Ultrathin Sirolimus-Eluting Bioresorbable Polymer DES as a Standard of Care and Comparison

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Disclosure

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
Institutional Grant/Research Support	Biotronik, Boston Scientific, Medtronic CardioVascular, Medinol, Orbus Neich
Consulting Fees/Honoraria	Biotronik, Boston Scientific Corporation, Medtronic CardioVascular, Cardinal Health
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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Drug Eluting Stent Innovation

Perspective

- Persistence of adverse events with both first generation and contemporary permanent polymer-based DES presents an opportunity for iterative improvement
- Advancements include thinner struts, stent design modifications, improvement in polymer biocompatibility and most recently the development of bioresorbable polymers
  - BP control drug release while allowing simultaneous (or subsequent) dissolution of the polymer material, eliminating the stimulus for chronic inflammation and hypothetically restoring the stent phenotype to an inert bare metal stent
- Although previous comparative studies have reported statistical non-inferiority between bioresorbable and permanent polymer DES, no study to date has demonstrated a statistically meaningful difference in clinical outcomes

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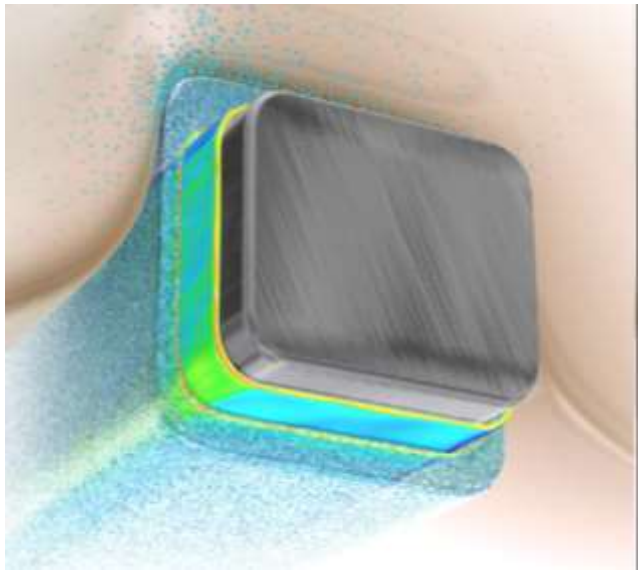
Orsiro Ultrathin Strut (BP SES) Stent System

Stent material	L-605 Cobalt-Chromium
Strut thickness	60 µm*
Polymer material	Poly-L-lactic acid (PLLA)
Polymer type	Bioresorbable, asymmetric circumferential thickness; scission begins immediately with 24 month complete degradation
Passive coating	Amorphous silicon carbide
Antiproliferative drug	Sirolimus (1.4 µg/mm^2), >80% eluted in first 90 days



*For 2.25mm to 3.0mm diameter stents, 80 µm for >3.0 mm diameter stents

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Randomised Clinical Trials Involving Orsiro BP SES

	BIOFLOW II	BIOFLOW IV	BIOSCIENCE	BIO-RESORT
Location	Europe	Europe, Japan	Switzerland	Netherlands
Design	Randomised 2:1 vs. Xience Prime	Randomised 2:1 vs. Xience Prime/Xpedition	Randomised (1:1 vs Xience Prime)	Randomised (1:1:1, Orsiro, Synergy, Resolute Integrity)
Primary Endpoint	LLL @ 9 Months	TVF @ 12 Months	TLF @ 12 Months	TVF @ 12 Months
Enrollment	452 (298 Orsiro, 154 Xience)	579 (387 Orsiro, 192 Xience)	2,119 (1,063 Orsiro, 1,056 Xience)	3,514 (1,172 Synergy, 1,169 Orsiro, 1,173 Resolute Integrity)
Inclusion	1 to 2 de novo lesions Separate arteries	1 to 2 de novo lesions Separate arteries	All-comers	All-comers
Follow-up	1, 6, 12 months and 2 to 5 year clinical 9 month clinical and angiographic (60 IVUS patients)	1, 6, 12 months and 2 to 5 year clinical	1, 6, 12 months and 2 to 5 year clinical	1 and 12 month and 2 to 5 year clinical

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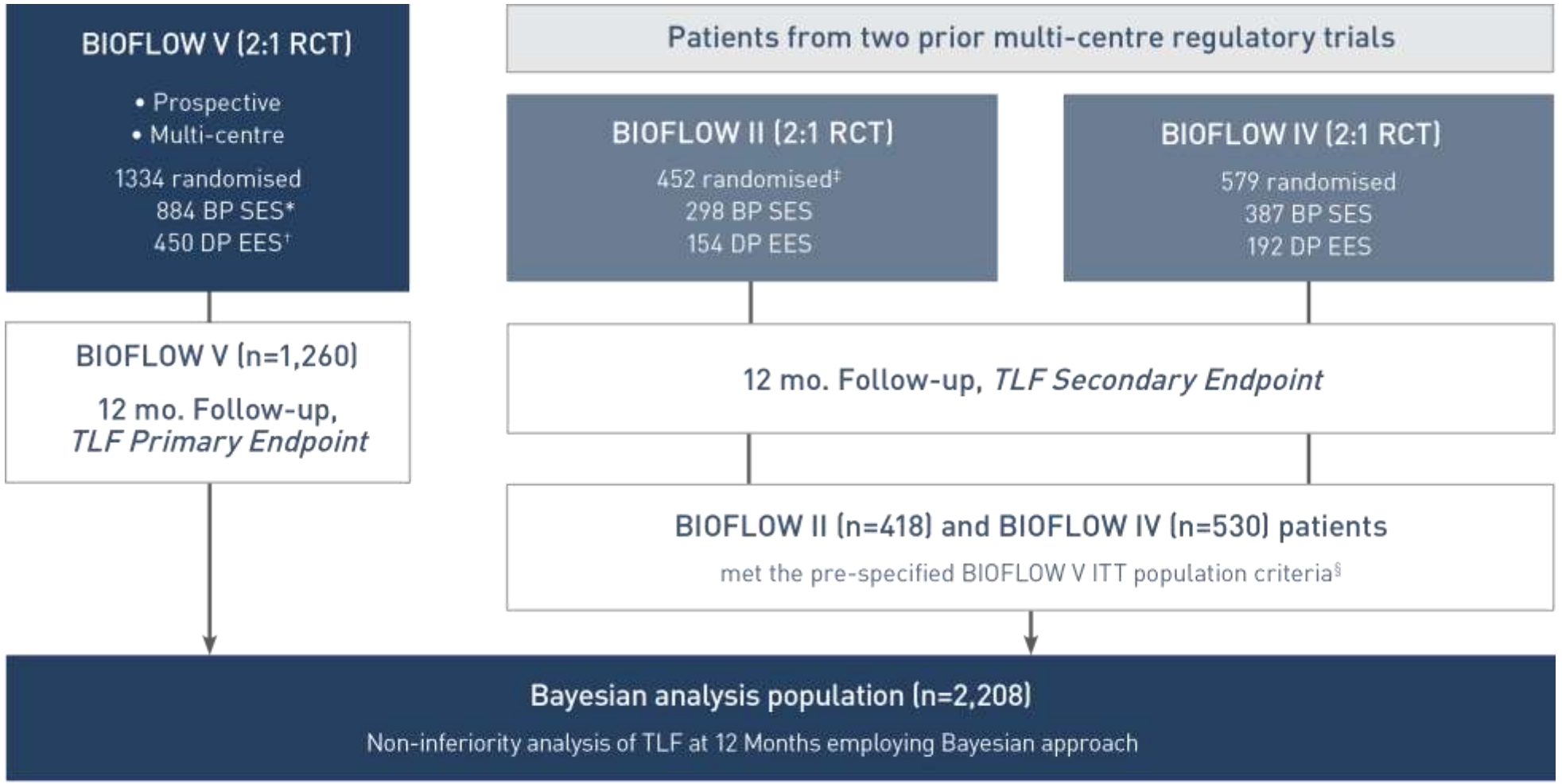
BIOFLOW V

Trial Design



* BP SES: Bioresorbable polymer sirolimus-eluting stent(s)
†DP EES: Durable polymer everolimus-eluting stent(s)
‡Six additional patients were enrolled and received a randomization assignment in BIOFLOW II, 4 experienced procedural complications prior to stenting and two patients withdrew consent prior to stenting but did not receive any study stent, and were excluded from the ITT population.
§ BIOFLOW V ITT population criteria: BIOFLOW V enrolment criteria, at least 330 days of follow-up or experienced an endpoint event prior to 330 days.

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Key Enrollment Criteria

Inclusion Criteria

- Age ≥ 18 years
- IHD, stable or unstable angina, or silent ischaemia
- ≤ 3 de novo target lesions in ≤ 2 native target vessels (TV)
- RVD ≥ 2.25 mm and ≤ 4.0 mm
- LL ≤ 36 mm
- TIMI flow > 1
- Eligible for DAPT therapy (aspirin + P_2Y_{12})
- Provided informed consent

Exclusion Criteria

- Recent (< 72 hours prior to procedure) STEMI or hemodynamically unstable NSTEMI/ ACS patients
- Chronic total occlusions, bypass grafts
- Bifurcations with side branch > 2.0 mm
- In-stent restenosis or active stent thrombosis
- LVEF < 30%
- Prior PCI within 30 days (non-TV) or within 9 months (TV)
- Planned staged PCI post-procedure
- Renal impairment > 2.5 mg/dL or 221 µmol/L or dialysis dependent
- Excessively tortuous/ angulated or severely calcified (operator visual assessment)

Doros et al. Am Heart J DOI: http://dx.doi.org/10.1016/j.ahj.2017.08.001

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BIOFLOW V

Enrollment

- 1,334 patients randomised between May 2015 and March 2016
  - 884 Orsiro and 450 Xience
- Patients enrolled in 13 countries in North America (665), Europe (390), Israel (231), Asia (36), and Australia and New Zealand (12)
- 12 month follow-up completed May 2017

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Baseline Clinical Characteristics

Clinical Characteristics	BP SES (N=884)	DP EES (N=450)
Age, years	64.5 ± 10.3	64.6 ± 10.7
Female	25.3%	27.1%
Hypertension	79.7%	80.5%
Hyperlipidemia	78.9%	82.4%
Diabetes mellitus	34.0%	37.0%
Prior MI	27.4%	25.9%
Prior PCI	36.8%	33.0%
Prior CABG	7.1%	5.2%
Current smoking	23.6%	22.7%
Clinical presentation		
Stable angina	48.4%	47.4%
Acute coronary syndrome	51.4%	49.6%

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Baseline Angiographic Characteristics

Angiographic Characteristics	BP SES (N=1,051 lesions)	DP EES (N=561 lesions)
Target lesion vessel		
Left anterior descending	41.0%	41.2%
Left circumflex	26.6%	26.0%
Right coronary artery	32.4%	32.8%
Thrombus	1.0%	0.9%
Bifurcation lesion	14.8%	15.0%
Moderate/severe calcification	24.0%	26.7%
Moderate/severe tortuosity	58.8%	61.5%
ACC/AHA lesion class B2/C	72.6%	75.9%

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Procedural Characteristics

Angiographic/Procedural Results	BP SES (N=1,051 lesions)	DP EES (N=561 lesions)
Lesion length	13.3 ± 7.6	13.2 ± 7.7
Reference vessel diameter	2.6 ± 0.5	2.6 ± 0.6
No. target lesions/pt*	1.2 ± 0.4	1.3 ± 0.5
% diameter stenosis, pre	55.4 ± 13.3	55.9 ± 13.5
% diameter stenosis, post	7.1 ± 9.8	7.4 ± 9.8
Post-dilation performed	47.7%	46.2%
No. stents/lesion*	1.07 ± 0.3	1.13 ± 0.4
Stent length/lesion	20.8 ± 9.1	21.8 ± 10.5
Overlapping stents*	9.4%	15.0%

**P*<0.05 for comparison

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Procedural Outcomes

	BP SES	DP EES	*P* value
Lesion success*	1102/1107 (99.5%)	579/583 (99.3%)	0.505
Device success†	1082/1107 (97.7%)	566/583 (97.1%)	0.415
Procedure success‡	827/881 (93.9%)	401/445 (90.1%)	0.019

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***Lesion success** defined as attainment of < 30% residual stenosis of the target lesion using any percutaneous method.

†**Device success** defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only.

‡**Procedure success** defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only without occurrence of in-hospital major adverse cardiac events (MACE; composite of all-cause death, Q-wave or non-Q-wave MI, and any clinical-driven TLR).

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30 Day Outcomes

	BP SES (N=884)	DP EES (N=450)	*P* value
All-cause death	0.1%	0.2%	1.000
Myocardial infarction	4.3%	6.9%	0.050
In-hospital MI	3.9%	6.7%	0.029
MI >3X ULN	2.3%	4.5%	0.04
MI >5X ULN	0.8%	2.4%	0.02
TLR	0.5%	0.7%	0.694
Stent thrombosis	0.3%	0.2%	1.000
TLF	4.2%	7.1%	0.026
TVF	4.3%	7.1%	0.037

All data represented as intention to treat
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Primary Endpoint: 12 Month Target Lesion Failure

	Orsiro BP SES (n=884)	Xience DP EES (n=450)	*P* value
Target lesion failure	6.2%	9.6%	0.040
Cardiac death	0.1%	0.7%	0.115
Target vessel MI	4.7%	8.3%	0.016
Clinically-driven TLR	2.0%	2.4%	0.686

All data represented as intention to treat

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BIOFLOW V
Pooled Bayesian Analysis: BIOFLOW V, II and IV Trials

	Orsiro BP SES (n=1466)	Xience DP EES (n=742)	Rate difference	Posterior probability	
Target lesion failure (Bayesian analysis)				Noninferiority margin 3.85%	Superiority (post-hoc)
12-Month Rate, posterior mean ± estimate of SD (%), 95% Credible Interval	6.3 ± 0.8 (4.9, 7.9)	8.9 ± 1.2 (6.7, 11.4)	-2.6 (-5.5, 0.1)	100.0%	96.9%

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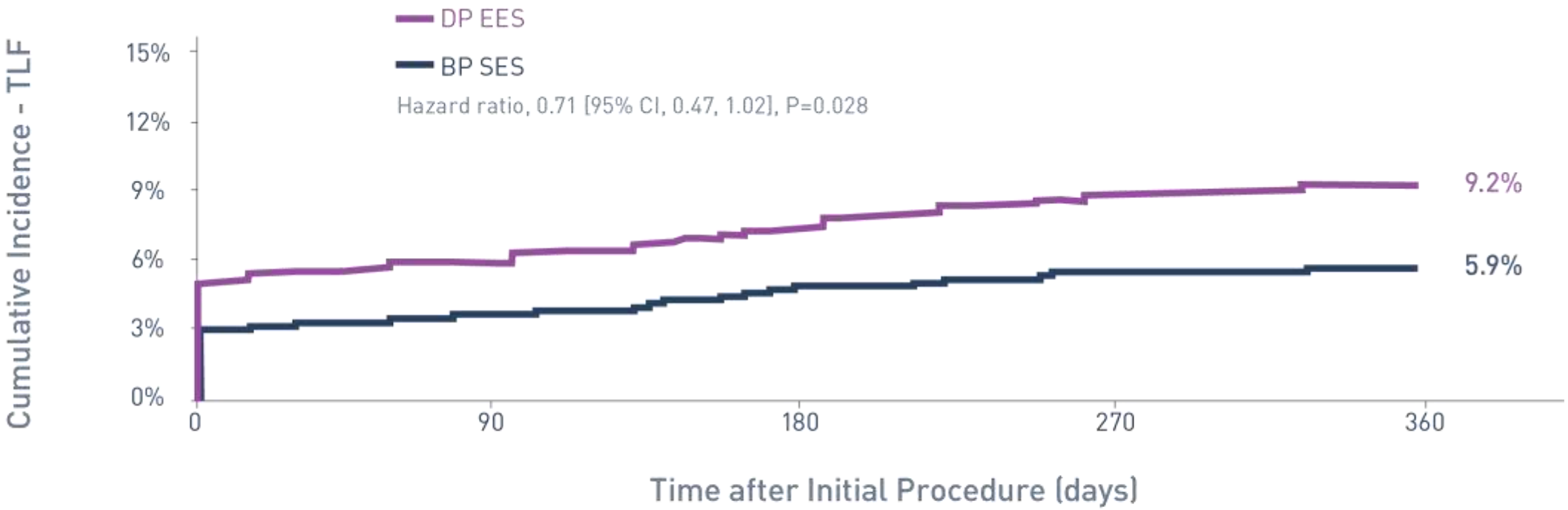
BIOFLOW V
Primary Endpoint: 12 Month Target Lesion Failure



No. at Risk					
DP EES	450	421	411	400	392
BP SES	884	848	828	814	792

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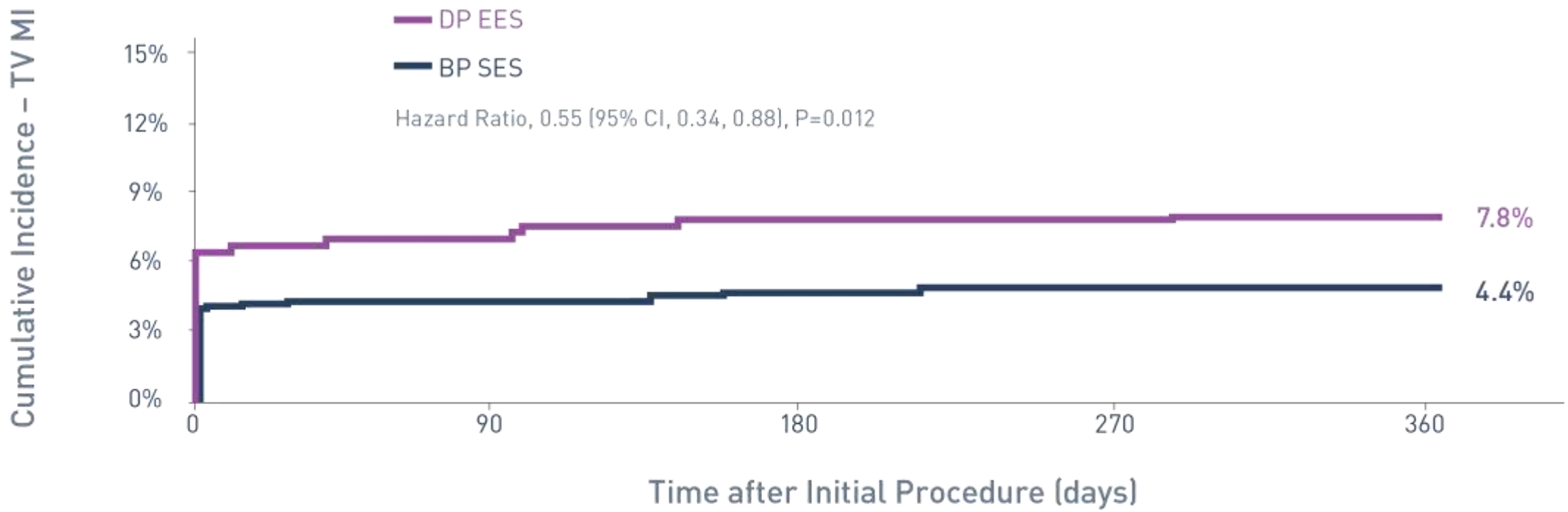
BIOFLOW V
12 Month Target Vessel-Related Myocardial Infarction



No. at Risk					
DP EES	450	421	411	400	392
BP SES	884	848	828	814	792

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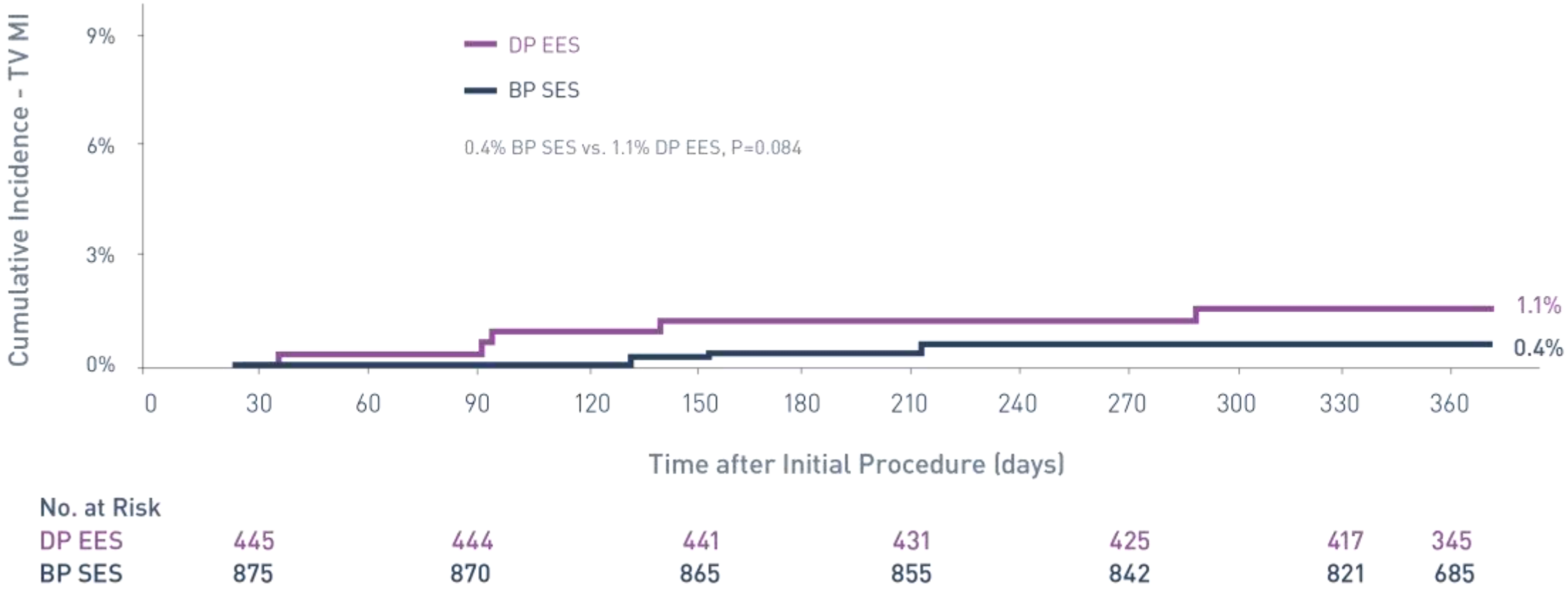
BIOFLOW V
Landmark Analysis: Target Vessel MI, 30 Days to 12 Months



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Stent Thrombosis

12 Month DAPT Adherence: 92.1% BP SES, 91.2% DP EES

	BP SES (N=884)	DP EES (N=450)	*P* value
Stent Thrombosis			
Any stent thrombosis	0.5%	1.2%	0.175
Definite	0.5%	0.7%	0.694
Definite/Probable	0.5%	0.7%	0.694
Timing of Event (Definite/Probable ST)			
Acute (≤ 24 hours)	0.1%	0.0%	1.000
Sub-acute (> 24 hours and ≤ 30 days)	0.2%	0.2%	1.000
Late (> 30 days and ≤ 1 year)	0.1%	0.5%	0.264
Timing of Event (Any ST)			
Acute (≤ 24 hours)	0.1%	0.0%	1.000
Sub-acute (> 24 hours and ≤ 30 days)	0.2%	0.2%	1.000
Late (> 30 days and ≤ 1 year)	0.1%	0.9%	0.047

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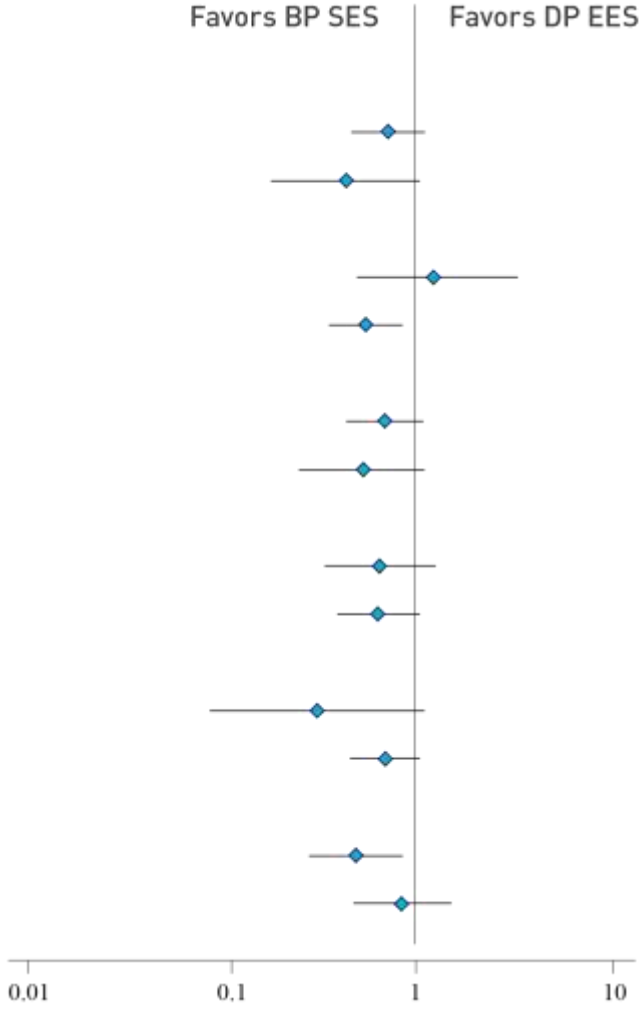
Target Lesion Failure at 12 Months by Subgroups

Subgroup	BP SES (N=884)	DP EES (N=450)	HR and 95% CI	P Value for Interaction
	no. of events / total no. (%)			
Vessel Size				0.37
Small Vessels*	43/554 (7.8)	31/290 (10.7)	0.71 (0.45, 1.13)	
Large Vessels	9/269 (3.3)	10/135 (7.4)	0.45 (0.18, 1.10)	
Age				0.16
>75	12/124 (9.7)	6/71 (8.4)	1.20 (0.45, 3.21)	
≤75	40/709 (5.6)	35/356 (9.8)	0.56 (0.35, 0.88)	
Gender				0.61
Male	39/628 (6.2)	28/312 (9.0)	0.69 (0.42, 1.11)	
Female	13/205 (6.3)	13/115 (11.3)	0.54 (0.25, 1.16)	
Diabetes				0.91
Diabetic	18/280 (6.4)	15/153 (9.8)	0.66 (0.33, 1.31)	
Non-diabetic	34/552 (6.2)	26/273 (9.5)	0.63 (0.38, 1.05)	
Lesion Length				0.25
>26 mm	4/78 (5.1)	6/36 (16.7)	0.31 (0.09, 1.11)	
≤ 26 mm	48/746 (6.4)	35/387 (9.0)	0.69 (0.45, 1.07)	
ACS†				0.24
ACS	24/426 (5.6)	23/209 (11.0)	0.50 (0.28, 0.89)	
Non-ACS	28/407 (6.9)	18/218 (8.3)	0.82 (0.45, 1.48)	



*Small vessels defined as ≤ 2.75mm.
†ACS defined as: subjects with unstable angina or any elevated cardiac enzymes at baseline (any pre procedure CK, CK MB or Troponin out of normal range).

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BIOFLOW V
Multivariable Analysis of Target Vessel MI

	Odds Ratio [95% CI]	*P* value
Orsiro vs. Xience	0.56 [0.35, 0.91]	0.020
Number of stents implanted (per patient)	1.13 [0.58, 2.19]	0.729
Subjects with two vessels treated	1.82 [0.79, 4.23]	0.162
Number of target lesions (per patient)	1.14 [0.52, 2.53]	0.743
Total stent lengths (mm) (sum per patient)	1.00 [0.98, 1.03]	0.934
History of MI	1.69 [1.02, 2.81]	0.041
Subjects with overlapping stents vs. without	1.43 [0.61, 3.36]	0.410

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TLF According to Stent Diameter

TLF to 12 Months	Orsiro (n = 884)	Xience (n = 450)	Difference [95% CI]	Posterior Probability of Interaction
Study stent diameter ≤ 3.0 mm	6.8% (36/531)	9.8% (26/266)	-3.0% [-7.4%, 1.0%]	0.616
Study stent diameter > 3.0 mm	5.2% (15/290)	9.3% (14/150)	-4.2% [-9.8%, 0.8%]	

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Revisiting the Thin Strut Hypothesis (or Principle)

- Thinner stent struts produce less inflammation, vessel injury, neointimal proliferation and thrombus formation compared with thicker struts[1]

- Over 15 years of DES iteration, progression to thinner struts is associated with lower rates of target vessel MI

  - Stainless steel (132 µm to 140 µm) to chromium alloys (81 µm to 91 µm) translate to ~40% to ~80% reductions in both procedural and late-term target vessel MI[2]

- In BIOFLOW V, an ~20 µm difference between BP SES and DP EES is associated with 40% reduction in TV MI

[1]Kolandaivelu. Cirulation 2011; Soucy. EuroIntervention 2010; Kastrati. Circulation 2001; Pache. JACC 2003
[2]ENDEAVOR III; SPIRIT III; ENDEAVOR IV; ENDEAVOR Pooled Analysis; SPIRIT IV

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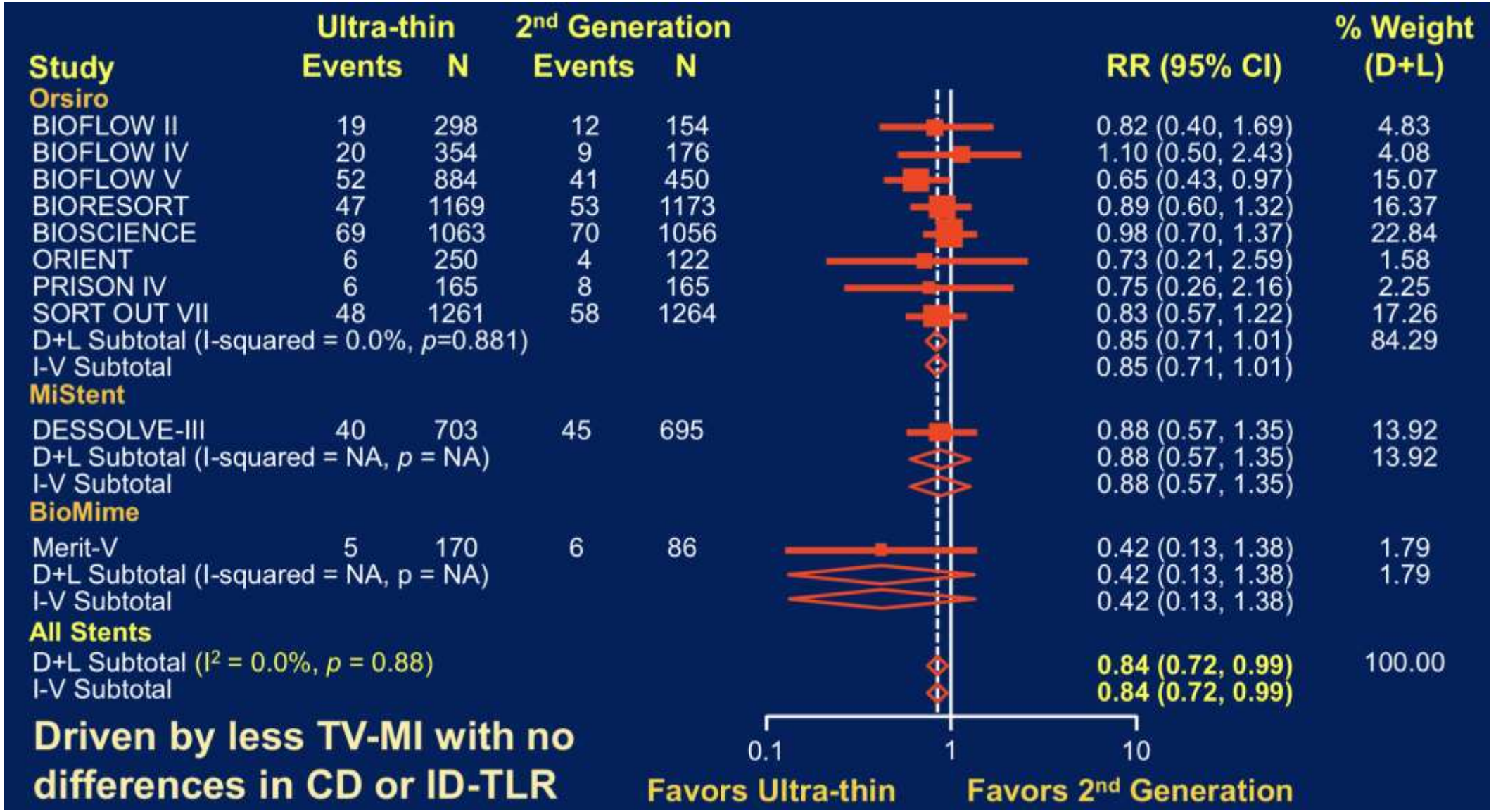
Ultra-thin (<70 μm) vs Thicker Strut 2nd Generation DES: 1-yr TLF

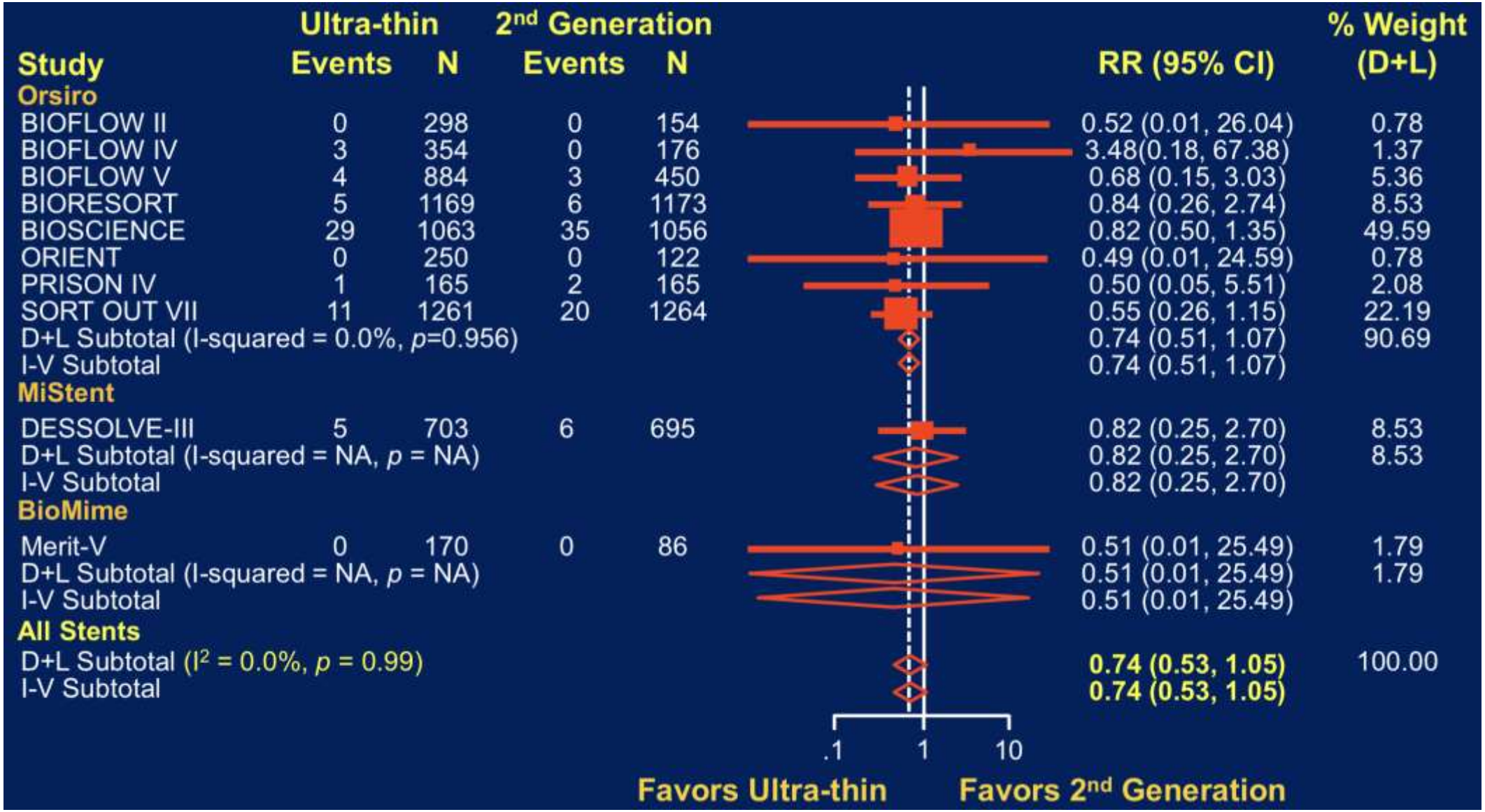
10 RCTs, 11,658 pts: Orsiro (60 μm), MiStent (64 μm), BioMime (65 μm)



Bangalore et al. Submitted

Ultra-thin (<70 μm) vs Thicker Strut 2nd Generation DES: 1-yr Def/Prob Stent Thrombosis

10 RCTs, 11,658 pts: Orsiro (60 μm), MiStent (64 μm), BioMime (65 μm)



Bangalore et al. Submitted

Orsiro Bioresorbable Polymer, Ultra-Thin Strut DES Conclusions

- In an international, randomised trial (BIOFLOW V), treatment with the ultrathin strut Orsiro BP SES was superior to the Xience DP EES regarding 12 month TLF and MI
  - Differences in MI observed early but persisted in landmark analysis
- Revascularization with Orsiro BP SES was associated with favorably low TLR and stent thrombosis
- Bayesian pooled analysis including patient level outcomes from BIOFLOW II and IV trials demonstrated unequivocal non-inferiority with mean TLF treatment difference of -2.6 % favoring Orsiro and posterior probability of superiority 96.9%
- Results are consistent with both prior and evolving evidence supporting ultra-thin strut DES as a contribution toward improved outcomes; *level setting expectations regarding when, where and how differences will be observed*
- These results endorse the safety and efficacy of the ultrathin Orsiro BP SES in patients representative of those treated in clinical practice and advance a new standard for DES comparison

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