased, although not significantly between patients with continued DAPT as compared to those who stopped (0.2 vs 0.6%, p = 0.16) [33]. Several substudies focusing on elderly patients undergoing nonurgent PCI [34] and diabetic patients [35] have been published from the eHEALING registry. The data demonstrated that TVF occurred significantly more often in elderly patients compared with younger patients (age <65 years; 7.0% vs age 65–74 years; 11.7% vs age ≥75 years; 11.7%; p < 0.001).

Recently, a prospective randomized trial evaluating the Genous stent in combination with or without a paclitaxel-coated balloon was performed in 120 patients with de novo coronary artery lesion [36]. Angiographic follow-up at 6 months (follow-up rate 96%) demonstrated treatment with paclitaxel-coated balloon plus the

![Figure 3. Scanning electron microscopy images in the pig coronary model at 14 days following deployment of Genous stent and sirolimus-eluting stent in single and overlapping configuration.](image-url)
Genous stent was superior to Genous stent alone, with an in-stent late loss of 0.34 ± 0.45 versus 0.88 ± 0.48 mm (p < 0.001). The re-stenosis rate was reduced from 23.2 to 5.1% (p = 0.006) with no definite or probable stent thrombosis in either group.

Overall, in stable patients, the Genous stent has performed well with MACE rates no greater than 17.3% at 1 year with the exception of a single-center prospective study where MACE rates were 28.0% at 1 year for the treatment of older patients (≥75 years) with de novo lesions [37]. In this study, a total of eight deaths occurred, five of which were cardiac deaths. Additionally, two patients suffered from nonfatal acute MI and 22 patients had clinically justified TLR. Definite ST was also observed in an additional two patients.

Genous clinical trials in high-risk patients

A summary of the clinical results of the Genous stent in high-risk patients is provided in Table 1. High risk, in general, was defined as meeting two or more of the following criteria: diabetes, acute coronary syndrome, heart failure, proximal vessel disease, multivessel disease, B2/C type lesion, bifurcation lesion and long lesion. Miglionico et al. studied the outcome of 80 high-risk patients treated with Genous stent with 14 ± 4 months follow-up who received aspirin indefinitely, whereas clopidogrel was discontinued 2 months after angioplasty (patients with acute coronary syndromes were continued for 9 months) [38]. The incidence of MACE was 16%; ten patients underwent percutaneous TLR and three patients had reintervention of a nontarget vessel. There was no incidence of stent thrombosis. Similarly, the study by Low et al. showed no evidence of Academic Research Consortium defined stent thrombosis at a mean follow-up of 34 months with MACE rates at 16% in patients with ST elevation MI (STEMI) [39].

In the TRIAS trial, 193 patients with lesions carrying a high risk of restenosis were randomly treated with the Genous stent or the paclitaxel-eluting stent (PES) [40,41]. At 1 year, the rate of TVF was 17.3% in the Genous stent and 10.5% for the PES. No incidence of stent thrombosis was observed in the Genous stent, however in the PES, four patients (4.2%) on DAPT had a definite stent thrombosis. At 2 years, a non-significant difference in TLR between the Genous stent and PES was observed (20.4 vs 15.8%). Stent thrombosis was again absent in the Genous group at 2 years as compared to five lesions (in four patients) in the PES group. However, results of the TRIAS HR trial, an investigator-initiated, prospective, multicenter, single-blind, randomized clinical trial did not establish noninferiority when comparing the Genous endothelial capturing stent with DES in patients carrying lesions with a high risk of restenosis at 12 months (target lesion failure [TLF]: 17.4 vs 7.0%) [42].

Co et al. assessed the use of the Genous stent in primary percutaneous intervention in 120 patients with acute STEMI without cardiogenic shock [43]. DAPT was given for 1 month and statin therapy started immediately after the procedure. The cumulative MACE event rate was 4.2% at 30 days, 5.8% at 6 months and 9.2% at 1 year. Definite stent thrombosis rate at 1 year was 1.7%, one patient presented with an acute and another patient with subacute stent thrombosis, and no incidence of LST.

Chong et al. studied the intermediate-term efficacy and safety of the Genous with a sirolimus-eluting bioabsorbable polymer stent (CURA) and BMS in patients undergoing primary PCI for acute MI. The number of patients enrolled in the study was 366, treated with 95

Figure 4. Published late lumen loss values for all clinical Genous™ studies.
Table 1. Overview of Genous™ clinical studies.

<table>
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<th>Study name or first author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Indication</th>
<th>Mean FU (months)</th>
<th>Event type</th>
<th>Genous event rate (%)</th>
<th>Angiographic or IVUS FU (%)</th>
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AMI: Acute myocardial infarction; DES: Drug-eluting stent; FU: Follow-up; IVUS: Intravascular ultrasound; MACE: Major adverse cardiac event; PCI: Percutaneous coronary intervention; STEMI: ST elevation myocardial infarction; TVF: Target vessel failure.
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<td>Stable or unstable angina or a non-STEMI</td>
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<td>TVF ST</td>
<td>17.3</td>
<td>8 month FU – angiographic (54 and 39%)</td>
<td>[40]</td>
</tr>
<tr>
<td>Single-center prospective</td>
<td>Lee</td>
<td>2010</td>
<td>321</td>
<td>STEMI</td>
<td>12</td>
<td>MACE ST</td>
<td>12.2</td>
<td>No routine angiographic or IVUS FU</td>
<td>[46]</td>
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<tr>
<td>Single-center prospective</td>
<td>Beijk</td>
<td>2010</td>
<td>178</td>
<td>De novo bifurcation lesion</td>
<td>12</td>
<td>TVF ST</td>
<td>12.4</td>
<td>No routine angiographic or IVUS FU</td>
<td>[45]</td>
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<td>Single-center prospective</td>
<td>Scacciatella</td>
<td>2011</td>
<td>61</td>
<td>High risk and no option for DES</td>
<td>24</td>
<td>MACE ST</td>
<td>18.0</td>
<td>No routine angiographic or IVUS FU</td>
<td>[59]</td>
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<td>TRIAS</td>
<td>2011</td>
<td>98</td>
<td>Nonurgent de novo with a high risk of restenosis</td>
<td>24</td>
<td>TVF ST</td>
<td>20.4</td>
<td>No routine angiographic or IVUS FU</td>
<td>[41]</td>
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<tr>
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<td>2011</td>
<td>95</td>
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<td>34</td>
<td>MACE ST</td>
<td>16.0</td>
<td>8 month FU – angiographic (82%)</td>
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<td>304</td>
<td>Nonurgent de novo with a high risk of restenosis</td>
<td>12</td>
<td>TVF ST</td>
<td>17.4</td>
<td>No routine angiographic or IVUS FU</td>
<td>[42]</td>
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<td>2011</td>
<td>2651</td>
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<td>12</td>
<td>TVF ST</td>
<td>7.0</td>
<td>No routine angiographic or IVUS FU</td>
<td>[34]</td>
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<td>2011</td>
<td>1403</td>
<td>Patients between 65 and 74 years with a nonurgent PCI</td>
<td>12</td>
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<td>8.8</td>
<td>No routine angiographic or IVUS FU</td>
<td>[34]</td>
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<td>No routine angiographic or IVUS FU</td>
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<td>2949</td>
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<td>12</td>
<td>TVF ST</td>
<td>8.8</td>
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**Abbreviations:** AMI: Acute myocardial infarction; DES: Drug-eluting stent; FU: Follow-up; IVUS: Intravascular ultrasound; MACE: Major adverse cardiac event; PCI: Percutaneous coronary intervention; STEMI: ST elevation myocardial infarction; TVF: Target vessel failure.
Accelerating endothelialization of coronary stents

were treated with the Genous stent, 53 with CURA and 218 with BMS [44]. At 2 years, MACE rates for the Genous stent was 13.7% which were comparable with BMS (19.7%) and DES (15.1%) (p = 0.38). One patient in the Genous group had an acute stent thrombosis with no incidence of LST.

Beijk et al. evaluated 1-year clinical outcome in patients treated with the Genous stent for bifurcation lesions using provisional T-stenting techniques and compared these to historical control groups with an identical BMS [45]. A total of 178 consecutive patients with de novo bifurcation lesions treated with the Genous stent were compared with 465 consecutive patients treated with BMS. At 1 year, the cumulative rate of the primary end point was 12.4% in the Genous group as compared with 17% in the BMS group. The cumulative rate of definite ST was 0.6% in the Genous group as compared with 0.4% in the BMS group. These results showed favorable outcomes in the treatment of bifurcation lesions, however, the results were statistically nonsignificant.

In the largest high risk patient study, Lee et al. investigated the effectiveness of the Genous stent in treatment of patients with acute STEMI [46]. A total of 321 patients receiving 357 Genous stents with a cumulate MACE event rate of 8.1% at 30 days, 10.0% at 6 months and 12.2% at 1 year. One patient developed acute stent thrombosis and another two had subacute stent thrombosis with no incidence of LST. Similar MACE rates were also observed in other high-risk studies except in a single study where the authors report MACE rates of 24% at 6 months with highest incidence of stent thrombosis (6%) in the Genous stent as compared with none in the bare cobalt–chromium group [47].

In a more recent study, Klomp et al. assessed the 1 and 3 year clinical outcome in a large cohort of unselected patients treated with the Genous stent [45,48]. Four hundred and five unselected patients were treated with the EPC-capturing Genous stent, with the majority of patients having complex lesions and high risk of restenosis. At 1 year, TLF (the composite cardiac death, MI and TLR) was 13.3% with the occurrence of definite LST at 0.5%. At 3 years, TLF rates were at 18.3% with no further incidence of very LST. Patients with a high risk of restenosis also showed a higher incidence of TLF as compared with those with low risk (1 year: 16.4 vs 8.7%; p = 0.03). Overall, Genous stent outcomes of high-risk patients have been promising, in particular in patients unable to receive DAPT for long periods of time.

**Technological advancement of the Genous coronary stent**

The ability to capture circulating EPCs on the stent surface to accelerate healing could have an advantage over BMS or DES, especially in high-risk patient populations. EPCs have the capability to migrate, proliferate and differentiate into endothelial lineage cells [20]. In culture, EPCs have been shown to differentiate into mature ECs as assessed by molecular markers and function [49]. EPC-derived ECs have also been used to develop endothelialized blood vessels, a field that routinely seeks novel autologous cell sources to develop patient-specific tissue, as nonendothelialized blood vessels are prone to thrombosis [50]. Moreover, enhancement of EPCs has been shown indirectly to inhibit in-stent restenosis in preclinical models [51,52].

The immobilized antihuman CD34 coating of the Genous stent is unique, as it represents the only coronary stent on the market that promotes healing by sequestering circulating EPCs. The Genous bioengineered surface features antibodies immobilized on the stent surface, a significant bioengineering feat that provides a stable shelf-life technology that allows the capture of circulating EPCs. Although there are many surface antigens present in circulating EPCs (e.g., CD133, CD34, CD31, CD45, von Willebrand factor, CD146 and VEGFR2) that promote EPC mobilization, CD34 has been shown to be more specific for capturing EPCs [53]. However it is worth noting that not all captured CD34+ EPCs will either differentiate into mature ECs or accelerate endothelial adhesion, as the CD34+ marker used to phenotype EPCs is nonspecific, and it is also expressed by both hematopoietic stem cells and mature ECs [54]. Overall, the circulating peripheral blood contains <1% of circulating endothelial precursor cells that express CD34, VEGFR2 and AC133 [54]. A subpopulation of CD34+ hematopoietic stem cells, which has been shown to play a role in vascular maintenance and repair, are the CD34+/KDR+ cells [55]. These cells (CD34+/KDR+) are not directly mobilized from bone marrow but are generated from circulating multipotent CD34+ cells following interaction at platelet-rich sites of vascular injury and exposure to shear stress [55]. This mechanism is consistent with the EPC capture in a recently stented vessel implanted with the Genous stent. Ultimately though, the heterogeneity in cell capture will need to be better characterized, nevertheless,
the therapeutic concept of rapid endothelialization using autologous progenitor cells is exciting. Other attempts to modify the stent surface to promote greater cellular healing include increasing surface roughness [56] and binding of the Arg-Gly-Asp (RGD) peptide [57], however, these technologies need further validation.

Conclusion
DAPT certainly helps prevent thrombotic events following stenting, however, DES still remain at risk of LST. Autopsy studies of patients dying from LST have shown that stents with >30% uncovered struts are at nine-times greater risk of thrombosis. Given the increased concern of late thrombosis following DES implantation, EPC-based technologies and strategies that enhance endothelialization are of great interest in order to accelerate healing. The Genous stent was designed to capture circulating EPCs with the idea that DAPT following stenting can be shortened or eliminated as compared with DES in patients at high risk of thrombosis. Moreover, the recovery of endothelial function would prevent platelet and inflammatory cell adhesion to stented surfaces and decrease late loss. Preclinical studies have successfully demonstrated that Genous stents endothelialize at a faster rate as compared with BMS and DES. In clinical studies, the overall safety and efficacy of the Genous stent has been demonstrated in several nonrandomized studies and large registries. Angiographic follow-up studies have shown peak late lumen loss at 6–12 months in the range of 0.6 to 1.1 mm, with significant reduction at 18 months. Clinical results have also shown, in stable patients at 6–24 months, that MACE rates ranged from 6 to 20%. Furthermore, stent thrombosis rates were lower in comparison to DES. In STEMI patients, stent thrombosis rates have shown similar incidences of stent thrombosis in the Genous stent as compared with BMS, except in one randomized study. Further studies are warranted to demonstrate the efficacy of the Genous stent in randomized trials comparing the Genous and BMS as well as comparison to current DES in both stable and unstable patients with increased risk of stent thrombosis including acute MI, left main and vein grafts.

Future perspective
Although the Genous stent has displayed excellent results in terms of stent thrombosis, the late lumen loss has been inferior to current DES. Therefore, a next-generation Genous stent, the ‘Combo’ stent, has been developed in which the EPC-capturing technology (on the luminal surface) is combined with an antiproliferative drug (on the abluminal surface) to minimize the hyperproliferative reaction to the damaged vessel wall to suppress late loss. The efficacy and safety of the Combo stent has recently been investigated in a preclinical model demonstrating superior results in terms of endothelialization and equivalency of neointimal thickness as compared to first- and second-generation DES [26, 27].

Fully biodegradable coronary stents are currently being introduced to the market because

Executive summary

Background
- Delayed healing, characterized by incomplete endothelialization, is the primary substrate underlying drug-eluting stent (DES) thrombosis.
- Endothelial progenitor cells (EPCs) possess the ability to migrate to areas of vascular injury and differentiate into mature endothelial cells.
- Recruiting EPCs to injured arterial segments after stenting is an attractive approach to accelerate healing.

Genous™ bioengineered stent
- A novel ‘prohealing’ stent coated with immobilized antihuman CD34 monoclonal antibody was designed to capture circulating EPCs.
- The Genous is based on the R stent platform, a unique dual helix design made from 316 stainless steel. Recently, a second generation has been developed from cobalt–chromium with thinner struts (81 µm).
- Preclinical studies have shown accelerated endothelialization of the Genous stent as compared with bare metal stents and DES.
- A first-in-man study provided the safety and efficacy of the Genous stent with no evidence of stent thrombosis at 9 months.

Genous clinical performance
- In de novo stable lesions the Genous stent major adverse cardiac event rates range from 6 to 20% at 6–24 months with a low rate of stent thrombosis (<2%).
- In high-risk ST elevation myocardial infarctions, the major adverse cardiac event rates range from 12.2 to 28% at 12 months with stent thrombosis between 0 and 6%.
- Late lumen loss at 6–12 months are in the range of 0.6 to 1.1 mm, greater than DES, however, late loss has been shown to decrease significantly at 18 months.

Future perspective
- Prohealing approach in combination with antiproliferate drugs will help reduce late loss while maintaining low stent thrombosis.
- Fully biodegradable stents could potentially alleviate adverse events associated with permanent polymer metallic DES.
- Better characterization of the plaque prior to stenting may help lower late stent thrombosis.
they could potentially ease adverse events such as LST. As these stents degrade over time, the potential for LST due to nonendothelialized strut or remaining polymer is alleviated. Moreover, biodegradable stents can negate some of the other issues related to permanent metallic stents such as overhang at ostial lesions and the potential for long-term positive remodeling of the stented vessel (i.e., no long-term ‘jailing’ of the vessel).

Major changes for optimal treatment of coronary disease, however, may not come from new devices but rather from accurate assessment of the extent and type of disease by catheter-based imaging techniques. Second-generation IVUS and, more impressively, optical coherence tomography, can provide plaque morphology of tissue components, including identification of high-risk thin cap fibroatheroma. This will require clinical proof and the economic cost will have to be weighed before they can be utilized in routine clinical practice.

Financial & competing interests disclosure
R Virmani is a consultant for Medtronic AVE, Abbott Vascular, WL Gore, Biosensors International, Terumo, Atrium Medical, Arsenal Medical and Lutonix. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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** of considerable interest


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