Short-term effects of Nano+™ polymer-free sirolimus-eluting stents on native coronary vessels: an optical coherence tomography imaging study

Pannipa Suwannasom[1,2], MD; Edouard Benit[3], MD; Olivier Gach[4], MD, PhD; Clemens von Birgelen[5], MD, PhD; Sjoerd H. Hofma[6], MD, PhD; Xu Bo[7], MBBS; Yao-Jun Zhang[8], MD, PhD; Shimpei Nakatani[1], MD; Yuki Ishibashi[1], MD, PhD; Yoshinobu Onuma[1,9], MD, PhD; Hector M. García-García[1,9], MD, PhD; Runlin Gao[7], MD; Patrick W. Serruys[10]*, MD, PhD

1. Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; 2. Northern Region Heart Center, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; 3. Hasselt Heart Centre, Jessa Ziekenhuis, Hasselt, Belgium; 4. CHU de Liege, Liege, Belgium; 5. Thoraxcentrum Twente, University of Twente, Enschede, The Netherlands; 6. Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands; 7. National Center for Cardiovascular Diseases, Fu Wai Hospital, Beijing, China; 8. Nanjing First Hospital, Nanjing Medical University, Nanjing, China; 9. Cardialysis BV, Rotterdam, The Netherlands; 10. International Centre for Circulatory Health, NHLI, Imperial College London, London, United Kingdom

KEYWORDS

- drug-eluting stent
- neointimal hyperplasia
- optical coherence tomography
- polymer-free stent

Abstract

Aims: Newly developed drug-eluting stents (DES) aim to promote early endothelialisation and prevent stent thrombosis. We sought to evaluate the extent of neointima growth by optical coherence tomography (OCT) three months after implantation of a polymer-free stent with a nano-sized-pore surface eluting sirolimus.

Methods and results: In this prospective, multicentre, open-label study, patients were enrolled with documented stable angina or silent ischaemia and planned intervention for up to two *de novo* coronary lesions (in different vessels), with lesion length of ≤18 mm. The primary OCT endpoint was the percentage of in-stent neointimal volume obstruction at three months. The secondary endpoints included binary restenosis, stent thrombosis and device-oriented composite endpoints: a composite of cardiac death, myocardial infarction (MI) non-attributable to non-target vessel and clinically indicated target lesion revascularisation at three months. A total of 45 patients with 47 lesions were enrolled from four European sites. Eventually, 43 patients with 45 lesions underwent OCT examination at three months (one case was excluded for poor image quality and one case due to catheter dysfunction). The median and interquartile range of in-stent neointimal volume obstruction was 8.2% (4.7-10.7), of strut coverage was 93.0% (83.2-96.5) and of incomplete apposed struts was 0% (0.0-0.9), respectively. At three months, the mean angiographic in-stent late lumen loss was 0.17±0.27 mm. No case of stent thrombosis, cardiac death or clinically indicated target lesion revascularisation was reported at three months.

Conclusions: Polymer-free sirolimus-eluting stents with a nano-sized-pore surface are effective in inhibiting neointimal tissue proliferation and promoting early vascular healing with high strut coverage at three-month follow-up. (ClinicalTrials.gov number: NCT01925027).

*Corresponding author: P.O. Box 2125, 3000 CC Rotterdam, The Netherlands.
E-mail: patrick.w.j.c.serruys@gmail.com

Introduction

Bare metal stents (BMS) have practically been replaced by drug-eluting stents (DES), as previous trials have shown a reduction of in-stent-restenosis and repeat revascularisation[1-4]. To prevent the formation of neointimal hyperplasia, current DES are coated with a thin polymer film which regulates the amount of drug that is eluted into the treated vessel. Accumulating evidence shows that permanent polymer could trigger a chronic inflammatory response, which is characterised by a delayed re-endothelialisation, resulting in incomplete strut coverage and the potential for late stent thrombosis (LST)[5-7]. Based on these considerations, newer generations of DES have focused on the safety profile, changing from durable polymer to biodegradable polymer and ultimately to polymer-free stents in order to diminish vascular inflammation further. The assessment of vascular repair (i.e., to quantify strut coverage) after stent implantation by using optical coherence tomography (OCT) has shown that strut coverage is higher in biodegradable polymer stents than in permanent polymer stents[8,9]. So far, there have been only a few studies assessing strut coverage at a very short-term time point (three months). Also, there have been only two OCT studies[10,11] which examined the patterns of strut coverage in polymer-free stents. In the present study, the polymer-free stent with a nano-sized-pore surface has been considered as an alternative modality of local drug delivery. We hypothesised that polymer-free stents have an early arterial healing, thereby reducing the risk of late stent thrombosis, and a controlled growth of neointima, which may reduce the likelihood of restenosis. In our present study, we sought to evaluate the extent of three-month neointimal coverage after the implantation of polymer-free nano-sized-pore surface sirolimus-eluting stents (SES) (Nano+™, Lepu Medical, Beijing, China).

Methods

TRIAL DESIGN

We performed a prospective, multicentre, single-arm, open-label study in coronary artery disease patients enrolled in four European investigational sites between August 2013 and June 2014. Selection criteria included: 1) patients who had documented stable angina or silent ischaemia demonstrated by positive functional study with a *de novo* target lesion of >50% diameter stenosis; 2) planned intervention on up to two *de novo* lesions in different epicardial vessels; 3) lesion length of less than 18 mm; 4) native coronary artery of 2.5-4.0 mm diameter; and 5) patient and physician agreement to follow-up visits including angiographic and OCT assessment at three months. Major clinical exclusion criteria included: 1) evidence of ongoing acute myocardial infarction in ECG prior to procedure; 2) left ventricular ejection fraction <30%; and 3) known hypersensitivity or contraindication to medication or material in the study. Angiographic exclusion criteria included: severe tortuous, calcified or angulated coronary anatomy of the study vessel which in the opinion of the investigator would result in suboptimal imaging or excessive risk of complication from placement of an OCT catheter; target lesion in left main stem; target lesion involving a side branch >2.0 mm in diameter; aorto-ostial lesion (within

3 mm of the aorta junction); total occlusion or TIMI flow 0 prior to wire crossing; target vessel containing visible thrombus; restenotic lesion; arterial or saphenous vein graft lesions or lesions distal to a diseased arterial or saphenous vein graft.

All major adverse cardiac events were adjudicated by an independent clinical events committee, and a data safety monitoring board monitored patient safety. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent.

STUDY DEVICE

The Nano+™ is a drug-coated stent which consists of a stainless steel platform crimped onto a delivery system which includes a high-pressure, semi-compliant balloon incorporated into the distal tip of a rapid exchange delivery catheter system. The strut thickness is 91 μm. The two ends of the stent present a sinusoidal curve shape while the middle parts have a special cyclic structure, all aligning in a helix shape (**Figure 1A** and **Figure 1B**). A large number of pores are present on the adluminal stent surface (**Figure 1C** and **Figure 1D**). The pore diameter is 400 nm and occupies only 1/800 of the stent thickness. The delivery system has a crossing profile of 0.93 mm with two radiopaque markers at the ends of the balloon to facilitate proper stent placement. For this trial, the Nano+ stent was available in five nominal stent diameters (2.5-4.0 mm), and eight lengths (9-36 mm). In summary, the stent releases the antiproliferative agent from the pores directly into the vessel wall without the use of any drug-eluting polymer as coating. Nano+ has a sirolimus dose of 2.2 μg/mm^2 and 85% of the drug is released within 30 days.

CORONARY STENT PROCEDURE

All patients received dual antiplatelet therapy before the procedure (oral aspirin 160-300 mg per day and clopidogrel or prasugrel or ticagrelor). Intraprocedural anticoagulation was achieved with unfractionated heparin as per standard practice. After the procedure, all patients were required to receive aspirin 75-100 mg per day indefinitely and a once daily dose of clopidogrel 75 mg or prasugrel 10 mg or ticagrelor 90 mg bid for the whole length of the study. Three types of biomarker (creatinine kinase, creatinine kinase-MB and troponin T or I) were sampled at least 24 hours prior to PCI and determined pre-discharge or within 48 hours, whichever came first. The highest value per reference was taken into consideration for adjudication of myocardial infarction. Patients will have clinical follow-up at six months and one year.

QUANTITATIVE CORONARY ANALYSIS

Two-dimensional quantitative coronary analysis (QCA) was performed at an independent core lab (Cardialysis BV, Rotterdam, The Netherlands) with the CAAS system (CAAS 5.9; Pie Medical BV, Maastricht, The Netherlands). The region of interest was the stented segment and the peri-stent segment, defined as 5 mm proximal and distal to the stent edge. The following parameters for QCA were computed: minimal luminal diameter (MLD), percentage of diameter stenosis (%DS) and reference vessel diameter (RVD). Binary
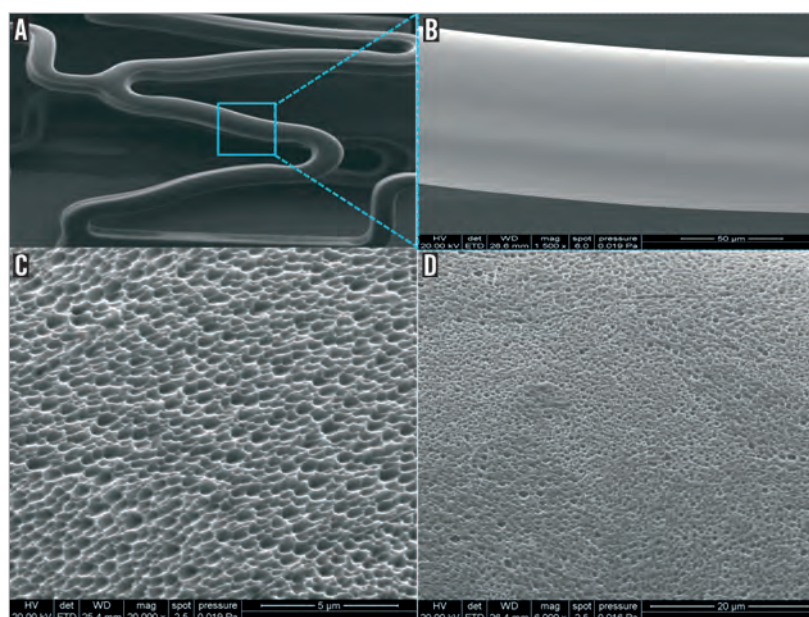
Figure 1. *Stent design. Strut design after expansion (A). The strut thickness is 91 μm (B), and a large number of sirolimus-filled pores are present on the adluminal stent surface. Electron microscopy shows the size of the nano pores at a magnification of 20,000x (C) and 6,000x (D).*

restenosis was defined as a diameter stenosis of 50% or more in any of the studied segments (stent and peri-stent segments) at follow-up. Late loss was defined as the difference between post-procedure MLD and follow-up MLD.

OCT IMAGING AND ANALYSIS

At three-month follow-up, OCT was performed using the three different frequency-domain OCT systems (C8 ILUMIEN OPTIS PCI Optimization System and Dragonfly II™ OCT catheter; C7-XR™ OCT Intravascular Imaging System and Dragonfly™ catheter; both consoles and catheters are from St. Jude Medical, St. Paul, MN, USA; LUNAWAVE OFDI System and FastView™ OFDI Imaging Catheter; Terumo, Tokyo, Japan). The intravascular imaging catheter was placed distal to the region of interest. OCT imaging commenced at a pullback speed of 18 mm/sec which retrieved images at 180 frames per second by Dragonfly II™ catheter, 20 mm/sec, 100 frames per second by Dragonfly™ catheter, and 20 mm/sec, 158 frames per second by FastView™ catheter.

All OCT images were analysed at an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) by analysts who were blinded to patient and procedural information. QIvus 2.2 software (Medis, Leiden, The Netherlands) was used. Cross-sectional OCT images were analysed at 1 mm intervals. Stent and luminal cross-sectional areas (CSA) were measured, and the neointimal cross-sectional area was calculated as the stent CSA minus the luminal CSA. The stent volume (SV), lumen volume (LV) and neointimal volume (NV=SV- LV) were also computed. Percentage of in-stent neointimal volume obstruction (%NVO) was calculated as NV/SV x 100%. Neointimal thickness was defined as the distance between the endoluminal surface of the neointima and the luminal surface of the strut reflection at the mid-point of the strut

and on a line perpendicular to the neointima and strut. A covered strut was defined as having neointimal thickness more than 0 μm[12]. The percentage of covered struts was calculated as the number of covered struts ×100 divided by the number of total struts which were analysable. Incomplete strut apposition was defined as a clear separation between strut and vessel wall with a distance greater than the thickness of the strut (91 μm). The spread-out sheets of each individual stent were created displaying struts using colour codes for coverage status. The graphics were obtained by correlating the longitudinal distance of each strut from the distal edge of the scaffold with the angle defining its circumferential position with respect to the centre of gravity of the vessel in each OCT pullback, taking as reference 0° the position at 3 o'clock[13-17].

In addition, the healing index to quantify the degree of vessel healing was calculated[18,19]. This score combines the following parameters: a) presence of intraluminal defect (%ILD; ILD area both free from the wall and attached to lumen/stent area) is assigned a weighting factor of "4"; b) presence of both malapposed and uncovered struts (%MU) is assigned a weighting factor of "3"; c) presence of uncovered struts alone (%U) is assigned a weighting factor of "2"; d) presence of malapposition alone (%M) is assigned a weighting factor of "1"; and finally e) presence of neointimal volume obstruction of more than 30% will be calculated by %NVO minus 30 then assigned a weighting factor of "1" (if neointimal volume was less than 30% , this factor was omitted). The parameters used to compute the healing index are shown in **Figure 2**.

STUDY ENDPOINTS

The primary endpoint was the percentage of in-stent neointimal volume obstruction at three-month follow-up. The secondary endpoints were angiographic, OCT and clinical endpoints.
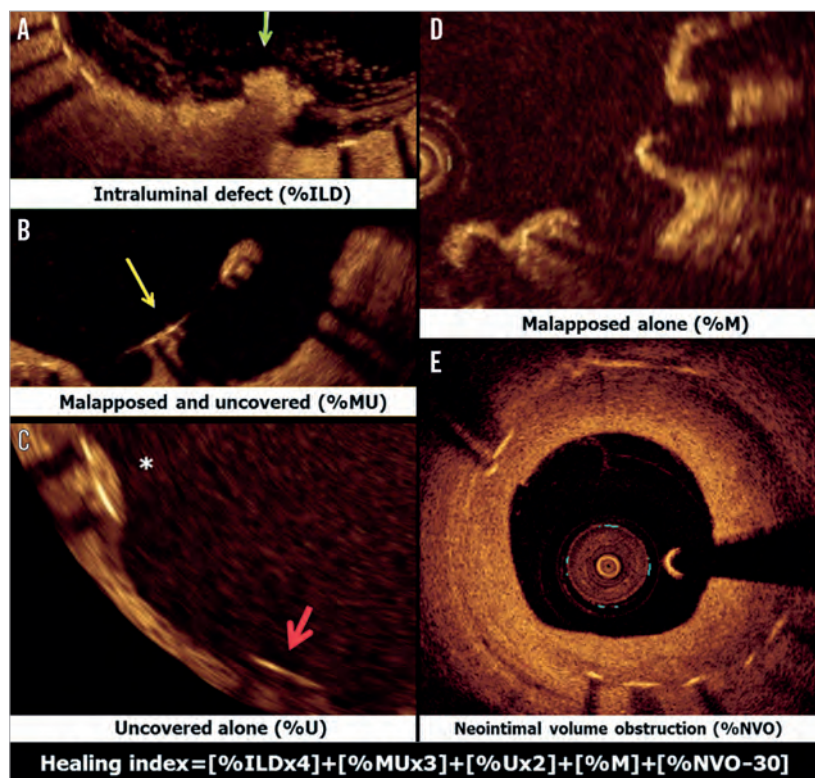
Figure 2. *Example of five parameters used for healing index calculation. The healing index was weighted according to OCT findings. The score was calculated from the presence of: (i) intraluminal defect area (A, green arrow); (ii) malapposed and uncovered struts (B, yellow arrow); (iii) uncovered struts alone (C, red arrow, as opposed to struts labelled with an asterisk which were covered struts); (iv) malapposition alone (D, all four struts were malapposed with good neointimal coverage); and (v) neointimal volume obstruction more than 30% (E). This parameter will be omitted if neointimal volume obstruction less than 30%. ILD: intraluminal defect; M: malapposition; MU: malapposed and uncovered; NVO: neointimal volume obstruction; U: uncovered*

The angiographic endpoints were binary restenosis, late lumen loss, MLD and percentage of diameter stenosis (%DS) post-procedure and at three months. The OCT endpoints were neointimal area and volume, mean stent area and volume, mean lumen area and volume, minimal stent area and volume, minimal lumen area and volume, neointimal thickness of the strut coverage, percentage of covered struts, and incomplete strut apposition area at three months. The clinical endpoints of this study were: 1) device-oriented composite endpoints (DOCE) and their individual components; 2) acute success; 3) stent thrombosis (ST) according to the definitions of the Academic Research Consortium[20].

Definitions of clinical endpoints

The device-oriented composite endpoints (DOCE) were defined as cardiac death, myocardial infarction not clearly attributable to a non-intervention vessel, and clinically indicated target lesion revascularisation. The definition of cardiac death included any death with immediate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia); deaths related to the procedure, including those related to concomitant therapy; unwitnessed death; and death of unknown cause. In this study, the per protocol definition for MI was the World Health Organization (WHO) MI definition[21], i.e., the development of new pathological Q-waves or creatinine kinase rise of two or more times the upper limit of normal (ULN) accompanied by a creatinine kinase-MB rise. Other definitions were equally assessed in enzymatic terms as follow: 1) the third universal definition of myocardial infarction (TUD)[22] is defined by an elevation of cardiac troponin values >5x the upper reference limit in patients with normal baseline value; 2) the SCAI definition[23] is defined by an elevation of CK-MB >10x ULN or, in the absence of CK-MB measurements, elevation of cardiac troponin (cTn T or I) >70x ULN. Some of these criteria require additional criteria, such as symptoms, new ischaemic ECG changes or new LBBB, angiographic loss of patency of a major coronary artery or side branch or persistent slow- or no-flow or embolisation, or imaging demonstrating new loss of viable myocardium or regional wall motion abnormality.

Target lesion revascularisation is defined according to the definition of the Academic Research Consortium[20]. Acute success was a composite of: 1) device success defined as successful implantation of the study device with less than 30% residual stenosis by visual assessment; 2) procedural success is considered successful if there is post-procedure in-stent diameter stenosis <30% by visual assessment and TIMI 3 at post-procedure or TIMI 2 at pre-and post-procedure and no occurrence of in-hospital DOCE.

SAMPLE SIZE AND STATISTICAL METHODS

For the Nano+ OCT study, no formal sample size calculation was performed as there were no previous data concerning the expected magnitude of the effect. The endpoint analyses presented in this report were performed on an intention-to-treat basis. Categorical variables were summarised with frequencies and percentages. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile ranges depending on the distribution of the data. The Student's t-test or non-parametric test was used to compare continuous variables. The statistical software used in this study was SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

ROLE OF THE FUNDING SOURCE

The investigators designed the study. Data collection and data analysis were performed at an independent central research organisation (Cardialysis BV, Rotterdam, Netherland). The sponsor had no role in data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

PATIENT AND PROCEDURAL CHARACTERISTIC

A total of 45 patients were enrolled in the study (details of recruitment are provided in the Appendix). **Table 1** shows baseline clinical characteristics, risk factors and current medication. The mean age of patients was 64.0±9.8 years with male predominance. The lesion characteristics are shown in **Table 2**. The right coronary artery was the most frequently treated vessel and half of the patients had a B2 lesion classification. The number of study stents implanted was 1.1 per lesion, with overlapping stents in four lesions. Procedural success was achieved in 44 patients; one patient did not meet the criteria of procedural success since this patient had sustained a periprocedural MI.

ANGIOGRAPHIC RESULTS

The QCA data at pre-procedure, post-procedure and at three months in all 47 lesions are shown in **Table 3**. The %DS was 60.9±10.8 before the intervention, 9.9±5.5 after the intervention, and 12.9±8.6 after three months. The procedure-induced acute lumen gain was 1.50±0.38 mm. At three-month follow-up, late lumen loss was 0.17±0.27 mm, and there was no evidence of binary restenosis (%DS >50%).

OPTICAL COHERENCE TOMOGRAPHY ANALYSIS

OCT was performed in 43 patients (two patients were excluded from the analysis due to poor OCT image quality [n=1] and OCT catheter dysfunction [n=1]). **Table 4** presents the results of OCT analysis of the primary endpoint. A total of 45 lesions containing 7,005 struts were included in the analysis, with a mean of 155.7±53.2 struts being analysed per lesion. Neointima volume obstruction was 8.2% (IQR 4.74-10.72). The median percentage of covered struts was 93.0% (IQR 83.2-96.5). **Figure 3A** shows the cumulative frequency of the percentage of covered struts: approximately two thirds of patients had more than 90% strut coverage after three months. Median neointimal

Table 1. Baseline characteristics of patients.

		N=45 patients
Age (years), mean±SD		64.0±9.8
Men, n (%)		33 (73.3)
Current smokers, n (%)		6 (13.3)
Diabetes, n (%)		5 (11.1)
Hypertension, n (%)		24 (53.3)
Hyperlipidaemia, n (%)		6 (13.3)
Family history of CAD, n (%)		19 (42.2)
Previous CABG, n (%)		1 (2.2)
Previous PCI, n (%)		10 (22.2)
Previous myocardial infarction, n (%)		10 (22.2)
Stable angina, n (%)		30 (66.7)
Silent ischaemia, n (%)		6 (13.3)
Current cardiac medication before index procedure	Aspirin, n (%)	39 (86.7)
	Clopidogrel, n (%)	12 (26.7)
	Beta-blocker, n (%)	30 (66.7)
	Statin, n (%)	32 (71.1)
Antiplatelet regimens in the first three months	Aspirin, n (%)	45 (100.0)
	Clopidogrel, n (%)	40 (88.9)
	Prasugrel, n (%)	1 (2.2)
	Ticagrelor, n (%)	4 (8.9)

Data are mean±standard deviation or number (%). CABG: coronary artery bypass graft; CAD: coronary artery disease; PCI: percutaneous coronary intervention

Table 2. Baseline target lesions and procedural characteristics.

	N=45 patients/ 47 lesions
Target vessel	
Left anterior descending, n (%)	6 (12.8)
Left circumflex artery, n (%)	14 (29.8)
Right coronary artery, n (%)	27 (57.4)
AHA/ACC lesion classification	
B1, n (%)	20 (42.6)
B2, n (%)	25 (53.2)
C, n (%)	2 (4.3)
Moderate to heavy calcification, n (%)	8 (17.0)
Diameter stenosis (%)	60.9±10.8
Obstruction length (mm)	12.7±4.4
Total nominal length of implanted stents per lesion (mm)	20.0±9.2
Overlapping stents, n (%)	4 (8.5)
Reference vessel diameter (mm)	2.83±0.46
Minimal lumen diameter (mm)	1.10±0.35
Mean lumen diameter (mm)	2.51±0.39
Acute success	
Device success (lesion level), n (%)	47/47 (100.0)
Procedure success (patient level), n (%)	44/45 (97.8)

Data are mean±standard deviation or number (%). AHA/ACC: American Heart Association/American College of Cardiology

Table 3. Quantitative coronary angiographic follow-up results (intention to treat, N=47).

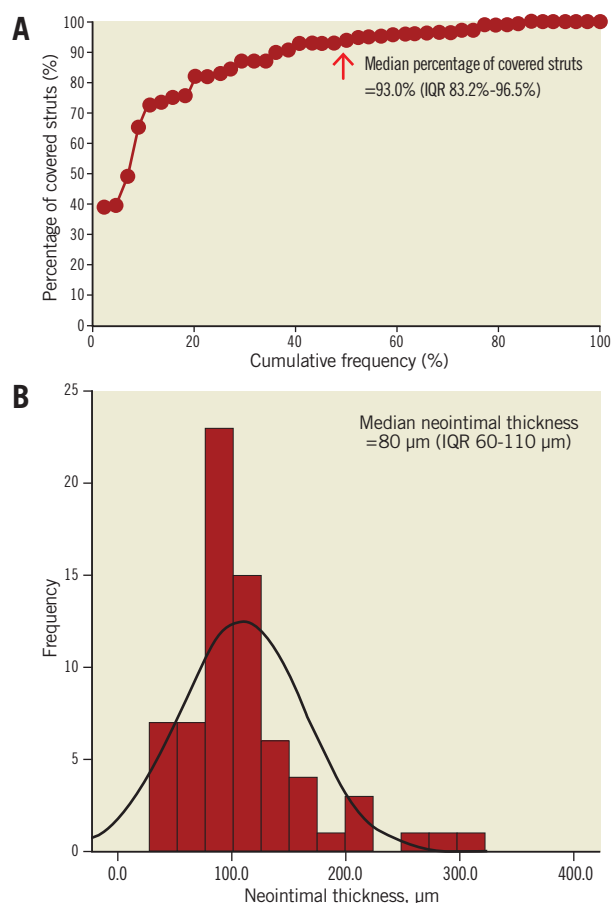| Variable		Pre-procedure	Post-procedure	3-month follow-up
Reference vessel diameter (mm)	In-stent	2.83±0.46	2.89±0.42	2.79±0.41
	In-segment		2.81±0.46	2.73±0.43
Diameter stenosis (%)	In-stent	60.9±10.7	9.9±5.49	12.9±8.6
	In-segment		18.1±7.6	18.2±8.2
Minimal lumen diameter (mm)	In-stent	1.10±0.35	2.59±0.34	2.43±0.40
	In-segment		2.29±0.41	2.23±0.41
Mean lumen diameter (mm)	In-stent	2.51±0.39	2.98±0.39	2.86±0.40
	In-segment		2.92±0.40	2.82±0.39
Stent length (mm)	In-stent		17.61±7.78	17.51±7.66
	In-segment		26.56±7.76	26.44±7.62
Acute gain (mm)	In-stent		1.50±0.38	
	In-segment		1.20±0.41	
Late loss (mm)	In-stent			0.17±0.27
	In-segment			0.06±0.19
Binary restenosis	In-stent			0 (0.0)
	In-segment			0 (0.0)

Figure 3. *Cumulative frequency curve of percentage of covered struts (A) and histogram of neointimal thickness (B).*

thickness at three months was 80 (IQR 60-100) μm and maximum neointimal thickness was 300 (IQR 220-350) μm. **Figure 3B** presents the distribution of neointimal thickness in all lesions. A total of 51 out of 7,005 struts were malapposed; the median percentage of ISA was 0% (IQR 0.0-0.86). Among malapposed lesions, a mean area of ISA >2 mm^2 was present in only two lesions. There was no thrombus area larger than 300 μm^2. **Figure 4** shows an example of a vessel treated with the Nano+ stent at three-month follow-up. **Figure 5** demonstrates spread-out vessel charts in an individual case, including the healing score and percentage of strut coverage from all 45 OCT pullbacks. The median healing index was 16.2 (IQR 7.5-33.6): the lowest score was 0 and the highest score was 177.7.

CLINICAL ENDPOINTS AND OUTCOMES

The three-month device-oriented composite endpoint (DOCE) rate was 2.2% (one patient), which resulted from a single periprocedural MI according to the per protocol definition (WHO MI definition) **(Table 5)**. The cause of the periprocedural MI was a coronary dissection (type F) after stent post-dilation, resulting in the need for bail-out implantation of overlapping stents. In **Table 6**, all cardiac biomarkers are tabulated according to the current MI definitions. All three types of cardiac biomarker were available in 97.8% of patients (44/45), while in one patient (2.2%) only creatinine kinase-MB and troponin were available. Overall, creatinine kinase and creatinine kinase-MB ratios were normal, while the troponin ratio was 9.04±35.67 times greater than ULN from the excessive increase of troponin in the case with periprocedural MI. When we subcategorised periprocedural myocardial infarction according to all current enzymatic criteria, there was a wide range of values exceeding the ULN (from 2.3% to 24.4%) depending on the definition. There was no stent thrombosis up to three months.

Discussion

The Nano+ study has assessed new criteria of coronary arterial healing three months after implantation of polymer-free SES. In this study, at three months the Nano+ stent showed: i) a low

Table 4. Optical coherence tomography results (intention to treat).

Overall (N=45 lesions)	Median (IQR 25-75)
Strut level analysis	
Total analysed struts, n	7,005
Mean number of struts per cross-section, n	143 (128.0-169.0)
Percentage of covered struts‡	93.0 (83.2-96.5)
Neointimal thickness, μm	80 (60-110)
Number of malapposed struts, n*	51
Percentage of malapposed struts¶‡	0.00 (0.00-0.86)
Percentage of strut presence of both malapposed and uncovered‡	0.00 (0.00-0.57)
Cross-section-level analysis	
Total analysed cross-sections, n	1,406
Minimum lumen area, mm²	5.73 (4.21-6.47)
Lumen area, mm²	7.02 (5.72-8.42)
Stent eccentricity index	0.90 (0.88-0.92)
Minimum stent area, mm²	6.57 (5.86-7.45)
Stent area, mm²	7.58 (6.69-9.04)
Neointimal area, mm²	0.62 (0.36-0.90)
Mean ISA area, mm²	0.00 (0.00-0.03)
Lesion-level analysis	
Total analysed lesion, n	45
Mean area of ISA >2 mm², n (%)	2 (4.4)
Thrombus area >300 μm², n (%)	0
Neointima volume, mm³	10.13 (6.05-16.21)
Stent volume, mm³	138.67 (96.14-173.59)
Lumen volume, mm³	129.92 (86.61-159.00)
Total malapposition volume, mm³	0.00 (0.00-0.39)
Percentage of neointima volume obstruction	8.20 (4.74-10.72)
Healing index (no unit)	16.2 (7.5-33.6)

*sum of all ISA struts, ¶based on crude analysis, ‡parameter used in healing index calculation. ISA: incomplete stent apposition

Table 5. Clinical outcomes at 3-month follow-up (intention to treat).

Clinical outcome	In-hospital (N=45/45)	3 months (N=45/45)
Cardiac death	0	0
Myocardial infarction	1 (2.2)	0
Periprocedural MI according to the WHO MI definition	1 (2.2)	0
Spontaneous MI	0	0
Clinically indicated target lesion revascularisation	0	0
Device-oriented composite endpoint (DOCE)		
CD, MI not clearly attributable to a non-intervention vessel, and CI-TLR	1 (2.2)	0
Definite/probable ST	0	0

CD: cardiac death; CI-TLR: clinically indicated target lesion revascularisation; DOCE: device-oriented clinical events; MI: myocardial infarction; ST: stent thrombosis; WHO: World Health Organization

percentage of neointimal volume obstruction; ii) a high percentage of covered struts; iii) a low number of malapposed struts comparable to other DES platforms; and iv) an acceptable neointimal thickness when compared to DES which have been investigated at the same time point **(Table 7)**. Quantitative coronary angiographic analysis showed standard acute lumen gain, low late lumen loss and no (binary) restenosis and, at three-month follow-up, there was no stent thrombosis and there were no major adverse cardiac events other than a single periprocedural MI.

The Nano+ stent is one of the polymer-free drug-eluting stents which have been tested recently[24]. This particular stent is made of 91 μm-thick 316L stainless steel struts and utilises nano-sized pores on its adluminal surface as a reservoir for drug elution. This stent has a similar efficacy and safety profile when compared to the durable polymer sirolimus-eluting stent in the treatment of stable CAD patients[24]. However, it has not yet been investigated whether this novel concept (polymer-free drug-eluting stent with a nano-sized-pore

Table 6. Cardiac biomarkers <48 hrs after index procedure.

	Total CK 44/45 (97.8%)	CK-MB 45/45 (100%)	Troponin (T and I) 45/45 (100%)
Mean ratio of enzyme vs. ULN	0.69±0.40	0.83±1.13	9.04±35.67 (range 0.11-280)
	n (%)	n (%)	n (%)
>1x ULN	3 (6.8)	9 (20.0)	21 (46.7)
>2x ULN	1 (2.3)¶ (WHO)	5 (11.1)	13 (28.9)
>3x ULN	0 (0)	3 (6.7) (Ext-H in the absence of CK)	11 (24.4)
>5x ULN	0 (0)	0 (0) (SCAI for CK-MB plus additional criteria)	8 (17.8) (TUD)
>10x ULN	0 (0)	0 (0) (SCAI for CK-MB)	7 (15.6)
>35x ULN	0 (0)	0 (0)	1 (2.2) (SCAI for cTn plus additional criteria)
>70x ULN	0 (0)	0 (0)	1 (2.2)¶ (SCAI for cTn)

¶Patients with protocolar periprocedural MI (WHO definition). The enzymatic criteria of periprocedural MI are provided as follow: 1) WHO[21] CK >2x ULN accompanied by CK-MB rise; 2) Ext-H[51] CK >2x ULN accompanied by CK-MB rise, if no CK was measured, elevation of the CK-MB >3x UNL, if CK and CK-MB were not measured, elevation of cTn >3x UNL; 3) TUD[22] cTn >5x ULN; 4) SCAI[23] CK-MB >10x ULN, or in the absence of CK-MB measurements, elevation of cTn >70x ULN. CK: creatinine kinase; CK-MB: creatinine kinase-MB; cTn: cardiac troponin; Ext-H: extended historical myocardial infarction definition; SCAI: Society for Cardiovascular Angiography and Interventions; TUD: third universal definition of myocardial infarction; ULN: upper limit normal

Table 7. Comparison of degree of vascular healing assessed by OCT in different type of DES (first-generation, polymer-free, biodegradable polymer and second-generation DES) at 3 months±1 month.

Author/year	Time point	Study stent, n (strut thickness)	% covered	% uncovered	%ISA	Neointimal thickness, µm	%NVO	Acute gain (mm)	Late loss (mm)
First-generation DES									
Takano et al[12] 2006	3 mo	CYPHER=21 (STh: 140 µm)	NA	15% (range 0-27)	16% (range 1-33)	29 (range 0-510)	NA	NA	NA
Polymer-free DES									
Moore et al[10] 2009	3 mo	CYPHER=12 (STh: 140 µm) Yukon=12 (STh: 87 µm)	88.3 (11.8) vs. 97.2 (6.1)¶	NA	2.2 (2.1) vs. 1.2 (1.1)¶	77.2 (25.6) vs. 191.2 (86.7)	NA	NA	0.06 (0.29) vs. 0.16 (0.33)
BICARE FIM[11] 2014	4 mo	SES + probucol N=25 (STh: 91 µm)	98.93	1.07¶	0.22¶	NA	NA	1.83 (0.44)	0.14 (0.19) with 1 binary stenosis
DEMONSTRATE[52] 2014	3 mo 1 mo	Cre8 DES=19 (STh: 80 µm) Multilink8=19 (STh: 81 µm)	NA	1.59 (2.10) vs. 0.86 (1.38)	4.18 (5.09) vs. 1.21 (1.72)	70 (40) vs. 160 (120)	NA	NA	0.10 (0.33) vs. 0.43 (0.36)
Nano+	3 mo	SES=45 (STh: 91 µm)	93.0 (83.2-96.5)¶	NA	0.00 (0.00-0.86)	80 (60-110)	8.2 (4.7-10.7)	1.50 (0.38)	0.16 (0.27)
Biodegradable polymer DES									
Kim BK et al[9] 2013	3 mo	BES=30 (STh: 112 µm) SES=30 (STh: 140 µm)	NA	14.7 (0-23.4) vs. 8.6 (0.7-21.5)¶G	0.1 (0.0-1.0) vs. 0.1 (0.0-1.0)¶	30 (20) vs. 40 (30)	NA	1.9 (0.5) vs. 1.9 (0.5)	0.1 (0.2) vs. 0.2 (0.4)
BuMA-OCT[29] 2014	3 mo	BuMA=33 (STh: 100 µm) EXCEL=36 (STh: 120 µm)	94.2% vs. 90.0%¶	NA	1.28% vs. 1.80%¶	70 (30) vs. 60 (20)	5.7 (5.0-7.6) vs. 5.3 (4.1-6.4)	1.61 (0.59) vs. 1.51 (0.49)	0.06 (0.09) vs. 0.07 (011)
DESSOLVE I 2013 Attizzani GF et al[30]	4 mo	MiStent*=10 (STh: 64 µm)	NA	14.34 (15.35)¶	3.74 (7.35) ¶	71.73 (39.78)	8.01 (6.21)	NA	NA
DESSOLVE I 2013 Ormiston J et al[31]	4 mo	MiStent*= 10 (STh: 64 µm)	NA	7.3 (range 0.4-46.3)	0.4 (range 0-22.7)	2.6 (range 0.6-24.6)	7.0 (range 2.3-22.9)	NA	0.03 (range -0.22-0.21)
Second-generation DES									
Endeavor OCT[42] 2009	3 mo	Endeavor=31 (STh: 91 µm)	99.9 (0.4) (ACS & SIHD)	NA	0.2	NA	NA	1.7 (0.6)	0.5 (0.3)
Kim SJ et al[39] 2013	3 mo	EES=36 (STh: 81 µm) ZES=24 (STh: 91 µm)	77.1 vs. 81.5	NA	2.3 vs. 1.4	58.7 (47.0) vs. 126.1 (131.5)	NA	1.92 (0.59) vs. 1.98 (0.41)	0.06 (0.10) vs. 0.22 (0.31)
Kim S et al[41] 2013	3 mo	ZES=20 (STh: 91 µm) EES=20 (STh: 81 µm)	NA	6.2 (6.9) vs. 4.7 (5.1)¶	0.7 (2.2) vs. 0.7 (1.7)¶	74 (41) vs. 75 (35)	NA	1.54 (0.44) vs. 1.43 (0.53)	0.13 (0.24) vs. 0.10 (0.15)
Nishinari et al[40] 2013	2,4,6, 8,10 weeks	Endeavor=4 (STh: 91µm) at 10 weeks	NA	19.2 (5.6)	0.0	146.2 (49.9)	NA	NA	NA
Hashikata et al[43] 2014	3 mo	R-ZES=20 (STh: 91 µm)	93.6 (3.5)*	NA	3.1 (2.2)*	54.1 (5.9)	NA	NA	NA

Data are reported as mean (SD) or median (IQR 1st–3rd) or median (range). ¶ Data analysed per strut level. *The report did not provide the level of statistical analysis. BES: biolimus-eluting stent; DES: drug-eluting stent; EES: everolimus-eluting stent; G: generalised estimating equation model (GEE); ISA: incomplete stent apposition; NA: not available; NVO: neointimal volume obstruction; R-ZES: Resolute zotarolimus-eluting stent; SES: sirolimus-eluting stent; STh: strut thickness; ZES: zotarolimus-eluting stent

surface) accelerates the tissue coverage (and possibly re-endothelialisation) while still preserving the ability to inhibit excessive neointimal formation.

The new generation of the OCT system provides an axial image resolution of 10-20 µm that allows precise assessment of neointimal proliferation, especially the lack of tissue coverage and the presence of residual thrombi; both parameters have been associated with an increased risk of stent thrombosis[5,25,26].

SHORT-TERM OCT STUDIES IN POLYMER-FREE DRUG-ELUTING STENTS

Amongst the other DES, there are three coating-free stent platforms similar to the Nano+ stent **(Table 7)**: 1) the Yukon® Choice stent[10,27] (Translumina GmbH, Hechingen, Germany) which is made of 316L stainless steel with an 87 µm strut thickness, eluting drug from a modified microporous surface; 2) the BioFreedom™[27,28] (Biosensors Europe SA, Morges, Switzerland) is a 316L stainless steel stent with
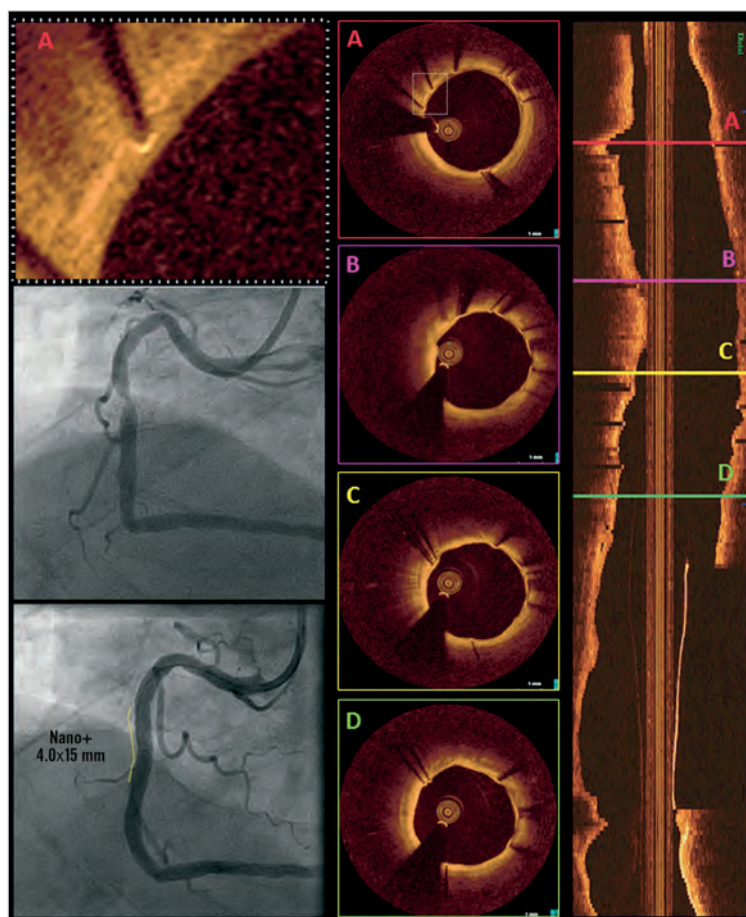
Figure 4. *Example of optical coherence tomography findings. Left middle and lower panels demonstrate pre- and post-procedure coronary angiography of right coronary artery, respectively. A Nano+ stent 4.0×15 mm was implanted into the right coronary artery. A three-month follow-up OCT image shows the longitudinal view (right panel) with corresponding cross-section sampling from four different in-stent segments (A to D, middle panels). A zoom-in image in white dotted frame (A, left upper panel) shows that the stent struts are covered with bright, homogeneous tissue and smooth luminal surface with neointimal thickness of 85.3 µm; percentage of covered struts is 95.1 with a healing index of 9.7.*

119 µm strut thickness, which has adluminal microabrasion allowing retention and elution of antiproliferative drugs; 3) the BICARE™[11] (Lepu Medical) has a platform identical to the present device but with a dual drug elution of sirolimus and probucol. The drug concentrations are 1.6 µg/mm² for sirolimus and 0.8 µg/mm² for probucol. The published data on these two devices (Yukon and BICARE) demonstrated the safety of these devices, and at three-month follow-up they showed similar tissue coverage (on OCT) and late lumen loss (on QCA) to the Nano+ stent in this present study.

SHORT-TERM OCT STUDIES IN BIODEGRADABLE POLYMER DRUG-ELUTING STENTS

There are two biodegradable polymer stent trials in which OCT data are available at short-term follow-up, the BuMA-OCT trial and the DESSOLVE I trial. In the BuMA-OCT trial[29], stent strut coverages were compared between a PLGA polymer with electro-grafting base layer sirolimus-eluting stent (SES) (BuMA™; SINOMED, Tianjin, China) and a PLA polymer SES (EXCEL; JW Medical Systems,

Weihai, China); the data showed that both the BuMA and the EXCEL stent had low percentages of neointimal volume obstruction (5.3% and 5.7%) which are similar to the Nano+ stent, but the BuMa and EXCEL stents had a relatively higher percentage of malapposed struts. In the DESSOLVE I trial[30,31], the device used was the MiStent® sirolimus-eluting stent (cobalt-chromium stent with a 64 micron strut thickness coated with polylactide-coglycolic acid and sirolimus; Micell Technologies, Inc., Durham, NC, USA), and the vascular reaction after implantation at four, six and eight months was investigated by OCT[30,31]. The Nano+ stent in our present study seems to have rates of covered struts and malapposition which are comparable to those of the MiStent in the DESSOLVE I trial.

SHORT-TERM OCT STUDIES IN SECOND-GENERATION DRUG-ELUTING STENTS

The second-generation DES with thinner cobalt-chromium struts, improved crossability, trackability and biocompatibility, have been globally adopted in daily practice. Second-generation DES showed
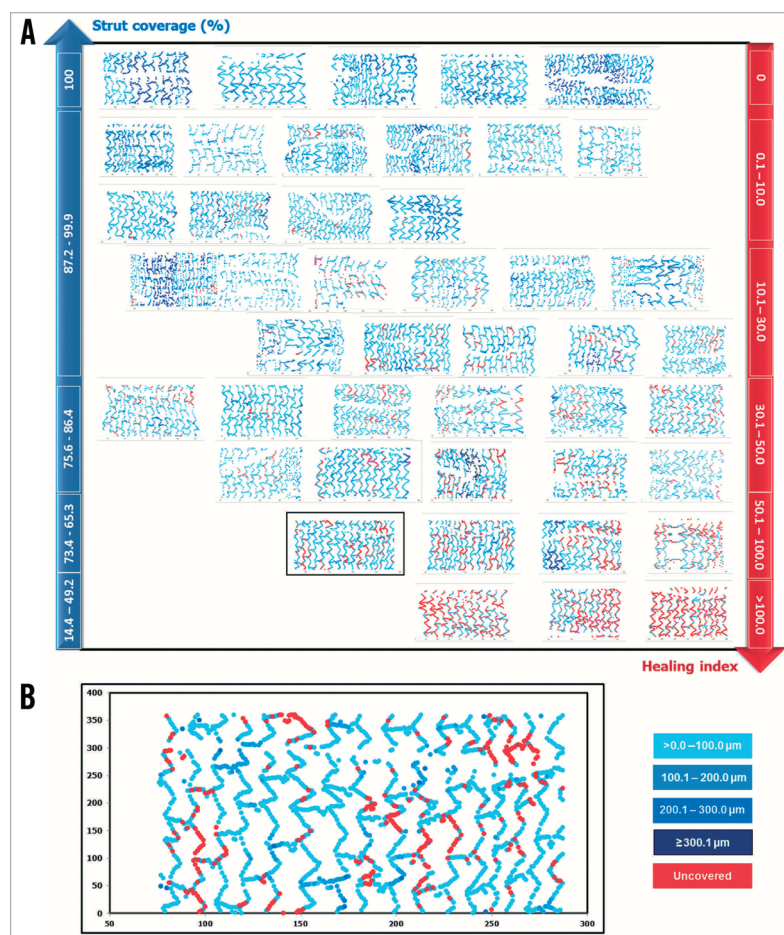
Figure 5. *Spread-out vessel chart of all stents. A) Percentage of covered struts and healing index. The blue vertical axis on the left-hand side shows the percentage of covered struts, while the red vertical axis on the right-hand side shows the healing index. Struts are colour-coded according to covered and uncovered status. Covered struts are depicted in blue: light blue indicates a neointimal thickness more than 0 µm to 100.0 µm, blue indicates a neointimal thickness 100.1-200.0 µm, navy blue indicates a neointimal thickness 200.1-300.0 µm, dark blue indicates a neointimal thickness more than 300.1 µm, and red indicates uncovered struts. B) Zoom-in spread-out vessel chart in which all struts are colour-coded according to coverage status: percentage of covered struts is 73.5 with a healing index of 54.*

a lower number of malapposed struts[32], a lower revascularisation rate[33,34], and a lower MACE[34,35] rate at long-term follow-up than first-generation DES.

The vascular healing after implantation of such new-generation devices replacing first-generation DES has also been assessed at medium-term follow-up (between nine and 12 months or later). The OCT data showed that new-generation DES have more complete neointimal coverage and lower strut malapposition rates than the first-generation DES[36-38]. The short-term OCT assessment of second-generation DES has been investigated in two devices, the XIENCE V® everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, CA, USA) and the Resolute® zotarolimus-eluting stent (R-ZES) (Medtronic CardioVascular, Santa Rosa, CA, USA). These studies showed a wide range of strut coverage (77.1-99.9%) and malapposed struts (0-3.1%)[39-43]. The plausible explanation for the heterogeneity of results might be the difference in analytic approach in calculating the percentage of covered struts or malapposed struts. Räber et al have reported the impact of various statistical analyses in OCT trial interpretation: the crude and the GEE-based percentages are clearly higher than the percentage from aggregated and multilevel analysis methods[44]. In addition, the wide variation in the percentage of covered struts might be the consequence of: 1) the generation of OCT systems, for instance the quality of the images of the recent OFDI system is by far superior to the earlier generation of OCT (M2/M3); 2) the criteria used to define strut coverage. The thickness criteria can vary from an absolute threshold of 0 µm to a minimum threshold of 10 µm (or more); or coverage may simply be defined by the presence of any covering tissue layer detectable on visual inspection. In the present study, the Nano+ stent showed coverage and malapposition rates which were comparable to the rates in second-generation DES.

APPLICATION OF HEALING INDEX FOR ASSESSING CORONARY ARTERIAL HEALING

The healing index was first reported in the TROFI study[18,19]. Vascular healing depends upon multiple factors (coverage, malapposition, exuberant neointimal proliferation and intraluminal defect). The benefit of the healing index methodology is that it standardises the assessment of the speed and degree of "healing" in patients treated

with different types of stent, assessed at different time points. The healing indices provided in **Table 8** were studied in the LEADERS trial[8] (Biolimus A9 BioMatrix Coroflex stent vs. Sirolimus-eluting Cypher stent), RESOLUTE trial[16] (zotarolimus-eluting Resolute stent vs. everolimus-eluting Xience metallic stents), ABSORB trial[45] (everolimus-eluting BVS) and TROFI trial (Biolimus A9 in a STEMI population). The healing index of the Nano+ stent can be compared with the healing indexes of other stents **(Table 8)**. The most influential factors of the healing index are the percentage of uncovered struts and number of ISA: both are low in the present study. Therefore, the Nano+ stent showed a low score of the healing index that can be appreciated at three months in comparison with other stents also investigated at the same time point.

CLINICAL IMPORTANCE OF STRUT COVERAGE ASSESSED BY OCT
It has been hypothesised that the ongoing inflammation process, triggered by durable polymer coating, may cause unfavourable clinical outcomes[46,47]: polymer-free stents have the potential to decrease this issue, resulting in a lower number of uncovered struts, malapposition or evagination[48] which are attributed to durable polymer-coated DES. In the literature, the OCT study criteria for lack of coverage (e.g., Ratio of Uncovered to Total Stent Struts Per Cross Section: RUTTS) are mainly derived from histopathological studies[5,49]. These studies have demonstrated that the lack of neointimal coverage after implantation is an important factor for late and very late stent thrombosis, since healthy endothelial tissue plays a key role in preventing thrombus formation. These observations have triggered extensive clinical research on the relevance of early tissue coverage (as assessed by OCT) for long-term outcomes of new DES. The OCT approach has shown its accuracy in detecting uncovered stent struts when compared to light and electron microscopy in a porcine model[50]. However, to date OCT has not been able to provide information on the type of tissue coverage, an observation which could become more relevant for the long-term clinical outcome.

Limitations
The present study is limited by the absence of post-procedural OCT images for comparison with the OCT images during follow-up. Post-procedural OCT data would have enabled us to understand the progression or regression of strut malapposition during the follow-up period. In addition, this study was a small single-arm trial without the use of a comparator.

Conclusions
Polymer-free sirolimus-eluting stents with a surface of nano-sized pores are effective in inhibiting neointimal tissue proliferation and promoting early vascular healing with high strut coverage at three-month follow-up.

Impact on daily practice
The novel concept of local drug delivery from metallic DES has been modified to decrease sequelae from chronic exposure to permanent polymer and to promote endothelisation. The Nano+ stent is a polymer-free sirolimus eluting stent utilising nano-sized pores on its adluminal surface as a reservoir for drug elution. At three months, the Nano+ stent showed a rapid strut coverage process although the level of actual strut coverage is similar to other current stent technologies in daily practice. Strut coverage has been shown to be a significant factor in the reduction of stent thrombosis; this current study reports promising data from the use of this platform.

Appendix
LIST OF THE INVESTIGATORS WHO CONTRIBUTED TO CASES ENROLLED IN THE NANO+ TRIAL
Principal investigators and recruiting sites: Belgium: Dr Edouard Benit, Hasselt Heart Centre, Jessa Ziekenhuis, Hasselt, Belgium, total enrolment=24 patients; Dr Olivier Gach, CHU de Liege, Liege, Belgium,

Table 8. Comparison of healing index among different stent types with period of evaluation and patient setting.

Patient status	n	time point	mean±SD	median (range)
In stable patients				
Sirolimus-eluting durable polymer	29	9 months	43.3±36.2	26.1 (4.6-127.4)
Biolimus A9-eluting biodegradable polymer	22	9 months	35.2±25.0	36.7 (1.1-79.6)
Sirolimus polymer-free stent Nano+™	45	3 months	30.3±38.9	16.2 (0.0-177.7)
Zotarolimus-eluting biocompatible durable polymer	17	13 months	18.7±20.4	15.2 (0.0-79.0)
Everolimus-eluting biocompatible durable polymer	15	13 months	10.8±15.3	3.4 (0.0-47.7)
Everolimus-eluting fully biodegradable BVS	28	6 months	9.4±13.3	3.1 (0.0-53.7)
In STEMI patients				
Biolimus A9-eluting biodegradable polymer	25	post-PCI	202.8±41.5	198.1 (67.9-344.3)
Biolimus A9-eluting biodegradable polymer	25	6 months	13.4±19.6	9.0 (0.0-97.2)
Biolimus A9-eluting biodegradable polymer+thrombectomy	26	post-PCI	206.3±38.7	200.6 (101.9-358.7)
Biolimus A9-eluting biodegradable polymer+thrombectomy	26	6 months	20.1±22.2	15.1 (0.0- 96.9)

BVS: bioresorbable vascular scaffold; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction. The STEMI patients have been published in the TROFI study[18,19]. All data of the patients in the stable group have been reported (LEADERS: Biolimus A9 vs. sirolimus-eluting durable polymer; RESOLUTE: zotarolimus and everolimus metallic stents; ABSORB: everolimus BVS).

total enrolment=15 patients; Dr Clemens von Birgelen, Thoraxcentrum Twente, University of Twente, Enschede, The Netherlands, total enrolment=4 patients; Dr Sjoerd H. Hofma, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands, total enrolment=2 patients.

Conflict of interest statement

C. von Birgelen has been a consultant to Boston Scientific and Medtronic and has received lecture fees from MSD and AstraZeneca; the research department of the Thoraxcentrum, Twente has received institutional research grants from Biotronik, Boston Scientific, and Medtronic. All of the other authors have no conflicts of interest to declare.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R; RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.

2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-23.

3. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE; ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation*. 2006;114:798-806.

4. Kang SH, Park KW, Kang DY, Lim WH, Park KT, Han JK, Kang HJ, Koo BK, Oh BH, Park YB, Kandzari DE, Cohen DJ, Hwang SS, Kim HS. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. *Eur Heart J.* 2014;35:1147-58.

5. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation*. 2007;115:2435-41.

6. Wenaweser P, Daemen J, Zwahlen M, van Domburg R, Jüni P, Vaina S, Hellige G, Tsuchida K, Morger C, Boersma E, Kukreja N, Meier B, Serruys PW, Windecker S. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol.* 2008;52:1134-40.

7. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Jüni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet.* 2007;369:667-78.

8. Barlis P, Regar E, Serruys PW, Dimopoulos K, van der Giessen WJ, van Geuns RJ, Ferrante G, Wandel S, Windecker S, van Es GA, Eerdmans P, Jüni P, di Mario C. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. *Eur Heart J.* 2010;31:165-76.

9. Kim BK, Ha J, Mintz GS, Kim JS, Shin DH, Ko YG, Choi D, Jang Y, Hong MK. Randomised comparison of strut coverage between Nobori biolimus-eluting and sirolimus-eluting stents: an optical coherence tomography analysis. *EuroIntervention.* 2014;9:1389-97.

10. Moore P, Barlis P, Spiro J, Ghimire G, Roughton M, Di Mario C, Wallis W, Ilsley C, Mitchell A, Mason M, Kharbanda R, Vincent P, Sherwin S, Dalby M. A randomized optical coherence tomography study of coronary stent strut coverage and luminal protrusion with rapamycin-eluting stents. *JACC Cardiovasc Interv.* 2009;2:437-44.

11. Yu M, Xu B, Kandzari DE, Wu Y, Yan H, Chen J, Qian J, Qiao S, Yang Y, Gao RL. First report of a novel polymer-free dual-drug eluting stent in de novo coronary artery disease: results of the first in human BICARE trial. *Catheter Cardiovasc Interv.* 2014;83:405-11.

12. Takano M, Inami S, Jang IK, Yamamoto M, Murakami D, Seimiya K, Ohba T, Mizuno K. Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation. *Am J Cardiol.* 2007;99:1033-8.

13. Gutierrez-Chico JL, van Geuns RJ, Koch KT, Koolen JJ, Duckers H, Regar E, Serruys PW. Paclitaxel-coated balloon in combination with bare metal stent for treatment of de novo coronary lesions: an optical coherence tomography first-in-human randomised trial, balloon first vs. stent first. *EuroIntervention.* 2011;7: 711-22.

14. Gutierrez-Chico JL, Radu MD, Diletti R, Sheehy A, Kossuth MB, Oberhauser JP, Glauser T, Harrington J, Rapoza RJ, Onuma Y, Serruys PW. Spatial distribution and temporal evolution of scattering centers by optical coherence tomography in the poly(l-lactide) backbone of a bioresorbable vascular scaffold. *Circ J.* 2012;76:342-50.

15. Nakatani S, Onuma Y, Ishibashi Y, Eggermont J, Zhang YJ, Campos CM, Cho YK, Liu S, Dijkstra J, Reiber JH, Perkins L, Sheehy A, Veldhof S, Rapoza R, van Es GA, Garcia-Garcia HM, van Geuns RJ, Serruys PW; ABSORB Cohort B investigators. Temporal evolution of strut light intensity after implantation of bioresorbable polymeric intracoronary scaffolds in the ABSORB cohort B trial-an application of a new quantitative method based on optical coherence tomography. *Circ J.* 2014;78:1873-81.

16. Gutierrez-Chico JL, van Geuns RJ, Regar E, van der Giessen WJ, Kelbaek H, Saunamaki K, Escaned J, Gonzalo N, di Mario C, Borgia F, Nuesch E, Garcia-Garcia HM, Silber S, Windecker S, Serruys PW. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial. *Eur Heart J.* 2011;32:2454-63.

17. Raber L, Zanchin T, Baumgartner S, Taniwaki M, Kalesan B, Moschovitis A, Garcia-Garcia HM, Justiz J, Pilgrim T, Wenaweser P, Meier B, Jüni P, Windecker S. Differential healing response attributed to culprit lesions of patients with acute coronary syndromes and stable coronary artery after implantation of drug-eluting stents: an optical coherence tomography study. *Int J Cardiol.* 2014;173:259-67.

18. Onuma Y, Thuesen L, van Geuns RJ, van der Ent M, Desch S, Fajadet J, Christiansen E, Smits P, Holm NR, Regar E, van Mieghem N, Borovicanin V, Paunovic D, Senshu K, van Es GA, Muramatsu T, Lee IS, Schuler G, Zijlstra F, Garcia-Garcia HM, Serruys PW; TROFI Investigators. Randomized study to assess the effect of thrombus aspiration on flow area in patients with ST-elevation myocardial infarction: an optical frequency domain imaging study--TROFI trial. *Eur Heart J.* 2013;34:1050-60.

19. Garcia-Garcia HM, Muramatsu T, Nakatani S, Lee IS, Holm NR, Thuesen L, van Geuns RJ, van der Ent M, Borovicanin V, Paunovic D, Onuma Y, Serruys PW. Serial optical frequency domain imaging in STEMI patients: the follow-up report of TROFI study. *Eur Heart J Cardiovasc Imaging.* 2014;15:987-95.

20. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

21. World Health Organization. Myocardial Infarction Community Registers. Public Health in Europe, Paper No. 5. Copenhagen: WHO; 1976.

22. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation.* 2012;126:2020-35.

23. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol.* 2013;62:1563-70.

24. Zhang Y, Chen F, Muramatsu T, Xu B, Li Z, Ge J, He Q, Yang Z, Li S, Wang L, Wang H, He B, Li K, Qi G, Li T, Zeng H, Peng J, Jiang T, Zeng Q, Zhu J, Fu G, Bourantas CV, Serruys PW, Huo Y. Nine-month angiographic and two-year clinical follow-up of polymer-free sirolimus-eluting stent versus durable-polymer sirolimus-eluting stent for coronary artery disease: the Nano randomized trial. *Chin Med J (Engl).* 2014;127:2153-8.

25. Sianos G, Papafaklis MI, Daemen J, Vaina S, van Mieghem CA, van Domburg RT, Michalis LK, Serruys PW. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol.* 2007;50:573-83.

26. Cheneau E, Leborgne L, Mintz GS, Kotani J, Pichard AD, Satler LF, Canos D, Castagna M, Weissman NJ, Waksman R. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. *Circulation.* 2003;108:43-7.

27. Abizaid A, Costa JR Jr. New drug-eluting stents: an overview on biodegradable and polymer-free next-generation stent systems. *Circ Cardiovasc Interv.* 2010;3:384-93.

28. Urban P, Abizaid A, Chevalier B, Greene S, Meredith I, Morice MC, Pocock S. Rationale and design of the LEADERS FREE trial: A randomized double-blind comparison of the BioFreedom drug-coated stent vs the Gazelle bare metal stent in patients at high bleeding risk using a short (1 month) course of dual antiplatelet therapy. *Am Heart J.* 2013;165:704-9.

29. Qian J, Zhang YJ, Xu B, Yang YJ, Yan HB, Sun ZW, Zhao YL, Tang YD, Gao Z, Chen J, Cui JG, Mintz GS, Gao RL. Optical coherence tomography assessment of a PLGA-polymer with electro-grafting base layer versus a PLA-polymer sirolimus-eluting stent at three-month follow-up: the BuMA-OCT randomised trial. *EuroIntervention.* 2014;10:806-14.

30. Attizzani GF, Bezerra HG, Ormiston J, Wang W, Donohoe D, Wijns W, Costa MA. Serial assessment by optical coherence tomography of early and late vascular responses after implantation of an absorbable-coating Sirolimus-Eluting stent (from the first-in-human DESSOLVE I trial). *Am J Cardiol.* 2013;112:1557-64.

31. Ormiston J, Webster M, Stewart J, Vrolix M, Whitbourn R, Donohoe D, Knape C, Lansky A, Attizzani GF, Fitzgerald P, Kandzari DE, Wijns W. First-in-human evaluation of a bioabsorbable polymer-coated sirolimus-eluting stent: Imaging and clinical results of the DESSOLVE I Trial (DES with sirolimus and a bioabsorbable polymer for the treatment of patients with de novo lesion in the native coronary arteries). *JACC Cardiovasc Interv.* 2013;6: 1026-34.

32. Guagliumi G, Musumeci G, Sirbu V, Bezerra HG, Suzuki N, Fiocca L, Matiashvili A, Lortkipanidze N, Trivisonno A, Valsecchi O, Biondi-Zoccai G, Costa MA; ODESSA Trial Investigators. Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare-metal and drug-eluting stents. *JACC Cardiovasc Interv.* 2010;3:531-9.

33. Maeng M, Tilsted HH, Jensen LO, Krusell LR, Kaltoft A, Kelbaek H, Villadsen AB, Ravkilde J, Hansen KN, Christiansen EH, Aaroe J, Jensen JS, Kristensen SD, Botker HE, Thuesen L, Madsen M, Thayssen P, Sorensen HT, Lassen JF. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. *Lancet.* 2014;383:2047-56.

34. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, Cutlip DE, Sudhir K, Hou L, Koo K, Stone GW.

5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv.* 2013;6:1263-6.

35. Dangas GD, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, Sudhir K, Smith RS Jr, Cao S, Theodoropoulos K, Cutlip DE, Lansky AJ, Stone GW. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv.* 2013;6:914-22.

36. Kim JS, Jang IK, Kim TH, Takano M, Kume T, Hur NW, Ko YG, Choi D, Hong MK, Jang Y. Optical coherence tomography evaluation of zotarolimus-eluting stents at 9-month follow-up: comparison with sirolimus-eluting stents. *Heart.* 2009;95:1907-12.

37. Choi HH, Kim JS, Yoon DH, Hong KS, Kim TH, Kim BK, Ko YG, Choi D, Jang Y, Hong MK. Favorable neointimal coverage in everolimus-eluting stent at 9 months after stent implantation: comparison with sirolimus-eluting stent using optical coherence tomography. *Int J Cardiovasc Imaging.* 2012;28:491-7.

38. Kim JS, Kim BK, Jang IK, Shin DH, Ko YG, Choi D, Hong MK, Cho YK, Nam CW, Hur SH, Choi JH, Song YB, Hahn JY, Choi SH, Gwon HC, Jang Y. ComparisOn of neointimal coVerage betwEen zotaRolimus-eluting stent and everolimus-eluting stent using Optical Coherence Tomography (COVER OCT). *Am Heart J.* 2012;163:601-7.

39. Kim SJ, Lee H, Cho JM, Park CB, Kim W, Kato K, Yonetsu T, Kim CJ, Jang IK. Comparison of zotarolimus-eluting stent and everolimus-eluting stent for vascular healing response: serial 3-month and 12-month optical coherence tomography study. *Coron Artery Dis.* 2013;24:431-9.

40. Nishinari M, Shimohama T, Tojo T, Shiono T, Shinagawa H, Kameda R, Aoyama N, Izumi T. Two-week interval optical coherence tomography: imaging evidence on neointimal coverage completion after implantation of the Endeavor zotarolimus-eluting stent. *Catheter Cardiovasc Interv.* 2013;82:E871-8.

41. Kim S, Kim JS, Shin DH, Kim BK, Ko YG, Choi D, Cho YK, Nam CW, Hur SH, Jang Y, Hong MK. Comparison of early strut coverage between zotarolimus- and everolimus-eluting stents using optical coherence tomography. *Am J Cardiol.* 2013;111:1-5.

42. Kim JS, Jang IK, Fan C, Kim TH, Park SM, Choi EY, Lee SH, Ko YG, Choi D, Hong MK, Jang Y. Evaluation in 3 months duration of neointimal coverage after zotarolimus-eluting stent implantation by optical coherence tomography: the ENDEAVOR OCT trial. *JACC Cardiovasc Interv.* 2009;2:1240-7.

43. Hashikata T, Tojo T, Namba S, Kitasato L, Hashimoto T, Kameda R, Shimohama T, Yamaoka-Tojo M, Ako J. Neointimal coverage of zotarolimus-eluting stent at 1, 2, and 3 months' follow-up: an optical coherence tomography study. *Heart Vessels.* 2014 Nov 2. [Epub ahead of print].

44. Räber L, Zaugg S, Windecker S, Jüni P. Intricacies in the analysis and interpretation of optical coherence tomography findings. *EuroIntervention.* 2014;9:1374-7.

45. Gutiérrez-Chico JL, Gijsen F, Regar E, Wentzel J, de Bruyne B, Thuesen L, Ormiston J, McClean DR, Windecker S, Chevalier B, Dudek D, Whitbourn R, Brugaletta S, Onuma Y, Serruys PW. Differences in neointimal thickness between the adluminal and the abluminal sides of malapposed and side-branch struts in a polylactide bioresorbable scaffold: evidence in vivo about the abluminal healing process. *JACC Cardiovasc Interv.* 2012;5:428-35.

46. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation.* 2004;109:701-5.

47. John MC, Wessely R, Kastrati A, Schömig A, Joner M, Uchihashi M, Crimins J, Lajoie S, Kolodgie FD, Gold HK, Virmani R, Finn AV. Differential healing responses in polymer- and nonpolymer-based sirolimus-eluting stents. *JACC Cardiovasc Interv.* 2008;1:535-44.

48. Radu M, Räber L, Kalesan B, Muramatsu T, Kelbaek H, Heo JH, Jørgensen E, Helqvist S, Farooq V, Brugaletta S, Garcia-Garcia H, Jüni P, Saunamäki K, Windecker S, Serruys P. Coronary evaginations are associated with positive vessel remodelling and are nearly absent following implantation of newer-generation drug-eluting stents: an optical coherence tomography and intravascular ultrasound study. *Eur Heart J.* 2014;35:795-807.

49. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

50. Templin C, Meyer M, Müller MF, Djonov V, Hlushchuk R, Dimova I, Flueckiger S, Kronen P, Sidler M, Klein K, Nicholls F, Ghadri JR, Weber K, Paunovic D, Corti R, Hoerstrup SP, Lüscher TF, Landmesser U. Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. *Eur Heart J.* 2010;31:1792-801.

51. Vranckx P, Cutlip DE, Mehran R, Kint P-P, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention.* 2010;5:871-4.

52. Prati F, Romagnoli E, Valgimigli M, Burzotta F, De Benedictis M, Ramondo A, Mehran R, Stella PR. Randomized comparison between 3-month Cre8 DES vs. 1-month Vision/Multilink8 BMS neointimal coverage assessed by OCT evaluation: the DEMONSTRATE study. *Int J Cardiol.* 2014;176:904-9.