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

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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).

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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Bare metal stents (BMS) have practically been replaced by drug-eluting stents (DES), as previous trials have shown a reduction of in-stent-restenosis and repeat revascularisation[1-4].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

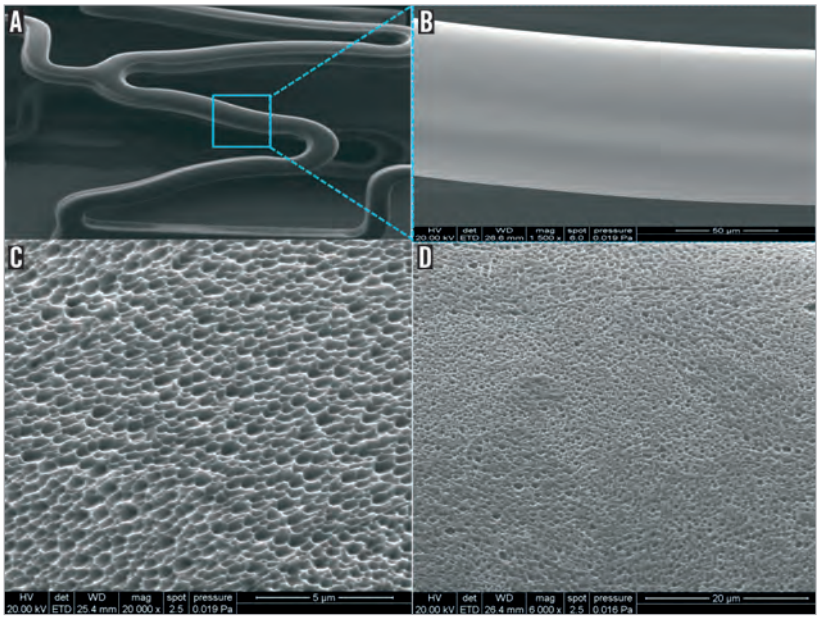

Figure 1. *Stent design. Strut design after expansion (A). The strut thickness is 91 µm (B), and a large number of sirolimus-filled pores are present on the adluminal stent surface. Electron microscopy shows the size of the nano pores at a magnification of 20,000x (C) and 6,000x (D).*

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.

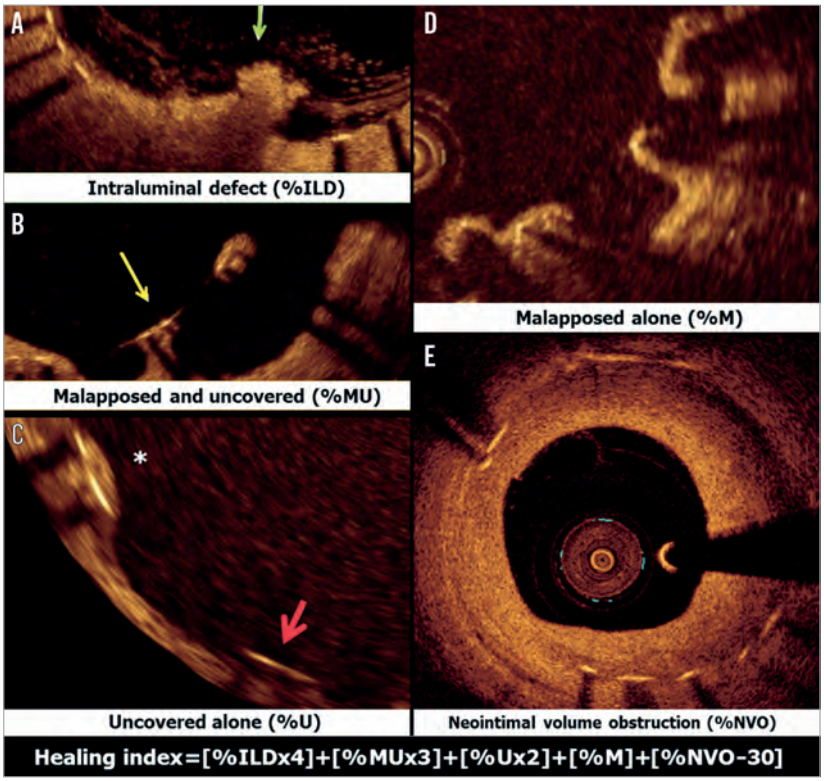

Figure 2. *Example of five parameters used for healing index calculation. The healing index was weighted according to OCT findings. The score was calculated from the presence of: (i) intraluminal defect area (A, green arrow); (ii) malapposed and uncovered struts (B, yellow arrow); (iii) uncovered struts 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)

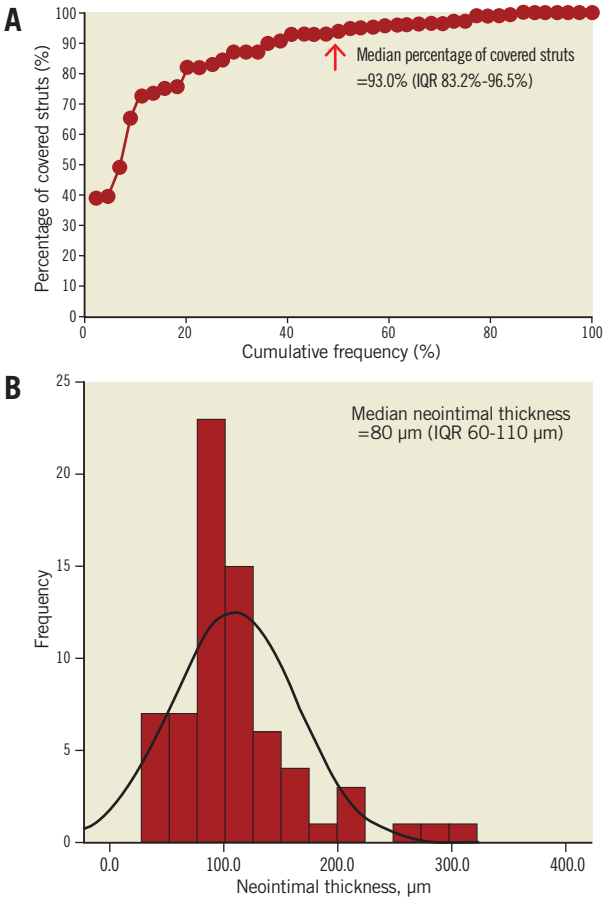

Figure 3. *Cumulative frequency curve of percentage of covered struts (A) and histogram of neointimal thickness (B).*

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, mm^2	5.73 (4.21-6.47)
Lumen area, mm^2	7.02 (5.72-8.42)
Stent eccentricity index	0.90 (0.88-0.92)
Minimum stent area, mm^2	6.57 (5.86-7.45)
Stent area, mm^2	7.58 (6.69-9.04)
Neointimal area, mm^2	0.62 (0.36-0.90)
Mean ISA area, mm^2	0.00 (0.00-0.03)
Lesion-level analysis	
Total analysed lesion, n	45
Mean area of ISA >2 mm^2, n (%)	2 (4.4)
Thrombus area >300 $µm^2$, n (%)	0
Neointima volume, mm^3	10.13 (6.05-16.21)
Stent volume, mm^3	138.67 (96.14-173.59)
Lumen volume, mm^3	129.92 (86.61-159.00)
Total malapposition volume, mm^3	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

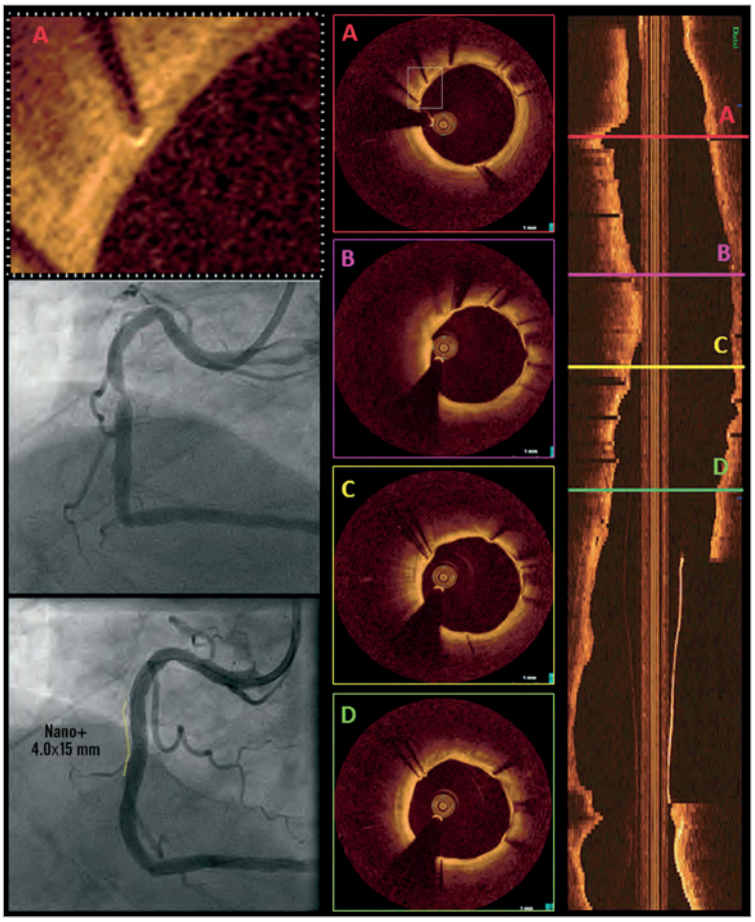

Figure 4. *Example of optical coherence tomography findings. Left middle and lower panels demonstrate pre- and post-procedure coronary angiography of right coronary artery, respectively. A Nano+ stent 4.0×15 mm was implanted into the right coronary artery. A three-month follow-up OCT image shows the 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/mm^2 for sirolimus and 0.8 μg/mm^2 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

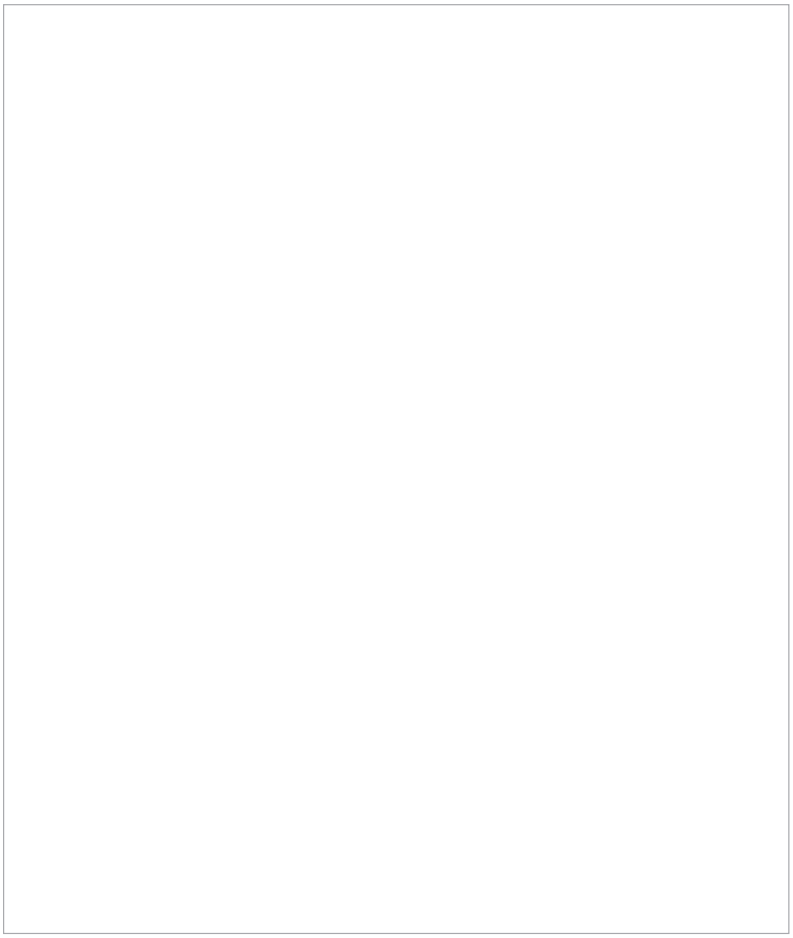

Figure 5. *Spread-out vessel chart of all stents. A) Percentage of covered struts and healing index. The blue vertical axis on the left-hand side shows the percentage of covered struts, while the red vertical axis on the right-hand side shows the healing index. Struts are colour-coded according to covered 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.

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