A randomized comparison of paclitaxel-eluting balloon* versus everolimus-eluting stent for the treatment of any in-stent restenosis

*The DARE trial (**D**rug-eluting b**A**lloon for in-stent **Re**stenosis)*

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***DEB Not approved in US**

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• B.Braun, Abbott Vascular
• Consulting Fees/Honoraria	• Company Names
• Major Stock Shareholder/Equity	• Company Names
• Royalty Income	• Company Names
• Ownership/Founder	• Company Names
• Intellectual Property Rights	• Company Names
• Other Financial Benefit	• Company Names

Background

- In-stent restenosis (ISR) still a major challenge
- DES & BMS ISR is mostly treated by (repeat) DES

- Drug-eluting balloon (DEB*) is an alternative treatment
- DEB negates the need for additional stent implantation

- No trials of DEB vs DES for any ISR (BMS and DES)

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DARE trial design

- Multicenter randomized non-inferiority trial
- Patients with any ISR (DES or BMS)
- 1:1 randomization to SeQuent Please paclitaxel-eluting balloon* or Xience everolimus-eluting stent
- Primary endpoint: 6-month in-segment MLD

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Inclusion criteria

- Any restenosis of stented vessels or surgical grafts
- DES or BMS ISR
- >50% in-stent and <5mm out of the stent
- Reference diameter of ≥ 2.0 to 4.0 millimeters
- Amendable to PCI treatment with either DEB or DES
- Amendable to 1 year dual antiplatelet therapy.

Exclusion criteria

- Restenosis in a biodegradable or non-CE marked stent
- GFR <30mL/min, exception when on dialysis.
- STEMI
- Expected need PCI in the same vessel < 6 months.

Statistical Plan

Power calculation assumptions

- 6-month in-segment MLD mean 2.1mm
- Standard deviation 0.6mm
- Non-inferiority margin of 0.4mm

- to reject the null hypothesis of inferiority with 80% power.
- 112 analyzable patients per group
- Attrition rate of 20%
- ***2x 135 patients (=270 total)***

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Trial organisation

Steering Committee
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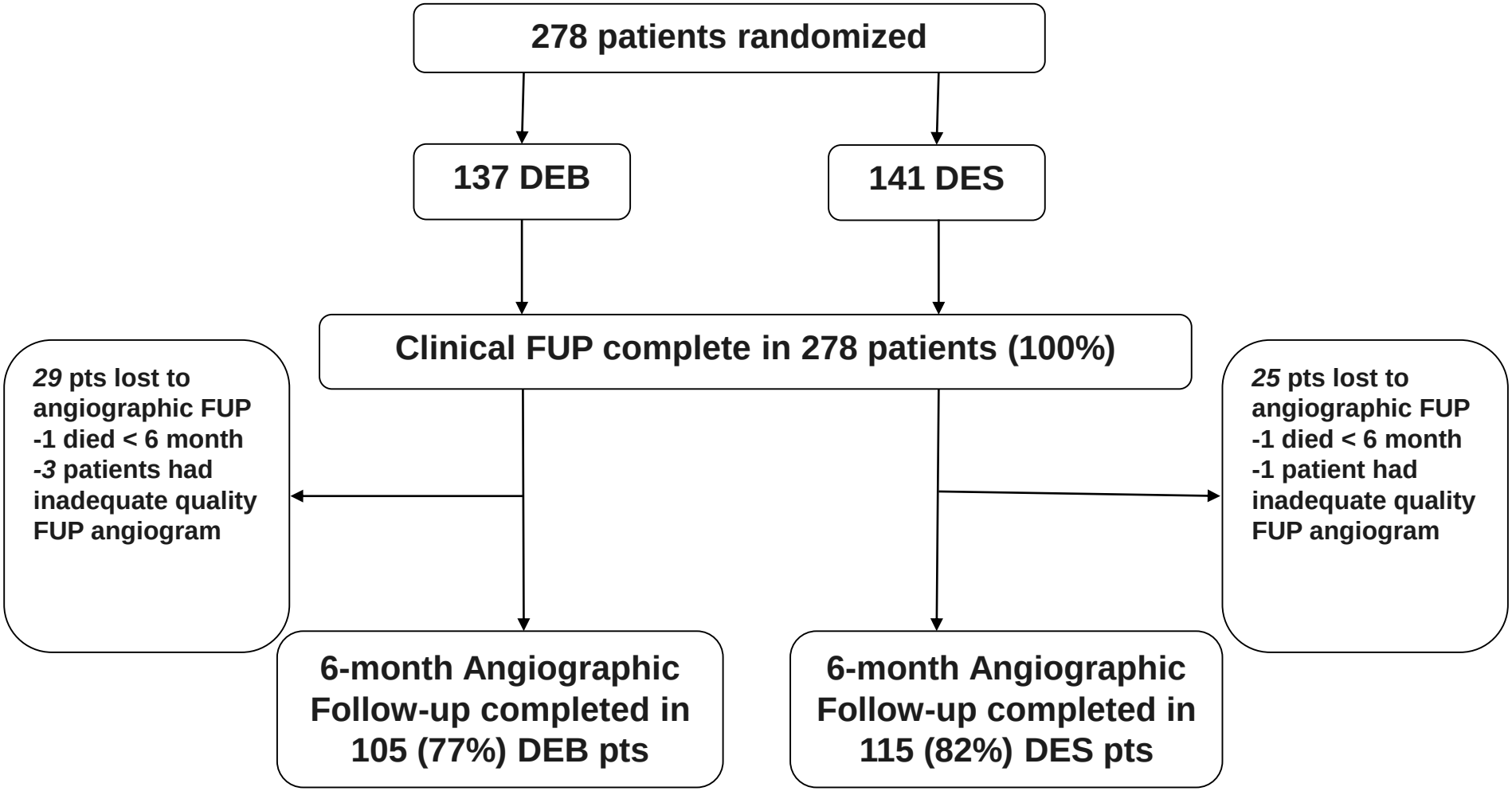
Data collection and analysis
Esther Scheunhage, Kirsten Boerlage-van Dijk, Ze-Yie Yong, Esther Wiegerinck, Gilbert Wijntjens, Bimmer Claessen, Jeroen Vendrik

Participating sites

Center	Principal Investigator	No of pts enrolled
Academic Medical Center, University of Amsterdam, the Netherlands	José P.S. Henriques & Jan Baan jr	90
Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands	René J. van der Schaaf	63
Albert Schweitzer Hospital, Dordrecht, the Netherlands	Atilla Dirkali	53
Tergooi Ziekenhuis Blaricum, the Netherlands	E. Karin Arkenbout	17
Radboud University, Nijmegen, The Netherlands	Marleen van Wely	17
Amphia Ziekenhuis, Breda, the Netherlands	Martijn Meuwissen	16
Isala Klinieken, Zwolle, the Netherlands	Marcel Gosselink	13
Vrije Universiteit Medical Center, Amsterdam, the Netherlands	Niels J. van Royen	9

Study Flow Chart



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Baseline Characteristics

	Drug-eluting Balloon	Drug-eluting Stent	P-value
	n=137	n=141	
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
Risk factors			
Diabetes	31% (42)	33% (46)	0.73
Hypertension	64% (87)	67% (94)	0.58
Hypercholesterolemia	59% (81)	60% (84)	0.94
Current smoker	17% (23)	13% (18)	0.34
Clinical presentation			0.78
Stable angina	44% (54)	42% (58)	
Acute coronary syndrome	56% (74)	58% (74)	

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Baseline Characteristics

	Drug-eluting Balloon	Drug-eluting Stent	P-value
	n=137	n=141	
Target vessel			0.71
Left anterior descending 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
BMS	45% (60)	43% (60)	
DES	49% (67)	53% (75)	
Unknown	7.3% (10)	4.3% (6)	
Focal in-stent restenosis	51% (54)	53% (64)	0.42

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Procedural Characteristics

	Drug-eluting Balloon	Drug-eluting Stent	P-value
MLD, mm	0.77±0.33	0.79±0.35	0.73
RVD, mm	2.56±0.43	2.59±0.54	0.46
Predilation	100% (137)	85.1% (120)	<0.0001
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
Postdilation	16% (22)	57% (80)	<0.001
Max. postdil balloon diameter (mm)	3.2±0.5	3.3±0.5	0.36
DEB duration of inflation (sec)	61±22	n/a	n/a

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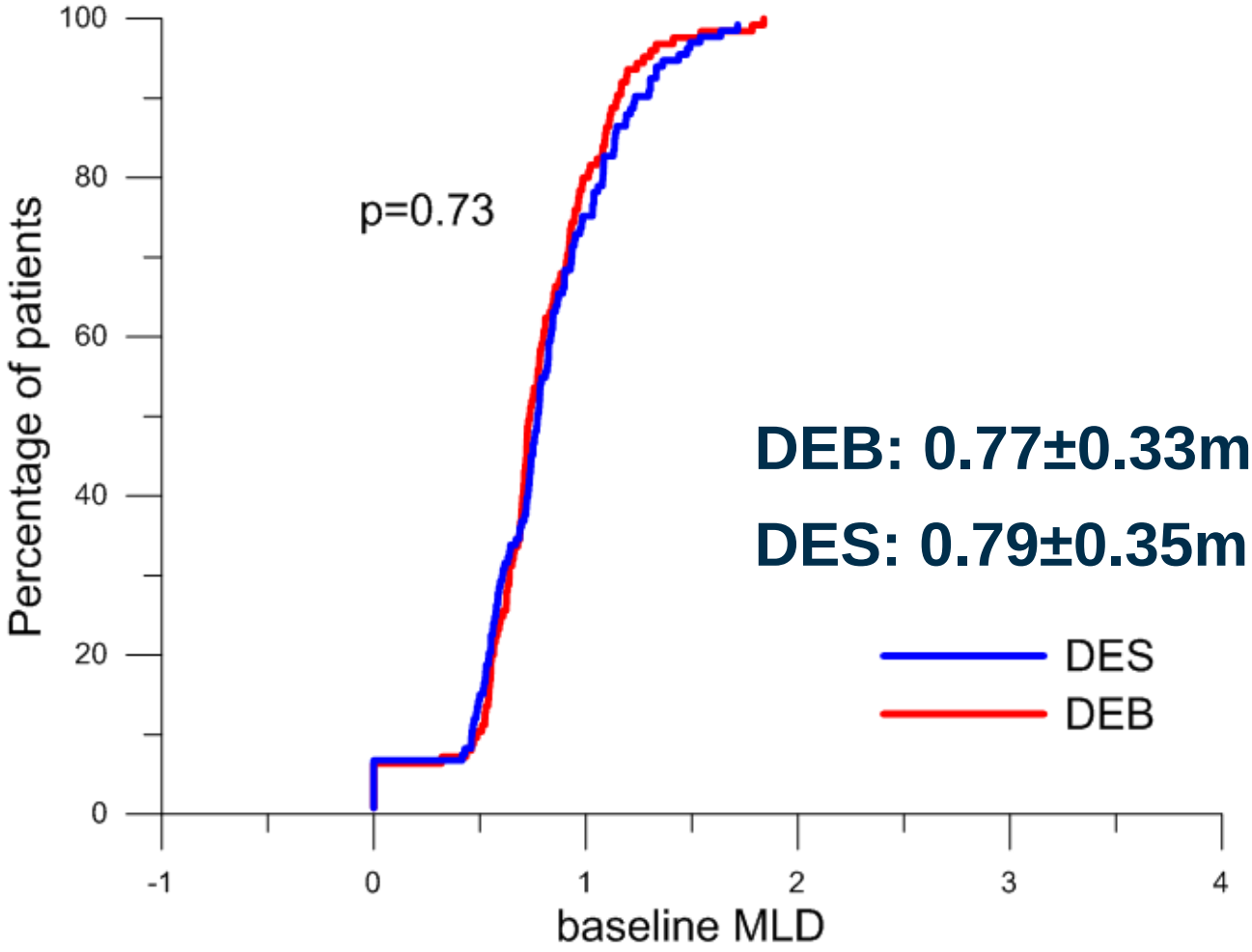
Baseline MLD



DEB: 0.77±0.33mm vs.

DES: 0.79±0.35mm, p=0.73

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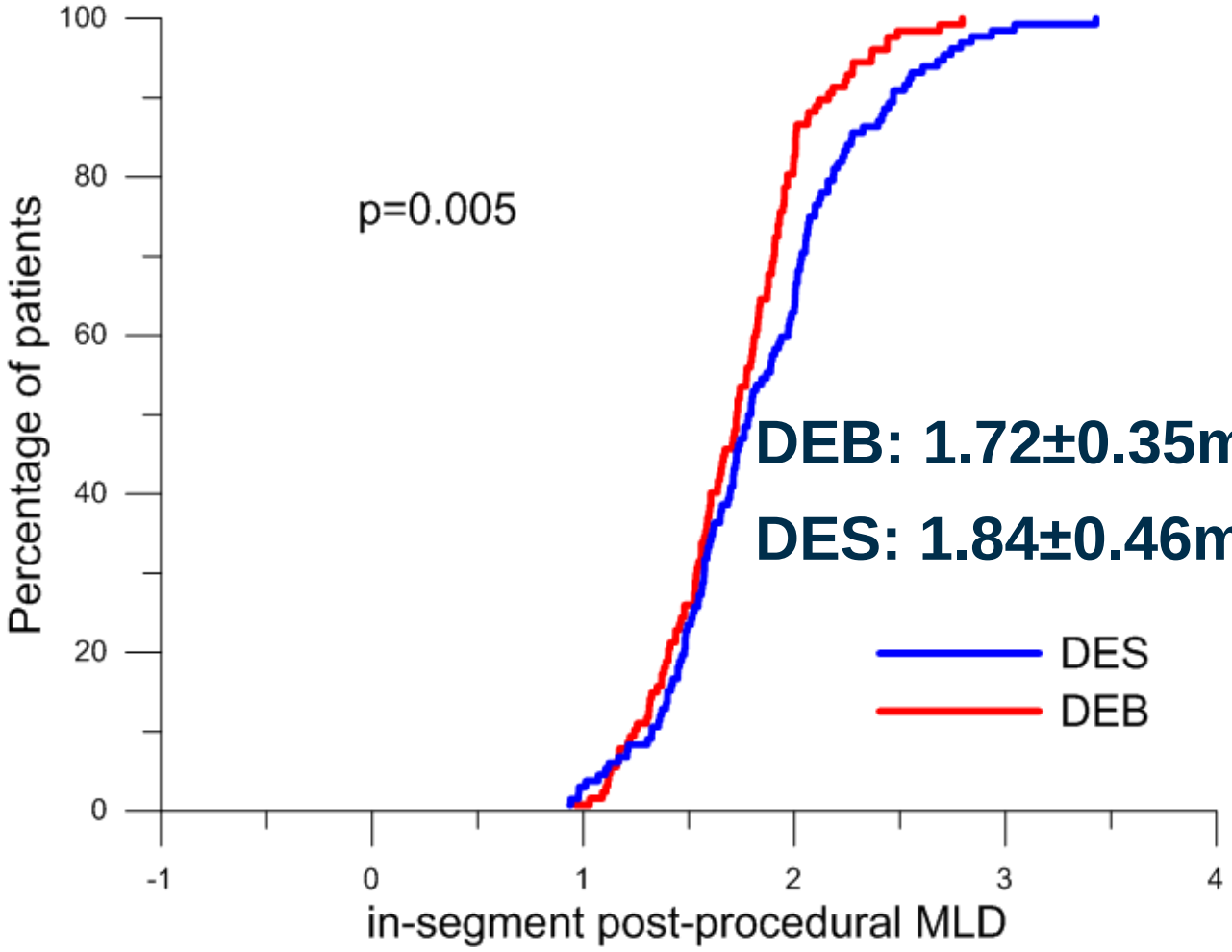
Post-procedural MLD



DEB: 1.72±0.35mm vs.

DES: 1.84±0.46mm, p=0.005

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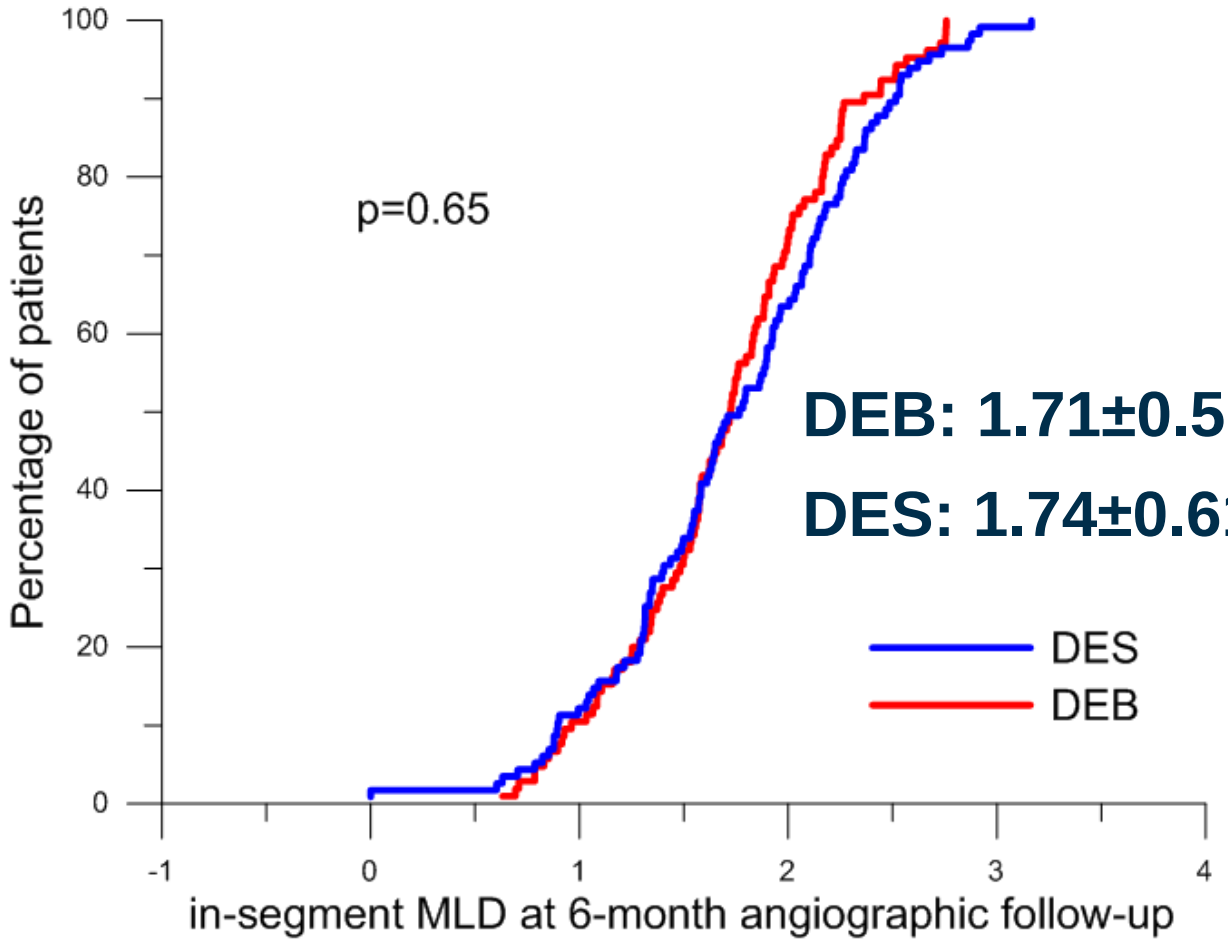
In-segment MLD @ 6 months



DEB: 1.71±0.51mm vs.

DES: 1.74±0.61mm, p=0.65

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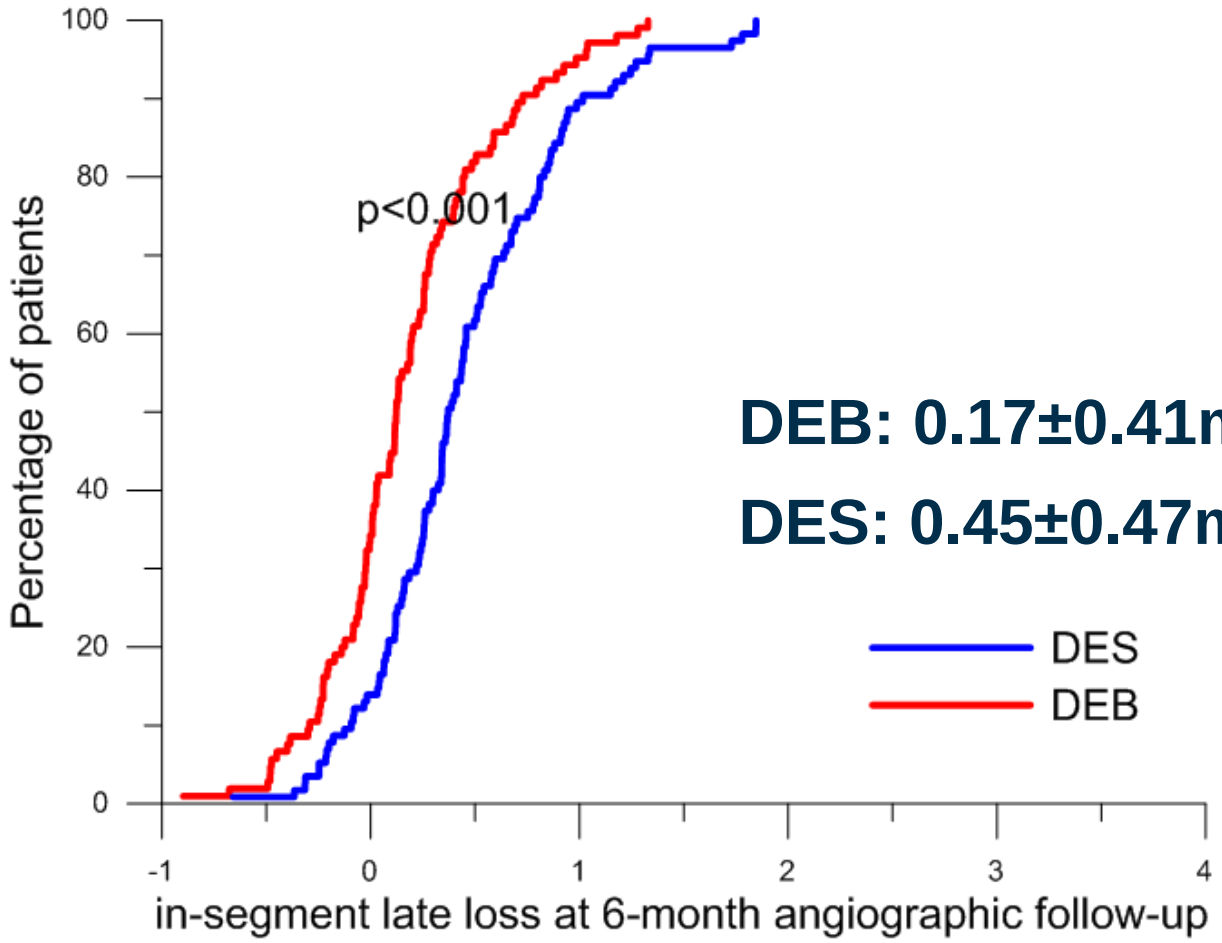
Late loss @ 6 months



DEB: 0.17±0.41mm vs.

DES: 0.45±0.47mm, p<0.001

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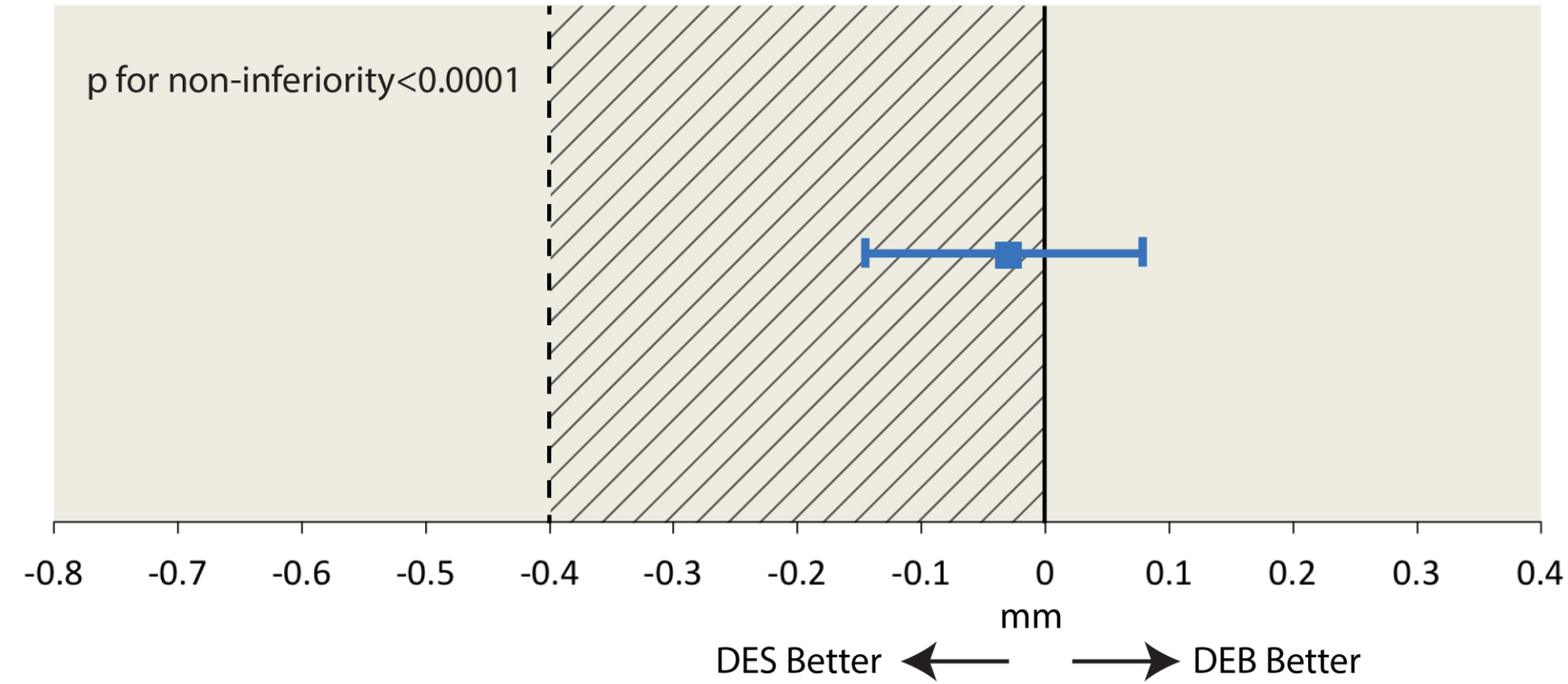
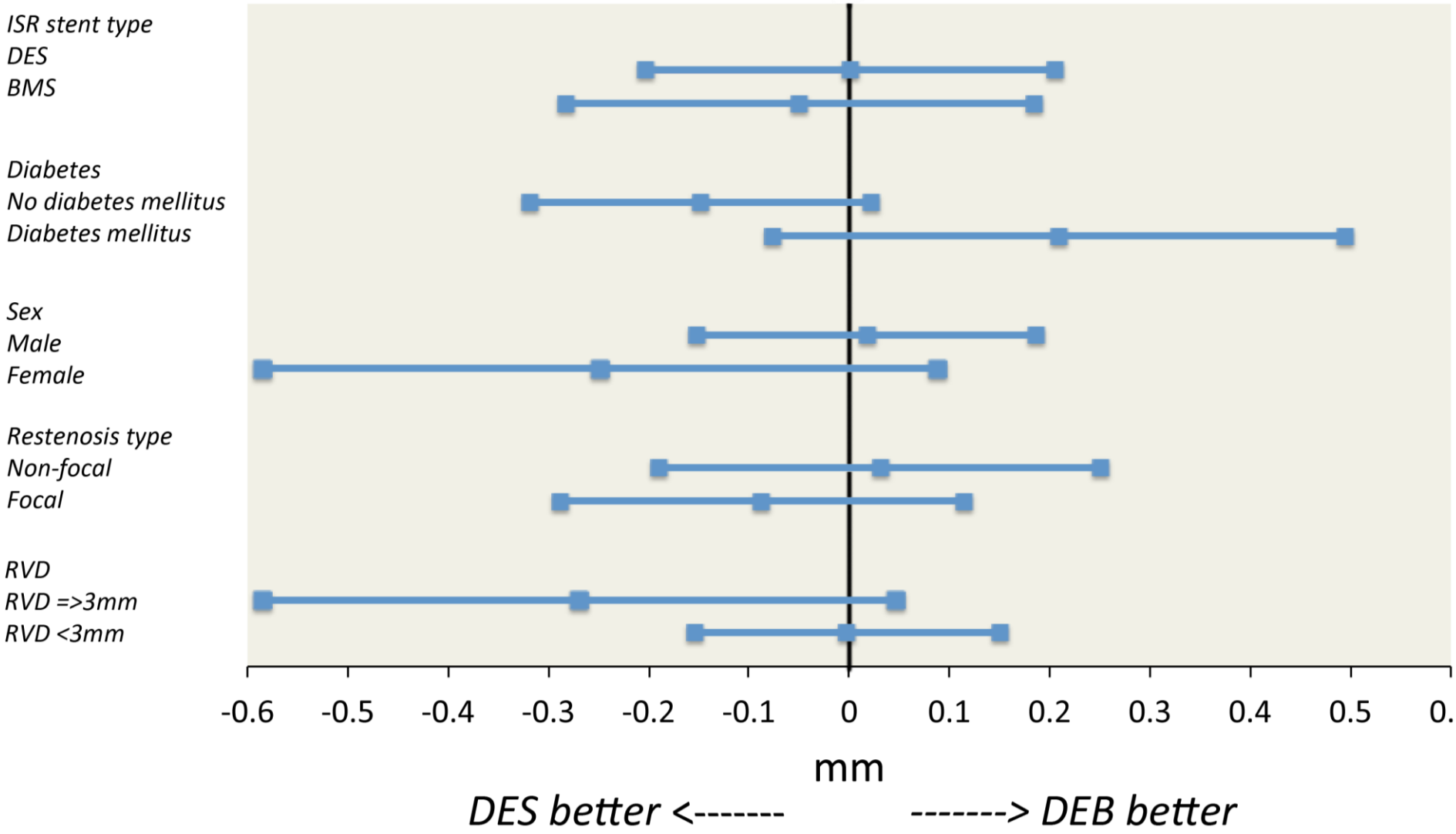
Primary Endpoint

point estimate and 90% confidence interval of difference between DEB and DES groups in minimal lumen diameter at 6-month angiographic follow-up



The point estimate of the difference in MLD between DEB and DES was -0.03mm and the 95% lower confidence limit (LCL) LCL -0.16mm, indicating noninferiority (p<0.0001)

Mean difference in 6-month MLD major subgroups



Clinical Endpoints

	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 MI	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 PCI	8.8% (12)	5.7% (8)	0.36
TVR CABG	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

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Limitations

- Long inclusion period (5 years)
- Procedural differences between groups
- No ISR lesion preparation (scoring balloons?)
- Not powered for clinical endpoints

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Conclusion Dare Trial

- **Non-inferiority of Sequent Please DEB vs Xience DES for any ISR (in-segment MLD @ 6-months FUP)**
- **Greater acute gain with DES vs. DEB, offset by greater DES late loss at 6-month follow-up**
- **Therefore, the DEB appears to be an alternative therapy for any ISR negating the need for additional stent**
- **No differences in clinical endpoints, including TVR**
- **Confirming European guidelines class 1A DEB for ISR**

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