CLINICAL RESEARCH
CORONARY INTERVENTIONS

Evaluation of vascular healing of polymer-free sirolimus-eluting stents in native coronary artery stenosis: a serial follow-up at three and six months with optical coherence tomography imaging

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Abstract

Aims: Our aim was to assess vascular response after polymer-free sirolimus-eluting stent (SES) implantation by using an optical coherence tomography (OCT)-derived vascular healing score (HS), quantifying the deficiency of healing.

Methods and results: In a prospective, multicentre, single-arm, open-label study, OCT examinations were performed at three months in 45 patients (47 lesions). Per protocol, 24 lesions which had not reached adequate vascular healing according to study criteria were scheduled for OCT examination at six months. The HS was calculated at two time points. Serial OCT imaging demonstrated that the proportion of covered stent struts increased from a median of 87.1% at three months to 98.6% at six months (p<0.001). The neointimal thickness increased from a median of 82.8 μm to 112.2 μm (p<0.001), whereas the median percentages of malapposed struts were 0.2% and 0.0% at the two respective time points. Neointimal volume obstruction increased from 6.3% to 12.8%, and the HS decreased from a median of 28.1 at three months to 2.4 at six months.

Conclusions: In patients who had inadequate vascular healing three months after polymer-free SES implantation, serial OCT showed almost complete vascular healing at six months. (ClinicalTrials.gov Identifier: NCT01925027)

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Abbreviations

BMS	bare metal stent
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
HS	healing score
ISA	incomplete stent apposition
LLL	late lumen loss
OCT	optical coherence tomography
%NVO	percentage of in-stent neointimal volume obstruction
RUTTS	ratio of uncovered to total stent struts per section
SES	sirolimus-eluting stent

Introduction

Optical coherence tomography (OCT) provides excellent imaging resolution of implanted devices and coronary arteries. At follow-up, OCT sheds light on the vascular healing process for the various coronary stent platforms[1-3]. Post-mortem data, demonstrating the relationship between uncovered stent strut and stent thrombosis, have been reported[4]. The impact of permanent polymer drug-eluting stents (DES) on long-term complications (late and very late stent thrombosis) from delayed vascular healing has been well described in the literature[5,6]. Consequently, intensive clinical research has focused on the potential relationship between OCT findings (uncovered strut and stent malapposition) and clinical outcomes.

Complications created by the polymer have motivated researchers to design new coronary stent platforms without a polymer coating. To evaluate the status of vascular healing systematically, the healing score (HS) has been introduced in clinical research[7,8]. The advantage of the HS is that it permits a relative assessment of the speed and degree of vascular "healing" in patients treated with different types of stent and at different points in time. The Nano+™ polymer-free stent (Lepu Medical Technology Co., Ltd., Beijing, China) is a polymer-free sirolimus-eluting stent (SES) which elutes the drug sirolimus from a reservoir made of abluminal nanomeric cavities, aimed at minimising long-term complications that have been related to the polymer coating. Prior OCT examinations three months after Nano+ implantation in 47 lesions showed that the strut coverage rate was 93.0%[9].

The aim of our present study was to provide mechanistic insights into the vascular healing process after implantation of polymer-free SES, as assessed in the vascular healing process by serial assessment of lesions with OCT that were treated with polymer-free SES at three and six months.

Methods

PATIENT POPULATION

The Nano+ OCT study is a prospective, multicentre, single-arm, open-label study in coronary artery disease patients. The inclusion and exclusion criteria have been described previously[9]. Briefly, the inclusion criteria are: 1) stable angina or silent ischaemia demonstrated by positive functional study with a *de novo* target lesion of >50% diameter stenosis (%DS); 2) planned intervention in 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 in diameter. All patients had OCT assessment scheduled at three-month follow-up. Whenever the pre-specified criteria were not fulfilled on three-month OCT imaging, the patients were scheduled for additional OCT assessment at six months. For the purposes of this study which aimed at assessing vascular healing serially at three months and six months, the data were exclusively reported in lesions which had OCT assessment at both time points. The study protocol was approved by all institutional ethics committees and informed consent was obtained from every patient before any intervention was performed.

DEVICE DESCRIPTION

The Nano+ stent is a drug-eluting stainless steel stent with a strut thickness of 91 μm. A large number of pores with a diameter of 400 nm are present on the abluminal stent surface. The device releases sirolimus from the abluminal pores directly (i.e., without using a polymer coating) into the vessel wall. A total of 85% of the drug is released within 30 days.

OCT ACQUISITION AND ANALYSIS

The details of OCT acquisition have been previously described[9]. All OCT images were analysed at an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) with QIvus 2.2 software (Medis, Leiden, The Netherlands). The stent and lumen areas were semi-automatically traced at 1 mm intervals.

At three-month follow-up, all lesions were evaluated by pre-specified OCT criteria, derived from the literature[4,7,10,11]. These criteria were: (i) percentage of covered struts >90%; (ii) no frame with a ratio of uncovered to total stent struts (RUTTS) of >30%; (iii) incomplete stent apposition area (ISA) ≤2 mm^2; (iv) intraluminal defect area (ILD) <300 μm^2. If these were not fulfilled, the patients were scheduled for additional OCT assessment at six months. A covered strut was defined as having a neointimal thickness >0 μm[8,12]. A RUTTS was calculated in every cross-section from the number of uncovered struts divided by the total number of struts[4]. Incomplete strut apposition was defined as a separation between strut and vessel wall with a distance greater than the thickness of the strut (i.e., >91 μm). An intraluminal defect was defined as an irregularly shaped structure, either free from the vessel wall or attached to the vessel wall or the stent.

To quantify the degree of vascular healing, the healing score (HS) was calculated at every time point. Details of the HS components have been described[8]. The score consisted of five parameters, as follows: (a) percentage of intraluminal defect (%ILD); (b) percentage of malapposed and uncovered struts (%MU); (c) percentage of uncovered struts alone (%U); (d) percentage of malapposition alone (%M); (e) presence of neointimal volume obstruction more than 30% (%NVO). The parameters were weighted according to the following formula: HS=[% ILD×4]+[% MU×3]+[% U×2]+[% M]+[% NVO −30%]. Whenever %NVO was less than 30, the last component was set as 0.

TREATMENT ALLOCATION AND FOLLOW-UP PROCEDURE

All patients in this trial underwent stent implantation according to standard procedures. All patients received aspirin 75-100 mg per day indefinitely and a daily dose of clopidogrel 75 mg or prasugrel 10 mg or ticagrelor 90 mg bid for at least four months after the index procedure.

Following the OCT examination at three months, all OCT pullbacks were assessed off-line by an independent core lab. When all pre-specified OCT criteria were met, patients were allowed to stop DAPT at four months but were advised to continue aspirin indefinitely according to standard guidelines[13]. In contrast, if any of the OCT criteria were not met, the patients were scheduled for repeat angiography and OCT examination at six months according to the protocol. If the six-month OCT findings met all criteria, the patients were allowed to stop DAPT at seven months; otherwise, the patients were requested to continue DAPT for at least 12 months after the index procedure.

Patients who stopped DAPT at either four or seven months according to the OCT findings were followed up at hospital or by a telephone call one month after their discontinuation of DAPT (five or eight months) in order to assess their vital status and to confirm the absence of serious adverse events after the discontinuation of DAPT.

QUANTITATIVE CORONARY ANALYSIS

Two-dimensional quantitative coronary analysis (QCA) was performed at an independent core lab (Cardialysis BV) with the CAAS system (CAAS 5.9; Pie Medical BV, Maastricht, The Netherlands), using validated quantitative methods[14].

STUDY ENDPOINTS

The primary endpoint was the change of HS from three to six months. The secondary angiographic endpoints were binary restenosis, late lumen loss (LLL), minimal lumen diameter (MLD) and %DS at six months. The secondary OCT endpoints were neointimal area and volume; mean stent lumen diameter, area and volume; minimal stent lumen diameter, area, and volume; mean neointimal thickness of the strut coverage; percentage of covered struts; and percentage of incomplete strut apposition area at six months.

Statistical analysis

The statistical analysis was performed by SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Categorical variables were summarised with frequencies and percentages. The continuous variables were reported as mean±standard deviation (SD) or median and interquartile ranges (IQR 1st-3rd) as appropriate. The Wilcoxon signed-rank test was used to compare continuous variables between serial OCT and QCA data. The categorical variables were compared by Fisher's exact test. A two-sided p-value <0.05 was considered statistically significant.
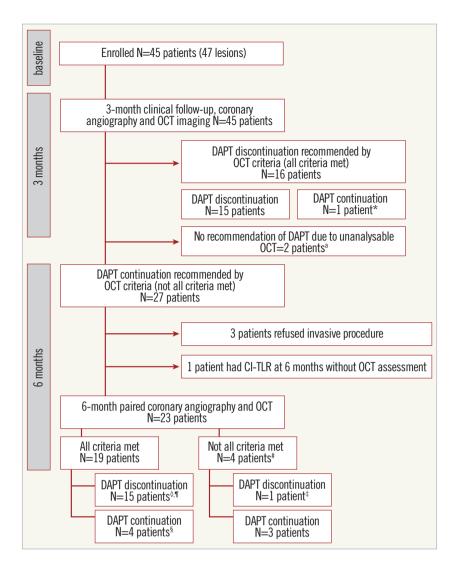
Results

BASELINE CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS

The study population is described in **Figure 1**. A total of 45 patients with 47 lesions received Nano+ stents and all patients under-

went repeat coronary angiography and OCT examination at three months. Twenty-seven patients (28 lesions) did not meet all OCT criteria at three months and were scheduled for OCT examination at six months. Out of 27 patients, three patients refused to undergo six-month invasive angiography while one patient underwent clinically indicated target lesion revascularisation without OCT assessment at 185 days. Finally, 23 patients with 24 lesions had serial coronary angiography and OCT assessment at three and six months. Baseline clinical and angiographic characteristics are presented in **Table 1**.

Table 1. Baseline clinical and angiographic characteristics.

	Overall n=45 patients/ 47 lesions	Serial population n=23 patients/ 24 lesions
Age (years), mean±SD	64.0±9.8	68.6±9.5
Men, n (%)	33 (73.3)	18 (78.3)
Current smokers, n (%)	6 (13.3)	1 (4.3)
Diabetes, n (%)	5 (11.1)	4 (17.4)
Hypertension, n (%)	24 (53.3)	12 (52.2)
Hyperlipidaemia, n (%)	37 (82.2)	19 (82.6)
Family history of CAD, n (%)	19 (45.2)	8 (34.8)
Previous CABG, n (%)	1 (2.2)	1 (4.3)
Previous PCI, n (%)	10 (22.2)	5 (21.7)
Previous myocardial infarction, n (%)	10 (22.2)	5 (21.7)
Stable angina, n (%)	30 (66.7)	16 (69.6)
Silent ischaemia, n (%)	6 (13.3)	3 (13.0)
Target vessel		
Left anterior descending, n (%)	27 (57.4)	12 (50.0)
Left circumflex artery, n (%)	6 (12.8)	4 (16.7)
Right coronary artery, n (%)	14 (29.8)	8 (33.3)
AHA/ACC lesion classification		
B1, n (%)	20 (42.6)	8 (33.3)
B2, n (%)	25 (53.2)	15 (62.5)
C, n (%)	2 (4.3)	1 (4.2)
Moderate to heavy calcification, n (%)	8 (17.0)	6 (25.0)
Obstruction length (mm)	12.7±4.4	12.9±4.1
Diameter stenosis (%)	60.9±10.8	61.3±10.4
Reference vessel diameter (mm)	2.83±0.46	2.81±0.47
Minimal lumen diameter (mm)	1.10±0.35	1.09±0.37
Mean lumen diameter (mm)	2.51±0.39	2.49±0.38
Total nominal length of implanted stents per lesion (mm)	20.0±9.2	21.7±11.5
Number of devices implanted per lesion (mm)	1.1±0.4	1.2±0.5
Mean nominal device diameter (mm)	3.6±1.5	3.19±0.41
Overlapping stents, n (%)	4 (8.5)	2 (8.7)

Data based on patients who had both OCT and coronary angiography at 3 and 6 months. Data are mean±standard deviation or number (%).
AHA/ACC: American Heart Association/American College of Cardiology

Figure 1. *Study flow chart and follow-up. *One patient was advised to continue DAPT according to his physician's opinion. ᵃTwo patients stopped clopidogrel after six-month OCT assessment due to fulfilment of OCT criteria. #No definite, probable, possible stent thrombosis reported at eight-month clinical follow-up. ‡Clopidogrel was stopped due to dental procedure. ◊Two patients had indication to use anticoagulant after stent implantation. One patient discontinued aspirin at one month and the other discontinued aspirin at three months after the index procedure. Both patients took the combination of anticoagulant and clopidogrel until six-month follow-up. After clopidogrel was discontinued at six months, the patients took only anticoagulant therapy. ¶One patient underwent CABG due to progression of distal left main disease. §One patient had non-clinically indicated TLR at 184 days. CI-TLR: clinically indicated target lesion revascularisation; DAPT: dual antiplatelet therapy; OCT: optical coherence tomography*

SERIAL ANGIOGRAPHIC AND OCT EXAMINATIONS AT THREE MONTHS AND SIX MONTHS

The QCA assessment at three and six months is shown in **Table 2**. The in-stent MLD was 2.46±0.38 mm at three months and 2.25±0.45 mm at six months. The in-stent LLL was 0.14±0.06 mm at three months and 0.35±0.08 mm at six months.

The OCT analyses are shown in **Table 3**. At three months, 95.8% (23 lesions) had at least one frame with RUTTS >30% and decreased to 12.5% (three lesions) at six months. Of note, 14 lesions (58.3%) had a percentage of covered strut <90% at three months while at six months only two lesions (8.3%) had such an incomplete coverage. The median number of frames

with RUTTS >30% decreased from 3.5 frames (range 1.3-7.0) at three months to 0.0 frames at six months. There was no case with an intraluminal defect >300 μm² at either time point.
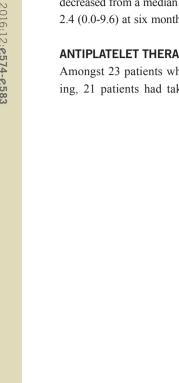
The proportion of covered stent struts increased from a median of 87.1% (75.4%-92.9%) at three months to 98.6% (95.6%-100.0%) at six months **(Figure 2)**. The median of neointimal thickness increased from 82.8 μm (69.3-98.7) to 112.2 μm (97.9-146.6) between three and six months. Only one case still had persistent malapposition at six months and there was no newly detected stent malapposition. The median percentage of malapposed struts at three and six months was 0.2% (IQR 0.0%-1.9%) and 0.0% (IQR 0.0%-0.0%), respectively. The %NVO increased between three and six months

from 6.3% (IQR 4.1%-9.6%) to 12.8% (IQR 8.5%-18.0%). The percentage of residual area stenosis increased from 14.6% (IQR 7.0%-23.6%) to 21.0% (IQR 7.5%-32.8%), p=0.002. The HS significantly decreased from a median of 28.1 (IQR 12.3-49.9) at three months to 2.4 (0.0-9.6) at six months **(Figure 3, Figure 4)**.

ANTIPLATELET THERAPY

Amongst 23 patients who received six-month repeat OCT imaging, 21 patients had taken the following DAPT at six months:

aspirin and clopidogrel 18 (85.7%) patients, aspirin and ticagrelor 2 (9.5%) patients, and aspirin and prasugrel in one (4.8%) patient.

CLINICAL OUTCOMES

Throughout the eight-month period, no definite, probable or possible stent thrombosis was reported among the 27 patients. There were three patients who underwent revascularisation after six-month angiographic follow-up. Two patients received target lesion
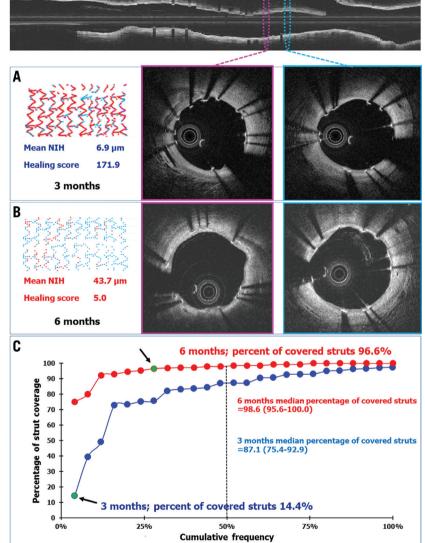

Figure 2. *Example of optical coherence tomography and cumulative frequency curve of percentage of covered struts at three months and six months in 24 paired lesions. Top panel shows the longitudinal view with corresponding cross-section samplings from two different in-stent segments (pink and blue ellipse). The follow-up OCT cross-sections at three months (middle and right-hand panel A) and six months (middle and right-hand panel B) are shown in coloured frames corresponding to the coloured cross-sections in the longitudinal view. The coverage of struts improved from three to six months. Panel A (left) shows a colour-coded spread-out sheet depicting a high proportion of uncovered struts (red dots) to covered struts (blue dots). At six-month follow-up (panel B, left), the spread-out sheet shows an improvement of strut coverage (fewer red dots). The HS dramatically decreased from 171.9 at three months to 5.0 at six months. The cumulative frequency curves of the percentage of covered struts at three months (blue) and six months (red) are shown in panel C. The green dots indicated by black arrows illustrate a shift from low to high percentage of strut coverage from three months to six months.*
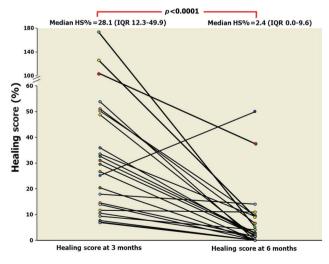
Table 2. Quantitative coronary angiography at 3 months and 6 months.

	3 months n=24 lesions	6 months n=24 lesions	p-value
Reference vessel diameter (mm)			
In-stent	2.84±0.43	2.77±0.44	0.03
In-segment	2.77±0.46	2.71±0.46	0.08
Minimal lumen diameter (mm)			
In-stent	2.46±0.38	2.25±0.45	0.001
In-segment	2.25±0.39	2.09±0.46	0.03
Mean lumen diameter (mm)			
In-stent	2.95±0.36	2.79±0.36	<0.001
In-segment	2.89±0.37	2.75±0.39	<0.001
Diameter stenosis (%)			
In-stent	12.7±9.1	17.6±12.3	0.02
In-segment	18.8±7.9	22.7±10.8	0.04
Late loss (mm)			
In-stent	0.14±0.06	0.35±0.08	<0.001
In-segment	0.06±0.04	0.22±0.07	0.005
Binary restenosis			
In-stent	0 (0.0%)	0 (0.0%)	1.0
In-segment	0 (0.0%)	0 (0.0%)	1.0

Data are mean±standard deviation or number (%). *p*-values were calculated by Wilcoxon signed-rank test.

Figure 4. *Spread-out sheets demonstrating the coverage status of the individual stents/patients at two time points (three and six months). Upper panel (A) demonstrates the coverage status of the individual stents at three months, while the lower panel (B) demonstrates the coverage status of the same stents at six months. Struts are colour-coded according to their coverage status. Uncovered struts are depicted as red while covered struts are depicted as blue, with deepening colour of blue indicative of a thicker neointima (light blue colour indicates a neointimal thickness more than 0 µm to 100.0 µm, sustained 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).*
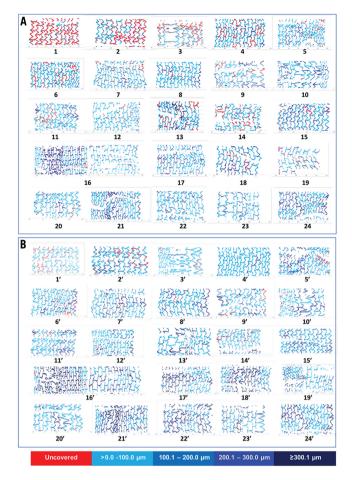
revascularisation and one patient underwent coronary bypass due to stable angina and progression of distal left main disease.

Discussion

The present study was to provide a mechanistic interpretation of the vascular healing process in polymer-free SES in which the relative lack of neointimal growth was documented at three months. The main findings are: 1) an improvement in vascular healing, as assessed by the HS, was documented by a decrease of HS from

28.1 at three months to 2.4 at six months; 2) the angiographic late lumen loss and %NVO on OCT at six months were 0.35 mm and 12.8%, respectively; and 3) the absence of any definite or probable stent thrombosis up to eight months.

Initially, there was heterogeneity in the healing process at three months; three lesions had a percentage of covered struts <50%. The extremely low coverage might be related to: i) the presence of ISA, as malapposed struts generate high shear flow disturbance that is known to be a factor of retardation of neointimal growth[15]; ii) unfavourable characteristics of circulating endothelial progenitor cell in individual patients[16]; and iii) a heterogeneity in drug effect, potentially due to defective manufacturing of a particular stent batch.

Figure 3. *Temporal change of healing index at three-month and six-month follow-up in 24 paired lesions.*

Table 3. Optical coherence tomography analysis at 3 months and 6 months.

	3 months n=24 lesions	6 months n=24 lesions	*p*-value
Strut level analysis			
Total analysed struts, n	3,833	3,812	
Number of struts per cross-section, n	7.9±1.2	7.7±1.1	0.32
Percentage of covered struts	87.1 (75.4-92.9)	98.6 (95.6-100.0)	<0.001
Mean neointimal thickness, µm	82.8 (69.3-98.7)	112.2 (97.9-146.6)	<0.001
Number of malapposed struts, n	41	10	
Percentage of malapposed struts, %	0.2 (0.0-1.9)	0 (0.0-0.0)	0.008
Percentage of both malapposed and uncovered struts present, %	0.0 (0.0-0.7)	0 (0.0-0.0)	0.09
Cross-section level analysis			
Number of cross-sections per lesion, n	18 (16-21)	18 (17-21)	0.25
Mean reference lumen area, mm^2	7.08 (5.27-8.51)	6.69 (5.49-7.36)	0.003
Minimal lumen area, mm^2	5.85 (4.49-6.98)	5.25 (3.87-6.01)	<0.001
Mean lumen area, mm^2	7.75 (6.39-8.51)	6.69 (5.87-7.89)	<0.001
Minimal stent area, mm^2	6.68 (5.98-7.42)	6.53 (5.77-7.41)	0.10
Mean stent area, mm^2	8.25 (6.72-9.27)	7.63 (6.76-9.23)	0.03
Neointimal area, mm^2	0.47 (0.35-0.73)	0.81 (0.67-1.21)	<0.001
Mean ISA area, mm^2	0.01 (0.00-0.07)	0.00 (0.00-0.00)	0.01
Number of frames with RUTTS >30% per lesion	3.5 (1.3-7.0)	0.0 (0.0-0.0)	<0.001
Lesion-level analysis			
Healing score	28.1 (12.3-49.9)	2.4 (0.0-9.6)	<0.001
Mean area of ISA >2 mm^2, n (%)	0 (0.0%)	0 (0.0%)	0.56
Intraluminal defect area >300 µm^2, n (%)	0 (0.0%)	0 (0.0%)	1.00
Neointima volume, mm^3	7.5 (5.9-14.2)	13.7 (11.6-24.8)	<0.001
Percentage of neointimal volume obstruction	6.3 (4.1-9.6)	12.8 (8.5-18.0)	<0.001
Stent volume, mm^3	140.1 (101.2-172.2)	139.6 (102.5-158.0)	0.86
Lumen volume, mm^3	134.0 (99.6-159.7)	120.1 (93.4-145.7)	0.57
Mean lumen eccentricity index	0.87 (0.82-0.89)	0.87 (0.83-0.89)	0.33
Mean stent eccentricity index	0.89 (0.85-0.92)	0.90 (0.87-0.92)	0.12
Residual area stenosis	14.6 (7.0-23.6)	21.0 (7.5-32.8)	0.002

Data are median (interquartile 1st-3rd) or mean±standard deviation. *p*-values were calculated by Wilcoxon signed-rank test.

CAN PATHOLOGICAL CRITERIA BE APPLIED AS AN INDICATOR OF OPTIMAL VASCULAR HEALING?

The OCT quantitative criteria used in the present study were derived from a post-mortem histopathological study that showed a strong correlation of late stent thrombosis with RUTTS and the number of uncovered struts[4]. Our OCT analysis at three months showed that 95.8% of lesions had RUTTS >30% while the percentage of strut coverage <90% was observed in 58.3%. These findings reflect the weak relationship between OCT surrogate markers and their clinical prognostic value. The anatomopathological criteria seem to overestimate the deficiencies of vascular healing status and they appear to be too stringent. The issues of applying the pathological criteria to clinical research are the following. 1) The criteria were derived from a post-mortem study of patients with late stent thrombosis and may thus reflect a certain selection bias since the denominator (patients alive having uncovered and malapposed struts) is unknown while the numerator

(autopsied patients with stent thrombosis) is known. To prove the prognostic value of uncovered and malapposed struts in clinical practice, a huge sample size to show statistical significance would be needed. Since the incidence of stent thrombosis with a combination of uncovered or malapposed struts is very low, the correlation may never be established. 2) The criteria were derived in the era of first-generation DES which had thicker struts that promoted recirculation zones with low endothelial shear stress behind the struts – a biological trigger for stent thrombosis[17]. 3) The conventional DAPT used in these anatomopathological cases (ticlopidine or clopidogrel) was not as potent as contemporary antiplatelet agents such as ticagrelor or prasugrel.

CAN OCT CRITERIA BE APPLIED AS GUIDANCE FOR DUAL ANTIPLATELET DURATION?

The current analysis showed that only one third of lesions had adequate vascular healing at three months whereas vascular healing

was almost complete at six months, without stent thrombosis. The present study did not pretend to detect lesions that were going to develop stent thrombosis: the study protocol recommended continuation of DAPT in order potentially to prevent patients from developing stent thrombosis. Previously, there has been sufficient evidence showing that abbreviated DAPT duration of three months[18] or six months[19-22] after polymer-coated DES implantation for low to moderate-risk patients is safe. It has recently been demonstrated that DAPT duration can even be abbreviated to only one month after polymer-free DES implantation, as reported in the LEADERS FREE trial[23]. In the LEADERS FREE trial, a polymer-free umirolimus-coated stent was compared with a bare metal stent (BMS) in high risk of bleeding patients who underwent PCI. The results showed that a polymer-free umirolimus-coated stent was superior to a BMS with respect to the composite of cardiac death, myocardial infarction, or stent thrombosis when used with a one-month course of DAPT. The rate of stent thrombosis did not differ significantly between the two groups, and more than half of the stent thromboses in both groups occurred during the first 30 days, when patients were prescribed DAPT. Consequently, invasive imaging is not a pragmatic requirement to determine whether DAPT has to be continued longer than three or six months in polymer-free DES, as reported in the present study. However, the consideration of abbreviated DAPT duration should be applied in specific stent platforms and in relation to similar lesion characteristics to those assessed in clinical trials.

ANGIOGRAPHIC LATE LUMEN LOSS AND OCT FINDINGS IN POLYMER-FREE DES

The LLL of the Nano+ stent at three and six months was 0.17 mm and 0.35 mm, respectively. These results are comparable to previous data of a polymer-free rapamycin-eluting stent that had an LLL of 0.16 mm[24] and 0.47 mm[25] at three months and six to eight months, respectively. Although Nano+ had a higher angiographic in-stent LLL as compared to the first and second generation of DES (both permanent and biodegradable polymer-coated)[26-28], the risk of target lesion revascularisation may still be low (<5% to 10%), according to the findings of a previous study with early-generation DES[29]. A higher LLL may not necessarily translate into a higher target lesion revascularisation rate among different DES platforms[30].

A recent study that compared FFR and MLA by OCT has clearly demonstrated that, with the exception of left main disease, an MLA >1.96 mm^2 is not generally associated with an FFR <0.80[31]. In our present study, the MLA was, in general, much higher than this meta-analysis-derived threshold that was recently proposed by D'Ascenzo et al[31].

Limitations

The limitations of this prospective study are: (1) a relatively small sample size that was not powered to demonstrate the relationship between OCT findings and clinical outcomes, as stated in the protocol; (2) the lesions that were treated in the present study were simple lesions, therefore favourable vascular healing might be expected in these relatively short and less complex lesions;

(3) a serial OCT follow-up was solely performed in inadequate vascular healing lesions at three months, which is a potential cause of selection bias; (4) the lack of a direct comparison between the study devices and contemporary DES that are used in routine clinical practice; and (5) the criteria of covered stent was defined as having a neointimal thickness more than 0 μm, which may not be practical in clinical use.

Conclusion

In patients treated with polymer-free SES, serial OCT showed almost complete vascular healing at six months, even when coverage was insufficient at three months. This suggests an adequate safety and efficacy profile of the device at that point in time. The implication of these findings should be evaluated in a large clinical trial.

Impact on daily practice

The Nano+ is a polymer-free DES that elutes sirolimus from a reservoir made of abluminal nanomeric cavities without the presence of a polymer. The healing score (HS), derived from OCT assessment, showed that the polymer-free SES develops an almost complete vascular healing within six months.

Guest Editor

This paper has been guest edited by Carlo Di Mario, MD, PhD, FESC, FACC, FRCP, FSCAI; NIHR Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom.

Conflict of interest statement

C. von Birgelen is a consultant to Boston Scientific and Medtronic and has received lecture fees from MSD and AstraZeneca; the research department has received institutional research grants from Biotronik, Boston Scientific, and Medtronic. P.W. Serruys and Y. Onuma are members of the advisory board of Abbott Vascular. The other authors have no conflicts of interest to declare. The Guest Editor has no conflicts of interest to declare.

References

1. 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.

2. 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.

3. 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.

4. 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.

5. 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.

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. 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.

8. Raber L, Onuma Y, Brugaletta S, Garcia-Garcia HM, Backx B, Iniguez A, Jensen LO, Cequier-Fillat A, Pilgrim T, Christiansen EH, Hofma SH, Suttorp M, Serruys PW, Sabate M, Windecker S. Arterial healing following primary PCI using the Absorb everolimus-eluting bioresorbable vascular scaffold (Absorb BVS) versus the durable polymer everolimus-eluting metallic stent (XIENCE) in patients with acute ST-elevation myocardial infarction: rationale and design of the randomised TROFI II study. *EuroIntervention.* 2015 August 13;11. [Epub ahead of print].

9. Suwannasom P, Benit E, Gach O, von Birgelen C, Hofma SH, Bo X, Zhang YJ, Nakatani S, Ishibashi Y, Onuma Y, García-García HM, Gao RL, Serruys PW. Short-term effects of Nano+™ polymer-free sirolimus-eluting stents on native coronary vessels: an optical coherence tomography imaging study. *AsiaIntervention.* 2015;1:57-70.

10. Prati F, Di Vito L, Biondi-Zoccai G, Occhipinti M, La Manna A, Tamburino C, Burzotta F, Trani C, Porto I, Ramazzotti V, Imola F, Manzoli A, Materia L, Cremonesi A, Albertucci M. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: the Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention.* 2012;8:823-9.

11. 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.

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. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.

14. van der Zwet PM, Reiber JH. A new approach for the quantification of complex lesion morphology: the gradient field transform; basic principles and validation results. *J Am Coll Cardiol.* 1994;24:216-24.

15. Foin N, Gutierrez-Chico JL, Nakatani S, Torii R, Bourantas CV, Sen S, Nijjer S, Petraco R, Kousera C, Ghione M, Onuma Y, Garcia-Garcia HM, Francis DP, Wong P, Di Mario C, Davies JE, Serruys PW. Incomplete stent apposition causes high shear flow disturbances and delay in neointimal coverage as a function of strut to wall detachment distance: implications for the management of incomplete stent apposition. *Circ Cardiovasc Interv.* 2014;7:180-9.

16. De Winter RJ, Klomp M. Understanding the role of endothelial progenitor cells in cardiovascular disease, coronary artery lesion progression, and in-stent restenosis. *JACC Cardiovasc Interv.* 2010;3:87-9.

17. Koskinas KC, Chatzizisis YS, Antoniadis AP, Giannoglou GD. Role of endothelial shear stress in stent restenosis and thrombosis: pathophysiologic mechanisms and implications for clinical translation. *J Am Coll Cardiol.* 2012;59:1337-49.

18. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y; RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol.* 2012;60:1340-8.

19. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fuca G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation.* 2012;125:2015-26.

20. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation.* 2012;125:505-13.

21. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, Tolg R, Seyfarth M, Maeng M, Zrenner B, Jacobshagen C, Mudra H, von Hodenberg E, Wohrle J, Angiolillo DJ, von Merzljak B, Rifatov N, Kufner S, Morath T, Feuchtenberger A, Ibrahim T, Janssen PW, Valina C, Li Y, Desmet W, Abdel-Wahab M, Tiroch K, Hengstenberg C, Bernlochner I, Fischer M, Schunkert H, Laugwitz KL, Schömig A, Mehilli J, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Trial Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J.* 2015;36:1252-63.

22. Gilard M, Barragan P, Noryani AA, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, Le Breton H, Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P, Champagnac D, Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Boschat J, Morice MC. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multi-center ITALIC trial. *J Am Coll Cardiol.* 2015;65:777-86.

23. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iñiguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC; LEADERS FREE Investigators. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med.* 2015;373:2038-47.

24. 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.

25. Mehilli J, Byrne RA, Wieczorek A, Iijima R, Schulz S, Bruskina O, Pache J, Wessely R, Schömig A, Kastrati A; Intracoronary Stenting and Angiographic Restenosis Investigators--Test Efficacy of Rapamycin-eluting Stents with Different Polymer Coating Strategies (ISAR-TEST-3). Randomized trial of three rapa-mycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J.* 2008;29:1975-82.

26. 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. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.

27. Regar E, Serruys PW, Bode C, Holubarsch C, Guermonprez JL, Wijns W, Bartorelli A, Constantini C, Degertekin M, Tanabe K, Disco C, Wuelfert E, Morice MC; RAVEL Study Group. Angiographic findings of the multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. *Circulation.* 2002;106:1949-56.

28. Serruys PW, Ong AT, Piek JJ, Neumann FJ, van der Giessen WJ, Wiemer M, Zeiher A, Grube E, Haase J, Thuesen L, Hamm C, Otto-Terlouw PC. A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial. *EuroIntervention.* 2005;1:58-65.

29. Ellis SG, Popma JJ, Lasala JM, Koglin JJ, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Stone GW. Relationship between angio-graphic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. *J Am Coll Cardiol.* 2005;45:1193-200.

30. Pocock SJ, Lansky AJ, Mehran R, Popma JJ, Fahy MP, Na Y, Dangas G, Moses JW, Pucelikova T, Kandzari DE, Ellis SG, Leon MB, Stone GW. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol.* 2008;51:23-32.

31. D'Ascenzo F, Barbero U, Cerrato E, Lipinski MJ, Omede P, Montefusco A, Taha S, Naganuma T, Reith S, Voros S, Latib A, Gonzalo N, Quadri G, Colombo A, Biondi-Zoccai G, Escaned J, Moretti C, Gaita F. Accuracy of intravascular ultrasound and opti-cal coherence tomography in identifying functionally significant coronary stenosis according to vessel diameter: A meta-analysis of 2,581 patients and 2,807 lesions. *Am Heart J.* 2015;169:663-73.