Prohealing Endothelial Progenitor Cell Capture Stents
Do the Cells Captured Explain the Clinical Outcomes?

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Since the early days of percutaneous transluminal angioplasty, it has been recognized that balloon inflation disrupts the endothelial monolayer and injures normal arterial segments. This initiates a repair process that is mediated by platelets, inflammatory cells, and circulating progenitor cells that are recruited to sites of injury. There has been recent interest in the prohealing properties of endothelial progenitor cells (EPCs). Early studies identified these cells by expression of the surface antigen CD34 and demonstrated that they promoted reendothelialization after balloon injury. Because of the fact that these cells are relatively rare in the circulation (0.005%–0.01% of the total white blood cell count), it is not surprising that a stent was designed to capture circulating EPCs and sequester the cells to promote rapid reendothelialization, to decrease thrombogenicity, and to prevent restenosis. To accomplish this, the stent incorporated a monoclonal CD34 antibody in a proprietary polysaccharide intermediate coating that was adhered to a stainless steel stent; in 2010, the stent platform was changed to cobalt chromium.

The safety and efficacy of the EPC capture stent have been studied extensively in clinical registries and randomized trials. The Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth (HEALING) registries established a safety profile for the stent but demonstrated what would become a common theme; the stent did not decrease late lumen loss (LLL) to the same degree observed for drug-eluting stents (DES). This finding was attributed initially to variation in the number of circulating EPCs because of differences in the use of statins that were found to increase EPCs 1.9-fold and to lower LLL (1.1±0.07 versus 0.53±0.06 mm) in statin-treated compared with non–statin-treated patients. Therefore, the HEALING-IIB study mandated statin treatment before the index procedure; however, LLL at 6 and 18 months (0.76±0.50 and 0.67±0.54 mm, respectively) remained higher than that observed for DES and was associated with a clinically driven target lesion revascularization rate of 6.3% at 6 months and 9.4% at 12 and 24 months. Similarly, the e-HEALING registry, a postmarketing study of patients with complex lesions, reported a target lesion revascularization rate of 7.9% and a stent thrombosis rate of 1.1% at 12 months. The EPC capture stent was also compared with paclitaxel DES in the randomized TRI-stent Adjudication Study. At 12 months, the EPC capture stent was associated with greater in-stent LLL (1.14±0.06 versus 0.55±0.06 mm; P<0.0001) and a higher nonsignificant target vessel failure rate (17.3% versus 10.5%). This was similar to what was observed in the HEALING registries and higher than for newer generation DES. Another randomized trial of 1.300 patients comparing the EPC capture stent with DES was halted prematurely when an interim analysis found that 12-month target lesion failure rate were 17.4% for the EPC capture stent and only 7.0% for the DES.

These disappointing results led investigators to rethink about how to best use EPC stent technology. The stent was next trialed in conjunction with a drug-eluting balloon (DEB). This study of 120 patients with de novo lesions found a reduction in LLL in patients treated with the DEB+stent as compared with the stent alone (0.34±0.45 versus 0.88±0.48 mm; P<0.001) with a decrease in the restenosis rate from 23.2% to 5.1%, P=0.039 at 6 months. Although encouraging, adoption of this strategy requires comparison with a DES. Also, it should be noted that the observed LLL improves only slightly the LLL seen in the DEB+stent arm (0.41±0.51 mm) in Paclitaxel-Eluting PTCA Balloon in Coronary Artery Disease III that failed to demonstrate noninferiority when trialed against a sirolimus DES in de novo coronary lesions.

The original EPC capture stent was modified subsequently to elute drug from the abluminal side of the stent while retaining its luminal cell capture properties. This combination stent, with half the dose of drug of a standard DES, tested well in preclinical large animal studies. Compared with a sirolimus DES, the combination stent decreased neointimal thickness and improved reendothelialization. Results from the first-in-man Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coated bioengineered StEnt trial have also been reported. In low-risk patients, the combination stent was noninferior to a paclitaxel DES with a LLL at 9 months of 0.39±0.45 versus 0.44±0.56 mm. As expected, clinically driven event rates were low, and there were no stent thrombosis events in either group by 12 months. The investigators acknowledged several limitations of the study, including recognition that the LLL for the combination stent remained greater than what has been observed for first-generation sirolimus DES (0.24 mm, including diabetes mellitus).

Taken together, the studies indicate that the prohealing EPC capture stents do not outperform or perform, as well as contemporary DES. The obvious explanation is related to the complexities surrounding what markers define an EPC and how these cells modulate reendothelialization. The concept that CD34 identifies a cell as an EPC is based on the original...
seminal study that isolated and characterized these cells. Since that study, there has been significant controversy about what surface markers are required to call a cell an EPC as CD34 is also expressed by mesenchymal and other hematopoietic stem cells, mast cells, dendritic cells, and smooth muscle progenitor cells. Thus, EPC capture stents may be selecting other CD34+ cells, some of which may promote neointima formation. Although there is evidence that isolated CD34+ cells can be driven toward an endothelial lineage ex vivo, this requires special culture conditions and may not have relevance for the EPC capture stent. Also, it has been determined that 5% to 10% of CD34+ cells are actually mature circulating endothelial cells. Whether these cells seed injured vessels once captured is also unknown.

A related issue is how the EPCs direct reendothelialization. The original premise was that captured EPCs would incorporate into the vessel to form a new endothelial monolayer. Instead, it is now thought that the EPCs are recruited to sites of vascular injury where they occupy areas of denuded endothelium acting as placeholders and secreting factors that stimulate proliferation and migration of resident endothelium. Furthermore, our current understanding of the duration of EPC retention, viability, and functionality by the stent is limited. Also, it will be of interest to determine whether these parameters are altered by exposure to cytostatic or cytotoxic drugs eluted from stents, although by design this exposure should be minimal. Nonetheless, a small ex vivo study indicates that these drugs decrease EPC proliferation, migration, and decrease viability.

The current iteration of the EPC capture stent may still have clinical use if it continues to demonstrate noninferior or equivalent LLL when compared with contemporary limus-eluting DES or reduces the duration of dual-antiplatelet therapy. Future EPC capture stent designs should consider advances made in surface marker characterization of EPCs with the potential to multiplex several antibodies to the stent. Also, it is plausible to consider a cell therapy approach with isolation and ex vivo expansion of EPCs followed by EPC capture stent placement and infusion of an EPC-enriched cell fraction. Only through continued advances in our understanding of the biology of EPCs, preclinical studies using appropriate models that recapitulate human disease, and carefully planned clinical trials will be able to recognize the full potential of the EPC stent platform.

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References

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