Ultrathin Strut Drug Eluting Stents in Complex Patients

Setting New Standards 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	Boston Scientific Corporation, Medtronic CardioVascular, Biotronik, 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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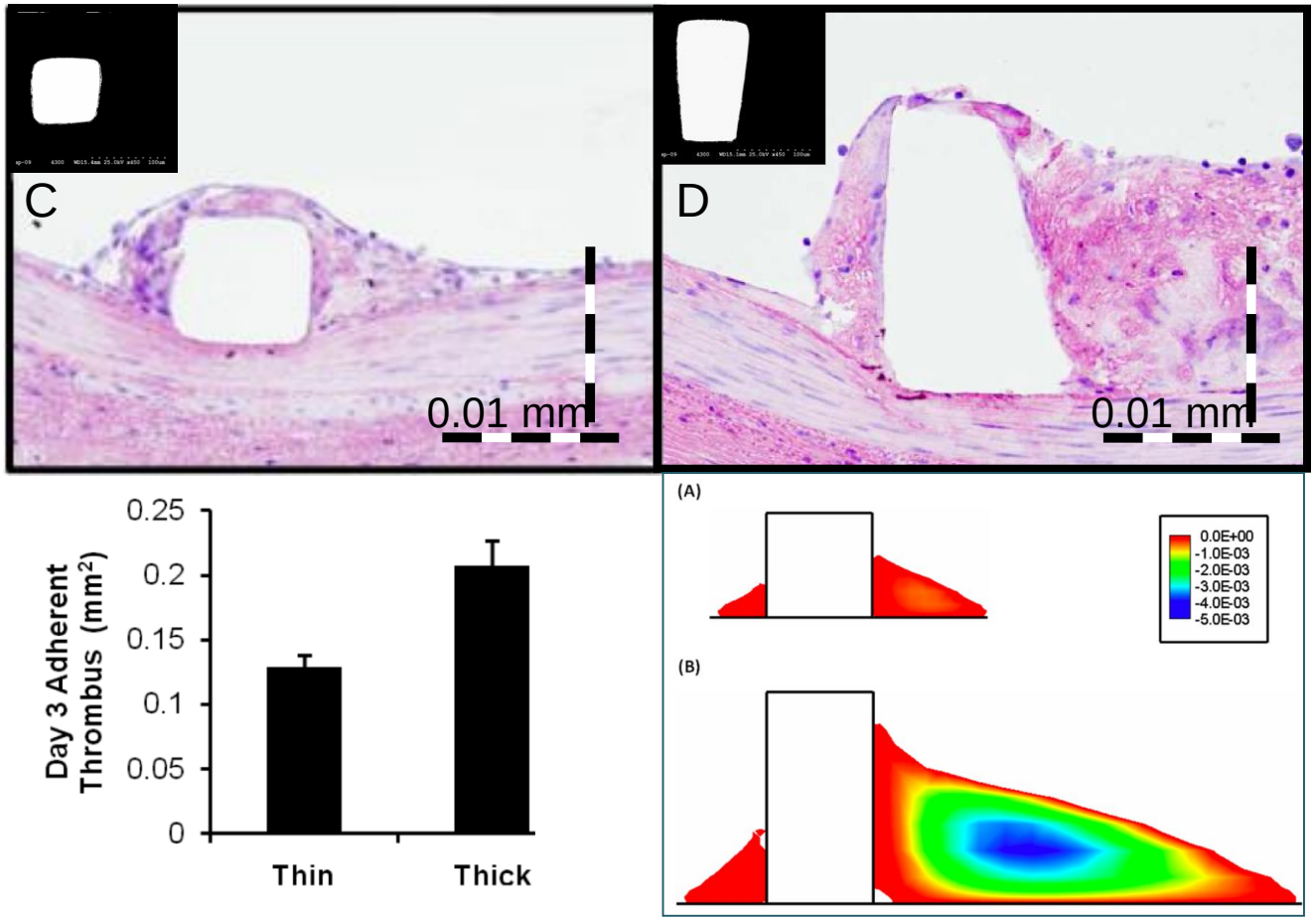
Revisiting the Thin Strut Hypothesis (or Principle)

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



[1]Kolandaivelu. Cirulation 2011; Soucy. EuroIntervention 2010; Kastrati. Circulation 2001; Pache. JACC 2003

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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 ~45% reductions in TV MI and TLR and >50% reduction in ST at 2 years

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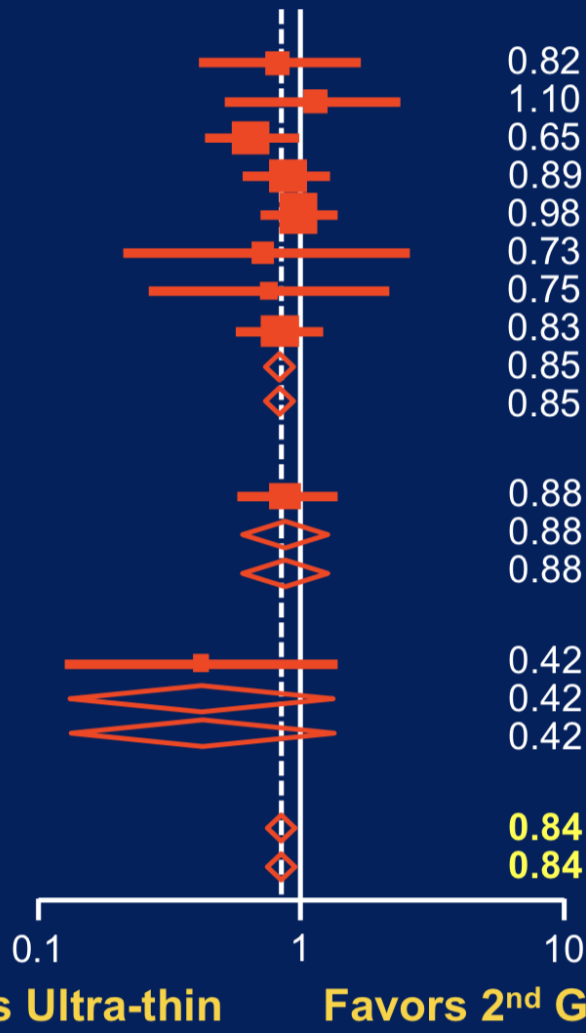
Ultra-thin (<70 μm) vs Thicker Strut 2nd Generation DES: 1-yr TLF

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

Study	Ultra-thin Events	Ultra-thin N	2nd Generation Events	2nd Generation N	RR (95% CI)	% Weight (D+L)
Orsiro						
BIOFLOW II	19	298	12	154	0.82 (0.40, 1.69)	4.83
BIOFLOW IV	20	354	9	176	1.10 (0.50, 2.43)	4.08
BIOFLOW V	52	884	41	450	0.65 (0.43, 0.97)	15.07
BIORESORT	47	1169	53	1173	0.89 (0.60, 1.32)	16.37
BIOSCIENCE	69	1063	70	1056	0.98 (0.70, 1.37)	22.84
ORIENT	6	250	4	122	0.73 (0.21, 2.59)	1.58
PRISON IV	6	165	8	165	0.75 (0.26, 2.16)	2.25
SORT OUT VII	48	1261	58	1264	0.83 (0.57, 1.22)	17.26
D+L Subtotal (I-squared = 0.0%, *p*=0.881)					0.85 (0.71, 1.01)	84.29
I-V Subtotal					0.85 (0.71, 1.01)	
MiStent						
DESSOLVE-III	40	703	45	695	0.88 (0.57, 1.35)	13.92
D+L Subtotal (I-squared = NA, *p* = NA)					0.88 (0.57, 1.35)	13.92
I-V Subtotal					0.88 (0.57, 1.35)	
BioMime						
Merit-V	5	170	6	86	0.42 (0.13, 1.38)	1.79
D+L Subtotal (I-squared = NA, p = NA)					0.42 (0.13, 1.38)	1.79
I-V Subtotal					0.42 (0.13, 1.38)	
All Stents						
D+L Subtotal (I^2 = 0.0%, *p* = 0.88)					**0.84 (0.72, 0.99)**	100.00
I-V Subtotal					**0.84 (0.72, 0.99)**	

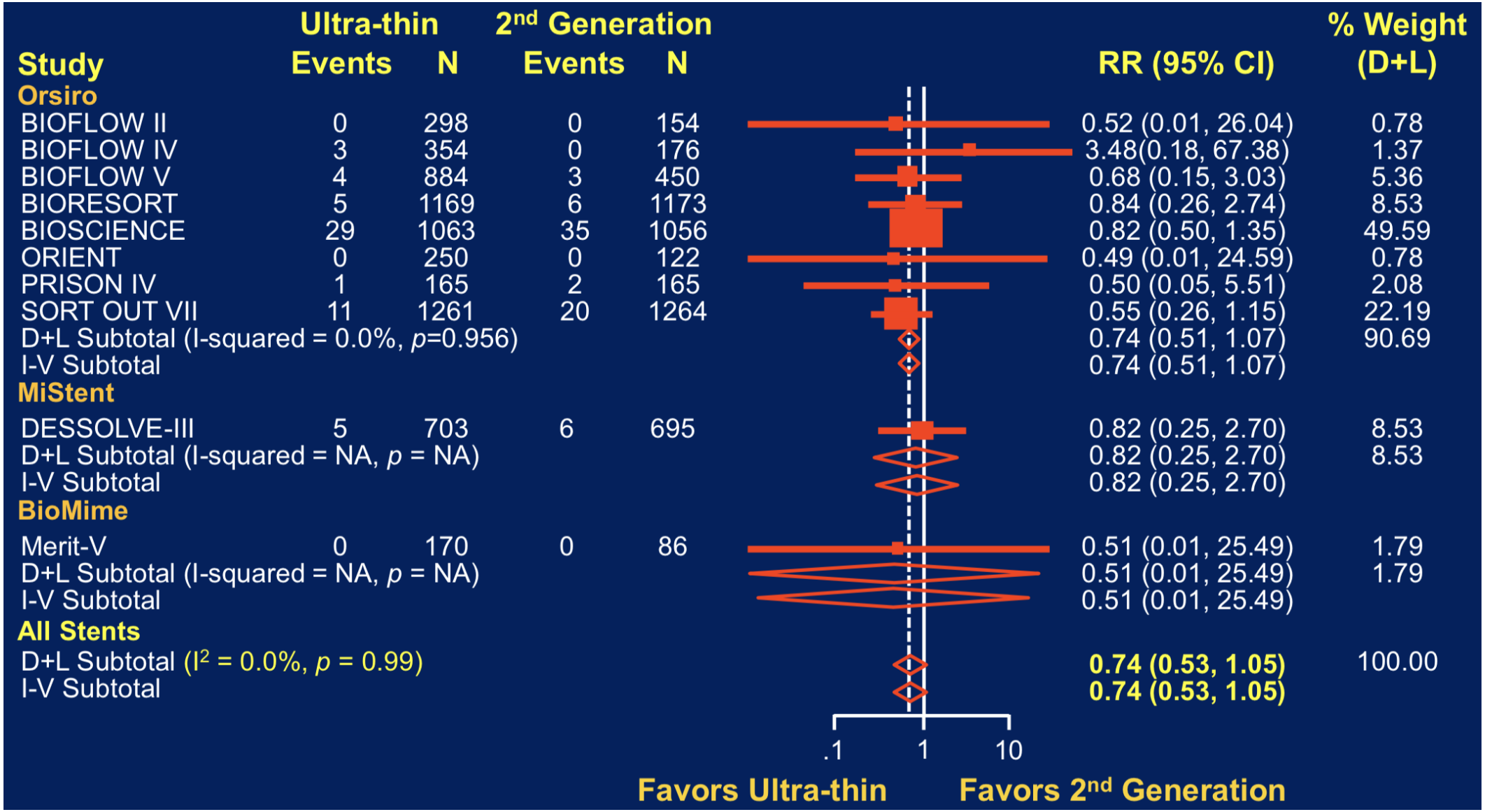


Driven by less TV-MI with no differences in CD or ID-TLR

Bangalore et al. Circ Interventions 2018

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

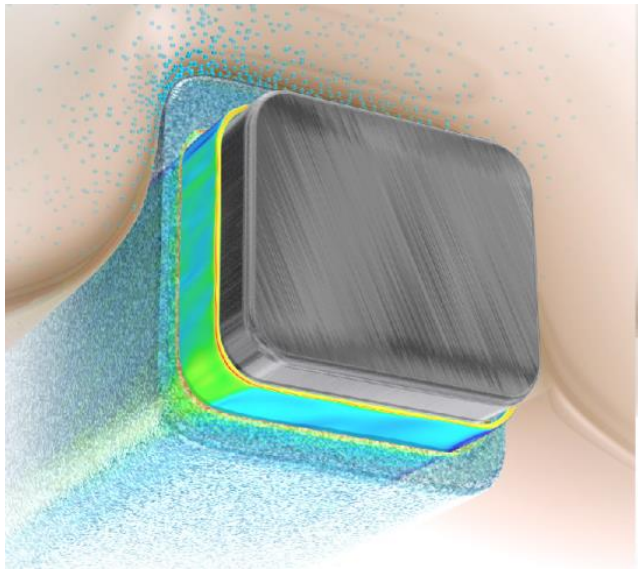
10 RCTs, 11,658 pts: Orsiro (60 μm), MiStent (64 μm), BioMime (65 μm)



Bangalore et al. Circ Interventions 2018

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
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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BIOFLOW V

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

Kandzari et al. Lancet 2017

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BIOFLOW V

2 Year Outcomes

	Orsiro BP SES (n=884)	Xience DP EES (n=450)	*P* value
Target lesion failure	7.5%	11.9%	0.015
Cardiac death	0.6%	0.5%	1.0
Target vessel MI	5.3%	9.5%	0.01
Ischemia-driven TLR	2.6%	4.9%	0.04
Cardiac Death/MI	7.0%	10.4%	0.047
Definite Stent Thrombosis	0.5%	1.2%	0.17
Definite Late/Very Late ST	0.1%	1.0%	0.045

All data represented as intention to treat

Kandzari et al. JACC 2018

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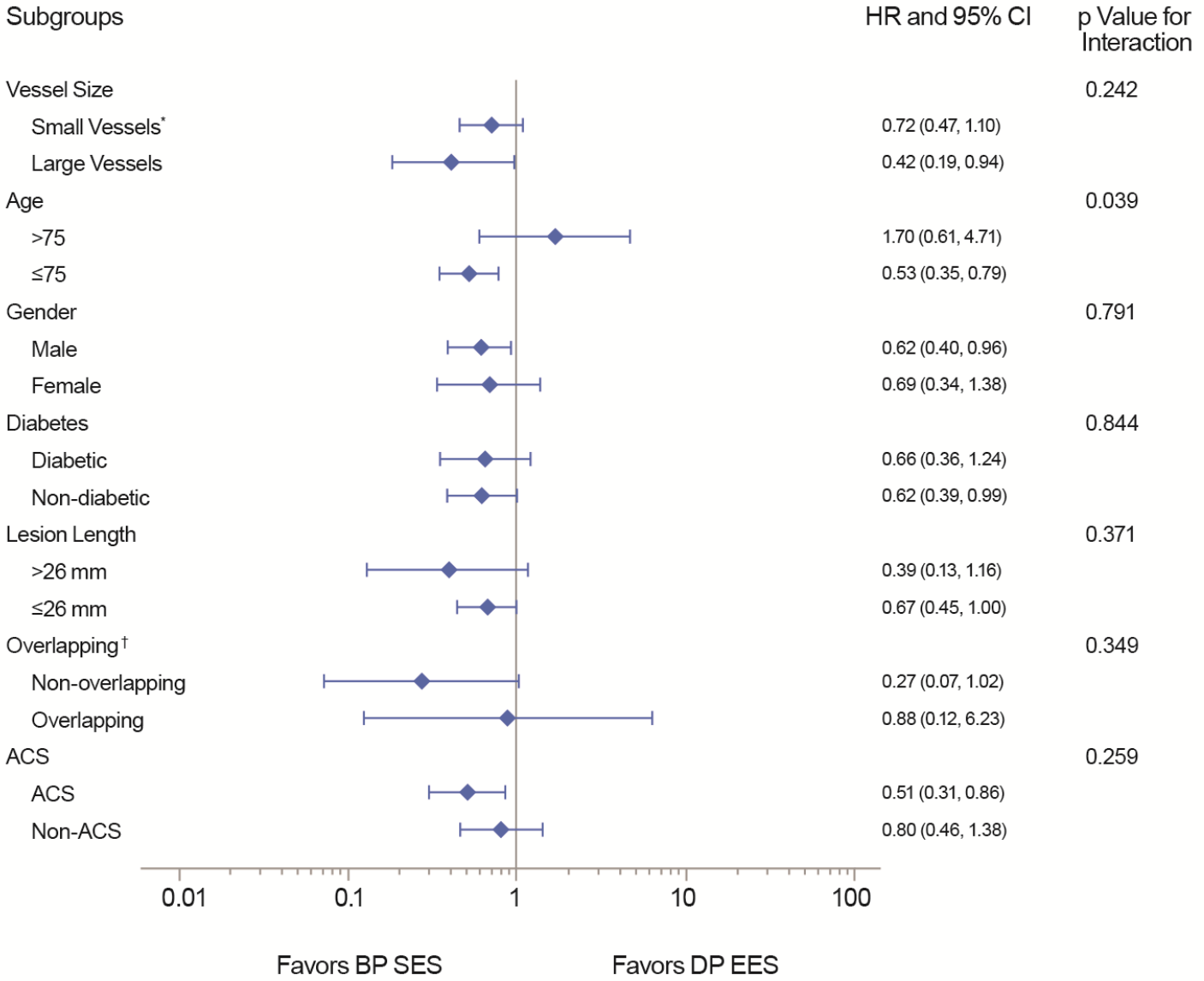
BIOFLOW V

Target Lesion Failure at 2 Years by Subgroups



*Small vessels defined as 2.75 mm or smaller. † Non-overlapping vs. Overlapping stents subgroup analysis is only performed on subjects with lesion length > 26 mm.

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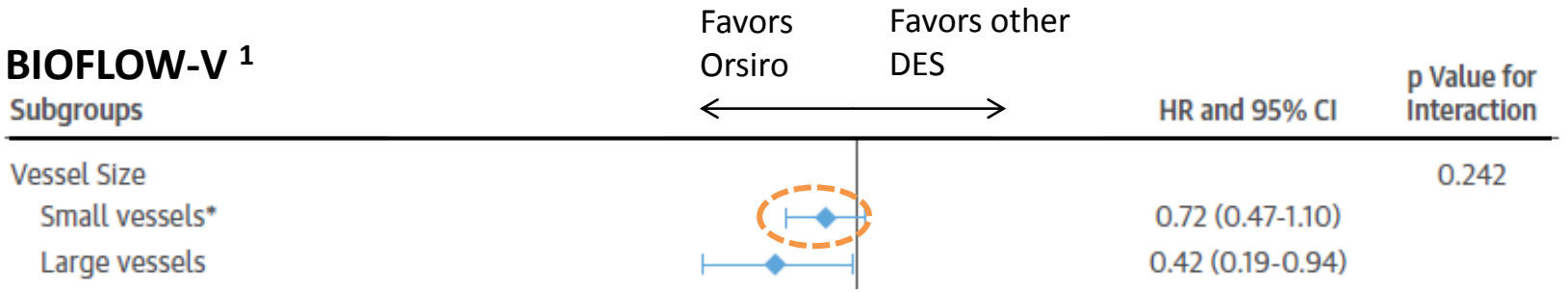
Small Vessel Disease*

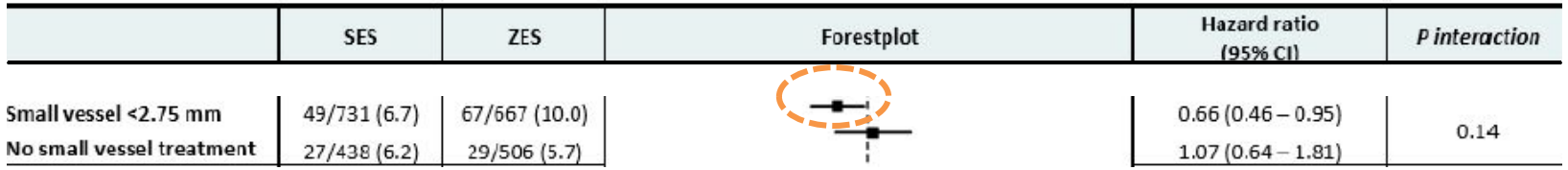
Subgroup Analyses from BIOFLOW V, BIORESORT and BIOSCIENCE

BIOFLOW-V [1]



2y TLF

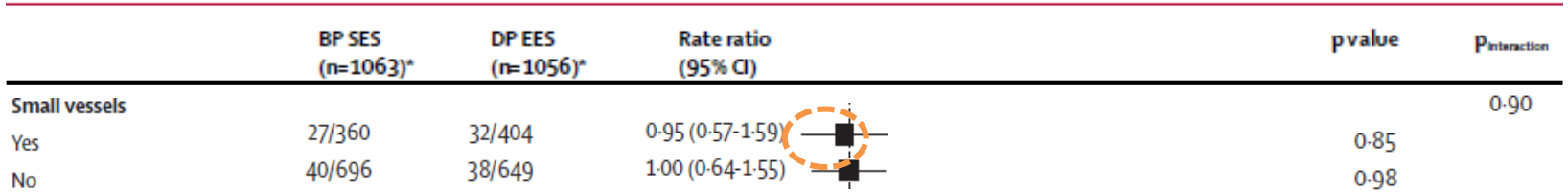
BIO-RESORT [2]



	SES	ZES	Forestplot	Hazard ratio (95% CI)	*P interaction*
Small vessel <2.75 mm	49/731 (6.7)	67/667 (10.0)		0.66 (0.46 – 0.95)	0.14
No small vessel treatment	27/438 (6.2)	29/506 (5.7)		1.07 (0.64 – 1.81)	

2y TVF

BIOSCIENCE [3]



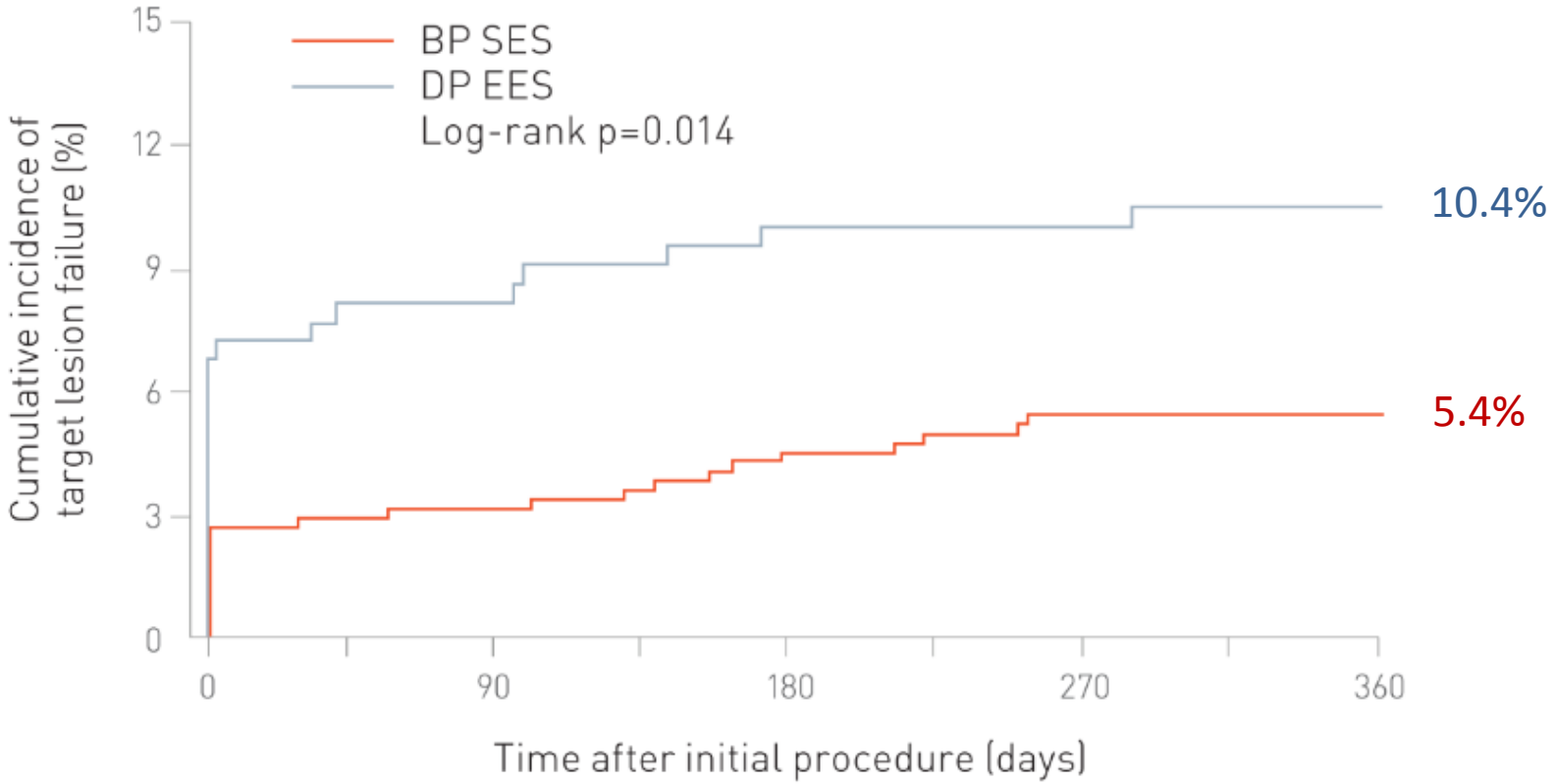
	BP SES (n=1063)*	DP EES (n=1056)*	Rate ratio (95% CI)	pvalue	$p_{interaction}$
Small vessels					0·90
Yes	27/360	32/404	0·95 (0·57-1·59)	0·85	
No	40/696	38/649	1·00 (0·64-1·55)	0·98	

1y TLF

*Small vessels defined as ≤2.75 mm

BIOFLOW V

Acute Coronary Syndrome Subgroup Analysis



Number at risk

BP SES	454	438	430	417	336
DP EES	223	206	200	192	160

Roguin, Kandzari, Waksman et al. Circ Cardiovasc Interv 2018

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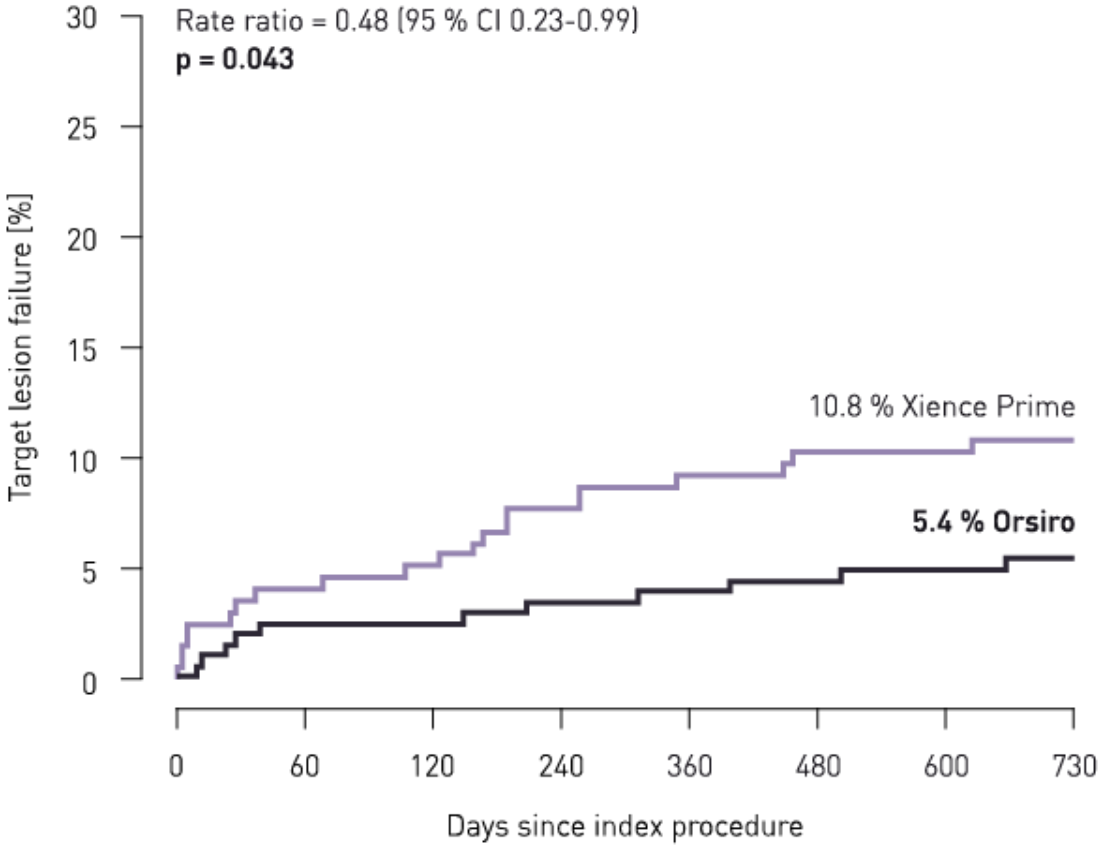
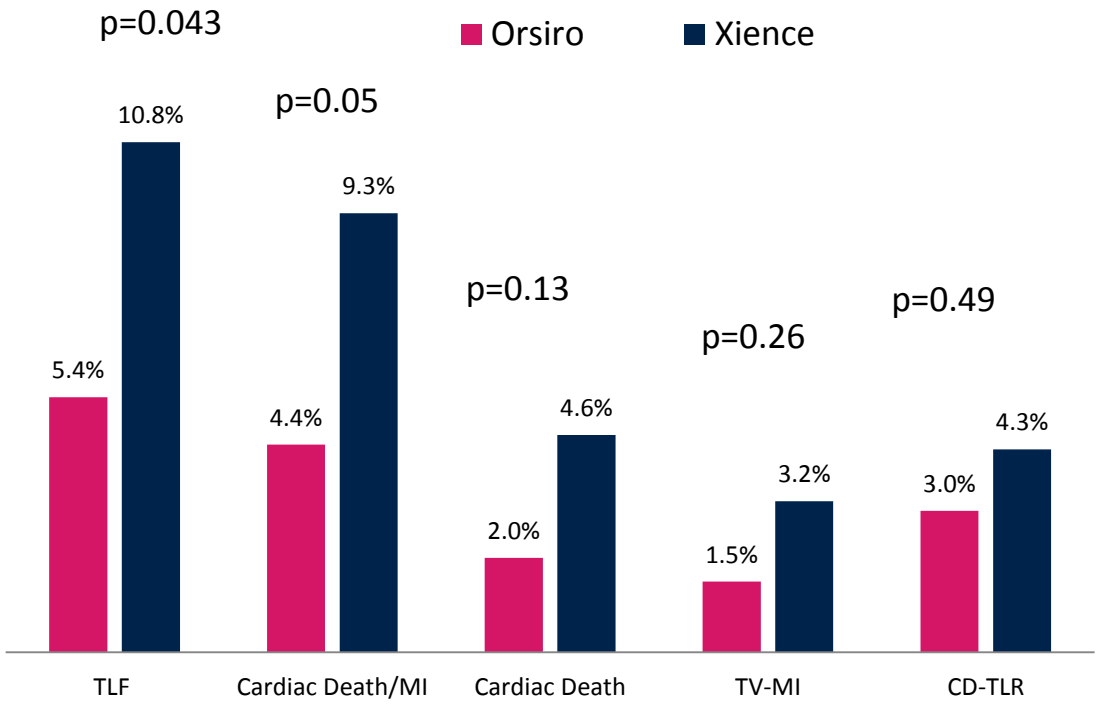
BIOFLOW V

STEMI Subgroup Analysis





Source: Piccolo R, EuroPCR 2016, Oral presentation

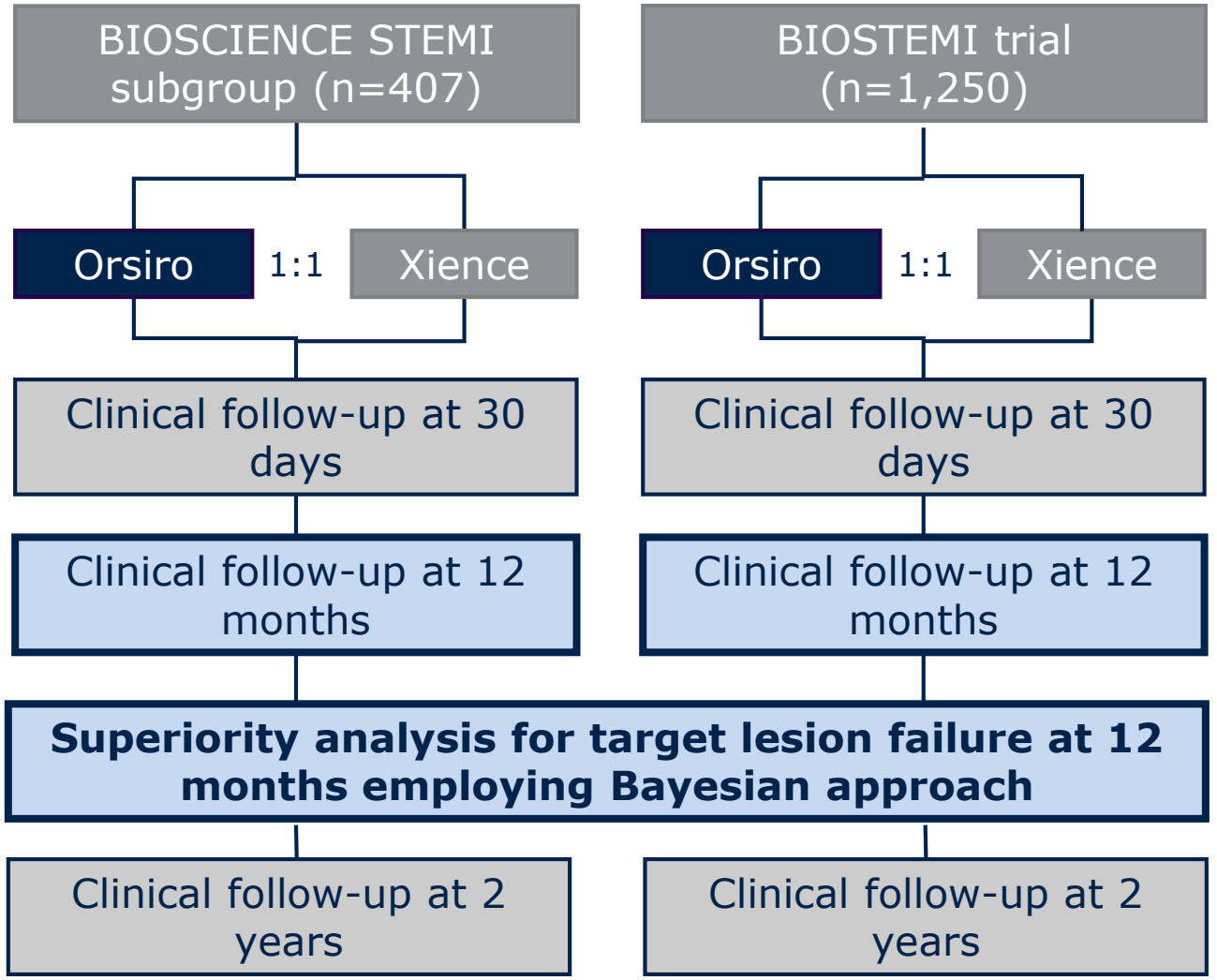
BIOSTEMI

DESIGN
Prospective, multicenter, randomized, controlled, superiority trial.

OBJECTIVE
To investigate the superiority of ultrathin-strut Orsiro BP-SES to Xience DP-EES in STEMI patients undergoing primary PCI.

COORDINATING CLINICAL INVESTIGATORS
Prof. Dr. Thomas Pilgrim, Bern, Switzerland
Dr. Juan F. Iglesias, Lausanne, Switzerland
PD Dr. Olivier Muller Lausanne, Switzerland

PRIMARY ENDPOINT
Target Lesion Failure (TLF) at 12 months, defined as a composite of cardiac death, target vessel re-infarction, or clinically-indicated TLR.



Iglesias et al. Eurointervention 2018

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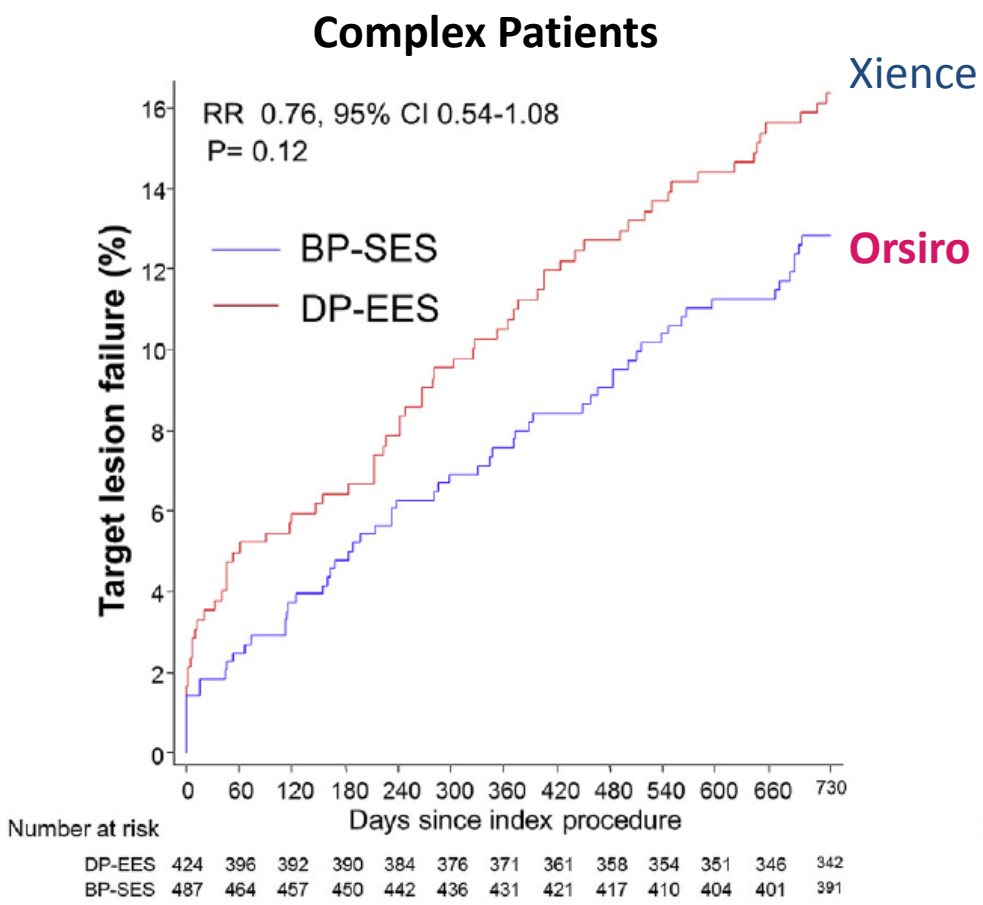
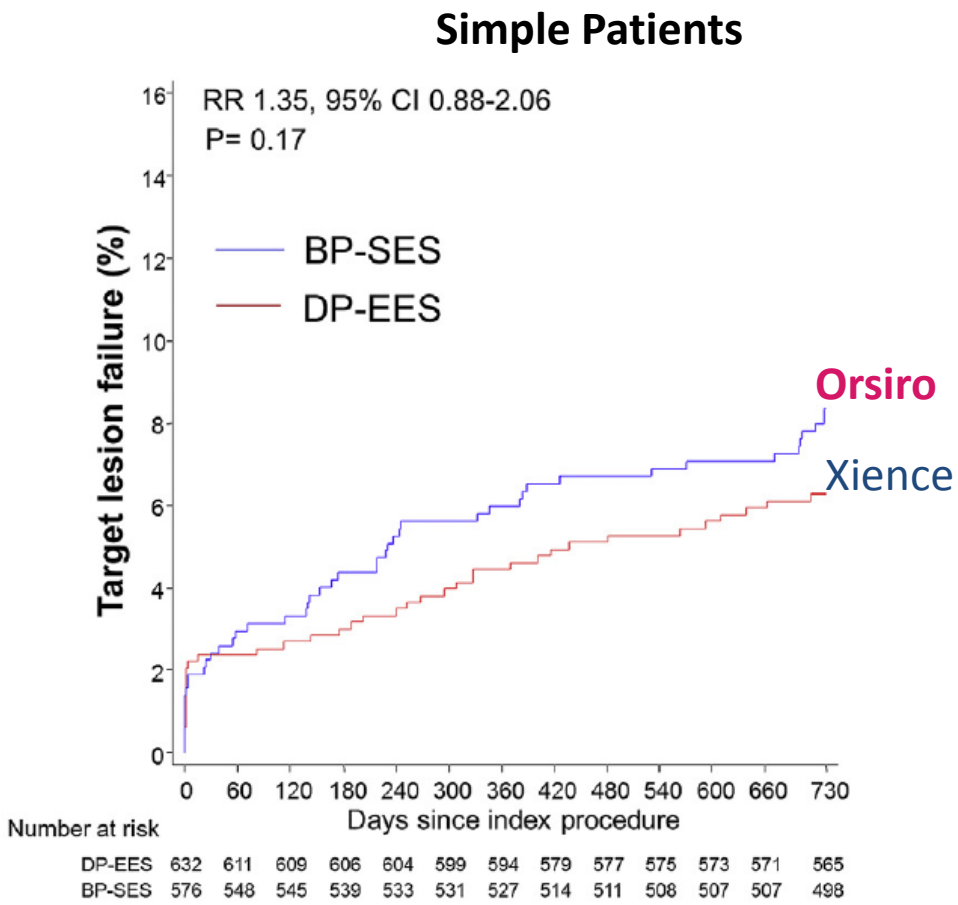
BIOSCIENCE

Impact of Patient and Lesion Complexity on Target Lesion Failure





- **Complex patients** defined by the presence of at least 1 of the following:
  - STEMI within 24 hours
  - Left ventricular ejection fraction 30%
  - Renal dysfunction (glomerular filtration rate <60 ml/min)
  - Insulin treated diabetes
  - Treatment of ostial lesion, bypass graft, unprotected left main lesion, or >2 vessels.

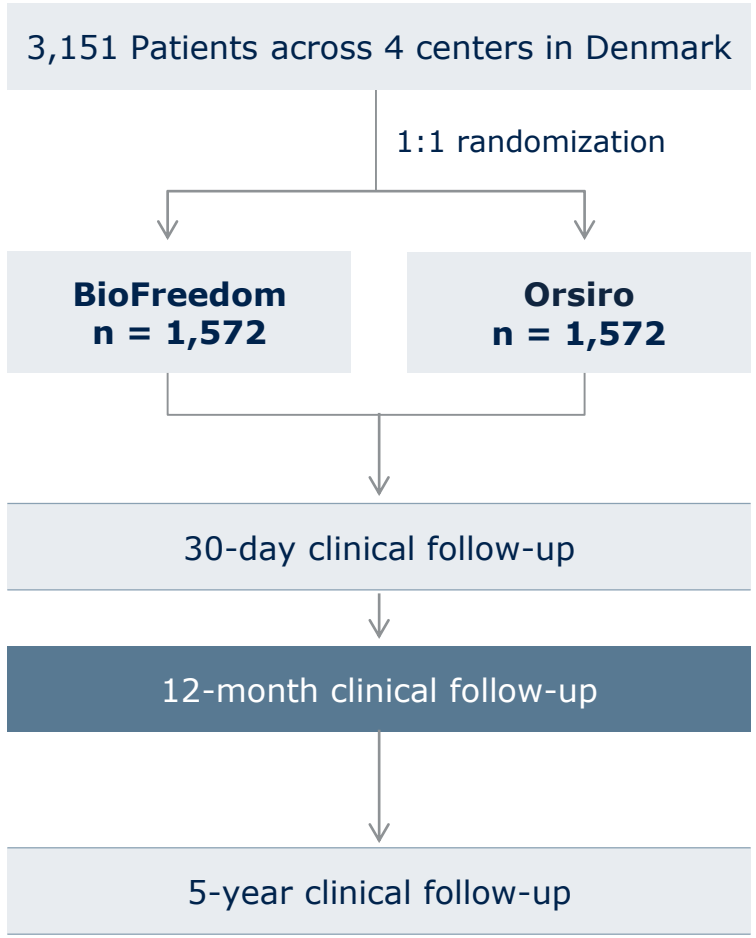
Koskinas K et al. Am J Cardiol 2017

SORT OUT IX

Design
Randomized, multicenter, single-blind, all-comers, two-arm, non-inferiority trial comparing BioFreedom to Orsiro

Objective
To compare the safety and efficacy of the polymer free biolimus A9-coated BioFreedom stent and the thin strut biodegradable polymer sirolimus-eluting Orsiro stent in an all-comer population

Primary Endpoint
Target lesion failure: a composite of cardiac death, myocardial infarction (not related to other than index lesion) or target lesion revascularization within 1 year

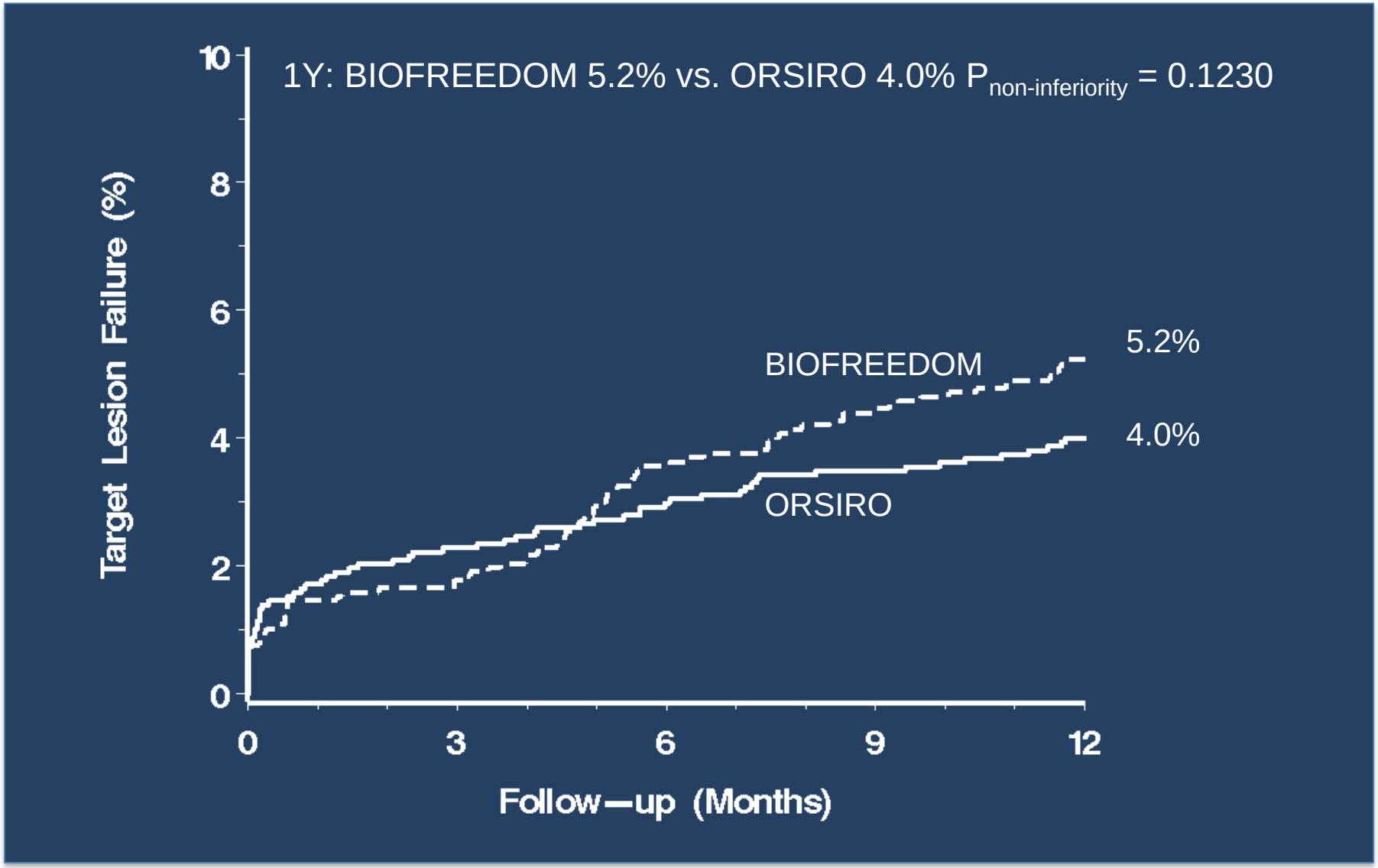


NCT02623140

STEMI 24%
B2/C 61%
Bifurcation 20%
CTO 5%

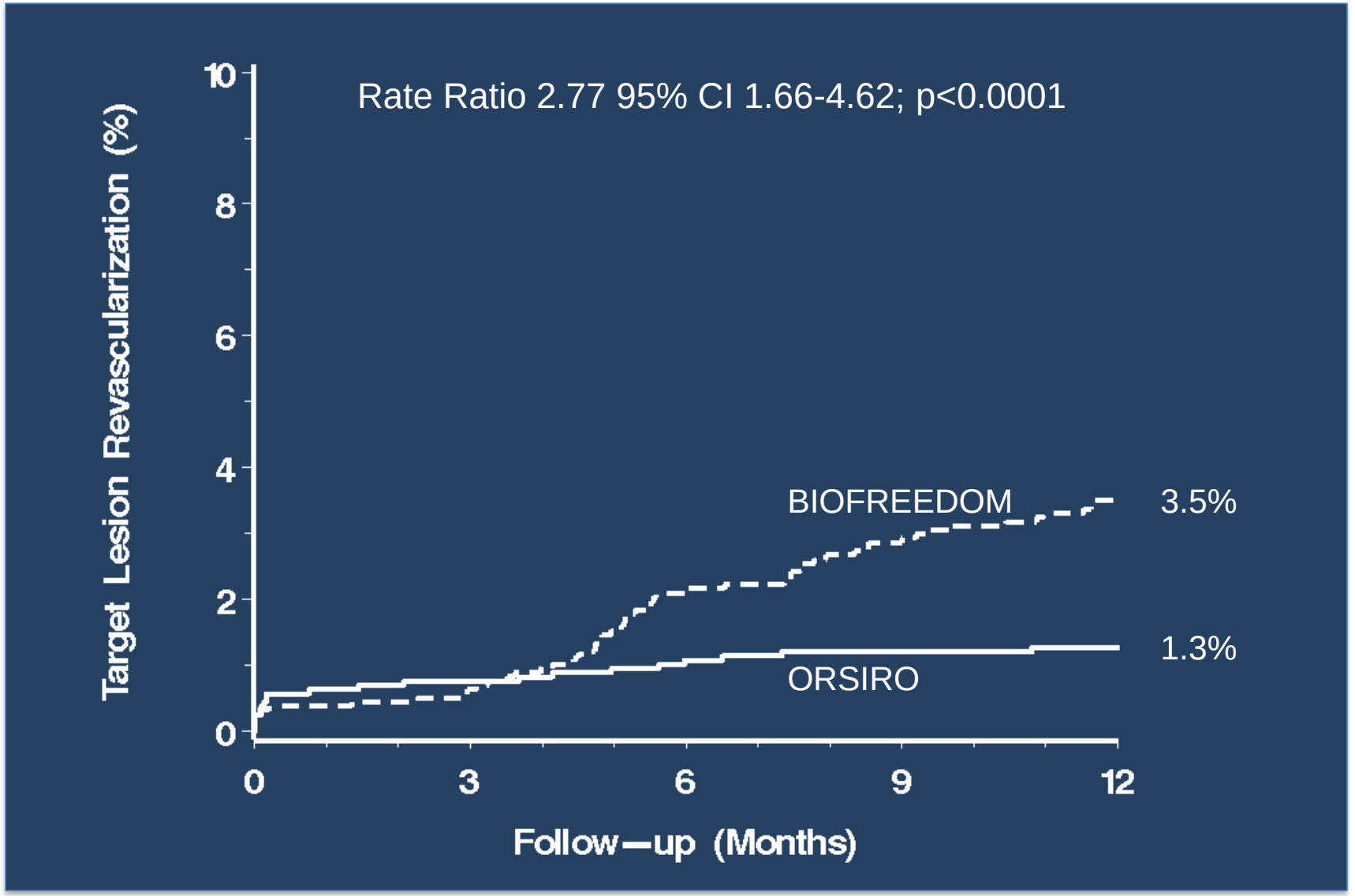
Okkels Jensen et al. on behalf SORT OUT IX Investigators, TCT 2018 – Oral presentation

SORT OUT IX
Primary Endpoint: TLF at 1 Year



Okkels Jensen et al. on behalf SORT OUT IX Investigators, TCT 2018 – Oral presentation

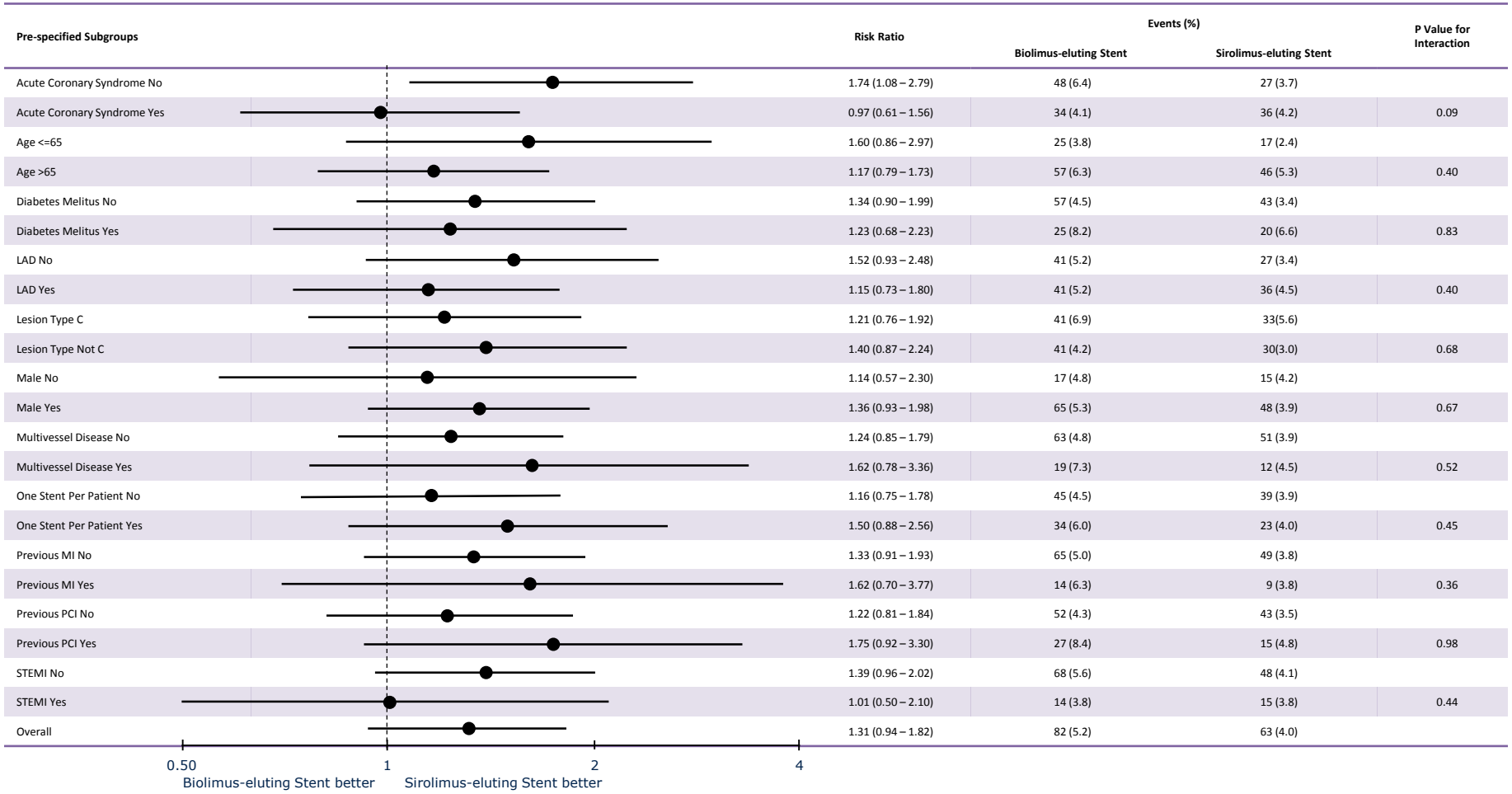
SORT OUT IX
Target Lesion Revascularization at 1 Year



Okkels Jensen et al. on behalf SORT OUT IX Investigators, TCT 2018 – Oral presentation

SORT OUT IX

TLF at 1 Year: Subgroup Analysis



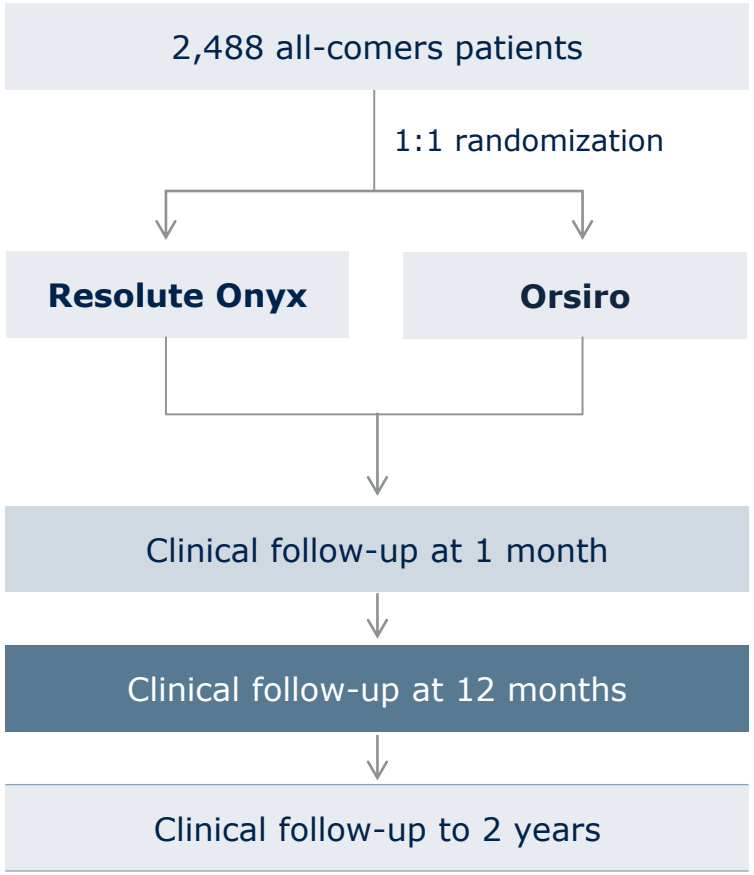
Pre-specified Subgroups	Risk Ratio	Events (%)		P Value for Interaction
		Biolimus-eluting Stent	Sirolimus-eluting Stent	
Acute Coronary Syndrome No	1.74 (1.08 – 2.79)	48 (6.4)	27 (3.7)	
Acute Coronary Syndrome Yes	0.97 (0.61 – 1.56)	34 (4.1)	36 (4.2)	0.09
Age <=65	1.60 (0.86 – 2.97)	25 (3.8)	17 (2.4)	
Age >65	1.17 (0.79 – 1.73)	57 (6.3)	46 (5.3)	0.40
Diabetes Melitus No	1.34 (0.90 – 1.99)	57 (4.5)	43 (3.4)	
Diabetes Melitus Yes	1.23 (0.68 – 2.23)	25 (8.2)	20 (6.6)	0.83
LAD No	1.52 (0.93 – 2.48)	41 (5.2)	27 (3.4)	
LAD Yes	1.15 (0.73 – 1.80)	41 (5.2)	36 (4.5)	0.40
Lesion Type C	1.21 (0.76 – 1.92)	41 (6.9)	33(5.6)	
Lesion Type Not C	1.40 (0.87 – 2.24)	41 (4.2)	30(3.0)	0.68
Male No	1.14 (0.57 – 2.30)	17 (4.8)	15 (4.2)	
Male Yes	1.36 (0.93 – 1.98)	65 (5.3)	48 (3.9)	0.67
Multivessel Disease No	1.24 (0.85 – 1.79)	63 (4.8)	51 (3.9)	
Multivessel Disease Yes	1.62 (0.78 – 3.36)	19 (7.3)	12 (4.5)	0.52
One Stent Per Patient No	1.16 (0.75 – 1.78)	45 (4.5)	39 (3.9)	
One Stent Per Patient Yes	1.50 (0.88 – 2.56)	34 (6.0)	23 (4.0)	0.45
Previous MI No	1.33 (0.91 – 1.93)	65 (5.0)	49 (3.8)	
Previous MI Yes	1.62 (0.70 – 3.77)	14 (6.3)	9 (3.8)	0.36
Previous PCI No	1.22 (0.81 – 1.84)	52 (4.3)	43 (3.5)	
Previous PCI Yes	1.75 (0.92 – 3.30)	27 (8.4)	15 (4.8)	0.98
STEMI No	1.39 (0.96 – 2.02)	68 (5.6)	48 (4.1)	
STEMI Yes	1.01 (0.50 – 2.10)	14 (3.8)	15 (3.8)	0.44
Overall	1.31 (0.94 – 1.82)	82 (5.2)	63 (4.0)	

A Randomized Trial Evaluating a Thin Composite Wire Strut Durable Polymer-Based DES Compared with an Ultra-Thin Strut Bioresorbable Polymer-Based DES in an All-Comers Patient Population - BIONYX

Design
International, multi-center, assessor- and patient-blinded, investigator-initiated, prospective, non-inferiority 1:1 randomized controlled trial comparing Resolute Onyx with Orsiro in an all-comers population

Objective
Evaluate the safety and effectiveness of Resolute Onyx compared to Orsiro in 2,488 all-comers patients

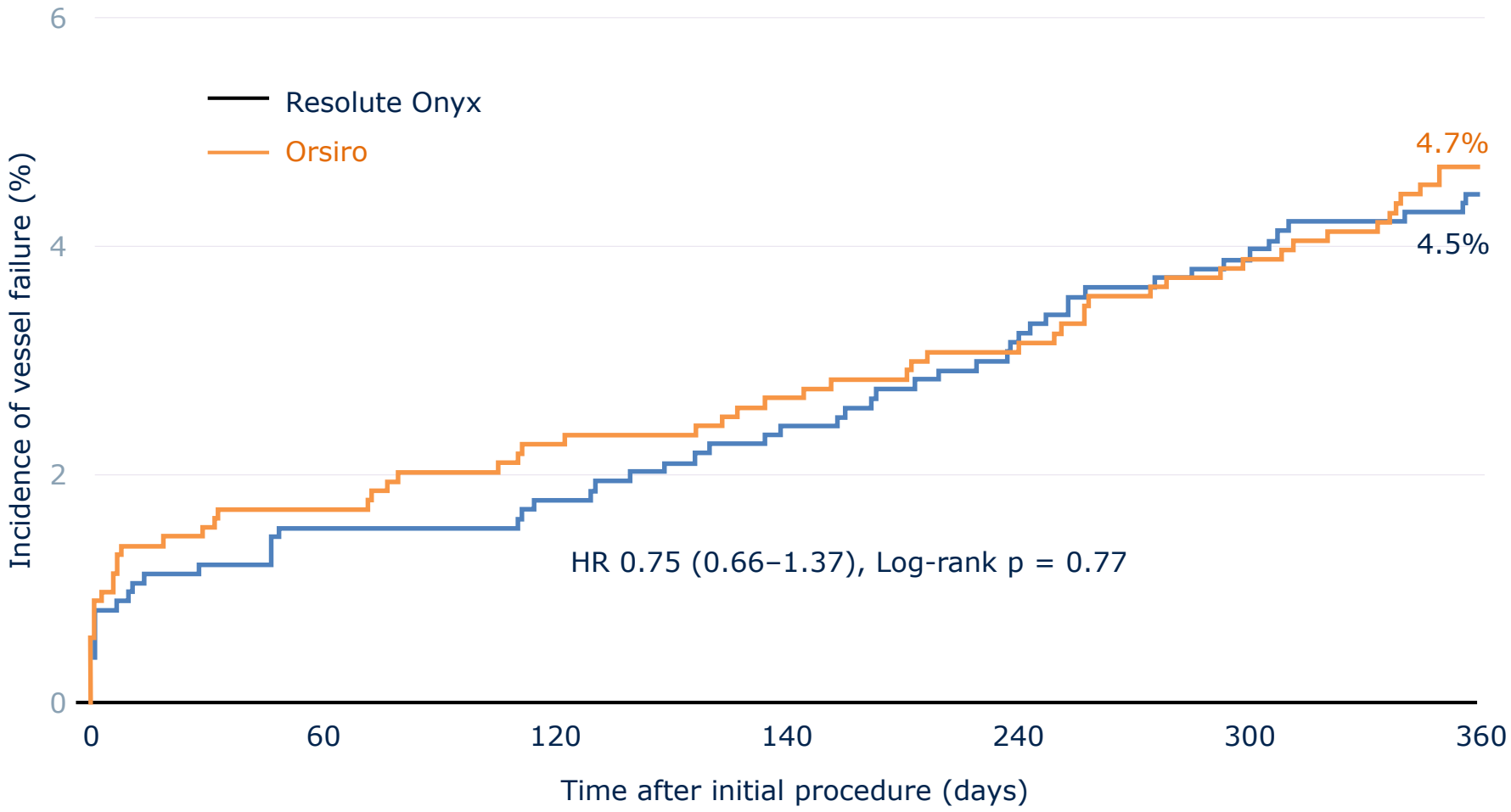
Primary Endpoint
Target Vessel Failure (TVF) rate at 12 months



~ 50% NSTEMI/STEMI
~ 20% Diabetes
~ 18% Multivessel PCI
~ 79% B2/C
~ 31% Bifurcation
~ 15% Severe Ca^{2+}
~ 3% CTO

Von Birgelen. TCT2018; Lancet 2018

BIONYX
Primary Endpoint: TVF at 1 Year

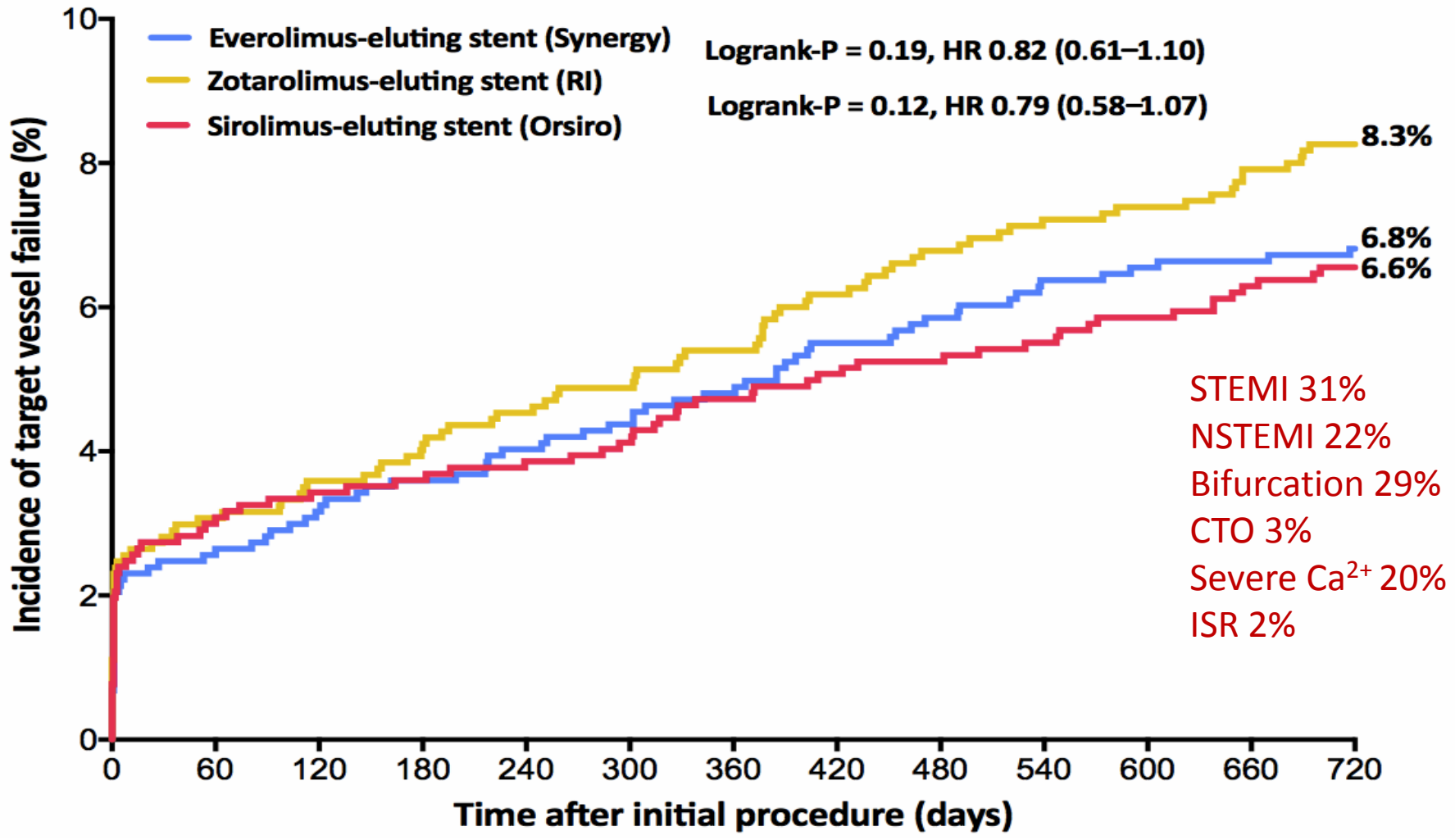


Von Birgelen. TCT2018; Lancet 2018

BIORESORT

Target Vessel Failure, 2 Years

N=3,514 All Comers

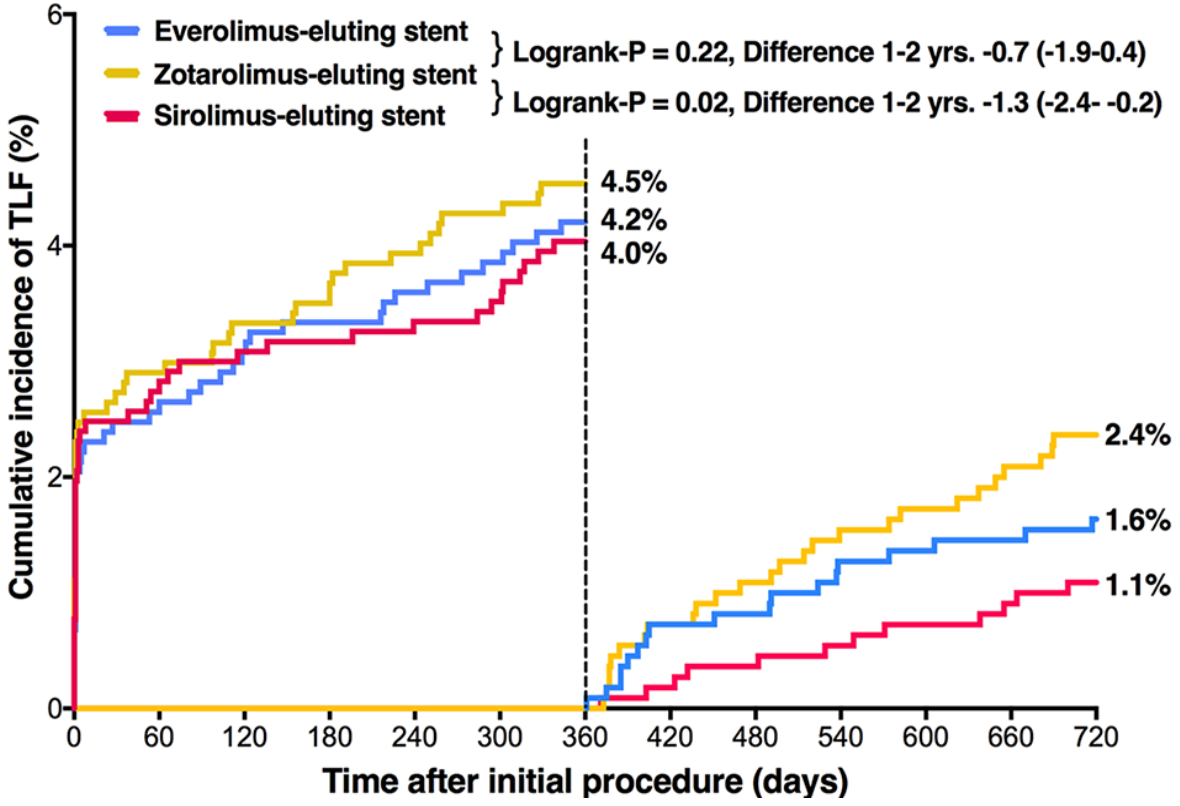


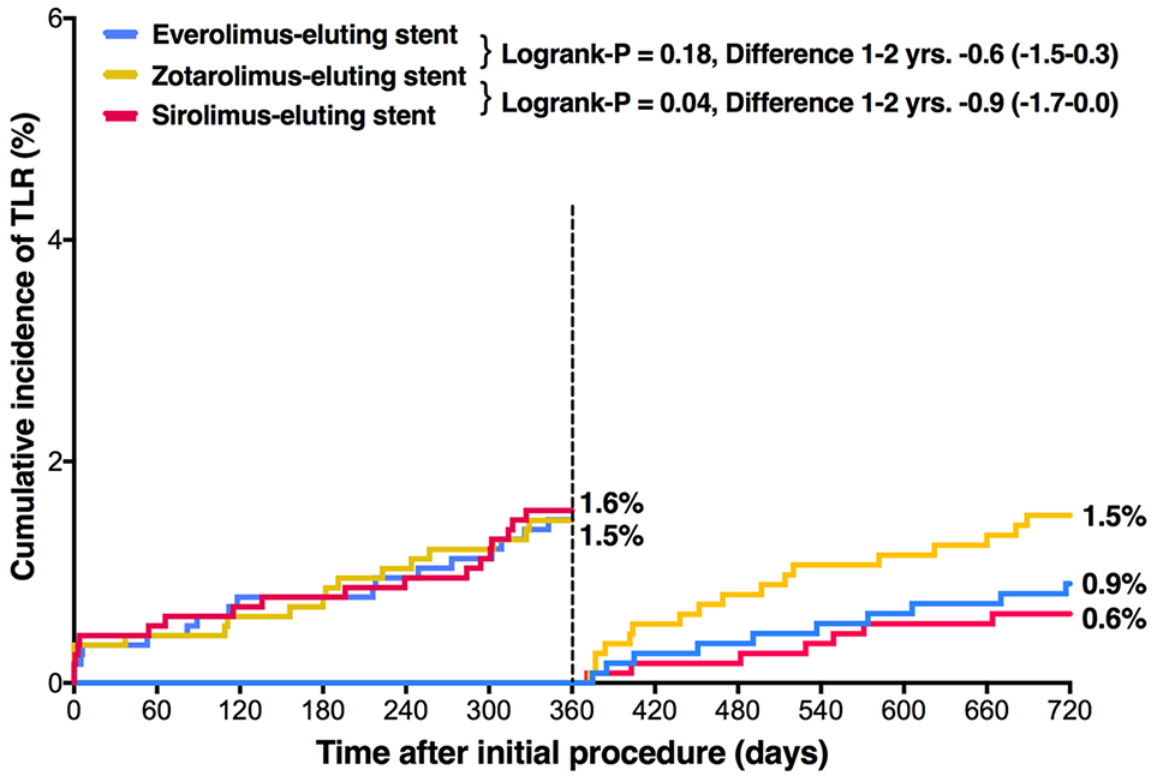
STEMI 31%
NSTEMI 22%
Bifurcation 29%
CTO 3%
Severe Ca^{2+} 20%
ISR 2%

Kok, von Birgelen et al. EuroPCR 2018; Eurointervention 2018

BIORESORT

Target Lesion Failure and TLR, Landmark Analyses 1 to 2 Years

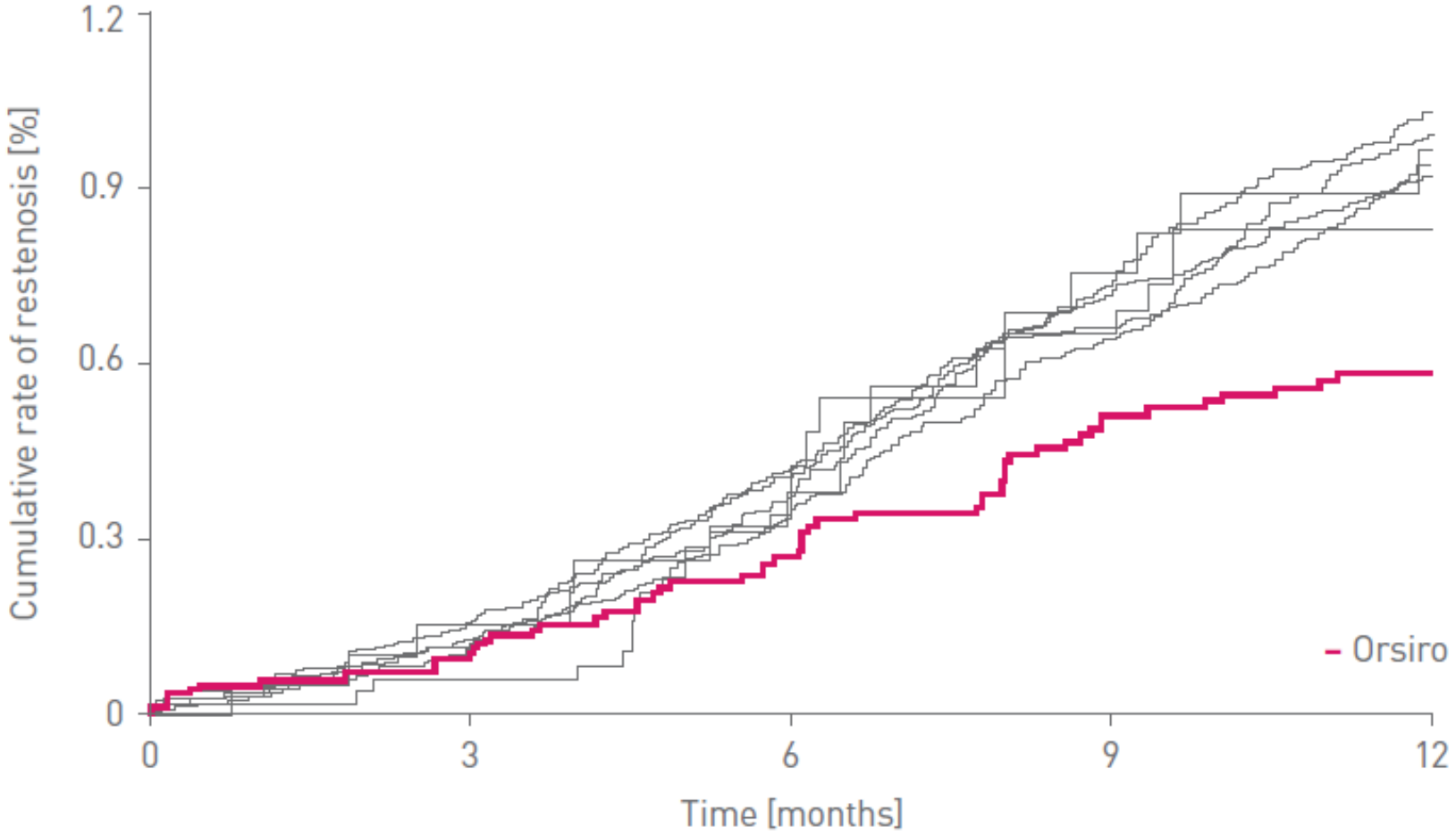




Kok, von Birgelen et al. EuroPCR 2018; Eurointervention 2018

SCAAR Registry

Clinical Restenosis Through 1 Year in Sweden, 2007 Through January 2018



For stents implanted at least 1000 times

Adapted from SCAAR: http://www.ucr.uu.se/swedeheart/images/stories/stent_reports/20180123/9Restenosis_first_year_in_most_used_stents.gif,

**other DES include: Resolute Integrity, Promus Premier, Synergy, Biofreedom, Resolute Onyx, Xience ProX

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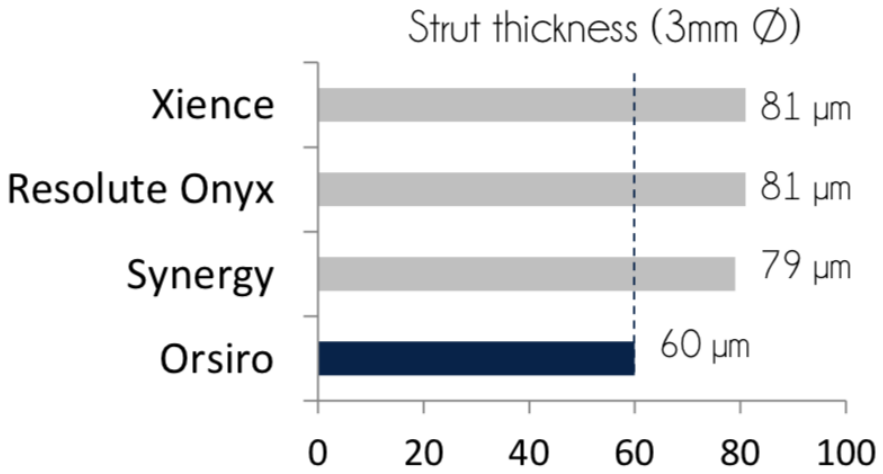
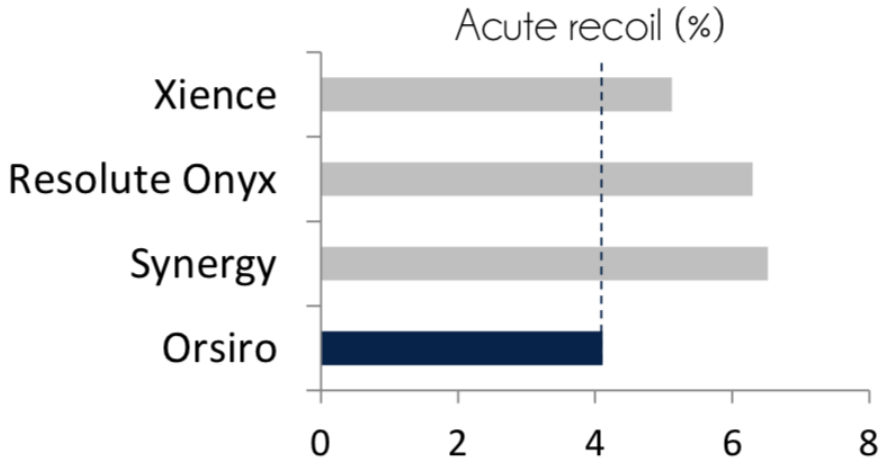
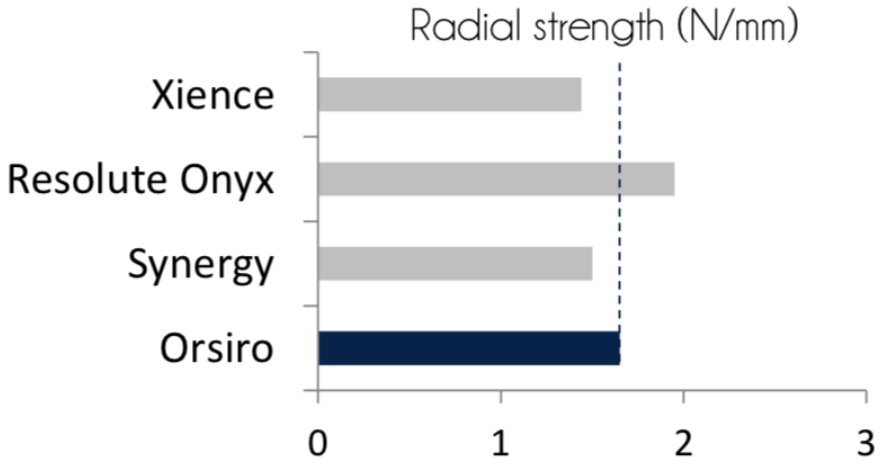
Comparative Properties of Ultrathin Strut vs Thin Strut DES

Struts are not Unidimensional







Bench test performed by independent laboratory - IIB // BIOTRONIK data on file

Source: S James, Evaluating the broad clinical utility of ultrathin bioabsorbable polymer DES; Oral presentation; Presented at: EuroPCR 2018; MAY 24

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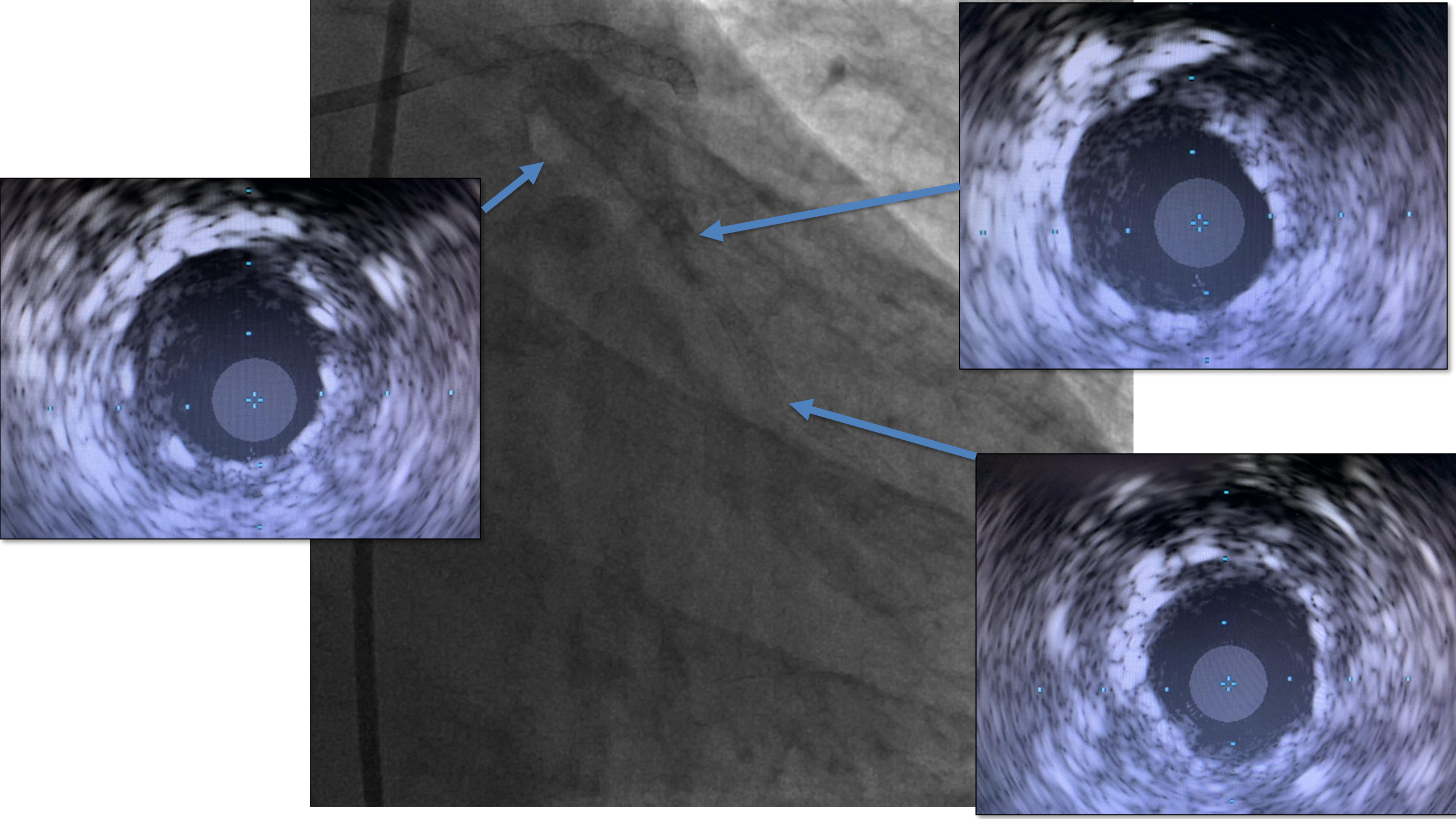

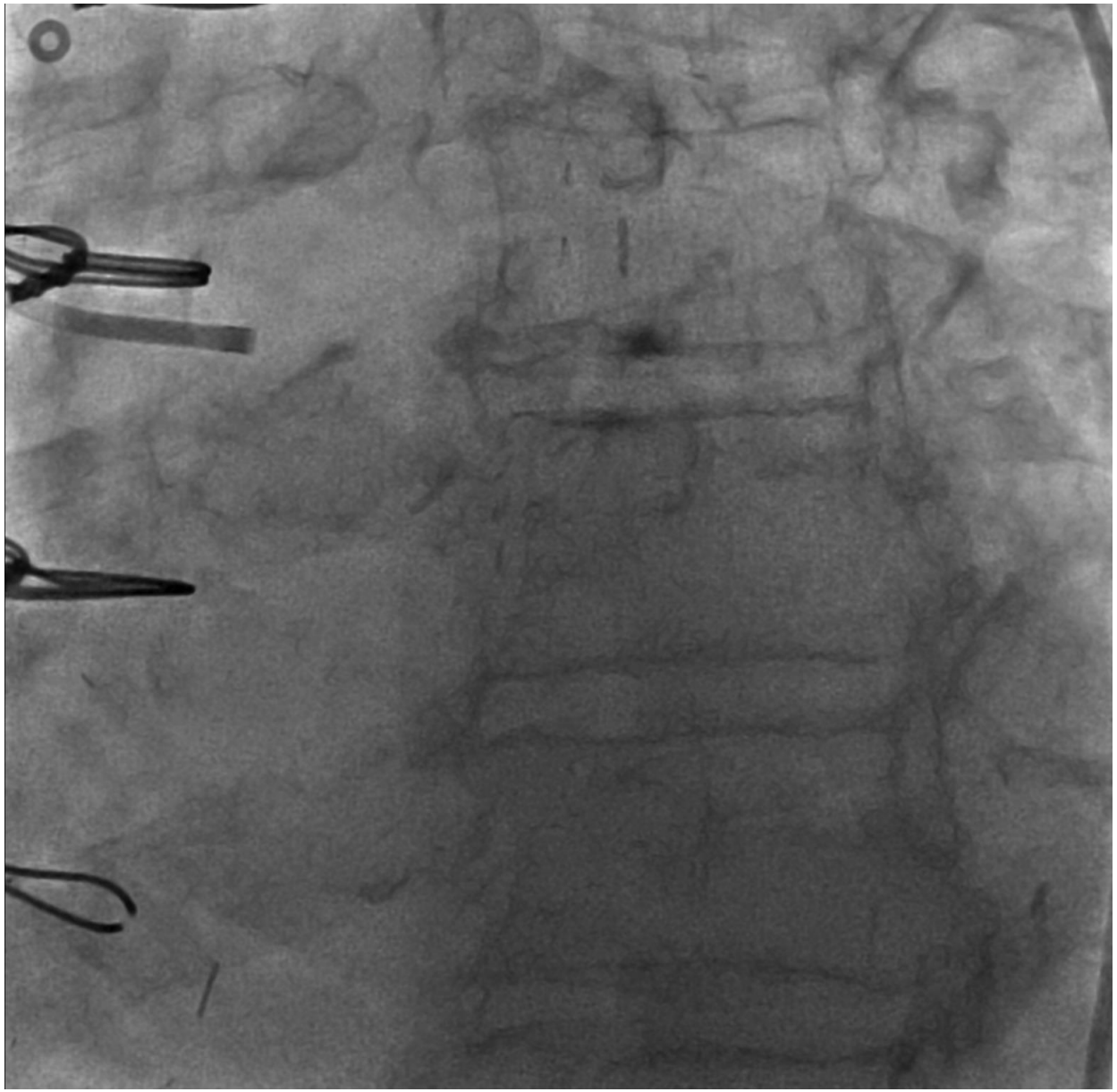

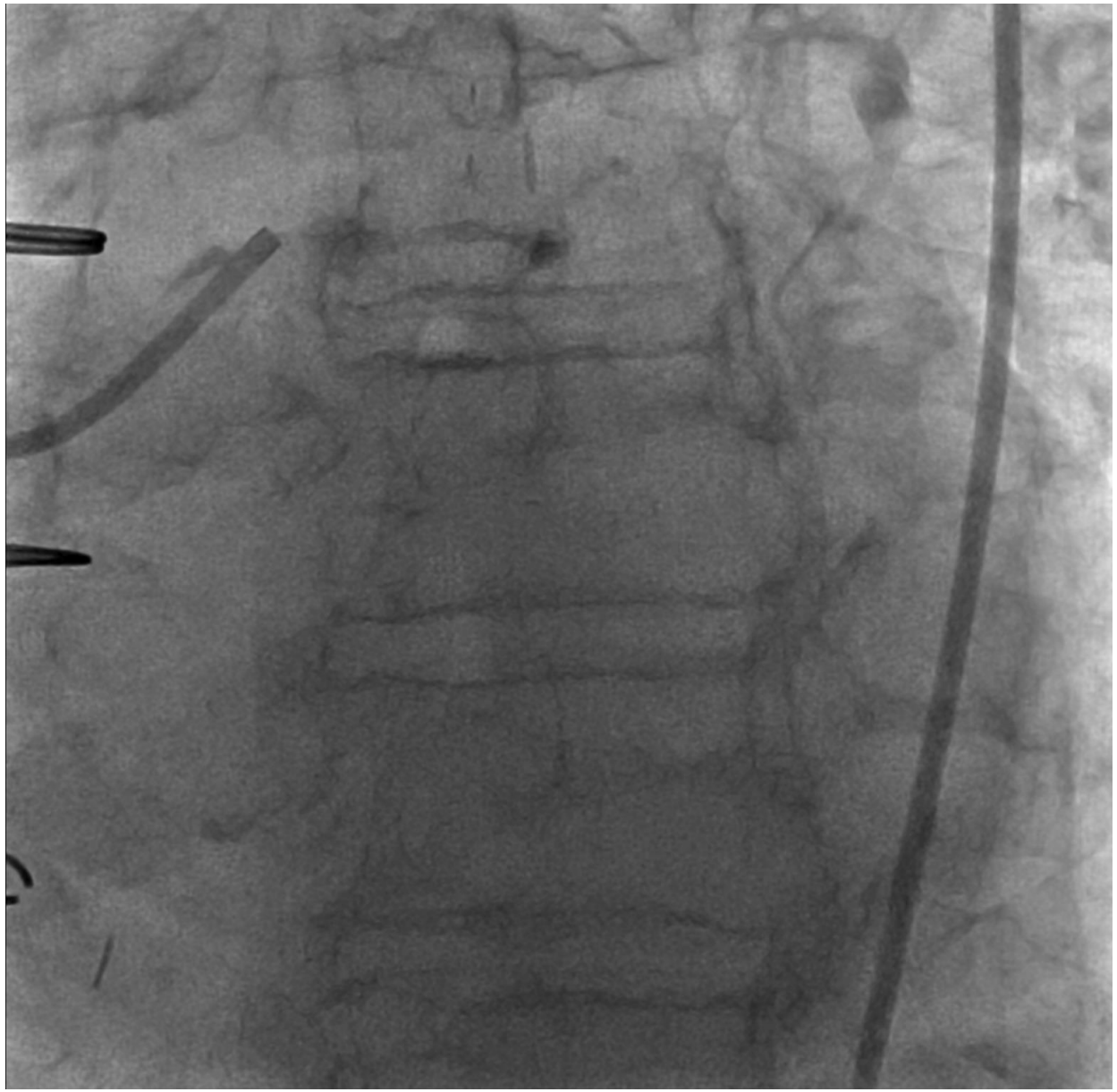

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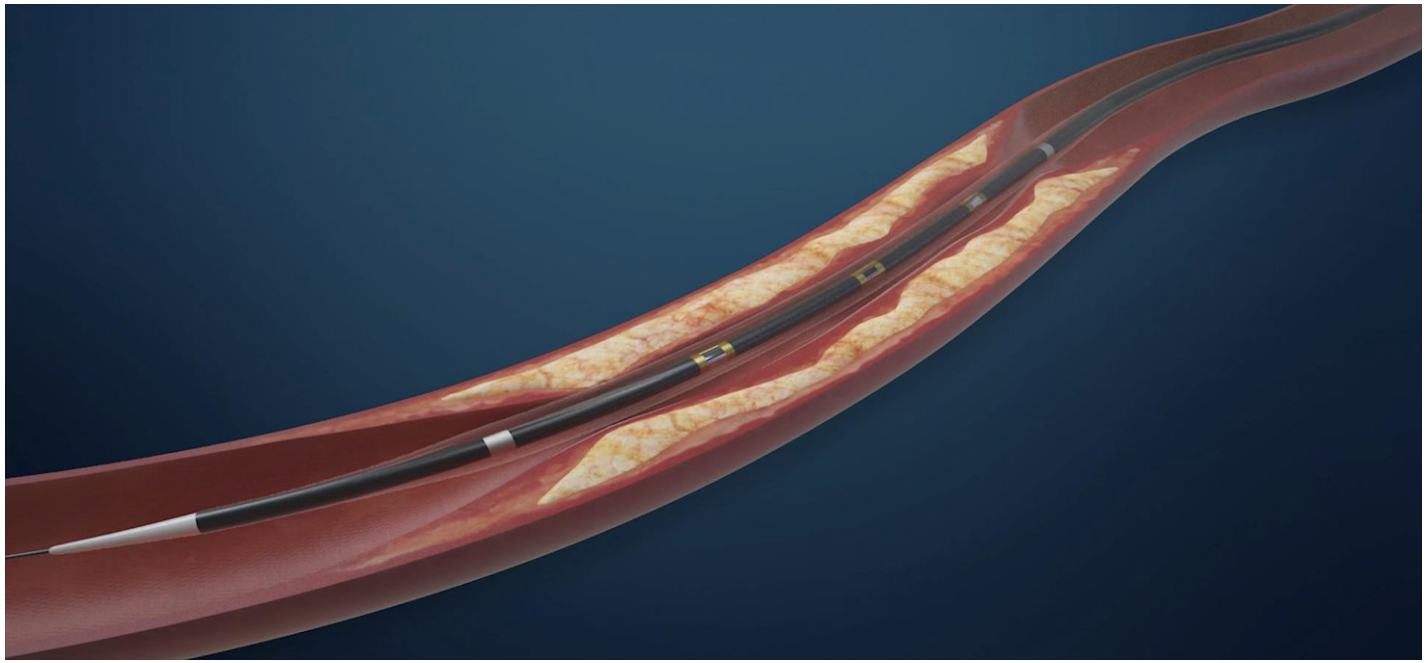
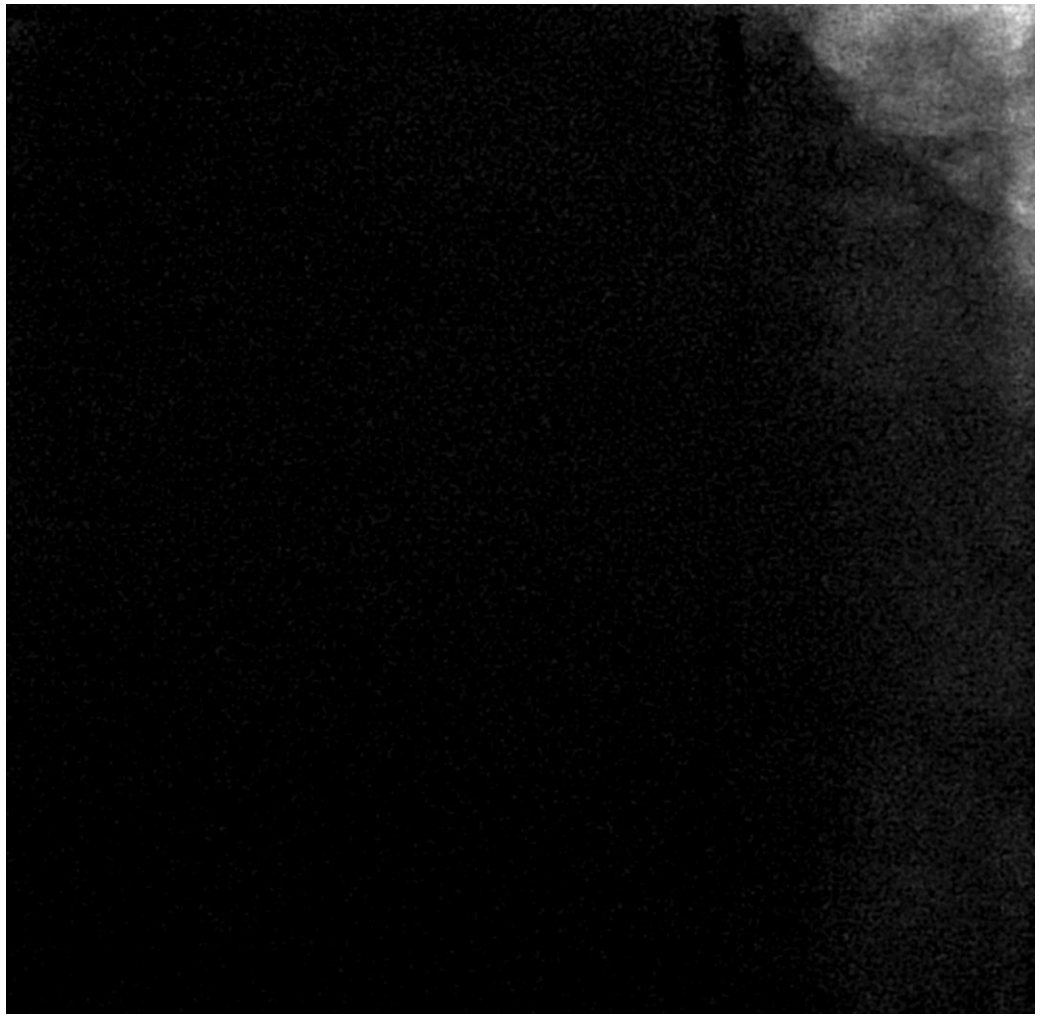
Intravascular Lithotripsy (IVL)
Shockwave Medical





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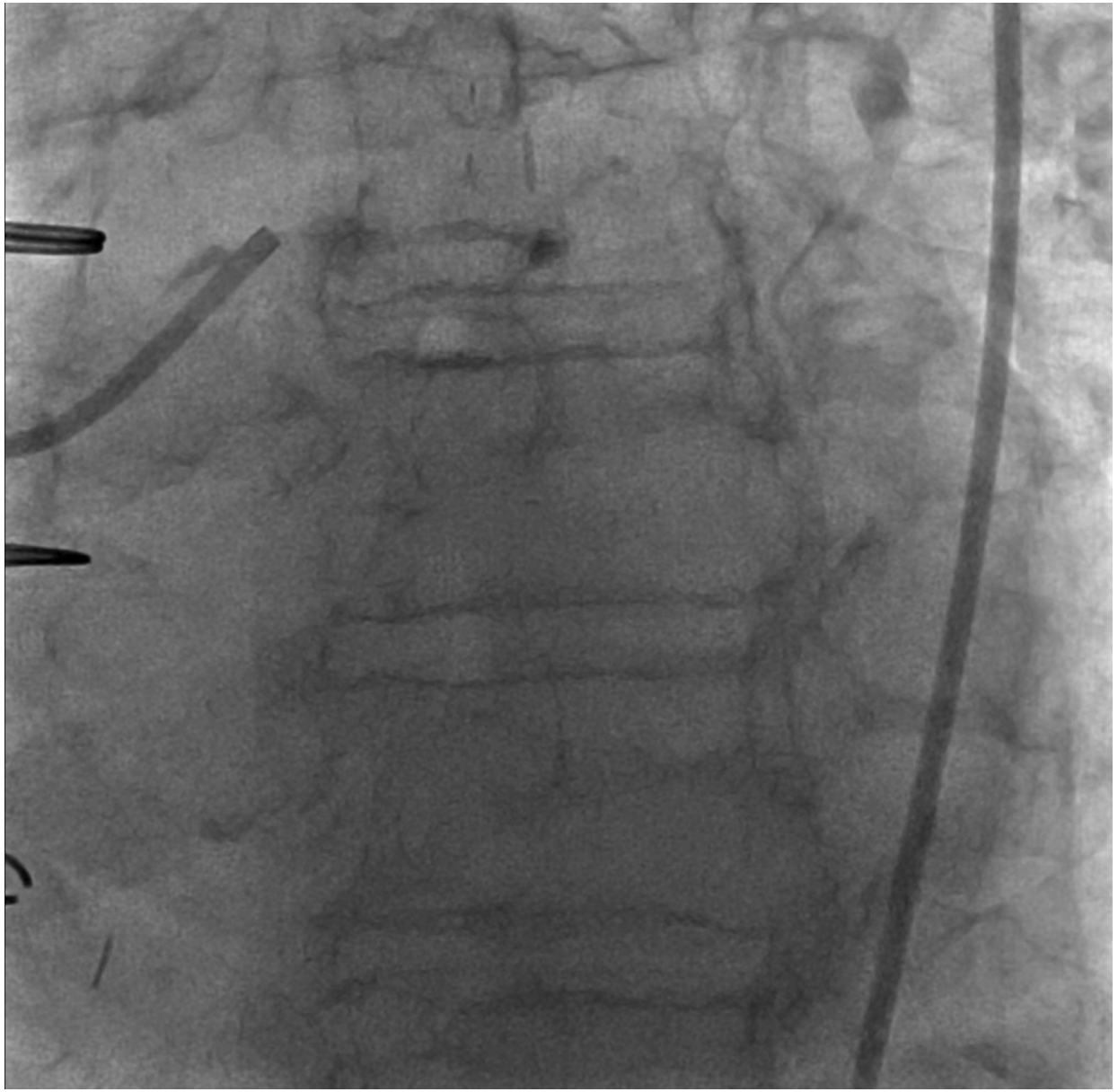

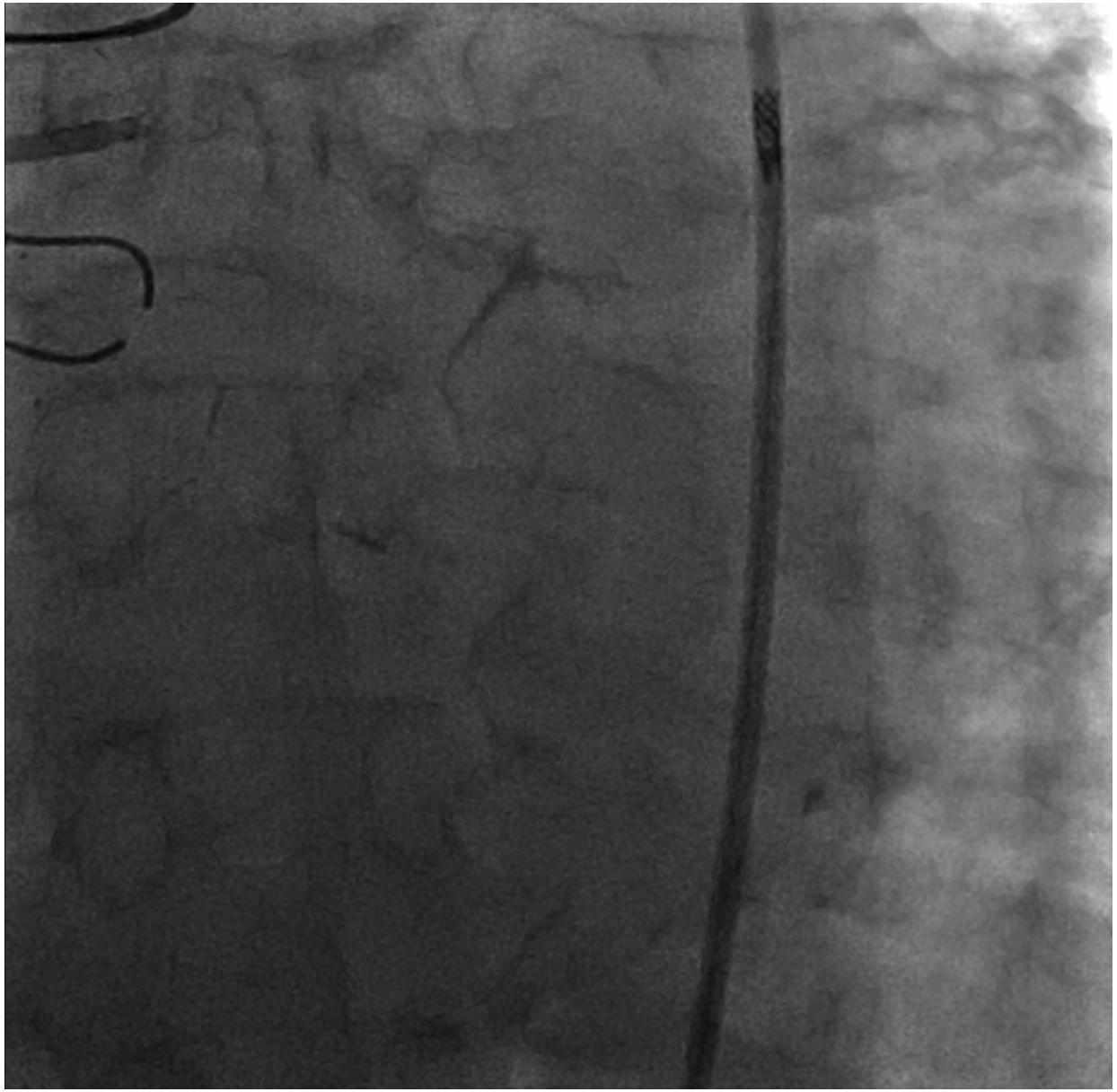

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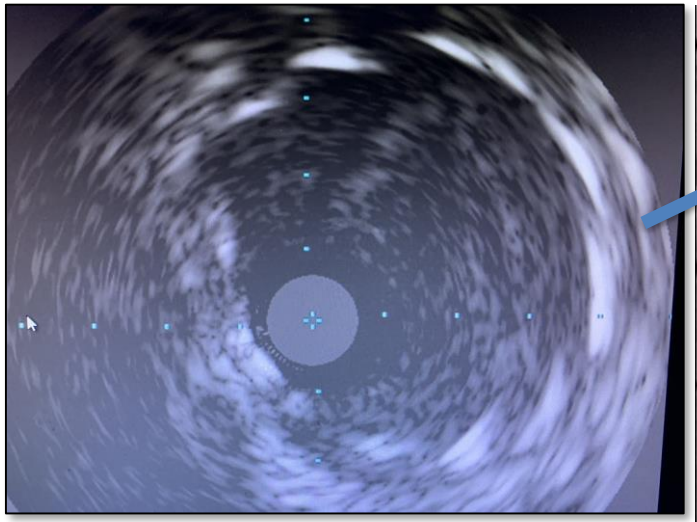

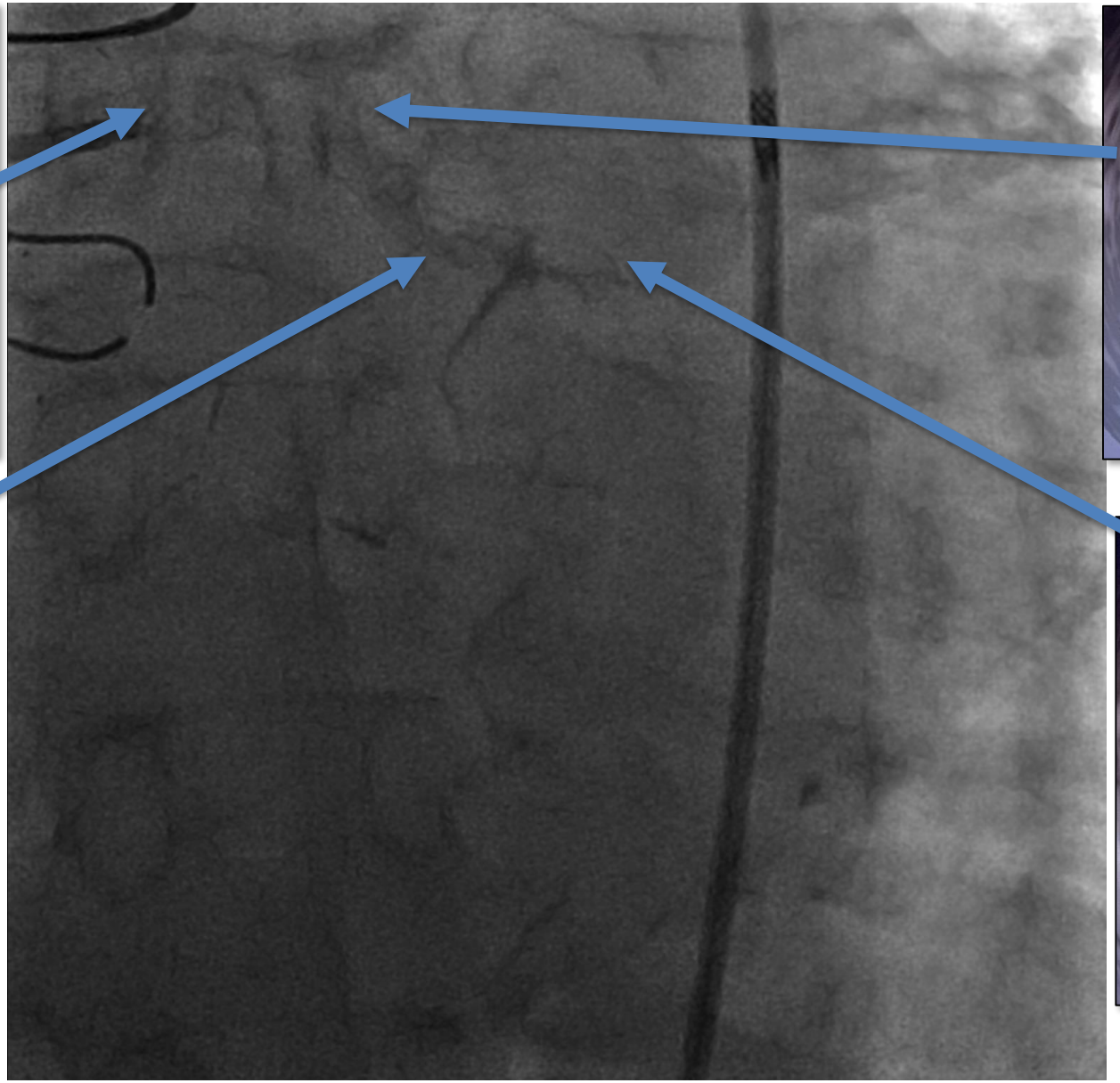

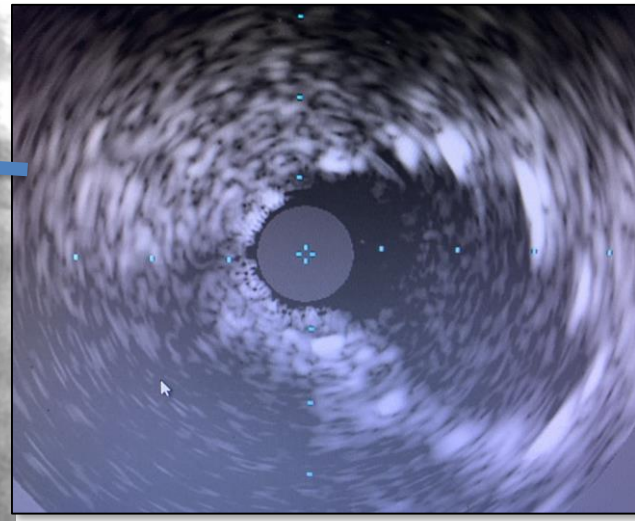

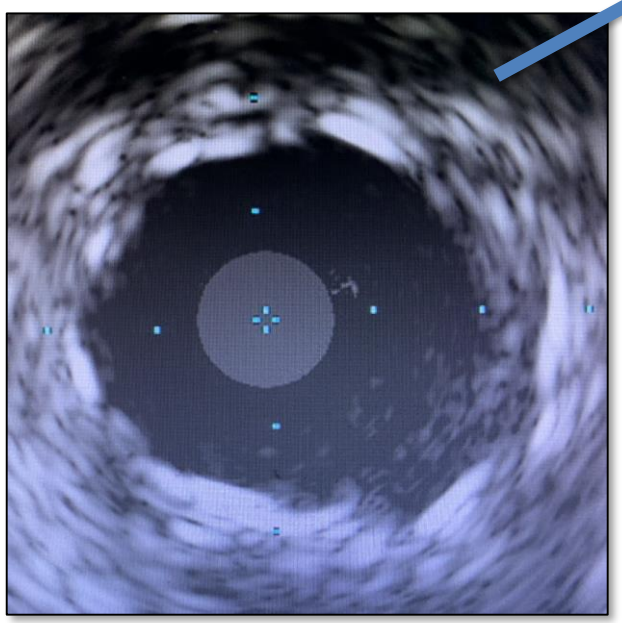

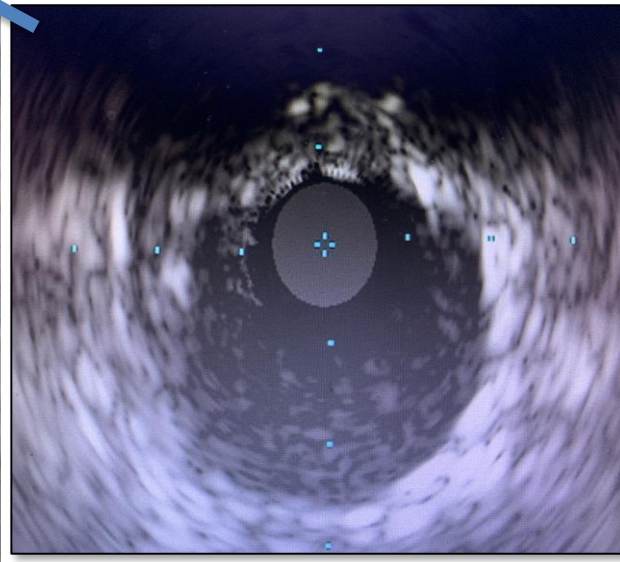

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Ultra-Thin Strut DES in Complex Indications and Lesions

Conclusions

- Emerging evidence suggests significantly lower MI, ST and TLR with ultrathin strut DES vs thin strut DES
  - Clinical observations supported by preclinical studies demonstrating improved healing and reduced injury, thrombus deposition
- Treatment with Orisiro ultrathin strut BP SES indicates comparable, if not superior, clinical outcomes compared with thin strut EES and ZES in RCTs inclusive of complex patient indications and anatomy
- Evolution of ultrathin strut stent designs indicates improved performance (deliverability, trackability) without compromising radial strength and scaffolding properties
  - Stent performance and characteristics represent multiple variables other than strut thickness alone

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