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A Randomized Comparison of Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent for the Treatment of Any In-Stent Restenosis

The DARE Trial

Jan Baan, Jr, MD, PhD,[a] Bimmer E. Claessen, MD, PhD,[a] Kirsten Boerlage-van Dijk, MD, PhD,[b] Jeroen Vendrik, MD,[a] René J. van der Schaaf, MD, PhD,[b] Martijn Meuwissen, MD, PhD,[c] Niels van Royen, MD, PhD,[d] A.T. Marcel Gosselink, MD, PhD,[e] Marleen H. van Wely, MD,[f] Atilla Dirkali, MD,[g] E. Karin Arkenbout, MD, PhD,[h] Robbert J. de Winter, MD, PhD,[a] Karel T. Koch, MD, PhD,[a] Krischan D. Sjauw, MD, PhD,[a] Marcel A. Beijk, MD, PhD,[a] M. Marije Vis, MD, PhD,[a] Joanna J. Wykrzykowska, MD, PhD,[a] Jan J. Piek, MD, PhD,[a] Jan G.P. Tijssen, PhD,[a] José P.S. Henriques, MD, PhD[a]

ABSTRACT

OBJECTIVES The authors sought 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) in-stent restenosis (ISR).

BACKGROUND The treatment of ISR remains challenging in contemporary clinical practice.

METHODS In a multicenter randomized noninferiority trial, patients with any ISR were randomly allocated in a 1:1 fashion to treatment with a DEB (SeQuent Please paclitaxel-eluting balloon, B. Braun Melsungen, Melsungen, Germany), or a DES (XIENCE everolimus-eluting stent, Abbott Vascular, Santa Clara, California). The primary endpoint was noninferiority 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 $26 \pm 10\%$ vs. $30 \pm 10\%$; $p = 0.03$). 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 noninferior to DES (DEB 1.71 ± 0.51 mm vs. DES 1.74 ± 0.61 mm; p for 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 noninferior 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. (J Am Coll Cardiol Intv 2018;11:275–83) © 2018 by the American College of Cardiology Foundation.

From the [a]Division of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [b]Division of Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; [c]Division of Cardiology, Amphia Ziekenhuis, Breda, the Netherlands; [d]Division of Cardiology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; [e]Division of Cardiology, Isala Klinieken, Zwolle, the Netherlands; [f]Division of Cardiology, Radboud University, Nijmegen, the Netherlands; [g]Division of Cardiology, Albert Schweitzer Ziekenhuis, Dordrecht, the Netherlands; and the [h]Division of Cardiology, Tergooi Ziekenhuis, Blaricum, the Netherlands. The DARE study was financially supported through a research grant provided by B. Braun Melsungen. The grant givers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Dr. Baan has received an unrestricted research grant from B. Braun Melsungen and Abbott Vascular. Dr. Piek is a member of the medical advisory board for Abbott Vascular; and a consultant for Philips/Volcano. Dr. Henriques has received an unrestricted research grant from B. Braun Melsungen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

DAPT = dual antiplatelet therapy

DEB = drug-eluting balloon(s)

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

ISR = in-stent restenosis

MLD = minimal lumen diameter

PCI = percutaneous coronary intervention

The aim of percutaneous coronary intervention (PCI) is to restore optimal blood flow in narrowed coronary arteries. Ever since the introduction of this nonsurgical 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, and so on) or paclitaxel (4). However, depending on patient and lesion characteristics, in-stent restenosis (ISR) still occurs in 3% to 20% of patients, even with the use of DES (5). Currently, implantation of new-generation DES is standard clinical practice. However, bare-metal stents (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, BMS, DES, and more recently, drug-eluting balloon (DEB) angioplasty (6). DEB 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).

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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, Melsungen, Germany) compared with the everolimus-eluting stent (EES) (XIENCE, Abbott Vascular, Santa Clara, California) in the treatment of any ISR.

METHODS

STUDY DESIGN. The DARE (Drug-Eluting Balloon for In-Stent Restenosis) trial was an investigator-initiated, prospective multicenter randomized 2-arm trial with blinded evaluation of endpoints. The study was conducted in accordance with the declaration of Helsinki and was registered on January 29, 2010 (Netherlands Trials Register 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. 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 trial protocol is available in the Online Appendix.

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 <5 mm 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 >4.0 mm 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-segment elevation myocardial infarction, and restenosis in a bioresorbable scaffold.

Written informed consent was obtained before the procedure. After successful pre-dilation of the ISR lesion, patients were randomly assigned in a 1:1 ratio to treatment with either a DEB (SeQuent Please paclitaxel-eluting balloon) or an EES (XIENCE prime or XIENCE expedition). 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 $P2Y_{12}$ 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 intraprocedural 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 was inflated at a pressure of 6 to 8 atm for the duration of

minimally 30 s, but optimally 60 s. In case of very long lesions, the use of 2 or more subsequent DEB was allowed, using a small overlap. For patients randomized to the EES arm, a stent size was chosen that can be deployed to the diameter as the last-used predilation balloon. The stent length was chosen so that the initial stent length plus 2 to 3 mm 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, received 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° difference using 6-F or larger catheters at 25 frames per second using an image intensifier setting of 5 inch (13 cm) or 7 inch (18 cm). 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. Intracoronary nitroglycerine was administered before acquisition of the angiogram.

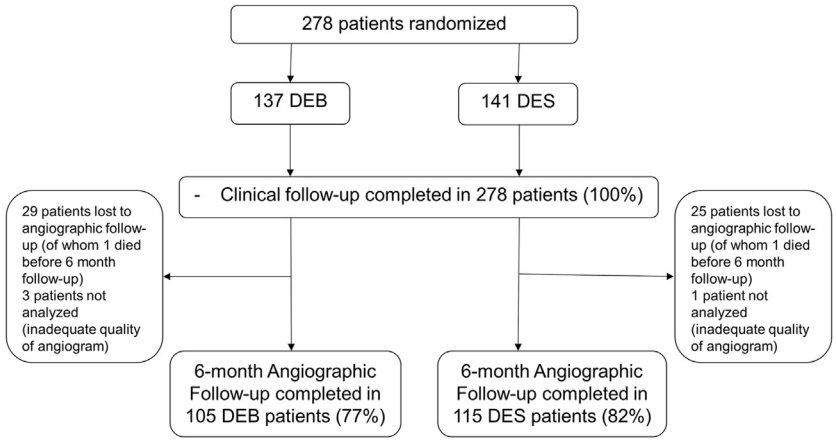
Angiographic follow-up was scheduled within 6 months (±1 month) after the index procedure, using the same projections and guidelines as during baseline coronary angiography. If the target lesion has been treated within 6 months from baseline PCI, no study follow-up coronary angiography was performed. In that case, the pre-procedural angiogram was used for endpoint assessment.

All study follow-up coronary angiograms were analyzed 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 6-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 5 mm outside of the new EES (in patients in the EES arm). Secondary angiographic endpoints included in-stent and in-segment angiographic binary restenosis at 6 months (defined as the presence of a stenosis of ≥50% at angiographic follow-up), In-stent and in-segment percent diameter stenosis at 6 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 untreated vessel), target vessel revascularization (either by PCI or coronary artery bypass grafting), stent thrombosis (definite or probable according to Academic Research Consortium criteria) (12), and cardiac death (all deaths were considered cardiac unless an unequivocal noncardiac 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 pathological Q waves on the electrocardiogram (ECG) or ECG changes indicative of ischemia; 2) pathological findings of an acute myocardial infarction; and 3) development of new pathological 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 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 noninferiority comparison of the DEB compared with the EES for the primary endpoint of MLD at 6-month angiographic follow-up. To satisfy the noninferiority hypothesis, the upper limit of the 1-sided 95% confidence limit for the difference in MLD between DEB and EES had to exceed a pre-specified margin of −0.4 mm, which reflects preservation of approximately 50% of the gain for DES relative to conventional BMS. This is equivalent to noninferiority testing at a 5% 1-sided α level. The MLD at 6-month follow-up was expected to be 2.1 mm in DEB-treated and in DES-treated patients with a SD of 0.6 mm. With 112 analyzable patients per treatment group, the study has 80% power to reject the null hypothesis of inferiority of DEB

FIGURE 1 Trial Flowchart



DEB = drug-eluting balloon; DES = drug-eluting stent(s).

to DES. To account for an attrition rate of 20%, we aimed to randomize 270 patients.

The mean ± SD for continuous variables was calculated in each group and compared using the Student *t* test or Mann-Whitney *U* test. Binary variables are reported as counts and percentages, and the chi-square or Fisher exact tests were used where appropriate to assess differences between the 2 groups. The two one-sided test was used to test noninferiority. 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, New York) and XLstat version 19.4 (Addinsoft, New York, New York) 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 [IQR]: 1.1 to 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**. Pre-dilation was used in 100% of patients in the DEB arm. Post-dilation 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 mm vs 1.72 ± 0.35 mm; $p = 0.007$) 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 of the difference in MLD between DEB and DES was −0.03 mm and 95% lower confidence limit −0.16 mm, respectively, indicating noninferiority (p for noninferiority <0.0001). In-segment MLD in both groups was not significantly different (DEB 1.71 ± 0.51 mm vs. DES 1.74 ± 0.61 mm; $p = 0.65$). There were no interactions in terms of the primary endpoint with selected subgroups (**Figure 2**). Additional analyses are provided in the Online Appendix.

TABLE 1 Baseline Characteristics

	Drug-Eluting Balloon (n = 137)	Drug-Eluting Stent (n = 141)	p Value
Age, yrs	66 ± 11	65 ± 10	0.28
Male	72 (98)	84 (118)	0.02
Time to restenosis, yrs	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 ± SD, % (n), or median (interquartile range). *Defined as estimated glomerular filtration rate <60 ml/min/m^2 by MDRD (Modification of Diet in Renal Disease) formula. †Data available for 260 patients.

TABLE 2 Procedural Characteristics

	Drug-Eluting Balloon (n = 137)	Drug-Eluting Stent (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	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 intrastent	32 (34)	34 (41)	
Proliferative	10.3 (11)	5.8% (7)	
Occlusive	5.6 (6)	6.7 (8)	
Pre-dilation	100 (137)	85.1 (120)	<0.0001
Maximum pre-dilation 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
Post-dilation	16 (22)	57% (80)	<0.0001
Maximum balloon diameter, mm	3.2 ± 0.5	3.3 ± 0.5	0.36
Maximum post-dilation pressure, atm	15.5 ± 4.4	18.8 ± 4.3	0.002
DEB duration of inflation, s	61 ± 22		n/a

Values are % (n) or mean ± SD. *Available for 227 patients.
DEB = drug-eluting balloon; N/R = not reported.

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 versus 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 noninferiority 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 versus 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 4 randomized clinical trials comparing a DEB with a current-generation DES have been published (7–9,20). 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 (21–23). 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. (20) 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 ± 0.6 mm vs. 2.01 ± 0.6 mm; p < 0.001) (9). The need for TVR was

TABLE 3 Angiographic Characteristics

	Drug-Eluting Balloon	Everolimus-Eluting Stent	p Value
Pre-procedure (N = 257)	125	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	127	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	105	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

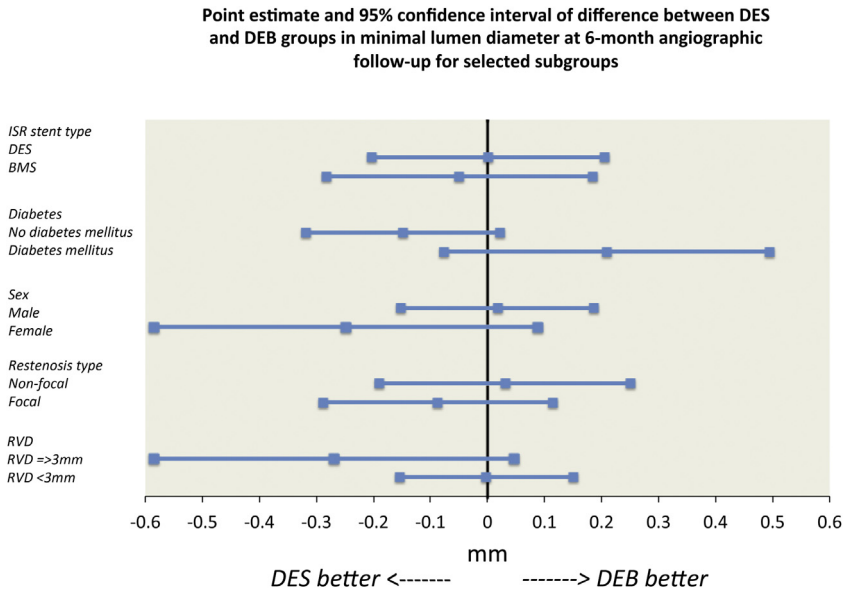
Values are n or mean ± SD.
MLD = minimal lumen diameter; RVD = reference vessel diameter.

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. (20) showed superior angiographic outcomes with the DEB compared with the EES (12-month late lumen loss 0.02 vs. 0.19 mm; p = 0.0004). In the SEDUCE trial, 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 the RIBS V trial, MLD at 9 months was significantly greater in the EES arm (2.13 mm vs. 2.54 mm; p = 0.006). The RIBS IV trial (N = 309) enrolled only patients with DES ISR, and showed superiority of the EES versus the DEB in terms of both angiographic endpoints (MLD at angiographic follow-up 2.03 ± 0.7 mm vs. 1.80 ± 0.6 mm; 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, for example, 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 pre-dilation versus scoring balloon pre-dilation followed by DEB therapy (24), Pre-dilation with a scoring balloon resulted in significantly greater MLD at 6- to 8-month angiographic follow-up (1.95 ± 0.55 mm vs. 1.77 ± 0.68 mm; 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 the DARE trial, TVR rates were similar in both treatment arms, which is in line with the results from the RIBS V (7) and SEDUCE (8) trials and the study by Pleva et al. (20)

FIGURE 2 Average Mean Difference in 6-Month MLD in Selected Subgroups



Bar indicates point estimate for difference in minimal lumen diameter and its 95% confidence interval. None of the interactions were statistically significant. BMS = bare-metal stent(s); ISR = in-stent restenosis; MLD = minimal lumen diameter; RVD = reference vessel diameter; other abbreviations as in Figure 1.

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 with the XIENCE EES in noninferiority 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.

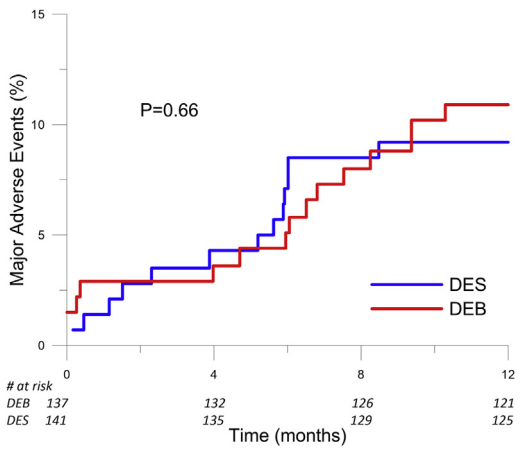
TABLE 4 Kaplan-Meier Estimates of Major Adverse Clinical Events at 12-Month Follow-Up

	Drug-Eluting Balloon (n = 137)	Drug-Eluting Stent (n = 141)	p Value
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

Values are % (n). *Defined as death, target vessel-related myocardial infarction, and target vessel revascularization.
TVR = target vessel revascularization.

STUDY LIMITATIONS. 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.

FIGURE 3 Kaplan Meier Estimates of Major Adverse Events at 12-Month Follow-Up



Event rates at 12 months: DEB 10.9% versus DES 9.2%; p = 0.66. Abbreviations as in Figure 1.

CONCLUSIONS

In patients with in-stent restenosis, treatment with DEB was noninferior compared with DES 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 DEB is an attractive treatment option for ISR, which negates the need for additional stent implantation.

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ADDRESS FOR CORRESPONDENCE: Dr. Jan Baan Jr., Department of Cardiology, B2-115, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: j.baan@amc.uva.nl.

PERSPECTIVES

WHAT IS KNOWN? The treatment of ISR remains challenging in contemporary clinical practice. Currently, the most widely used treatment for ISR is (repeat) DES implantation. The use of a DEB offers an alternative treatment option that negates the need for additional stent implantation.

WHAT IS NEW? In this largest trial of DEB versus DES for any ISR to date (N = 278), the use of a DEB was noninferior 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 the DARE study 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 with DES for ISR in adequately powered, large-scale randomized clinical trials.

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

APPENDIX For an expanded Methods section, list of participating centers and study personnel, and a supplemental figure and tables, please see the online version of this paper.