Evaluation of a novel stent technology: the Genous EPC capturing stent
Klomp, M.

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6 | **Endothelial progenitor cells**

6.1 Understanding the role of endothelial progenitor cells in cardiovascular disease, coronary artery lesion progression, and in-stent restenosis

Robbert J de Winter and Margo Klomp

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Bone-marrow derived, circulating endothelial progenitor cells (EPCs) were first described by Asahara et al. in 1997.1 They discovered that EPCs have regenerative capacities and play an important role in vessel wall homeostasis. While animal studies have shown that these progenitor cells beneficially influence the repair of endothelial cells after injury and the progression of atherosclerosis,23 the role of EPCs in humans is less well understood.

In subjects with cardiovascular risk factors, such as hypertension and diabetes mellitus, studies have shown that the number of circulating EPCs is reduced, and their function adversely affected.45 In contrast, elevated EPC levels were seen in patients that suffered an acute myocardial infarction6 and patients that underwent a percutaneous coronary intervention (PCI).7 Unfortunately, studies reporting on the number of circulating EPCs in patients with coronary artery disease (CAD) fail to show agreement. Some studies report that the EPC number is reduced in patients with atherosclerotic disease,8,9 whereas other studies report that EPC levels are indeed increased in CAD patients.10,11 There is accumulating evidence that a reduced number of EPCs is associated with the occurrence of ischemic cardiovascular events in patients with angiographically documented coronary artery disease.12,13

Further assessment of circulating EPCs as surrogate biological markers might be helpful to identify novel therapeutic approaches to enhance endogenous vascular repair and favorably modify the progression of cardiovascular disease. The establishment of a healthy, functional endothelial layer may not only improve vascular homeostasis, but by abluminal secretion of anti-inflammatory and anti-proliferative factors may also reduce neointimal formation following stent placement. Currently, the novel bio-engineered Genous™ Endothelial Progenitor Cell Capturing Stent (OrbusNeich Medical Technologies Inc., FL, USA) coated with anti-human CD34+ antibodies attracting circulating EPCs is available in many countries for the treatment of patients with clinically significant CAD.14 Animal studies have shown that after only 60 minutes of incubation, a confluent monolayer of adherent CD34+ cells was formed covering the stent struts.15-17 In two small non-randomized studies (HEALING-FIM and HEALING II) the safety and efficacy of the EPC-capturing stent was demonstrated in patients with non-complex coronary artery lesions. The multicenter, randomized TRIAS program is ongoing, in which the EPC capturing stent is compared to drug-eluting stents and patients with either progression of coronary atherosclerosis (N=22), and patients with in-stent restenosis (N=30). The number of cells in each patient was prospectively measured the day before PCI and correlated with quantitative coronary angiographic assessments of in-stent restenosis and lesion progression on follow-up angiograms. No significant differences among the groups were found regarding the baseline clinical and angiographic characteristics although the overall and subdivided subject numbers were all small. Absolute numbers of EPCs, both CD34+/KDR+, CD34-/KDR+, CD133+/KDR+, and angiographic outcome at 8 months. A total of 155 consecutive patients with stable angina underwent PCI with a bare-metal stent, and 20 healthy controls without CAD were also studied. At 8-month follow-up, the patients were subdivided in 3 groups based on their angiographic characteristics: patients without progression of CAD and without in-stent restenosis (N=103), patients with progression of coronary atherosclerosis (N=22), and patients with in-stent restenosis (N=30). The number of cells in each population was prospectively measured the day before PCI and correlated with quantitative coronary angiographic assessments of in-stent restenosis and lesion progression on follow-up angiograms. No significant differences among the groups were found regarding the baseline clinical and angiographic characteristics although the overall and subdivided subject numbers were all small. Absolute numbers of EPCs, both CD34+/KDR+ and CD133+/KDR+, were higher in patients with in-stent restenosis compared to patients without in-stent restenosis and controls. In addition, the number of CD14+/CD45+ cells was higher in patients with restenosis compared to patients with lesion progression, patients in the stable CAD group and in the control group. In contrast to previous (cross-sectional) studies, there was no significant difference in levels of EPCs between those with CAD and normal controls. Pelliccia et al concluded that patients which develop restenosis after bare-metal stent placement have higher baseline numbers of subpopulations of EPCs that incorporate into endothelial cells or play a role in arteriogenesis compared with controls and patients with either progression of coronary atherosclerosis or stable disease. Specifically regarding the development of in-stent restenosis, the authors speculate that an abnormal engraftment of CD34+ and CD133+ EPCs causing excessive intima proliferation and in-stent restenosis may occur particularly among patients who have greater levels of EPCs at time of PCI. The results of Pelliccia et al. are in contrast to those from a prior report on patients treated with the EPC-attracting Genous Stent. In that study, Duckers et al.18 observed that decreased in-stent late lumen loss was associated with higher levels of circulating EPCs. These inter-study differences may be explained by distinctions in study designs or cell populations measured. In the study by Duckers et al. EPCs were assessed 6 months following PCI, no bare metal stents were used, and the cells identified as EPCs were 7AAD−/CD45+/CD34+/KDR+, so-called “viable” EPCs.

Considering these and other varied observations, one could conclude that despite meaningful investigations, the biology and clinical significance of EPCs in cardiovascular disease remain poorly understood. It is possible, for example, that the CD34+ population may be comprised...
of precursors of both endothelial and fibroblast phenotypes. It is also illustrative that there is not a uniform unit of measure when assessing the number of circulating EPCs. In different studies the number of EPCs has been expressed as number of cells per 1000 white blood cells, percentage per 100 peripheral mononuclear cells, FACS events per 10000 counts, number of cells per μL, or "viable" EPCs per 100 μL. Again comparing the studies by Pelliccia et al. and Duchers et al., even though both included similar patients with stable angina, there is a several hundred-fold difference in the number of EPCs reported. It is also not known if it is the CD34+/KDR+/CD45- cells, the CD133+/KDR+/CD45- cells, or other cells that are responsible for colony forming in the functional colony forming unit (Hill) assay.4

In summary, Pelliccia et al. conclude that patients with restenosis have higher numbers of subpopulations of EPCs compared with controls and with patients with either progression of coronary atherosclerosis or stable disease. These results are appreciated and hopefully will be followed by observations from other investigators. For the future several areas must be further pursued, including the characterization of bone-marrow derived circulating endothelial progenitor cells and subpopulations, the determination of factors that influence their number, function and biological significance both in healthy subjects and in patients with cardiovascular disease, and the standardization of measurements and units of measure in order to interpret results from different laboratories.

References


