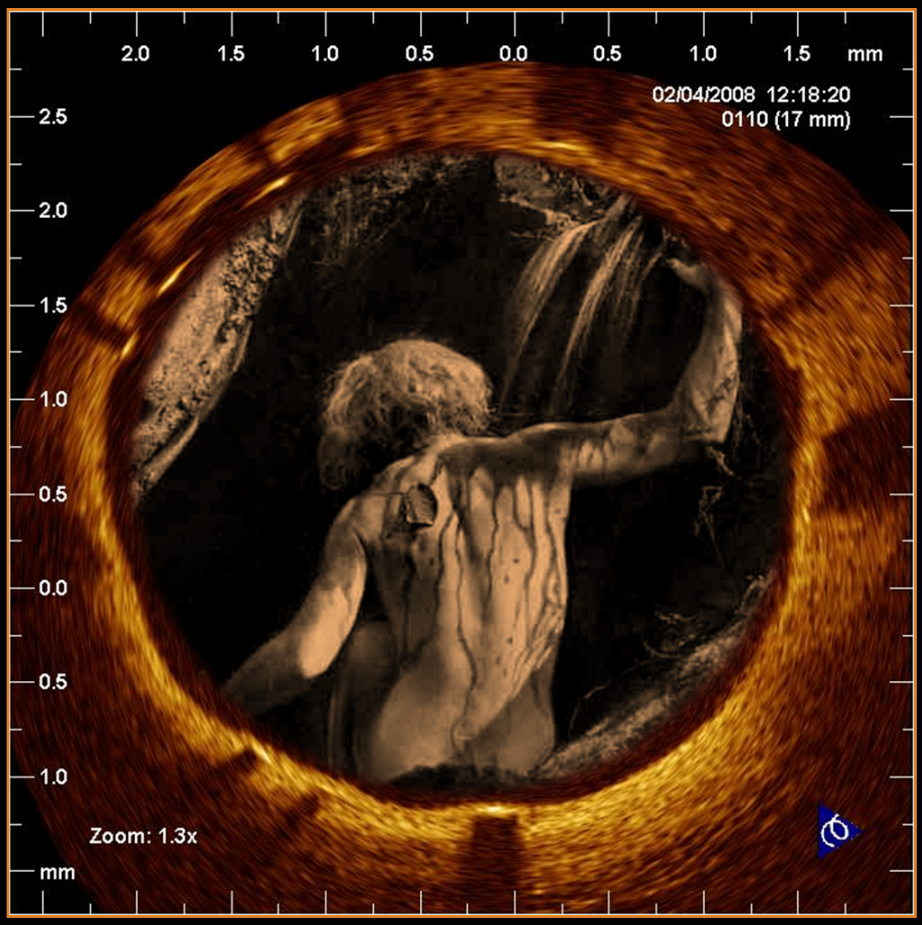
In vivo evaluation of neointimal healing after stenting with optical coherence tomography



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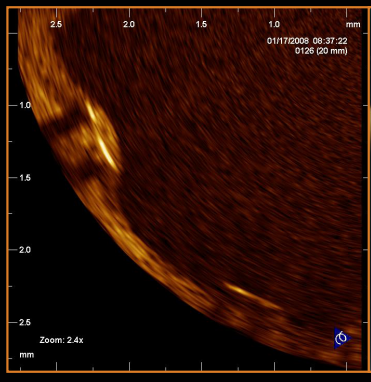

IN VIVO EVALUATION OF NEOINTIMAL HEALING AFTER STENTING WITH OPTICAL COHERENCE TOMOGRAPHY

Juan Luis Gutiérrez-Chico

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Front cover illustration: Composition about Siegfried's myth, by Juan Luis Gutiérrez-Chico. It contains images from the film *Siegfried*, from the series *Die Nibelungen* (directed by Fritz Lang); the picture *Das Blatt*, by the illustrator Klaus Busch; and optical coherence tomography images obtained in the Erasmus Medical Centre, Rotterdam.

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In vivo evaluation of neointimal healing after stenting with optical coherence tomography

In vivo beoordeling van neointimale heling na stentplaatsing met Optische Coherentie Tomografie

Proefschrift

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Doctoral committee

Promotor:	Prof. Dr. Patrick W Serruys
Co-promotor:	Dr. Evelyn Regar
Internal committee:	Ton van der Steen
	Eric Boersma
	Francesco Prati
Plenary committee:	Ulf Landmesser
	Michael Joner
	José Ramón González-Juanatey

To all those great persons who supported me patiently while I followed great names.
To all those who fill my heart with Music.

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"La experiencia es una llama que no alumbra sino quemando".

(Experience is a flame that does not illuminate but burning)

La Corte de Carlos IV

Benito Pérez Galdós

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Quoting Professor Patrick W Serruys, promoter of this thesis, the history of interventional cardiology has undergone four revolutions[1]. As in many other aspects of life, each revolution arose to solve a specific problem, but it often generated new problems itself, or left some aspects insufficiently solved, so the stimulus to keep on improving the results has been always present to date.

THE PROBLEM: CORONARY HEART DISEASE
The 1st revolution: balloon angioplasty

Ischemic heart disease is still today the first cause of mortality in the world, especially in the developed countries[2-4]. The vast majority of cases are due to atherosclerosis, a complex systemic degenerative process resulting in cholesterol accumulation in the extra-cellular space of the arterial intima, with inflammation, foam-cells formation, and necrosis[5-8]. The clinical manifestations of coronary atherosclerosis comprise from stable angina, due to flow-limiting stenosis of the artery, to acute myocardial infarction or sudden death, when the atheroma gets complicated by thrombotic phenomena[9].

The first revolution in the treatment of this disease came in 1977, when Andreas Grüntzig performed the first coronary balloon angioplasty[10-12]. The inflation of a balloon in a narrowed coronary vessel resulted in smash of the atheroma plaque and enlargement of the lumen, thus solving the flow limitation imposed by the stenosis. The success of this therapy was however mitigated by the risk of acute coronary occlusion due to extensive dissection requiring emergency bypass surgery[13-16] and also by high restenosis rates at follow-up (about 30-50% after 1 year)[15, 17-23]. The mechanism of restenosis had at least two differentiated components: constrictive remodelling of the vessel, defined as reduction in the area of the elastic external lamina (accounting for 73% of the lumen reduction) and neointimal hyperplasia (accounting for 27% of the lumen reduction)[24-26].

THE PROBLEM: RESTENOSIS DUE TO ARTERIAL REMODELLING
The 2nd revolution: coronary stenting

The advent of bare metal coronary stents solved the main drawbacks of balloon angioplasty: acute vessel occlusion and restenosis. This technology was able to tackle eventual dissections occurring during the balloon inflation and to prevent the subsequent arterial recoil, thus reducing the rates of acute and subacute coronary occlusion to 2.6%[27]. The radial strength of the metallic scaffold could counterbalance effectively that of elastic recoil and prevent constrictive remodelling at the external elastic lamina, acknowledged as the main mechanism of restenosis[24-26]. Two landmark randomised trials, BENESTENT and STRESS, published

simultaneously in the same issue of the same journal, compared the performance of coronary stenting vs. balloon angioplasty, demonstrating the safety and superior performance of bare metal stents in terms of higher angiographic and clinical success during the procedure, lower need for emergency coronary bypass surgery and lower restenosis rates at follow-up (22-32% at seven months)[28, 29]. These results represented a crucial leap forward for percutaneous coronary interventions, thus starting to become autonomous from surgery and to claim for their own niche in the therapeutic panoply against coronary heart disease. Stenting became the second revolution.

Nonetheless, the restenosis rates were still high (22-32% in the pivotal trials[28, 29]). The second mechanism of restenosis, neointimal hyperplasia, although it only contributed to 27% of the lumen reduction after balloon angioplasty[24-26], was still present and unaffected by stenting, leading to failure of the intervention in up to 20.0 – 50.3% of unselected cases[30, 31].

Moreover, this new technique left a foreign metallic body inside the coronary vessel permanently. It is known that the metallic surface of the stent in contact with the circulating blood exerts a pro-thrombotic effect through different mechanisms. The electromechanical conductance of the metal promotes the adsorption of plasma proteins, most of them negatively charged at human blood pH[32-38]. Most of the adsorbed proteins are fibrinogen and albumin[32, 35, 36, 39-42], but also fibronectin, vitronectin and von Willebrand factor[43]. The negative charge of the platelets membrane enhances in vitro their adhesion to the metallic surface and subsequent activation[33, 34, 44-46], but in vivo the platelets do not interact directly with the metallic surface, but rather with the adsorbed protein coat[32, 35, 36, 39-43, 47], more precisely with the fibrinogen through the GP IIb/IIIa receptor[35, 36, 48-51]. The ratio of fibrinogen / albumin adsorbed is directly proportional to the platelet adhesion and activation[32, 35, 42, 47], i.e. preferential adsorption of albumin results in passivation of the surface[35, 36]. The hydrophilicity of the surface material seems to favour higher fibrinogen / albumin ratios in the adsorption, and therefore higher platelet adhesion and activation[35]. As additional mechanisms, the coagulation factor XII adsorbs preferentially to negatively-charged metallic surfaces, resulting in activation of the intrinsic pathway of the coagulation cascade[52-56]. Finally, the metallic surface activates the complement system by the alternative pathway; the factor sC5b-9 induces activation of platelets and leukocytes and expression of p-selectin in the platelet membrane, contributing to create a prothrombotic milieu[57-59]. In summary, bare metal stents tended to get thrombosed in contact with the circulating blood, thus requiring specific anti-thrombotic treatment after implantation. Initially this therapy included aspirin, dipyridamole and warfarin[28, 29, 60, 61], but in the following years the combination of aspirin with a thienopyridine demonstrated to be more effective in the prevention of stent thrombosis and to have a better safety profile[62-66].

The second revolution in interventional cardiology, the bare metal stent (BMS), was tarnished by neointimal hyperplasia, resulting in restenosis in 20.0 – 50.3% of real-world cases[30, 31] and created a new problem, stent thrombosis, requiring specific attention.

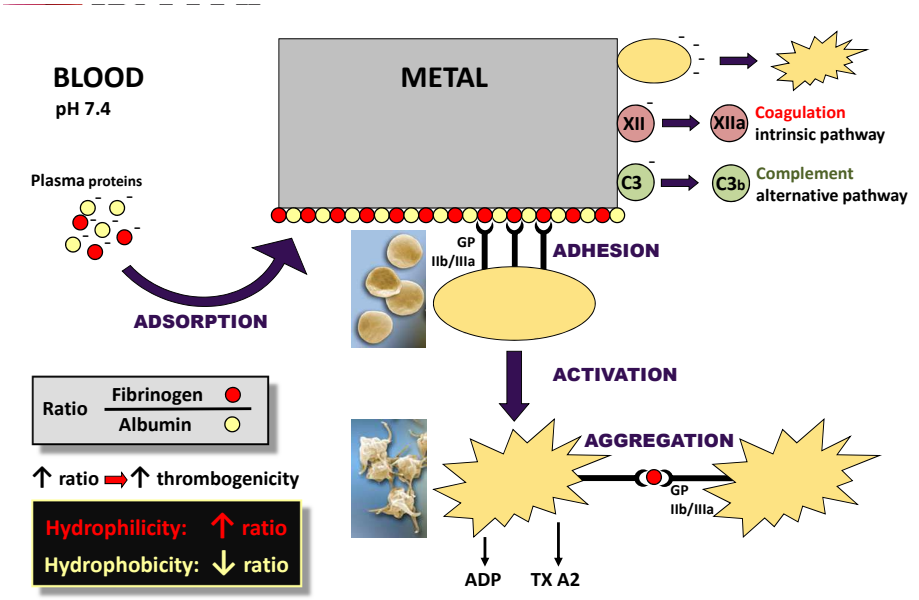

Figure 1:
Pathophysiology of thrombogenicity on metallic surfaces.

THE PROBLEM: RESTENOSIS DUE TO NEOINTIMAL HYPERPLASIA

The 3rd revolution: drug-eluting stents

The third revolution in interventional cardiology came with the concept of using metallic stents with enough radial force to prevent constrictive remodelling and also able to inhibit neointimal hyperplasia through the sustained elution of an antiproliferative agent. These break-through devices were named drug-eluting stents (DES) and exerted specific actions against the main mechanisms involved in restenosis[24-26]. Intravascular ultrasound (IVUS) studies proved the concept of an efficient suppression of neointimal proliferation achieved by the elution of sirolimus[67, 68]. In pioneer large scale trials, RAVEL, SIRIUS and TAXUS-IV, drug-eluting stents reduced the restenosis rates to 7.9 - 8.9 % at 9 months[69-71]. After these results interventional cardiology started to rival by-pass surgery as best therapeutic option for revascularization of coronary heart disease: a true revolution.

However the Congress of the European Society of Cardiology held in Barcelona in 2006 undermined this initial enthusiasm: the results of several registries and meta-analysis coincided to report higher rates of late and very late stent thrombosis in DES than in BMS[72-75]. Moreover, DES seemed to increase cardiac[73], non-cardiac[74] and overall mortality[75] with respect to BMS as well. The news had a tremendous impact on the cardiology community: the recommenda-

tions of dual anti-platelet therapy were extended up to 12 months and the interest for evidence about long-term safety of DES grew enormously. Registries of all-comers treated with DES showed stent thrombosis rates of 0.53% per year, with a continued increase to 3% over four years[76, 77]. In patients with complex multivessel disease (ARTS II), the rate of combined definite, probable and possible stent thrombosis was as high as 9.4% at five years, accounting for 32% of MACE events[78].

Pathology and imaging studies played an instrumental role in elucidating the mechanism of late and very late stent thrombosis. Since the BMS era, pathology had described the presence of uncovered struts in fatal cases of stent thrombosis[79, 80]. As for late stent thrombosis (>30 days, ≤365 days after stent implantation), several angioscopy studies reported signs of delayed healing in DES, with still considerable amounts of uncovered struts after the 6th month, when dual anti-platelet therapy was normally interrupted[81-84]. As for very late stent thrombosis (>365 days after stent implantation), pathology described also delayed neointimal healing and incomplete endothelialization in experimental studies or autopsies of fatal cases[85-88], but the mechanism for this incomplete neointimal coverage seemed to go beyond the failure to restore the endothelial continuity because of the antiproliferative potency of the drug and to involve also an inflammatory reaction[88-92]. The implantation of these devices elicited an inflammatory reaction in the vessel wall[91, 93], presumably due to the polymeric coating[93] and inducing some positive (expansive) remodelling[91]. Hydrophobic polymeric coatings induced an inflammatory reaction more intense than hydrophilic polymers[94, 95]. Moreover, the presence of intense eosinophilic infiltrates in the vessel wall[88] and in the thrombus harvested from patients with an episode of very late stent thrombosis[90] suggested an additional inflammatory mechanism, mediated by a delayed type IVb hypersensitivity reaction, recruiting preferentially eosinophils. This hypersensitivity reaction was supposed to be triggered by the polymer rather than by other components of the device, given the timing of onset (later than 90 days, when the drug is no longer detectable in the vessel wall) and the presence of polymer fragments surrounded by giant cells[88, 91].

Intense investigational efforts were then undertaken to improve the haemocompatibility (reduced thrombogenicity) and biocompatibility (reduced inflammation) of the DES, preserving their efficacy in preventing restenosis. Several approaches were then tested, with variable outcomes: thinner struts[67, 68, 96]; hydrophobic fluoropolymers with improved haemocompatibility profiles[97-101] and eventually inducing fluoropassivation[102-104]; hydrophilic polymers with improved biocompatibility profile[105-111]; polymer-free corrugated abluminal surfaces[112-118]; non-polymeric mineral carriers (hydroxyapatite)[119-121]; elution from reservoirs[122-130]; non-stent-based local delivery systems, comprising intrapericardial administration[131], double-balloon catheter[132], porous balloon[133] and drug-coated balloons (DCB)[134-146]; biodegradable polymers in solely abluminal coating, engineered to provide sustained kinetics of release for the antiproliferative drug, coupled with the hydrolysis and degradation of the polymer up to its complete resorption and disappearance[115, 147-166]; or endothelial-progenitor-cells-capturing stents[167-170].

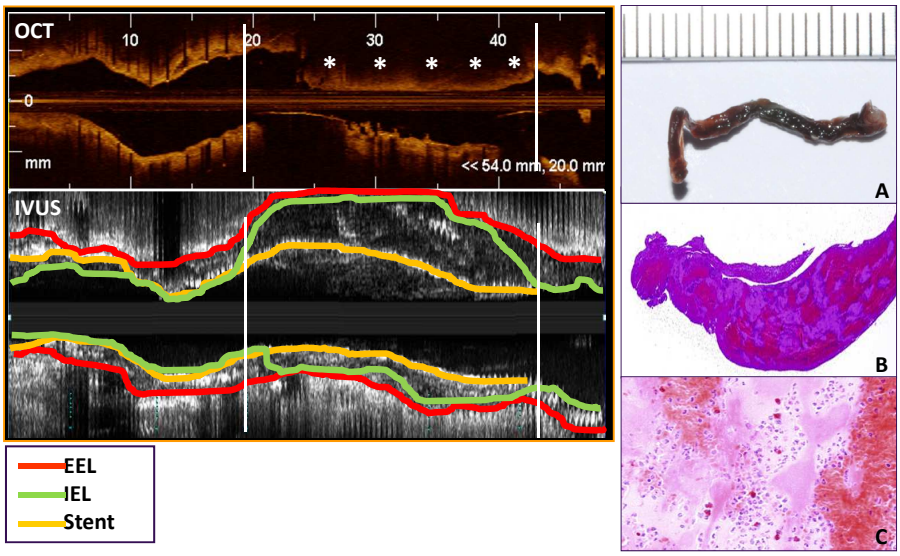

Figure 2:
Case of definite very late stent thrombosis associated to late-acquired malapposition, illustrated by matched OCT and IVUS studies (left panels). Intraluminal thrombus (asterisks) can be clearly seen in the OCT longitudinal view (left upper panel), within the region of interest delimited by two vertical white bars. The matched IVUS longitudinal view (left lower panel) shows positive remodelling of the external elastic lamina together with enlargement of the internal elastic lamina and massive malapposition of the stent. The thrombus harvested from the coronary artery (right panel A) presented intense eosinophilic infiltration in the histological analysis (right panel, B and C). These findings suggest a delayed hypersensitivity mechanism with intense inflammatory reaction, resulting in weakening of the vessel wall, late-acquired malapposition and stent thrombosis.
Images courtesy of Dr. Lorenz Räber, Inselspital, Bern, CH.

THE PROBLEM: STENT THROMBOSIS

Looking for a solution: Evaluation of the neointimal healing after stenting

This PhD thesis took shape in this context of deep concern about DES thrombosis in parallel with an unprecedented momentum of technological innovation intended to promote optimal neointimal healing after DES implantation. Aristotle defined virtue as an intermediate state between the opposed vices of excess and deficiency[171]. Thus "optimal" neointimal healing could be defined in Aristotelian terms as an intermediate degree of neointimal proliferation between the vice for excess (neointimal hyperplasia, resulting in stent restenosis) and the vice for deficiency (incomplete neointimal coverage, augmenting the risk of stent thrombosis). Furthermore, this intermediate degree could be delimited more precisely as the minimal neointimal proliferation that warrants coverage of the whole metallic surface of the stent without flow-compromising re-narrowing of the vessel. The scope of this thesis is the qualitative and quantitative evaluation in vivo of the neointimal healing process after

stenting, which determines the clinical outcome of the intervention at a great extent. The neointimal healing response can be evaluated in vivo by invasive imaging techniques: coronary angiography, IVUS, angioscopy and optical coherence tomography.

Coronary angiography – quantitative coronary angiography (QCA)

Coronary angiography is still today the workhorse invasive imaging technique for diagnostic and interventional procedures. The simple injection of a radiopaque contrast medium into the coronary arteries provides clear real-time luminograms, that translate into accurate and highly reproducible measurements for clinical decision-making and for research applications[172, 173]. In the BMS era restenosis (the vice for excess in the neointimal reaction) could be efficiently assessed by quantitative coronary angiography (QCA) through percent diameter stenosis (% DS), a parameter derived from the minimal lumen diameter (MLD) in the segment of interest with respect to the interpolated reference vessel diameter at that point. Thus, restenosis was defined on a binary basis as a % DS equal to or greater than an arbitrary threshold of 50%[21, 61, 174-176]. Although angiographic restenosis had poor clinical predictive value for the need of revascularization on individual subjects[177], the restenosis rates in clinical trials were well correlated with the rates of revascularization, thus fitting the principle of angiographic surrogate endpoints[178-180]. With the advent of DES, however, the restenosis rates were reduced below 10%[69-71], so the sample sizes and the costs required to find relevant differences in comparative trials using binary restenosis as primary endpoint increased considerably. Late lumen loss (LLL) became then the parameter of choice to evaluate neointimal hyperplasia and the trend to restenosis. Contrary to binary restenosis, LLL is a continuous variable, very sensitive to subtle differences between devices, well correlated with the propensity to binary restenosis, following a curvilinear and monotonic relation, independent from the type of stent type and from the reference vessel diameter, that permits to increase the power and to reduce the sample sizes required to find significant differences in clinical trials[180-183]. Thus, although QCA can evaluate restenosis efficiently, it loses accuracy in presence of overlapping vessels, foreshortening or calcium in the vessel wall. It gives scarce and often unreliable information about the mechanical settlement of the stent (sizing, expansion, apposition) and no information at all about the completeness or incompleteness of neointimal coverage (the vice for defect). Furthermore, the methodology developed to quantify restenosis by QCA relies solely on the point of MLD, disregarding the regional distribution of the lumen re-narrowing.

Intravascular ultrasound (IVUS)

IVUS can improve the accuracy of the coronary luminogram in cases of overlapping, foreshortened or calcified vessels, because it is not affected by these limitations. IVUS provides also detailed information about the mechanical aspects of the stent and can accurately quantify neointimal hyperplasia along the whole stented segment at conventional longitudinal

intervals of 1mm, reporting minimal and also mean diameters, areas and volumes. Unlike QCA, IVUS can image also the vessel wall extracting information about the plaque burden, plaque morphology or calcium distribution. Like QCA, IVUS can reliably discern whether the neointimal response is exaggerated or not. Indeed trials comparing DES vs. BMS used IVUS to confirm that DES reduced the extent of neointimal proliferation[184-188]. However, its axial resolution (100 μm) still results insufficient to assess the completeness of coverage, because the thin neointimal layer covering DES struts is often below this resolution.

Coronary angioscopy

After several investigators reported higher rates of late / very late stent thrombosis and higher late mortality rates in DES than in BMS in the Congress of the European Society of Cardiology in Barcelona in 2006[72-75], the interest to study the neointimal reaction after stenting shifted from the quantification of restenosis to the opposite pole of the spectrum: the evaluation of the completeness of neointimal healing. At that point, the only imaging technique able to detect uncovered struts and ready for immediate in vivo clinical application was coronary angioscopy. The availability of the technique was limited to a few frontline centers in Japan and Asia. The performance of the study was cumbersome for the patient and for the operator, since it required occlusion of the coronary vessel and removal of the blood in order to obtain good quality images. Finally, unlike the accurate objective quantification provided by QCA or IVUS, angioscopy had limited quantitative abilities, relying on a rather qualitative and subjective evaluation of the images obtained often from a manual and irregular pullback. In spite of all these drawbacks, angioscopy was the first technique to evaluate systematically in vivo the completeness of coverage, making an instrumental contribution to our current understanding of the mechanisms underlying the phenomenon of late DES thrombosis[81-84]. A semi-quantitative approach was used to grade the neointimal coverage, based on a classification with 4 ordered categories[82, 84]:

- *Grade 0* - stent struts exposed.
- *Grade 1* - struts covered but bulging into the lumen.
- *G*rade 2 - struts embedded but visible translucently.
- *Grade 3* - struts fully embedded and invisible.

Minimum, maximum and predominant grades of coverage observed within the stented segment were normally reported.

It must be noticed that this semi-quantitative grading used in angioscopy follows the "*winter coat principle: everything covered, and the thicker the better*". Thick neointimal responses obtain higher scores, no matter if they are functionally maladaptive or the consequence of inefficient neointimal suppression. Likewise, once the neointimal healing proliferation has been completed, subsequent processes of intima maturation resulting in thickening of the layer will translate into an increase in the angioscopy grades, especially the maximum[82, 189].

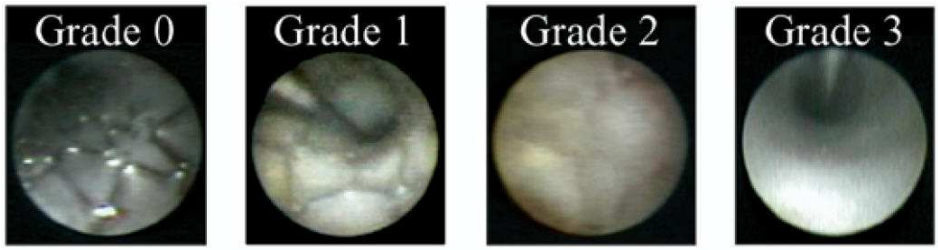

Figure 3:
Grading of the neointimal coverage assessed by coronary angioscopy.
Modified from Awata et al. J Am Coll Cardiol 2008; 52(9): 787–92.

Optical coherence tomography

The interest to assess the completeness of coverage boosted the development of Optical Coherence Tomography (OCT) for coronary applications. OCT uses near-infrared light (NIR) to generate cross-sectional images of the coronary arteries. NIR has shorter wavelength and higher frequency than ultrasound, therefore OCT images have 10-fold higher resolution than IVUS images, at the expense of lower penetration into the tissue[190, 191]. OCT provides an axial resolution of 10-15 μm, thus enabling accurate evaluation of the tissue coverage after stenting. OCT-derived tissue coverage correlates well with histological neointimal healing and endothelialization after stenting in animal models[192-196], thus constituting a valid in-vivo surrogate to assess the completeness of coverage, with superior diagnostic performance to that of IVUS[192]. The high resolution of OCT enables the visualization and objective measurement of details that had remained elusive for the other imaging techniques hitherto. With the first time-domain systems, occlusion of the coronary artery and blood removal was required, similarly to angioscopy[190, 197, 198]. However, since NIR radiation has very high signal-to-noise ratio that enables very fast pullback speeds, acquisition is also feasible with non-occlusive techniques, taking advantage of the viscosity and the transparency of ordinary angiographic contrast media to remove transiently the blood from the coronary artery for the short time needed to complete the pullback[199, 200]. The newest Fourier-Domain systems of interferometry enable even faster pullbacks[190, 201], so currently the non-occlusive technique prevails and the acquisition of OCT images is extremely simplified. This technology is becoming rapidly available worldwide.

OCT can analyse the whole stented segment at conventional longitudinal intervals of 1mm or even shorter. Neointimal hyperplasia and restenosis can be assessed using minimal and mean diameters, areas and volumes, like in IVUS studies, but OCT can go further and perform a detailed analysis strut by strut. Per strut analysis usually reports coverage as a binary outcome and the thickness of coverage as a continuous outcome. Binary coverage has been the primary endpoint in most OCT trials and studies hitherto[111, 159, 202-207]. It is considered a

surrogate for the completeness of neointimal healing, which is believed to be protective against stent thrombosis. An important caveat is the inability of OCT to detect thin layers of neointima below its axial resolution (10-20 μm, limited sensitivity), and to discern between neointima and other material like fibrin or thrombus (limited specificity). The latter becomes an issue at very early phases after stenting, when the prevalence of struts covered by fibrin is high. Endothelial cells can be found on the metallic surface of the stent as early as day 5 after implantation in a swine model, but these endothelial cells restore the endothelial continuity very seldom, and areas devoid of endothelium appear covered by granulation tissue or fibrin[208]. Thus, DES are completely covered with fibrin (not with neointima) 1-3 days after implantation, but the low discriminative power of OCT results in false coverage rates of 45-76%[196]. The analysis of optical density might overcome this limitation in the future and discern between neointima and fibrin[196]. Since the greatest interest is to assess intimal coverage at later phases, months or years after stent implantation, when the prevalence of fibrin-covered struts is low, the practical impact of this limitation is minimal[195].

In contrast with angioscopy, it must be noticed that the evaluation of neointimal coverage in OCT follows the "*bikini principle: everything covered, but the less the better*". Binary coverage will be exactly the same, irrespective of the neointimal rim thickness, and will not augment after processes of intima maturation and thickening. Thick neointimal responses are reflected in high values of the thickness of coverage per strut and considered the consequence of inefficient neointimal suppression. OCT is the imaging technique that best accommodates the definition of optimal neointimal healing as "the minimal neointimal proliferation that warrants coverage of the whole metallic surface of the stent without flow-compromising re-narrowing of the vessel". Thus, the optimal neointimal healing is considered to be that with high binary coverage rates but with low thickness of coverage.

Most of the studies compiled in this PhD thesis will use OCT for the evaluation of the neointimal response after stenting, taking advantage of its ease of acquisition, the high resolution of the images, the accuracy and reproducibility of the measurements and the unlimited analytical capabilities

THE PROBLEM: THE CAGE

The 4th revolution: bioresorbable vascular scaffolds (BVS)

Although DES had efficiently reduced the restenosis rates to 7.9 - 8.9 %[69-71], this technology had several flaws that remained incompletely solved: late and very late stent thrombosis rates were high after implantation of 1st generation devices; the polymer and the metal were foreign bodies exerting chronically a pro-inflammatory action on the vessel wall[91, 93] and posing the risk for catastrophic delayed hypersensitivity reactions[88-90]; finally the metallic stent caged the artery, interfering with normal vascular physiology (abnormal vasoconstriction

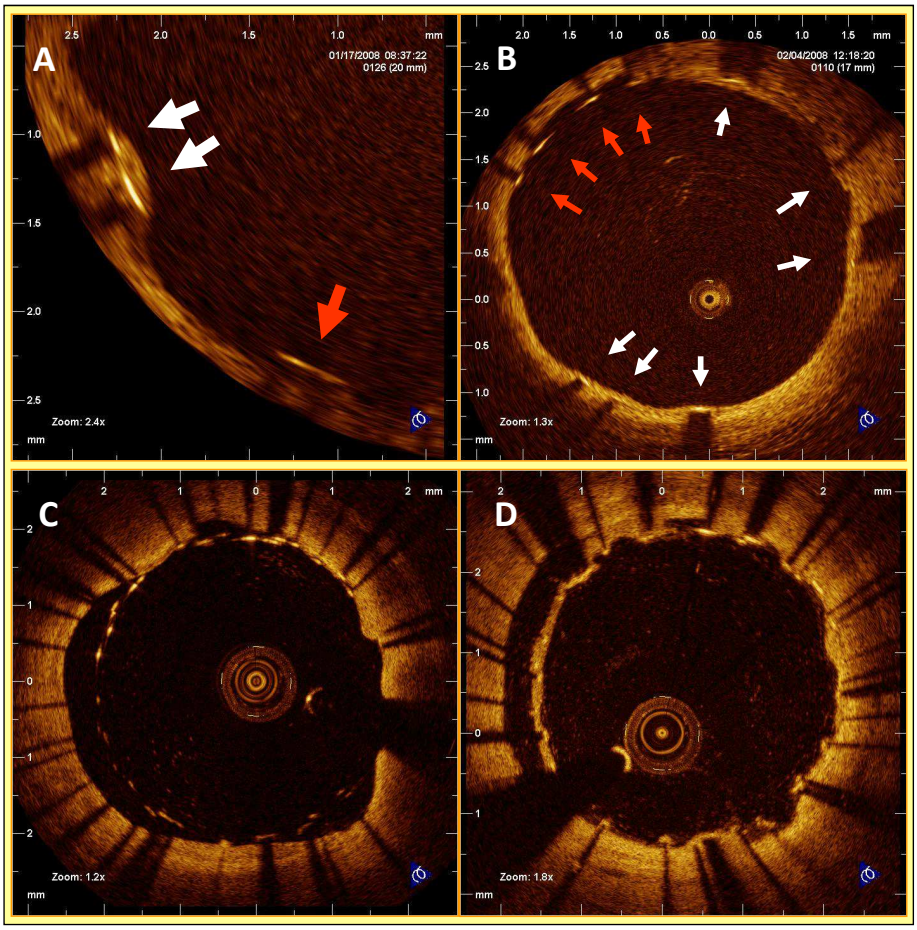

Figure 4:

Assessment of coverage by OCT as a binary outcome (A and B): struts are classified as covered if a rim of tissue can be seen over the whole reflecting surface of the strut (white arrows) or as uncovered if the reflecting surface of the strut is totally or partially exposed to the lumen of the vessel (red arrows). The lower panel presents matched cross-sections corresponding to an overlapping region of two undersized nitinol self-expandable stents immediately post-stent implantation (C) and at 6 month follow-up (D): notice the neointimal bridges trying to cover the grossly malapposed areas.

was observed distal to the stent in vasomotion tests after infusion of acetylcholine, probably as consequence of structural or functional defects in the endothelium[209]) and preventing an eventual late luminal gain.

Among all the scientific and technological approaches implemented to address DES limitations, one must be highlighted and deserves specific mention: the bioresorbable vascular scaffolds (BVS). These devices constitute a genuine breakthrough in the treatment of coronary heart disease and have been heralded as the fourth revolution in interventional cardiology[1], since they can potentially yield the same efficacy as DES in terms of restenosis prevention,

overcoming all their aforementioned limitations. Currently there exist several bioresorbable devices available for treatment of coronary stenosis[210-215], but the Abbott Vascular BVS was pioneer in the development for clinical use, so we will focus on it as paradigm.

The BVS (Abbott Vascular, Santa Clara, CA, USA) consists of a semicrystalline poly(L-lactide) (PLLA) backbone and conformal coating of amorphous poly(D,L-lactide) (PDLLA) containing the antiproliferative agent, everolimus. The molecular weight of the BVS polymers is degraded primarily through hydrolysis of the ester bonds present in each monomer subunit. Crystalline residues with characteristic dimension less than 2 μm are phagocytosed by macrophages. Ultimately, PLLA and PDLLA degrade to lactate, which is metabolised via the Krebs' cycle and other metabolic pathways[216]. Hydrolysis is a slow process evolving in three phases: 1) In the revascularization phase (0-3 months) the hydrolysis erodes the surface of the structure, degrading the PDDLA coating and thus releasing the everolimus. The oriented crystallites that comprise the load-bearing structural elements lose molecular weight because of surface hydrolysis, but they preserve their structural organization, so the radial strength of the device remains intact. These features of the design are of capital importance to prevent recoil, constrictive remodelling and neointimal hyperplasia. 2) In the restoration phase (3-6 months), the hydrolysis starts to affect the tie chains that connect oriented crystallite domains so the structural organization slowly disintegrates and the device loses progressively radial strength. After the 3rd month neither recoil nor remodelling play a relevant role, so the radial strength is no longer necessary, and the neointimal healing reaction is stopped. Chromatography studies show very low molecular weight in the scaffold, but relatively small loss in total mass, suggesting the scission of the polymers in smaller domains, losing their structural integrity. At the end of the restoration phase, a natural vasomotor response has been restored in the vessel. The device remains there, but as a totally passive implant that does not interfere with the normal physiology of the vessel. 3) Finally, in the resorption phase (6-24 months) the polymer remnants are slowly hydrolysed and substituted by a matrix of proteoglycans and finally by functional smooth muscle cells. Complete polymer resorption occurs approximately two years after implantation[217, 218]. BVS has delivered acceptable and durable clinical and angiographic results up to 4 years follow-up[218-223], with low MACE rates of 3.4-7.1%, depending on the series[221, 223]. The revision 1.1 has reduced restenosis rates to 2.4% at 6 month[222], with lumen late loss as low as 0.27mm at 12 month[223].

Based on these initial results, the BVS promises to solve all the limitations of DES without compromise of their anti-restenotic efficacy: no single case of spontaneous thrombosis of the scaffold has been reported up to 4 years follow-up in the revision 1.0 (hence, after complete resorption of the device)[218-221] and up to 1 year follow-up in the revision 1.1[222, 223], vasomotion is restored 12 months after implantation[218, 223], and in some series late lumen enlargement has been reported[218]. These encouraging outcomes stem from relatively small series of selected patients and require confirmation in larger studies. Furthermore, the relative fragility of the PLLA polymer as compared with the metallic alloys, might become an insurmountable

limitation in the treatment of heavily calcified lesions, thus precluding the use of BVS in some patients.

BVS is not only revolutionizing the treatment of coronary heart disease, but also the conventional imaging approach used in the study of intracoronary devices. In contrast to metallic stents, BVS is translucent to optical radiation and totally radiolucent to gamma radiation, with the only exception of the radiopaque platinum markers at the edges. The translucency of the processed polylactide used in the BVS makes it particularly suitable for optical coherence tomography (OCT) imaging. The optical radiation can penetrate the translucent polymer with significant backscattering occurring only at the borders of struts where the refractive index of the medium changes. Alternatively, the strut core has been characterized as a "black box"[218, 219, 222], signifying the absence of refractive index changes within the material. Thus, the abluminal side of an implanted intracoronary device becomes accessible for an invasive imaging technique for the first time. The study of the BVS by OCT demands a specific methodology, differentiated from that applied with metallic stents, affecting the assessment of apposition or coverage. The assessment of neointimal coverage on the BVS is particularly challenging due to the convolution of the signals generated by the polymer and the neointimal rim. Both signals have very similar optical impedance and become indiscernible in a standard OCT analysis using log-transformed images. This thesis would not be complete without a special chapter dedicated to the evaluation of the neointimal healing after implantation of the BVS, indeed one of the most challenging, inspiring and interesting parts of this compilation. The opportunity of getting involved in the scientific development of this fascinating technology has been a truly privilege that secures my eternal gratitude to Erasmus Medical Center, to Cardialysis BV and to Professor Patrick W Serruys.

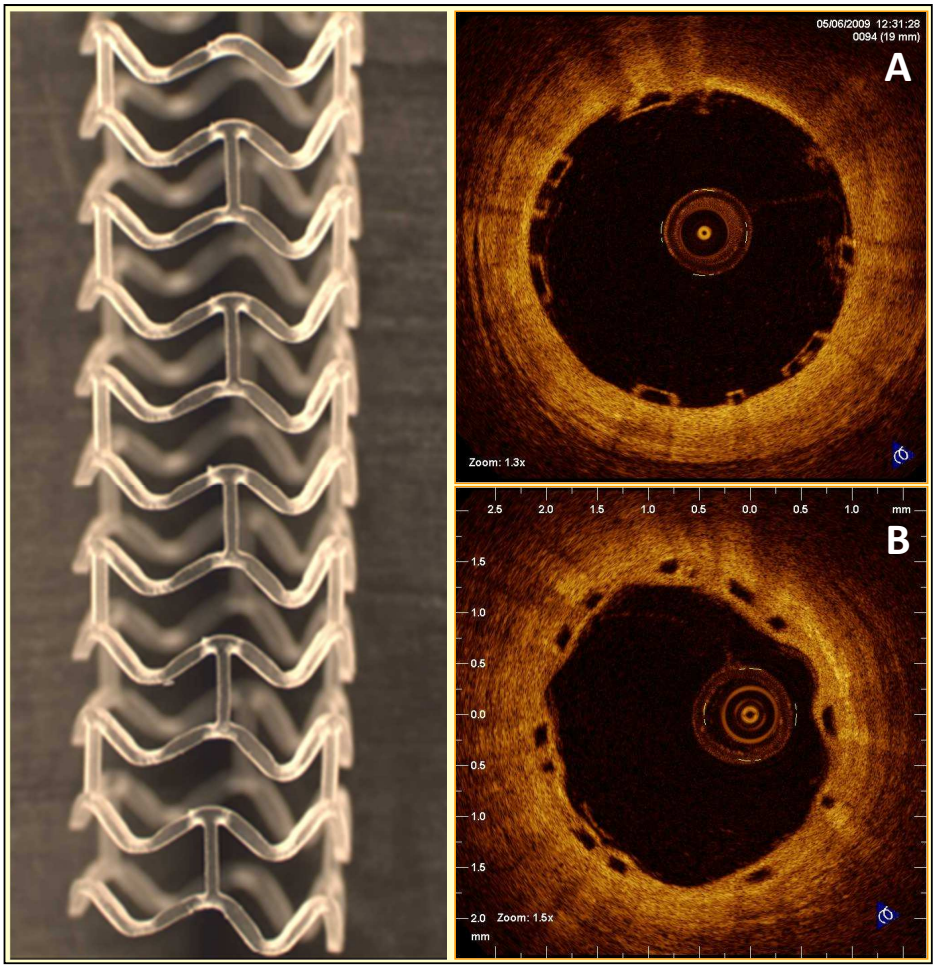

Figure 5:
Bioresorbable vascular scaffold (left) imaged by OCT immediately post-implantation (right A) and at 6 month follow-up (right B). Notice the translucency of the polymer allows detailed visualization of the abluminal side of the struts and of the underlying tissue.

AIMS OF THE THESIS

The aim of this thesis is to evaluate in vivo the neointimal healing response elicited by different interventional approaches and specific device designs aimed to optimize the restoration of the endothelial continuity after stent implantation. For that purpose, most of the hereby presented studies will take advantage of the accuracy, resolution and versatility offered by OCT, although other invasive imaging techniques are also applied when required.

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"Was man von der Minute ausgeschlagen,

gibt keine Ewigkeit zurück".

(What one refuses in one minute,
no eternity will return)

Resignation

Friedrich Schiller

PART 1

DRUG-COATED BALLOONS

CHAPTER 1

Rationale for the use of drug-coated balloons

Drug-coated balloons.

Gutiérrez-Chico JL, Serruys PW.

Controversies and Consensus in Imaging and Interventions, 2011.

http://c2i2.digithalamus.com/web11-01/drug-coated-balloons.asp

LEAD AUTHOR BIOGRAPHY

Juan Luis Gutiérrez-Chico studied Medicine in Valladolid University (Spain). He completed his first PhD in the Department of Cardiovascular Imaging of "Clínico San Carlos" Hospital (Madrid) under the direction of Drs. Zamorano and Macaya (2007). Master degree in Statistics by Barcelona University (2008). He worked in Benjamin Franklin Hospital (Berlin) and Inselspital (Bern) before becoming interventional cardiologist. Currently he works in the Erasmus MC (Rotterdam, NL) on invasive evaluation of intracoronary devices, under Dr. Serruys' supervision. His main areas of expertise are optical coherence tomography, healing after stenting, biocompatible and bioresorbable polymers, drug-coated balloons, bifurcations and biomechanics.

ABSTRACT

Drug-coated balloons (DCB) have the potential advantages with respect to drug-eluting stents (DES) of being polymer-free and enabling an even transfer of the drug along the vessel wall, instead of creating a peri-strut drug gradient. This scenario seems more favourable for a complete reendothelialization, without compromising an efficient inhibition of neointimal hyperplasia.

Paclitaxel is the antiproliferative drug of all currently available DCB, at a concentration of 2-3 μg/mm^2 of balloon surface. Paclitaxel is markedly hydrophobic and cannot be transferred onto the vessel wall unless it is bound to a hydrophilic carrier. The role of this carrier is of capital importance to determine the clinical efficacy of the DCB.

DCB with hydrophilic carriers have proven to be clinically and angiographically superior to plain-balloon angioplasty and to paclitaxel-eluting stents for the treatment of coronary in-stent restenosis. The same type of DCB has proven to be superior to plain balloon angioplasty for the treatment of de novo femoropopliteal stenosis. The combination of DCB with a bare metal stent might represent an alternative to DES for the treatment of de novo coronary lesions in selected cases. The role of DCB in bifurcations or small coronary vessels is still has to be determined.

INTRODUCTION

Aristotle wrote that virtue is always between two vices that fall short of and exceed, respectively, what is right. For Interventional Cardiology keeping the neointimal response after stenting within a "virtuous" range is still a challenge. In the bare metal stent (BMS) era the main concern was the vice for excess of neointimal hyperplasia, namely restenosis, that occurred in 20.0 – 50.3% of the cases 6 months after implantation[1]. Drug-eluting stents (DES) inhibit neointimal proliferation and have efficiently reduced the restenosis rates to 7.9 - 8.9% at 9 months[1]. However, these encouraging results have been tempered by some reports suggesting higher incidence of late and very late stent thrombosis in DES[2-5], due to incomplete neointimal healing[6] with incomplete endothelialization of the metallic struts[7] (the vice for defect). In the DES the antiproliferative drug is paradoxically eluted from the same metallic struts that should be ideally endothelialized, creating a drug gradient that plays against the healing of the metallic scaffold. Moreover, other mechanisms have been also implicated in DES thrombosis, like inflammation. The polymer containing and releasing the drug might induce inflammation of the vascular layers[8], trigger a delayed hypersensitivity reaction[9,10] and stent thrombosis[9,10].

The need for drug-coated balloons (DCB) can be understood as an attempt to overcome the limitations of DES. They represent the most advanced step in a group of therapies named "non-stent-based local delivery of antiproliferative drugs", comprising different experimental techniques, like double balloon catheter[11], porous balloon[12] or intrapericardial administration of paclitaxel[13]. DCB have been tested clinically in several indications and are ready to be part of the routine armamentarium of the modern cathlab. The appealing principles of DCB mechanism of action are 1) the drug transferred from the DCB onto the vessel wall inhibits neointimal hyperplasia efficiently and prevents restenosis (prevents the vice for excess), 2) the drug is transferred evenly along the vessel wall, instead of creating a peri-strut gradient, what seems a more favourable scenario for complete endothelialization of the struts (prevents the vice for defect). Furhtermore, the absence of polymer permits to circumvent the pro-inflammatory and pro-thrombotic phenomena that this component might elicit.

THE DEVELOPMENT OF DCB: A PHARMACOKINETIC DILEMMA

The concept of DCB has been long time confronted to a question that seemed impossible to be answered satisfactorily: "how could a brief local application of an antiproliferative drug for a few seconds have a biological effect on a process prolonged up to 3 months?" Actually the question entails two major challenges: 1) the transfer time is very short compared to the sustained elution of DES; 2) the marked hydrophobicity of the antiproliferative drugs hinders their diffusion in hydrophilic milieus like the vessel wall. The physicochemical and

pharmacokinetic dilemma does not have an easy solution: hydrophobic drugs could bind tightly to fixed tissue components and have a prolonged effect, but their diffusion into the hydrophilic vessel wall is problematic (they form micelles that prevent an adequate contact with the vessel wall and an efficient uptake); conversely, hydrophilic drugs permeate easily the vessel layers, but they are also easily washed out, thus being unlikely to exert the expected biological effect. Scepticism seems more than justified.

Paclitaxel is a markedly hydrophobic molecule, hence its transfer onto the arterial wall during the time of a balloon inflation is minimal. However, an interesting observation opened new perspectives: addition of paclitaxel to the contrast media iopromide (used for coronary angiography) during percutaneous coronary stenting resulted in a therapeutic effect inhibiting neointimal hyperplasia, in spite of the limited contact time[14-16]. The viscosity of the contrast media could prolong the contact time at some extent, but not to explain a therapeutic effect. The key mechanism seems to be the affinity of the hydrophilic iopromide for the hydrophobic paclitaxel: the former facilitates the tissular uptake of the latter up to the adventitia[17]. Once in the target tissue, paclitaxel would bind to fixed hydrophobic components, becoming resistant to clearance and exerting a prolonged biological effect. This finding represents the pharmacokinetic basics for the development of DCB: combining a hydrophobic active drug (that remains) with a hydrophilic carrier (that diffuses), both with mutual affinity.

COMPONENTS OF A DCB

Most of the commercially available DCB to date have three components: the balloon catheter, the active drug and the carrier. The most compelling evidence about efficacy of DCB stems from devices with this kind of design. Actually, some companies that started manufacturing paclitaxel-coated balloons without carrier have recently revised their product and incorporated a hydrophilic carrier.

The balloon catheter

The balloon is usually a compliant or semi-compliant rapid-exchange balloon catheter. The balloon exerts the same mechanical action than any conventional angioplasty balloon, dilating the target lesion and enlarging the lumen to restore a normal coronary flow. However the balloon catheter of a DCB has a second function at least as important as the first one: it puts the drug in contact with the vessel wall to enable its diffusion. The conformability of a balloon to the lumen shape and consequently the contact surface and the transfer of the drug might be better at low-pressure inflation. In this regard a systematic preparation of the coronary lesions, using predilatation, atherectomy or cutting-balloon as required might be advisable, to allow a final DCB balloon inflation as smooth as possible, to optimize the drug transfer.

The active antiproliferative drug

Paclitaxel is hitherto the drug of choice in all the commercially available DCB, due to their aforementioned pharmacokinetic properties for local delivery[17], at a dose of 2-3 μg/mm^2 of balloon surface area. Paclitaxel binds to the β subunit of tubulin and hyper-stabilizes the microtubules of the cell, thus inhibiting the mitosis. Other hydrophobic agents could be also tested for this application in the next future.

The carrier

The carrier plays a capital role in the efficacy of the DCB, since it determines the amount of drug lost in the transit, and its transference to the vessel wall. A balloon coated just with paclitaxel (without carrier) will suffer negligible loss of the hydrophobic drug during the transit, but the paclitaxel transference to the vessel wall will be also very low during balloon inflation. Manufacturers of this kind of devices recommended repeat balloon inflations, in an attempt to increase the contact time without provoking ischemia. The association of paclitaxel to a hydrophilic carrier (iopromide, e.g.) will result in considerable loss of paclitaxel load during transit, but also in a high transference rate of the drug into the vessel wall[17-19]. Manufacturers of these devices recommend a single prolonged inflation. The hydrophilic carrier could partly explain the efficacy of some DCB[18,20-22], compared to the poor performance of other DCB using carriers of a different type or no carrier[18,23].

In presence of a hydrophilic carrier, the longer the transit time, the lower the paclitaxel dose reaching the target. In order to minimize the transit time, systematic pre-dilatation of the target lesion should be performed before the DCB applications.

The formulation employed will determine the pharmacokinetic properties and the diffusion of the active agent. Some animal studies suggest that paclitaxel diffuses not only in a radial direction from the balloon surface, but also distally and proximally following the longitudinal axis of the vessel[19]. This finding is at variance with the evidence from paclitaxel-eluting stents using reservoirs technology: in the first experimental designs neointimal hyperplasia was maximal at the bridge sites, where no wells for paclitaxel reservoirs had been initially implemented[24]. It is unknown if the alleged longitudinal diffusion is effective to prevent edge restenosis, and actually some clinical studies with DCB suggest that geographical mismatch (no drug delivery to a stented or injured vessel segment) is associated with restenosis and target lesion revascularization (TLR)[25]. Until more solid evidence is available in this regard, it is recommended to extend the balloon applications some mm beyond the stent edges or target segment to avoid geographical miss.

The fourth element: the stent

Some companies have assembled pre-mounted BMS on DCB for the treatment of de novo lesions. These combinations are aimed to be an alternative to DES with interesting advantages: polymer-free, limited exposure to the antiproliferative drug and homogeneous distribution of the drug along the vessel wall. Animal studies also suggest that the loss of paclitaxel during vascular transit is lower in folded DCB with a crimped stent than in plain DCB[18].

CURRENTLY AVAILABLE DEVICES

Paclitaxel-coated balloons with hydrophilic carrier

Paccocath (Bayer Schering Pharma AG, Berlin, Germany) and **SeQuent Please** (B Braun Melsungen AG, Vascular Systems, Berlin, Germany) use a hydrophilic iopromide-derived carrier. The concentration of paclitaxel is 3 µg/mm^2 of balloon surface. 16% of the total paclitaxel load is transferred to the vessel wall during a single 30" balloon inflation, and this amount exerts an efficient neointimal inhibition[18]. This technology has been the pioneer in developing the concept of DCB, and has generated the most solid clinical evidence.

Dior (Eurocor GmbH, Bonn, Germany) has also a paclitaxel concentration of 3 µg/mm^2 of balloon surface, but it followed initially a carrier-free design: paclitaxel coated a microporous balloon surface, being the balloon three-folded to minimize the transit loss. However, the poor clinical performance of the first Dior generation forced the company to incorporate a hydrophilic Shellac carrier. Shellac is a hydrophilic natural resin. The 2nd Dior generation has a Paclitaxel-Shellac (1:1) coating in layers, obtained through micropipetting. The layered and non-crystalline nature of the coating might make it very robust and resistant to scratching.

The **IN.Pact Falcon** DCB (Invatec, Italy) has a paclitaxel concentration of 3 µg/mm^2 and a proprietary hydrophilic FreePac carrier. The **Moxy** DCB (Lutonix, Mapple Grove, MN, USA) has a paclitaxel concentration of 2 µg/mm^2 and a proprietary hydrophilic non-disclosed carrier. No more specific information can be provided about these two devices.

Paclitaxel-coated balloons with a pre-mounted BMS

Coroflex-DEBlue is the combination of a Coroflex Blue BMS with the Sequent Please DCB (B Braun Melsungen AG, Vascular Systems, Berlin, Germany). The **Magical system** is a CoCr BMS pre-mounted on a Dior balloon (Eurocor, Bonn, Germany).

Porous balloons for paclitaxel delivery

GENIE (Acrostak, Winterthur, Switzerland), is a liquid drug delivery catheter available in various diameters and shaft lengths. After determining the vessel diameter and lesion length, the balloons are inflated with diluted paclitaxel.

EVIDENCE ABOUT DCB

DCB have been tested in different clinical coronary scenarios, like in-stent restenosis (ISR), de novo coronary lesions, small vessels non-amenable for stenting or bifurcations, but also in peripheral femoropopliteal stenosis.

In-stent restenosis

Treatment of ISR is currently a favoured indication for DCB, because the optimal therapeutic approach to ISR is still a matter of debate. Re-stenting with DES has proven to be superior to brachytherapy and to plain balloon angioplasty[26,27], but it cannot be considered an optimal solution, because double stent layers have been associated to delayed neointimal healing[28] and suboptimal clinical outcomes[29].

DCB have proven to be superior to plain-balloon angioplasty for the treatment of ISR in randomized trials. Paccocath DCB has less incidence of major adverse cardiovascular events (MACE), mainly due to a significant reduction in TLR, lower in-segment late lumen loss and lower rates of binary restenosis[30,31]. Compared to paclitaxel-eluting stents (PES), the SeQuent Please DCB has proven lower in-segment late loss and a statistically non-significant trend to lower binary restenosis and MACE, the latter mainly driven by the larger need for TLR with PES[32]. In the scope of these results, DCB has emerged as the best currently available therapy for ISR.

De novo coronary lesions

The combination of a BMS premounted on a DCB resulted in larger inhibition of neointimal hyperplasia than sirolimus-eluting stent (SES) in animal coronary overstretch models[33]. However, this combination failed to prove non-inferiority vs. SES for the treatment of human de novo coronary lesions in the PEPCAD-III trial[34]. The recently presented "De Novo" trial compared the OCT neointimal volume obstruction of the Moxy DCB used in combination with a non-premounted BMS depending on the sequence of application (DCB first vs. BMS first). No significant difference in efficacy endpoints were found between both sequences of application[35], and the reported endpoints are similar to those historically reported for paclitaxel-eluting stents. These OCT results constitute an additional evidence of the biological effect of DCB (figure 1).

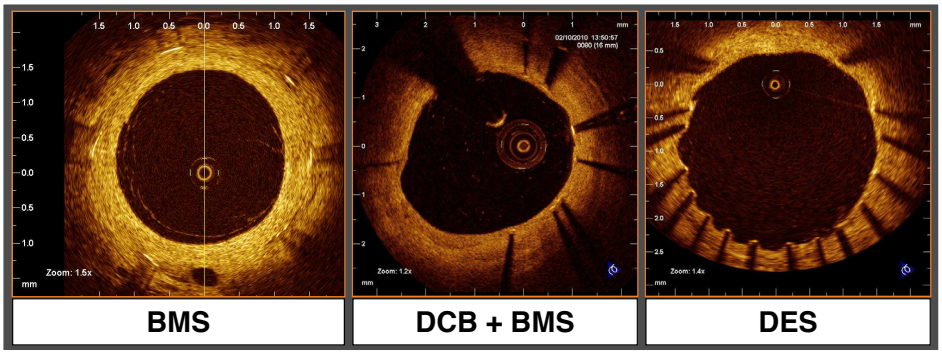

Figure 1: Examples of typical neointimal hyperplasia reaction 6-9 months after bare metal stent (BMS), after the combination of a drug-coated balloon (DCB) with a BMS and after a drug-eluting stent (DES), as observed with optical coherence tomography. Notice how the thin layer covering the stent struts in the combination DCB-BMS is closer to the one observed after DES than to the typical thick layer after BMS, suggesting a clear biological effect of the paclitaxel transferred during the balloon inflation.

Small coronary vessels

PEPCAD I was a multi-centric registry of the Sequent-Please DCB for treatment of small vessels (2.25 - 2.8mm). Cross-over to stenting or plain balloon angioplasty occurred in 30% of the cases. At 6 months follow-up in-segment late loss and binary restenosis were 0.28±0.53mm and 19,0%, respectively; TLR 14% and MACE 18%. Only 10% of the cases suffered acute elastic recoil requiring bailout intervention[36].

The randomized PICOLETTO trial compared the carrier-free Dior vs. PES for treatment of small coronary vessels (≤ 2.75 mm diameter) in 57 patient with stable or unstable angina. The DCB failed to prove non-inferiority; indeed percent diameter stenosis (the primary endpoint), binary restenosis and minimal lumen diameter were significantly worse in those treated with DCB at 6 months follow-up. Although clinical outcomes were comparable in terms of death and MI, there was still a trend towards higher TLR with the DCB[23].

The role of DCB in treatment of small coronary vessels is still to define. The inability to counteract acute recoil and late remodelling will be probably a severe limitation precluding good results in the future.

Bifurcations

The DEBIUT registry enrolled 20 patients with bifurcation lesions, who sequentially had the main branch and then the side branch treated with the Dior DCB, followed by provisional stenting of only the main branch using a BMS. In no case stenting of the side branch was required. At 4-month follow-up there were no MACE events; however no angiographic data were reported[37].

More recently the PEPCAD V study enrolled 28 patients with bifurcation lesions, the majority of them class 011 or 111 of Medina. Both branches were treated with the SeQuent Please DCB, followed by provisional stenting of the main branch with a BMS; 14% of side branches eventually received a stent. At 9-month follow-up, whilst there were significant reductions in both main-branch and side-branch late lumen loss, and only 1 TLR, of concern were the two late stent thrombosis events in patients receiving DCB and BMS in the main branch[38].

DCB have currently no clear indication and no clear advantage for the treatment of coronary bifurcations.

Peripheral artery disease

DCB with iopromide-based additive have proven to be superior to plain balloon angioplasty[39,40] and to balloon angioplasty with paclitaxel dissolved in the contrast media[39] for the treatment of de novo femoropopliteal stenosis, in terms of late loss at 6 months[39] and TLR rates at 3 years follow-up[40].

KEY LEARNING POINTS

1) Currently there is compelling evidence that DCB efficiently inhibit neointimal hyperplasia, stemming from clinical and imaging studies.
2) The hydrophilic carrier plays a capital role in the transfer of the drug onto the vessel wall and determines the efficacy of the device, or the lack of it.
3) DCB have proven superiority with respect to the hitherto predicate treatments for ISR and femoropopliteal stenosis.
4) DCB in combination with BMS might be an alternative for the treatment of de novo coronary lesions in selected cases.
5) The role of DCB for the treatment of bifurcations or small coronary vessels is still to define.

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CHAPTER 2

Basic components of drug-coated balloons

Moxy® drug-coated balloon: a novel device for the treatment of coronary and peripheral vascular disease.

Gutiérrez-Chico JL, Regar E, van Geuns RJ, Garg S, Schultz C, van Mieghem N, Duckers H, Serruys PW

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DESCRIPTION

The Moxy Drug-Coated PTCA/PTA Balloon is a paclitaxel-coated balloon with a hydrophilic carrier to optimize the drug release onto the vessel wall. It represents an interesting alternative to drug-eluting stent (DES) for the percutaneous treatment of in-stent restenosis, de novo-coronary lesions or peripheral artery disease.

HISTORY

Adoption of DES has reduced coronary restenosis rates to 7.9 - 8.9% at 9 months[1-3], but this benefit is compromised by a higher incidence of late and very late stent thrombosis[4-8]. The polymer component of DES may contribute to inflammation of the vascular layers[9], eventually resulting in thrombosis[10-12], and the antiproliferative drug is eluted from the same metallic struts that should ideally be endothelialized, creating a drug-gradient that prevents proper neointimal healing. In this perspective, drug-coated balloons (DCB) represent an interesting alternative, since they don't utilize polymers and the drug is distributed along the vessel wall without creating a peri-strut gradient.

DCB have three components: the balloon, the drug and the carrier, which is a critical component. The balloon is usually compliant or semi-compliant. The antiproliferative drug is paclitaxel at a dose of 2-3 μg/mm^2 in all the currently available devices. Paclitaxel is markedly hydrophobic, therefore alone it has very limited transfer onto the vessel wall during the short time of a balloon inflation. However, once delivered to tissue it diffuses through the vessel wall and binds to fixed hydrophobic components of the tissue, becoming resistant to wash out and exerting a prolonged biological effect[13]. The carrier is the substance that enables the transfer of the hydrophobic paclitaxel onto the tissues of the vessel wall through a hydrophilic milieu. It plays a critical role in the pharmacokinetics and in the efficacy of the different devices tested. The carrier also determines the amount of drug lost in transit. Thus a carrier-free balloon will suffer negligible loss of paclitaxel (hydrophobic) during transit, but the drug transference to the vessel wall will also be minimal. The hydrophilic carrier (e.g., iopromide) increases transference rate of the drug onto the vessel wall[13-15] but also loss of paclitaxel during transit.

Lutonix (Maple Grove, MN) has developed a DCB with a proprietary hydrophilic carrier for coronary and peripheral applications.

TECHNICAL SPECIFICATIONS

Description of the Moxy DCB

The Moxy DCB is a standard angioplasty catheter with a highly specialized drug coating on the balloon portion. The device consists of a dual lumen shaft in two separate designs: Rapid Exchange (Rx) and Over-the-Wire (OTW), for coronary and peripheral applications, respectively. The coronary Rx system is compatible with 0.014" guidewire and 5 Fr guide catheters. The peripheral OTW system is compatible with 0.018" guidewire, 7 Fr guide catheters and 6 Fr sheaths.

The Moxy DCB is semi-compliant with a low-profile tapered tip (Figure 1). The balloon is made from a polyamide material capable of achieving high inflation pressures (>16atm for Rx and >12atm for OTW). Two radiopaque marker bands are located at the proximal and distal ends of the balloon to facilitate fluoroscopic visualization of the DCB during delivery and placement. The proximal portion of the DCB catheter includes a female luer lock hub connected to the inflation lumen used to inflate and deflate the balloon. Each product has a balloon protector and stainless steel stylet to protect the balloon prior to use.

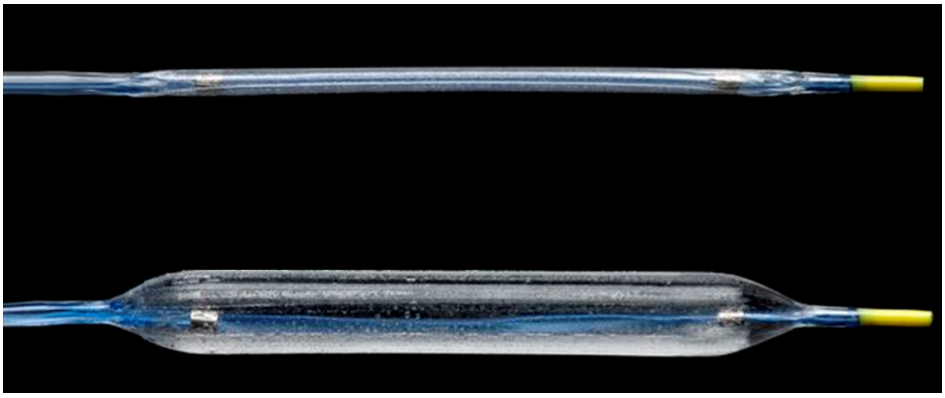

Figure 1: Moxy drug-coated semi-compliant balloon in folded and inflated positions.

Description of the Lutonix Drug Coating

The Lutonix drug coating is a non-polymer based formulation consisting of the anti-proliferative agent Paclitaxel and a proprietary hydrophilic carrier that is designed to minimize the loss of drug during transit and to optimize the drug uptake by target vessel tissue during angioplasty. Paclitaxel is evenly distributed along the working length of the balloon at a surface concentration of 2µg/mm^2 (33% lower than other DCBs)..The proprietary carrier was selected among more than 200 substances tested as the one providing the best coating uniformity, pharmacokinetic profile and transfer efficiency.

INDICATIONS FOR USE

Coronary in-stent restenosis (ISR)

Treatment of ISR is currently a favoured indication for DCB, because the optimal therapeutic approach to ISR is still a matter of debate. Re-stenting with DES has proven to be superior to brachytherapy[16,17] and to plain balloon angioplasty[18,19], but it cannot be considered an optimal solution, because double stent layers have been associated to delayed neointimal healing[20] and suboptimal clinical outcomes[21].

Other DCB with paclitaxel at a dose of 3µg/mm^2 and hydrophilic carrier have proven to be superior to plain-balloon angioplasty for the treatment of ISR in randomized trials. DCB have less incidence of major adverse cardiovascular events (MACE), mainly due to a significant reduction in target lesion revascularization (TLR), lower in-segment late lumen loss and lower rates of binary restenosis[22,23]. Compared to paclitaxel-eluting stents (PES), DCB have proven lower in-segment late loss and a statistically non-significant trend to lower binary restenosis and MACE, the latter mainly driven by the larger need for TLR with PES[24]. In the scope of these results, DCB has emerged as the best currently available therapy for ISR.

The Moxy DCB is currently being tested for the treatment of coronary ISR in an observational registry titled PERVIDEO I (ClinicalTrials.gov Identifier: NCT00916279).

De novo coronary lesions

The combination of DCB (paclitaxel-coated at 3µg/mm^2, hydrophilic carrier) with BMS results in larger inhibition of neointimal hyperplasia than sirolimus-eluting stent (SES) in animal coronary overstretch models[25]. However, this combination failed to prove non-inferiority vs. SES for the treatment of human de novo coronary lesions[26].

The ongoing De Novo Pilot Study (NCT00934752) is a multicenter study assessing performance of the Moxy DCB in combination with a BMS (Multilink Vision, Abbot Vascular, Santa Clara, CA, USA) for treatment of de novo coronary lesions. This study incorporates a randomized, single-blind, open-label design to better understand outcomes based on the sequence of application (DCB first vs. BMS first) with OCT-derived neointimal volume as the primary endpoint.

Small coronary vessels

A randomized clinical trial comparing a carrier-free DCB vs. PES for treatment of small coronary vessels (≤ 2.75 mm diameter) was prematurely stopped due to disappointing results of the DCB in an interim analysis[27]. Vessel recoil and the absence of a carrier to facilitate drug transfer might explain these results.

The PEPCAD I registry used a DCB with hydrophilic carrier for treatment of lesions in vessels with 2.25 – 2.80 mm of diameter. Cross-over to stenting or plain balloon angioplasty occurred in 30% of the cases. At 6 months follow-up in-segment late loss and binary restenosis were 0.28±0.53mm and 19,0%, TLR 14% and MACE 18%. Only 10% of the cases suffered acute elastic recoil requiring bailout intervention[28].

DCB might be an alternative for treatment of small coronary vessels, but their role for this indication still requires further clarification. Moxy DCB is not being clinically tested for this indication to date.

Coronary bifurcations

The feasibility of treating sequentially both branches of a bifurcation with DCB, followed by provisional stenting of the main vessel with BMS, has been tested in small series of patients[29,30]. There are no comparative data vs. other strategies and the report of 2 stent thrombosis has raised some concerns[31]. The role of DCB for the treatment of bifurcations is still unclear. Moxy DCB is not being clinically tested for this indication to date.

Peripheral artery disease

DCB are superior to plain balloon angioplasty[32,33] for the treatment of de novo femoropopliteal stenosis. Treatment with another DCB (paclitaxel-coated at 3µg/mm^2, hydrophilic carrier) resulted in significantly lower late loss at 6 months[34] and lower TLR rates at 2 years follow-up[35].

Further evidence of DCB efficacy is being investigated in the LEVANT I multicenter, single blind, randomized, controlled trial (NCT00930813) which compares the Moxy OTW peripheral balloon vs. plain balloon angioplasty for the treatment of de novo femoropopliteal stenosis.

TIPS AND TRICKS FOR USE

The following comments about tips and tricks for use of the Moxy DCB are based on current evidence but also in the personal experience of the main operators involved in the different clinical studies.

In order to minimize the transit time and hence the loss of paclitaxel, systematic predilation is recommended. This also minimizes potential disruption of the drug coating from the mechanical stress during difficult lesion crossing. For the treatment of ISR, where the neointimal tissue is usually fibrotic and "slippery" for hydrophilic balloons, predilation is recommended and may require the use of non-compliant devices or cutting balloons. The aggressiveness of pre-dilatation may depend on the lesion characteristics (e.g. calcification) and indication (e.g. ISR vs. *de novo* lesions).

Although some studies suggest that paclitaxel diffuses into the vessel wall not only in a radial direction, but also distal and proximally following the longitudinal axis of the vessel[36], it is somewhat unknown if this longitudinal diffusion is effective to prevent stent edge restenosis. Some clinical studies suggest that geographical mismatch (no drug delivery to a stented or injured vessel segment) is associated with restenosis and TLR[37]. Until more solid evidence is available in this regard, if the DCB is used in combination with a BMS for treatment of *de novo* coronary lesions, it is recommended to extend the balloon applications beyond the stent edges (2-5 mm).

The conformability of a balloon to the lumen shape of the vessel is better at low-pressure inflation, suggesting the possibility that transfer of paclitaxel may be optimal at lower atmospheres.

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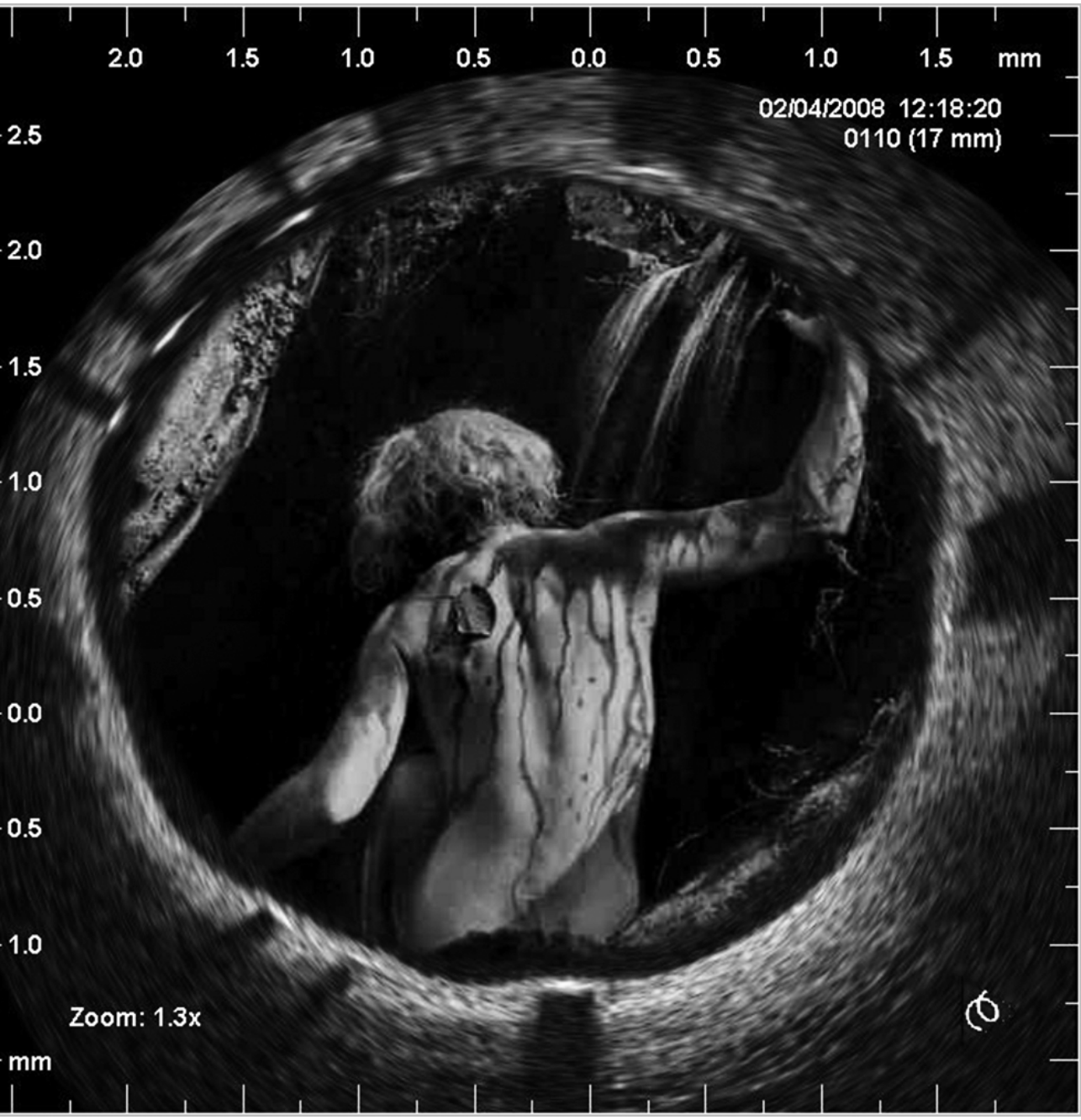
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CHAPTER 3

DCB in combination with BMS for treatment of de novo coronary lesions

Paclitaxel-coated balloon in combination with bare metal stent for treatment of de novo coronary lesions: an optical coherence tomography first-in-human randomized trial balloon-first vs. stent first.

Gutiérrez-Chico JL, van Geuns RJ, Koch K, Koolen J, Duckers HJ, Regar E, Serruys PW

EuroIntervention 2011;7:711-722.

ABSTRACT

Aims: To test the efficacy of sequential application of drug-coated balloon (DCB) and bare metal stent (BMS) for treatment of de novo coronary lesions, comparing the sequence of application (DCB first vs. BMS first).

Methods and results: In a multicenter pilot trial, 26 patients with de novo coronary lesions were randomized to receive a paclitaxel-coated balloon application followed by BMS implantation (DCB first) or viceversa (BMS first). Quantitative coronary angiography (QCA) and optical coherence tomography (OCT) were performed post-procedure and at 6 months, with OCT % neointimal volume obstruction as primary endpoint. Longitudinal geographical miss was only observed in DCB first (23.1 vs. 0.0%, p=0.220). Implantation of BMS first resulted in fewer malapposed struts (p=0.013) but similar coverage at 6 months. No significant difference was found regarding the primary endpoint (25.5 vs. 24.9%, p=0.922), mean thickness of coverage (261 vs. 225µm, p=0.763), late loss (0.53 vs. 0.45mm, p=0.833), binary restenosis (27.3 vs. 16.7% in-segment, p=0.640) or clinical endpoints.

Conclusion: Sequential application of DCB and not-premounted BMS for treatment of de novo coronary lesions results in efficient inhibition of neointimal hyperplasia. The sequence of application (DCB first vs. BMS first) does not seem to influence the outcome, except for better apposition in BMS first.

Key words: Coronary vessels; coronary stenosis; angioplasty, transluminal percutaneous coronary; angioplasty, balloon; paclitaxel; stents.

CONDENSED ABSTRACT

In a multicentre trial, 26 patients with de novo coronary lesions were randomized to receive a novel paclitaxel-coated balloon application followed by bare metal stent implantation (DCB first) or viceversa (BMS first). Longitudinal geographical miss was only observed in DCB first (23.1 vs. 0.0%, p=0.220). BMS first resulted in fewer malapposed struts (p=0.013) but similar coverage at 6 months by optical coherence tomography (OCT). No significant difference was found regarding OCT percent neointimal volume obstruction (25.5 vs. 24.9%, p=0.922, primary endpoint), mean thickness of coverage (261 vs. 225µm, p=0.763), angiographic late loss (0.53 vs. 0.45mm, p=0.833) or clinical endpoints.

LIST OF ABBREVIATIONS

BMS: Bare-metal stent
DCB: Drug-coated balloon
DES: Drug-eluting stent
ISA: Incomplete stent apposition
MACE: Major acute cardiovascular event
MLA: Minimal lumen area
MLD: Minimal lumen diameter
NASB: Non-apposed side-branch struts
NIH: Neointimal hyperplasia
OCT: Optical coherence tomography
PCI: Percutaneous coronary intervention
PES: Paclitaxel-eluting stent
QCA: Quantitative coronary angiography
RVD: Reference vessel diameter
SES: Sirolimus-eluting stent
TLR: Target lesion revascularization
TVR: Target vessel revascularization

INTRODUCTION

Drug-eluting stents (DES) have efficiently reduced the restenosis rates to 7.9 - 8.9 % at 9 months[1], due to the sustained elution of an antiproliferative agent that inhibits neointimal hyperplasia. However some reports have suggested an eventually higher incidence of late stent thrombosis[2-5]. In all these cases, the common pathological finding was an incomplete neointimal healing[6] with incomplete endothelialization of the metallic struts[7]. In DES the antiproliferative drug is eluted from the struts, creating a peri-strut gradient that plays against a proper healing. Likewise, the polymer containing and releasing the drug might induce inflammation and thrombosis[8-10].

Drug-coated balloons (DCB) represent an alternative to DES for inhibiting neointimal hyperplasia. DCB transfer the drug evenly along the vessel wall, instead of creating a peri-strut gradient, what seems a more favourable scenario for complete endothelialization of the struts. However this technology must circumvent two limitations: first, the marked hydrophobicity of the antiproliferative drugs hinders their diffusion in a hydrophilic milieu like the vessel wall; second, the transfer time is very short, compared to the sustained elution of DES. A hydrophilic carrier with affinity for the drug facilitates its transfer onto the vessel wall. This mechanism would explain why the combination of paclitaxel with the contrast media iopromide during injection for coronary angiography results in a therapeutic effect inhibiting neointimal hyperplasia[11-13], even though the contact time with the vessel wall is limited to a few seconds: the hydrophilic iopromide would act as carrier for the hydrophobic paclitaxel, facilitating its transfer into the tissue up to the adventitia[14]. Once in the tissue, paclitaxel would bind to fixed lipophilic compounds, becoming resistant to wash-out and exerting a prolonged effect[14].

In swine coronary overstretch models, DCB combining paclitaxel with a hydrophilic iopromide-based carrier have proven dose-dependant reduction of the neointimal area, with complete endothelialization of all the struts and reduction of inflammatory markers[15]. In the clinical setting the same device was superior to plain balloon angioplasty[16,17] and to paclitaxel-eluting stent (PES)[18] for the treatment of in-stent restenosis. For de novo coronary lesions, the combination of DCB with BMS results in larger inhibition of neointimal hyperplasia than a sirolimus-eluting stent (SES) in porcine coronary overstretch models[19]. These studies used a DCB with a hydrophilic iopromide-based carrier, and BMS premounted on the DCB. There is scarce information about the efficacy of this combination in the clinical setting. Moreover, the effect of sequential application of DCB and BMS for treatment of de novo coronary lesions, and the impact of the sequence (DCB first vs. BMS first) are unknown. Hypothetically, sequential application might increase the risk of "geographical miss" (mismatching between the DCB-treated and the stented segments) compared to premounted devices, especially if

DCB is applied first. On the other hand, application of DCB first might enhance the diffusion of the drug onto the vessel wall, with better contact than in the presence of an interposed stent.

METHODS

The De Novo Pilot Study (NCT00934752) was a multicenter, prospective, single-blind, open-label randomized trial assessing the performance of the Moxy DCB (Lutonix Inc, Maple Grove, MN, USA) in combination with an independent not-premounted BMS for treatment of de novo coronary lesions, comparing the effect of the sequence of application (DCB first vs. BMS first) on the extent of neointimal hyperplasia (NIH) at 6 months.

Study population and allocation to treatment

The study enrolled patients with stable/unstable angina or with documented silent ischemia, and one de novo coronary stenosis ≥50% and <100%, ≤18mm length, with a reference vessel diameter (RVD) ≥2.5 and ≤3.25mm and amenable for percutaneous coronary intervention (PCI). Exclusion criteria included: 1) Myocardial infarction or thrombolysis in previous 72 hours, 2) History of stroke within the past 6 months, 3) Intervention required in >2 coronary lesions, or in one additional lesion lying in the same vessel as the study lesion 4) Coronary intervention within 60 days before the index procedure or planned after it, 5) Any previous intervention on the target coronary vessel, 6) Left ventricular ejection fraction < 25%, 7) Target lesion located in the left main coronary artery, or involving bifurcation of vessels ≥2.5mm, 8) Planned use of adjunctive coronary devices (e.g. cutting-balloon, atherectomy).

Patients were screened for eligibility before entering the procedure. All potentially eligible patients provided informed signed consent for enrolment. Final inclusion was done after verifying the eventual successful treatment of the non-study lesion and after the guidewire had crossed the target lesion without complications. Patients were randomly allocated on a 1:1 basis to receive treatment with Moxy DCB before BMS (DCB first) or after BMS (BMS first) using computer generated-sequences, in blocks stratified by centre.

The study was conducted in accordance with Good Clinical Practice, Declaration of Helsinki and local regulations, and protocol was approved by the Ethical Committees of the centres involved in the trial: Erasmus MC, Rotterdam; Academic MC, Amsterdam and Catharina Ziekenhuis, Eindhoven, NL.

Study endpoints and sample size calculation

The primary endpoint of the trial was the in-stent percent neointimal volume obstruction at 6 months assessed by optical coherence tomography (OCT). No evidence about the expected magnitude of the effect was available when the trial was designed, and therefore no formal sample size calculation based on the primary endpoint could be done. Based on unpublished data from other ongoing OCT trials, a minimum number of 10 patients per treatment arm was considered necessary to provide reliable and non-trivial results, and to detect a significant deviation in any of the arms from the results obtained with DES.

Secondary endpoints of the study included OCT endpoints (apposition at baseline and at 6 months; coverage at 6 months), quantitative coronary angiography (QCA) endpoints (late lumen loss, percent diameter stenosis, binary restenosis defined as diameter stenosis ≥50%) and clinical endpoints (composite of cardiac death, myocardial infarction [MI] and clinically-driven target lesion revascularizatio [TLR]; stent thrombosis; major/minor bleeding).

Study devices

The DCB used in this study was the Moxy catheter (Lutonix, Maple Grove, MN, USA), model 9001. It is a standard rapid exchange semi-compliant balloon, coated by paclitaxel at a surface concentration of 2 μg/mm^2, and by a proprietary hydrophilic non-polymeric carrier. The device was available at 2.5 and 3.0mm diameter, and at 18 and 30mm length for this study. All patients were stented with the Multi-link Vision/MiniVision stent (Abbott Vascular, Santa Clara, CA, USA). It is a cobalt-chromium BMS with a strut thickness of 81μm, available at 2.5, 2.75 and 3.0mm diameter, and at 15, 18 and 23mm length for this study.

Description of the intervention

Before the intervention all subjects received aspirin 100-325mg and clopidogrel 75mg daily for 3 days or in a loading dose of 300mg. Use of glycoprotein IIb/IIIa inhibitors was left at the operator's discretion. Intravenous heparin or other thrombin inhibitor was administered to maintain an activated clotting time ≥250 seconds (or ≥200 seconds if a glycoprotein IIb/IIIa inhibitor was being administered) during the procedure. The interventions were performed with a ≥6F guiding catheter. Systematic predilatation of the target lesion was mandatory regardless the allocation to treatment. The implanted BMS had to cover the whole target lesion length. The DCB should extend at least 2mm beyond the distal and proximal margins of the stent and of the segment exposed to predilatation, A single DCB inflation ≥ 30 seconds was mandatory. If necessary, post-dilatation could be performed with the DCB catheter or with other shorter compliant or non-compliant balloon. After optimization of the result,

intracoronary nitroglycerin was administered and final angiography and OCT pullback were recorded. Optimization of the result based on OCT images was strongly discouraged.

Follow-up

Subjects with a single study-lesion were kept on dual anti-platelet therapy with aspirin and clopidogrel for 3 months. In case a non-study lesion had been also treated during the same procedure, duration of anti-platelet therapy could be extended to meet the requirements of the devices employed.

Clinical follow-up visits were scheduled at 30 days, 6, 12 and 24 months. Angiographic and OCT follow-up were performed at 6 months.

QCA analysis

QCA analysis was performed with the CAAS II system[20] (Pie Medical BV, Maastricht, The Netherlands) in a core-lab setting (Cardialysis BV, Rotterdam, NL). An in-DCB region of interest was defined as that coronary segment between the two radiopaque markers of the DCB during inflation. In-segment region comprised the in-DCB segment plus 5mm proximal and 5mm distal. MLD was automatically detected by the software. RVD at the point of MLD was calculated by the software by interpolation. Percent diameter stenosis was calculated as: (1-[MLD/RVD])*100

OCT study and analysis

OCT pullbacks were obtained post-procedure and at 6 months follow-up with a Fourier-domain C7 system, using a Dragonfly catheter (Lightlab Imaging, Westford, MS, USA) at a rotation speed of 100 frames/sec using non-occlusive technique[21]. After infusion of intracoronary nitroglycerine, the optical catheter was withdrawn by a motorized pullback at a constant speed of 20 mm/second, while Iodixanol 320 contrast (Visipaque™, GE Health Care, Cork, Ireland) was infused through the guiding catheter at a continuous rate of 2-6 ml/sec.

OCT pullbacks were analysed offline in a core-laboratory (Cardialysis BV, Rotterdam, the Netherlands) by independent investigators blinded to the allocation and to clinical and procedural characteristics of the patients, using proprietary software (Lightlab Imaging, Westford, Massachusetts, USA). Cross-sections at 1mm intervals within the stented segment and 5mm proximal and distal to the stent edges were analyzed. Lumen and stent areas were calculated in each analysed cross-section. A metallic strut typically appears as a bright signal-intense structure with dorsal shadowing. Apposition was assessed strut by strut at baseline and follow-up by measuring the distance between the strut marker and the lumen contour[22]. The marker of each strut was placed at the endoluminal leading edge, in the mid-point of its

long-axis, and the distance was measured following a straight line connecting this marker with the gravitational centre of the vessel. Struts located at the ostium of side branches, with no vessel wall behind, were labelled as non-apposed side-branch (NASB) struts and excluded from the analysis of apposition. Struts were classified as malapposed (ISA, incomplete stent apposition) during the statistical analysis if their distance to lumen contour was ≥100µm, threshold resulting from rounding up the sum of the strut thickness (81µm) plus the axial resolution of OCT (14µm). Tissue coverage thickness was measured only at follow-up from the marker of each visible strut to the endoluminal edge of the tissue coverage, following a straight line connecting the strut marker with the gravitational centre of the vessel. A strut was considered non-covered when the thickness of coverage was 0µm. If the thickness of

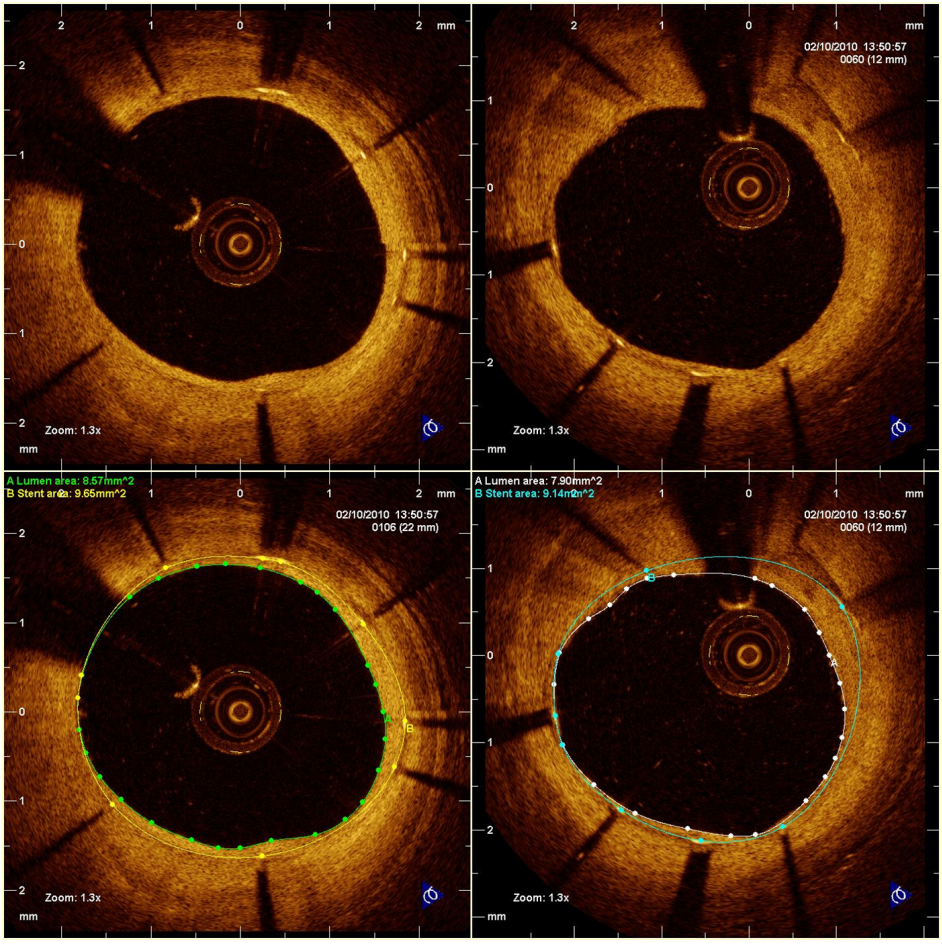

Figure 1:

Examples of cross-sections in the optical coherence tomography studies 6 months after treatment with the combination of Moxy DCB and BMS (upper panel): neointimal hyperplasia (NIH) area is calculated as [stent area – lumen area] (lower panel).

coverage was ≥60μm for any of the struts in the cross-section, neointimal hyperplasia (NIH) area was calculated (Figure 1). From lumen, stent and NIH areas and stent length, the corresponding volumes were calculated. In-stent percent neointimal volume obstruction (primary endpoint) was calculated as: (NIH volume / Stent volume) * 100

To summarize the spatial distribution of the non-covered struts along the stents, "spread-out vessel graphics" were created by correlating the longitudinal distance from the distal edge of the stent to the strut (abscises) with the angle where the struts were located in the circular cross-section section with respect to the gravitational centre of the vessel (ordinates), taking as reference 0º the position at three o'clock. The resultant graphic represented the stented vessel, as if it had been cut longitudinally along the reference angle 0º and spread out on a flat surface.

Assessment of longitudinal and axial mismatch (geographical miss)

Longitudinal geographical miss, defined as presence of ballooned or stented segments not covered in their whole length by the DCB application, was assessed by angiography in both treatment groups, using the stent and the edge markers of the corresponding balloons as references.

Axial geographical miss, defined as inability of the inflated DCB to contact the vessel wall at some regions of the stented segment, was exploratorily assessed in the group B (stent first), by means of graphics comparing the final stent area with the nominal area of the inflated DCB per cross-section. Thus, in those portions where stent area was bigger than the nominal inflated DCB area, axial geographical miss would be more likely to occur. This graphics were contrasted vs. the NIH area distribution along the stent, to explore a potential association between axial geographical miss and the extent of NIH.

Statistical analysis

Results are reported as mean±standard deviation for continuous variables, and as count (percent) for nominal variables. Continuous variables were compared with U-Mann-Whittney's test. Nominal variables were compared with Pearson's chi-square, or Fisher's exact test if the expected frequency was <5 in any cell.

In the OCT per strut analysis, the proportions of uncovered and ISA struts were analyzed using multi-level logistic regression models with random effects at 3 different levels: 1) treatment arm, 2) patient, 3) stent. Mean thickness of coverage was analyzed using a multi-level linear regression model with random effects at the same 3 levels, after logarithmic transform. Overlap segments were considered as separate units of clustering.

Clinical endpoints followed a hierarchical events model. Backward step logistic regression and proportional hazards Cox regression were used for 30 days and 6 months results, respectively.

All statistical analyses were performed according to the intention-to-treat principle, using the SAS v8.2 package (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Figure 2 shows the flow chart of the study. Between the 24th of June and the 15th of December 2009, 26 patients were enrolled and randomized. Two patients, both in the DCB-first group, withdrew consent after randomization, one of them before the 30 days visit, the other one between 30 days and 6 months. One of the angiographies and OCT studies in the BMS-first group were lost. One OCT study in each group was considered of insufficient quality to be analyzed. One patient in BMS-first underwent implantation of other type of stent than the one established per protocol (Skylor, Invatec S.p.a., Roncadelle, Brescia, Italy). Considering

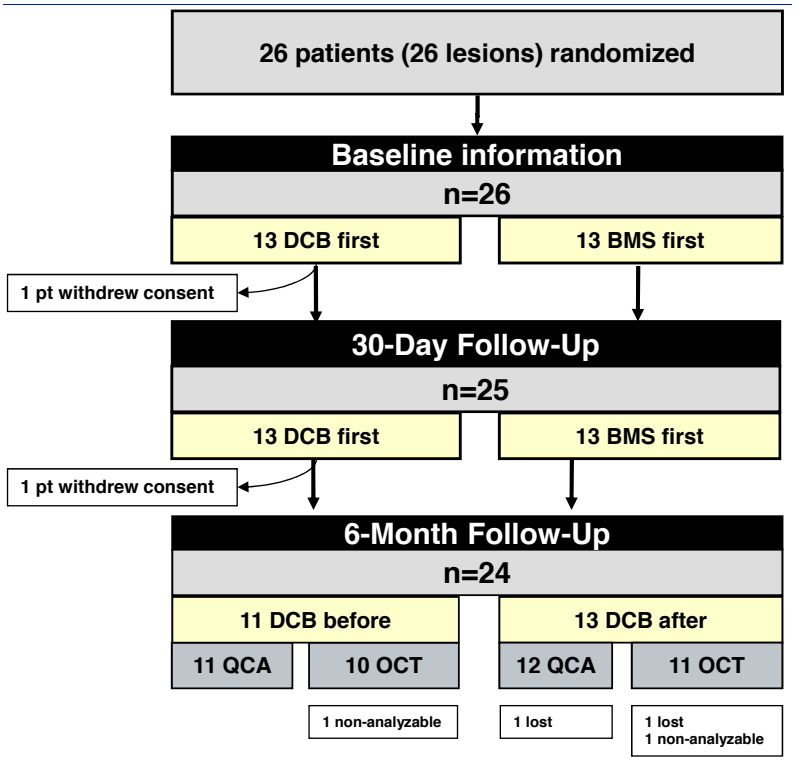

Figure 2:
Flow chart of the study patients, with allocation to treatment and loss at follow-up.

the similar characteristics of both types of stent, the steering committee decided not to exclude the patient from the analysis. Tables 1 and 2 show the baseline clinical and procedural characteristics of the patients, with no significant imbalance. Longitudinal geographical miss was only found in DCB first, although the difference did not reach statistical significance.

Table 3 presents the results of the QCA analysis. In spite of randomization, patients allocated to BMS-first had significantly smaller vessels than patients in DCB-first (RVD: 2.41 vs. 2.81mm, p=0.026, respectively). Late loss was non-significantly different between the groups (0.45 vs. 0.53 mm in-DCB, p=0.833).

Table 4 presents the OCT in-stent areas and volumetric analysis. Lumen and stent areas parallel the QCA findings of smaller vessels in BMS-first. There was no significant difference in in-stent % NIH volume obstruction (primary endpoint of the trial) between DCB-first and

Table 1: Baseline clinical characteristics of the groups.

	DCB before BMS n=13	**BMS before DCB n=13**	**p-value**	**All n=26**
Age (years)	57.4 ± 10.9	58.2 ± 11.0	0.724	57.8 ± 10.7
Male	10 (76.9%)	9 (69.2%)	1.000*	19 (73.1%)
BMI (kg/m2)	28.2 ± 4.6	26.8 ± 3.2	0.614	27.5 ± 3.9
Hypertension	7 (53.8%)	7 (53.8%)	1.000	12 (46.2%)
Hypercholesterolemia	9 (69.2%)	10 (76.9%)	1.000*	7 (26.9%)
Diabetes mellitus	3 (23.1%)	2 (15.4%)	1.000*	5 (19.2%)
Insulin	1 (7.7%)	0 (0.0%)	1.000*	1 (3.8%)
Oral antidiabetics	2 (15.4%)	2 (15.4%)	1.000*	4 (15.4%)
Smoking	9 (69.2%)	6 (46.2%)	0.234	11 (57.7%)
Ex-smoker	6 (46.2%)	4 (30.8%)	0.420	10 (38.5%)
Current smoker	3 (23.1%)	2 (15.4%)	1.000*	5 (19.2%)
Family history	9 (69.2%)	6 (46.2%)	0.226*	15 (57.7%)
Renal insufficiency	1 (7.7%)	0 (0.0%)	1.000*	1 (3.8%)
Stroke/TIA	1 (7.7%)	0 (0.0%)	1.000*	1 (3.8%)
CHF	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)
Previous MI	4 (30.8%)	4 (30.8%)	1.000*	8 (30.8%)
Previous PCI	2 (15.4%)	1 (7.7%)	1.000*	3 (11.5%)
Previous CABG	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)
Clinical indication				
Unstable angina	5 (38.5%)	6 (46.2%)	0.691	11 (42.3%)
Stable angina	8 (61.5%)	6 (46.2%)	0.431	14 (53.8%)
Silent ischemia	0 (0.0%)	1 (7.7%)	1.000*	1 (3.8%)

*Fisher's exact test.

BMI: Body mass index; BMS: Bare metal stent; BP: Blood pressure; CABG: Coronary artery by-pass graft; CHF: Cardiac heart failure; DCB: Drug-coated balloon; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; TIA: Transient ischemic attack.

Table 2: Procedural characteristics of the groups.

			DCB before BMS n=13	BMS before DCB n=13	p-value	All n=26
Diseased vessels	RCA		5 (38.5%)	6 (46.2%)	0.691	11 (42.3%)
	LAD		7 (53.8%)	6 (46.2%)	0.695	13 (50.0%)
	LCX		3 (23.1%)	7 (53.8%)	0.107	10 (38.5%)
Treatment vessel	RCA		5 (38.5%)	2 (15.4%)	0.378*	7 (26.9%)
	LAD		5 (38.5%)	6 (46.2%)	0.691	11 (42.3%)
	LCX		3 (23.1%)	5 (38.5%)	0.673*	8 (30.8%)
Moderate/heavy calcification			2 (15.4%)	1 (7.7%)	1.000*	3 (11.5%)
Bifurcation involved			1 (7.7%)	3 (23.1%)	0.593*	4 (15.4%)
DCB	Transit time (sec)		65.3 ± 33.2	68.7 ± 34.0	0.649	66.9 ± 32.8
	Time inflation (sec)		56.0 ± 21.6	61.2 ± 20.7	0.413	58.5 ± 20.9
	Max inflation press (atm)		9.0 ± 2.9	8.5 ± 2.9	0.880	8.8 ± 2.8
Need for a 2nd DCB			1 (7.7%)	2 (15.4%)	1.000*	3 (11.5%)
BMS	Nr stents implanted		1.2 ± 0.4	1.1 ± 0.3	0.511	1.2 ± 0.4
	Need for additional stents		3 (23.1%)	1 (7.7%)	0.593*	4 (15.4%)
		Residual stenosis	1 (7.7%)	0 (0.0%)	1.000*	1 (3.8%)
		Lesion not covered by BMS	1 (7.7%)	0 (0.0%)	1.000*	1 (3.8%)
		Dissection	2 (15.4%)	1 (7.7%)	1.000*	3 (11.5%)
Device success			13 (100.0%)	13 (100.0%)	NA	26 (100.0%)
Post-dilatation			7 (53.8%)	5 (38.5%)	0.431	12 (46.2%)
Longitudinal geographical miss			3 (23.1%)	0 (0.0%)	0.220*	3 (11.5%)
Angiographic complications						
	Coronary dissection not repaired		1 (7.7%)	0 (0.0%)	1.000*	1 (3.8%)

*Fisher's exact test.

BMS: Bare metal stent; DCB: Drug-coated balloon; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery.

Table 3: Quantitative coronary angiography (QCA) results.

	DCB before BMS	BMS before DCB	p-value	All
Lesion length (mm)	10.7 ± 4.9	11.2 ± 5.1	0.960	10.9 ± 4.9
RVD (mm)	2.81 ± 0.45	2.41 ± 0.37	**0.026**	2.61 ± 0.45
MLD (mm)	1.07 ± 0.28	0.91 ± 0.23	0.204	0.99 ± 0.26
% diam stenosis	61.8 ± 9.4	61.9 ± 8.1	0.920	61.8 ± 8.6
In-DCB				
Acute gain (mm)	1.42 ± 0.45	1.09 ± 0.42	0.087	1.26 ± 0.46
Late loss (mm)	0.53 ± 0.52	0.45 ± 0.57	0.833	0.49 ± 0.54
Binary restenosis	1 (9.1%)	2 (16.7%)	1.000*	3 (13.0%)
In-segment				
Acute gain (mm)	1.20 ± 0.40	0.90 ± 0.41	0.098	1.06 ± 0.43
Late loss (mm)	0.52 ± 0.65	0.31 ± 0.41	0.651	0.41 ± 0.54
Binary restenosis	3 (27.3%)	2 (16.7%)	0.640*	5 (21.7%)

Table 4: Optical coherence tomography (OCT) areas and volumes: in-stent analysis.

		DCB before BMS 10 pt, 11 stents	BMS before DCB 12 pt, 12 stents	p-value	All 22 pt, 23 stents
Post-implant	**Stent length (mm)**	14.91 ± 6.47	17.48 ± 3.77	0.151	16.25 ± 5.28
	Min stent area (mm^2)	7.77 ± 2.36	5.30 ± 1.46	**0.013**	6.49 ± 2.28
	Mean stent area (mm^2)	9.11 ± 2.38	6.50 ± 1.79	**0.013**	7.75 ± 2.44
	Stent volume (mm3)	134.99 ± 75.77	114.71 ± 41.86	0.928	124.41 ± 59.94
	% frames with ISA	18.7 ± 17.7	7.2 ± 9.5	0.091	12.7 ± 14.9
	Max ISA area (mm^2)	1.21 ± 1.41	0.47 ± 0.65	0.190	0.82 ± 1.12
	ISA volume (mm3)	2.14 ± 1.89	0.70 ± 1.08	0.051	1.39 ± 1.66
	ISA volume (%of stent vol)	2.24 ± 2.53	0.52 ± 0.77	0.118	1.34 ± 2.00
6 months follow-up	**MLA (mm^2)**	4.94 ± 2.88	3.48 ± 2.41	0.270	4.21 ± 2.69
	Mean lumen Area (mm^2)	6.86 ± 2.91	5.14 ± 2.17	0.193	6.00 ± 2.65
	Lumen volume (mm3)	95.75 ± 57.32	90.68 ± 38.56	0.748	93.22 ± 47.74
	% frames with ISA	4.06 ± 7.05	0.57 ± 1.88	0.270	2.31 ± 5.34
	Max ISA area (mm^2)	0.43 ± 0.68	0.03 ± 0.09	0.243	0.23 ± 0.52
	ISA volume (mm3)	0.56 ± 0.88	0.02 ± 0.08	0.243	0.29 ± 0.67
	ISA volume (% of stent vol)	0.37 ± 0.75	0.02 ± 0.08	0.243	0.20 ± 0.55
	Max NIH area (mm^2)	4.02 ± 1.77	2.93 ± 1.74	0.151	3.48 ± 1.80
	NIH volume (mm3)	30.14 ± 23.71	27.35 ± 14.41	0.974	28.74 ± 19.20
	% NIH vol obstruction	25.3 ± 15.9	24.9 ± 13.5	0.922	25.1 ± 20.8

BMS-first groups (25.5 vs. 24.9%, p=0.922, respectively). No correction for stent volume was required for the primary endpoint, because % NIH volume obstruction is by definition corrected for stent size. Table 5 presents the OCT areas and volumetric analysis of the stent edges. The exploratory assessment of axial geographical miss in BMS-first (figure 3) did not show any clear association between axial DCB-BMS mismatch and the extent of local NIH. In the per-strut analysis, apposition immediately post-implantation tended to be worse in DCB first compared to BMS first (table 6). Although the absolute proportion of ISA struts was substantially reduced in both groups at 6 months, the difference became then significant (0.1 vs. 2.3%, p<0.0001). Also the proportion of uncovered struts tended to be higher in DCB-first than in BMS-first (9.1% vs. 5.3%, p=0.237, respectively), without significant differences in thickness of coverage (p=0.575). After correction for vessel size (mean stent area), the difference in proportion of ISA struts still remained significant at 6 months (p=0.013). The spread-out vessel charts summarize the spatial distribution and clustering of uncovered struts (figure 4). Uncovered struts cluster in some subjects, in some regions within a stent, or around the overlap segment.

Table 7 summarizes the clinical and safety secondary endpoints at 30 days and 6 months follow-up. Median follow-up time was 181 days (IQ range: 171 – 186.25): 176 days in group A (IQ range: 162.5 – 185), 181 days in group B (IQ range: 175 – 188).

Table 5: Optical coherence tomography (OCT) areas and volumes: analysis of the stent edges.

Post-implant		DCB before BMS	BMS before DCB	p-val	All
Proximal edge	n	10	12		22
	Length (mm)	4.12 ± 1.54	4.94 ± 0.30	0.418	4.57 ± 1.11
	MLA (mm^2)	7.03 ± 3.37	5.73 ± 2.50	0.314	6.32 ± 2.92
	Mean lumen area (mm^2)	8.35 ± 3.44	6.79 ± 2.32	0.254	7.50 ± 2.92
	Lumen volume (mm3)	33.66 ± 13.96	33.29 ± 10.93	0.628	33.46 ± 12.09
	% frames with dissection	15.00 ± 24.15	20.83 ± 36.32	0.974	18.18 ± 30.82
Distal edge	n	9	11		20
	Length (mm)	4.47 ± 1.27	4.30 ± 1.29	0.941	4.37 ± 1.25
	MLA (mm^2)	5.88 ± 1.79	4.54 ± 1.71	0.201	5.14 ± 1.83
	Mean lumen area (mm^2)	6.97 ± 1.52	5.32 ± 1.79	0.056	6.06 ± 1.84
	Lumen volume (mm3)	30.44 ± 10.45	23.27 ± 10.77	0.201	26.50 ± 10.97
	% frames with dissection	18.15 ± 29.68	16.67 ± 26.87	1.000	17.33 ± 27.41
6 months follow-up					
Proximal edge	n	10	11		21
	Length (mm)	4.64 ± 1.21	5.00 ± 0.00	1.000	4.83 ± 0.83
	MLA (mm^2)	5.57 ± 2.11	4.88 ± 2.68	0.557	5.20 ± 2.39
	Mean lumen area (mm^2)	7.87 ± 2.75	6.33 ± 2.98	0.314	7.06 ± 2.91
	Lumen volume (mm3)	37.24 ± 16.59	31.63 ± 14.89	0.512	34.30 ± 15.59
Distal edge	n	9	11		20
	Length (mm)	5.00 ± 0.00	4.20 ± 1.40	0.175	4.56 ± 1.09
	MLA (mm^2)	5.15 ± 1.97	3.83 ± 2.70	0.370	4.42 ± 2.43
	Mean lumen area (mm^2)	6.05 ± 1.82	4.54 ± 3.14	0.261	5.22 ± 2.68
	Lumen volume (mm3)	30.25 ± 9.11	20.31 ± 16.03	0.175	24.79 ± 14.00

DISCUSSION

To the best of our knowledge this is the first randomized trial testing the efficacy of a DCB with an OCT primary endpoint. The results suggest that the sequential application of DCB and not-premounted BMS for the treatment of de novo coronary lesions is feasible and inhibits neointimal hyperplasia efficiently. The overall in-stent NIH volume obstruction (primary endpoint) and the mean thickness of coverage (25.1% and 242µm, respectively) are comparable to the ones reported for paclitaxel-eluting stents (22.2 – 25.8%, 200 - 240µm)[23,24], lower than in some DES and far from those in BMS (53.9%, 530µm)[23]. Also the proportion of uncovered struts (7%) is in the range of paclitaxel-eluting stents (5 – 7%), lower than in sirolimus eluting stents (8%), but higher than in BMS (1%)[23,24]. These OCT findings constitute an additional evidence of the biological effect exerted by DCB in the modulation of neointimal hyperplasia after stenting. Clinical and angiographic studies had already proven the concept consistently[16-18], but this is the first time to quantify this effect with OCT, what will be interesting for the design of future studies.

Table 6: Optical coherence tomography (OCT) analysis of apposition and coverage per strut: prespecified analysis and after correction by vessel size (mean stent area).

	DCB first	BMS first	OR (95% CI)	p-val	All
Post-implant	10 patients 10 lesions 11 stents 1849 struts	12 patients 12 lesions 12 stents 2025 struts			22 patients 22 lesions 23 stents 3874 struts
Apposition					
Well-apposed	1644 (88.9%)	1902 (93.9%)	0.53 (0.24, 1.15) 0.54 (0.21, 1.42)*	0.106 0.213*	3546 (91.5%)
ISA	187 (10.1%)	110 (5.4%)	1.91 (0.81, 4.51) 1.82 (0.66, 5.04)*	0.139 0.247*	297 (7.7%)
NASB	18 (1.0%)	13 (0.6%)	1.51 (0.45, 5.07) 1.81 (0.51, 6.39)*	0.507 0.357*	31 (0.8%)
6 months follow-up	10 patients 10 lesions 11 stents 1580 struts	11 patients 11 lesions 11 stents 1785 struts			21 patients 21 lesions 22 stents 3365 struts
Apposition					
Well-apposed	1536 (97.2%)	1779 (99.7%)	**0.10 (0.02, 0.55)** 0.21 (0.03, 1.68)*	**0.008** 0.143*	3315 (95.8%)
ISA	37 (2.3%)	2 (0.1%)	**25.57 (5.58, 117.47)** **12.56 (1.70, 93.10)***	**<0.0001** **0.013***	39 (1.2%)
NASB	7 (0.4%)	4 (0.2%)	1.79 (0.21, 14.92) 0.63 (0.09, 4.26)*	0.592 0.638*	11 (0.3%)
Coverage					
Covered struts	1437 (90.9%)	1690 (94.7%)	0.47 (0.14, 1.63) 0.89 (0.25, 3.11)*	0.237 0.857*	3127 (92.9%)
Thickness of coverage (μm)	261 (238)*	225 (195)*			242 (217)
Corrected mean (μm)†	104	132	0.78 (0.32, 1.90) 1.15 (0.43, 3.08)*	0.575 0.763*	

Data reported as # (%), except for the thickness of coverage, reported as mean (SD).

*Estimation of the effect after correction by vessel size (mean stent area).

† Ln transformed. Estimate or the effect and confidence intervals represent group A/group B ratio.

Table 7: Clinical and safety secondary endpoints at 30 days and 6 months.

	30d				6m			
	DCB before BMS n=13	BMS before DCB n=13	p-value	All n=26	DCB before BMS n=13	BMS before DCB n=13	p-value	All n=26
Death	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)
MI	0 (0.0)	1 (7.7)	0.232	1 (3.8)	0 (0.0)	2 (15.4)	0.166	2 (7.7)
TVR	1 (7.7)	0 (0.0)	0.232	1 (3.8)	3 (23.1)	2 (15.4)	0.628	5 (19.2)
TLR	0 (0.0)	0 (0.0)	NA	0 (0.0)	2 (15.4)	2 (15.4)	0.987	4 (15.4)
Death, MI, TLR	0 (0.0)	1 (7.7)	0.232	1 (3.8)	2 (15.4)	4 (30.8)	0.432	6 (23.1)
Bleeding	0 (0.0)	2 (15.4)	0.086	2 (7.7)	0 (0.0)	2 (15.4)	0.149	2 (7.7)
Stent thrombosis	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)

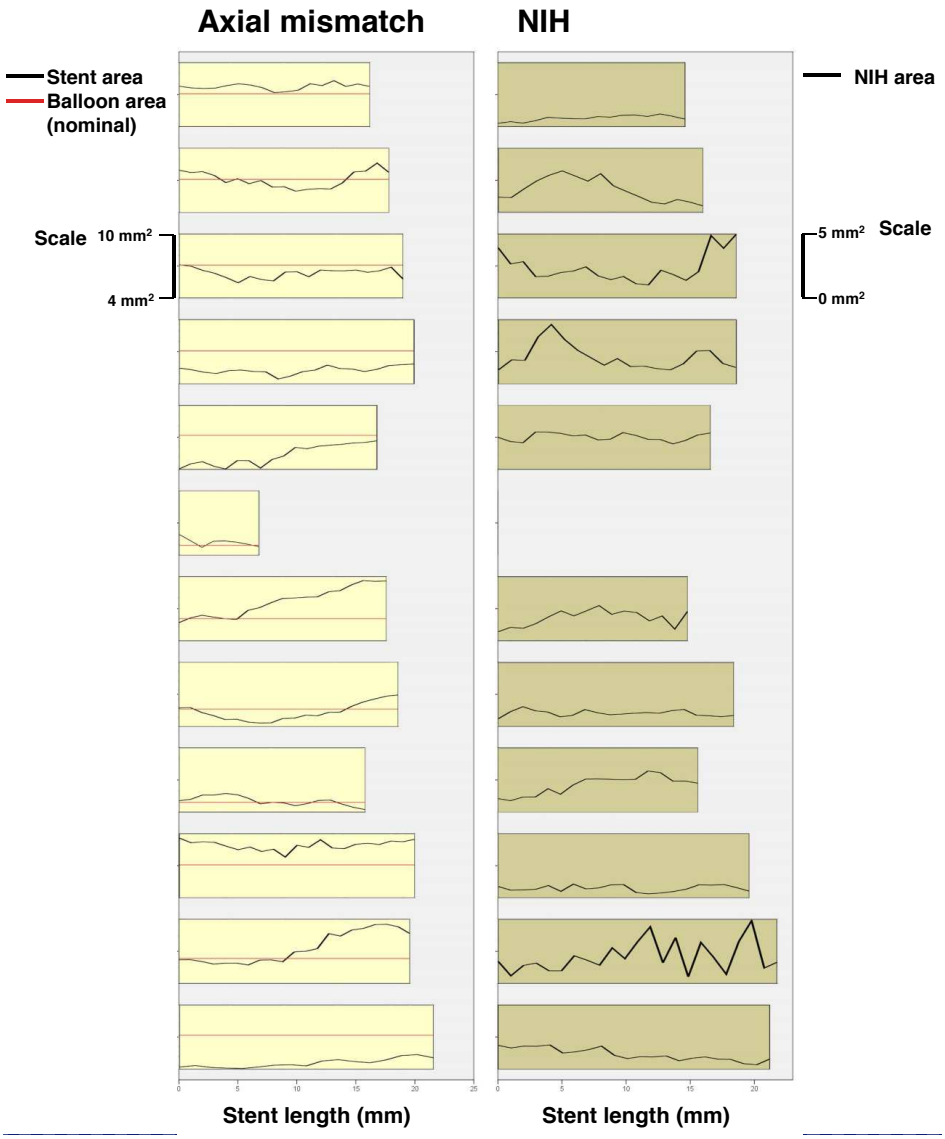

Figure 3:

Exploratory assessment of axial geographical miss post-implantation (left panel) and its eventual association with local neointimal hyperplasia (NIH, right panel) in the group B of the study (BMS before DCB).

The bars in the left panel represent the length of each implanted stent. The black and red lines represent the stent area and the nominal area of the inflated balloon, respectively, in each cross-section. Thus, in those regions where the stent area is higher than the nominal inflated balloon area (black above red), axial mismatch would be more likely to occur. The black line in the right panel represents the local NIH area at 6 months in the corresponding stents. At first glance, no clear relation between NIH and axial geographical miss can be concluded.

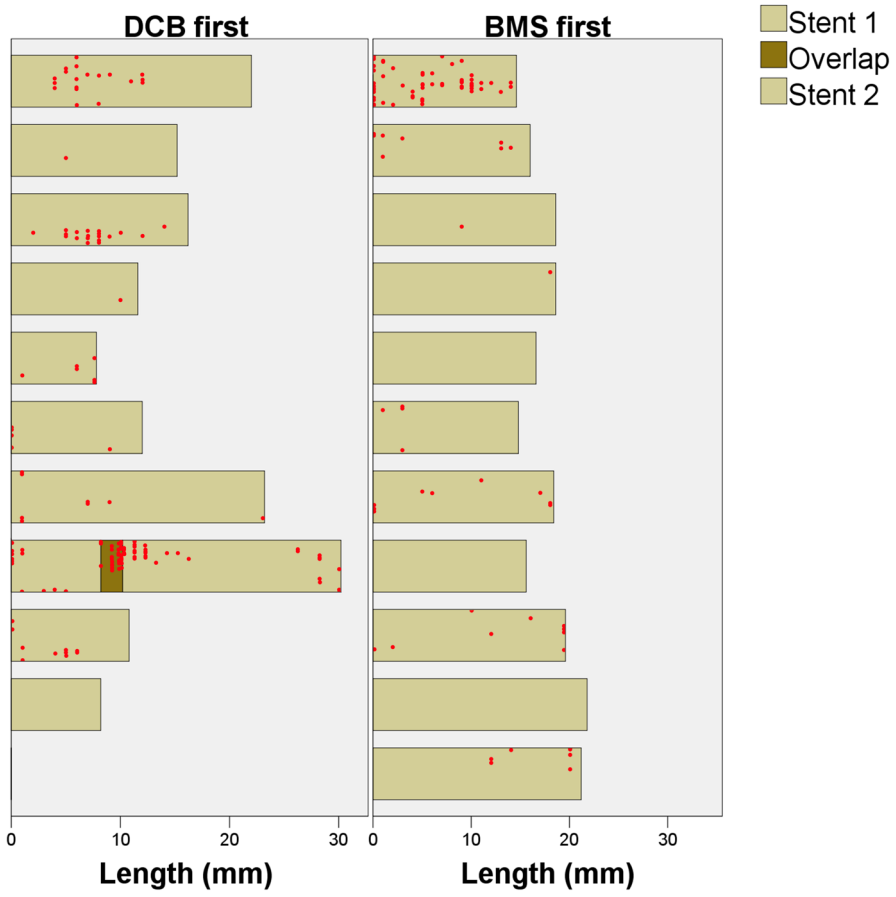

Figure 4:

Spread-out-vessel charts showing the spatial distribution of uncovered struts at 6 months in both treatment groups. The graphic summarizes the clustering effect at the three levels: 1) allocation to treatment (right vs. left panel), 2) patient/lesion (bars are summaries per patient/lesion), 3) stent. The regional clustering within the stented region is also represented.

The sequence "BMS first" translated into better apposition than "DCB first", as reflected by significantly lower proportion of ISA struts and a non-significant trend to lower ISA areas and volumes. Although initially the sequence "BMS first" seemed to have also better coverage profile (higher proportion of covered struts at 6 months, with thinner tissue coverage), the log transform suggests that the neointimal coverage is actually comparatively thicker in this group, and the adjusted analysis suggests that these differences in coverage are mainly due to the smaller vessel size than to the allocation to treatment. Therefore both therapeutic strategies are comparable in terms of coverage at 6 months, but the sequence BMS first results in better apposition. Except from this advantage, there were no significant differences between treatment

groups in the primary endpoint or in any of the remaining secondary endpoints. Thereafter the initial working hypothesis could not be confirmed. The results about the primary endpoint and struts coverage do not suggest that the application of DCB first actually results in better contact with the vessel wall, better transfer of the paclitaxel and therefore more effective action. Likewise, the idea that the implantation of BMS first would reduce the incidence of longitudinal geographical miss and hence be more efficient in real-world practice in spite of an eventually suboptimal contact between the DCB and the vessel wall, was not either confirmed: although no single case of geographical miss was certainly observed in the group "BMS first", this did not seem to have any impact in any of the efficacy endpoints.

The results of this exploratory study suggest that the deployment of BMS first might ease the recognition of the target region and reduce the longitudinal geographical miss. However, this strategy might also result in an incomplete contact between the DCB and the vessel wall at some points, when the former is inflated inside the stent (axial geographical miss). The documentation of axial mismatch is more challenging. In this study we introduce a graphic method to assess axial geographical miss, as already explained, and explore its potential association with regional NIH. The results, however, do not suggest any direct relation in this respect. Likewise, although axial mismatch is a common finding among the patients in BMS-first, this does not entail worse outcome in any of the tested endpoints. It seems that geographical miss, either longitudinal or axial, influences the results at a lesser extent than currently believed. A potential explanation for this finding might be the diffusion kinetics of paclitaxel. Posa et al. demonstrated in a coronary swine model that paclitaxel diffuses not only axially but also longitudinally into the vessel wall after DCB application[25]. Thus, a homogeneous inhibitory effect might be achieved, even though the contact with the vessel wall were suboptimal or the application were slightly distant from the target point. Further investigation to clarify these findings is warranted.

The spread-out vessel charts offer an intuitive graphic representation of the spatial distribution and clustering of struts uncoverage. For instance, the effect of stent overlap can be easily understood with this representation. The graphic also depicts the complexity of healing after stenting, still poorly understood, with large interindividual and regional variability within some patients. This marked clustering phenomenon highlights the importance of choosing an appropriate statistical method for the analysis of OCT data, in order to avoid misleading conclusions.

Limitations

This was a pilot study with small sample size, conceived to explore the effect of a novel DCB on the treatment of de novo coronary lesions. The results of several efficacy variables were in the expected ranges of paclitaxel-eluting stents, what is a relevant finding, but careful extrapolation of these results must be warned, because this was not a proper comparative

study vs. a different device. Likewise, a bigger sample size might have contributed to understand better the role played by the sequence of application.

Randomization resulted in a homogeneous distribution of all the control variables, except the vessel size. Although the primary endpoint was by definition corrected for vessel size, a statistical correction was required for the other efficacy endpoints. Sensitivity analysis including mean stent area as covariate circumvented this limitation in the per strut analysis. Mean stent area resulted to be a significant confounding factor for apposition (only affecting the proportion of NASB struts: the bigger the vessel, the more NASB struts) and for coverage (the bigger the vessel, the more proportion of uncovered struts and the thinner the coverage). The results of this sensitivity analysis, in which the inclusion of vessel size in the model significantly modified the magnitude of some effects, and in some cases even reversed the sense of the association, are also hereby reported.

Angiographic late loss was slightly higher than initially expected in this trial (overall in-stent 0.49mm), despite the relatively small size of the vessels. Other paclitaxel-coated balloons with hydrophilic carriers had reported in-stent late loss of 0.09 and 0.19mm for the treatment of in-stent restenosis[16,18]. Likewise, the rates of binary restenosis (overall in-segment 21.7%) at 6 months are clearly higher than previously reported by other DCB in other clinical scenarios (in-segment 5-7%)[16,18]. These findings might be related to the reduced paclitaxel dose of the Moxy balloon or to a less efficient transfer of the drug by the carrier. Further investigation will be required to better understand the reasons why this technology yields optimal results, comparable to paclitaxel-eluting stents, in some cases, but cannot avoid restenosis in others.

CONCLUSION

Sequential application of a paclitaxel-coated balloon in combination with a not-premounted BMS for the treatment of de novo coronary lesions is feasible and results in efficient inhibition of neointimal hyperplasia. The sequence of application (balloon first vs. BMS first) does not seem to influence the outcome, except for a significantly better apposition if the BMS is deployed first.

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"Il raziocinio è un lume che uno può accendere quando voule obbligar gli altri a vedere, e può soffiarci sopra quando non vuo più veder lui".

(Reason is a light that one can turn on to compel the others to see, but one can also blow on it when oneself does not want to see any more)

Dell'invenzione

Alessandro Manzoni

PART 2

COVERED STENTS

CHAPTER 4

Covered stent in saphenous vein graft

"Over-and-Under" pericardial covered stent with paclitaxel balloon in a saphenous vein graft.

Wykrzykowska JJ, Gutiérrez-Chico JL, van Geuns RJ.

Catheter Cardiovasc Interv 2010;75:964-966.

ABSTRACT

Treatment of vein graft disease remains a challenge in interventional cardiology because of the risk of embolization and no-reflow phenomenon. Currently available distal protection devices have their limitations. The PTFE-covered stents may be well suited for venous graft lesion treatment, but those available commercially to date have poor crossing profiles, and deliverability and high rates of restenosis. We report the first use of over-and-under pericardium-covered stent in combination with drug-eluting balloon to treat venous graft disease.

CASE PRESENTATION

A 75-year-old man with past history of anterior myocardial infarction in 1981 and subsequent bypass surgery with venous graft to the LAD/D1 and venous graft to the RCA, subsequent RCA graft occlusion and LAD graft ostial stenting in 2007, now returned with symptoms of unstable angina. His risk factors included poorly controlled diabetes treated with insulin, hypercholesterolemia, hypertension and significant family history. Diagnostic angiography revealed severe three vessel disease with significant right coronary artery disease and ostial LAD graft in-stent restenosis.

We performed direct stenting with Xience V 3.0 X 28 mm (Xience V, Abbott, Santa Barbara, CA) of the RCA without complications. The attention was then turned to the graft. A 6 Fr JR4 catheter provided good support and the lesion was crossed easily with a Pilot 50 hydrophilic wire (Pilot 50, Abbott, Santa Barbara, CA). Given the risk of embolization in this 28-year-old graft, we elected to use a covered "over-and-under" equine pericardial covered stent (ITGI Medical, Or Akiva, Israel) combined with an application of the paclitaxel drug eluting balloon (Dior, EuroCor, Bonn, Germany). In addition to angiography (Figure 1A), intravascular ultrasound (IVUS) grey scale with a 20 MHz Eagle eye S5 Volcano catheter (Eagle Eye S5, Volcano Corp., San Diego, CA) was performed showing severe in stent restenosis (Figure 1B). The lesion was predilated with a non-compliant balloon given some degree of calcification seen on IVUS (Figure 1 B, C). A 3.5 x 20 mm Dior paclitaxel eluting balloon was applied at 6-8 atms for 30 seconds twice. Optical Coherence Tomography (OCT) with C7 Lightlabs sytem (C7-XR, LightLab Imaging Inc, Westford, MA) was also performed after predilation to size the vessel. 3.5 x 23 mm "Over-and-under" pericardial stent delivered easily and was deployed at 16 atms. Postdilation with a 3.5 x 15 mm non-compliant balloon was performed at 18 atms to achieve the most optimal result. OCT was repeated showing good stent apposition and presence of stent suture lines (Figure 2; arrows). Final angiography showed good result with

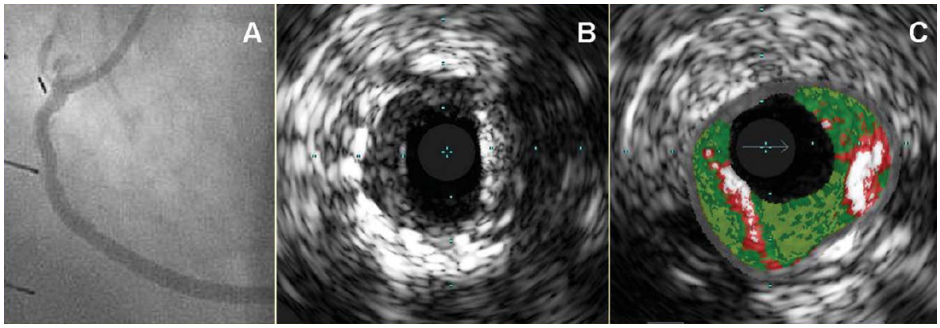

Figure 1:
A. Baseline angiography showing ostial graft in-stent restenosis. B. Initial IVUS assessment showing the MLD with complex plaque and calcifications. C. IVUS-VH.

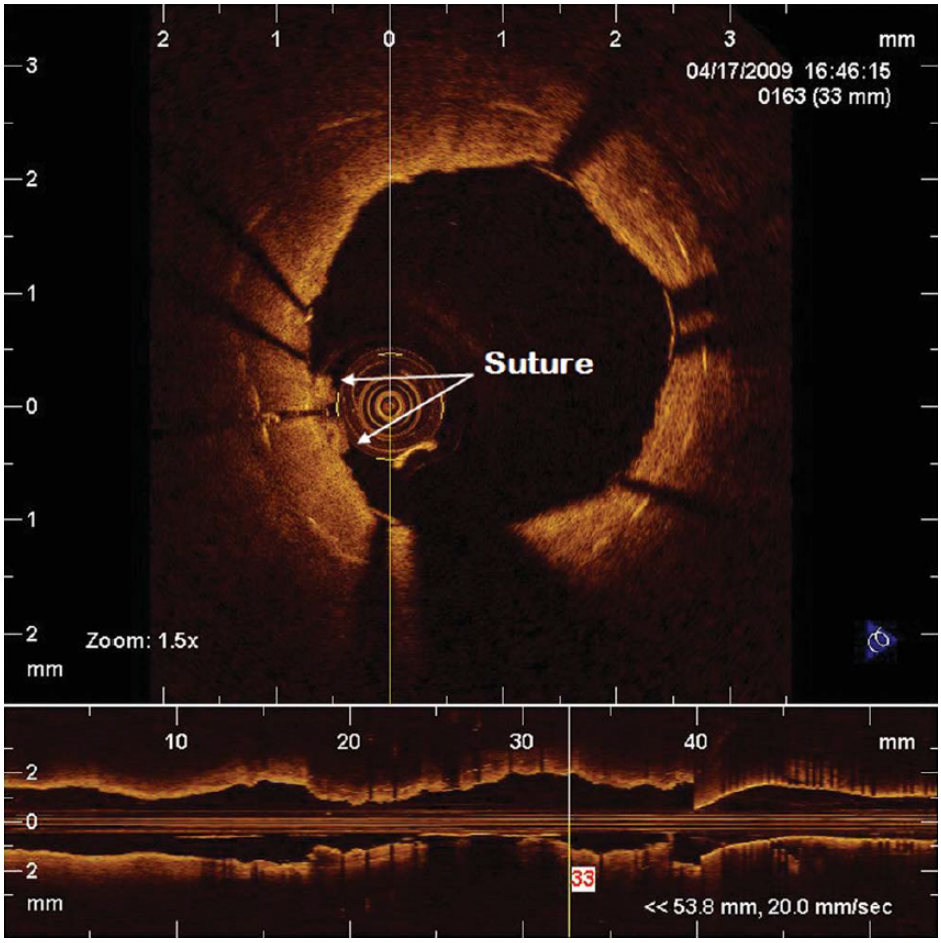

Figure 2:
OCT after stenting showing good apposition and presence of suture lines (arrows).

TIMI III flow (Figure 3). The patient tolerated the procedure well without biomarker evidence of periprocedural infarction.

The patient returned 6 months later with symptoms of unstable angina and both angiography and OCT demonstrated in-segment (edge) restenosis. This was treated with an everolimus eluting Xience V stent with good result.

CASE DISCUSSION

Interventions on venous grafts continue to present a challenge to an interventional cardiologist. Particularly grafts older than 20 years, as in our case, tend to have high degree

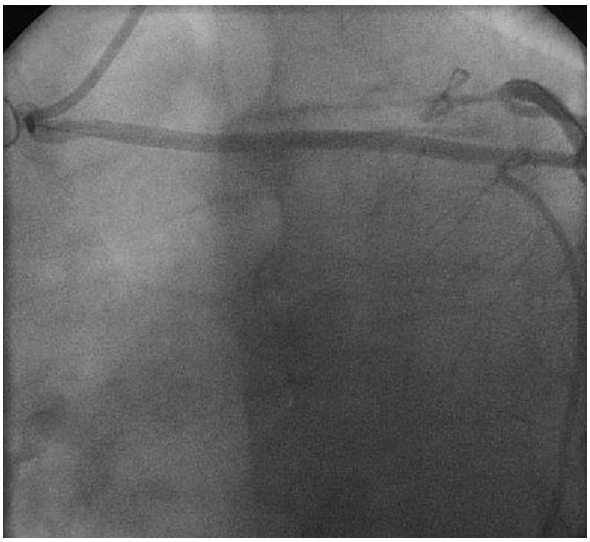

Figure 3: Final angiography with TIMI III flow.

of friable atheromatous plaque, which is prone to embolization and may cause no-reflow phenomenon with periprocedural myocardial infarction and its consequent mortality.[1] Angiographic assessment of plaque burden does not predict with high accuracy the risk of periprocedural complications and which patients would benefit from devices such as distal protection devices.[2] Distal protection devices have been shown to reduce complications, however, they suffer from certain limitations.[3] Protruding friable plaque through the stent struts may continue to micro-embolize post-stent placement.

Covered stents would appear to be well suited for treatment of venous graft atheroma. PFTE covered devices such as Jomed stent were limited, however, by poor flexibility and deliverability as well as in-stent restenosis.[4] Our own group has circumvented the latter problem by placing a drug eluting stent within the covered stent.[5] "Over-and-under" pericardial covered stent is a novel technology that may be more deliverable and have a better crossing profile.[6] It is more biocompatible than PTFE and therefore promises to have less in-stent restenosis. Unfortunately, in this case the patient returned with in-segment restenosis potentially due to the shorter length of the drug eluting balloon than the pericardium covered stent. This maybe also due to the fact that the first generation Dior balloon with lower concentration of paclitaxel was used and therefore less drug was delivered at the edges of the stent.

The manner of deployment is such that stent edges deploy before the middle of the stent, thereby effectively trapping the friable atheroma behind the pericardium and preventing embolization. Our patient had no biomarker evidence of microembolization and no periprocedural myocardial infarction. To further minimize the risk of in-stent restenosis, we pretreated the vessel with a paclitaxel drug-eluting balloon. This technology has been shown to be effective for treatment of in-stent restenosis and de novo disease.[7-9] To our knowledge,

this is the first report of combined use of the drug eluting balloon with a pericardium covered "over-and-under" stent. A systematic registry or randomized study will be needed to further assess the safety and feasibility as well as efficacy of the combined use of the two devices. Careful assessment of the drug elution profile and how it is altered by the presence of the pericardium, as well as weather application directly on the vessel wall versus on the pericardium post-stenting is preferable will be needed, to prevent edge restenosis as seen in this case. In addition as illustrated here, particular attention to ensuring drug elution at the edges of the stent is important for future restenosis risk.

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"De querer ser a creer que se es ya, va la distancia de lo trágico a lo cómico".

(From "wanting to be" to "believing to be" goes the distance between tragedy and comedy)

Meditaciones del Quijote

José Ortega y Gasset

PART 3

SELF-EXPANDABLE BARE METAL STENTS

CHAPTER 5

Self-expandable stents for vulnerable plaque treatment

Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT).

Wykrzykowska JJ, Diletti R, Gutiérrez-Chico JL, van Geuns RJ, van der Giessen WJ, Ramcharitar S, Duckers HE, Schultz C, de Feyter P, van der Ent M, Regar E, de Jaegere P, Garcia-Garcia HM, Pawar R, Gonzalo N, Ligthart J, de Schepper J, van den Berg N, Milewski K, Granada JF, Serruys PW.

EuroIntervention 2012;8:945-954.

ABSTRACT

Aims: The aim of the pilot SECRITT trial was to evaluate the safety and feasibility of sealing the high risk IVUS and optical coherence tomography-derived thin cap fibroatheroma (TCFA), with a dedicated nitinol self-expanding vShield device.

Methods and results: After screening with angiography, fractional flow reserve (FFR), intravascular ultrasound virtual histology (IVUS-VH) and optical coherence tomography (OCT), 23 patients met enrolment criteria (presence of non-obstructive VH-derived TCFA lesion with thin cap on OCT) and were randomised to vShield (n=13) versus medical therapy (n=10). In the shielded group, baseline percent diameter stenosis was 33.2±13.5%, FFR was 0.93±0.06. At six-month follow-up in shielded patients percent diameter stenosis further decreased to 18.7±16.9% and FFR remained the same 0.93±0.05. Average late loss was 0.24±0.13 mm. Average baseline fibrous cap thickness was 48±12 µm. After shield placement at six-month follow-up neo-cap formation was observed with average cap thickness of 201±168 µm. There were no dissections after shield placement and no plaque ruptures. In addition, mean stent area of 8.76±2.16 mm2 increased to 9.45±2.30 mm^2, that is by 9% at six-month follow-up. The number of malapposed struts decreased from 10.7% to 7.6% and the number of uncovered struts at six months was 8.1%. There were no device-related major adverse cardiovascular events (MACE) events at six-month follow-up.

Conclusion: High risk plaque passivation and sealing with a vShield self-expanding nitinol device appears feasible and safe. A long-term larger randomised study with streamlined screening criteria is needed to evaluate the efficacy of this approach over medical therapy.

ABBREVIATIONS

TCFA: thin cap fibroatheroma
CSA: cross-sectional area
MI: myocardial infarction
ARC: Academic Research Consortium
ISA: incomplete stent apposition
MACE: major adverse cardiovascular events
IVUS: intravascular ultra-sound
IVUS-VH: intravascular ultrasound virtual histology
OCT: optical coherence tomography
PCI: percutaneous coronary intervention
QCA: quantitative coronary angiography
FFR: fractional flow reserve

INTRODUCTION

Our current understanding of the pathogenesis of acute coronary syndrome, the progression of coronary artery disease and sudden death is that 70% of the time patients with atherosclerosis and fatal myocardial infarction incur plaque rupture of the so-called thin cap fibroatheroma and in the rest of the cases pathology reveals plaque erosion or calcified nodule[1-3]. Many of these plaques have gone undetected by conventional coronary angiography because the underlying lesion was non-obstructive (<50% diameter stenosis) due to the so-called Glagov effect (positive remodelling at the site of large plaque burden). High-risk plaque is defined as a large lipid pool , thin cap (less than 65 µm) and macrophage dense inflammation, as well as positive remodeling[2, 4-6]. The majority of these plaques occur in the proximal portion of the three major epicardial coronary arteries[7, 8]. It is also becoming clear that obstructive plaques (with minimal luminal area < 4mm^2) can also be high risk and identify a patient at risk of future events. In fact these plaques have been shown to result in the highest number of events in the PROSPECT trial[9], the first prospective natural history study of atherosclerosis using multimodality imaging. Currently there are two strategies to manage patients with thin cap fibroatheromas: 1) Conservative medical therapy based on the premise that none of the imaging modalities to-date have been able to identify reliable features of the plaque that render it prone to major adverse cardiac events, and 2) focal treatment to seal and passivate the plaque. The latter approach has been recently demonstrated in the VELETI trial to prevent progression of disease in vein grafts with non-obstructive lesions[10]. The SECRITT trial is a randomised, controlled pilot study that evaluates the safety and feasibility of sealing the high risk IVUS and OCT-derived TCFA with a dedicated nitinol self-expanding vShield device. As such, it is the first trial of a dedicated device for treatment of "vulnerable plaque" in native coronary arteries.

METHODS

Device description

The vProtect™ luminal shield system (Prescient Medical, Inc., Doylestown, PA, USA) consists of the self-expanding (nitinol) vascular shield **(Figure 1A)** and a rapid exchange delivery system. The delivery system is compatible with 0.014" guidewires and 6 Fr guiding catheters. The delivery system consists of a distal outer sheath that houses the luminal shield and an inner body with radiopaque markers at the distal and proximal ends of the shield. The luminal shield is constructed from a nickel-titanium alloy with an austenitic finish. The shield has a wall thickness that is less than 70 µm and has been designed with the objective to match the elastic properties of the TCFA. The shield is available in 3.5 mm, 4.0 mm and 4.5 mm diameter

with a length of 15 mm for all the diameters. This allows vessels of between 2.75 mm to 4.0 mm to be treated. The distinctive feature of the shield is the hysteresis between the inward radial resistive force and the outward force exerted on the vessel wall. The latter is very low not exceeding 100 mm Hg **(Figure 1B)** thereby minimising the trauma to the vessel wall and potential for plaque rupture during the deployment.

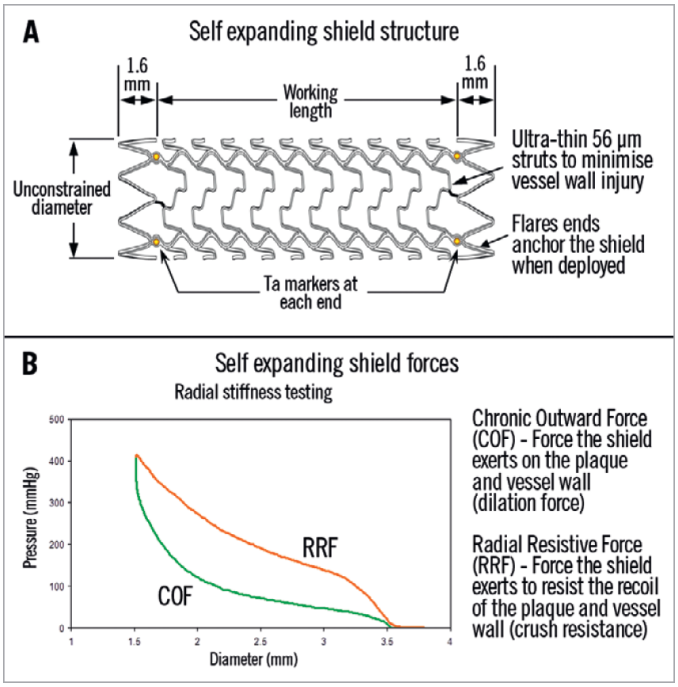

Figure 1:

A) Device design and structure highlighting the ultra-thin struts and tantalum markers to allow for positioning. B) Hysteresis curve between radial resistive force and chronic outward force (COF) exerted by the device on the vessel wall. In the case of the vShield, COF is around 100 mmHg, minimising vessel trauma and allowing for gentle continued expansion over time (9% at six months).

Study design and patient population

SECRITT is a clinical prospective pilot, open, single centre randomised study assessing the safety and feasibility of shielding the non-obstructive IVUS-derived TCFA, and the effects on the prevention of plaque progression at six months follow-up. Patients over the age of 18 admitted with stable or unstable coronary syndromes (including non-ST-elevation myocardial infarction) and an angiogram demonstrating the need for PCI in one or more lesion, and concomitant presence of angiographically and haemodynamically non-obstructive IVUS-derived TCFA were eligible for the study. After obtaining informed consent and successful treatment of the culprit lesion **(Figure 2)** patients were randomised 1:1 to treatment with the shield

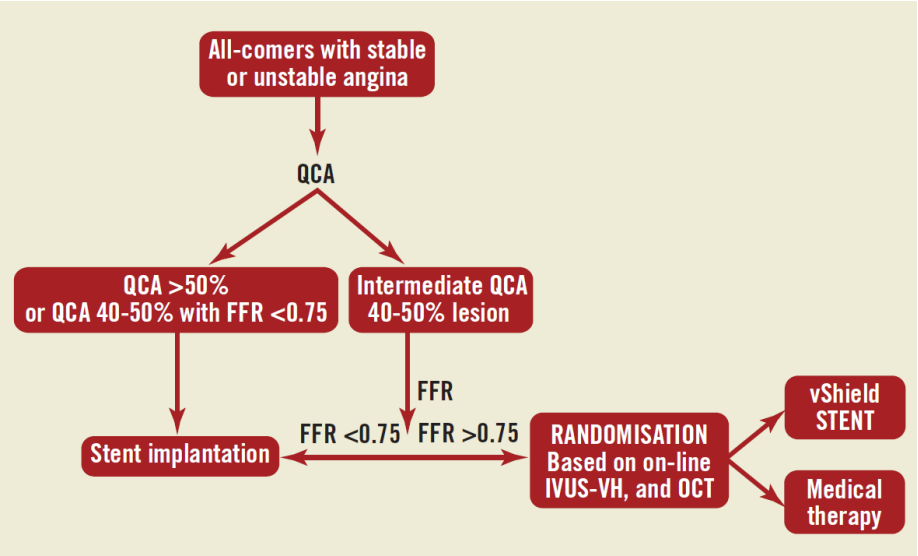

Figure 2:
Flow chart.

device or medical therapy. Exclusion criteria were as follows: acute myocardial infarction, prior coronary artery bypass graft (CABG), significant left main disease, cardiogenic shock, renal insufficiency (cr >1.5 mg/dL), resuscitation or intubation, cerebrovascular event within the last 30 days, major bleeding event within the last 30 days, severe hypertension refractory to medical therapy, history of significant trauma or surgery within the last six weeks, know nickel allergy, allergy to aspirin or clopidogrel that cannot be treated, pregnancy, coexisting condition with life expectancy <12 months and vessel diameter on angiography of <2.5 or >4.0 mm. All patients in the study were on aspirin therapy and received clopidogrel loading dose (600 mg) or were on maintenance clopidogrel dose. Anticoagulation during the procedure was achieved with heparin (with goal of ACT >300 msec). After the procedure all patients received aspirin and clopidogrel. All patients were treated with anti-cholesterol medications with the goal of low-density lipoprotein <70 mg/dL. The study protocol was approved by the institutional ethics committee and all patients provided signed informed consent.

Study lesion definition

Lesions qualified as study lesions if: 1) they were angiographically intermediate with 40-50% diameter stenosis, and 2) had an FFR of more than 0.75 (pathway B in the flow chart, **Figure 2**), and 3) fulfilled the criteria for IVUS-derived TCFA. Cap thickness and presence of the lipid pool was also documented by OCT.

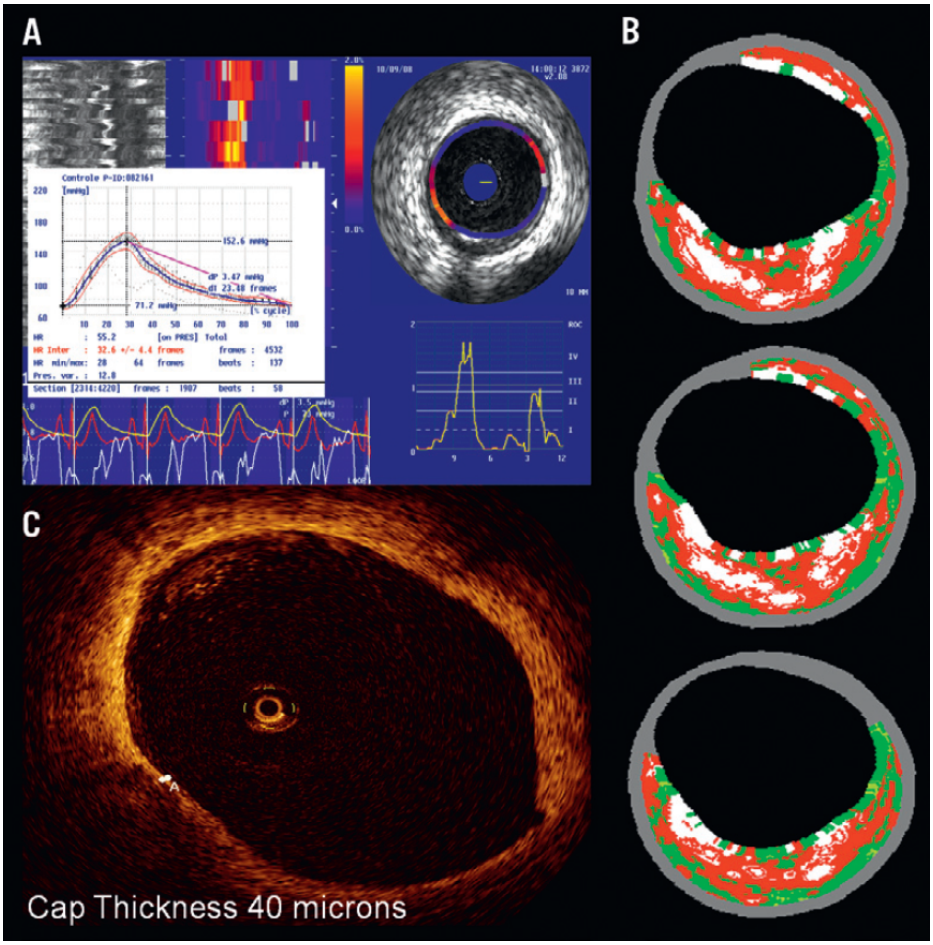

Figure 3:
Example of baseline imaging for one of the enrolled patients. A) In the upper left, palpogram showing stain value of 1.4% (ROC III-IV); B) In the upper right corresponding matched TCFA on IVUS VH analysis with plaque burden of 56% and necrotic core of 34% in three consecutive frames; C) In lower left corner, matched OCT frame showing cap thickness of 40 µm.

Quantitative angiography

The target coronary segment was filmed in two orthogonal planes that had been prescribed after viewing of the preceding angiogram. Quantitative coronary angiography (QCA) was performed following administration of 100-200 micrograms of nitroglycerine to assess the proper length and diameter of the vessel. A final angiogram was made under the same rotation and skew angles following intracoronary nitroglycerine administration. A QCA off-line using CMS-Medis quantitative angiography (Medis, Leiden, The Netherlands) was made to quantify the final result. The following measures were obtained for each lesion: minimal luminal diameter, reference vessel diameter and percent diameter stenosis. Late loss was

calculated from the difference between minimal luminal diameter immediately post shielding and at six-month follow-up. Restenosis was defined as the presence of in-lesion >50% diameter stenosis at follow-up.

Fractional flow reserve assessment

Fractional flow reserve was measured with a sensor-tipped 0.014" angioplasty guidewire (WaveWire/WaveMap; Volcano Therapeutics, Inc., Rancho Cordova, CA, USA; or PressureWire; Radi Medical Systems, Uppsala, Sweden). After crossing the target lesion with the wire, hyperaemia was induced with intravenous infusion of 140 µg/kg/min of adenosine (Adrecar; Sanofi, Munich, Germany) for a total of two minutes. The maximum pressure gradient used to calculate FFR was defined as the ratio of the mean post-stenotic pressure to the mean aortic pressure, measured by the guiding catheter, during maximal hyperaemia. FFR of ≥0.75, was considered functionally not significant and constituted the enrolment criterion. Exact FFR measurement at baseline and at six-month follow-up was recorded.

IVUS-VH acquisition and analysis

Details regarding the validation of the technique, have previously been reported[11, 12]. Briefly, IVUS-VH uses spectral analysis of IVUS radiofrequency data to construct tissue maps that are correlated with a specific spectrum of the radiofrequency signal and assigned colour codes (fibrous [labelled green], fibrolipidic [labelled greenish-yellow], necrotic core [labelled red] and calcium [labelled white]).

IVUS-VH data was acquired using either the In-Vision Gold console (in the same pullback as palpography) or the S5 imaging system, and a 20 MHz Eagle Eye® Gold catheter (all: Volcano Therapeutics, Inc., Rancho Cordova, CA, USA). The IVUS-VH sampling rate during pullback is gated to peak R-wave and is therefore dependent on heart rate.

IVUS B-mode images were reconstructed from the radio frequency (RF) data by customised software (IVUS Lab Version 4.4; Volcano Therapeutics INC., Rancho Cordova, CA, USA). Semi-automated contour detection of both lumen and the media-adventitia interface was performed and the RF data was normalised using a technique known as "blind deconvolution", an iterative algorithm that deconvolves the catheter transfer function from the backscatter, thus accounting for catheter-to-catheter variability. Compositional data obtained for every slice was expressed as mean percent for each component.

Pullback of 40 mm was performed after administration of 100- 200 micrograms of intracoronary nitroglycerine and incorporated the segment at least 5 mm proximal and distal to the region of interest. Pullback speed was 0.5 mm/sec.

Online analysis was performed to look for IVUS-defined thin-cap fibroatheroma (ID-TCFA) (enrolment criterion). The analysis was subsequently repeated off-line by two independent

observers blinded to patient clinical data and randomisation to verify the presence of ID-TCFA. After tracing the lumen and external elastic membrane diameters, plaque, lumen and total vessel area and volumes were computed for the segment of interest. The three consecutive cross-sections with >40% plaque burden and >10% necrotic core in contact with the lumen were identified and their quantitative characteristics and measurements were recorded. In addition, minimal luminal area (MLA) was measured.

IVUS-Palpography acquisition and analysis

Intravascular ultrasound palpography is a technique that allows the assessment of local mechanical tissue properties. At a defined pressure difference, soft tissue (e.g., lipid-rich) components will deform more than hard tissue components (e.g., fibrous-calcified)[13-15]. In coronary arteries, the tissue of interest is the vessel wall, while the blood pressure with its physiologic changes during the heart cycle is used as the excitation force. Radiofrequency data obtained at different pressure levels are compared to determine the local tissue deformation.

Each palpogram represents the strain information for a certain cross-section over the full cardiac cycle. Palpograms will be acquired using a 20 MHz phased-array IVUS catheter (Eagle-Eye®; Volcano Therapeutics Inc. , Rancho Cordova, CA, USA). Cine runs, before and during contrast injection were performed to define the position of the IVUS catheter. Digital radiofrequency data was acquired using a custom-designed workstation.

During the recordings, data was continuously acquired at a pullback speed of 0.5 mm/sec using an automated pullback device (Track Back II; Volcano Therapeutics Inc., Rancho Cordova, CA, USA) with simultaneous recording of the ECG and the aortic pressure. The data was stored on a DVD and sent to the imaging core lab for offline analysis (Cardialysis BV, Rotterdam, The Netherlands).

The local strain was then calculated from the gated radiofrequency traces using cross-correlation analysis and displayed colour-coding, from blue (for 0% strain) via red through to yellow (for 2% strain). This colour-coded information was superimposed on the lumen vessel boundary of the cross-sectional IVUS image.

Using previously described methodology, plaque strain values were assigned a Rotterdam Classification (ROC) score ranging from one to four (ROC I: 0-0.5%; ROC II: 0.6-<0.9%; ROC III: 0.9-1.2%; ROC IV: >1.2%). A cross-sectional area (CSA) was defined as a high strain when it had a high strain region (ROC III-IV) that spanned an arc of at least 12° at the surface of a plaque (identified on the IVUS recording) adjacent to low-strain regions (<0.5%). The highest value of strain in the cross-section is taken as the strain level of the CSA.

Highest strain value pre and post-shielding and was recorded and colocalisation with the IVUS-VH derived TCFA performed using timestamps.

TD and OFDI-OCT acquisition and analysis

The OCT M3 time domain optical coherence tomography (TD-OCT) and C7 optical frequency domain imaging optical coherence tomography (OFDI-OCT) systems used in this study (LightLab Imaging Inc., Westford, MA, USA) have been described previously[16-21]. Briefly, the OCT catheter was advanced distal to the stented lesion over a conventional coronary guidewire in the case of the C7 system or, in the case of the M3 system, the OCT imaging wire (ImageWire™; Lightlab Imaging Inc., Westford, MA, USA) was directly advanced past the lesion. The OCT catheter was then withdrawn proximal to the stented segment and the lesion visualised using an automated pullback system at 20 mm/sec in the case of the C7 system and 3.0 mm/sec in the case of the M3 system. During image acquisition, coronary blood flow was replaced by continuous flushing of contrast at 3.0-4.0 ml/sec using a power injector (Mark V ProVis; Medrad, Inc., Indianola, PA, USA) at 300 psi. Cross-sectional images were acquired at 100 frames/sec for the C7 and 20 frames/sec for the M3. During the baseline study documentary OCT was performed to measure and record the thickness of the fibrous cap overlying the lipid pool corresponding to the area of the ID-TCFA. A significant lipid pool was defined as a heterogeneous area of attenuated OCT signal, present in more than one quadrant of the vessel wall. The thinnest cap measurement was recorded. The assessment of the shield with OCT post implantation was used to assess procedure-related trauma to the vessel wall (plaque prolapse, presence of filling defects, proximal and distal edge dissection), and at six-months follow-up to assess shield strut apposition and tissue coverage and to measure the thickness of neo-cap. The thickness of the cap was measured every 1 mm within the shielded segment (15 frames per shield) using 360 degree analysis off-line software. In addition, shield areas were measured immediately post-shielding and at six-months follow-up to assess the degree of continued shield expansion with OCT.

A detailed per strut analysis was provided to illustrate the potential advantage of this device in treatment of these necrotic core rich non-obstructive lesions as compared to drug-eluting balloon expandable stents.

Measurements were repeated off-line by two independent observers using Lightlabs imaging software.

Follow-up and study endpoints

The primary endpoint of the study was the acute change in the lesion strain pattern immediately after shielding and acute device and angiographic success. Secondary endpoints of the study included: 1) change in the fibrous cap thickness from baseline to six-months post-shielding, 2) change in the stent area, 3) percent diameter stenosis at baseline and at follow-up, late loss and binary restenosis rate, and 4) cumulative incidence of major adverse cardiac events (death, MI and revascularisation) at six-month follow-up. Stent thrombosis oc-

currence was defined and classified according to the Academic Research Consortium (ARC) criteria[22].

Sample size calculation and statistical analysis

The study population was statistically based on the change in study lesion strain patterns immediately post-stenting, as noted in the ABSORB trial[23]. In this trial the mean of the maximal strain/cross-section/patient decreased from 0.44±0.25 to 0.00±0.01. Based on the assumptions for these, the sample size was calculated as detailed below.

Assumptions for the sample size calculation using a paired t-test:

- mean difference between pre- and post-treatment equal to zero
- alpha=0.05;
- mean pre=0.4;
- mean post=0.0;
- SD of difference pre-post=0.3;
- 90% power.

To assess the change in strain observed on palpography post-treatment, paired (pre-and post-) data of nine patients would have been needed. However, in order to account for the patients lost to follow-up, we aimed to enrol a total of 15 patients in each arm of the trial.

Discreet variables are presented as counts and percentages. Continuous variables are expressed as means $\pm$ standard deviation.

RESULTS

Patient enrollment

From June 2008 until February 2010 over 100 patients were approached for participation in the trial. Forty-eight signed informed consent, but only 23 patients met inclusion and enrolment criteria (including presence of ID-TCFA) and were enrolled in the trial. Thirteen patients were randomised to shield device and 10 randomised to medical therapy but with one patient crossing over to the shield arm. Baseline clinical characteristics of the patients enrolled are summarised in **Table 1**. Notably 24% of the patients were diabetic and 65% had multivessel disease. Of the 13 shielded patients, 11 completed full angiographic and imaging follow-up. Of the 10 control patients only five completed full angiographic and imaging follow-up.

Table 1. Baseline clinical characteristics for the overall population

Characteristic		N=23
Age		67 (range 50-82)
Gender (male)		76%
Current smoking		18%
Hypertension		71%
Hypercholesterolemia		76%
Diabetes melitus		24%
Prior MI		41%
Prior PCI		58%
Angina type:		
	Stable	76%
	Unstable	24%
Multivessel disease		65%
Non-culprit vessel (TCFA vessel)		
	LAD	24%
	LCX	24%
	RCA	52%

Angiographic and FFR analysis

In 24% of the cases, proximal or mid left anterior descending (LAD) artery was the site of the TCFA , in 24% the left circumflex LCx coronary artery and in 52% cases the right coronary artery (RCA). In the shielded group, baseline percent diameter stenosis was 33.2±13.5% with minimum lumen diameter (MLD) of 2.01±0.39 mm **(Table 2)**. Baseline FFR was 0.93±0.06. Post-stenting percent diameter stenosis decreased to 21.0±10.7 in the shielded patients and MLD increased to 2.43±0.44 mm. At six-month follow-up in shielded patients, percent diameter stenosis further decreased to 18.7±16.9% with MLD of 2.19±0.33 mm and FFR remained

Table 2: Serial angiographic and FFR assessment in shielded and control groups.

QCA	Baseline			6 months follow-up	
	Shielded group		Control group (n=5)	Shielded group (n=11)	Control group (n=5)
	Pre-stenting (n=11)	Post-stenting (n=11)			
MLD (mm)	2.01+0.39	2.43+0.44	1.87+0.54	2.19+0.33	1.78+0.49
RVD (mm)	2.95+0.39		2.93+0.44	2.72+0.46	3.08+0.50
% diameter stenosis	33.2+13.5	21.0+10.7	35.4+16.3	18.7+16.9	39.0+19.3
Late loss (mm)				0.24+0.13	0.22+0.12
FFR	0.93+0.06		0.93+0.05	0.93+0.05	0.82+0.29

the same (0.93±0.05). Average late loss was 0.24±0.13 mm. FFR in the control group at six months was 0.82±0.29 compared to 0.93±0.05 at baseline.

IVUS-VH analysis and palpography

At the site of the TCFA lesion baseline plaque burden was 60.6±8.8%, percent necrotic core in contact with the lumen was 34.7±6.3% averaged over three consecutive frames. Average MLA was 6.8±2.4 mm2 **(Table 3 and Figure 3)**. At follow-up, the five control patients showed no increase in plaque burden or necrotic core observed over time and no MLA decrease.

Average strain before shield placement was 0.71%±0.53% (ROC score of II on average). This decreased acutely post-shield placement to 0.1%±0.09% (ROC score of I).

Table 3: IVUS VH and palpography baseline and acute data summary

Parameter	(n=23)
MLA mm^2	6.8 ± 2.4
% plaque burden	60.6 ± 8.8
% necrotic core	34.7 ± 6.3
% strain pre-shield	0.71 ± 0.53
% strain post-shield	0.1 ± 0.09

OCT analysis and data

As previously reported by our group[24], deployment of the self-expanding shield resulted in minimal trauma to the vessel wall, particularly when compared to the balloon-expandable devices. There were no proximal or distal edge dissections and no filling defects. Length of intra-stent dissections was also minimal.

Table 4: Optical coherence tomography at baseline, post-shield and at 6 month follow-up.

	Shielded (pre-shield/acute post-shield)	Shielded 6 months follow-up
Cap thickness / mean neointimal thickness (μm)	48 ± 12 (range 30-70)	201 ± 168 (range 50-608)
Presence of lipid pool	100%	
Mean lumen area mm^2	9.03 ± 2.29	8.36 ± 2.87
Mean stent area mm^2	8.76 ± 2.16	9.45 ± 2.30 (9% increase)
Minimum lumen area mm^2	7.23 ± 2.85	6.12 ± 2.75
Malapposed struts	185/1721 (10.7%)	159/2072 (7.6%)
Uncovered struts		167/2072 (8.1%)

Average baseline fibrous cap thickness was 48±12 µm with a range of 30-70 µm. After shield placement at six-month follow-up neo-cap formation was observed with average cap thickness of 201±168 µm (range 50-608 µm) **(Table 4)**. The patient with 608 µm of neo-cap formation at baseline had adjacent calcifications that required high pressure (16 atms) post-dilation of the shield with resultant barotrauma and more exuberant healing response.

In addition, mean stent area of 8.76±2.16 mm2 increased to 9.45±2.30 mm2, that is by 9% at six-month follow-up (**Table 4** and **Figure 4**). The number of malapposed struts decreased from 10.7% to 7.6% and the number of uncovered struts at six months was 8.1%.

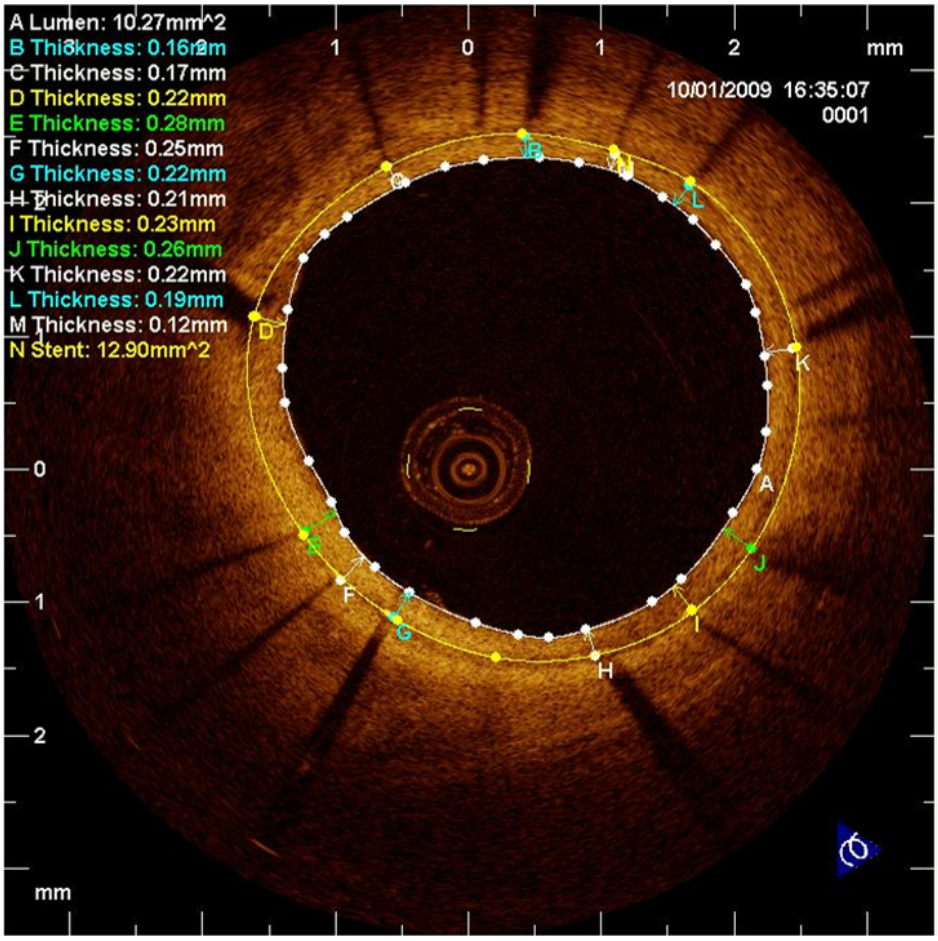

Figure 4:
Example of per-strut OCT analysis and appearance of vShield at six-month follow-up with uniform strut coverage of around 200 µm and no malapposition.

Detailed per strut analysis

A total of 11 stents were evaluated at baseline. In two patients there was a high degree of malaposition due to undersizing of the device. Mean incomplete stent apposition (ISA) area was 0.36±0.47 mm2. Mean prolapse area was 0.009±0.17 mm2. Of the 1,721 stent struts counted at baseline 1,521 were well apposed, 185 (10.7%) were malapposed and 15 were in front of side branches. There were no dissections seen. Mean thrombus area was 0.015 mm2.

At six-month follow-up 12 stents were evaluated with a total length of 142.95 mm. Mean lumen area was 8.36±2.87 mm2 (decreased by 7.4%). Mean stent area increased to 9.45±2.30 mm2 (by 9%), implying continued stent expansion. Mean ISA area was 0.88±0.85 mm2. Of the total of 2,072 struts evaluated, 1,910 were well apposed, 159 were malapposed (7.6%; decrease from baseline), and three were in front of a side branch. Of all struts 8.1% were non-covered. Of the well-apposed struts, 93.2% were covered, while of the malapposed struts 78% were covered.

Clinical events

There were no device-related MACE events **(Table 5)**. One of the control (non-shielded) patients returned within two weeks of the procedure with an unstable coronary syndrome and crossed

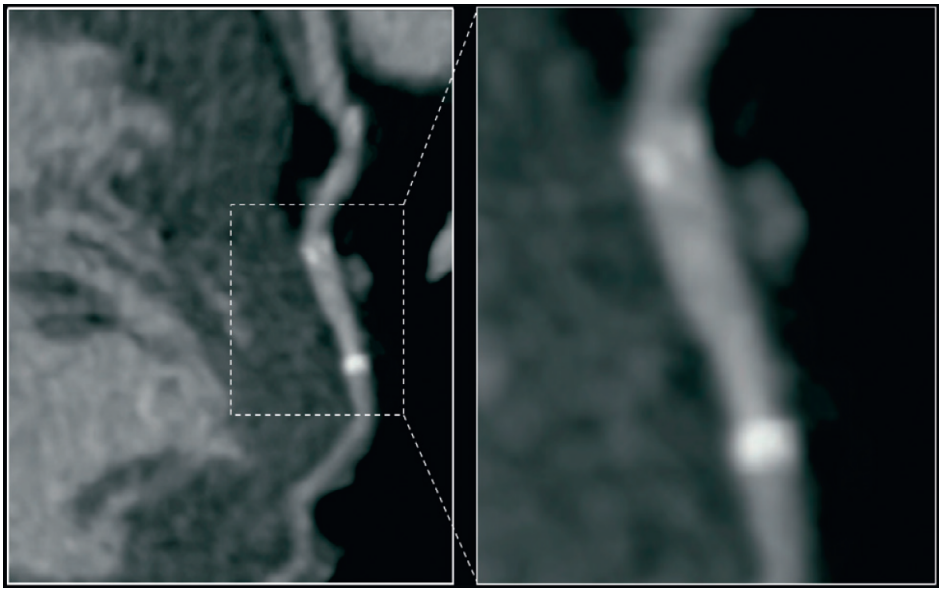

Figure 5:
MSCT image of vShield at six months. There is no beam-hardening artefact from nitinol struts (except for tantalum markers at the edges) allowing for good non-invasive evaluation of patency.

Table 5: Cummulative incidence of MACE rate at 6-month follow-up

	Shield arm (n=13)	Medical therapy arm (n=10)
MACE	0	1
Death	0	0
MI	0	0
Clinically-driven revascularization	0	1 (cross-over to shield)
Revascularisation related to the target lesion/shielded vessel	0	0

over to the shield arm. There were no stent thrombosis events. Lastly, non-invasive assessment of shield patency with MSCT appears feasible owing to its thin nitinol struts **(Figure 5)**.

DISCUSSION

In this first-in-man experience with shielding of vulnerable plaque (thin-cap fibroatheroma) using a self-expanding nitinol shield, we demonstrate the feasibility and preliminary efficacy of the approach. The device delivery was successful in all 13 patients who were randomised to the shield and there were no MACE events related to the shield device treatment at six-month follow-up. The treatment strategy employed in this protocol is based on the fact that most myocardial infarctions (MI) result not from a critical blockage, but from lesions that are non-flow limiting[25-30]. In individuals who have undergone angiography in the months preceding myocardial infarction, the culprit lesions most often show <50% diameter stenosis[27]. Moreover, it has been shown on a previous angiogram that only approximately 15% of acute MI arise from lesions of <60% stenosis[11]. These lesions, however, have a substantial plaque volume/percent plaque burden. The coronary flow is not obstructed because of outward (positive) remodelling. Longer-term prognosis of a patient might depend on far more detailed plaque assessment than angiography and on adequate treatment of plaques at risk of rupture.

The use of IVUS-VH to identify vulnerable plaques (ID-TFCA) is well documented and is comparative to what has been demonstrated from documented plaque ruptures. ID-TCFA is currently defined as a lesion fulfilling the following criteria in at least three consecutive cross-sectional areas (CSA): 1) necrotic core ≥10% without evident overlying fibrous tissue, 2) lumen obstruction ≥40%. In addition, the ID-TCFA must demonstrate positive remodelling by having a remodelling index (RI) >1.05. In a study population of 21 patients Garcia-Garcia[12] found, in 13 patients, 42 ID-TCFA that fulfil the IVUS-VH criteria. This meant that on average there are approximately three ID-TCFA per patient. Documented plaque ruptures were reported by Rioufol[31] in 2002 in 24 patients referred for PCI after a first acute coronary syndrome (ACS) with a troponin I elevation. He found that there were 50 plaque ruptures corresponding to 2.08 vulnerable plaques per patients presenting with an ACS, which is in

accordance with Garcia-Garcia's IVUS-VH findings. Interestingly, plaque rupture on the culprit lesion was found only in nine patients (37%). In 19 patients (79%) at least one plaque rupture was found somewhere other than the culprit lesion, in a different artery in 70% and in both other arteries in 12.5% of the patients. This reinforces the importance of identifying and treating vulnerable plaques and the fact that they can be remotely associated from the culprit lesion causing the presenting symptom. This also constitutes the rationale for the treatment of intermediate non-flow limiting lesions with signs of vulnerability. Accuracy of thin-cap atheroma detection can be further increased by combining IVUS-VH imaging with OCT imaging of the lesion, which due to its micron resolution can allow the measurement of the thickness of the fibrous cap. Sawada [32] has shown that out of 126 lesions examined with two modalities only 28 (22%) fulfill thin-cap fibroatheroma criteria by both IVUS-VH and OCT with thin cap defined as < 65 microns. For these reasons, we have chosen in this study to perform a very detailed multimodality examination of plaque before enrolling patients in the study. The examinations that each patient underwent were: 1) angiography, 2) FFR, 3) palpography (off-line), 4) IVUS-VH, and 5) OCT online at baseline. This was followed by post-shielding assessment with: 1) angiography, 2) palpography, and 3) OCT. At six-month follow-up the assessment included: 1) angiography, 2) FFR, 3) palpography/ IVUS, and 4) OCT. With such extensive examination and procedure times, which was challenging for patients, personnel and operators, enrolment in the study was rather slow (23 patients in under two years), and several patients (particularly in the control arm) were unwilling to participate in the follow-up catheterisation. The use of stringent criteria for enrolment was justified in this pilot study; the protocol may have been more successful had we used a simple combination of non-invasive coronary MSCT assessment (for positive remodelling, plaque burden, 3-D strain and flow) combined with intraprocedural OCT (to measure cap thickness and show presence of a lipid pool). In the future, angiography, FFR and IVUS/palpography assessment should be replaced by non-invasive methodologies such as MSCT or combined MSCT-FDG-PET examination[33] which after evaluation against invasive technologies could potentially provide equivalent information before the start of the invasive procedure[34-36].

We have been able to demonstrate here that the self-expanding device is ideally suited for treatment of thin-cap fibroatheromas. The self-expanding nature of the device causes minimal trauma to the vessel wall, minimising the risk of thin-cap rupture and necrotic core embolisation. We had no periprocedural MI in this patient cohort. Furthermore, the device is well apposed and continues to expand gently by 9% over six months, minimising the risk of having malapposed and uncovered struts. While there is no drug coating and the device is bare metal, the combination of thin nitinol struts and lack of traumatic balloon expansion result in minimal neointimal formation. Eight percent of the struts were still uncovered at six months with average neo-cap of 201 μm and late loss of 0.13 mm which is comparable to some of the state-of-the-art drug-eluting stents. There were no stent thrombosis events. The continued gentle expansion of the device is similar to that observed by Granada et al in

the first-in-man trial of the vShield device in moderate stable lesions, which was completed recently[37] and also comparable to the results achieved with the Stentys stent (STENTYS Inc., Princeton, NJ, USA) in the Apposition study[38].

The number of patients enrolled and lack of events made it impossible to determine whether placement of the shield and plaque passivation demonstrated by OCT offered an advantage over standard medical therapy with aspirin, clopidogrel and statins. The ability to prevent plaque growth and disease progression to a significant lesion was demonstrated recently in the VELETI trial of paclitaxel-eluting stent treatment versus medical therapy in graft disease[10].

Limitations

The present report is a pilot study and the number of patients is limited, and should therefore be considered exploratory and hypothesis-generating, without formal statistical hypothesis.

The limited number of patients made any meaningful statistical analysis rather difficult and thus the data are presented for most part in a qualitative fashion.

Moreover, an important limitation was failure to complete the full projected study enrolment and lack of angiographic/imaging follow-up in a large proportion of non-shielded control arm patients. In addition, since only 4.4% of the VH-derived TCFA lesions result in event rates at three years based on the finding of the PROSPECT study[9] (in the absence of MLA<4 mm2 or >70% plaque burden), despite our extensive use of imaging such as concomitant OCT we may have failed to identify truly high-risk plaques.

CONCLUSION

Passivation of the thin-cap fibroatheroma with a self-expanding nitinol vShield device appears to be safe and feasible. A larger cohort study with long-term follow-up will be needed to evaluate this device as a treatment for necrotic core rich lesions.

CONFLICT OF INTEREST STATEMENT

In the past, J. de Schepper was an employee of Prescient Medical. The other authors have no conflicts of interest to declare.

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"Celui qui se juge trop important pour de petits travaux est souvent trop petit pour les travaux importants".

(Whoever considers himself too important for little jobs is often too little for the important jobs)

Jacques Tati

PART 4

METALLIC DRUG-ELUTING STENTS WITH RESERVOIRS

CHAPTER 6

Efficacy of drug elution from reservoirs

Effect of paclitaxel elution from reservoirs with bioabsorbable polymer compared to a bare metal stent for the elective percutaneous treatment of de novo coronary stenosis: the EUROSTAR-II randomised clinical trial.

Silber S, Gutiérrez-Chico JL (equally contributed), Behrens S, Witzenbichler B, Wiemer M, Hoffmann S, Slagboom T, Harald D, Suryapranata H, Nienaber C, Chevalier B, Serruys PW.

EuroIntervention 2011;7:64-71.

ABSTRACT

Aims: To compare the angiographic and clinical performance of a paclitaxel-eluting stent using reservoirs technology and a bioresorbable polymer, without surface coating (CoStar), vs. an equivalent bare metal stent (BMS) using identical metallic platform.

Methods and results: 303 patients (335 lesions) with de novo coronary artery stenosis suitable for elective percutaneous treatment were randomized in an international multi-centre single-blind trial to receive the CoStar stent (n=152) or the equivalent BMS (n=151). At 8 months, the primary endpoint of in-segment binary restenosis was significantly lower in the CoStar than in the BMS group (17.6 vs. 30.3%, p=0.029). In-stent late loss (0.41 vs. 0.81mm; p<0.0001) and all the other angiographic secondary endpoints also favoured CoStar. The composite of cardiac death, myocardial infarction related to the target vessel and target lesion revascularization was significantly lower at 8 months in the CoStar arm (19.7 vs. 29.1%; hazard ratio 0.54, 95% CI; 0.34 – 0.87; p=0.010), mainly due to lower incidence of target lesion revascularization (15.1 vs. 26.5%; hazard ratio 0.45, 95% CI: 0.27 – 0.76; p=0.002).

Conclusions: As compared with a bare metal stent of identical design, the Paclitaxel elution from reservoirs results in significantly less binary restenosis, less late loss and lower revascularization rates at 8 months. Therefore, based on these data, the CoStar Paclitaxel-eluting stent was found to be effective and safe.

Key words: Angioplasty, transluminal percutaneous coronary; coronary stenosis; paclitaxel; stents; drug-eluting stents.

CONDENSED ABSTRACT

303 patients with de novo coronary lesions were randomized to receive the paclitaxel-eluting CoStar stent with reservoirs technology (n=152) or an equivalent BMS using identical metallic platform (n=151). At 8 months in-segment binary restenosis (primary endpoint) and in-stent late loss were significantly lower in the CoStar group (17.6 vs. 30.3%, p=0.029; 0.41 vs. 0.81mm; p<0.0001, respectively). The composite of cardiac death, myocardial infarction and target lesion revascularization (TLR) was also significantly lower at 8 months in the CoStar arm (19.7 vs. 29.1%; hazard ratio 0.54, p=0.010), mainly due to lower incidence of TLR (15.1 vs. 26.5%; hazard ratio 0.45, p=0.002).

INTRODUCTION

Patients receiving bare metal stents (BMS) suffer from restenosis in 20.0 – 50.3% due to excessive neointimal proliferation[1]. Due to their ability to inhibit cellular proliferation, drug-eluting stents (DES) have reduced the restenosis rates to 7.9 - 8.9 %[2-5]. However some reports have suggested an eventually higher incidence of late and very late stent thrombosis in DES[6-10], with the common pathological finding of delayed neointimal healing and incomplete endothelialization in fatal cases[11-15]. The mechanism for delayed neointimal healing and stent thrombosis seems to go beyond the antiproliferative potency of the drug and involve also other factors, like the thickness of the struts[16], cracking of the polymer[17], polymer-induced inflammatory reaction[14,18-22] or inappropriate kinetics of drug release[23,24]. In some first generation DES a specific inflammatory reaction has been described, with presence of intense eosinophilic infiltrates in the vessel wall[14] and in the thrombus harvested from patients suffering very late stent thrombosis[19], that might be mediated by delayed type IVb hypersensitivity, recruiting preferentially eosinophils. This hypersensitivity is likely triggered by the polymer rather than by other components of the device[21], given the timing of onset (later than 90 days, when the drug is no longer detectable in the vessel wall) and the presence of polymer fragments surrounded by giant cells[14,22]. Also inadequate pharmacokinetics of the device are known to be potentially harmful: excessive drug release during the early phase of repair might cause not only delayed healing but also toxicity, leading to smooth muscle cells necrosis, positive remodelling and acquired malapposition[23].

Intense research efforts are currently aimed to optimize DES design features, to improve its safety profile and to promote complete neointimal healing, in order to prevent stent thrombosis. Reservoir technology offers considerable advantages with respect to surface polymer coating: struts are honeycombed with laser-cut holes or wells that act as drug reservoirs. This design permits precise control of the spatial drug release (abluminal/ adluminal/ bidirectional) and optimization of the temporal elution rate using inlaid stacked layers of drug and polymer[25]. The polymer layers can be bioresorbable and disappear after elution of the drug, thus circumventing the problem of delayed hypersensitivity and late inflammatory reactions associated to thrombotic phenomena. The lack of surface polymer coating avoids also the risk of cracking as previously described[17], although stents with reservoirs require a specific design, with specifically engineered hinge points and bridges, to increase its flexibility and deliverability as well as preserve the structural and functional integrity of the reservoirs after the deployment stress[25].

The CoStar stent (previously Conor MedSystems, Menlo Park, CA, USA, now Cordis Corporation, Bridgewater, NJ) consists of a new cobalt-chromium platform (Unistar, Conor MedSystems, Menlo Park, CA, USA) with reservoirs containing a bioresorbable poly-(lactide-co-glycolide) (PLGA) polymer and paclitaxel at a dose of 10µg/17mm of stent. The enhanced flexibility was achieved by a new stent design with bridge elements and ductile hinges

(figure 1). The elution of the drug is solely abluminal and prolonged to 30 days, coupled to the progressive degradation of the PLGA polymer by hydrolysis. This release formulation is the result of an evidence-based clinical selection process among other formulations, being the one with lowest incidence of major adverse cardiovascular events (MACE)[26] and lowest angiographic late loss[27]. The thickness of the struts is 90µm. The CoStar stent failed to prove non-inferiority vs. a first-generation surface-coating paclitaxel-eluting stent (Taxus Express, Boston Scientific, Maple Grove, MN, USA) in the COSTAR-II trial[28]. Furthermore, the performance of the CoStar stent in this study was assumed not to be significantly different from the "imputed" i.e. theoretically constructed, virtual BMS[27]. These results questioned the efficacy of reservoirs DES as drug-delivery technology. Purpose of this study was to compare the performance of the CoStar reservoirs DES vs. a BMS of identical design but with empty reservoirs.

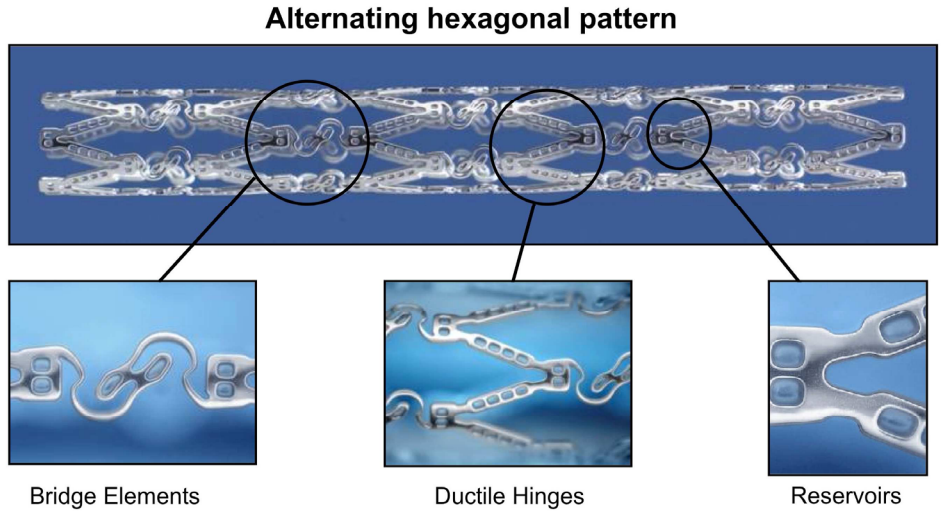

Figure 1: Design of the CoStar DES.
The new cobalt-chromium platform has reservoirs containing a bioresorbable poly-(lactide-co-glycolide) (PLGA) polymer and paclitaxel at a dose of 10µg/17mm of stent. Its enhanced flexibility was achieved by a new stent design with bridge elements and ductile hinges.

METHODS

The EUROSTAR-II trial was an international multi-centre , randomized, single-blind trial evaluating the efficacy and safety of the CoStar paclitaxel-eluting stent with reservoir technology vs. a control of the identical BMS platform without drug or polymer (Unistar, Conor Med-Systems, Menlo Park, CA, USA) for elective treatment of de novo lesions in native coronary arteries.

Study endpoints

Primary endpoint for the study was in-segment binary restenosis rate at 8 months by quantitative coronary angiography (QCA). Angiographic secondary endpoints at 8 months were: 1) In-stent and In-segment late lumen loss, 2) In-stent and In-segment minimal lumen diameter (MLD). Clinical secondary endpoints were 1) MACE at 30 days and 8 months, defined as an adjudicated composite of death that cannot be clearly attributed to a non-cardiac cause or non-intervention vessel, new myocardial infarction (MI, Q- or non-Q-Wave) that cannot be clearly attributed to a non-intervention vessel, according to World Health Organization criteria[29] and target vessel revascularization (TVR); 2) clinically-driven TVR and 3) clinically-driven TLR. Combined secondary endpoints were: 1) Device success, defined as attainment of <50% in-stent residual stenosis by QCA as final result of the intervention, in absence of device malfunction, and 2) Procedural success, defined as attainment of <50% in-stent residual stenosis by QCA as final result of the intervention, in absence of in-hospital MACE.

Sample size calculation

This trial was designed as a superiority one-sided trial of the DES vs. the control arm using the BMS of identical design. Based on prior studies, the estimated incidence of the primary endpoint was estimated in 5% for the CoStar DES intervention arm[27] and in 15% for the UniStar BMS active control arm[26]. On these assumptions and for a one-sided α error of 0.05, a minimum sample size of 131 patients per treatment arm was calculated to yield a greater than 80% power of finding a significant difference, using the normal method with Fleiss' correction. Accounting for up to 10% patients lost to follow-up, the final sample size calculation resulted in 146 patients per group.

Study population

Patients between 18-80 years of age, with stable or unstable angina pectoris or with a positive functional test for ischemia and up to two discrete de novo lesions in native coronary arteries, amenable to treatment with percutaneous coronary intervention (PCI) using the study stents were enrolled into the trial. Eligible lesions had to be between 50% and 99% diameter stenosis, reference vessel diameter (RVD) 2.5-3.5mm and length ≤25mm by visual estimation that could be treated with a single study stent. TIMI flow pre-intervention had to be ≥ I. Study lesions should not have undergone any previous interventional procedure of any kind, and no additional treatment should be planned for the patient in the following 30 days. Exclusion criteria were: cerebrovascular event or transient ischemic attack within the prior 6 months, percutaneous or surgical coronary revascularization within the prior 30 days, acute myocardial infarction within the prior 72 hours, cardiogenic shock, unstable ventricular

arrhythmias, left ventricular ejection fraction <30%, serum creatinine >2.5 mg/dL, known hypersensitivity to any of the components of the study devices or to the procedure medication, episode of gastrointestinal bleeding in the preceding 3 months, contraindication for dual antiplatelet therapy, any other clinical condition conferring the patient a life expectancy <2 years, presence of >2 lesions (or >1 lesion in the same coronary artery) requiring treatment, target lesion involving a bifurcation with a side branch >2mm in diameter, detection of intraluminal thrombus visible in the angiography and planned used of adjunctive coronary devices (e.g. cutting-balloon or atherectomy).

All patients in the trial provided written informed consent before enrolment, and were randomly allocated on a 1:1 basis to receive the CoStar paclitaxel-eluting stent with reservoir technology or the UniStar BMS with identical, but empty reservoirs. Allocation to treatment used a random computer-generated sequence of numbers, and sequentially numbered sealed envelopes available at each study site. The patient, but not the operator, was kept blinded to the allocation. The study was conducted in accordance with Good Clinical Practice, Declaration of Helsinki and local regulations, and protocol was approved by the Ethical Committees of the centres involved in the trial.

Description of the intervention and follow-up

All patients received 100 mg of aspirin at least one hour before the intervention and a minimum loading dose of 300mg of clopidogrel prior or immediately following the procedure. Use of glycoprotein IIb/IIIa inhibitors was left at the operator's discretion. Intravenous heparin was administered during the procedure to keep an activated clotting time ≥250 seconds, or 200-250 if a glycoprotein IIb/IIIa receptor blocker was administered.

The interventions were performed with a ≥6F guiding catheter. Direct stenting or predilatation with a balloon shorter and at least 0.5mm smaller in diameter than the study stent were both allowed. The study stents (as described above) were available at 2.5, 3.0 and 3.5mm diameter, and at 10, 16, 22, 28 and 33mm length. The implanted stent had to cover the whole target lesion length and the entire ballooned segment in case of predilatation, extending at least 2mm beyond on each side. Use of additional stents had to be avoided, except in the cases of insufficient lesion coverage or bailout procedure. If the patient required additional bailout stents, these had to be identical to

the initial study stents implanted. The stent was deployed at an inflation pressure between nominal and rated burst pressure to achieve full expansion, complete apposition and a final diameter stenosis <10%. If necessary the stent could be postdilated with a balloon shorter than the stent length at the operator's discretion. IVUS guidance was allowed but not mandatory. Systematic monitoring of ECG and cardiac serum markers was performed in all patients after the procedure and before discharge.

After the intervention, patients were kept on dual antiplatelet therapy with 100mg of aspirin and 75mg of clopidogrel daily for a minimum of 6 months, followed by daily aspirin indefinitely. Clinical follow-up visits were scheduled 30 days and 8 months post-procedure, and angiographic follow-up at 8 months.

Quantitative coronary angiography (QCA) analysis

Coronary angiography was performed according to standard procedures[30]. QCA analysis was performed with the CAAS II system[31] (Pie Medical BV, Maastricht, The Netherlands) in a core-lab setting (Bio-Imaging Technologies, Leiden, NL) by analysts blinded to patients' characteristics and to the allocation to treatment. The analysis results were reported for the stented segment (in-stent) and for the segment comprising 5mm proximal and distal to the stent edges (in-segment). MLD was automatically detected by the software. RVD at the point of MLD was calculated by the software by interpolation. % diameter stenosis was calculated as: (1-[MLD/RVD])*100. Binary restenosis was defined as % diameter stenosis ≥50%. In-Stent and In-Segment late lumen loss was defined as the difference between MLD at 8 months follow-up and the respective post-procedure MLD.

Statistical analysis

Results are reported as mean±standard deviation for continuous variables, and as count (percent) for nominal variables. Continuous variables were compared with Fisher's t-test for independent samples. Nominal variables were compared with Pearson's chi-square, or Fisher's exact test if the expected frequency was <5 in any cell.

Clinical and safety endpoints followed a hierarchical events model. Incidences of the different endpoints at 30 days were calculated and compared as risk ratios. Results at 8 months were analyzed as events-free survival using Cox proportional hazards regression and log rank tests.

All statistical analyses were performed according to the intention-to-treat principle, using the PASW 17.0.2 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

303 patients (335 lesions) were enrolled in the EUROSTAR-II trial at 18 different European sites: 152 in the CoStar DES group, and 151 in the Unistar BMS group (figure 2). Tables 1 and 2 show the baseline characteristics of patients and lesions, respectively, with no significant difference in any of the variables tested, except for a larger proportion of prior coronary artery bypass graft in the UniStar group (p=0.010). QCA analysis did not show significant differences

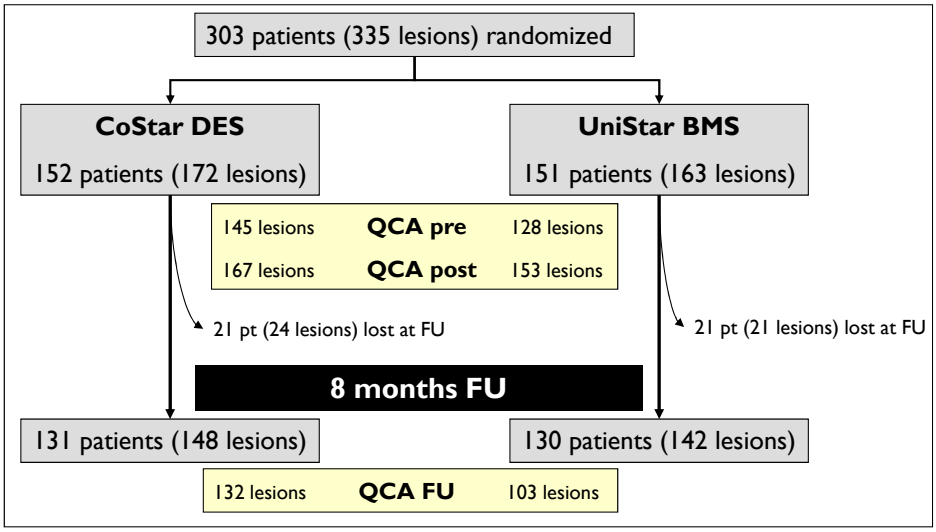

Figure 2: Flow chart of the study.
FU: Follow-up; QCA: Quantitative coronary angiography suitable for analysis.

in the pre-procedural analysis of the lesions (table 3). Both groups were also comparable with respect to QCA results post-stenting, except for a slightly higher residual diameter stenosis in the CoStar than in the UniStar subgroup (21.2 vs. 18.62%, respectively; p=0.030).

42 patients (13.9%) were lost for angiographic follow-up: 21 (13.8%) and 21 (13.9%) in the CoStar and UniStar groups, respectively. Clinical follow-up was completed in all patients at 8 months. Median FU time was 243 days, inter-quartile range (217 – 250 days). The primary endpoint (in-segment % binary restenosis) was significantly reduced in the Costar arm: 17.6 vs. 30.3%, p=0.029; (table 3, figure 3). Significant differences in favour of CoStar were also found in all the angiographic secondary endpoints (table 3, figures 3-5).

Regarding the clinical and safety endpoints, no significant difference was found between groups at 30 days (table 4). However, the incidence of MACE was significantly reduced at 8 months in the CoStar arm (19.7 vs. 29.1%; hazard ratio 0.54, 95% CI; 0.34 – 0.87; p=0.010). Similar death, and MI rates were found at 8 months in both treatment groups, but the incidence of TLR was significantly lower in CoStar (15.1 vs. 26.5%; hazard ratio 0.45, 95% CI: 0.27 – 0.76; p=0.002). A single case of stent thrombosis was registered in the UniStar group seven days after the intervention (subacute), and classified as definite according to ARC criteria[32].

DISCUSSION

The results of this EUROSTAR-II trial prove the efficacy of reservoirs technology for inhibition of neointimal hyperplasia and clinically relevant prevention of restenosis, compared

Table 1: Baseline characteristics of the patients.

	CoStar DES (n=152)	UniStar BMS (n=151)	p-value
Male	113 (74.3%)	104 (68.9%)	0.291
Age (years)	64.9 ± 9.2	66.2 ± 9.4	0.228
Weight (kg)	82.8 ± 13.3	81.5 ± 12.5	0.417
Height (cm)	171.1 ± 8.0	171.1 ± 8.9	0.985
BMI (kg/m^2)	28.2 ± 4.0	27.8 ± 3.6	0.361
Risk factors			
Hypertension	102 (67.1%)	113 (74.8%)	0.138
Hypercholesterolemia	92 (60.5%)	94 (62.3%)	0.758
Diabetes mellitus	40 (26.3%)	34 (22.5%)	0.442
Insulin therapy	15 (9.9%)	14 (9.3%)	0.860
Smoking	71 (46.7%)	64 (42.4%)	0.449
Current smoker	30 (19.7%)	28 (18.5%)	0.792
Peripheral vascular disease	12 (7.9%)	4 (9.3%)	0.669
Stroke / TIA	7 (4.6%)	4 (2.6%)	0.363
Renal insufficiency	13 (8.6%)	10 (6.6%)	0.526
CHF	6 (3.9%)	5 (3.3%)	0.767
Chronic respiratory disease	7 (4.6%)	8 (5.3%)	0.781
Prior MI	41 (27.0%)	41 (27.2%)	0.972
Prior PCI	56 (36.8%)	47 (31.1%)	0.294
Pior CABG	3 (2.0%)	13 (8.6%)	**0.010**
LVEF (%)	62.2 ± 13.0	61.1 ± 12.9	0.464
Clinical indication			0.390
Stable angina	101 (66.4%)	101 (66.9%)	0.935
Unstable angina	29 (19.1%)	35 (23.2%)	0.382
Silent ischemia	22 (14.5%)	15 (9.9%)	0.228

to an identical BMS platform. The primary endpoint (in-segment % binary restenosis) was significantly lower in the group treated with a CoStar DES than in the group treated with the UniStar BMS. Other secondary endpoints addressing the inhibition of neointimal hyperplasia and prevention of restenosis, like late loss, or incidence of TVR and TLR, were also significantly in favour of the reservoirs DES. The reservoirs DES also proved to be superior in secondary clinical endpoints, like the incidence of the composite of death, MI and TLR, although this clinical superiority was mainly due to the reduction of TLR, showing similar rates of death and MI. This finding is consistent with the angiographic findings, and can be interpreted as efficient and clinically relevant prevention of restenosis, without clinical safety concerns.

The results of the COSTAR-II study had questioned the efficacy of reservoirs DES[28]: the reservoir paclitaxel-eluting CoStar stent failed to prove non-inferiority vs. a first-generation surface-coating paclitaxel-eluting stent (Taxus Express, Boston Scientific, Maple Grove, MN,

Table 2: Baseline characteristics of the lesions and procedural results.

	CoStar DES (n=172)	UniStar BMS (n=163)	p-value
Target coronary vessel			
LM	1 (0.6)	1 (0.6)	1.000
LAD	67 (39.0)	66 (40.5)	0.774
LCX	41 (23.8)	44 (27.0)	0.507
RCA	62 (36.0)	51 (31.3)	0.357
Lesion length			0.855
Discrete (<10mm)	82 (48.2)	86 (53.1)	
Tubular (≥10; ≤20mm)	80 (47.1)	70 (43.2)	
Diffuse (>20mm)	8 (4.7)	6 (3.7)	
Ostial lesion	9 (5.2)	6 (3.7)	0.500
Bifurcation requiring double wiring	8 (4.7)	7 (4.3)	0.875
Eccentric	111 (66.5)	107 (66.0)	0.936
Irregular contour	25 (15.0)	29 (17.9)	0.473
Angulation			0.561
Mild	151 (87.8)	144 (88.3)	
Moderate	21 (12.2)	18 (11.0)	
Severe	0 (0.0)	1 (0.6)	
Moderate/severe tortuousity	21 (12.2)	20 (12.3)	0.986
Moderate/severe calcification	5 (2.9)	4 (2.5)	1.000
TIMI flow pre-procedure			0.287
0	0 (0.0)	0 (0.0)	
I	4 (2.4)	1 (0.6)	
II	11 (6.5)	15 (9.3)	
III	154 (91.1)	145 (90.1)	
Procedural results			
Direct stenting	111 (63.8%)	99 (60.0%)	0.472
Need for bailout 2nd stent	15 (8.6%)	14 (8.5%)	0.964
Reason for bailout 2nd stent			
Residual stenosis >50%	1 (6.7%)	1 (7.1%)	1.000
Coronary dissection	5 (33.3%)	12 (85.7%)	**0.008**
Lesion incompletely covered	9 (60.0%)	1 (7.1%)	**0.005**
Post-dilatation	18 (10.3%)	19 (11.5%)	0.730
TIMI flow post-procedure III	170 (100.0)	162 (100.0)	NA
Residual dissection	2 (1.2)	1 (0.6)	1.000
Device success	170 (98.8)	162 (99.4)	1.000

Results expressed as n(%).

Table 3: QCA analysis per lesion.

QCA results	CoStar DES (n=167)		UniStar BMS (n=153)		p-value
	Mean	SD	Mean	SD	
Lesion pre-stenting	n=145		n=128		
Length (mm)	15.12	7.58	15.16	7.69	0.971
RVD (mm)	2.74	0.51	2.73	0.48	0.860
MLD (mm)	1.12	0.37	1.05	0.30	0.129
% diameter stenosis	59.41	10.64	60.93	10.45	0.236
Results post-stenting					
In-stent	n=167		n=153		
Stent length (mm)	16.98	6.74	17.01	8.29	0.975
RVD (mm)	2.88	0.49	2.84	0.43	0.471
MLD	2.55	0.46	2.55	0.38	0.977
% diameter stenosis	11.21	8.32	10.30	8.24	0.322
In-segment	n=160		n=143		
Segment length (mm)	25.51	6.98	25.26	8.11	0.776
RVD (mm)	2.83	0.50	2.80	0.45	0.554
MLD	2.25	0.55	2.27	0.44	0.636
% diameter stenosis	**21.15**	10.53	**18.62**	9.65	**0.030**
Results at 8 months FU					
In-stent	n=132		n=103		
Stent length (mm)	17.08	7.07	16.57	8.69	0.639
RVD (mm)	2.82	0.52	2.80	0.46	0.735
MLD	**2.16**	0.65	**1.77**	0.57	**<0.0001**
% diameter stenosis	**23.79**	16.33	**36.95**	16.93	**<0.0001**
Late loss	**0.41**	0.48	**0.81**	0.49	**<0.0001**
Binary restenosis*	**12 (9.1%)**		**29 (28.2%)**		**<0.0001**
In-segment	n=125		n=89		
Segment length (mm)	25.63	7.36	24.85	8.60	0.479
RVD (mm)	2.81	0.50	2.79	0.45	0.720
MLD	**1.99**	0.66	**1.69**	0.52	**<0.0001**
% diameter stenosis	**30.18**	17.39	**39.56**	15.04	**<0.0001**
Late loss	**0.29**	0.50	**0.64**	0.49	**<0.0001**
Binary restenosis*	**22 (17.6%)**		**27 (30.3%)**		**0.029**

*Results expressed as n(%)

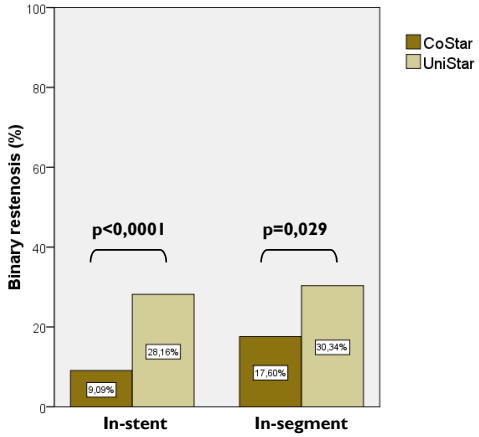

Figure 3: In-stent and in-segment binary restenosis (primary endpoint) of the CoStar DES and the UniStar BMS at 8 months follow-up.

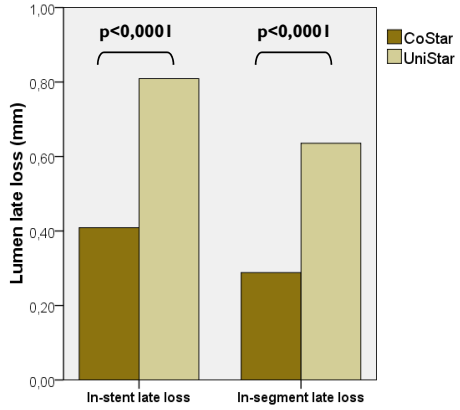

Figure 4: In-stent and in-segment absolute late lumen loss of the CoStar DES and the UniStar BMS at 8 months follow-up.

USA). Furthermore, in the COSTAR-II study, the performance of the CoStar reservoirs DES was assumed not to be significantly different from the "imputed" i.e. theoretically constructed, virtual BMS[27]. The hereby reported EUROSTAR-II trial was run simultaneously to the COSTAR-II trial. In contrast to COSTAR-II, EUROSTAR-II is the only randomized trial directly comparing the performance of the same reservoirs DES vs. an equivalent BMS platform of identical design. The EUROSTAR-II results definitely answer the question about the efficacy of reservoirs DES vs. BMS, at a higher level of evidence than indirect hypothetical placebo imputations of COSTAR-II. Our results are also more consistent with preceding evidence about the CoStar stent[25-27] and other reservoirs DES[33]. The hereby reported angiographic results for the CoStar DES (in-stent binary restenosis 9.1%, in-stent late loss 0.41mm) are in between the ones obtained in the CoStar-II trial (17.9%, 0.64mm, respectively)[28] and the values from preceding studies with the same device (0-5.7%, 0.28-0.38mm)[26,27]; being similar to Taxus Express

Table 4: Clinical follow-up results at 30 days and 8 months.

30 days FU	CoStar DES (n=152)	UniStar BMS (n=151)	Risk ratio			p-value
			Estimate	95% CI		
				Low	Up	
Death	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Cardiac	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Non cardiac	0 (0.0)	0 (0.0)	NA	NA	NA	NA
MI	1 (0.7)	2 (1.3)	0.50	0.05	5.42	0.995
Q-wave	0 (0.0)	1 (0.7)	NA	NA	NA	0.997
TVR	0 (0.0)	1 (0.7)	NA	NA	NA	0.997
TLR	0 (0.0)	1 (0.7)	NA	NA	NA	0.997
Stent thrombosis	0 (0.0)	1 (0.7)	NA	NA	NA	0.997
MACE (Cardiac death, MI, TLR)	1 (0.7)	3 (2.0)	0.33	0.03	3.15	0.611
Procedural success	148 (99.3)	140 (98.6)	1.01	0.98	1.03	0.967
8 months FU			**Hazard ratio**			**p-value**
			Estimate	95% CI		
				Low	Up	
Death	0 (0.0)	2 (1.3)	0.01	0.00	>1000	0.111
Cardiac	0 (0.0)	1 (0.7)	0.01	0.00	>1000	0.301
Non cardiac	0 (0.0)	1 (0.7)	0.01	0.00	>1000	0.223
MI	5 (3.3)	3 (2.0)	1.53	0.37	6.41	0.558
Q-wave	1 (0.7)	1 (0.7)	0.96	0.06	15.37	0.978
TVR	27 (17.8)	42 (27.8)	0.49	0.30	0.80	**0.003**
TLR	23 (15.1)	40 (26.5)	0.45	0.27	0.76	**0.002**
Stent thrombosis	0 (0.0)	1 (0.7)	0.02	0.00	>1000	0.312
MACE (Cardiac death, MI, TLR)	30 (19.7)	44 (29.1)	0.54	0.34	0.87	**0.010**

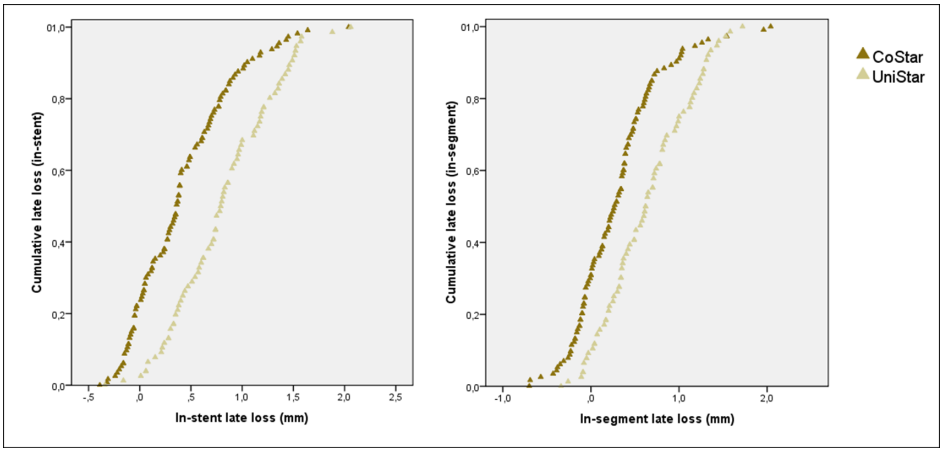

Figure 5: In-stent and in-segment late lumen loss cumulative curves of the CoStar DES and the UniStar BMS at 8 months follow-up.

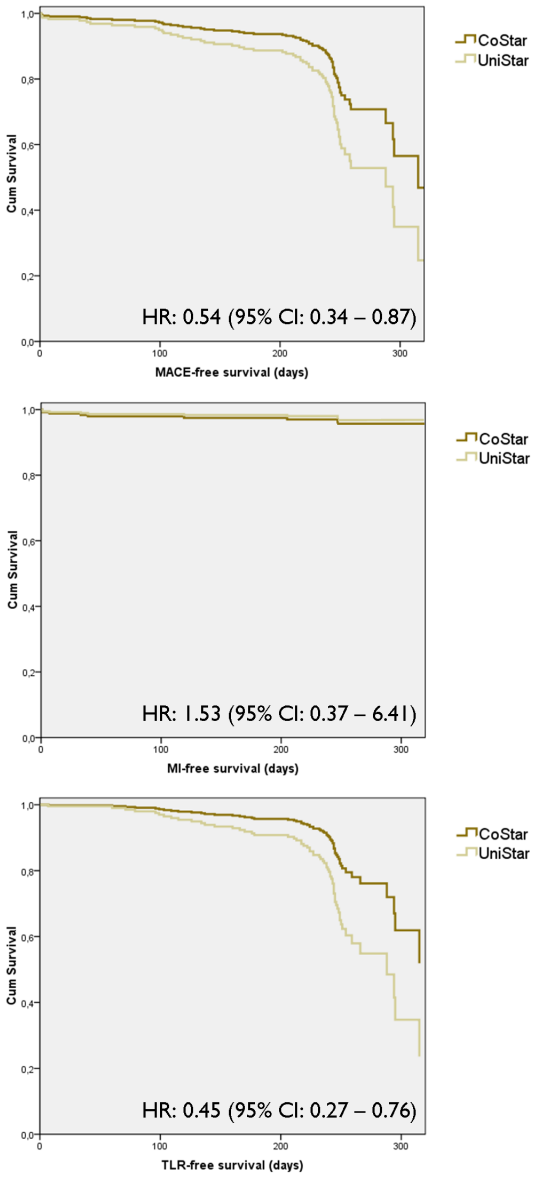

Figure 6: Event-free survival plots for the composite endpoint of major adverse cardiovascular events (MACE) at 8 months, comprising cardiac death (only 1 event, not represented in the charts), myocardial infarction (MI) and clinically-driven target lesion revascularization (TLR).

in its pivotal trial (5.5%, 0.39mm)[5]. The angiographic results for the UniStar BMS are also comparable to those reported for the BMS in TAXUS IV[5]. Putting into perspective the results of EUROSTAR-II with the preceding results, it seems that the first studies about the reservoirs CoStar DES overestimated its efficacy[26,27], but the present study proves that the reservoirs paclitaxel-eluting CoStar DES prevents restenosis compared to an equivalent BMS.

The incidence of MACE in this trial is however much higher than in any preceding study[5,26-28], so for the CoStar DES group as for the BMS control group. This excess of MACE is exclusively due to a much higher incidence of revascularization: TVR for the CoStar DES was 17.8%, whereas it was 8.1% in the COSTAR-II[28]; 2.8% in EUROSTAR-I[27] and 2.6% in PISCES[26]. Revascularization in the BMS group was also higher than in prior studies: TVR for the UniStar BMS was 27.8%, whilst it was 12.0% in the BMS arm of the TAXUS IV trial[5]. The reason explaining this excess of revascularization and consequently of MACE can be the coincidence in time of the clinical and angiographic follow-up at 8 months, resulting in some "oculostenotic" revascularizations performed during routine angiographic follow-up and accounted as clinically-driven. In fact the curves in figure 6 show a steep increase in both TLR and composite MACE around 244 days (8 months). In contrast, in COSTAR-II the primary clinical endpoint could not have been affected by the "oculostenotic" revascularization because it was defined at 8months with angiographic follow-up at 9 months. However the coincidence in time of the angiographic and clinical follow-up explains only partially these results: as compared with the TAXUS IV trial, binary restenosis was twice bigger in the CoStar than in the paclitaxel-surface coated Taxus Express stent, even though their late loss was similar and the restenosis rate in the BMS control arms was comparable[5]. Thus, the CoStar stent might be less efficient than Taxus for inhibition of neointimal hyperplasia, as suggested by COSTAR-II[28]. An optimized design of the honeycombed stent platform, and the different anti-proliferative drugs, with different dosage and kinetics of release, could have contributed to improve the clinical and angiographic outcomes of DES reservoir technology, as recently reported[33].

Limitations

This trial was performed on a selected population, with respect to clinical and angiographic features. This must be taken into account in the interpretation and generalization of the results.

Although the randomization process worked well in general, it resulted in the imbalanced distribution of the variable "prior coronary artery bypass graft surgery" between treatment groups. This imbalance might have biased the results at some extent, but the magnitude of this bias was deemed minor and therefore an eventual modification of the pre-specified statistical analysis was not considered to be justified.

Loss at angiographic follow-up was approx. 14%, therefore it remained in the range considered acceptable for the validity of studies with a primary angiographic endpoint. The attrition

at follow-up did not seem to affect selectively to any of the treatment groups. Nonetheless, some angiographic studies were discarded for QCA analysis due to insufficient quality. This might have introduced some selection bias in the results, although it affected both groups alike. In spite of this limitation, the QCA results are consistent with the clinical efficacy variables, less affected by loss or selection.

Although the absence of thrombotic events in the CoStar DES group is compatible with the hypothesis that a bioresorbable polymer might avoid delayed hypersensitivity reactions triggering very late thrombosis, this study, like all other DES randomized trials published so far, is underpowered for testing stent thrombosis and no valid conclusion can be stated in this regard.

CONCLUSION

As compared with an equivalent bare metal stent, paclitaxel elution from reservoirs resulted in significantly less binary restenosis, less late loss and lower revascularization rates at 8 months.. No safety concerns were observed.

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APPENDIX

This study was enabled by a study grant of BIOTRONIK, Berlin, Germany. The Steering Committee comprised Sigmund Silber, MD (principal investigator, Munich, Germany) as well as Harry Suryapranata, MD (Zwolle, The Netherlands) and Bernard Chevalier, MD (Massy, France). CRO and independent external monitoring was performed by DATATRAK, Bonn Germany. Data and Safety Monitoring Committee (DMSC) / Clinical Events Committee (CEC) members were Marcus Lins, MD, (Kiel, Germany), Didier Blanchard, MD, (Tours, France) and Jan Bart Hak, PhD, (Chairman, Groningen, The Netherlands).

"Rien n'a changé et pourtant tout existe d'une autre façon".

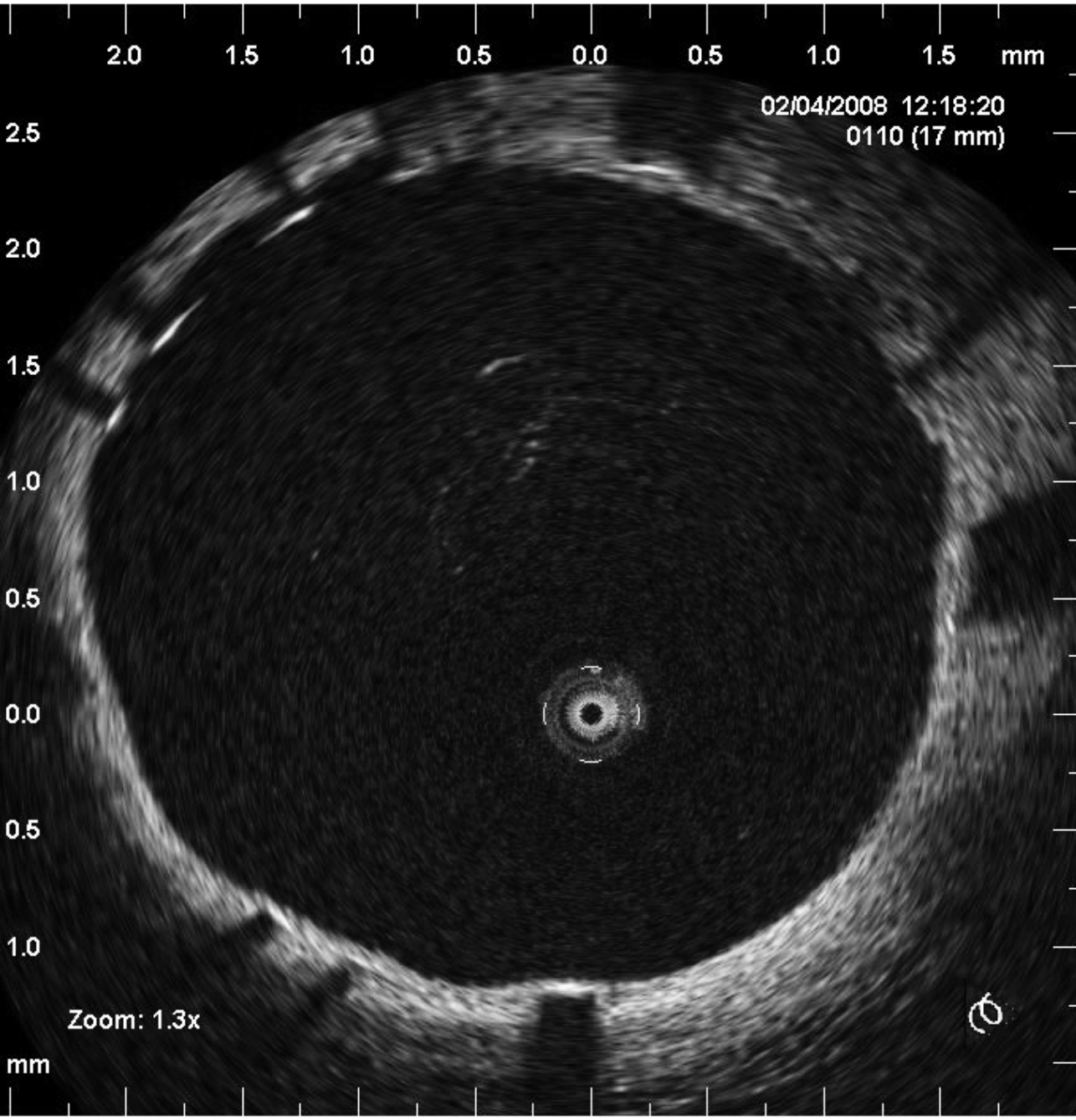
(Nothing has changed and however everything exists on a different way)

La Nausée

Jean-Paul Sartre

PART 5

METALLIC DRUG-ELUTING STENTS WITH BIOCOMPATIBLE POLYMERS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CHAPTER 7

Hydrophilic vs. hydrophobic polymers

Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13 months follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial.

Gutiérrez-Chico JL, van Geuns RJ, Regar E, van der Giessen WJ, Kelbæk H, Saunamäki K, Escaned J, Gonzalo N, di Mario C, Borgia F, Nüesch E, García-García HM, Silber S, Windecker S, Serruys PW.

Eur Heart J 2011;32:2454-2463.

STRUCTURED ABSTRACT

Aims: To compare the tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent (ZES) vs. a fluoropolymer-coated everolimus-eluting stent (EES) at 13 months, using optical coherence tomography (OCT) in an "all-comers" population of patients, in order to clarify the mechanism of eventual differences in the biocompatibility and thrombogenicity of the devices.

Methods and results: Patients randomized to angiographic follow-up in the RESOLUTE All Comers trial (NCT00617084) at pre-specified OCT sites underwent OCT follow-up at 13 months. Tissue coverage and apposition were assessed strut by strut, and the results in both treatment groups were compared using multilevel logistic or linear regression, as appropriate, with clustering at three different levels: patient, lesion and stent. 58 patients (30 ZES, 28 EES), 72 lesions, 107 stents and 23197 struts were analyzed. 887 and 654 uncovered struts (7.4% and 5.8%, p=0.378); 216 and 161 malapposed struts (1.8% and 1.4%, p=0.569) were found in the ZES and EES groups, respectively. Mean thickness of coverage was 116±99μm in ZES and 142±113μm in EES (p=0.466). No differences in percent neointimal volume obstruction (12.5±7.9 vs. 15.0±10.7%) or other areas-volumetric parameters were found between ZES and EES, respectively.

Conclusions: No significant differences in tissue coverage, malapposition or lumen/stent areas and volumes were detected by OCT between the hydrophilic-polymer coated ZES and the fluoropolymer-coated EES at 13 months follow-up.

Key words: Tomography, optical coherence; polymers; poly(vinylidene fluoride-co-hexafluoro propylene); zotarolimus; everolimus; drug-eluting stents; coronary vessels; Angioplasty, transluminal, percutaneous coronary.

ABBREVIATIONS

BMS: bare-metal stent
DES: drug-eluting stent.
EES: Everolimus-eluting stent
ISA: incomplete stent apposition.
IVUS: intravascular ultrasound.
MLA: minimal lumen area.
NASB: non-apposed side branch.
NIH: neointimal hyperplasia.
OCT: optical coherence tomography.
PCI: percutaneous coronary intervention.
QCA: quantitative coronary angiography
ZES: Zotarolimus-eluting stent

INTRODUCTION

The neointimal healing response after stenting strongly determines the long-term outcome. In the era of bare-metal stents (BMS) the concern was focused on an exaggerated neointimal proliferation, often leading to restenosis, that accounted for 20.0 – 50.3% of the cases[1]. Drug-eluting stents (DES) have reduced the restenosis rates to 7.9 - 8.9 %[1], due to their ability to inhibit cellular proliferation. However, since some reports suggested an eventually higher incidence of late and very late stent thrombosis in DES[2-5], the concern shifted to the opposite pole: avoiding an incomplete neointimal coverage of the metallic scaffold that might eventually pose a risk for stent thrombosis[6-10]. Intense research is currently aimed to promote optimal neointimal healing[11].

The neointimal healing response can be quantified in vivo by invasive imaging techniques. Intravascular ultrasound (IVUS) can quantify neointimal hyperplasia and discern whether it is exaggerated, but it cannot assess the completeness of healing, because the thin neointimal layer covering the DES struts is often below IVUS axial resolution (100 μm). Optical coherence tomography (OCT) provides an axial resolution of 10-15 μm, thus enabling accurate evaluation of tissue coverage after stenting. OCT coverage correlates well with histological neointimal healing and endothelialization after stenting in animal models[12-15], thus constituting an in-vivo surrogate to estimate the completeness of neointimal healing[14,15]. OCT has become an exploratory tool for the evaluation of healing in studies comparing different types of DES[16-18].

The polymers releasing the drug play a role in the modulation of the neointimal response after stenting. In first-generation DES some polymers were believed to induce allergic reactions and inflammation, resulting in incomplete neointimal healing and ultimately stent thrombosis[10,19]. The second generation of polymer coatings is designed to enhance biocompatibility and minimize the inflammatory reaction through different approaches[16,20]. The BioLinx polymer (Medtronic Inc., Santa Rosa, California, USA) comprises 3 different polymers: 1) the hydrophobic C10 acts as drug reservoir for a slow and sustained release, 2) the hydrophilic polyvinyl-pyrrolidinone improves biocompatibility, and 3) C19 contains both hydrophobic and hydrophilic polyvinyl pirrolidinone groups playing a role in the control of drug release and in the biocompatibility, respectively. The blend acts as an amphiphilic molecule, with topographic orientation of its hydrophilic components towards the surface in contact with the cells[21,22], thus improving the biocompatibility, since hydrophilic polymers do not induce activated monocyte adhesion[23], which is associated with local inflammation and vascular cells proliferation[24]. The BioLinx polymer also enables a finer and more sustained drug elution. In the porcine model 85% of the drug content is eluted into tissue during the first 60 days, and the remainder is completely eluted by 180 days[25]. Another contemporary biocompatible polymer is the fluoropolymer, poly(vinylidene fluoride-co-hexafluoropropylene). The fluoropolymer surface is hydrophobic, but elicits a biological response known as "fluoropassivation" which consists of minimizing the fibrin deposition and thrombogenicity,

reducing the inflammatory reaction and enhancing a faster neointimal healing[26,27]. Preferential affinity of fluorinated surfaces for albumin, with respect to fibrin, and the inhibitory effect of fluorination on platelets adhesion/activation or leucocytes recruitment have been postulated as mechanisms to explain this phenomenon.

The BioLinx polymer is a component of the Resolute stent (Medtronic, Santa Rosa, California, USA), together with the Driver BMS (Medtronic) and the antiproliferative agent zotarolimus, at a dose of 160μg/cm^2 [21]. The stent has proven excellent clinical and angiographic results in selected groups[28-30]. The RESOLUTE-All Comers trial (NCT00617084) compared for the first time the Resolute zotarolimus-eluting stent (ZES) vs. another DES (XIENCE V, Abbott Vascular , Santa Clara, California, USA) in an "all-comers" patient population, with a non-inferiority design[31]. XIENCE V is an everolimus-eluting stent (EES) at a dose of 100μg/cm^2 of stent surface, coated with a fluoropolymer, designed to release 80% of the everolimus in the first 30 days after deployment[32]. ZES proved to be non-inferior to EES for target-lesion failure, a composite of cardiac death, myocardial infarction and clinically indicated target-lesion revascularization[31]. Nevertheless, the interpretation of the stent thrombosis rates is still a matter of dispute: definite stent thrombosis was significantly higher in ZES than in EES (1,2% vs. 0.3%) at 1 year, but there were no significant differences in definite/probable stent thrombosis[31]. In order to better understand these clinical results, this OCT substudy of the RESOLUTE-All Comers trial compares the neointimal coverage of both devices 13 months after implantation.

METHODS

The design and main results from the RESOLUTE All Comers have been published elsewhere[31]. It was an international, multi-centre, prospective, randomized, open-label non-inferiority trial comparing the Resolute ZES, with BioLinx polymer vs. the XIENCE V EES, with fluoropolymer coating. Patient eligibility followed a real-world all-comers design, including patients with symptomatic coronary heart disease with every possible presentation or with silent ischaemia, with one or more coronary artery stenoses >50% in 2.25-4.00mm diameter vessels, susceptible to be treated with either of the two devices. There were no limitations regarding the number of lesions or vessels treated, or lesion length. Exclusion criteria comprised known allergy to anti-platelet /anti-thrombotic regimes, or to any of the components of the two stents of the study. Planned surgery in the following 6 months after PCI was also an exclusion criterion. The primary endpoint was target lesion failure, a composite of cardiac death, myocardial infarction (not clearly attributable to a non-target vessel) and clinically indicated target lesion revascularisation at 1 year follow-up.

Twenty percent of the patients were randomly selected for an angiographic sub-study, thus undergoing quantitative coronary angiography (QCA) at baseline and repeat angiography at 13 months follow-up. OCT was performed in patients in the angiographic sub-study

from selected sites in which OCT was available. The sample size was calculated for the angiographic substudy[31], but no formal sample size calculation based on an endpoint hypothesis was performed for the OCT substudy, because no evidence about the expected magnitude of the effect was available when the trial was designed. Based on unpublished data and on the expertise of the investigators with other ongoing OCT trials, a minimum number of 50 patients was considered necessary to provide reliable and non-trivial results.

Several clinical, angiographic and OCT variables were identified as secondary endpoints in the main RESOLUTE All Comers trial. The principal OCT endpoint was tissue coverage, evaluated as completeness of coverage (proportion of uncovered struts per stent) and as mean thickness of coverage. Additional OCT endpoints included apposition and standard areas and volumes.

OCT analysis

OCT pullbacks were obtained at 13 months follow-up with M2, M3 or C7 systems (Lightlab Imaging, Westford, Massachusetts, USA), depending on the site, using occlusive or non-occlusive technique, as appropriate[33] (Table 1).

Table 1: Characteristics of the different OCT systems* in the study.

	M2	M3	C7
Technique	Occlusive	Non-occlusive	Non-occlusive
Domain	Time	Time	Fourier
Catheter	ImageWire	ImageWire	Dragonfly
Rotation speed (frames/s)	15.6	20	100
Pullback speed (mm/s)	2	3	20
Patients with ZES	1	9	20
Patients with EES	2	9	17
Total	3	18	37

*All systems and catheters from Lightlab Imaging, Westford, Massachusetts, USA.
ZES: zotarolimus-eluting stent; EES: everolimus-eluting stent.

OCT pullbacks were analysed offline in a core-laboratory (Cardialysis BV, Rotterdam, the Netherlands) by independent analysts blinded to stent-type allocation and clinical and procedural characteristics of the patients, using proprietary software (Lightlab Imaging). Cross-sections at 1mm intervals within the stented segment and 5mm proximal and distal to the stent edges were analyzed. Lumen and stent areas were drawn in each analysed cross-section, and the derived incomplete stent apposition (ISA) or neointimal hyperplasia (NIH) areas were calculated as appropriate. A metallic strut typically appears as a bright signal-intense structure with dorsal shadowing. Apposition was assessed strut by strut by

measuring the distance between the strut marker and the lumen contour. The marker of each strut was placed at the endoluminal leading edge, in the mid-point of its long-axis, and the distance was measured following a straight line connecting this marker with the centre of gravity of the vessel[34] (Figure 1). Struts with distance to lumen contour larger than the sum of strut + polymer thickness were considered malapposed. This resulted in ISA thresholds of >97µm for ZES and >89µm for EES. Struts located at the ostium of side branches, with no vessel wall behind, were labelled as non-apposed side-branch (NASB) struts and excluded from the analysis of apposition (Figure 1).

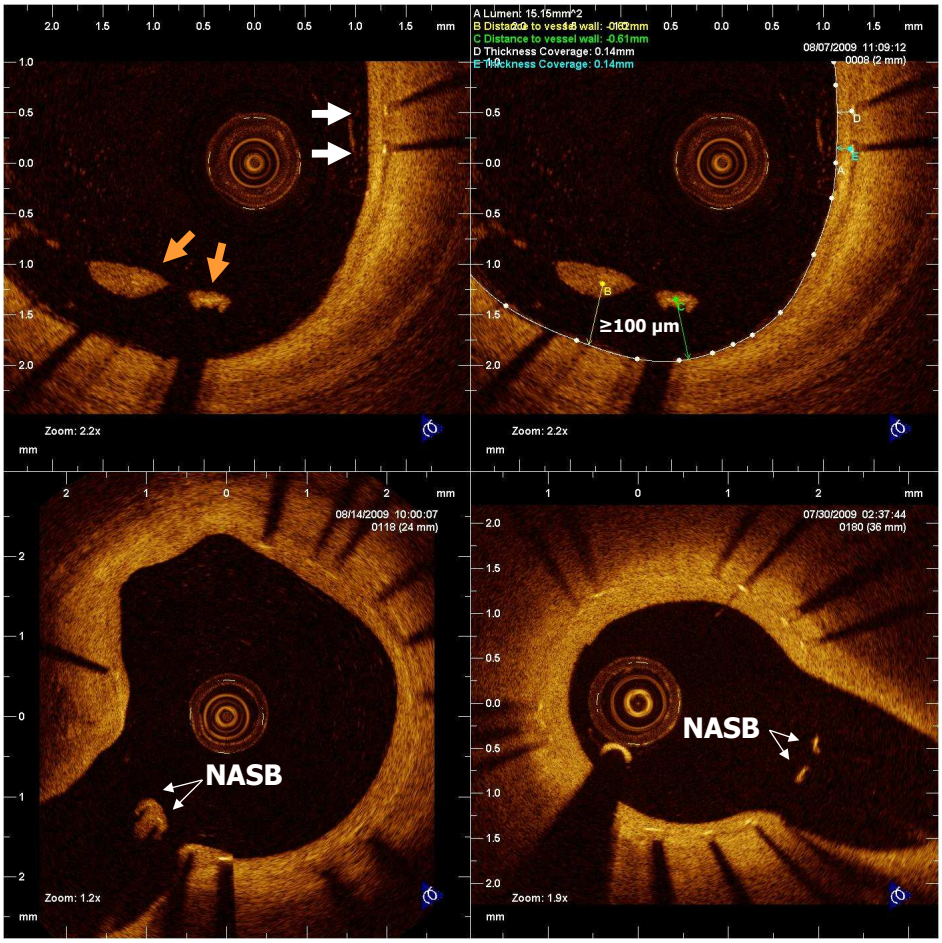

Figure 1:

Categories of apposition.

OCT cross-sections showing examples of struts in the 3 different categories of apposition: Well-apposed (white arrows), ISA (orange arrows) and NASB.

Struts were classified as uncovered if any part of the strut was visibly exposed to the lumen, or covered if a layer of tissue was visible over all the reflecting surfaces. In covered struts, thickness of coverage was measured from the strut marker to the endoluminal edge of the tissue coverage, following a straight line connecting the strut marker with the centre of gravity of the vessel (Figure 2).

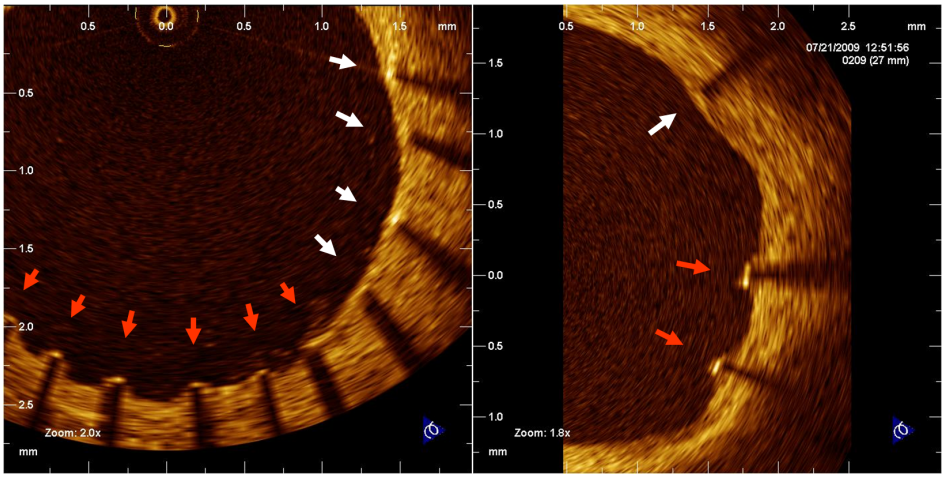

Figure 2:
Coverage.
OCT cross-sections showing examples of covered (white arrows) and non-covered struts (red arrows).

To summarize the spatial distribution of the uncovered struts along the stents, "spread-out vessel graphics" were created by correlating the longitudinal distance from the distal edge of the stent to the strut (abscises) with the angle where the struts were located in the circular cross-section section respect to the centre of gravity of the vessel (ordinates). The resultant graphic represented the stented vessel, as if it had been cut longitudinally along the reference angle 0º and spread out on a flat surface (Figure 3).

Statistical analysis

Results are reported as mean±standard deviation for continuous variables, and as count (percent) for nominal variables. Continuous variables with normal distribution were compared with Student's t-test for independent samples, or with U-Mann-Whittney in the case that normal distribution could not be assumed. Nominal variables were compared with Fisher's exact test.

In the per strut analysis, apposition was estimated through a categorical variable, comprising three possible excluding categories (well-apposed, ISA or NASB). Tissue coverage was

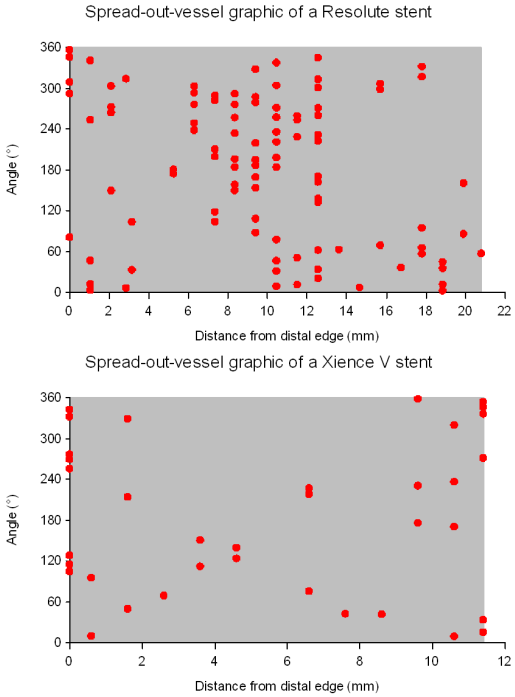

Figure 3:

Spread-out-vessel graphs.

The X-axis represents the distance from the distal edge of the stent to the strut; the Y-axis represents the angle where the strut is located in the circular cross section respect to the centre of gravity of the vessel. The result is a graphic representing the spatial distribution of the non-covered stents (red spots) along the stent, as if it had been cut along the reference angle (0º) and spread out on a flat surface.

estimated through the proportion of uncovered struts (dichotomous variable) and through the mean thickness of coverage (continuous). Dichotomous or categorical variables were analyzed using multi-level logistic regression models with random effects at 4 different levels: 1) treatment arm, 2) patient, 3) lesion, 4) stent. Likewise, continuous variables were analyzed using multi-level linear regression models with random effects at the same 4 levels. Overlapping stents and stents separated by a gap <5mm length within the same coronary segment were assigned to the same coronary lesion. Overlap segments were considered separate units of clustering at the stent level for the per strut multilevel analysis.

All statistical analyses were performed according to the intention-to-treat as specified in the protocol, using the SAS v8.2 package (SAS Institute Inc., Cary, North Carolina, USA). All tests were two-sided and p-value <0.05 was considered statistically significant.

Table 2: Baseline patient characteristics.

	ZES (n=30)	EES (n=28)	p-val
Age (years)	60.9 (12.5)	62.6 (8.9)	0.547
Males	23 (76.7%)	23 (82.1%)	0.749
BMI (kg/m^2)	83.7 (18.4)	28.8 (4.8)	0.476
Cardiovascular risk factors			
	18 (60.0%)	15 (53.6%)	0.791
	7 (23.3%)	7 (25%)	1.000
Insulin-requiring	0 (0.0%)	2 (7.1%)	0.229
Hypercholesterolemia	21 (70.0%)	20 (71.4%)	1.000
Smoking	18 (60.0%)	16 (57.1%)	1.000
Current smoker (<30d)	11 (36.7%)	9 (32.1%)	0.787
Family history of CHD	7 (35.0%)	11 (50.0%)	0.366
Antecedents			
	7 (25.0%)	9 (32.1%)	0.768
	8 (26.7%)	4 (14.3%)	0.336
With BMS	1 (3.3%)	3 (10.7%)	0.344
With DES	5 (16.7%)	1 (3.6%)	0.195
Previous CABG	2 (6.7%)	3 (10.7%)	0.665
Clinical presentation			
Stable angina	16 (53.3%)	11 (39.3%)	0.306
Unstable angina	3 (10.0%)	5 (17.9%)	0.464
Myocardial infarction	9 (30%)	10 (35.7%)	0.781
STEMI	6 (20.0%)	7 (25.0%)	0.757
Silent ischaemia	2 (6.7%)	2 (7.1%)	1.000
Serum creatinine (µmol/L)	76.2 (18.1)	87.4 (23.6)	**0.048***
Ejection fraction (%)	65 (10)	55 (11)	**0.041***
Angiographic characteristics			
Nr of diseased major vessels			
One	22 (73.3%)	22 (78.6%)	0.762
Two	7 (23.3%)	6 (21.4%)	1.000
Three	1 (3.3%)	0 (0.0%)	1.000
LM + 3 vessels	0 (0.0%)	0 (0.0%)	NA
Syntax score	14.13 (12.19)	14.19 (9.10)	0.984

* p≤0,05

Data presented as # of events(%) or mean(SD), as appropriate.

BMI: Body Mass Index; BMS: Bare Metal Stent; CABG: Coronary Artery By-pass Graft; CHD: Coronary Heart Disease; DES: Drug-eluting stent; DM: Diabetes Mellitus; EES: everolimus-eluting stent; LM: Left Main Stem; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; STEMI: ST elevation myocardial infarction; ZES: Zotarolimus-eluting stent.

RESULTS

2292 patients were enrolled in the RESOLUTE All Comers trial. 58 patients (30 ZES, 28 EES) with 107 stents in 72 lesions underwent OCT at 13 months. 9 out of 2718 (0.33%) cross-sections were deemed of insufficient quality for the quantitative analysis. In total 23197 struts were analyzed. Tables 2-4 show the baseline characteristics of patients, procedures and lesions, respectively, in both treatment arms. The randomization produced comparable groups, except patients who received EES had significantly higher serum levels of creatinine and lower left ventricular ejection fraction than the patients who received ZES. No clinical events were observed in the patients in the OCT substudy, except for a non-Q wave myocardial infarction in the EES group. No patient was excluded from the study on the basis of clinical outcomes.

Tables 5-6 show mean in-stent areas and volumes in non-overlapping and overlapping segments, respectively, without significant differences between both stent types. Table 7 shows the comparative results of the variables estimating apposition and tissue coverage.

Table 3: Procedural characteristics (per patient).

	ZES (n=30)	EES(n=28)	p-val
Contrast (ml)	264.0 (148.6)	265.8 (125.4)	0.962
Procedure duration (min)	59.1 (40.3)	56.7 (41.8)	0.826
Nr vessels treated	1.30 (0.54)	1.21 (0.42)	0.501
LAD	15 (50.0%)	13 (46.4%)	0.799
LCX	8 (26.7%)	9 (32.1%)	0.775
RCA	15 (50.0%)	11 (39.3%)	0.441
LM	1 (3.3%)	1 (3.6%)	1.000
Nr of lesions treated	1.4 (0.7)	1.5 (0.6)	0.711
Nr of stents implanted	2.0 (1.8)	2.4 (1.2)	0.381
Total stented length (mm)	40.1 (42.6)	47.9 (29.7)	0.428
Cross-over	0 (0.0%)	0 (0.0%)	NA
On-label use	13 (43.3%)	10 (35.7%)	0.600
Long lesion (>27mm)*	3 (12.0%)	3 (13.6%)	1.000
Small vessel (<2.5mm diameter)*	12 (48.0%)	15 (68.2%)	0.238
Antiplatelet therapy			
Dual at 6 months	28 (93.3%)	27 (96.4%)	1.000
Dual at 12 months	27 (90.0%)	26 (92.9%)	1.000
Aspirin at 12 months	28 (93.3%)	27 (96.4%)	1.000
Clopidogrel at 12 months	29 (96.7%)	27 (96.4%)	1.000

Data presented as # of events(%) or mean(SD), as appropriate.

EES: everolimus-eluting stent; LAD: Left anterior descending; LCX: Left Circumflex; LIMA: Left internal mammary artery; LM: Left Main Stem; RCA: Right coronary artery; SVG: Saphenous vein graft; ZES: Zotarolimus-eluting stent.

*Derived from QCA data.

Table 4: Lesions characteristics.

	ZES (n=36)	EES (n=36)	p-val
Target vessel			
LM	0 (0.0%)	1 (2.8%)	1.000
LAD	14 (38.9%)	15 (41.7%)	1.000
LCX	5 (13.9%)	6 (16.7%)	1.000
RCA	17 (47.2%)	14 (38.9%)	0.634
Pre-procedural TIMI flow			
0	6 (16.7%)	6 (16.7%)	1.000
I	1 (2.8%)	2 (5.6%)	1.000
II	3 (8.3%)	2 (5.6%)	1.000
III	26 (72.2%)	26 (72.2%)	1.000
Post-procedural TIMI flow			
II	1 (2.8%)	0 (0.0%)	1.000
III	35 (97.2%)	36 (100.0%)	1.000
TO	6 (16.7%)	6 (16.7%)	1.000
Ostial lesion	1 (2.8%)	1 (2.8%)	1.000
Bifurcation	8 (22.2%)	12 (33.3%)	0.430
Moderate or severe calcification	8 (22.2%)	5 (13.9%)	0.541
Angiographic edge dissections	1 (2.8%)	0 (0.0%)	1.000
Complications	0 (0.0%)	0 (0.0%)	NA
QCA characteristics			
Lesion length (mm)	16.6 (9.9)	13.8 (10.0)	0.297
Pre-stenting			
RVD (mm)	2.84 (0.56)	2.59 (0.54)	0.089
MLD (mm)	0.88 (0.58)	0.78 (0.51)	0.438
% diam stenosis	69(19)	70 (19)	0.942
Post-stenting			
In-stent			
RVD (mm)	2.91 (0.49)	2.82 (0.45)	0.401
MLD (mm)	2.44 (0.51)	2.40 (0.48)	0.717
% diam stenosis	16 (8)	15 (7)	0.476
In-segment			
RVD (mm)	2.83 (0.47)	2.66 (0.46)	0.116
MLD (mm)	2.15 (0.44)	2.01 (0.39)	0.161
% diam stenosis	24 (9)	24 (9)	0.923

* $p \leq 0,05$

Data presented as # of events(%) or mean(SD), as appropriate.

EES: everolimus-eluting stent; LAD: Left anterior descending; LCX: Left Circumflex; LIMA: Left internal mammary artery; LM: Left Main Stem; MLD: Minimal Lumen Diameter; QCA: Quantitative Coronary Angiography; RCA: Right coronary artery; RVD: Reference vessel diameter; TO: Total occlusion; ZES: Zotarolimus-eluting stent.

Lesion length and RVD were not available for 17 lesions due to initial TIMI flow 0/I; for one lesion in the ZES group the pre-stenting lesion length, RVD, MLD and % diameter stenosis could not be determined due to overlapping vessels.

Figure 4:

Spread-out-vessel graphics showing non-covered struts of the 109 stents and corresponding overlaps analyzed at 13 months. The graphic summarizes the spatial distribution of non-coverage and its clustering of at the four considered levels (allocation to treatment, patient, lesion, stent).