

The relationship between the number of preprocedural circulating endothelial progenitor cells and angiographic restenosis following coronary artery stent placement

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ABSTRACT

Objective In animals, endothelial progenitor cells (EPCs) beneficially influence the repair of the coronary vessel wall after damage by stent placement. However, their role in humans is less well understood. In the present study, the authors aimed to evaluate the relationship between the number of preprocedural EPCs defined as CD34+/KDR+/CD133+ cells and angiographic late loss as a measure of the growth of in-stent intimal hyperplasia.

Design, setting, patients and interventions The 59 study patients were treated in the authors' clinic with a Genous EPC capturing stent, a bare metal stent (BMS) or a drug-eluting stent, and angiographic follow-up occurred between 6 and 13 months.

Results The authors found no relationship between preprocedural EPCs and angiographic late loss, irrespective of stent type. Though statistically not significant, patients with a high number of preprocedural CD34 cells and treated with a Genous stent or BMS showed a numerically higher late loss (in Genous patients: 1.03 ± 0.76 mm vs 0.71 ± 0.50 mm, $p=0.15$; in BMS patients: 1.06 ± 0.73 mm vs 0.35 ± 0.62 mm, $p=0.08$).

Conclusions Considering these and other varied observations, further studies aimed at identifying the biological mechanism and the individual roles of EPCs and/or CD34 cells in endothelial repair after coronary vessel stenting are needed.

INTRODUCTION

One of the major long-term disadvantages of percutaneous coronary intervention (PCI) remains in-stent restenosis and the need for repeat revascularisation.^{1,2} Therefore, knowledge of the pathophysiological mechanism of smooth-muscle cell proliferation and in-stent-intimal hyperplasia is of great importance. Balloon inflation and stent placement cause arterial wall injury, which in turn induces a cascade of events including migration of bone marrow-derived circulating endothelial progenitor cells (EPCs) towards the site of injury.³ Animal studies have shown that these EPCs beneficially influence the repair of the endothelial lining after injury and the progression of atherosclerosis by means of their regenerative capacities and role in vessel-wall homeostasis.⁴ However, their role in humans is less well understood, and importantly,

research is hampered by the lack of a universal definition of the 'true' EPC.^{5,6}

Recently, a stent coated with immobilised anti-CD34 antibodies to capture circulating EPCs, the bio-engineered Genous EPC capturing stent, has been shown to enhance coronary endothelialisation in animal models.^{7–9} Several clinical studies have demonstrated the safety and efficacy of the device in patients.^{10–14}

The EPC attracting technology may be dependent on the number of EPCs circulating in the bloodstream at the time of device implantation. In the present study, we aimed to evaluate the relationship between the number of preprocedural EPCs and angiographic late loss in patients treated with a Genous stent, a bare metal stent (BMS) or a drug-eluting stent (DES).

METHODS

Setting

This study is a substudy of the TRI-stent adjudication study (TRIAS) Program, for which the trial design has been published.¹⁵ In short, the TRIAS Program consists of two separate trials, TRIAS high risk (HR) and TRIAS low risk (LR), with patients with clinically stable coronary artery disease and a clinical indication for treatment with a coronary stent. In the TRIAS HR trial, patients with a high risk of restenosis were randomised in a 1:1 ratio between treatment with the Genous stent or a first-generation DES. In the TRIAS LR trial, patients with a low risk of restenosis were randomised in a 1:1 ratio between the treatment with the Genous stent or the BMS. The Genous stent (Genous Bio-engineered R stent, OrbusNeich Medical Technologies, Fort Lauderdale, Florida) is coated with antihuman CD34+ antibodies that specifically target the circulating EPC population to enhance neovascularisation and arterial repair response.

All interventions were performed according to standard PCI guidelines. At the start of the procedure, all patients received aspirin 300 mg if not already on aspirin, 5000 IU of unfractionated heparin and 600 mg of clopidogrel. The use of periprocedural glycoprotein IIb/IIIa receptor inhibitors was left to the discretion of the operator. After the PCI, patients were treated with aspirin 100 mg indefinitely, and clopidogrel 75 mg daily was prescribed for 1 month when a Genous stent or

BMS was implanted and for 12 months when a DES was implanted. All patients were clinically followed for 1 year. Repeat angiography was performed according to our hospitals' standard operating procedure, and the recorded images were suitable for off-line quantitative coronary analysis (QCA).

Design of the current analysis

The current analysis involved all TRIAS patients recruited at the Academic Medical Center-University of Amsterdam between May 2008 and January 2009 with available EPC analysis and repeat angiography. Prior to the PCI procedure, an arterial blood sample was taken for EPC analysis. CD34 cell analysis was a component of the EPC analysis. All patients who had not undergone a repeat angiography for clinical reasons between 6 and 13 months' follow-up were invited for a repeat coronary angiogram at 13 months. The study population consisted of all patients with a repeat angiography between 6 and 18 months and with an analysable EPC blood sample. The primary objective of the current analysis was to evaluate the relationship between the number of preprocedural EPCs and angiographic late loss. The secondary objective was to evaluate the relationship between the number of preprocedural CD34 cells and the angiographic late loss per stent type implanted. The median EPC and CD34+ values were used as a cut-off value to establish a patient population with a low number of EPCs and CD34 cells and a patient population with a high number of EPCs and CD34 cells respectively.

The study complied with the principles of the Declaration of Helsinki regarding investigation in humans and was approved by the local institutional review board. All patients gave written informed consent prior to randomisation, blood withdrawal and per protocol study repeat angiography.

Quantitative analysis by flow cytometry

Arterial blood samples were taken from the patients minutes prior to the PCI procedure and collected in an EDTA tube. Within 2 h after sampling, the CD34 cells and EPCs, defined as CD34+/KDR+/CD133+ cells, were quantified by flow cytometry.¹⁶ All measurements were performed in duplicate. For this assay, 400 µl of whole peripheral blood was stained in duplicate with conjugated monoclonal antibodies anti-CD34-PerCP-Cy5.5 (BD Biosciences, San Jose, California), anti-KDR-APC (R&D Systems, Minneapolis, Minnesota), anti-CD133-PE (Miltenyi Biotec, Bergisch Gladbach, Germany) and anti-CD45-FITC (BD Biosciences) for a duration of 20 min. After lysis of erythrocytes with haemolytic buffer (155 mM NH₄Cl, 10 mM KHCO₃, 0.1 mM EDTA, pH 7.2), the cells were washed once with haemolytic buffer and once with phosphate-buffered saline containing 2 mM EDTA and 0.5% BSA, and finally resuspended in phosphate-buffered saline containing 2 mM EDTA and 0.5% BSA. A quantitative fluorescence analysis was performed using a FACS-CANTO flow cytometer and analysed with FACS Diva software (BD Biosciences). Prior to this study, extensive research was carried out to warrant the reproducibility of these data. First, we determined the amount of blood necessary to accurately measure EPCs. We analysed different volumes (25–400 µl) of the same blood sample in duplicate which showed that we can accurately measure samples between 100 and 400 µl of blood. Blood samples were analysed multiple times to assess the precision of our assay, showing a variability maximum of 4 EPCs/sample.

Quantitative coronary analysis

For adequate endpoint assessment, follow-up angiographic views were recorded using the same planes as used at baseline procedure. All angiograms were performed under routine

protocol by experienced operators and were recorded in such a way that they were suitable for off-line quantitative coronary analysis (QCA). Standard off-line QCA was performed by the AMC core lab using the QCA-CMS 6.0 system of Medis Medical Imaging Systems (Leiden, The Netherlands).

In-stent late loss was defined as the difference in minimal lumen diameter (MLD) between postprocedure and follow-up within both edges of the stent in millimetres, estimated by off-line QCA. The Percent Diameter Stenosis (% DS) is calculated as $100 \times (1 - \text{MLD} / \text{reference vessel diameter (RVD)})$ using the mean values from two orthogonal views (when possible) by off-line QCA. The Angiographic Binary Restenosis rate is defined as the percentage of patients with a stenosis of 50% or more of the luminal diameter at follow-up.

Statistical analysis

Continuous variables are summarised by mean \pm SD. A χ^2 test was used to compare the differences between categorical variables with Gaussian distribution. Continuous variables were compared with the Student unpaired t test. The statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) software version 16. A p value of <0.05 was considered statistically significant. Our study was an exploratory analysis for which no formal power calculation was performed.

RESULTS

Baseline characteristics

A total of 59 patients with 75 lesions had complete angiographic follow-up available and were enrolled in the current analysis. To compare the patients with a low number of EPCs with patients with a high number of EPCs, the cut-off value of 31.3 EPCs/ml was chosen. Baseline clinical characteristics are summarised in table 1. The baseline features of both groups compared well, except that there was a slightly higher percentage of current smokers and patients with hyperlipidaemia in patients with a high number of EPCs (p=0.04 and 0.02 respectively). There were slightly (although not statistically significantly) more patients with diabetes in the group with low EPCs.

Procedural characteristics including target coronary artery, number of lesions per patient, number and type of stent per lesion and vessel diameter were similar between the two groups (table 2). A total of 19 (50%) Genous stents were implanted in patients with a low EPC number and 16 (43%) with a high EPC number, 14 (37%) and 11 (30%) DES, and five (13%) and 10 (27%) BMS, respectively (p=0.32).

EPC analysis and angiographic results

Table 3 depicts the angiographic outcome by EPC count. In patients with a low number of EPCs, eight of the 38 presented with binary in-stent restenosis at follow-up versus 11 of the 37 patients with a high number of EPCs (p=0.39). The RVD, MLD and %DS compared well for both groups at the three angiographic time points: before stenting, after stenting and at follow-up.

There was no statistically significant difference in late loss (0.62 ± 0.68 mm and 0.74 ± 0.81 mm; p=0.48) and %DS at follow-up ($31.19 \pm 22.24\%$ and $35.76 \pm 26.34\%$; p=0.42) between patients with a low number of EPCs and high number of EPCs.

Table 4 depicts the late loss and %DS by EPC count and CD34 cell count for each type of stent implanted. The cut-off value of 1335 CD34 cells/ml was chosen based on the median value. Again, no statistically significant relationship was found. Patients with a low and high number of EPCs had a similar late loss (in Genous-treated patients: 0.85 ± 0.58 mm and

Table 1 Baseline clinical characteristics for all 59 patients with complete angiographic follow-up stratified by number of endothelial progenitor cells at baseline

	Endothelial progenitor cells/ml		p Value
	≤31.3 N=29	>31.3 N=30	
Age (years)	64±10	62±12	0.49
Male	20 (69%)	22 (73%)	0.71
Body mass index (kg/m ²)	28.1±3.7	26.8±3.5	0.19
Diabetes	9 (31%)	6 (20%)	0.33
Requiring oral medication/diet	6 (21%)	5 (17%)	—
Requiring insulin	3 (10%)	1 (3%)	—
Hypertension	18 (62%)	13 (43%)	0.15
Hyperlipidaemia	15 (52%)	24 (80%)	0.02
Family history of coronary artery disease	12 (41%)	10 (33%)	0.52
Current smoker	4 (14%)	11 (37%)	0.04
Previous myocardial infarction	5 (17%)	4 (13%)	0.68
Previous percutaneous intervention	2 (7%)	3 (10%)	0.67
Previous coronary artery bypass grafting	0 (0%)	0 (0%)	—
Clinical indication for percutaneous coronary intervention			0.17
No complaints-angiographic indication	2 (7%)	0 (0%)	—
Stable angina	19 (66%)	25 (83%)	—
Unstable angina	8 (28%)	5 (17%)	—
Aspirin therapy	28 (97%)	30 (100%)	0.31
β-Blocker	22 (76%)	28 (93%)	0.06
Statin therapy	24 (83%)	27 (90%)	0.42
Extent of coronary artery disease			0.56
One vessel	25 (86%)	26 (87%)	—
Two vessels	3 (10%)	4 (13%)	—
Three vessels	1 (3%)	0 (0%)	—

Values are n (%) or mean±SD.

0.90±0.75 mm; $p=0.83$) and similar %DS (in Genous-treated patients: 36.19±21.35% and 35.24±26.50%; $p=0.91$). Furthermore, no statistically significant difference was found in late loss and %DS between patients with low number of CD34 cells and patients with a high number of CD34 cells, for all three stent

types. Late loss in Genous-treated patients with a low and high number of CD34 cells was 0.71±0.50 mm and 1.03±0.76 mm; $p=0.15$, and percentage diameter stenosis was 29.44±17.48% and 41.73±27.16%; $p=0.12$, respectively. Figure 1A,B illustrates the EPC and CD34 cell analysis per stent type implanted.

Table 2 Lesion characteristics for the 75 treated lesions in the 59 enrolled patients, stratified by number of endothelial progenitor cells at baseline

	Endothelial progenitor cells/ml		p Value
	≤31.3 38 lesions	>31.3 37 lesions	
Target coronary artery			0.25
Left anterior descending	19 (50%)	12 (32%)	—
Left circumflex	7 (18%)	7 (19%)	—
Right	12 (32%)	18 (49%)	—
ACC/AHA lesion classification			0.29
A	5 (13%)	1 (3%)	—
B1	8 (21%)	7 (19%)	—
B2	15 (39%)	14 (38%)	—
C	10 (26%)	15 (41%)	—
Occluded artery	6 (16%)	7 (19%)	0.72
Type of stent			0.32
Genous endothelial progenitor cell capturing stent	19 (50%)	16 (43%)	—
Genous-treated patients enrolled in TRI-stent adjudication study low risk	13 (34%)	8 (22%)	—
Genous-treated patients enrolled in TRI-stent adjudication study high risk	6 (16%)	8 (22%)	—
Drug-eluting stent	14 (37%)	11 (30%)	—
Bare metal stent	5 (13%)	10 (27%)	—
Lesion length (mm)	16.89±7.38	22.78±16.67	0.06
Stent length (mm)	22.42±10.60	27.62±18.75	0.15
Stent diameter (mm)	3.28±0.49	3.35±0.37	0.46
Stents per lesion	1.16±0.37	1.27±0.56	0.31
Absolute gain in-stent (mm)	1.91±0.63	2.00±0.61	0.57

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

Table 3 Angiographic outcome by level of endothelial progenitor cells at baseline

	Endothelial progenitor cells/ml*		p Value
	≤31.3 38 lesions	>31.3 37 lesions	
Reference vessel diameter (mm)			
Before stenting	2.80±0.49	2.94±0.44	0.17
After stenting	2.94±0.42	3.11±0.37	0.06
At follow-up	2.87±0.48	3.04±0.43	0.11
Minimal lumen diameter (mm)			
Before stenting	0.73±0.51	0.68±0.46	0.70
After stenting	2.62±0.44	2.71±0.38	0.32
At follow-up	2.00±0.73	1.96±0.86	0.83
Diameter stenosis (%)			
Before stenting	71.52±18.92	74.12±17.53	0.55
After stenting	11.06±8.19	13.16±5.63	0.20
At follow-up	31.19±22.24	35.76±26.34	0.42
In-stent late loss (mm)	0.62±0.68	0.74±0.81	0.48
Binary restenosis	8 (21%)	11 (30%)	0.39

Values are n (%) or mean±SD.

*Endothelial progenitor cells are defined as CD34+/KDR+/CD133+ cells.
L, number of lesions.

DISCUSSION

In the current analysis, we found no relationship between preprocedural EPCs, defined as CD34+/KDR+/CD133+ cells, and angiographic late loss, as a measure of the growth of in-stent intimal hyperplasia, in patients treated with a coronary stent for stable coronary artery disease. This absence of an effect of preprocedural EPCs on in-stent-restenosis occurred whether a Genous EPC attracting stent, a BMS or a DES was implanted.

A comparison of the results of the present study with those of previous trials is not straightforward, owing to differences in study design, variance of cell populations measured and method of measurement, timing of blood sampling in relation to stent implantation, duration of follow-up and type of stent used at baseline. A study by Duckers *et al* including 63 patients showed that Genous-stent-treated patients with normal EPC titres, defined as 7AAD-/CD45+/CD34+/KDR+ cells, had a lower luminal late loss (0.53±0.06 mm) at 6-month angiographic

follow-up compared with patients with low EPC titres (1.01±0.07 mm; $p<0.001$).¹² However, in this study, EPCs were measured at the time of the follow-up angiography. In another study by Briguori *et al* including 136 patients, it was shown that patients with high EPC levels (CD34+/KDR+ and CD34+/VE-cadherin+ cells) at baseline had significantly less stenosis progression in the non-treated vessels at 24 months than patients with low levels of EPCs ($p=0.003$).¹⁰ However, in contrast, the study by Pelliccia *et al* including 155 patients demonstrated that BMS-treated patients with evidence of in-stent restenosis at 8-month follow-up had a higher number of EPCs at baseline (CD34+/KDR+/CD45- cells) compared with patients without in-stent restenosis and controls.¹⁷

Conceptually, one expects that in patients with higher number of circulating EPCs at the time of stent implantation a functional endothelial layer may be formed more rapidly. It is hypothesised that by rapidly forming a layer covering the stent struts, the inflammation process is suppressed, subsequently preventing the occurrence of significant neo-intimal hyperplasia. In our current analysis, however, we could not establish a relationship between the number of circulating EPCs at the time of stent implantation and angiographic late loss at 6–13 months. We therefore hypothesise that the absolute number of circulating EPCs may not be influencing the repair of the endothelial layer after arterial wall injury in humans as was previously demonstrated in animal studies.^{18 19}

Interestingly, late loss in patients with a high CD34 cell count and treated with a Genous stent or BMS, although not statistically significantly different, was numerically higher than in patients with a low CD34 cell count. Our study is a small study, and these findings may be hypothesis-generating at best. Since CD34 cells are pluripotent bone-marrow-derived stem cells, it is conceivable that some mobilised bone-marrow progenitors may differentiate into vascular smooth muscle cells and therefore aggravate the formation of in-stent restenosis, thereby explaining our findings.²⁰

CONCLUSION

Our study did not show any relationship between circulating EPCs at the time of stent implantation and angiographic

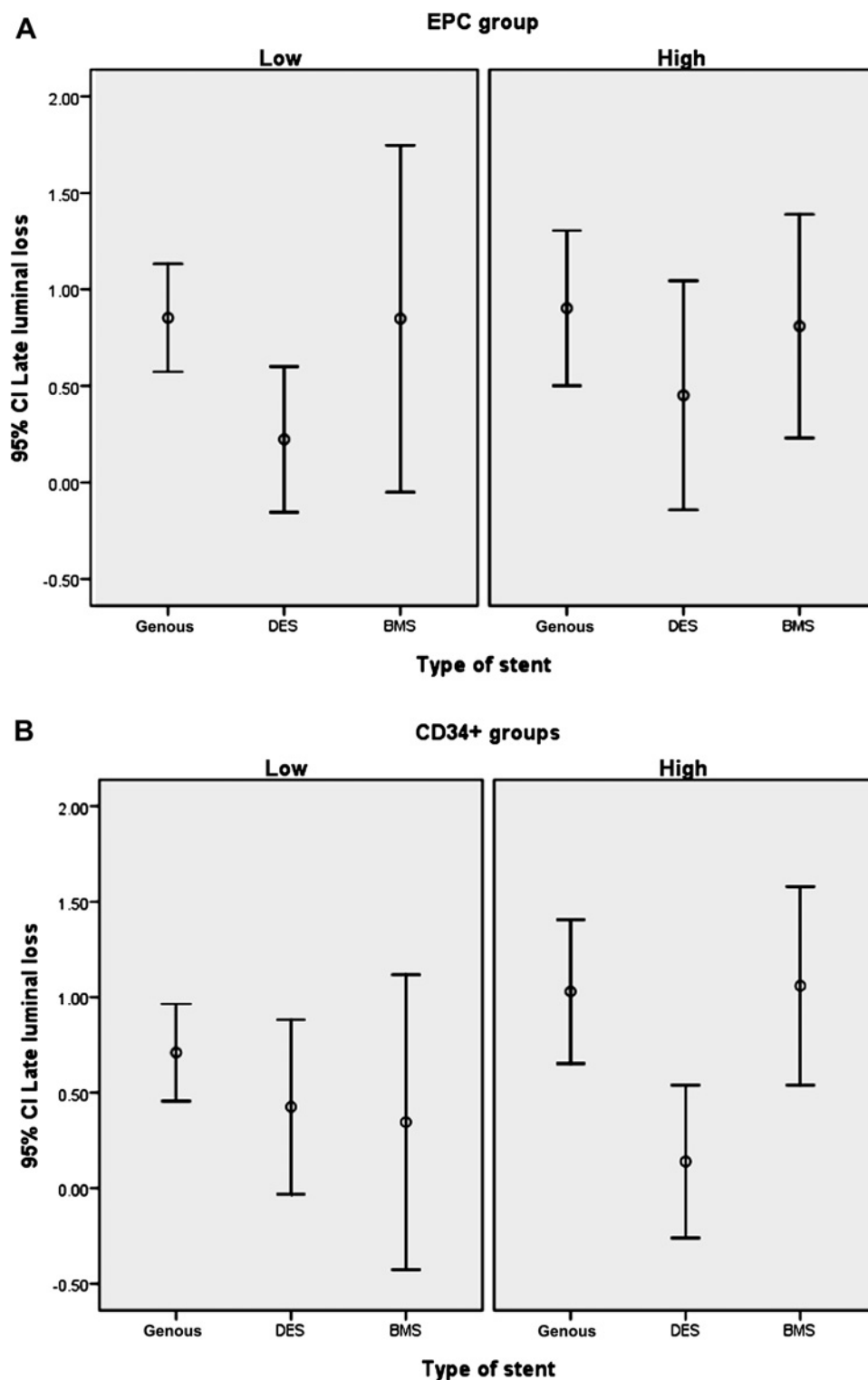
Table 4 Late loss and percentage diameter stenosis per stent type stratified by number of endothelial progenitor cells at baseline and by number of CD34 cells at baseline

	Endothelial progenitor cells/ml*		p Value	CD34 cells/ml		p Value
	≤31.3	>31.3		≤1335	>1335	
Genous endothelial progenitor cell capturing stent	(n=19)	(n=16)		(n=17)	(n=18)	
In-stent late loss (mm)	0.85±0.58	0.90±0.75	0.83	0.71±0.50	1.03±0.76	0.15
Diameter stenosis (%)	36.19±21.35	35.24±26.50	0.91	29.44±17.48	41.73±27.16	0.12
Bare metal stent (N=15)	(n=5)	(n=10)		(n=5)	(n=10)	
In-stent late loss (mm)	0.85±0.72	0.81±0.81	0.93	0.35±0.62	1.06±0.73	0.08
Diameter stenosis (%)	46.24±21.80	41.93±23.89	0.74	33.28±15.80	48.41±24.36	0.23
Drug-eluting stent (N=25)	(n=14)	(n=11)		(n=16)	(n=9)	
In-stent late loss (mm)	0.22±0.65	0.45±0.88	0.47	0.43±0.86	0.14±0.52	0.37
Diameter stenosis (%)	19.03±18.62	30.89±29.44	0.23	26.59±25.99	20.09±21.41	0.53
All lesions	(n=38)	(n=37)		(n=38)	(n=37)	
In-stent late loss (mm)	0.62±0.68	0.74±0.81	0.48	0.54±0.69	0.82±0.79	0.11
Diameter stenosis (%)	31.19±22.24	35.76±26.34	0.42	28.74±20.93	38.27±26.75	0.09

Values are n (%) or mean±SD.

*EPCs are CD34+/KDR+/CD133+ cells.

Figure 1 (A) Error bar graph showing the three levels of CD34+/KDR+/CD133+ cells (endothelial progenitor cells (EPCs)) and late luminal loss per stent type. (B) Error bar graph showing the three levels of CD34 cells and late luminal loss per stent type.



in-stent restenosis following coronary artery stent placement. This lack of an association was found, irrespective of stent type: Genous stent, BMS or DES. Although statistically not significant, patients with a high number of preprocedural CD34 cells and treated with a Genous stent or BMS showed a higher late loss. Considering ours and other varied observations, further studies aimed at identifying the biological mechanism and the individual roles of EPCs and/or CD34 cells in endothelial repair after coronary vessel stenting are therefore needed.

Limitations

The current analysis had several limitations. The number of patients with available preprocedural EPC sample and angiographic follow-up was relatively small. In addition, various definitions of EPCs have been used in the literature, thereby hampering the comparison between our current analysis and other studies. Moreover, angiographic follow-up data for patients with a clinical indication for a repeat angiogram were obtained between 6 and 13 months' follow-up, while all other patients were invited for a repeat coronary angiogram after

13 months. Finally, we and others have shown in-stent intimal hyperplasia tissue regression between 6 and 18 months after Genous stent implantation in contrast to DES, thus making the clinical implications of angiographic outcome at 6–13 months complex.

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Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the Medical Ethic Committee of the Academic Medical Center-University of Amsterdam.

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