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ABSTRACT

Background: The treatment of in-stent restenosis (ISR) remains challenging in contemporary clinical practice.

Objectives: To evaluate the relative performance of a drug-eluting balloon (DEB) and a drug-eluting stent (DES) in patients with any (bare metal or drug-eluting stent) ISR.

Methods: In a multicenter randomized non-inferiority trial, patients with any ISR were randomly allocated in a 1:1 fashion to treatment with a DEB (SeQuent Please paclitaxel-eluting balloon, BBraun Melsungen, Germany), or a DES (XIENCE everolimus-eluting stent, Abbott Vascular, Santa Clara, CA). The primary endpoint was non-inferiority in terms of in-segment minimal lumen diameter (MLD) at 6-month angiographic follow-up. Secondary endpoints included angiographic parameters at 6 months and clinical follow-up up to 12 months.

Results: A total of 278 patients of whom 56% had DES-ISR were randomized at 8 sites to treatment with DEB (n=141) or DES (n=137). As compared with DEB, DES was associated with larger MLD and lower % stenosis immediately post-procedure (1.84±0.46 vs 1.72±0.35, p=0.018 and 26±10% vs. 30±10%, p=0.03). Angiographic follow up was completed at 196±53 days in 79% of patients. With respect to the primary endpoint of in-segment MLD at 6 months, DEB was non-inferior to DES (DEB 1.71±0.51mm vs. DES 1.74±0.61mm, p *noninferiority* <0.0001). Target vessel revascularization at 12-month follow-up was similar in both groups (DES 7.1% vs DEB 8.8%, p=0.65).

Conclusions: In patients with ISR, treatment with DEB was non-inferior compared with DES in terms of 6-month MLD. There were no differences in clinical endpoints, including target vessel revascularization up to 12 months. Therefore, use of a DEB is an attractive treatment option for in-stent restenosis withholding the need for additional stent implantation.

KEY WORDS: In-stent restenosis, drug-eluting balloon, drug-eluting stent, percutaneous coronary intervention

CONDENSED ABSTRACT

Treating in-stent restenosis (ISR) remains challenging in contemporary clinical practice. The multicenter DARE trial randomized 278 patients with bare-metal stent or drug-eluting stent ISR to treatment with a drug-eluting stent (DES) or a drug-eluting balloon (DEB). Angiographic follow up was completed at 196±53 days in 79% of patients. With respect to the primary endpoint of in-segment minimal luminal diameter at 6 months, DEB was non-inferior to DES (DEB 1.71±0.51mm vs. DES 1.74±0.61mm, p *noninferiority* <0.0001). Target vessel revascularization at 12-month follow-up was similar in both groups (DES 7.1% vs DEB 8.8%, p=0.65).

ABBREVIATIONS

PCI= percutaneous coronary intervention

ISR= in-stent restenosis

DEB= drug-eluting balloon

DES= drug-eluting stent

BMS= bare-metal stent

EES= everolimus-eluting stent

DARE= drug-eluting balloon for in-stent restenosis

DAPT= dual antiplatelet therapy

MLD= minimal lumen diameter

SD= standard deviation

INTRODUCTION

The aim of percutaneous coronary intervention (PCI) is to restore optimal blood flow in narrowed coronary arteries. Ever since the introduction of this non-surgical technique in 1977 the phenomenon of restenosis has hampered its long-term efficacy.(1) With balloon angioplasty alone, restenosis rates >40% at 6-month follow-up were not uncommon.(2,3) The use of coronary artery stents led to an important reduction in restenosis rates, particularly with drug-eluting stents (DES) which are coated with antiproliferative drugs such as sirolimus (or one of its analogues e.g. everolimus, zotarolimus, etc.) or paclitaxel.(4) However, depending on patient- and lesion characteristics, in-stent restenosis (ISR) still occurs in 3-20% of patients, even with the use of DES.(5) Currently, implantation of new-generation DES is standard clinical practice. However, BMS are still used in a minority of patients (e.g. with increased bleeding risk or scheduled surgery) because of the shorter required duration of dual antiplatelet therapy (DAPT). Many techniques have been used to treat ISR, including conventional balloon angioplasty, cutting balloon angioplasty, intravascular brachytherapy, laser atherectomy, bare-metal stents (BMS), DES, and more recently, drug-eluting balloon (DEB) angioplasty. (6) Drug-eluting balloons allow for the delivery of an antiproliferative drug without the need for additional stent implantation which is an intuitively attractive treatment option for ISR lesions. Prior randomized studies have investigated the use of DEB in a population consisting of either exclusively BMS ISR or DES ISR patients, (7-11) however no study to date has enrolled patients with any ISR (i.e. BMS- and DES-ISR).

The DARE (drug-eluting balloon for in-stent restenosis) trial was designed to investigate the relative performance of the paclitaxel-eluting balloon (Sequent Please, B.Braun, Melsungen, Germany) compared with the everolimus-eluting stent (EES, XIENCE, Abbott Vascular, Santa Clara, CA) in the treatment of any in-stent restenosis.

METHODS

Study design

The DARE trial was an investigator-initiated, prospective multicenter randomized two-arm trial with blinded evaluation of endpoints. The study was conducted in accordance with the declaration of Helsinki and was registered on 01-29-2010 (NTR number NTR2189). The study was investigator-initiated and sponsored by the Academic Medical Center – University of Amsterdam. The study was financially supported through a research grant provided by B.Braun (Melsungen, Germany). The grant givers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Investigators of the Heart Center at the Academic Medical Center - University of Amsterdam designed the study, collected and managed the data, and performed the statistical analyses. The trial protocol was approved in Amsterdam by a central medical ethics committee and ethics committee approval was received in all participating centers according to local regulations. The authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Participants

Patients with ISR of a metallic coronary stent of any type (BMS or DES) were eligible for inclusion. Restenosis was defined as >50% diameter stenosis on visual assessment in-stent and/or <5mm out of the stent. Restenosis of all lesion types were eligible, including ostial, left main, bifurcation, chronic total occlusion, saphenous vein grafts, and arterial graft lesions. Exclusion criteria included reference vessel diameter <2.0 or >4.0mm by visual estimation, age <18 years, the impossibility to arrange a follow-up coronary angiography at 6 months after the baseline procedure, life expectancy <1 year, presentation with ST-elevation myocardial infarction, and restenosis in a bioresorbable scaffold.

Written informed consent was obtained prior to the procedure. After successful predilation of the ISR lesion patients were randomly assigned in a 1:1 ratio to treatment with

either a DEB (Sequent Please paclitaxel-eluting balloon, B.Braun, Melsungen, Germany) or an EES (XIENCE prime or XIENCE expedition, Abbott Vascular, Santa Clara, CA). Randomization was done in an open-label manner with an electronic web-based system in permuted blocks of varying size in each participating center.

Procedures and follow-up

All patients were pretreated with aspirin and a P2Y12 inhibitor (i.e. clopidogrel, prasugrel, or ticagrelor). Anticoagulation during the procedure was obtained with unfractionated heparin according to local protocols at each participating center. Use of glycoprotein IIb/IIIa inhibitors or other intra-procedural medication was at the discretion of the operator. Pre-dilation was protocol-mandated in both study arms, the technique for pre-dilation was left to the operator's discretion but aimed at full expansion of the previous implanted stent. For patients randomized to the DEB arm a balloon size with the same diameter as the last used pre-dilation balloon was used. The DEB is inflated at a pressure of 6-8 atmospheres for the duration of minimally 30 seconds, but optimally 60 seconds. In case of very long lesions, the use of 2 or more subsequent DEB's was allowed, using a small overlap. For patients randomized to the EES arm a stent size was chosen which can be deployed to the diameter as the last-used pre-dilation balloon. The stent length was chosen so that the initial stent length plus 2-3mm on both sides of the initial stents were covered. The decision to use a post-dilation balloon was left to the operator's discretion.

The treatment of dissections during ISR PCI was at the discretion of the operator. If additional stenting was deemed necessary, the protocol mandated the use of a BMS in patients randomized to the DEB arm and an EES in patients randomized to the EES arm. Treatment of additional non-ISR (*de novo)* lesions during the same procedure was performed at the operator's discretion.

Post-procedurally, all patients, regardless of randomized treatment assignment 12 months of DAPT followed by life-long aspirin. Repeat angiography was scheduled at 6 months (±1 month) in all patients. Clinical follow-up was obtained by telephone interview at 30 days, and at 1 year after the index procedure.

Quantitative Coronary Angiography

Baseline coronary angiography was performed in 2 different views with at least 30^0 difference using 6 French or larger catheters at 25 frames per second using an image intensifier setting of 5 inch (13cm) or 7 inch (18cm). Pre-procedural and final angiograms were obtained during breath hold without a guidewire in the coronary artery. Projections were selected without overlap of the target lesion, minimizing foreshortening of the segment of interest. Intra-coronary nitroglycerine was administered before acquisition of the angiogram.

Angiographic follow-up was scheduled within six months (±1 month) after the index procedure, using the same projections and guidelines as during baseline coronary angiography. If the target lesion has been treated within six months from baseline PCI, no study follow-up coronary angiography was performed. In that case, the pre-procedural angiogram was used for endpoint assessment.

All study follow-up coronary angiograms were analysed at the independent QCA Core Lab (Cordinamo, Wezep, the Netherlands) in a blinded fashion. QCA measurements were performed on a single “worst” projection (i.e., the projection in which the stenosis looks most severe)

Outcomes

The primary endpoint was minimal lumen diameter (MLD) at six-month angiographic follow-up. MLD was defined as the minimal diameter in up to 5 mm outside of both ends of the original stent (in patients in the DEB arm) and 5mm outside of the new EES (in patients in the EES arm). Secondary angiographic endpoints included in-stent and in-segment

angiographic binary restenosis (ABR) at six months (defined as the presence of a stenosis of ≥50% at angiographic follow-up), In-stent and in-segment percent diameter stenosis (%DS) at six months, and the presence of persisting dissection (i.e. dissection post-index-procedure that remained present at follow-up). Clinical endpoints included myocardial infarction (unless originating from an un-treated vessel), target vessel revascularization (either by PCI or CABG), stent thrombosis (definite or probable according to Academic Research Consortium criteria), (12) and cardiac death (all deaths were considered cardiac unless an unequivocal non-cardiac cause could be established). Myocardial infarction was defined according to "the myocardial infarction classification and criteria for diagnosis" by the Academic Research Consortium and is adapted from the Global Task Force definitions for myocardial infarction: 1) Typical rise and fall of biomarkers of myocardial necrosis and ischemic symptoms or development of new pathologic Q-waves on the ECG or ECG changes indicative of ischemia; 2) Pathological findings of an acute myocardial infarction; 3) Development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.(12) The composite endpoint of major adverse events (MAE) was defined as the occurrence of death, target vessel related myocardial infarction or target vessel revascularization. A masked Critical Event Committee centrally adjudicated all study endpoints.

Statistical analysis

The primary analysis was a non-inferiority comparison of the DEB compared to the EES for the primary endpoint of MLD at 6-month angiographic follow-up. To satisfy the non-inferiority hypothesis, the upper limit of the one-sided 95% confidence limit for the difference in MLD between DEB and EES had to exceed a pre-specified margin of -0.4mm, which reflects preservation of approximately 50% of the gain for drug-eluting stents relative to conventional bare metal stents. This is equivalent to non-inferiority testing at a 5% one-sided

α level. The MLD at 6-month follow-up was expected to be 2.1mm in DEB-treated and in DES-treated patients with a standard deviation (SD) of 0.6mm. With 112 analyzable patients per treatment group, the study has 80% power to reject the null hypothesis of inferiority of DEB to DES. To account for an attrition rate of 20%, we aimed to randomize 270 patients.

The means (±SD) for continuous variables were calculated in each group and compared using Student's t-test or Mann-Whitney u test. Binary variables are reported as counts and percentages, and the chi-square or Fisher's exact tests were used where appropriate to assess differences between the two groups. The Two One-Sided Test was used to test non-inferiority. The Kaplan-Meier method was used to estimate cumulative event rates, and the log-rank test was used to assess differences between both groups. Analyses were performed according to the intention-to-treat principle. A p-value of <0.05 was considered statistically significant. IBM SPSS statistics version 20.0 (IBM, Armonk, NY) and XLstat version 19.4 (Addinsoft, New York City, NY) were used to perform statistical analyses.

RESULTS

Between May 2010 and June 2015, 278 patients were enrolled at 8 sites. A total of 137 patients were randomized to the DEB arm and 141 patients were randomized to the DES arm. Figure 1 shows the flowchart for the trial. Baseline clinical characteristics were similar in both groups, with the exception of a larger proportion of male patients in the DES arm (table 1). Most lesions were located in the left anterior descending coronary artery in both groups. The proportion of BMS-ISR lesions was 45% in the DEB arm and 43% in the DES arm (p=0.39). Median time to ISR was 3.6 years (interquartile range 1.1-8.3 years). Most patients with DES-ISR were originally treated with –limus–eluting stents (83% in the DEB arm, 86.0% in the DES arm). Most ISR lesions were of the focal type (DEB 51%, DES 53%, p=0.42).

Procedural and angiographic characteristics at baseline and at the end of the index procedures are shown in tables 2 and 3. Predilation was used in 100% of patients in the DEB

arm. Postdilation was used in 16% of patients in the DEB arm and 57% in the DES arm (p<0.0001). No bail-out stenting after treatment with DEB had occurred. Immediately after the procedure, the MLD in the DES arm was larger compared with the DEB arm (1.84±0.46 vs 1.72±0.35, p=0.007) and % stenosis was significantly lower in the DES arm (26±10% vs. 30±10%, p=0.03).

Angiographic follow-up: Angiographic follow-up was obtained in 105 patients in the DEB arm (77%) and 115 patients in the DES arm (82%) at a mean follow-up duration of 196±53 days. Angiographic outcomes are presented in table 3. At 6-month follow-up the point estimate and 95% lower confidence limit (LCL) of the difference in MLD between DEB and DES was -0.03mm and 95% LCL -0.16mm, respectively, indicating non inferiority (p for non-inferiority <0.0001). In-segment MLD in both groups was not significantly different (DEB 1.71±0.51mm vs. DES 1.74±0.61mm, p 0.65). There were no interactions in terms of the primary endpoint with selected subgroups (figure2)

Clinical follow-up: Clinical follow-up was complete in 100% of patients up to 12 months. Clinical events are summarized in table 4. A total of 3 patients died, 1 in the DEB group and 2 in the DES group (0.7% vs. 1.4%, p=0.58). There were no instances of stent thrombosis up to 12 month follow-up. There was no difference in the incidence of TVR; 8.8% in the DEB arm vs. 7.1% in the DES arm, p=0.65. The incidence of composite major adverse events was similar in both groups and is shown in figure 3.

DISCUSSION

The randomized DARE trial demonstrated non-inferiority of a paclitaxel-eluting DEB compared with an everolimus-eluting DES in terms of 6-month MLD in the treatment of any BMS- and DES ISR. The current trial, which is the largest trial of DEB vs EES in ISR to date, adds important insights to the available clinical evidence on treatment strategies for ISR in both BMS and DES. A considerable number of observational studies and randomized trials

investigating the use of DEB and/or (obsolete) first-generation DES in the treatment of BMS- and DES-ISR have previously been performed. (10,11,13-19) However, only four randomized clinical trials comparing a DEB with a current-generation DES have been published. (7-9) In all these trials, the SeQuent Please DEB was compared with the XIENCE everolimus-eluting stent (EES). Both devices are currently the benchmark device in their class, with the XIENCE EES being the most intensively studied DES and the SeQuent Please paclitaxel-eluting balloon the most intensively studied DEB. (20-22) The RIBS V (restenosis intra-stent of bare-metal stents) trial, the SEDUCE (safety and efficacy of a drug-eluting balloon in coronary artery restenosis) trial, and the trial by Pleva et al. exclusively enrolled patients with BMS-ISR. The 189-patient RIBS V trial showed that use of the EES resulted in superior late angiographic findings (MLD at 9-month follow-up 2.36±0.6mm vs. 2.01±0.6mm, p<0.001). (9) The need for TVR was statistically similar in both groups, but numerically higher in the DEB arm (2% vs. 6 %, p=0.17). However, the 136-patient study by Pleva et al. showed superior angiographic outcomes with the DEB compared with the EES (12-month late lumen loss, 0.02 vs 0.19mm, p=0.0004). (23) In SEDUCE, optical coherence tomography was performed at 9-month follow-up showing a significantly lower percentage of uncovered struts in the DEB arm (1.4% vs 3.1%, p=0.025). (8) As in RIBS V, MLD at 9 months was significantly greater in the EES arm (2.13mm vs. 2.54mm, p=0.006). The RIBS IV trial (n=309) enrolled only patients with DES ISR, and showed superiority of the EES vs. the DEB in terms of both angiographic endpoints (MLD at angiographic follow-up 2.03±0.7mm vs. 1.80±0.6mm, p<0.01) and clinical endpoints (TVR at 1 year 10% vs. 18% p=0.04). (7)

In light of the previous data, the DARE trial confirms the feasibility of using a DEB in both BMS- and DES-ISR. In current clinical practice, the majority of stents implanted are next-generation DES, but BMS are still being used in selected cases. Therefore, the DARE trial population closely resembles daily clinical practice. As opposed to the aforementioned RIBS

IV, RIBS V, and SEDUCE trials, no significant difference in 6-month MLD were observed between the EES and DEB arms. However, we did observe greater acute lumen gain with EES as compared with DEB, which is in line with prior trials.(7-9) This difference in acute lumen gain could potentially be reduced by using more aggressive lesion preparation before DEB inflation e.g. by using scoring or cutting balloons; The ISAR-DESIRE 4 (Intracoronary stenting and angiographic results: Optimizing treatment of drug-eluting stent in-stent restenosis) trial, randomized 252 patients with DES ISR to conventional predilation versus scoring balloon pre-dilation followed by DEB therapy.(24) Predilation with a scoring balloon resulted in significantly greater MLD at 6- to 8-month angiographic follow-up (1.95±0.55mm vs 1.77±0.68mm, p=0.03). Moreover, a recent observational study demonstrated the feasibility of using a combination of excimer laser coronary angioplasty followed by DEB inflation in patients with DES-ISR. (25) In 80 patients with a mean age of 65±10 years, of whom 38% had diabetes mellitus, the binary angiographic restenosis rate at 9-month angiographic follow-up was 9%.

When selecting a treatment strategy for ISR the specific advantages and disadvantages of DES and DEB should be carefully weighed. Currently, (repeat) implantation of a DES arguably remains the most widely used treatment strategy. Using a DEB instead of an additional stent offers the advantage of delivering antiproliferative medication to the ISR lesion with no additional deployment of metal with acceptable angiographic and clinical outcomes. The SEDUCE trial showed a reduced number of exposed stent struts at angiographic follow-up with DEB compared with DES. (8) Therefore, the duration of DAPT could potentially be shortened when using a DEB. In the DARE trial, DAPT was recommended for 12 months in both DEB and DES arms. However, the RIBS-IV and RIBS-V trials recommended 3 months of DAPT after DEB and 12 months after DES suggesting that a DAPT duration of 3 months after DEB treatment is feasible and safe. The use of an

additional DES is associated with a statistically significant, but clinically unimpressive advantage in terms of angiographic parameters. Moreover, it is unclear whether use of additional next-generation DES leads to reduced need for TVR as compared with DEB inflation. The only trial to show a significantly reduced rate of TVR at 12 months was RIBS IV. (9) In DARE, TVR rates were similar in both treatment arms, which is in line with the results from RIBS V and SEDUCE. (7,8)

Alternative treatments options for ISR include alternative DEBs (multiple clinical trials are currently investigating novel DEBs coated with paclitaxel or sirolimus), alternative next-generation DES which have shown similar performance compared to the XIENCE EES in non-inferiority trials, coronary artery bypass grafting, intracoronary brachytherapy, cutting or scoring balloon angioplasty, bioresorbable vascular scaffolds, (26) and many more. However, the most readily available techniques with the most available clinical evidence remain the DEB and the DES. The DARE trial confirms the feasibility of both treatment strategies in ISR.

The following limitations of the DARE trial should be mentioned. First, the trial was not powered to detect differences in clinical endpoints such as target vessel revascularization, myocardial infarction, death, and stent thrombosis. An adequately powered trial to investigate hard clinical outcomes would be very difficult to perform given that it took 5 years to enroll 278 patients from 8 sites in the current trial. Unfortunately, a screening log was not prospectively collected for each participating site. The fact that both BMS- and DES-ISR lesions were included may be perceived as a limitation. Nonetheless, in daily clinical practice both DES and ISR occur, indicating the DARE trial population constitutes a representative sample. Furthermore, no long-term angiographic data were obtained, therefore the results from this trial should be extrapolated with caution to longer-term follow-up.

In conclusion, in patients with in-stent restenosis, treatment with drug-eluting balloon was non-inferior compared with drug-eluting stent in terms of 6-month minimal lumen diameter. There were no differences in clinical endpoints, including target vessel revascularization up to 12 months. Therefore, use of a drug-eluting balloon is an attractive treatment option for in-stent restenosis which negates the need for additional stent implantation.

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PERSPECTIVES

WHAT IS KNOWN?

The treatment of in-stent restenosis remains challenging in contemporary clinical practice. Currently, the most widely used treatment for in-stent restenosis is (repeat) drug-eluting stent (DES) implantation. The use of a drug-eluting balloon (DEB) offers an alternative treatment option that negates the need for additional stent implantation.

WHAT IS NEW?

In this largest trial of DEB vs. DES for any ISR to date (n=278), the use of a DEB was non-inferior in terms of minimal lumen diameter at 6-month follow-up. Moreover, there were no differences in clinical events between both treatment arms, although it should be noted that DARE was not powered to detect differences in clinical events.

WHAT IS NEXT?

Future research is warranted to investigate the safety and efficacy of the DEB as compared to DES for ISR in adequately powered, large-scale randomized clinical trials.

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FIGURE LEGEND

Figure 1: Trial Flowchart

DEB= drug-eluting balloon, DES= drug-eluting stent

Figure 2: Average mean difference in 6-month minimal lumen diameter in selected subgroups.

DES= drug-eluting stent, DEB= drug-eluting balloon, ISR= In-stent restenosis, DES= drug-eluting stent, BMS= bare-metal stent, RVD= reference vessel diameter. Bar indicates point estimate for difference in minimal lumen diameter and its 95% confidence interval. All interactions were not statistically significant.

Figure 3: Kaplan Meier Estimates of Major Adverse Events at 12-month follow-up

DEB= drug-eluting balloon, DES= drug-eluting stent. Event rates at 12 months: DEB 10.9% vs. DES 9.2%, p=0.66

Table 1. Baseline Characteristics

	Drug-eluting Balloon	Drug-eluting Stent	
	n=137	n=141	*P-value*
Age (years)	66±11	65±10	0.28
Male	72% (98)	84% (118)	0.02
Time to restenosis (years)	3.8 (0.94-8.5)	3.3 (1.3-8.2)	0.81
Previous myocardial infarction	53% (72)	52% (73)	0.60
Previous coronary artery bypass grafting	14% (19)	16% (22)	0.66
Chronic renal failure*	6.6% (9)	7.1% (10)	0.85
Risk factors			
Diabetes	31% (42)	33% (46)	0.73
Insulin dependent diabetes mellitus	10% (15)	18% (25)	0.11
Hypertension	64% (87)	67% (94)	0.58
Hypercholesterolemia	59% (81)	60% (84)	0.94
Family history of coronary artery disease	51% (70)	50% (70)	0.81
Current smoker	17% (23)	13% (18)	0.34
*Clinical presentation***			0.78
Unstable angina	44% (54)	42% (58)	
Acute coronary syndrome	56% (74)	58% (74)	
Medication at baseline			
Aspirin	86% (116)	92% (130)	0.09
Clopidogrel	42% (56)	47% (66)	0.37
Prasugrel	7.5% (10)	7.9% (11)	0.90
Ticagrelor	12% (17)	11% (16)	0.59
Coumarin derivates	17% (23)	11% (16)	0.18
Statin	87% (117)	92% (129)	0.20

Values are %, mean ± Standard deviation, or median (interquartile range)
* defined as estimated glomerular filtration rate <60ml/min/m2 by MDRD (modification of diet in renal disease) formula
** data available for 260 patients

Table 2. Procedural characteristics

	Drug-eluting Balloon	Drug-eluting Stent	
	n=137	n=141	*P-value*
Target vessel			0.71
Left anterior descending coronary artery	41% (56)	39% (55)	
Circumflex coronary artery	20% (28)	24% (34)	
Right coronary artery	37% (51)	35% (49)	
Left main coronary artery	0.0% (0)	0.7% (1)	
Saphenous vein graft	0.7% (1)	1.4% (2)	
Index stent type			0.87
Bare metal stent	45% (60)	43% (60)	
Biolimus-eluting	3.6% (5)	5.7% (8)	
Everolimus-eluting	23% (31)	22% (31)	
Sirolimus-eluting	10% (14)	11% (15)	
Zotarolimus-eluting	1.5% (2)	6.4% (9)	
Paclitaxel-eluting	9.5% (13)	7.8% (11)	
Tacrolimus-eluting	0.7% (1)	0.7% (1)	
Unknown	7.3% (10)	4.3% (6)	
*Classification of in-stent restenosis**			0.42
Focal	51% (54)	53% (64)	
Diffuse intra-stent	32% (34)	34% (41)	
Proliferative	10.3% (11)	5.8% (7)	
Occlusive	5.6% (6)	6.7% (8)	
Predilation	100% (137)	85.1% (120)	<0.0001
Maximum predilation pressure (atm)	13.8±4.5	N/R	n/a
Device length(mm)	22.4±4.4	22.1±8.6	0.72
Device diameter (mm)	3.3±0.9	2.9±1.1	0.001
Device maximum inflation pressure (atm)	N/R	15.5±3.7	n/a
Postdilation	16% (22)	57% (80)	<0.0001
Maximum balloon diameter (mm)	3.2±0.5	3.3±0.5	0.36
Maximum postdilation pressure (atm)	15.5±4.4	18.8±4.3	0.002
DEB duration of inflation (sec)	61±22		n/a

values are % N) or mean ± standard deviation

* available for 227 patients

Table 3. Angiographic characteristics

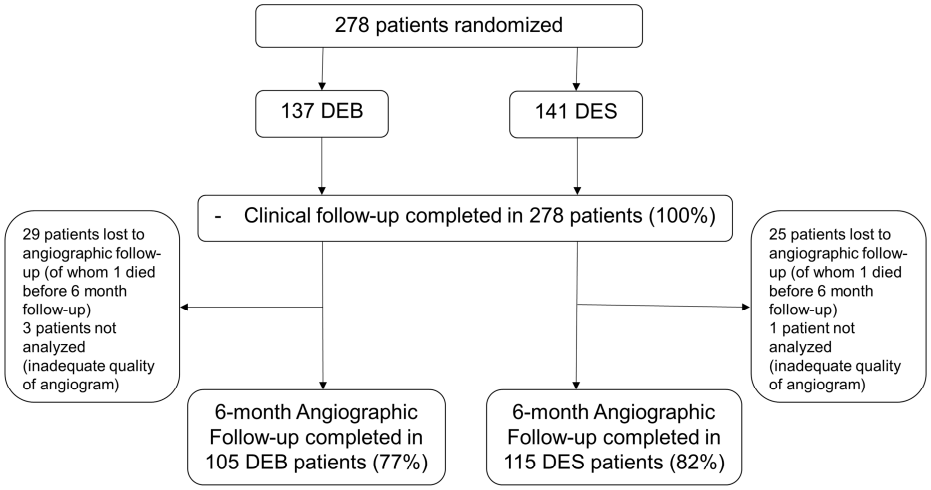
		Drug eluting balloon		Everolimus eluting stent	
					P-value
Pre-procedure (n=257)	n	125	n	132	
MLD, mm		0.77±0.33		0.79±0.35	0.73
RVD, mm		2.56±0.43		2.59±0.54	0.46
Stenosis, % of lumen diameter		69.7±11.8		69.3±12.5	0.80
Post-procedure	n	127	n	132	
In-lesion					
MLD, mm		1.86±0.38		2.2±0.41	<0.001
Stenosis, % of lumen diameter		26.8±12.0		15.6±11.7	<0.001
Acute gain, mm		1.09±0.45		1.40±0.44	<0.001
In-segment					
MLD, mm		1.72±0.35		1.84±0.46	0.018
Stenosis, % of lumen diameter		29.9±9.6		26.2±10.0	0.03
Acute gain, mm		0.97±0.42		1.06±0.48	0.12
6-Month follow-up	n	105	n	115	
In-lesion					
MLD, mm		1.79±0.55		1.98±0.66	0.02
Stenosis, % of lumen diameter		33.9±17.1		26.8±22.2	0.08
Binary Angiographic Restenosis		16.2%		19.1%	0.57
Late lumen loss		0.09±0.43		0.21±0.52	0.055
In-segment					
MLD, mm		1.71±0.51		1.74±0.61	0.65
Stenosis, % of lumen diameter		36.1±15.5		33.8±18.6	0.32
Binary Angiographic Restenosis		18.1%		20.9%	0.60
Late lumen loss		0.17±0.41		0.45±0.47	<0.001

MLD= minimal lumen diameter, RVD= reference vessel diameter

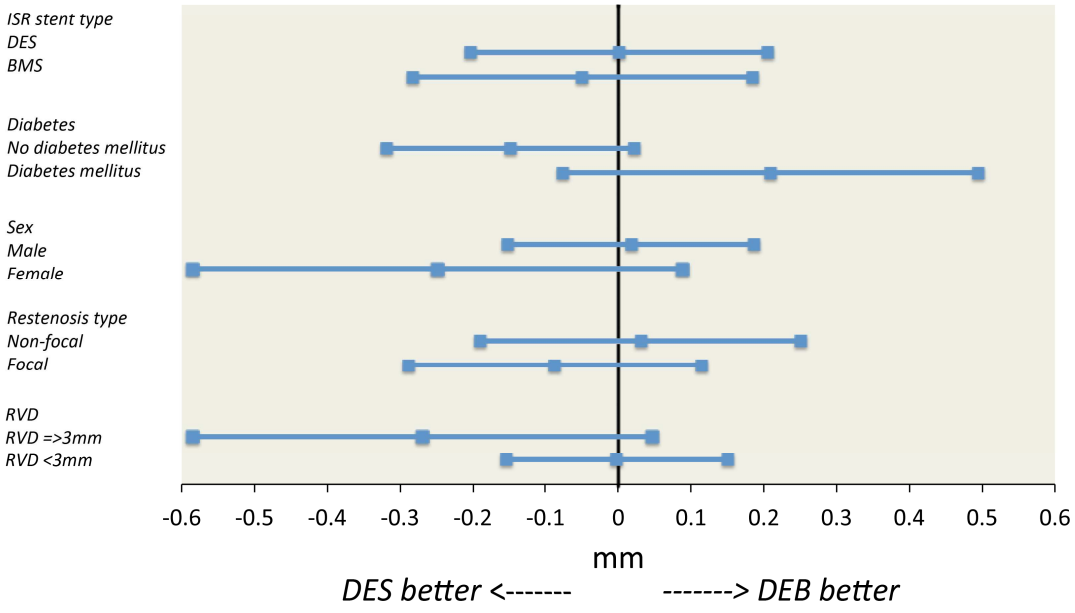
Table 4: Kaplan-Meier estimates of major adverse clinical events at 12-month follow-up

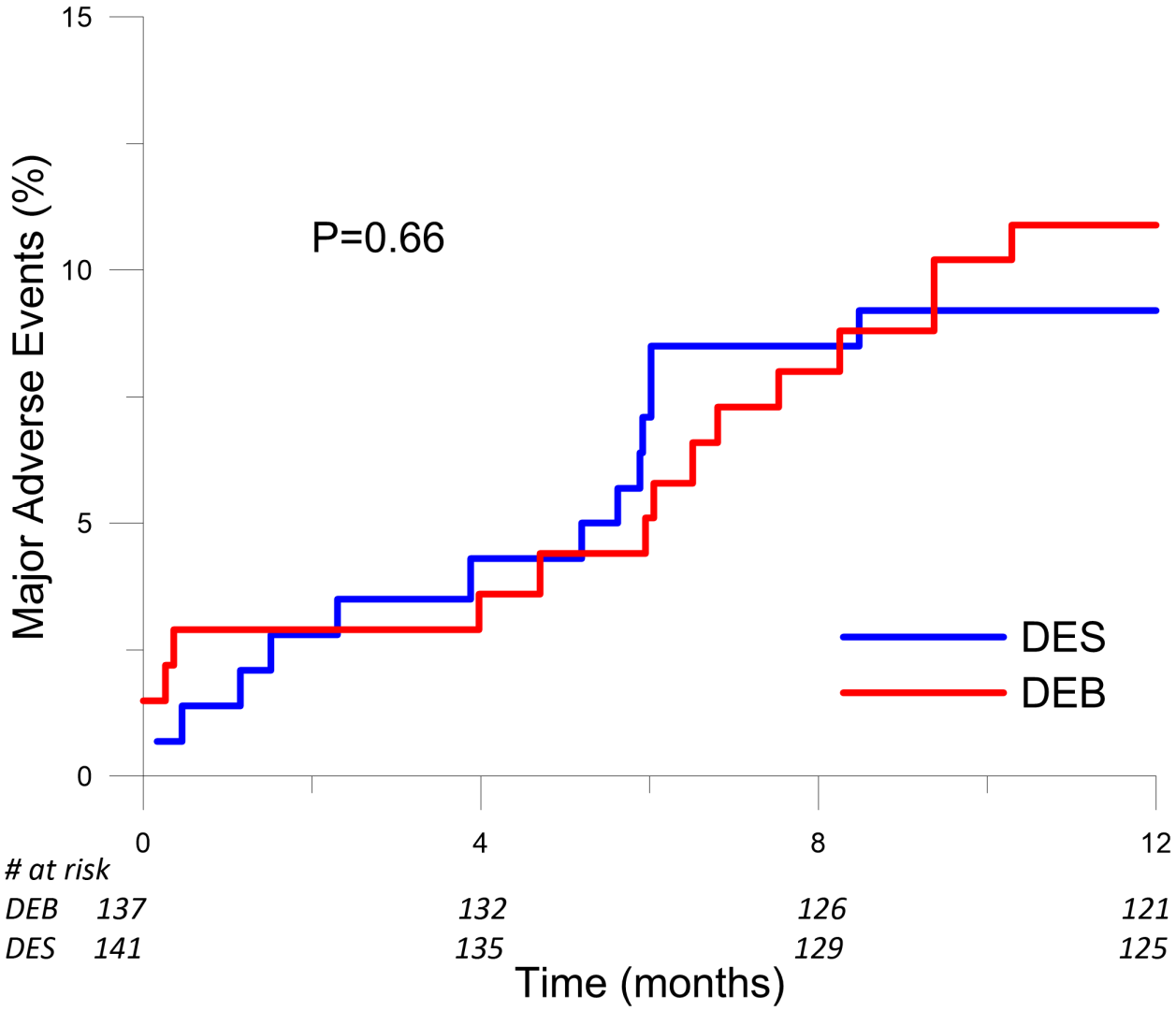
	Drug-eluting balloon	Drug-eluting stent	*p-value*
	n=137	n=141	
Death	0.7% (1)	1.4% (2)	0.58
Cardiac death	0	0.7% (1)	0.32
Myocardial infarction	2.2% (3)	2.8% (4)	0.74
Target vessel related myocardial infarction	1.4% (2)	0.7% (1)	0.54
Stent thrombosis	0	0	n/a
Stroke	0.7% (1)	1.4% (2)	0.58
Target vessel revascularization	8.8% (12)	7.1% (10)	0.65
TVR percutaneous coronary intervention	8.8% (12)	5.7% (8)	0.36
TVR coronary artery bypass graft surgery	0	1.4%(2)	0.16
Coronary artery bypass graft surgery all	0.7% (1)	4.3% (6)	0.06
Percutaneous coronary intervention all	13.9% (19)	11.3% (16)	0.58
Composite major adverse events*	10.9% (15)	9.2% (13)	0.66

***** defined as death, target vessel related myocardial infarction, and target vessel revascularization
Data presented as % (n), TVR= target vessel revascularization



Point estimate and 95% confidence interval of difference between DES and DEB groups in minimal lumen diameter at 6-month angiographic follow-up for selected subgroups




15
10
5
0
Major Adverse Events (%)
P=0.66
DES
DEB
0
4
8
12
at risk
DEB 137 132 126 121
DES 141 135 129 125
Time (months)