EuroIntervention 2020;15:1527-1533 published online October 2019

Bare metal or drug-eluting stent versus drug-coated balloon in non-ST-elevation myocardial infarction: the randomised PEPCAD NSTEMI trial

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A list of the study collaborators can be found in the Appendix paragraph.

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00723

KEYWORDS

- bare metal stent
- drug-eluting balloon
- drug-eluting stent
- NSTEMI

Abstract

Aims: Drug-coated balloons (DCB) may avoid stent-associated long-term complications. This trial compared the clinical outcomes of patients with non-ST-elevation myocardial infarction (NSTEMI) treated with either DCB or stents.

Methods and results: A total of 210 patients with NSTEMI were enrolled in a randomised, controlled, non-inferiority multicentre trial comparing a paclitaxel iopromide-coated DCB with primary stent treatment. The main inclusion criterion was an identifiable culprit lesion without angiographic evidence of large thrombus. The primary endpoint was target lesion failure (TLF; combined clinical endpoint consisting of cardiac or unknown death, reinfarction, and target lesion revascularisation) after nine months. Secondary endpoints included total major adverse cardiovascular events (MACE) and individual clinical endpoints. Mean age was 67±12 years, 67% were male, 62% had multivessel disease, and 31% were diabetics. One hundred and four patients were randomised to DCB, 106 to stent treatment. In the stent group, 56% of patients were treated with BMS, 44% with current-generation DES. In the DCB group, 85% of patients were treated with DCB only whereas 15% underwent additional stent implantation. During a follow-up of 9.2±0.7 months, DCB treatment was non-inferior to stent treatment with a TLF rate of 3.8% versus 6.6% (intention-to-treat, p=0.53). There was no significant difference between BMS and current-generation DES. The total MACE rate was 6.7% for DCB versus 14.2% for stent treatment (p=0.11), and 5.9% versus 14.4% in the per protocol analysis (p=0.056), respectively.

Conclusions: In patients with NSTEMI, treatment of coronary *de novo* lesions with DCB was non-inferior to stenting with BMS or DES. These data warrant further investigation of DCB in this setting, in larger trials with DES as comparator (ClinicalTrials.gov Identifier: NCT01489449).

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SUBMITTED ON 07/08/2019 - REVISION RECEIVED ON 1st 18/09/2019 / 2nd 18/10/2019 - ACCEPTED ON 23/10/2019

DOI: 110.4244/EIJ-D-19-00723

Abbreviations

ARC	Academic Research Consortium
BMS	bare metal stent
DCB	drug-coated balloon
DES	drug-eluting stent
ITT	intention-to-treat
NSTEMI	non-ST-elevation myocardial infarction
POBA	plain old balloon angioplasty
PP	per protocol
PTCA	percutaneous transluminal coronary angioplasty
TLF	target lesion failure

Introduction

Andreas Grüntzig introduced percutaneous transluminal coronary angioplasty (PTCA) in 1977[1]. The next important step in coronary percutaneous transluminal intervention was the development of bare metal stents (BMS), reported for the first time in 1987[2], initially to treat flow-limiting dissections. Later it became apparent that stents resulted in better acute outcomes and reduced the restenosis rate by about 10% in absolute terms compared to PTCA only[3]. However, the implantation of coronary stents was initially complicated by an unacceptably high rate of acute and subacute vascular closure. With the introduction of dual platelet aggregation inhibition in the mid 1990s, stent implantation became a safe procedure[4,5]. The still high restenosis rate with BMS was finally able to be reduced by local drug delivery from drug-eluting stents (DES)[6]. While DES of the first generation had increased thrombotic occlusion rates compared to BMS, this disadvantage was overcome in DES of the second generation. However, in long-term observational studies, the short- and medium-term benefit of stents over angioplasty was reversed. Patients treated with BMS in the course of a myocardial infarction showed very late thrombotic vascular occlusions and myocardial infarctions after an average of nine years, more than twice as often as patients treated with PTCA alone[7]. Furthermore, newer-generation DES also show a slight but linear increase in cardiovascular events which, according to current knowledge, appears not to plateau over time[8]. This has been suggested to be due to accelerated neoatherosclerosis[9].

Furthermore, interventional treatment of acute coronary syndromes is associated with an increased rate of acute and subacute stent thrombosis when compared with stable coronary heart disease. Therefore, the concept of avoiding permanent implants may be especially attractive for patients with acute coronary syndrome to prevent stent-associated acute and long-term complications. Drug-coated balloons (DCB) fulfil the requirements of "leaving nothing behind" to avoid stent-associated events. Small randomised studies[10] and registries[11-13] have confirmed the safety and efficacy of the "DCB only" concept in the treatment of coronary *de novo* disease. Recently, two trials with primary clinical endpoints have been published for small coronary vessels (the BASKET-SMALL 2 study[14]) and in patients with high bleeding risk (the DEBUT study[15]). However, no randomised controlled trial on this concept has been published in patients with acute coronary syndrome. The aim of this prospective, randomised, controlled multicentre trial was to compare the clinical outcome of patients with non-ST-elevation myocardial infarction (NSTEMI) treated either by DCB or by stent.

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Methods

STUDY DESIGN

Two hundred and ten patients with NSTEMI were enrolled in a randomised, controlled, non-inferiority multicentrre trial comparing a paclitaxel iopromide-coated DCB (SeQuent® Please and SeQuent® Please NEO, coated with 3 µg paclitaxel/mm² of balloon surface; B. Braun Melsungen AG, Berlin, Germany) with primary stent treatment (ClinicalTrials.gov Identifier: NCT01489449).

PATIENTS

The main inclusion criterion was clinical presentation with an NSTEMI defined by ischaemic symptoms (angina pectoris) >30 minutes, last symptoms within 72 hours before randomisation, positive cardiac troponin T, I, or hs-troponin above the 99th percentile, and an identifiable culprit lesion without angiographic evidence of large thrombus with intended early percutaneous coronary intervention (PCI).

PROCEDURES

After assessment of inclusion and exclusion criteria, patients were randomly assigned to undergo primary stent implantation or use of a DCB after lesion preparation according to the DCB Consensus Group recommendations[16]. The trial was initiated in December 2012, when BMS were still recommended in the setting of non-ST-elevation acute coronary syndrome[17]. During the course of the study, the investigators agreed to use new-generation limus-eluting DES.

The primary endpoint was target lesion failure (TLF; combined clinical endpoint consisting of cardiac or unknown death, myocardial reinfarction, and target lesion revascularisation) after nine months. Secondary endpoints included total major adverse cardiovascular events (MACE) consisting of all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI at other vessels. Furthermore, individual clinical endpoints were defined as secondary endpoints. All endpoints were defined according to the Academic Research Consortium (ARC) definitions[18]. For further details please refer to **Supplementary Appendix 1** and the CONSORT checklist **(Supplementary Appendix 2)**.

Results

PATIENTS

Two hundred and ten patients with NSTEMI were enrolled in this randomised study between December 2012 and January 2017. Mean age was 67±12 years, 67% were male, 62% had multivessel disease, and 31% were diabetics. One hundred and four patients were randomised to DCB treatment, 106 to stent treatment. **Table 1** summarises the baseline clinical data. In total, 243 lesions were treated, 123 in the DCB group and 120 in the stent group. In the stent group, 56% of patients were treated with BMS, 44% with

Table 1. Baseline clinical data.

	Total (%)	DCB group (%)	Stent group (%)	*p*-value
Number of patients	210	104	106	
Male	141 (67.1)	69 (66.3)	72 (67.9)	0.88
Age, years	66.5±12.3	66.0±11.4	67.0±13.1	0.54
Height, m	1.71±9.1	1.71±9.5	1.72±8.6	0.93
Weight, kg	83.7±17.3	84.2±18.6	82.2±16.0	0.68
Body mass index, kg/m^2	28.5±5.1	28.7±5.2	28.4±4.9	0.69
History of stroke	15 (7.1)	6 (5.8)	9 (8.5)	0.59
History of myocardial infarction	37 (17.6)	20 (19.2)	17 (16.0)	0.59
Peripheral artery disease	16 (7.6)	9 (8.7)	7 (6.6)	0.61
Diabetes mellitus	66 (31.4)	28 (26.9)	38 (35.8)	0.18
Hyperlipidaemia	100 (47.6)	52 (50.0)	48 (45.3)	0.58
Hypertension	175 (83.3)	82 (78.7)	93 (87.7)	0.10
Previous smoker	50 (23.8)	25 (24.0)	25 (23.6)	0.69
Current smoker	78 (37.1)	35 (33.7)	43 (40.6)	
Family history of coronary artery disease	58 (27.6)	27 (26.0)	31 (29.2)	0.34
Data are presented as mean value ± standard deviation or n (%).				

current-generation DES. In the DCB group, 85% of patients were treated with DCB only whereas 15% underwent additional stent implantation. Two lesions in the DCB group were treated with plain old balloon angioplasty (POBA) only, since no study device as well as no crossover stent could be advanced to the lesion. Procedural data are presented in **Supplementary Table 1**. No differences in length of hospital stay and medical treatment at discharge were observed between the groups **(Supplementary Table 2)**.

PRIMARY ENDPOINT

During a follow-up of 9.2±0.7 months, the TLF rate was 3.8% in patients randomised to DCB treatment versus 6.6% in those randomised to primary stenting (intention-to-treat; p=0.53; difference −0.03, 97.5% confidence interval [CI]: −0.1057 to 0.0506). Non-inferiority of DCB versus stent was able to be demonstrated according to Farrington and Manning with a non-inferiority level of −0.07 (90% CI: −0.0315 to 0.0867), a proportion difference of 0.0276, and a significance level of <0.0033 **(Table 2, Figure 1)**.

Table 2. Clinical events at 9-month follow-up.

	Total (%) N=210	DCB group (%) N=104	Stent group (%) N=106	*p*-value
Cardiac death	9 (4.3)	3 (2.9)	6 (5.7)	0.49
All-cause mortality	15 (7.1)	5 (4.8)	10 (9.4)	0.28
Myocardial infarction	3 (1.4)	0 (0)	3 (2.8)	0.24
Target lesion reintervention	2 (1.0)	1 (1.0)	1 (0.9)	1.0
Stroke	1 (0.5)	0 (0)	1 (0.9)	0.50
Percutaneous coronary intervention in other vessels	1 (0.5)	1 (1.0)	0 (0)	0.50
Stent/vessel thrombosis	0 (0)	0 (0)	1 (0.9) *	0.50
Total MACE (all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI in other vessels)	21 (10.5)	7 (6.7)	15 (14.2)	0.11
Primary endpoint TLF (cardiac death, myocardial reinfarction, or target lesion revascularisation)	11 (5.2)	4 (3.8)	7 (6.6)	0.53
Intention-to-treat analysis. Data are presented as n (%). * Unknown death 8 days post DES implantation.				

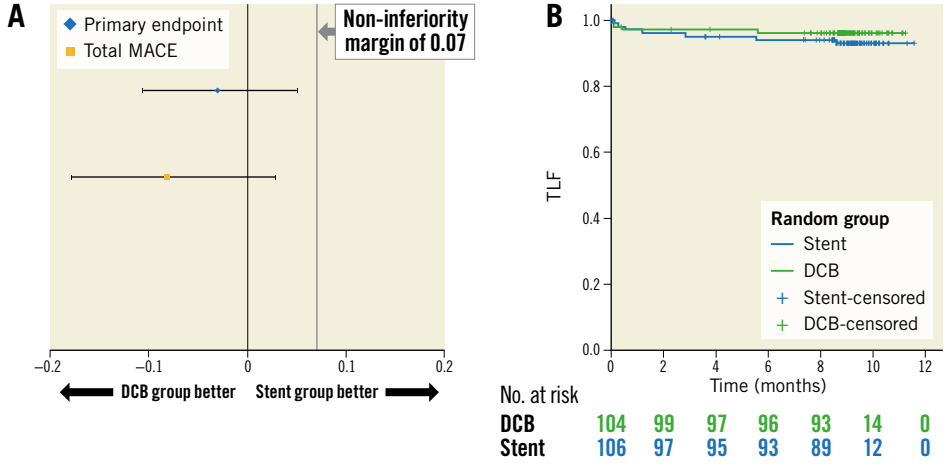

Figure 1. *Primary endpoint. A) Test for non-inferiority, intention to treat. Ratio of event rates (97.5% CI) for the primary endpoint target lesion failure (TLF consisting of cardiac death, myocardial reinfarction, or target lesion revascularisation) and total major adverse cardiac events (total MACE; all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI at other vessels). Confidence interval for TLF nine months: difference −0.03, 97.5% CI: −0.1057 to 0.0506. Confidence interval for total MACE nine months: difference −0.08, 97.5% CI: −0.1775 to 0.0291. B) Kaplan-Meier analysis of the primary endpoint TLF at nine months (intention to treat). P (log-rank)=0.360.*

There was no significant difference in TLF rates in the per protocol analysis **(Figure 2)** or between BMS and current-generation DES.

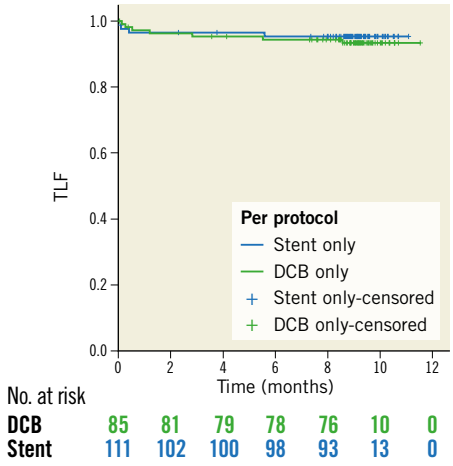

Figure 2. *Kaplan-Meier analysis of the primary endpoint target lesion failure (TLF consisting of cardiac death, myocardial reinfarction, or target lesion revascularisation) at nine months (per protocol). P (log-rank)=0.615.*

SECONDARY ENDPOINTS

Rates of death (4.8% vs 9.4%), myocardial infarction (0 vs 2.8%), target lesion reintervention (1.0% vs 0.9%), stroke (0 vs 0.9%), and PCI at other vessels (1.0% vs 0) did not differ significantly between patients randomised to DCB or stent treatment, respectively. In the DCB group, no acute or subacute thrombotic stent or vessel occlusions occurred. In the stent group, one patient died eight days after DES implantation when at home (unknown death).

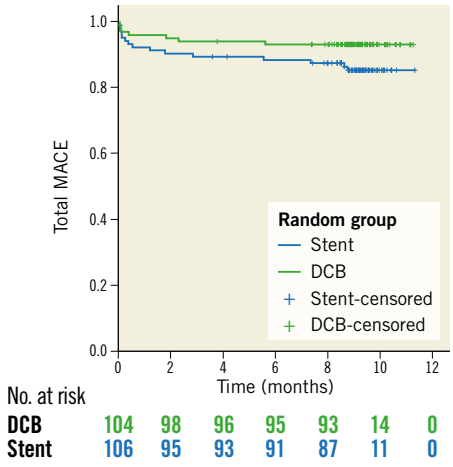

Figure 3. *Kaplan-Meier analysis of total MACE (all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI at other vessels) at nine months (intention to treat). P (log-rank)=0.082.*

The total MACE rate was 6.7% for DCB versus 14.2% for stent treatment (p=0.11) **(Figure 3)**, and 5.9% versus 14.4% in the per protocol analysis (p=0.056) **(Table 3, Supplementary Figure 1)**, respectively. No significant differences were observed between BMS and DES, whereas both treatments had higher event rates compared to "DCB only"; however, the latter difference was not statistically significant **(Supplementary Table 3, Supplementary Figure 2, Supplementary Figure 3)**.

Table 3. Clinical events at 9-month follow-up. Treatment per protocol (DCB only vs stent only).

	Total (%) N=196	DCB only (%) N=85	Stent only (%) N=111	*p*-value
Cardiac death	9 (4.6)	3 (3.5)	6 (5.4)	0.73
All-cause mortality	14 (7.1)	4 (4.7)	10 (9.0)	0.28
Death non-cardiac	5 (2.6)	1 (1.2)	4 (6.7)	0.39
Death other vessel	4 (2.0)	2 (2.4)	2 (1.8)	1.0
Death target vessel	1 (0.5)	1 (1.2)	0 (0)	0.43
Death unknown	4 (2.0)	0 (0)	4 (3.6)	0.13
Myocardial infarction	3 (1.5)	0 (0)	3 (2.7)	0.25
Target lesion reintervention	2 (1.0)	1 (1.2)	1 (0.9)	1.0
Stroke	1 (0.5)	0 (0)	1 (0.9)	1.0
Percutaneous coronary intervention in other vessels	1 (0.5)	0 (0)	1 (0.9)	1.0
Stent/vessel thrombosis	0 (0)	0 (0)	1 (0.9) *	0.50
Total MACE (all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI in other vessels)	21 (10.7)	5 (5.9)	16 (14.4)	0.056
Primary endpoint TLF (cardiac death, myocardial reinfarction, or target lesion revascularisation)	10 (5.1)	4 (4.7)	7 (6.3)	0.75

Data are presented as n (%). * Unknown death 8 days post DES implantation.

Discussion

Non-ST-elevation acute coronary syndrome is the most common trigger for invasive coronary diagnostics and interventions worldwide. Despite the lack of larger randomised trials on the preferred interventional technique, DES are regarded as the standard of care in most countries[19]. However, until now no single randomised study has demonstrated the superiority of DES compared with BMS or even POBA in the prevention of death and recurrent myocardial infarction[7].

The increased risk of thrombotic complications in acute coronary syndrome is a striking argument to avoid permanent implants. In recent years, there has been growing interest in the development and investigation of bioresorbable scaffolds. The promise of preventing medium- and long-term complications associated with leaving a foreign metallic stent within the vessel, by avoiding permanent implants, is indeed conceptually very attractive. However,

the price to be paid in the form of early and late thrombotic complications has so far been too high[20].

Drug-coated balloons cannot replace stents or scaffolds in all clinical situations. However, if used in accordance with the recommendations of the DCB Consensus Group[16,21], stent implantation might be avoided in many lesions. The main contraindications for DCB treatment are flow-limiting dissections and an unsatisfactory initial lumen gain. Contrary to the fears of some interventional cardiologists who were trained against the background of primary stent implantation, the "DCB only" procedure appears to be safe. In the Swedish SCAAR registry, for example, in almost 2,400 propensity-matched patients, not only was the rate of thrombotic vascular occlusion after DCB significantly lower after five years, but also and above all the acute occlusion rate due to DCB treatment was reduced compared with current-generation DES[12]. The present trial supports these findings since there were no cases of acute vessel closure in DCB-treated patients, which is in line with the findings from the BASKET-SMALL 2 trial in coronary arteries smaller than 3 mm[14] and the DEBUT trial in patients with high bleeding risk[15].

This finding seems surprising, but it is very plausible. The early reduction of vascular occlusions after stent implantation is related to the fixation of flow-limiting dissections, which are rare. However, the prevention of acute and subacute stent thrombosis is based mainly on the initiation of dual antiplatelet therapy[4,5]. For balloon angioplasty alone, the impact of this drug treatment has never been systematically investigated. The important first procedural step in the "DCB only" concept is to achieve sufficient lumen gain by adequate preparation of the lesion and to detect incident flow-limiting dissections. Inhibition of restenosis is a consequence of local drug application, which can also be achieved with DCB treatment. The special feature of the "DCB only" treatment is that it results in lumen enlargement after a few months post treatment[22,23], which can be considered a type of vascular restoration. This phenomenon is the basis for accepting a certain residual stenosis during the intervention. Of note, stent-based therapies do not show this effect.

Interestingly, patients in the stent group who had received a BMS showed similar event rates to those who had received the new-generation DES. The somewhat lower reintervention rate of DES was not sufficient to achieve a significant advantage over BMS. The 12-month duration of dual antiplatelet therapy in all patients may have played a role here, regardless of the stent type used. These results are in accordance with a current Cochrane meta-analysis in 12,503 patients presenting with acute coronary syndrome, in which there was no difference in survival between BMS and DES, but differences in the incidence of TLR were found[24].

The results of the present study support the safety of coronary intervention without stent implantation in patients with an increased thrombotic risk. After nine months, there was no statistically significant difference in all relevant clinical endpoints between primary stent therapy and DCB only. This means that, unlike bioresorbable stents, this approach does not increase the event rate within the first few months by avoiding permanent implants. However, superiority for DCB only may only be demonstrated in a longer-term follow-up. Patients in this study will be followed up for up to five years.

Limitations

Patients with NSTEMI represent a heterogeneous patient population. Using the DCB concept, lesions with a high thrombus burden were excluded because the concept of a single short-term drug application probably makes little sense here. The decision for inclusion in the study was always made immediately after diagnostic coronary angiography and before PCI. Following the presentation of the concept of DCB only in 2011[16], several studies in different indications were initiated to investigate this new concept in *de novo* lesions with a primary clinical endpoint. For small coronary vessels there was the BASKET-SMALL 2 study[14], for high bleeding risk the DEBUT study[15], and for ACS the PEPCAD NSTEMI study. When conducting these trials, it was difficult to find centres that wanted to accept this new and untested concept. In the participating centres it was usually the case that only one or two operators were willing to include patients at all. This explains the long recruitment time in some of the studies. In spite of this limitation, all three studies have delivered convincing results showing the safety and efficacy of DCB only in studies with primary clinical endpoints.

Based on the data available at the initiation of the study, BMS were initially used in the control group. Following the general recommendation of DES in the guidelines, the use of current-generation DES was recommended after inclusion of about half of the patients. Exclusive use of DES in the comparator arm would have been more favourable. Unfortunately, the study does not have sufficient statistical power for a subgroup comparison. Furthermore, there was no routine angiographic follow-up in the study, so event rates could be underestimated. The power of the study is limited regarding its primary endpoint and also the non-inferiority margin selected. Furthermore, event adjudication was carried out by local investigators without a centralised and independent clinical events committee.

Nevertheless, our findings are in concert with results of previous registries[11-13,25] and trials comparing DCB with stents in small coronary vessels[10,26,27] and normal-sized vessels in patients at high risk of bleeding[15]. In the BELLO study, for example, there was no difference between DCB and DES in the clinical events after one year in small coronary vessels[10], but after three years there was a significant advantage for DCB therapy in terms of reduction of major adverse events[28]. The recently presented DEBUT study compared 210 patients treated with "DCB only" versus BMS in patients at high risk of bleeding. The frequency of major adverse events after nine months was 12.4% for the BMS, while only 1.9% events occurred after DCB[15].

Conclusions

In conclusion, treatment of coronary *de novo* lesions with DCB was non-inferior to stenting with BMS or DES. These data warrant further investigation of DCB in this setting, in larger trials

with DES as comparator. Longer-term follow-up will scrutinise whether avoiding permanent implants is advantageous over traditional stent therapy in certain patients.

Impact on daily practice

DCB use for ISR therapy has a IA recommendation in the ESC guidelines. So far, there is no such recommendation for the treatment of *de novo* stenoses. For *de novo* lesions, randomised trials with primary clinical endpoints have demonstrated the safety and efficacy of DCB for small coronary vessels (BASKET-SMALL 2 trial), patients with high risk of bleeding (DEBUT trial) and now also patients with NSTEMI (PEPCAD NSTEMI trial).

Funding

Financial support was provided by B. Braun Melsungen AG, Berlin, Germany.

Appendix. Study collaborators

Johannes Brachmann, MD; *Klinikum Coburg, Coburg, Germany*; Anne Bärisch, MD; *Vivantes Klinikum im Friedrichshain, Berlin, Germany*.

Conflict of interest statement

B. Scheller is a shareholder of InnoRa GmbH, Berlin, and was named as co-inventor on patent applications submitted by Charité University Hospital, Berlin, Germany. M.A. Ohlow has received research support from Translumina and proctoring fees and travel support from Biosensors. T.K. Rudolph has received speaker's honoraria from Abbott Vascular. M. Böhm is supported by the Deutsche Forschungsgemeinschaft (SFB TTR 219, S-01) and has received research support from Medtronic and St. Jude. R. Degenhardt has received research support from B. Braun. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. CONSORT checklist.

Supplementary Figure 1. Kaplan-Meier total MACE (all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI at other vessels) at nine months (per protocol). DCB only versus stent only.

Supplementary Figure 2. Kaplan-Meier primary endpoint target lesion failure (consisting of cardiac death, myocardial reinfarction, or target lesion revascularisation) at nine months (per protocol). DCB only versus DES only versus BMS only.

Supplementary Figure 3. Kaplan-Meier total MACE (all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI at other vessels) at nine months (per protocol). DCB only versus DES only versus BMS only.

Supplementary Table 1. Procedural data.

Supplementary Table 2. Hospital stay and medication at discharge.

Supplementary Table 3. Clinical events at 9-month follow-up.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00723

Supplementary data

Supplementary Appendix 1. Methods

Study design

Two hundred and ten patients with NSTEMI were enrolled in a randomised, controlled, non-inferiority multicentre trial comparing a paclitaxel iopromide-coated DCB (SeQuent® Please and SeQuent® Please NEO, coated with 3 µg paclitaxel/mm² of balloon surface; B. Braun Melsungen AG, Berlin, Germany) with primary stent treatment (ClinicalTrials.gov Identifier: NCT01489449). The study was conducted at five departments of cardiology in Germany (Central Clinic, Bad Berka; University Hospital of Saarland, Homburg/Saar; Vivantes Klinikum im Friedrichshain, Berlin; University Hospital Cologne, Germany; Klinikum Coburg, Germany). Study coordination and data management were carried out by the Center for Clinical Research at the Cardiovascular Center Hospital Rotenburg an der Fulda, Germany. Financial support was provided by B. Braun Melsungen AG, Berlin, Germany. The study was performed according to the Declaration of Helsinki and WHO guidelines. All patients gave written informed consent. The local ethics committees approved the study.

Patients

The main inclusion criterion was clinical presentation with a non-ST-elevation myocardial infarction (NSTEMI) defined by ischaemic symptoms (angina pectoris) >30 minutes, last symptoms within 72 hours before randomisation, positive cardiac troponin T, I, or hs-troponin above the 99th percentile, and an identifiable culprit lesion without angiographic evidence of large thrombus with intended early percutaneous coronary intervention. Treatment of up to two lesions was allowed. Furthermore, patients had to be older than 18 years, have a diameter stenosis >70% (visual estimate) or TIMI flow less than 3, a vessel diameter of 2.5–3.5 mm. Patients had to sign informed consent for and agree to be available for all required post-procedure follow-up assessments as defined in the clinical protocol. Exclusion criteria included presentation with cardiogenic shock, ST-elevation myocardial infarction, no identifiable culprit lesion, in-stent restenosis lesions, indication for acute bypass surgery, culprit lesion in a venous bypass graft, contraindication for treatment with heparin, ASA and thienopyridines, other medical illness (i.e., cancer, liver disease or congestive heart failure) that may require cytostatic

or radiation therapy, cause the subject to be non-compliant with the protocol, confound the data interpretation or be associated with limited life expectancy (i.e., less than two years), women who were known or suspected to be pregnant, significant gastrointestinal bleed within the past six months, history of bleeding diathesis or coagulopathy or would refuse blood transfusions, or participating in another device or drug study within the last six months which may interfere with the interpretation of results of this study.

Procedures

After assessment of inclusion and exclusion criteria, patients were randomly assigned to undergo primary stent implantation or use of a DCB after lesion preparation according to the DCB Consensus Group recommendations [16]. The trial was initiated in December 2012, when bare metal stents were still recommended in the setting of non-ST-elevation acute coronary syndrome [17]. During the course of the study, the investigators agreed to use new-generation limus-eluting DES. Immediately following the procedure, heparin was discontinued. Cardiac catheterisation, intervention, and sheath removal was carried out according to hospital practice.

Dual antiplatelet therapy with aspirin plus clopidogrel, ticagrelor or prasugrel was continued orally for 12 months. Patients underwent clinical follow-up at 30 days, four months, and nine months post procedure. All endpoints and adverse events were evaluated in consensus by the investigators and the study coordination and data management centre. The investigators and the data collection centre remained blinded until the database was closed.

The primary endpoint was target lesion failure (TLF; combined clinical endpoint consisting of cardiac or unknown death, myocardial reinfarction, and target lesion revascularisation) after nine months. Secondary endpoints included total major adverse cardiovascular events (total MACE) consisting of all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI at other vessels. Furthermore, individual clinical endpoints were defined as secondary endpoints. All endpoints were defined according to the ARC definitions [18].

Statistical analysis

The primary objective of this trial was to compare the experimental (DCB) and the control intervention (stent) with respect to the TLF rate within nine months after implantation. Due to the sparseness of empirical data for the endpoint in the target population, the assumptions to be made for sample size calculation were uncertain and hence it was in doubt whether the desired power could actually be achieved in a fixed sample size design. For that reason, the study was performed with an adaptive interim analysis looking at the four-month MACE data of the first 200 included patients.

The null hypothesis H0 was tested with the non-inferiority test of Farrington and Manning at an overall one-sided significance level of a=0.025 with a non-inferiority margin of 7%. The secondary variables were analysed descriptively by tabulation and with Kaplan-Meier curves. Statistical analyses were conducted for the intention-to-treat (ITT) population consisting of all data of patients who were recruited and randomised in this study, and the per protocol (PP) population. The homogeneity of the intervention groups is described by comparison of the demographic data. Continuous variables were tested with the t-test and categorical variables with Fisher's exact test.

The role of the funding source

The study sponsor did not have any role in the study design, collection, analysis, and interpretation of data or writing of the report, and did not participate in the decision to submit the manuscript for publication. The principal investigator (B. Scheller) and R. Degenhardt had full access to all data. The corresponding author had final responsibility for the decision to submit for publication.

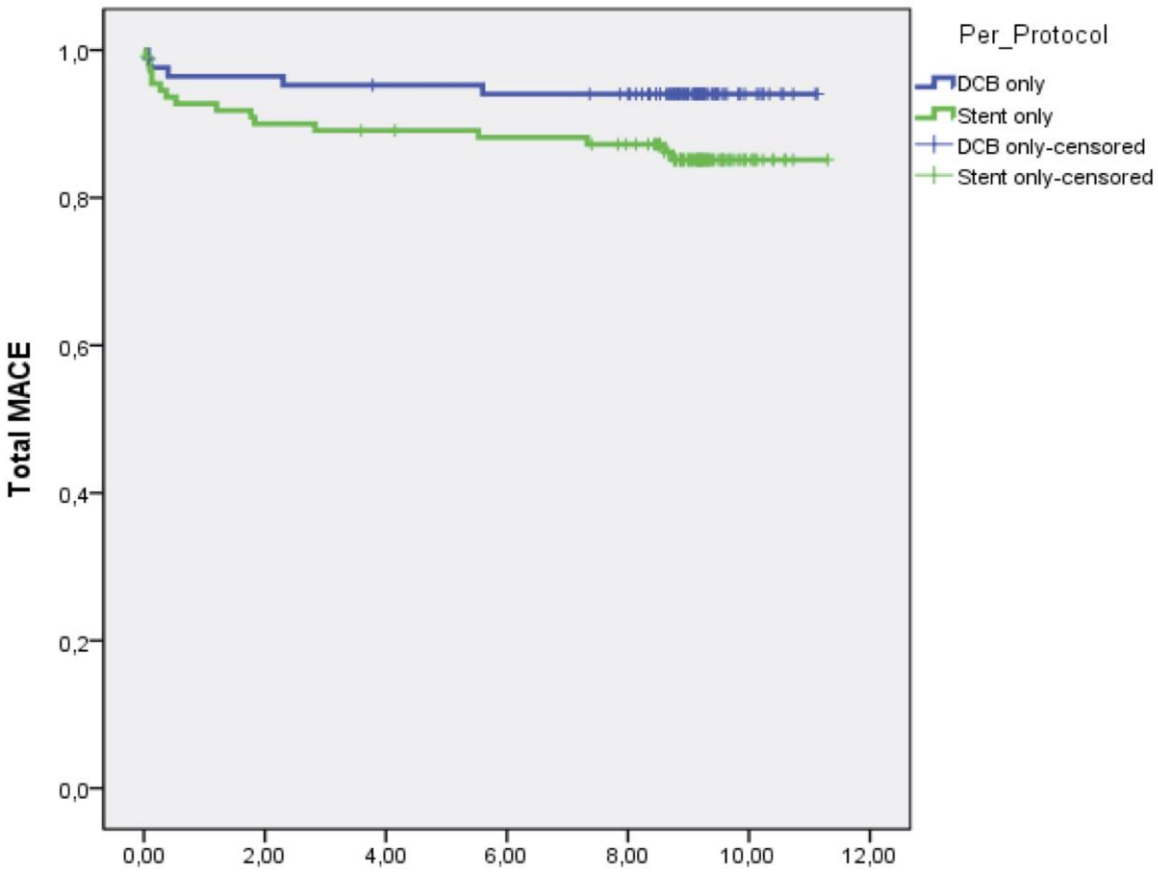
Supplementary Appendix 2. CONSORT checklist of information to include when reporting a randomised trial*

Section/Topic	Item no.	Checklist item	Reported on page no.
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	8
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	None
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	8
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	na
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	na

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	na
	11b	If relevant, description of the similarity of interventions	na
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	na
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8ff
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8ff
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8ff
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8ff
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8ff
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8ff
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10ff
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10ff
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10ff
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6

Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6

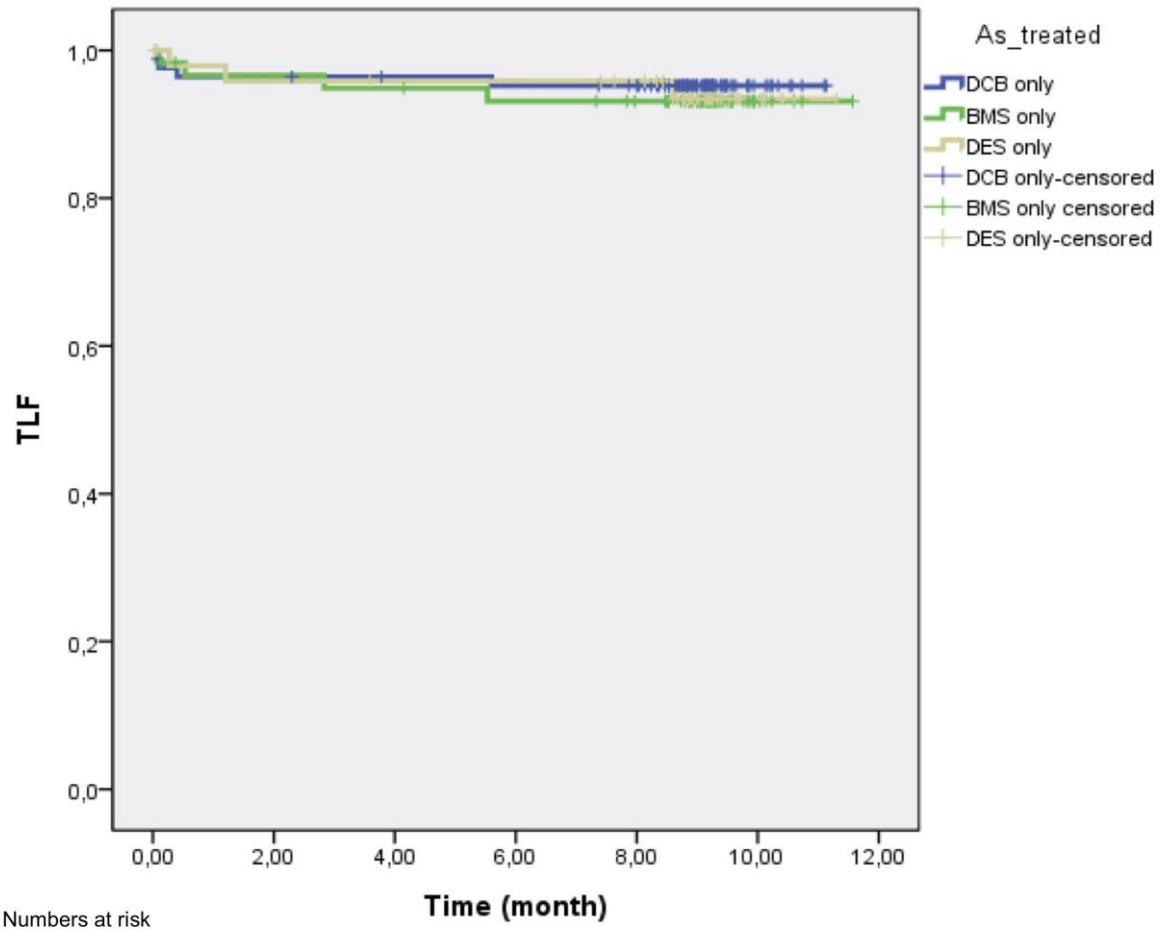
*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.



Numbers at risk

Month	0	2	4	6	8	10	12
DCB	85	81	79	78	76	10	0
Stent	111	99	97	95	91	12	0

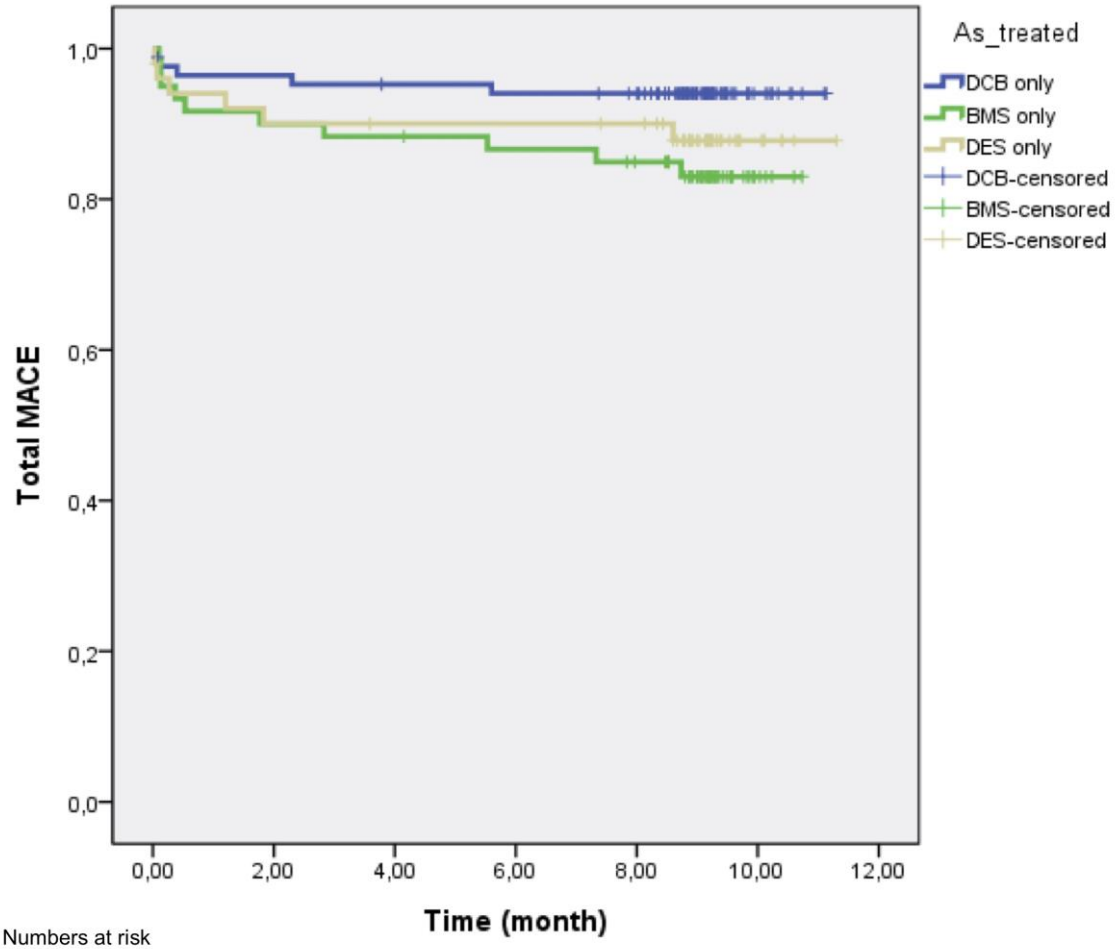
Supplementary Figure 1. Kaplan-Meier total MACE (all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI at other vessels) at 9 months (per protocol). DCB only versus stent only. P (log-rank)=0.060.



Numbers at risk

Month	0	2	4	6	8	10	12
DCB only	85	81	79	78	76	10	0
BMS only	60	56	55	53	50	6	0
DES only	51	46	45	45	43	7	0

Supplementary Figure 2. Kaplan-Meier primary endpoint target lesion failure (TLF consisting of cardiac death, myocardial reinfarction, or target lesion revascularisation) at nine months (per protocol). DCB only versus DES only versus BMS only. P (log-rank)=0.873.



Numbers at risk

Month	0	2	4	6	8	10	12
DCB only	85	81	79	78	76	10	0
BMS only	60	54	53	51	48	5	0
DES only	51	45	44	44	43	7	0

Supplementary Figure 3. Kaplan-Meier total MACE (all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI at other vessels) at nine months (per protocol). DCB only versus DES only versus BMS only. P (log-rank)=0.129.

Supplementary Table 1. Procedural data.

	Total (%)	DCB group (%)	Stent group (%)	***p*-value**
Number of patients	210	104	106	
Single-vessel disease	79 (37.6)	39 (37.5)	40 (37.7)	0.97
Two-vessel disease	76 (36.2)	37 (35.6)	39 (36.8)	
Three-vessel disease	56 (26.2)	28 (26.9)	27 (25.5)	
Treated lesions (N=243)				
Treated lesion	243 (100)	123 (50.6)	120 (49.4)	
LAD	97 (39.9)	51 (41.5)	46 (38.3)	0.79
LCX	84 (34.6)	40 (32.5)	44 (36.7)	
RCA	62 (25.5)	32 (26.0)	30 (25.0)	
Treated lesions per patient	1.11	1.18	1.13	0.32
Occluded lesion	10 (4.1)	3 (2.4)	7 (5.8)	0.21
Diameter stenosis before PCI, %	89.4±10.4	89.7±9.0	89.0±11.7	0.63
Predilatation	239 (98.4)	122 (99.2)	117 (97.5)	0.37
Length predilatation balloon, mm	18.0±4.4	18.6±4.6	17.4±4.1	0.038
Diameter predilatation balloon, mm	2.6±0.5	2.6±0.5	2.5±0.5	0.093
Inflation pressure predilatation, bar	12.3±2.4	12.6±2.3	12.0±2.5	0.094
Inflation time predilatation, sec	18.2±10.2	18.7±11.3	17.7±8.9	0.44
BMS	70 (28.8)	1 (0.8)	69 (57.5)	<0.0001
DES	59 (24.3)	8 (6.5)	51 (42.5)	
DCB only	103 (42.3)	103 (83.7)	0 (0)	
BMS+DCB	9 (3.7)	9 (7.3)	0 (0)	
POBA	2 (0.8)	2 (1.6)	0 (0)	
Stent length, mm			18.03±5.54	
Stent diameter, mm			3.03±0.42	
DCB length, mm		21.15±5.00		
DCB diameter, mm		2.81±0.49		
DCB pressure, bar		10.79±2.67		
DCB inflation time, sec		47.48±27.60		

Supplementary Table 1. Hospital stay and medication at discharge.

	Total (%)	**DCB group (%)**	**Stent group (%)**	***p*-value**
Duration of hospital stay, days	4.7±3.9	4.2±3.8	5.1±4.0	0.067
Clopidogrel	56 (26.7)	26 (25.0)	30 (28.3)	0.30
Ticagrelor	133 (63.3)	68 (65.4)	65 (61.3)	
Prasugrel	17 (8.1)	10 (9.6)	7 (6.6)	
No antiplatelet therapy (patient died in-hospital)	2 (1.0)	0 (0)	2 (1.9)	

Supplementary Table 3. Clinical events at 9-month follow-up.

	Total (%) N=196	**DCB only (%) N=85**	**BMS only (%) N=60**	**DES only (%) N=51**	***p*-value**
Cardiac death	9 (4.6)	3 (3.5)	3 (5.0)	3 (5.9)	0.80
All-cause mortality	14 (7.1)	4 (4.7)	6 (10.0)	4 (7.8)	0.46
Death non-cardiac	5 (2.6)	1 (1.2)	3 (5.0)	1(2.0)	0.34
Death other vessel	4 (2.0)	2 (2.4)	2 (3.3)	0(0)	0.45
Death target vessel	1 (0.5)	1 (1.2)	0 (0)	0 (0)	0.52
Death unknown	4 (2.0)	0 (0)	1 (1.7)	3 (6.0)	0.06
Myocardial infarction	3 (1.5)	0 (0)	2 (3.3)	1 (2.0)	0.26
Target lesion reintervention	2 (1.0)	1 (1.2)	1 (1.7)	0 (0)	0.67
Stroke	1 (0.5)	0 (0)	1 (1.7)	0 (0)	0.32
Percutaneous coronary intervention in other vessels	1 (0.5)	0 (0)	0 (0)	1 (2.0)	0.24
Stent/vessel thrombosis	1 (0.5)	0	0	1 (2.0) *	0.24
Total MACE (all-cause mortality, myocardial infarction, target lesion revascularisation, stroke, or PCI in other vessels)	21 (10.7)	5 (5.9)	10 (16.7)	6 (11.8)	0.11
Primary endpoint TLF (cardiac death, myocardial reinfarction, or target lesion revascularisation)	11 (5.6)	4 (4.7)	4 (6.7)	3 (5.9)	0.88

Treatment per protocol (DCB only vs BMS only vs DES only). * Unknown death 8 days post DES implantation.