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Year: 2012

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Corti, R

DOI: <https://doi.org/10.1093/eurheartj/ehr503>

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ZORA URL: <https://doi.org/10.5167/uzh-155146>

Journal Article

Published Version

Originally published at:

Corti, R (2012). A further step towards vascular reparative therapy. *European Heart Journal*, 33(11):1302-1304.

DOI: <https://doi.org/10.1093/eurheartj/ehr503>

A further step towards vascular reparative therapy

Roberto Corti*

Department of Cardiology, Universitätsspital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland

Online publish-ahead-of-print 2 May 2012

This editorial refers to ‘Endothelial-dependent vasomotion in a coronary segment treated by the ABSORB everolimus-eluting bioresorbable vascular scaffold system is related to plaque composition at the time of bioabsorption of the polymer: indirect finding of vascular reparative therapy?’[†], by S. Brugaletta *et al.*, on page 1325

Polymer-based drug-eluting stents (DES) have become the treatment of choice for most patients undergoing percutaneous coronary intervention (PCI). Although these stents efficiently reduce rates of restenosis and the need for vascular reintervention by 70% compared with bare metal stents (BMS), several risks closely related to the metallic cage and polymers have recently been reported. In addition, marked differences exist between various drug–polymer–device combinations that may translate into different biological responses. Different vascular healing responses to the stents could potentially explain differences in net clinical benefit. Poor endothelialization and coverage of the stent struts, fibrin deposition, and local inflammatory or hypersensitivity reactions at the site of DES implantation have been associated with increased risk of stent thrombosis.^{1,2} Recent studies indicated evidence for device-specific responses in the interference of DES with endothelial function.^{3–5}

The study of Brugaletta *et al.*⁶ brings new hope in cardiology, taking a new step towards vascular reparative therapy. This study suggests that in the near future we might be able to treat coronary lesions using absorbable drug-eluting scaffolds that will provide adequate radial strength to overcome the problem of vascular recoil and will fix local dissection occurring after lesion dilatation. In addition, they will inhibit smooth muscle cell proliferation and will finally allow complete recovery of coronary vasomotion. The latter will hold true not only in the vascular segment adjacent to the stent, such as at the proximal and distal segments after treatment with BMS,⁵ but also within the scaffolded segment. This will be the case after complete stent bioabsorption, providing optimal healing of the vessel wall.

The authors showed that at 1-year follow-up the vasoreactivity behaviour of the scaffolded segment did not differ substantially

from the physiological reaction observed distal to the stented segment. The ability of a coronary segment treated by the ABSORB bioresorbable vascular scaffold (BVS) device to react to vasoactive stimuli appears to correlate to the bioabsorption of the polymeric struts as detected by intravascular imaging technology. Taken together, these observations indicate that the stented segment might recover its healthy condition, allowing physiological vascular function.

These findings are very exciting and are in contrast with the current interventional therapy, leaving the patients with permanently caged vasculature by metallic prosthesis.⁷ In a sense, this therapy is reminiscent of the concept of plaque sealing by coronary angioplasty introduced several years ago by Bernhard Meier.⁸ This was based on the principles that a coronary stenosis subjected to balloon angioplasty will not progress to a total occlusion later on, unless it occludes abruptly during or immediately after the intervention. It was speculated that after disruption with the balloon, the healing mechanisms with intimal proliferation would provide a new, smooth, and elastic coat to the ruptured plaque. This new cap of intimal proliferation could potentially preclude plaque rupture and protect from coronary thrombosis. This principle could, however, not find a broad clinical application because of the risk of abrupt coronary occlusion induced by local coronary dissection after balloon angioplasty. In fact, the use of stents in PCI has rapidly been adopted in the interventional community, limiting the use of balloon angioplasty for selected lesions only. The introduction of bioabsorbable scaffolds could overcome most of the limitations of metallic stents.

This promising new technology is, however, still in an early phase of development. The vascular healing processes are expected to be very complex and difficult to investigate *in vivo*, therefore definitive demonstration of vascular reparative mechanisms using this device is expected to be a long process. New invasive imaging techniques such as optical frequency domain imaging allow precise analysis of strut coverage with microscopic resolution and have the potential to differentiate between fibrin- and neointimal-covered stent struts (*Figure 1*).⁹ In addition, there is compelling evidence that the healing process could be

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +41 44 255 1111, Fax: +41 44 255 4401, Email: roberto.corti@USZ.ch

[†] doi:10.1093/eurheartj/ehr466.

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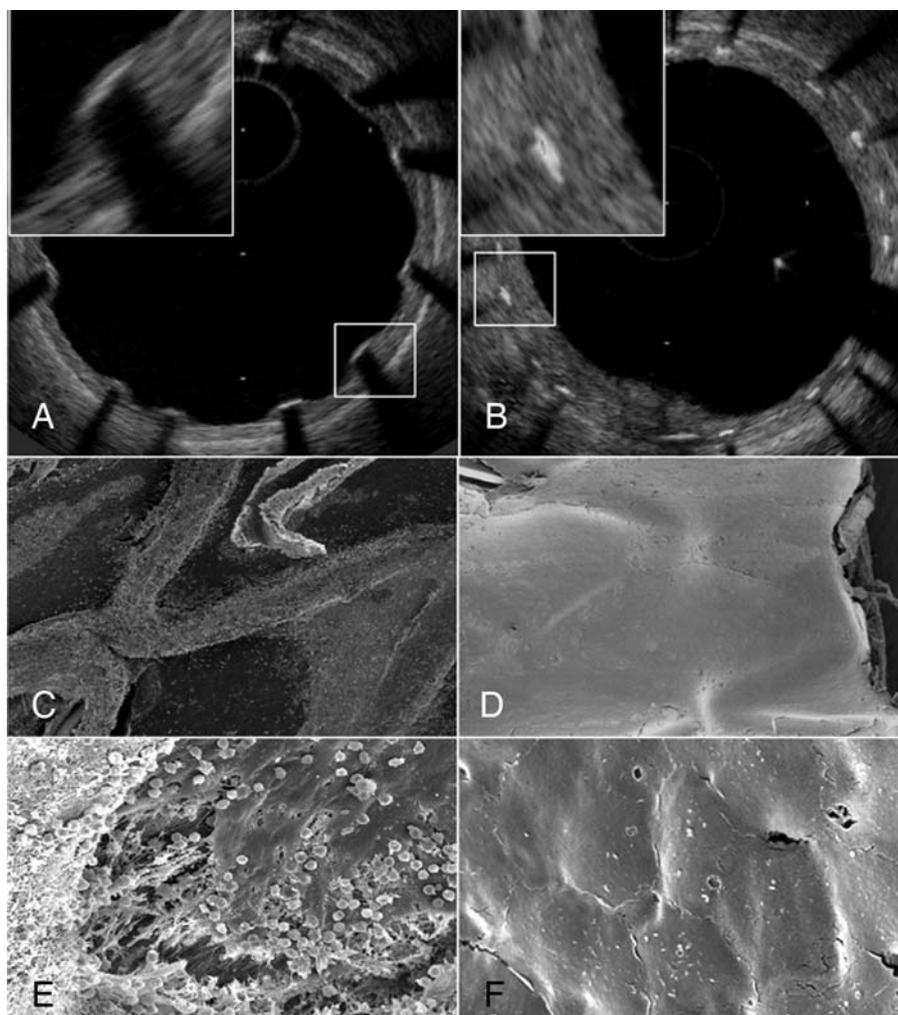


Figure 1 Optical frequency domain imaging allows precise analysis of strut coverage with a resolution of 10–20 μm . Selected examples of stent strut coverage in an experimental model at 3 days (A) and 4 weeks (B) after implantation. Electron microscopy revealed the presence of fibrin and strut-adherent blood cells at 1 week (C and E) and a complete layer of endothelial cells at 4 weeks (D and F). In humans, the coverage of metallic stent struts is often inhomogeneous, presenting covered and uncovered struts in the same stent. Original figure with permission of C. Templin.⁹

heterogeneous and vary from patient to patient; therefore, larger studies focused on different patient and lesion characteristics will be essential before introducing the new technology of BVS in the clinical arena.

Modern scaffolds have three main components: the metallic strut, the anti-proliferative drug, and the polymer in which the drug is immersed allowing for controlled release. Differences in each one of the main components could explain the clinical differences seen in randomized studies. The BVS device studied by Brugaletta *et al.*⁶ consists of two components: a polymer backbone of poly-L-lactide coated with a thin layer of poly-D,L lactide polymer containing the everolimus, a potent anti-proliferative drug. The polymer of the ABSORB BVS device is similar to the one used to cover the abluminal stent surface of the clinically available metallic DES Nobori (Terumo)¹⁰ and Biomatrix (Biosensors),¹¹ that showed superiority to first-generation DES using durable

polymers. Of particular interest was the relevant reduction in the risk of stent thrombosis. The vascular reaction to polymers could, however, differ among patients. Similarly, the way patients respond to drugs also varies, with some patients requiring a lower drug dose for equivalent benefit. Everolimus belongs to the limus family. Similar to sirolimus, zotarolimus, and biolimus, the biological effects of everolimus are mediated by the intracellular receptor FK506-binding protein 12. The FK506-binding protein 12–drug complex blocks progression from G₁ to S phase in the cell cycle, inhibiting smooth muscle cell progression and proliferation. Despite the similarity in the mechanism of action of these drugs, the presently clinically available stents eluting these drugs differ in their vascular effects.¹² The reported differences include coronary vasomotion distally to stented segments,³ neointima formation, and stent strut coverage. Such differences could potentially be explained by a different drug concentration or elution, as well as

by the different polymer used. Recent clinical data indicated that stents using absorbable polymer are more rapidly endothelialized¹³ than stents using a non-absorbable polymer, demonstrating superior clinical outcome in reducing the risk of stent thrombosis.¹⁴

The plumbing part of PCIs, consisting of re-establishing enough flow to prevent symptoms even at peak exercise, is important but should be only a secondary goal.¹⁵ The primary goal of interventional coronary treatment should become an improvement in the prognosis of the patients with coronary artery disease. This goal can only be achieved by a treatment that, after re-establishing normal flow conditions by lumen expansion, would allow complete recovery of the vascular function, which at least intuitively will only be possible by complete disappearance of the scaffold. Apart from removing the foreign material that may cause a thrombotic event, bioabsorbable stents have indisputable advantages of avoiding full metal jackets that can preclude coronary surgery and they do not interfere with non-invasive diagnostic tools.

Even though preliminary, the reported results seem to indicate hope for the vascular reparative therapy aimed for.

Conflict of interest: none declared.

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