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Clinical outcomes by optical characteristics of neointima and treatment modality in patients with coronary in-stent restenosis

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KEYWORDS

- drug-eluting balloon
- drug-eluting stent
- in-stent restenosis
- optical coherence tomography

Abstract

Background: Drug-coated balloons (DCB) and drug-eluting stents (DES) represent the currently recommended treatments for in-stent restenosis (ISR). Optical coherence tomography (OCT) allows detailed neointimal characterisation which can guide treatment strategies.

Aims: The aims of this study were first, to assess the relation between neointimal pattern and clinical outcomes following in-stent restenosis (ISR) treatment, and second, to explore a potential interaction between neointimal pattern and treatment modality relative to clinical outcomes.

Methods: Patients undergoing OCT-guided treatment (DCB or DES) of ISR in three European centres were included. Based on the median of distribution of non-homogeneous neointima quadrants, patients were categorised into low and high inhomogeneity groups.

Results: A total of 197 patients (low inhomogeneity=100 and high inhomogeneity=97) were included. There were no significant differences in terms of major adverse cardiac events (MACE) (p=0.939) or target lesion revascularisation (TLR) (p=0.732) between the two groups. The exploratory analysis showed a significant interaction between neointimal pattern and treatment modality regarding MACE (p_{int}=0.006) and TLR (p_{int}=0.022). DES showed a significant advantage over DCB in the high (MACE: HR 0.26 [0.10-0.65], p=0.004; TLR: HR 0.28 [0.11-0.69], p=0.006), but not in the low inhomogeneity group (MACE: p=0.917; TLR: p=0.797).

Conclusions: In patients with ISR treated with DCB or DES, there were no significant differences in terms of MACE or TLR between the low and high inhomogeneity groups. A significant interaction was observed between treatment modality and neointimal pattern with an advantage of DES over DCB in the high and no difference in the low inhomogeneity group. This warrants confirmation from prospective dedicated studies.

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Abbreviations

CI	confidence interval
DCB	drug-coated balloon
DES	drug-eluting stent
HR	hazard ratio
ISR	in-stent restenosis
MACE	major adverse cardiac events
MI	myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
QCA	quantitative coronary analysis
TLR	target lesion revascularisation

Introduction

In-stent restenosis (ISR) represents the most frequent treatment failure modality following percutaneous coronary intervention (PCI)[1]. Although use of newer-generation drug-eluting stents (DES) has significantly reduced its occurrence, contemporary randomised clinical trials have shown cumulative rates of target lesion revascularisation (TLR) of 7-10% at five-year follow-up[2], and real-world registries including surveillance angiography have shown even higher rates of angiographic restenosis[3].

Although several treatment strategies for ISR have been tested[4], drug-coated balloon (DCB) angioplasty and repeat DES implantation have emerged as the most effective therapeutic options[5,6]. However, one major limitation of clinical trials comparing treatment modalities for ISR is the isolated use of coronary angiography as a guide to treatment allocation; indeed, besides mere confirmation of ISR presence, such a coronary "luminogram" delivers little additional information to guide the treatment strategy.

In this regard, the use of high-resolution intravascular imaging techniques, such as optical coherence tomography (OCT), provides unique information regarding the mechanisms underlying ISR and the characteristics of neointimal tissue[7]. Based on its optical properties at OCT imaging, neointimal tissue has been subdivided into several patterns[8] that correlate with different histological substrates[9,10]. Such different patterns might impact on the outcomes of patients with ISR undergoing PCI in a way dependent on the treatment approach (DES or DCB). However, the number of studies investigating the correlation between OCT-defined neointimal pattern and clinical outcomes following different treatment modalities is extremely scant[11] and limited by either comparison of non-contemporary treatment options (such as plain old balloon angioplasty), short clinical follow-up, or isolated neointimal characterisation at one single frame.

This large multicentre European registry had two objectives: first, to assess whether the OCT neointimal pattern is related to the clinical outcomes of patients undergoing PCI for ISR; second, to explore whether there is an interaction between neointimal pattern and type of PCI – DCB or repeat DES – relative to clinical outcomes.

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Methods

PATIENT POPULATION AND STUDY ENDPOINTS

Patients presenting with ischaemic symptoms and/or evidence of myocardial ischaemia in three European centres (Hospital Universitario de La Princesa and Hospital Universitario Clínico San Carlos, Madrid, Spain [from 2010 to 2011]; Deutsches Herzzentrum, Munich, Germany [from 2012 to 2017]) who underwent intravascular OCT and subsequent PCI (either DES or DCB) for ISR were considered eligible for the study. Informed consent was obtained prior to each procedure. Ethics approval was waived since all procedures were required on a clinical basis. Treatment modality was at the discretion of the operator. Clinical follow-up was performed by office visit, phone contact or structured follow-up letter.

The primary endpoint of the study was the cumulative incidence of major adverse cardiac events (MACE), defined as a composite of all-cause death, myocardial infarction (MI) or clinically driven target lesion revascularisation (TLR). The secondary endpoint was clinically driven TLR. Individual components of the primary endpoint were also assessed separately. Further details regarding study endpoint definitions are provided in **Supplementary Appendix 1**.

ANGIOGRAPHIC AND OCT DATA ACQUISITION AND ANALYSIS

Baseline and post-procedural angiograms as well as raw data of OCT image acquisitions were recorded and assessed off-line in a core laboratory (ISAResearch Center, Munich, Germany). The angiographic pattern of ISR was classified according to Mehran's classification[12]. Quadrant-based neointimal characterisation was performed at the frame displaying the maximal % area stenosis as well as the five preceding and following analysed frames[13-15] **(Figure 1)**. Details and definitions regarding angiographic and OCT analysis are provided in **Supplementary Appendix 1**.

In order to investigate the relation between an increased expression of inhomogeneous quadrants and clinical outcomes, the study population was divided into low and high inhomogeneity groups, based on the median of distribution of non-homogeneous quadrants; analogously, the high inhomogeneity patient population was further classified into low and high neoatherosclerosis subgroups.

STATISTICAL ANALYSIS

Continuous data are presented as mean±SD or median (25th-75th percentiles) depending on the distribution pattern of the variable. Categorical data are presented as absolute and relative frequencies. Hypothesis testing of differences between the groups was performed using the Student's t-test or the Wilcoxon rank-sum test for continuous variables and the Pearson χ^2 test (or Fisher's exact test where any expected cell count of the contingency table was <5) for categorical variables.

To account for the clustered nature of the data, a linear mixed model was used for the analysis of OCT data. The model contained a fixed-effects term (neointimal pattern) and a random intercept as random-effects term for patient in case of frame-level analysis and as nested random-effects term for patient and frame for strut-level analysis.

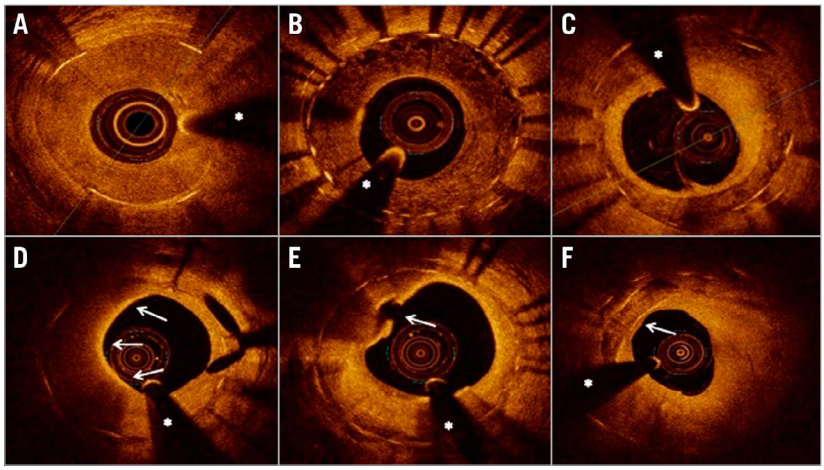

Figure 1. *Representative images of optical coherence tomography findings in patients presenting with in-stent restenosis. A) Homogeneous neointimal pattern. B) Heterogeneous neointimal pattern. C) Layered neointimal pattern. D) Macrophage infiltration involving a 180° neointimal arc (arrows from 6 to 12 o'clock). E) Neoatherosclerosis and ruptured thin-cap fibroatheroma (arrow). F) Neointimal calcification (arrow). * guidewire artefact.*

Event-free survival was estimated by the Kaplan-Meier method for each clinical outcome. Hazard ratios (HR) with two-sided 95% confidence intervals (95% CI) were calculated using Cox proportional hazards models. The two objectives of the study were addressed in a statistical two-step approach. First, we compared two patient groups defined by the OCT neointimal pattern (high and low inhomogeneity groups) regarding their clinical outcomes after PCI for ISR. The risk for the primary and secondary endpoints of the study was assessed using a) a univariable Cox proportional hazards model including only the OCT pattern of neointima as an independent variable, and b) a multivariable model including baseline clinical and angiographic characteristics in addition to the OCT pattern of neointima. Second, we assessed whether the relation between the OCT pattern of neointima and clinical outcomes is influenced by the type of PCI performed for treatment of ISR (DCB or DES). For this purpose, we entered the interaction between OCT pattern of neointima and PCI type into the multivariable model described above. In the case of a significant adjusted interaction between these two variables, we proceeded with an illustrative comparison of the outcomes for the two PCI types (DCB or DES) in each group of OCT pattern of neointima. All tests were two-sided and assessed at a significance level of 5%. Statistical analysis was performed using the R 3.6 Statistical Package (R Foundation for Statistical Computing, Vienna, Austria).

Results

BASELINE CLINICAL AND PROCEDURAL CHARACTERISTICS

A total of 197 patients undergoing PCI for ISR were included, with one lesion being imaged/treated per patient. Based on the median of the distribution of non-homogeneous quadrants, patients were categorised into low (n=100) and high (n=97) inhomogeneity groups. Treatment modality was DES implantation in 88 (44.7%) patients and DCB angioplasty in 109 (55.3%) patients. Baseline clinical, angiographic and procedural characteristics according to neointimal pattern are shown in **Table 1** and **Table 2**. There were

Table 1. Clinical characteristics according to the extent of inhomogeneity.

	Low inhomogeneity n=100	High inhomogeneity n=97	*p*-value
Age, years	66.9±10.6	66.9±10.1	0.978
Male	82 (82.0)	77 (79.4)	0.776
Current smoker	18 (18.0)	13 (13.4)	0.49
Ex-smoker	38 (38.0)	34 (35.1)	0.778
Body mass index (kg/m^2)	28.2±3.97	28.0±4.93	0.797
Hypercholesterolaemia	71 (71.0)	63 (64.9)	0.449
Arterial hypertension	93 (93.0)	84 (86.6)	0.211
Diabetes mellitus	45 (45.0)	37 (38.1)	0.406
Oral therapy	27 (27.0)	24 (24.7)	0.842
Insulin therapy	13 (13.0)	6 (6.19)	0.168
Previous myocardial infarction	56 (56.0)	52 (53.6)	0.846
Previous coronary artery bypass grafting	15 (15.0)	11 (11.3)	0.584
Clinical presentation			
Silent ischaemia	21 (21.0)	21 (21.6)	0.525
Stable angina pectoris	49 (49.0)	49 (50.5)	
Unstable angina pectoris	20 (20.0)	12 (12.4)	
Non-ST-segment elevation myocardial infarction	9 (9.0)	14 (14.4)	
ST-segment elevation myocardial infarction	1 (1.0)	1 (1.0)	
Multivessel disease	84 (84.0)	71 (73.2)	0.094
Affected vessels			
One vessel	16 (16.0)	26 (26.8)	0.072
Two vessels	19 (19.0)	23 (23.7)	
Three vessels	65 (65.0)	48 (49.5)	
Ejection fraction (%)	54.0±13.3	58.8±13.2	0.079

Data are shown as numbers (%) or mean±SD.

Table 2. Angiographic and procedural characteristics according to the extent of inhomogeneity.

	Low inhomogeneity n=100	High inhomogeneity n=97	*p*-value
Index stent interval, days	378 [198-1,772]	416 [215-2,015]	0.403
Target coronary vessel			
Left main coronary artery	1 (1.0)	2 (2.1)	0.266
Left anterior descending coronary artery	50 (50.0)	43 (44.3)	
Left circumflex coronary artery	18 (18.0)	28 (28.9)	
Right coronary artery	31 (31.0)	24 (24.7)	
Restenosis morphology			
Focal margin	9 (9.0)	13 (13.4)	0.065
Focal body	41 (41.0)	38 (39.2)	
Multifocal	12 (12.0)	2 (2.1)	
Diffuse intrastent	29 (29.0)	37 (38.1)	
Proliferative	3 (3.0)	4 (4.1)	
Complete occlusion	6 (6.0)	3 (3.1)	
Underlying stent type			
Bare metal stent	18 (18.0)	20 (20.6)	0.731
Drug-eluting stent	73 (73.0)	68 (70.1)	
Unknown	9 (9.0)	9 (9.3)	
Ostial lesion	18 (18.0)	19 (19.6)	0.918
Bifurcation lesion	26 (26.0)	29 (29.9)	0.652
Quantitative coronary angiography			
Reference diameter, mm	2.96±0.45	2.83±0.53	0.067
Lesion length, mm	13.3±6.79	13.8±7.66	0.633
Preprocedural minimal lumen diameter, mm	1.09±0.45	1.02±0.45	0.267
Post-procedural minimal lumen diameter, mm	2.44±0.47	2.50±0.48	0.388
Preprocedural diameter stenosis, %	63.5±13.6	65.3±13.7	0.358
Post-procedural diameter stenosis, %	19.4±11.5	17.5±9.1	0.196
Nominal balloon diameter, mm	3.34±0.46	3.28±0.51	0.337
Maximal balloon pressure, atm	16.9±4.4	17.3±4.9	0.552
Repeat drug-eluting stent implantation	40 (40.0)	48 (49.5)	0.232
Maximal stent diameter, mm	3.29±0.44	3.22±0.53	0.468
Total stented length, mm	30.3±15.8	29.3±12.9	0.791

Data are shown as counts (%), mean±SD, or median [25th-75th percentiles].

Table 3. Optical coherence tomography characteristics according to the extent of inhomogeneity.

	Low inhomogeneity n=100	High inhomogeneity n=97	*p*-value
Frames analysed	3,505	2,647	–
Struts analysed	33,298	24,967	–
Mean stent area, mm^2	6.50 (5.04-8.49)	6.59 (5.28-7.94)	0.533
Mean stent diameter, mm	2.87 (2.53-3.28)	2.89 (2.59-3.18)	0.755
Min. stent diameter, mm	2.74 (2.38-3.10)	2.74 (2.43-3.01)	0.652
Max. stent diameter, mm	3.03 (2.67-3.47)	3.06 (2.74-3.39)	0.837
Mean lumen area, mm^2	4.35 (2.91-6.28)	4.22 (3.01-6.17)	0.774
Min. lumen area, mm^2	2.00±1.34	2.34±1.42	0.087
Mean lumen diameter, mm	2.35 (1.91-2.82)	2.31 (1.95-2.80)	0.998
Min. lumen diameter, mm	2.15 (1.74-2.58)	2.13 (1.77-2.57)	0.977
Max. lumen diameter, mm	2.55 (2.09-3.07)	2.52 (2.14-3.04)	0.995
Mean area stenosis, %	29.4 (14.7-47.1)	27.9 (14.9-46.4)	0.635
Max. area stenosis, %	64.7±18.3	59.4±20.2	0.060
Neointimal area, mm^2	1.75 (0.94-2.97)	1.76 (0.95-2.94)	0.618
Mean neointimal thickness, µm	210.0 (110.0-390.0)	220.0 (120.0-390.0)	0.461
Stent underexpansion	77 (77.0)	63 (64.9)	0.101
Strut coverage, %	93.7	93.7	0.134
Strut malapposition, %	0.89	1.19	0.392
Mean malapposition distance, µm	160.0 (130.0-260.0)	180.0 (130.0-280.0)	0.978

Data are shown as counts (%) or median (25th-75th percentiles).

no relevant differences in the baseline characteristics between the two groups.

OPTICAL COHERENCE TOMOGRAPHY ANALYSIS

OCT morphometric data according to predominant neointimal type are shown in **Table 3**. Morphometric analysis included a total of 3,505 frames (33,298 struts) in the low inhomogeneity group and 2,647 frames (24,967 struts) in the high inhomogeneity group. There were no relevant between-group differences in terms of stent diameter/area, lumen diameter/area or neointimal thickness/area. Neointimal tissue characterisation was performed in a total of 7,675 quadrants; the proportion of inhomogeneous quadrants was 2.3% (0.0-6.4) in the low inhomogeneity group and 31.8% (18.2-60.7) in the high inhomogeneity group.

CLINICAL OUTCOMES

The median (25th-75th percentiles) follow-up was 701 (408-1,087) and 748 (361-1,083) days (p=0.962) in the low and high inhomogeneity groups, respectively. Clinical events and the primary and secondary endpoints are shown in **Table 4**. High neointimal inhomogeneity was not associated with a significantly higher risk of MACE (HR 1.02 [0.59-1.75], p=0.939) **(Figure 2)**, clinically driven TLR (HR 1.10 [0.63-1.93], p=0.732) **(Figure 3)**, or a composite of death or MI (HR 0.53 [0.14-2.08], p=0.372) **(Figure 4)**. We performed a multivariable analysis using two separate Cox proportional hazards models for the primary and secondary endpoints. The OCT pattern of neointima and PCI type for ISR (DES or DCB) were entered into these models along with several baseline clinical and angiographic characteristics such as age, gender, smoking habit, body mass index, hypercholesterolaemia, arterial hypertension, diabetes mellitus, history of MI, history of coronary artery bypass grafting, multivessel disease, target vessel, ostial lesion, bifurcation lesion, complete occlusive ISR,

Table 4. Clinical outcomes.

All patients				
Clinical event	**Low inhomogeneity n=100**	**High inhomogeneity n=97**	**Hazard ratio (95% CI)**	***p*-value**
Death	5	2	0.42 (0.09-2.08)	0.306
MI	1	1	1.04 (0.07-16.6)	0.978
Death or MI	6	3	0.53 (0.14-2.08)	0.372
CABG	2	1	0.53 (0.05-5.60)	0.603
Repeat PCI	22	24	1.18 (0.66-2.10)	0.571
TLR	24	25	1.10 (0.63-1.93)	0.732
MACE	27	26	1.02 (0.59-1.75)	0.939
Patients with high neointimal inhomogeneity				
Clinical event	**Drug-eluting stent n=48**	**Drug-coated balloon n=49**	**Hazard ratio (95% CI)**	***p*-value**
Death	0	2	–	0.505*
MI	0	1	–	0.990*
Death or MI	0	3	–	0.250*
CABG	1	0	–	0.990*
Repeat PCI	5	19	0.23 (0.09-0.61)	0.003
TLR	6	19	0.28 (0.11-0.69)	0.006
MACE	6	20	0.26 (0.10-0.65)	0.004
Patients with low neointimal inhomogeneity				
Clinical event	**Drug-eluting stent n=40**	**Drug-coated balloon n=60**	**Hazard ratio (95% CI)**	***p*-value**
Death	3	2	2.29 (0.38-13.70)	0.365
MI	1	0	3.06	0.800*
Death or MI	4	2	1.84 (0.56-16.7)	0.197
CABG	2	0	–	–
Repeat PCI	7	15	0.65 (0.27-1.60)	0.351
TLR	9	15	0.90 (0.39-2.05)	0.797
MACE	11	16	1.04 (0.48-2.25)	0.917
Patients with high neointimal inhomogeneity				
Clinical event	**High neoathero-sclerosis n=47**	**Low neoathero-sclerosis n=50**	**Hazard ratio (95% CI)**	***p*-value**
Death	2	0	–	0.464*
MI	0	1	–	0.970*
Death or MI	3	2	1.84 (0.32-10.7)	0.503
CABG	0	1	–	0.970*
Repeat PCI	10	14	0.70 (0.31-1.57)	0.391
TLR	10	15	0.65 (0.29-1.43)	0.289
MACE	11	15	0.69 (0.32-1.51)	0.366

* Fisher's exact test. CABG: coronary artery bypass grafting; CI: confidence interval; MACE: major adverse cardiac events; MI: myocardial infarction; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation

reference diameter (vessel size) and diameter stenosis before PCI (restenosis severity). In the multivariable model for the primary endpoint of MACE at two years, the adjusted p-value was 0.567 for the OCT pattern of neointima and 0.022 for the PCI type. In the multivariable model for the secondary endpoint of TLR at

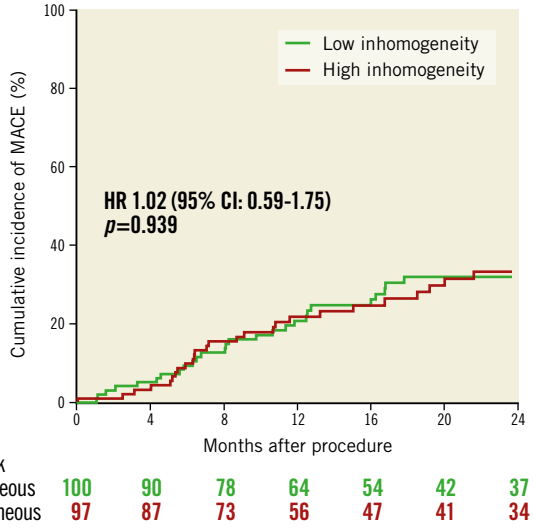

Figure 2. *Cumulative incidence of major adverse cardiac events in the low and high inhomogeneity subgroups.*

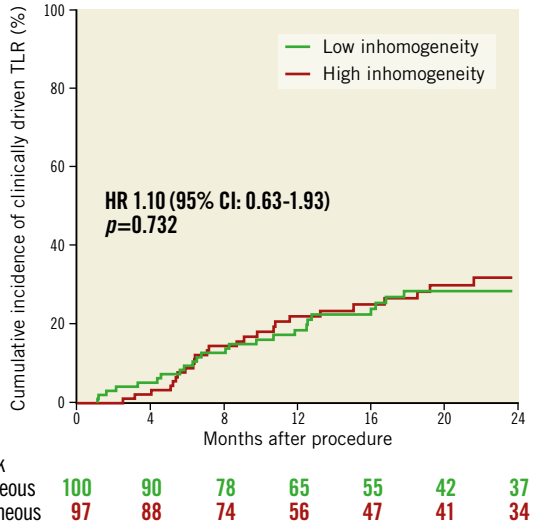

Figure 3. *Cumulative incidence of clinically driven target lesion revascularisation in the low and high inhomogeneity subgroups.*

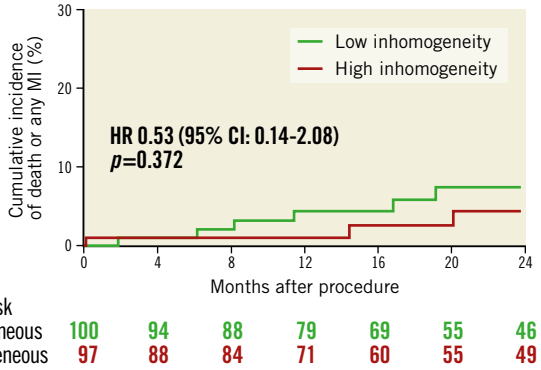

Figure 4. *Cumulative incidence of all-cause death or myocardial infarction in the low and high inhomogeneity subgroups.*

two years, the adjusted p-value was 0.350 for the OCT pattern of neointima and 0.013 for the PCI type. Subsequently, we assessed the interaction between the OCT pattern of neointima and PCI type for ISR (DES or DCB) by adding the interaction term OCT pattern of neointima * PCI type to these two multivariable models. There were statistically significant interactions for both MACE (p_{int}=0.006) and TLR (p_{int}=0.022) at two years.

INTERACTION BETWEEN NEOINTIMAL PATTERN, TREATMENT MODALITY AND CLINICAL OUTCOMES

The clinical, angiographic and procedural characteristics of the high and low inhomogeneity groups, respectively, according to treatment modality (DES or DCB) are shown in **Supplementary Table 1-Supplementary Table 4**. **Table 4** shows the clinical outcomes for each neointimal group according to treatment modality. Notably, DES was associated with a significant advantage over DCB in the high inhomogeneity group (MACE: HR 0.26 [0.10-0.65], p=0.004; TLR: HR 0.28 [0.11-0.69], p=0.006), but not in the low inhomogeneity group (MACE: HR 1.04 [0.48-2.25], p=0.917; TLR: HR 0.90 [0.39-2.05], p=0.797). The dependence of treatment effect of DES and DCB on the extent of inhomogeneity of the neointima is shown in **Figure 5** for the primary endpoint.

NEOATHEROSCLEROSIS

Clinical, angiographic and procedural characteristics according to the extent of neoatherosclerosis in the subgroup of patients with high inhomogeneity are shown in **Supplementary Table 5** and **Supplementary Table 6**. Clinical outcomes of patients in the high inhomogeneity group according to the extent of neoatherosclerosis are shown in **Table 4**. There were no relevant differences in terms of clinical outcomes between the two groups.

Discussion

Based on the results of available randomised clinical trials[5,6], current European guidelines recommend the use of either DES or DCB for the treatment of coronary ISR (class of recommendation I, level of evidence A)[16]. The main findings of the present study can be summarised as follows: i) in patients presenting with ISR and undergoing treatment with DCB or DES, there were no significant differences in terms of MACE or clinically driven TLR between the low and high inhomogeneity groups; ii) a significant interaction exists between treatment modality and neointimal pattern with an advantage of DES over DCB in the high inhomogeneity group and no difference in the low inhomogeneity group; iii) there were no relevant differences in terms of clinical outcomes between low and high neoatherosclerosis subgroups in the population of patients with high neointimal inhomogeneity.

The efficacy of DCB treatment relies on rapid initial transfer and subsequent tissue retention of the antiproliferative agent necessary for persistent suppression of cell proliferation[17]. DCB represents a particularly attractive treatment option due to its ability to provide favourable angiographic results without adding new stent layers. Such a mechanism of action suggests that the subset of smooth muscle cell-rich ISR lesions is particularly suitable for DCB treatment. OCT-histology correlation studies have shown an homogeneous neointimal pattern to correlate consistently with abundance of smooth muscle cells[10].

On the other hand, clinical outcomes following repeat DES implantation might be less dependent on underlying neointimal patterns compared to DCB angioplasty. However, repeat DES implantation is associated with potential drawbacks, mainly due to additional stent layers and neoatherosclerosis development. Histological and clinical studies have confirmed an accelerated

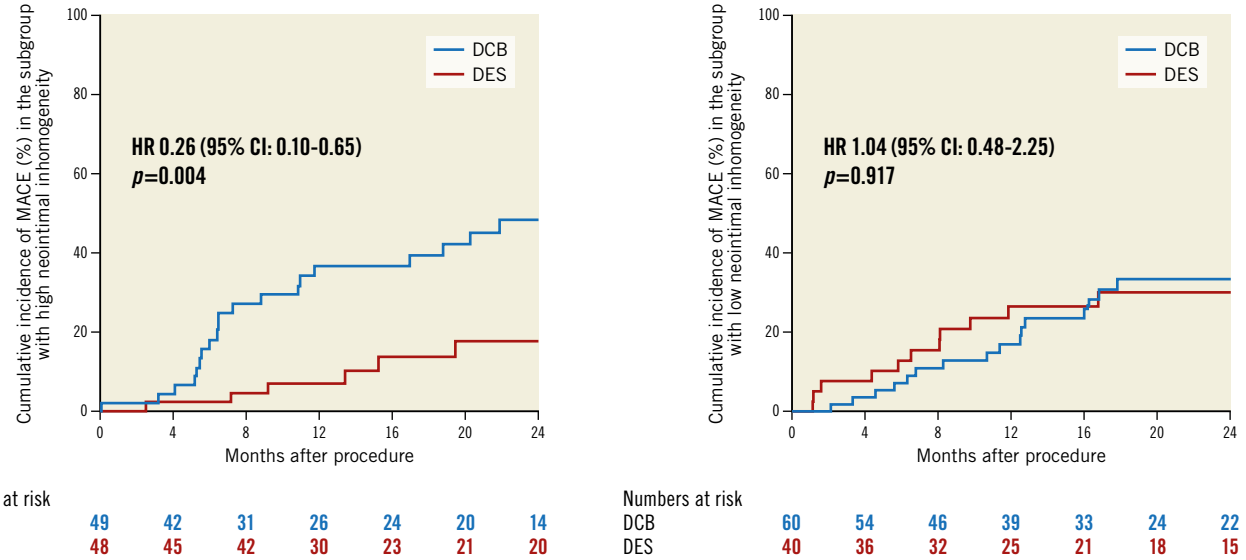

Figure 5. *Cumulative incidence of major adverse cardiac events according to treatment type (DES vs DCB) in the subgroups of patients with high (left) and low (right) inhomogeneity of the neointima. There was a significant interaction between neointimal pattern and treatment modality regarding MACE (p_{int}=0.006).*

course of neoatherosclerosis following DES implantation[14,18], which in turn triggers late adverse events, including repeat ISR and stent thrombosis[13,19].

Our findings are in keeping with those of Tada et al[11] who reported comparable TLR rates following DCB and repeat DES in patients with homogeneous neointima. From a practical standpoint, our results support the use of DES in ISR lesions with high neointimal inhomogeneity, while DCB angioplasty could be safely and effectively used in ISR lesions with low neointimal inhomogeneity. However, regardless of the treatment strategy adopted, the overall MACE rate remains considerable in patients presenting with ISR, highlighting the need for individualised treatment in this patient population.

To summarise, by tailoring treatment strategy to specific ISR lesion characteristics, incorporation of intravascular OCT in the treatment algorithm of ISR impacts positively on treatment outcomes in terms of efficacy and safety. Implementation of such an algorithm in clinical practice requires confirmation of our findings in specifically designed randomised clinical trials with relevant clinical and angiographic endpoints.

Our report has a number of strengths. First, it includes a detailed quadrant-based multi-frame neointimal characterisation for each ISR lesion. Indeed, categorisation of neointimal patterns based on the optical characteristics of a single frame[11,20,21] is limited by significant intra-lesion neointimal heterogeneity[13]. Second, analysis of OCT pullbacks was performed in a central core laboratory according to a standardised protocol, thereby minimising between-centre variability. Third, extended clinical follow-up, with a median follow-up of two years, should have allowed capture of late-occurring events, such as those related to the development of neoatherosclerosis.

Study limitations

Some limitations should be considered when interpreting the results of the present report. First, due to the retrospective nature of the study, its results should be interpreted as exploratory, that is hypothesis-generating. Second, the possible bias of patient and lesion selection should be considered, since patients presenting with ISR were not included consecutively. Third, treatment strategy was at the discretion of the operator and could represent an additional bias. Fourth, the index stent interval, despite not being different between groups, showed considerable variability and could represent an additional confounding factor.

Conclusions

In a large multicentre European registry including patients undergoing intravascular OCT prior to percutaneous treatment of ISR lesions with the two currently recommended strategies, there was no significant difference in terms of MACE or clinically driven TLR between patients with low and high inhomogeneity of the neointima. The exploratory analysis showed that a significant interaction exists between neointimal pattern and treatment modality, with DES showing a significant advantage over DCB in the high, but not in the low inhomogeneity group. This warrants confirmation from prospective dedicated studies.

Impact on daily practice

In patients presenting with ISR and undergoing treatment with either DCB or DES, there were no significant differences in clinical outcomes between the low and high neointimal inhomogeneity groups. The exploratory analysis showed a significant interaction between treatment modality and neointimal pattern, with a significant advantage of DES implantation as compared to DCB angioplasty in lesions with high neointimal inhomogeneity and comparable outcomes between the treatment strategies in lesions with low neointimal inhomogeneity. If confirmed by prospective dedicated studies, these results would support repeat DES implantation for lesions with high neointimal inhomogeneity, while DCB angioplasty could represent a particularly safe and effective treatment for lesions with low neointimal inhomogeneity.

Conflict of interest statement

N. Gonzalo reports personal fees from Abbott Vascular and Boston Scientific, outside the submitted work. M. Joner reports personal fees from Biotronik, OrbusNeich, AstraZeneca and Recor, grants and personal fees from Boston Scientific and Edwards, and grants from Amgen, outside the submitted work. S. Kufner reports speaker fees from AstraZeneca and Bristol Myers Squibb, not related to the current work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods: Study endpoint definitions; Angiographic data acquisition and analysis; OCT data acquisition and analysis; Qualitative neointimal characterisation.

Supplementary Table 1. Clinical characteristics in the high inhomogeneity group according to the type of treatment of in-stent restenosis.

Supplementary Table 2. Angiographic and procedural characteristics in the high inhomogeneity group according to the type of treatment of in-stent restenosis.

Supplementary Table 3. Clinical characteristics in the low inhomogeneity group according to the type of treatment of in-stent restenosis.

Supplementary Table 4. Angiographic and procedural characteristics in the low inhomogeneity group according to the type of treatment of in-stent restenosis.

Supplementary Table 5. Clinical characteristics according to the extent of neoatherosclerosis in the subgroup of patients with high neointimal inhomogeneity.

Supplementary Table 6. Angiographic and procedural characteristics according to the extent of neoatherosclerosis in the subgroup of patients with high neointimal inhomogeneity.

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Supplementary data

Supplementary Appendix 1. Methods

Study endpoint definitions

Death

The primary endpoint includes death from any cause.

Myocardial infarction

The definition of myocardial infarction used in the present study is adopted from the Third Universal Definition of Myocardial Infarction. Cardiac troponin was used as the preferred biomarker. Creatine kinase-myocardial band (CK-MB) and CK values were used in cases where troponin values were not available.

Myocardial infarction diagnosis required the detection of a rise and/or fall in cardiac biomarkers (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

– symptoms of ischaemia

– development of pathological Q-waves in the ECG

– new or presumed new ST segment–T-wave changes (ST–T changes) or new left bundle branch block (LBBB)

– imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Clinically driven target lesion revascularisation

Target lesion revascularisation was defined according to the Academic Research Consortium-2 consensus document as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion, with the latter being defined as the treated segment including the 5 mm margin proximal and distal to the stent. A revascularisation procedure was considered clinically indicated in case of documented percent diameter stenosis of ≥50% at coronary angiography coupled with any of the following: i) a positive history of recurrent angina pectoris presumably related to the target vessel; ii) objective signs of ischaemia at rest (ECG changes) or positive non-invasive functional test presumably related to the target vessel.

Angiographic data acquisition and analysis

Baseline and post-procedural angiograms were recorded and assessed off-line in a core laboratory (ISAResearch Center, Munich, Germany) with an automated edge-detection

system (Medis Medical Imaging Systems, Leiden, the Netherlands). Measurements were performed on cineangiograms recorded after intracoronary administration of nitroglycerine. The contrast-filled, non-tapered catheter tip was used for calibration. Quantitative analysis was performed on both "in-stent" and in-segment" areas (including the stented segment as well as both 5 mm margins proximal and distal to the stent).

OCT data acquisition and analysis

Following administration of intracoronary nitrates, OCT was performed with a non-occlusive imaging technique using commercially available OCT imaging systems (C7XR; ILUMIEN™ or ILUMIEN™ Optis™; St. Jude Medical, St. Paul, MN, USA). In brief, a rapid exchange imaging catheter (Dragonfly™ or Dragonfly™ Duo; St. Jude Medical) was advanced beyond the stented segment. An OCT pullback of the entire stented segment, including distal and proximal reference sites, was performed with contrast injection through the guiding catheter at 3-5 ml/sec. If the stented segment was too long to be imaged in a single pullback, an additional pullback was acquired using angiographic landmarks for appropriate imaging catheter position and view. In case of sub-occlusive or occlusive ISR lesions, small balloon dilatation (≤2.0 mm in diameter) at low pressure was performed to allow sufficient blood clearance and pullback quality.

Raw data of OCT image acquisitions were sent to a centralised core laboratory (ISAResearch Center, Munich, Germany) for off-line analyses. Quantitative and morphometric analyses were performed every 1 mm along the entire target segment by means of dedicated software (St. Jude Medical).

The first and last analysed frames of the stented segment were defined as OCT frames where stent struts were present in at least ¾ of the perimeter. Stent and lumen cross-sectional area were measured throughout the entire length of the stent. The number of stent struts was recorded for each analysed cross-section. Thickness of tissue coverage on the luminal side of each stent strut was measured at the mid point of the strut. Struts were classified as covered if the thickness of tissue covering the strut was ≥ the minimal axial resolution of OCT (20 μm). Struts were considered uncovered if any part of the strut was visibly exposed to the lumen. Incomplete stent strut apposition was considered present when the axial distance between the

strut's surface and the luminal surface was > the sum of the strut and polymer thickness plus the minimal axial resolution of OCT.

Distal and proximal reference measurements were performed in none or minimally diseased cross-sections within 10 mm from the stent edges. The reference area was calculated as the sum of the proximal and distal reference lumen areas divided by two. If the pullback did not include analysable proximal and/or distal non-stented reference segments, the reference area was derived from the most proximal and/or distal stented segments. Stent expansion index was calculated as the minimal stent area divided by the reference area with stent underexpansion defined by a stent expansion index <0.8.

Qualitative neointimal characterisation

Since previous studies have shown considerable intra-lesion neointimal heterogeneity, characterisation of neointimal tissue was performed not only at the frame displaying the maximal % area stenosis (%AS), but also in correspondence of the five preceding and following analysed frames. Each frame was subdivided into four quadrants (90°) and the neointimal characteristics separately characterised for each of them. Based on its properties at OCT imaging, neointimal tissue has been historically subdivided into three different patterns: i) homogeneous, ii) heterogeneous, and iii) layered; however, validation studies against the gold standard of histology have shown homogeneous patterns to correlate consistently with abundance of smooth muscle cells embedded in collagen/proteoglycan-rich tissue, while the remaining patterns revealed a multitude of corresponding histological components. Therefore, in order to apply a histopathology-based and treatment-oriented classification, neointimal tissue was categorised as homogeneous or inhomogeneous, the latter category including heterogeneous, layered or neoatherosclerosis quadrants. Atherosclerotic changes of the neointima were defined by the presence of one or more of the following: macrophage infiltration, lipid-laden tissue within the stent or neointimal calcification. In order to assess inter-observer variability in neointimal characterisation, a subgroup of 50 randomly chosen pullbacks was independently analysed by two experienced cardiologists. There was excellent inter-observer agreement regarding neointimal characterisation (Cohen's κ=0.931).

Supplementary Table 1. Clinical characteristics in the high inhomogeneity group according to the type of treatment of in-stent restenosis.

	Drug-eluting stent n=48	**Drug-coated balloon n=49**	***p*-value**
Age, years	66.8±11.7	67.1±8.4	0.876
Male	37 (77.1)	40 (81.6)	0.762
Current smoker	5 (10.4)	8 (16.3)	0.578
Ex-smoker	16 (33.3)	18 (36.7)	0.890
Body mass index (kg/m^2)	28.0±5.6	27.9±4.3	0.917
Hypercholesterolaemia	29 (60.4)	34 (69.4)	0.476
Arterial hypertension	37 (77.1)	47 (95.9)	0.015
Diabetes mellitus	14 (29.2)	23 (46.9)	0.111
Oral therapy	11 (22.9)	13 (26.5)	0.859
Insulin therapy	2 (4.2)	4 (8.2)	0.678
Previous myocardial infarction	30 (62.5)	22 (44.9)	0.125
Previous coronary artery bypass grafting	5 (10.4)	6 (12.2)	>0.999
Clinical presentation			0.125
Silent ischaemia	11 (22.9)	10 (20.4)	
Stable angina pectoris	19 (39.6)	30 (61.2)	
Unstable angina pectoris	9 (18.8)	3 (6.12)	
Non-ST-segment elevation myocardial infarction	8 (16.7)	6 (12.2)	
ST-segment elevation myocardial infarction	1 (2.1)	0 (0.0)	
Multivessel disease	30 (62.5)	41 (83.7)	0.034
Affected vessels			0.016
One vessel	18 (37.5)	8 (16.3)	
Two vessels	13 (27.1)	10 (20.4)	
Three vessels	17 (35.4)	31 (63.3)	
Ejection fraction (%)	60.8±15.5	56.4±9.8	0.196

Data are shown as counts (%) or mean±SD.

Supplementary Table 2. Angiographic and procedural characteristics in the high inhomogeneity group according to the type of treatment of in-stent restenosis.

	Drug-eluting stent n=48	**Drug-coated balloon n=49**	***p*-value**
Target coronary vessel			0.432
Left main coronary artery	1 (2.1)	1 (2.0)	
Left anterior descending coronary artery	25 (52.1)	18 (36.7)	
Left circumflex coronary artery	11 (22.9)	17 (34.7)	
Right coronary artery	11 (22.9)	13 (26.5)	
Restenosis morphology			0.111
Focal margin	9 (18.8)	4 (8.2)	
Focal body	15 (31.2)	23 (46.9)	
Multifocal	2 (4.2)	0 (0.0)	
Diffuse intrastent	17 (35.4)	20 (40.8)	
Proliferative	2 (4.2)	2 (4.1)	
Complete occlusion	3 (6.3)	0 (0.0)	
Ostial lesion	5 (10.4)	14 (28.6)	0.046
Bifurcation lesion	11 (22.9)	18 (36.7)	0.206
Quantitative coronary angiography			
Reference diameter, mm	2.79±0.57	2.87±0.49	0.481
Preprocedural minimal lumen diameter, mm	0.90±0.47	1.13±0.40	0.011
Post-procedural minimal lumen diameter, mm	2.75±0.48	2.25±0.34	<0.001
Preprocedural diameter stenosis, %	68.4±14.4	62.1±12.2	0.022
Post-procedural diameter stenosis, %	11.3±6.8	23.5±6.6	<0.001
Nominal balloon diameter, mm	3.34±0.57	3.21±0.44	0.234
Maximal balloon pressure, atm	19.3±3.9	15.3±5.0	<0.001
Maximal stent diameter, mm	3.22±0.53		
Total stented length, mm	29.3±12.9		

Data are shown as counts (%) or mean±SD.

Supplementary Table 3. Clinical characteristics in the low inhomogeneity group according to the type of treatment of in-stent restenosis.

	Drug-eluting stent n=40	**Drug-coated balloon n=60**	***p*-value**
Age, years	65.9±10.7	67.5±10.5	0.450
Male	33 (82.5)	49 (81.7)	>0.999
Current smoker	7 (17.5)	11 (18.3)	>0.999
Ex-smoker	17 (42.5)	21 (35.0)	0.585
Body mass index (kg/m^2)	27.9±4.23	28.3±3.82	0.562
Hypercholesterolaemia	30 (75.0)	41 (68.3)	0621
Arterial hypertension	37 (92.5)	56 (93.3)	>0.999
Diabetes mellitus	19 (47.5)	26 (43.3)	0.837
Oral therapy	14 (35.0)	13 (21.7)	0.214
Insulin therapy	2 (5.0)	11 (18.3)	0.101
Previous myocardial infarction	24 (60.0)	32 (53.3)	0.651
Previous coronary artery bypass grafting	6 (15.0)	9 (15.0)	>0.999
Clinical presentation			0.861
Silent ischaemia	8 (20.0)	13 (21.7)	
Stable angina pectoris	20 (50.0)	29 (48.3)	
Unstable angina pectoris	7 (17.5)	13 (21.7)	
Non-ST-segment elevation myocardial infarction	4 (10.0)	5 (8.3)	
ST-segment elevation myocardial infarction	1 (2.5)	0 (0.0)	
Multivessel disease	32 (80.0)	52 (86.7)	0.540
Affected vessels			0.541
One vessel	8 (20.0)	8 (13.3)	
Two vessels	6 (15.0)	13 (21.7)	
Three vessels	26 (65.0)	39 (65.0)	
Ejection fraction (%)	52.5±18.2	54.6±10.7	0.707

Data are shown as counts (%) or mean±SD.

Supplementary Table 4. Angiographic and procedural characteristics in the low inhomogeneity group according to the type of treatment of in-stent restenosis.

	Drug-eluting stent n=40	Drug-coated balloon n=60	*p*-value
Target coronary vessel			0.198
Left main coronary artery	0 (0.0)	1 (1.7)	
Left anterior descending coronary artery	24 (60.0)	26 (43.3)	
Left circumflex coronary artery	4 (10.0)	14 (23.3)	
Right coronary artery	12 (30.0)	19 (31.7)	
Restenosis morphology			0.983
Focal margin	4 (10.0)	5 (8.3)	
Focal body	16 (40.0)	25 (41.7)	
Multifocal	4 (10.0)	8 (13.3)	
Diffuse intrastent	13 (32.5)	16 (26.7)	
Proliferative	1 (2.5)	2 (3.3)	
Complete occlusion	2 (5.0)	4 (6.7)	
Ostial lesion	5 (12.5)	13 (21.7)	0.366
Bifurcation lesion	6 (15.0)	20 (33.3)	0.070
Quantitative coronary angiography			
Reference diameter, mm	2.94±0.43	2.98±0.47	0.232
Preprocedural minimal lumen diameter, mm	1.09±0.45	1.09±0.46	0.958
Post-procedural minimal lumen diameter, mm	2.76±0.41	2.22±0.39	<0.001
Preprocedural diameter stenosis, %	63.1±13.4	63.7±13.8	0.810
Post-procedural diameter stenosis, %	9.8±6.8	25.9±9.2	<0.001
Nominal balloon diameter, mm	3.42±0.58	3.29±0.36	0.219
Maximal balloon pressure, atm	18.1±4.1	16.1±4.5	0.023
Maximal stent diameter, mm	3.29±0.44		
Total stented length, mm	30.3±15.8		

Data are shown as counts (%) or mean±SD.

Supplementary Table 5. Clinical characteristics according to the extent of neoatherosclerosis in the subgroup of patients with high neointimal inhomogeneity.

	Low neoatherosclerosis n=50	**High neoatherosclerosis n=47**	***p*-value**
Age, years	65.6±9.48	68.3±10.6	0.194
Male	40 (80.0)	37 (78.7)	>0.999
Current smoker	6 (12.0)	7 (14.9)	0.905
Ex-smoker	18 (36.0)	16 (34.0)	>0.999
Body mass index (kg/m^2)	28.8±4.71	27.1±5.05	0.092
Hypercholesterolaemia	31 (62.0)	32 (68.1)	0.678
Arterial hypertension	42 (84.0)	42 (89.4)	0.634
Diabetes mellitus	20 (40.0)	17 (36.2)	0.858
Oral therapy	12 (24.0)	12 (25.5)	>0.999
Insulin therapy	4 (8.0)	2 (4.3)	0.678
Previous myocardial infarction	30 (60.0)	22 (46.8)	0.272
Previous coronary artery bypass grafting	8 (16.0)	3 (6.38)	0.241
Clinical presentation			0.039
Silent ischaemia	11 (22.0)	10 (21.3)	
Stable angina pectoris	19 (38.0)	30 (63.8)	
Unstable angina pectoris	8 (16.0)	4 (8.5)	
Non-ST-segment elevation myocardial infarction	11 (22.0)	3 (6.4)	
ST-segment elevation myocardial infarction	1 (2.0)	0 (0.0)	
Multivessel disease	32 (64.0)	39 (83.0)	0.06
Affected vessels			0.085
One vessel	18 (36.0)	8 (17.0)	
Two vessels	9 (18.0)	14 (29.8)	
Three vessels	23 (46.0)	25 (53.2)	
Ejection fraction (%)	60.0±12.9	57.0±13.8	0.417

Data are shown as counts (%) or mean±SD.

Supplementary Table 6. Angiographic and procedural characteristics according to the extent of neoatherosclerosis in the subgroup of patients with high neointimal inhomogeneity.

	Low neoatherosclerosis n=50	**High neoatherosclerosis n=47**	***p*-value**
Target coronary vessel			0.983
Left main coronary artery	1 (2.0)	1 (2.1)	
Left anterior descending coronary artery	22 (44.0)	21 (44.7)	
Left circumflex coronary artery	14 (28.0)	14 (29.8)	
Right coronary artery	13 (26.0)	11 (23.4)	
Restenosis morphology			0.224
Focal margin	8 (16.0)	5 (10.6)	
Focal body	19 (38.0)	19 (40.4)	
Multifocal	0 (0.0)	2 (4.3)	
Diffuse intrastent	18 (36.0)	19 (40.4)	
Proliferative	4 (8.0)	0 (0.0)	
Complete occlusion	1 (2.0)	2 (4.3)	
Ostial lesion	9 (18.0)	10 (21.3)	0.88
Bifurcation lesion	15 (30.0)	14 (29.8)	>0.999
Quantitative coronary angiography			
Reference diameter, mm	0.99±0.46	1.04±0.44	0.612
Preprocedural minimal lumen diameter, mm	2.49±0.42	2.51±0.54	0.836
Post-procedural minimal lumen diameter, mm	65.7±14.4	64.8±13.0	0.746
Preprocedural diameter stenosis, %	16.6±9.1	18.4±9.0	0.327
Post-procedural diameter stenosis, %	3.29±0.45	3.26±0.57	0.707
Nominal balloon diameter, mm	18.0±5.0	16.5±4.7	0.121
Maximal balloon pressure, atm	23 (46.0)	25 (53.2)	0.614
Maximal stent diameter, mm	3.24±0.44	3.20±0.60	0.798
Total stented length, mm	30.4±14.8	28.6±12.1	0.756

Data are shown as counts (%) or mean±SD.