
Capturing circulating endothelial progenitor cells: a new concept tested in the HEALING studies

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Stenting has become a standard procedure in percutaneous coronary interventions (PCI).¹ The Achilles' heel of stenting—the stent-related restenosis—has been almost (but not totally) resolved by many drug-eluting stents (DES). Today, DES are used in over 80% in the USA and in Switzerland with lower penetration rates in other countries. The new Achilles' heel of stenting with DES, however, seems to be late stent thrombosis:²⁻⁴ due to delayed healing, DES require longer addition of clopidogrel to acetylsalicylic acid drug. If clopidogrel is discontinued too early, stent thrombosis with its inherent high mortality, is a possible threat. Therefore, a new concept was developed, enhancing the speed of stent healing by capturing circulating endothelial progenitor cells from the blood stream onto a specially designed stent.⁵⁻⁷

The stent design

The Genous Bio-engineered R stent received CE mark on August 11, 2005 for use in a group of selected patients eligible for balloon angioplasty with symptomatic ischemic heart disease due to *de novo* and/or restenotic coronary artery lesions.⁸ The stent is comprised of 3 distinct components; the R stent™, the Evolution2 PTCA balloon catheter, and the

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endothelial progenitor cells (EPC) antibody surface on the stent. The R stent™ is made from medical grade 316L stainless steel, which has a well characterized biosafety profile as an implant material. The Evolution Delivery System is a low profile Rapid Exchange PTCA dilatation catheter. The R stent™ and the Evolution2 catheter have received CE mark approval and are currently commercially available in Europe as the R stent™ Evolution2.

The Genous Bio-engineered R stent consists of the 316L stainless steel coronary stent coated with a biocompatible matrix. Covalently attached to this matrix is a layer of murine, monoclonal, antihuman CD34 antibody. The antibody specifically targets CD34+ cells in circulation. The antibody is specific to surface antigens present on circulating EPC and when it is attached to the stent the antibody creates an immunoaffinity surface for preferentially capturing these circulating cells.

Clinical evaluations with the Genous Bio-engineered R stent

HEALING I

The HEALING-FIM study was a single center evaluation of an Orbus-designed proto-

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type EPC capture stent technology conducted at the ThoraxCenter at Erasmus University Medical Center, Rotterdam to demonstrate the safety and feasibility of the EPC capture stent technology.⁶ Sixteen patients with coronary artery disease were successfully treated with the implantation of anti-hCD34 antibody stents designed to capture circulating endothelial progenitor cells directly from the blood. Complete procedural and angiographic success was achieved in all 16 patients. The nine-month composite major adverse cardiac and cerebrovascular events (MACCE) rate was 6.3% as a result of a symptom-driven target vessel revascularization (TVR) in a single patient. There was no other MACCE despite only 1 month of clopidogrel. At six-month follow-up, the mean angiographic late luminal loss was 0.63±0.52 mm and percent stent volume obstruction was 27.2±20.9%. This first human clinical investigation of this technology demonstrates that the EPC capture coronary stent is safe and feasible for the treatment of *de novo* coronary artery disease.

HEALING II

The objective of multicenter HEALING II study is to demonstrate the safety and stent-related healing response to the Genous Bio-engineered R stent. The 10 centers participating in HEALING II include 4 centers in the Netherlands, and 3 centers each in Belgium and Germany. Patient enrollment was completed in October 2004 with 63 patients included. All of the patients were monitored clinically with follow-up examinations conducted at hospital discharge, 30 days and 6 months postimplantation, with quantitative angiographic and volumetric intravascular ultrasound assessment at 6 months postimplantation; additional patient clinical examinations are currently underway at 9 and 18 months and a repeat angiography at 18 months postprocedure.

The patient population consisted of 67% males with the average age of 61 years. In terms of medical history, 46% had hypertension, 13% had diabetes, 67% were hyperlipidemic, and 52% had a family history of car-

diovascular disease.⁹ In terms of the target lesion, 40% were left anterior descending arteries, and 57% were B2/C lesions. The average lesion length as measured by the core lab was 9.83 mm, average reference vessel diameter was 2.63 mm and the baseline minimal luminal diameter was 0.98 mm. Procedural and angiographic success was achieved in 62 of the 63 patients for a success rate of 98.4%. In 1 case there was a failure to cross the lesion where the stent delivery system was successfully retrieved. There was no subacute thrombosis despite the protocol recommendation for only one month of dual antiplatelet therapy. Two minor bleeding complications were reported, both events were development of a hematoma at the entry puncture site that manifest during the initial procedure and were resolved prior to patient release from the hospital; however, neither of these events were determined to be directly attributable to the study device.

An analysis of the 6 month data was presented at the 2005 TCT and revealed the following: the clinically driven target lesion revascularization (TLR) rate at 6 months was 6.3% with an overall MACE rate of 7.9%.

When HEALING II was set up, it was recognized that it would be critical to assess EPC levels in the HEALING II patients to mechanistically understand the functionality of the EPC capture device. The subsequent analysis of the relationship of EPC levels to clinical outcomes measured the quantity of EPCs circulating in the bloodstream and identified 2 patient subsets – those with low and normal levels of EPCs. A strong correlation was observed between EPC quantity and clinical responses. All restenotic and cardiac events were restricted to patients with low EPCs. For patients with normal EPC levels there were no TLR or MACE at 6 months follow-up. In addition, late loss for the normal EPC group was 0.48 mm and the resulting binary restenosis rate, defined as greater than 50% blockage, was 0%, indicating a healthy healed artery.

Furthermore, the vast majority of patients with normal EPC levels were on statin therapy while most in the low EPC group were not. HEALING II patients on statins exhibit

ed more than double the number of EPCs than those not on statins.

These findings are instrumental to the design of the upcoming HEALING III randomized study. HEALING III will assess the effect of statin therapy combined with EPC capture and bare metal stents. HEALING III will be initiated in early 2006.

In conclusion, EPC titer directly correlates with angiographic and IVUS outcome and identifies patients likely to respond to EPC capture stenting. The TLR/TVR events were restricted to the low EPC group and patients without statin therapy at the time of implant were generally restricted to the low EPC group.

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