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Randomized Comparison of Bare Metal or Drug-Eluting Stent versus Drug Coated Balloon in Non-ST-Elevation Myocardial Infarction - PEPCAD NSTEMI

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Short title: **PEPCAD NSTEMI**

Classifications: **NSTEMI; Bare metal stent; Drug-eluting balloon; Drug-eluting stent**

Abbreviations

percutaneous transluminal coronary angioplasty (PTCA)

bare metal stent (BMS)

drug eluting stent (DES)

drug coated balloon (DCB)

non-ST-Elevation Myocardial Infarction (NSTEMI)

target lesion failure (TLF; combined clinical endpoint consisting of cardiac or unknown death, myocardial reinfarction, and target lesion revascularization)

academic research consensus (ARC)

intention-to-treat (ITT)

per protocol (PP)

plain old balloon angioplasty (POBA)

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 stent.

Methods and Results

210 patients with NSTEMI were enrolled in a randomized, controlled, non-inferiority multicenter 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 revascularization) after 9 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. 104 patients were randomized 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 noninferior to stent treatment with a TLF of 3.8% vs 6.6% (intention-to-treat, p=0.53). There was no significant difference between BMS and current generation DES. Total MACE rate was 6.7% for DCB vs 14.2% for stent treatment (p=0.11), and 5.9% vs. 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).

Condensed Abstract

Two hundred and ten patients with Non-ST-Elevation Myocardial Infarction were randomized. Mean age was 67±12 years, 67% were male, 62% had multivessel disease, and 31% were diabetics. 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 noninferior to stent treatment with a target lesion failure (TLF) of 3.8% vs 6.6% (intention-to-treat, p=0.53). Total MACE rate was 6.7% for DCB vs 14.2% for stent treatment (p=0.11), and 5.9% vs. 14.4% in the per protocol analysis (p=0.056), respectively.

Introduction

Andreas Grüntzig introduced 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 could finally 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 has been 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 9 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 that according to current knowledge appears not to plateau over time [8], which 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) fulfill the requirements of ‘leaving nothing behind’ to avoid stent-associated events. Small randomized studies [10] and registries [11-13] confirmed the safety and efficacy of the 'DCBonly' concept in the treatment of coronary de-novo disease. Recently two trials with primary clinical endpoint have been published for small coronary vessels (BASKET SMALL 2 study [14]) and in patients with high bleeding risk (DEBUT study [15]). However, no randomized controlled trial on this concept have been published in patients with acute coronary syndrome. The aim of this prospective, randomized, controlled multicenter trial was to compare the clinical

outcome of patients with Non-ST-Elevation Myocardial Infarction (NSTEMI) treated either by DCB or stent.

Methods

Study design

Two hundred and ten patients with NSTEMI were enrolled in a randomized, controlled, non-inferiority multicenter trial comparing a paclitaxel iopromide coated DCB (SeQuent™ Please and SeQuent™ Please Neo, coated with 3 µg paclitaxel/mm² 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 a non-ST-elevation myocardial infarction (NSTEMI) defined by ischemic symptoms (angina pectoris) > 30 minutes, last symptoms within 72 hours before randomization, positive cardiac troponin T, I, or hs-Troponin above 99th percentile, and an identifiable culprit lesion without angiographic evidence of large thrombus with intended early percutaneous coronary intervention.

Procedures

After assessment of inclusion and exclusion criteria, patients were randomly assigned to undergo primary stent implantation or using 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.

The primary endpoint was target lesion failure (TLF; combined clinical endpoint consisting of cardiac or unknown death, myocardial reinfarction, and target lesion revascularization) after 9 months. Secondary endpoints included total major adverse cardiovascular events (total MACE) consisting of all-cause mortality, myocardial infarction, target lesion revascularization, stroke, or PCI at other vessels. Furthermore, individual clinical endpoints were defined as secondary endpoints. All endpoints were defined according to the ARC definition [18].

Results

Patients

Two hundred and ten patients with non-ST-elevation myocardial infarction were enrolled in this randomized 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 randomized to DCB treatment, 106 to stent treatment. Table 1 summarizes the clinical baseline 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 current generation DES. In the DCB group, 85% of patients were treated with DCB only whereas 15% underwent additional stent implantation. Two lesions of the DCB group were treated with POBA only, since no study device as well as no cross-over stent could be advanced to the lesion. Supplementary table 1 presents the procedural data. 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, TLF was 3.8% in patients randomized to DCB treatment vs 6.6% randomized to primary stenting (intention-to-treat; p=0.53; difference -0.03, CI(97.5) = -0.1057 to 0.0506). Non-inferiority of DCB vs stent could be demonstrated according to Farrington and Manning with a non-inferiority level of -0.07 (CI(90) = -0.0315 to 0.0867), a proportion difference of 0.0276, and a significance level of <0.0033 (Table 2, Figure 1). There was no significant difference in TLF rates in the per protocol analysis (Figure 2) and between BMS and current generation DES.

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 vessel (1.0% vs. 0) did not differ significantly between patients randomized to DCB or stent treatment, respectively. In the DCB group no acute and subacute thrombotic stent or vessel occlusions occurred. In the stent group, one patient died eight days after DES implantation when being already at home (unknown death).

Total MACE rate was 6.7% for DCB vs 14.2% for stent treatment (p=0.11; Figure 3), and 5.9% vs. 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 'DCBonly'; however, the latter difference was not statistically significant (Supplementary table 3, Supplementary Figure 2, Supplementary Figure 3).

Discussion

Non-ST-elevation acute coronary syndrome is the most common trigger for invasive coronary diagnostics and interventions worldwide. Despite the lack of larger randomized trials on the preferred interventional technique, drug eluting stents (DES) are regarded as the standard of care in most geographies [19]. However, until now no single randomized study has demonstrated superiority of DES compared with bare metal stents (BMS) or even plain old balloon angioplasty (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], they might allow to avoid stent implantation in many lesions [11]. The main contraindications for DCB treatment are flow-limiting dissections and an unsatisfactorily initial lumen gain. Contrary to the fears of some interventional cardiologists who were trained against the background of primary stent implantation, the 'DCBonly' 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 mainly based 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 'DCBonly' 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 'DCBonly' treatment is that it results in lumen enlargement after a few months post treatment [22, 23], which can be considered as a type of vascular restoration. This phenomenon is the basis for accepting a certain residual stenosis during the intervention. Of note, stent-based therapies are not showing 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 reinvention 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, who found no difference in survival between BMS and DES, but differences in the incidence of TLR [24].

The results of the present study support the safety of coronary intervention without stent implantation in patients with an increased thrombotic risk. After 9 months, there was no statistically significant difference in all relevant clinical endpoints between primary stent therapy and DCBonly. This means that unlike bioresorbable stents, this approach does not increase the event rate within the first few months to avoid permanent implants. However, superiority for DCBonly may only be demonstrated in a longer-term follow-up. Patients in this study will be followed up for up to 5 years.

Limitations

Patients with NSTEMI represent a heterogeneous patient population. Adapted to 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 DCBonly in 2011 [25], 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 this 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 centers that wanted to accept this new and untested concept. In the participating centers 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 3 studies have delivered convincing results showing the safety and efficacy of DCBonly 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 favorable. 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 done by local investigators without a centralized and independent Clinical Event Committee.

Nevertheless, our findings are in concert with results of previous registries [11, 13, 26, 27] and trials comparing DCB with stents in small coronary vessels [10, 28, 29] 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 3 years there was a significant advantage for DCB therapy in terms of reduction of major adverse events

[30]. The recently presented DEBUT study compared 210 patients treated with 'DCBonly' versus BMS in patients at high risk of bleeding. The frequency of major adverse events after 9 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 scrutinize whether avoiding permanent implants is advantageous over traditional stent therapy in certain patients.

Impact on daily practice

DCB use for ISR therapy has an IA recommendation in the ESC guidelines. So far, there is no such recommendation for the treatment of de-novo stenoses.

For de-novo lesions, randomized 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).

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Appendix: Collaborators

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Conflict of Interest Statement

BS is shareholder of InnoRa GmbH, Berlin, and was named as co-inventor on patent applications submitted by Charité university hospital, Berlin, Germany. MAO received research support from Translumina and proctoring fees and travel support from Biosensors. TKR received speakers' honoraria from Abbott Vascular. MB is supported by the Deutsche Forschungsgemeinschaft (SFB TTR 219, S-01) and received research support from Medtronic and St Jude. RD received research support from B.Braun. The other authors declare no other conflict of interest.

Figure legends

Figure 1: **(A) Test for non-inferiority, intention to treat. Ratio of event rates (97.5% CI) for the primary endpoint (TLF target lesion failure consisting of cardiac death, myocardial reinfarction, or target lesion revascularization) and total major adverse cardiac events (total MACE; all-cause mortality, myocardial infarction, target lesion revascularization, stroke, or PCI at other vessel). Confidence interval for TLF 9 months: difference -0.03, 97.5% CI= -0.1057 to 0.0506. Confidence interval for total MACE 9 months: difference -0.08, 97.5% CI= -0.1775 to 0.0291. (B) Kaplan-Meier Primary Endpoint Target Lesion Failure (TLF target lesion failure consisting of cardiac death, myocardial reinfarction, or target lesion revascularization) at 9 months (intention to treat). P (LogRank) = 0.360.**

Figure 2: **Kaplan-Meier Primary Endpoint Target Lesion Failure (TLF target lesion failure consisting of cardiac death, myocardial reinfarction, or target lesion revascularization) at 9 months (per protocol). P (LogRank) = 0.615.**

Figure 3: **Kaplan-Meier Total MACE (all-cause mortality, myocardial infarction, target lesion revascularization, stroke, or PCI at other vessel) at 9 months (intention to treat). P (LogRank) = 0.082.**

Tables

	Total (%)	DCB Group (%)	Stent Group (%)	p
Number of patients [N]	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
Weigth [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
Hyperlipidemia	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

Table 1: Clinical baseline data.

	Total (%) N=210	DCB Group (%) N=104	Stent Group (%) N=106	p
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 other vessel	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 revascularization, stroke, or PCI at other vessel)	21 (10.5)	7 (6.7)	15 (14.2)	0.11
Primary endpoint TLF (cardiac death, myocardial reinfarction, or target lesion revascularization)	11 (5.2)	4 (3.8)	7 (6.6)	0.53

Table 2: Clinical events at 9 months follow-up. Intention to treat analysis. * unknown death 8 days post DES implantation.

	Total (%) N=196	DCB only (%) N=85	Stent only (%) N=111	p
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-cardial	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 other vessel	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 revascularization, stroke, or PCI at other vessel)	21 (10.7)	5 (5.9)	16 (14.4)	0.056
Primary endpoint TLF (cardiac death, myocardial reinfarction, or target lesion revascularization)	10 (5.1)	4 (4.7)	7 (6.3)	0.75

Table 3: Clinical events at 9 months follow-up. Treatment per protocol (DCB only vs Stent only). * unknown death 8 days post DES implantation.

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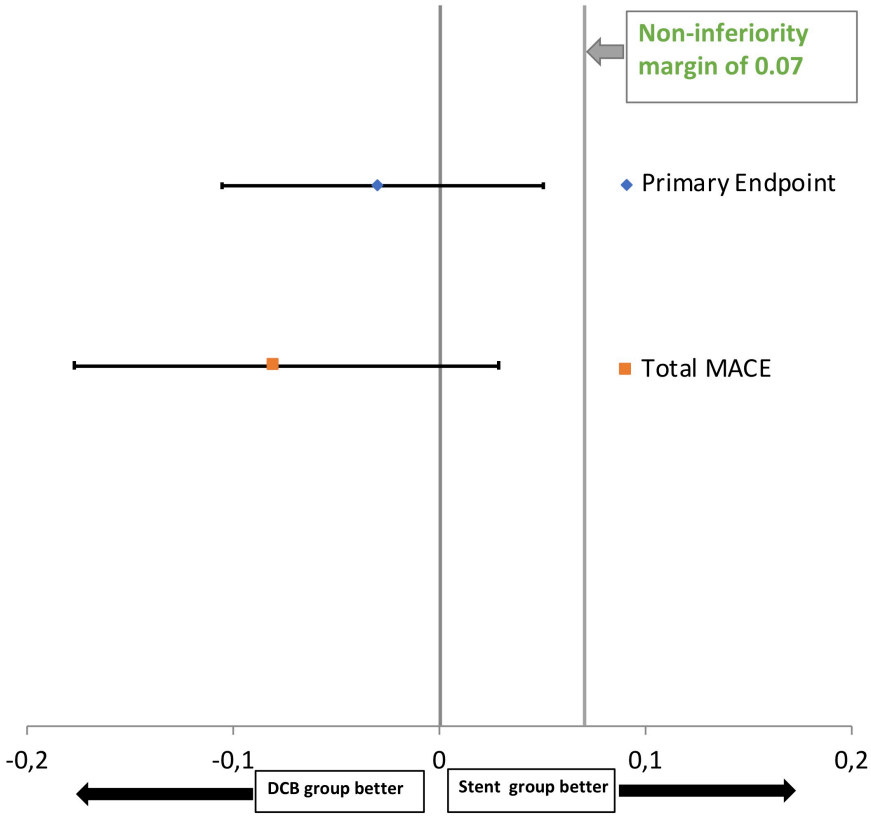
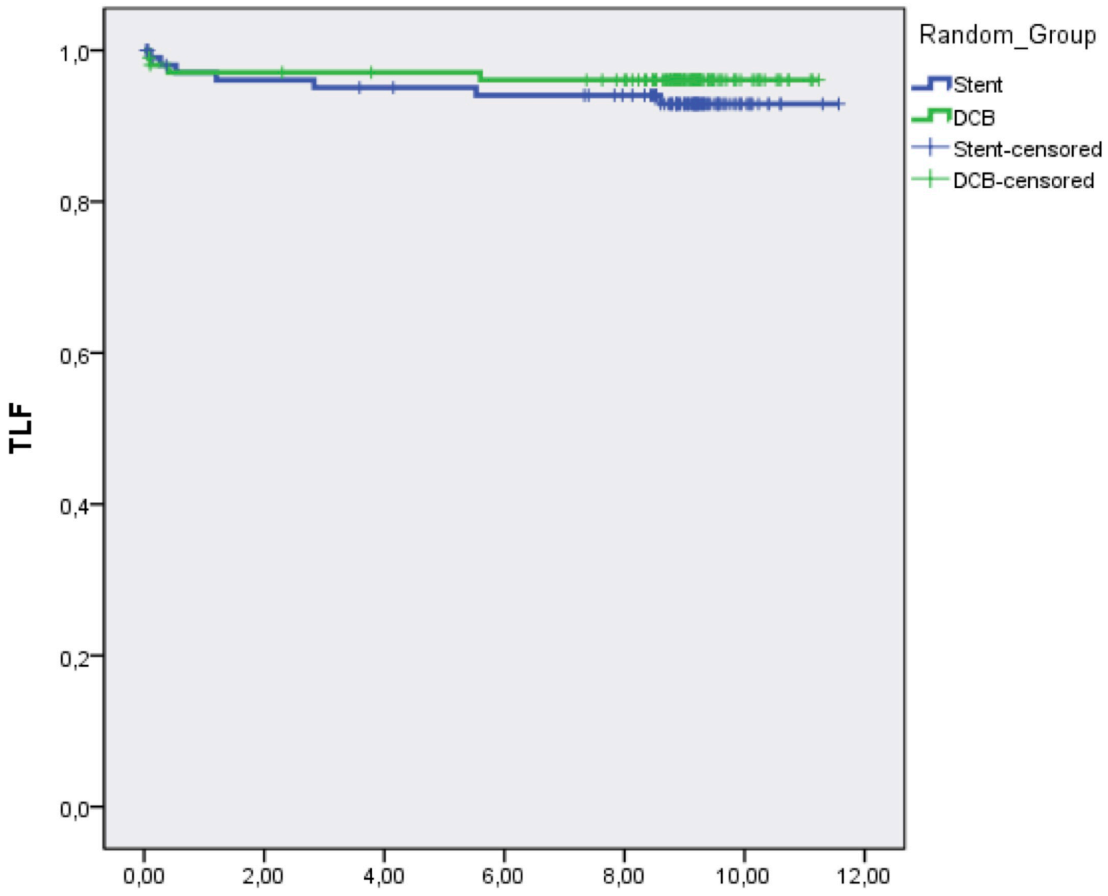
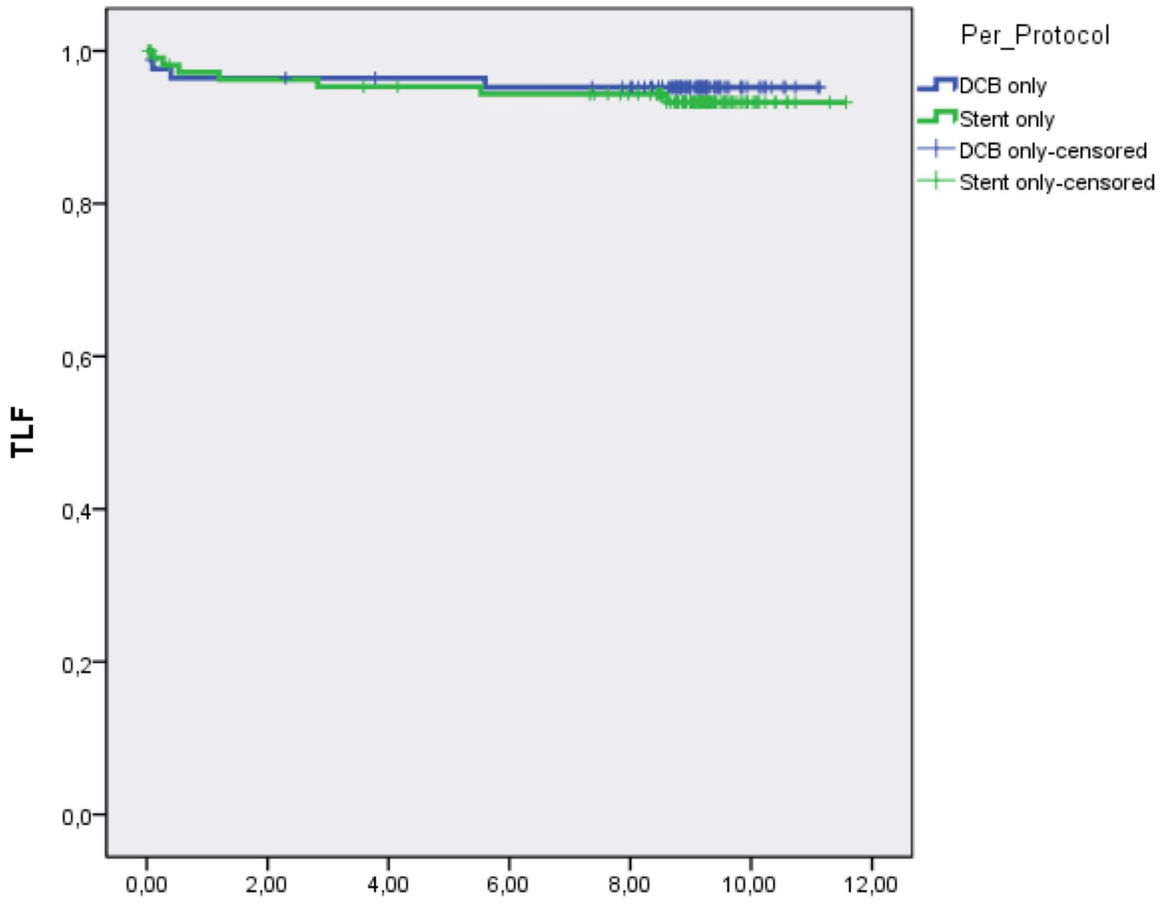




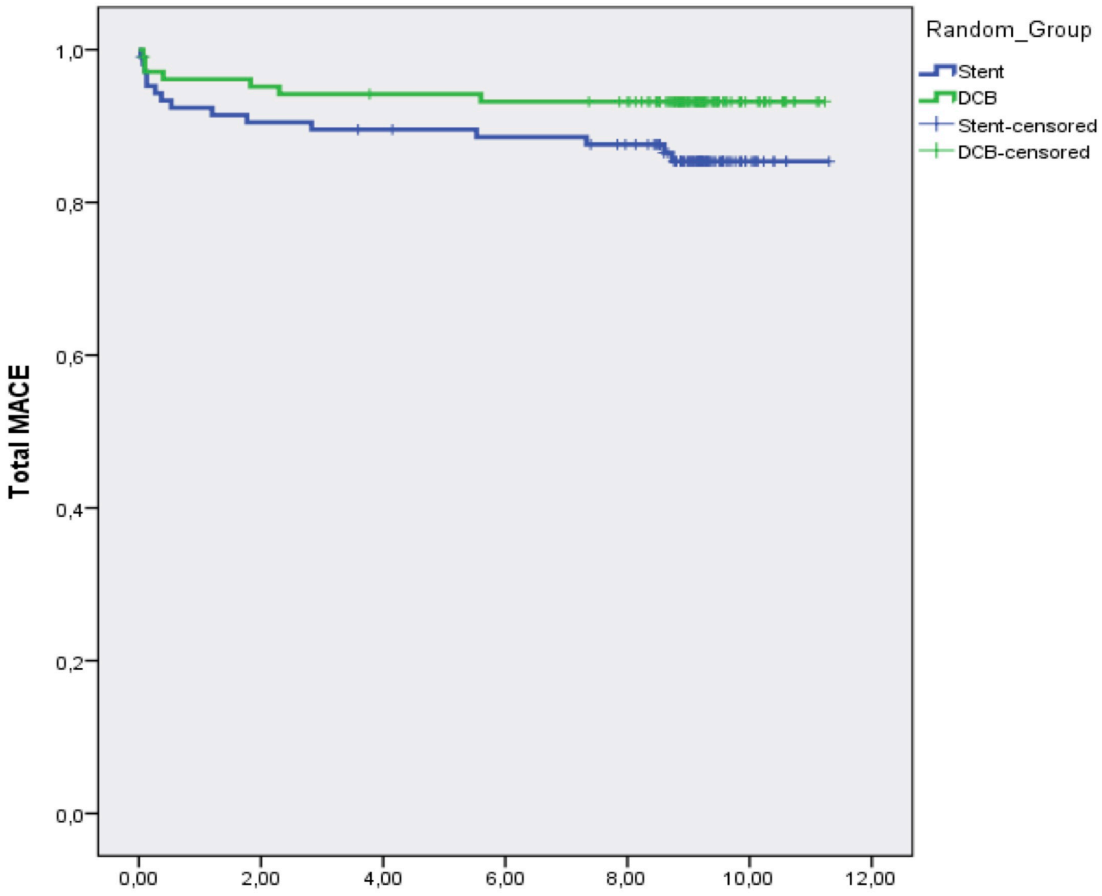
Numbers at risk

Month	0	2	4	6	8	10	12
DCB	104	99	97	96	93	14	0
Stent	106	97	95	93	89	12	0



Numbers at risk

Month	0	2	4	6	8	10	12
DCB	85	81	79	78	76	10	0
Stent	111	102	100	98	93	13	0



Numbers at risk

Month	0	2	4	6	8	10	12
DCB	104	98	96	95	93	14	0
Stent	106	95	93	91	87	11	0

Randomized Comparison of Bare Metal or Drug-Eluting Stent versus Drug Coated Balloon in Non-ST-Elevation Myocardial Infarction - PEPCAD NSTEMI

Supplementary Material

Methods

Study design

Two hundred and ten patients with NSTEMI were enrolled in a randomized, controlled, non-inferiority multicenter trial comparing a paclitaxel iopromide coated DCB (SeQuent™ Please and SeQuent™ Please Neo, coated with 3 µg paclitaxel/mm² 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 was done 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 ethical committees approved the study.

Patients

The main inclusion criterion was clinical presentation with a non-ST-elevation myocardial infarction (NSTEMI) defined by ischemic symptoms (angina pectoris) > 30 minutes, last symptoms within 72 hours before randomization, positive cardiac troponin T, I, or hs-Troponin above 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, having a diameter stenosis > 70% (visual estimate) or TIMI flow less than III, 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 the 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 is 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 will refuse blood transfusions, or participating in another device or drug study within the last 6 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 using 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 catheterization, intervention, and sheaths 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, 4 months, and 9 months post procedure. All endpoints and adverse events were evaluated in consensus by the investigators and the study coordination and data management center. The investigators and the data collection center 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 revascularization) after 9 months. Secondary endpoints included total major adverse cardiovascular events (total MACE) consisting of all-cause mortality, myocardial infarction, target lesion revascularization, stroke, or

PCI at other vessels. Furthermore, individual clinical endpoints were defined as secondary endpoints. All endpoints were defined according to the ARC definition [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 9 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 months 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 analyzed descriptively by tabulation and with the Kaplan-Meier curves. Statistical analyses were conducted for the intention-to-treat population (ITT) consisting of all data of patients who were recruited and randomized in this study, and the per protocol population (PP). 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 funding source

The study sponsor did not have any role in 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 Principle Investigator (BS) and RD had full access to all data. The corresponding author had final responsibility for the decision to submit for publication.

Supplementary Figure legends

Supplementary Figure 1: **Kaplan-Meier Total MACE (all-cause mortality, myocardial infarction, target lesion revascularization, stroke, or PCI at other vessel) at 9 months (per protocol). DCB only vs. Stent only. P (LogRank) = 0.060.**

Supplementary Figure 2: **Kaplan-Meier Primary Endpoint Target Lesion Failure (TLF target lesion failure consisting of cardiac death, myocardial reinfarction, or target lesion revascularization) at 9 months (per protocol). DCB only vs. DES only vs. BMS only. P (LogRank) = 0.873.**

Supplementary Figure 3: **Kaplan-Meier Total MACE (all-cause mortality, myocardial infarction, target lesion revascularization, stroke, or PCI at other vessel) at 9 months (per protocol). DCB only vs. DES only vs. BMS only. P (LogRank) = 0.129.**

Supplementary Tables

	Total (%)	DCB Group (%)	Stent Group (%)	p
Number of patients [N]	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 lesion (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 lesion 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		

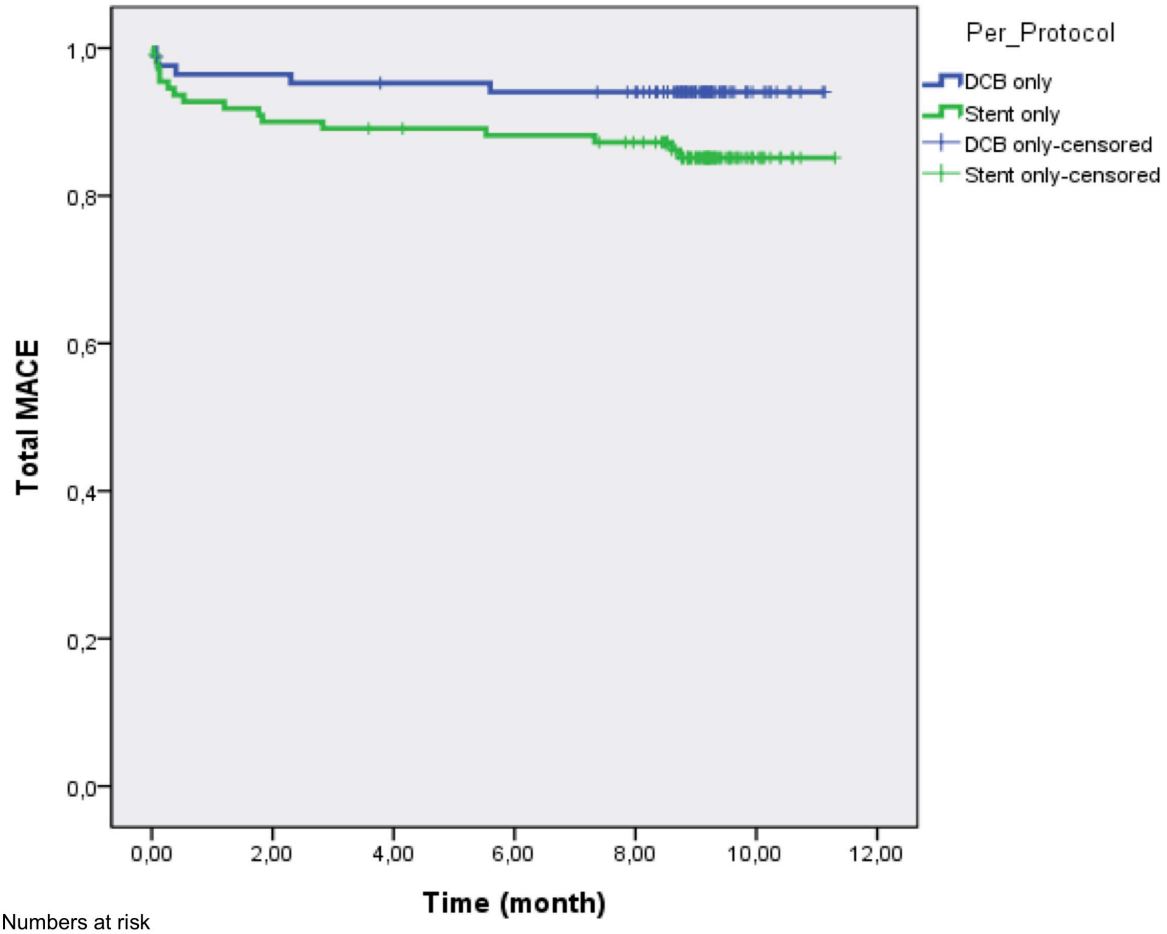
Supplementary table 1: Procedural data.

	Total (%)	DCB Group (%)	Stent Group (%)	p
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 2: Hospital stay and medication at discharge.

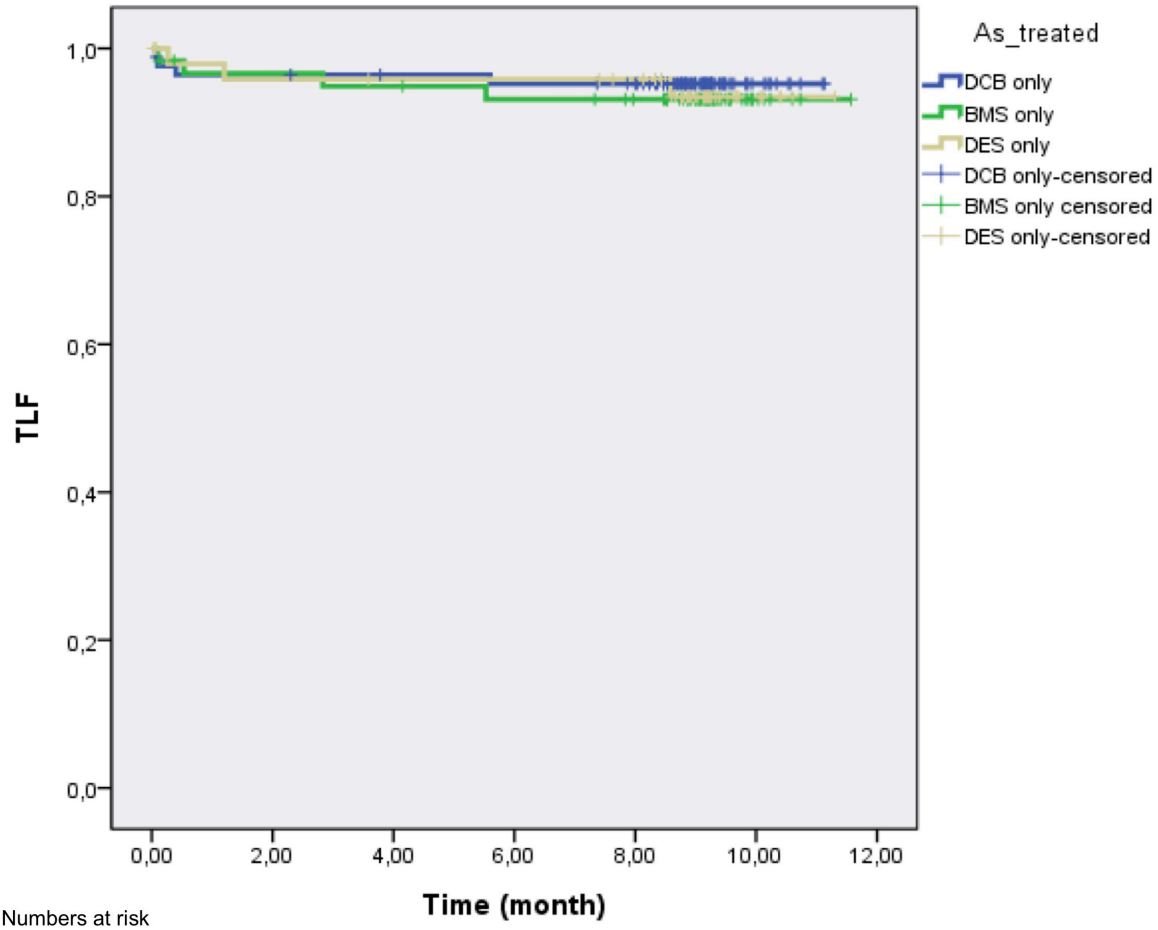
	Total (%) N=196	DCB only (%) N=85	BMS only (%) N=60	DES only (%) N=51	p
Cardiac death	9 (4.6)	3 (3.5)	3 (5.0)	3 (5.9)	0.80
All-cause mortality	14 (7.1)	4 (4.7)	6 (10.0)	4 (7.8)	0.46
Death non-cardial	5 (2.6)	1 (1.2)	3 (5.0)	1(2.0)	0.34
Death other vessel	4 (2.0)	2 (2.4)	2 (3.3)	0(0)	0.45
Death target 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 other vessel	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 revascularization, stroke, or PCI at other vessel)	21 (10.7)	5 (5.9)	10 (16.7)	6 (11.8)	0.11
Primary endpoint TLF (cardiac death, myocardial reinfarction, or target lesion revascularization)	11 (5.6)	4(4.7)	4 (6.7)	3 (5.9)	0.88

Supplementary table 3: Clinical events at 9 months follow-up. Treatment per protocol (DCB only vs BMS only vs DES only). * unknown death 8 days post DES implantation.



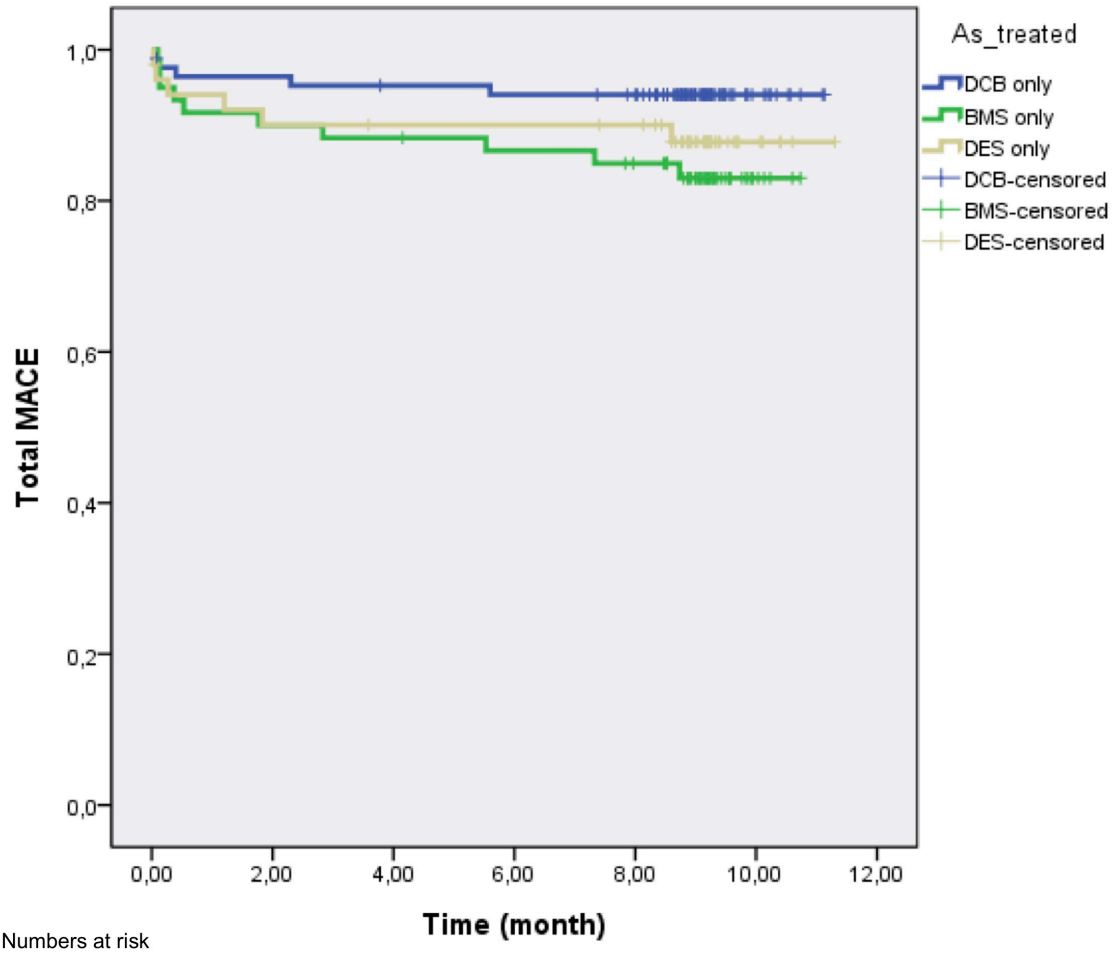
Numbers at risk

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



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



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

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.