DES Evolution

Bioresorbable Polymer DES as a Standard in Trials and Clinical Practice

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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
Grant/Research Support	Abbott Vascular, Boston Scientific, Medinol Medtronic CardioVascular, Biotronik, Thoratec
Consulting Fees/Honoraria	Boston Scientific Corporation, Medtronic CardioVascular
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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What are the requirements of DES in 2016?

Drug-eluting stent trials: too much non-inferiority, too little progress?

What are our expectations for a new generation DES?

- *Is 'as good as' good enough? Is at least 50% as good acceptable?*
- *Must a 'new, but similar' DES demonstrate similar head-to-head outcomes or is inference good enough?*
- *Are preclinical (endothelialization) and mechanistic (OCT, vasomotion) data sufficient to support a new DES with limited human experience?*

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Evolution of DES Randomized Trials

"CIs are broad and overlapping, reflecting the overall low incidence of events. This is an ongoing issue in trials of emerging DES technology, making the design of trials powered to detect safety benefit with comparator stents largely infeasible."

Byrne, R. A. et al. J Am Coll Cardiol 2011;58:1325-1331

Meta-Analyses, Network Meta-Analyses…

RCT remain standard for regulatory approval

[1]Leon et al. JACC Intv 2010; [2]Stone TCT 2010; [3]Stone TCT 2010; [4]Park JAMA 2009, [5]Windecker et al. Lancet 2008; [6]Kedhi et al. Lancet 2009; Smits TCT 2010; [7]Serruys NEJM 2010

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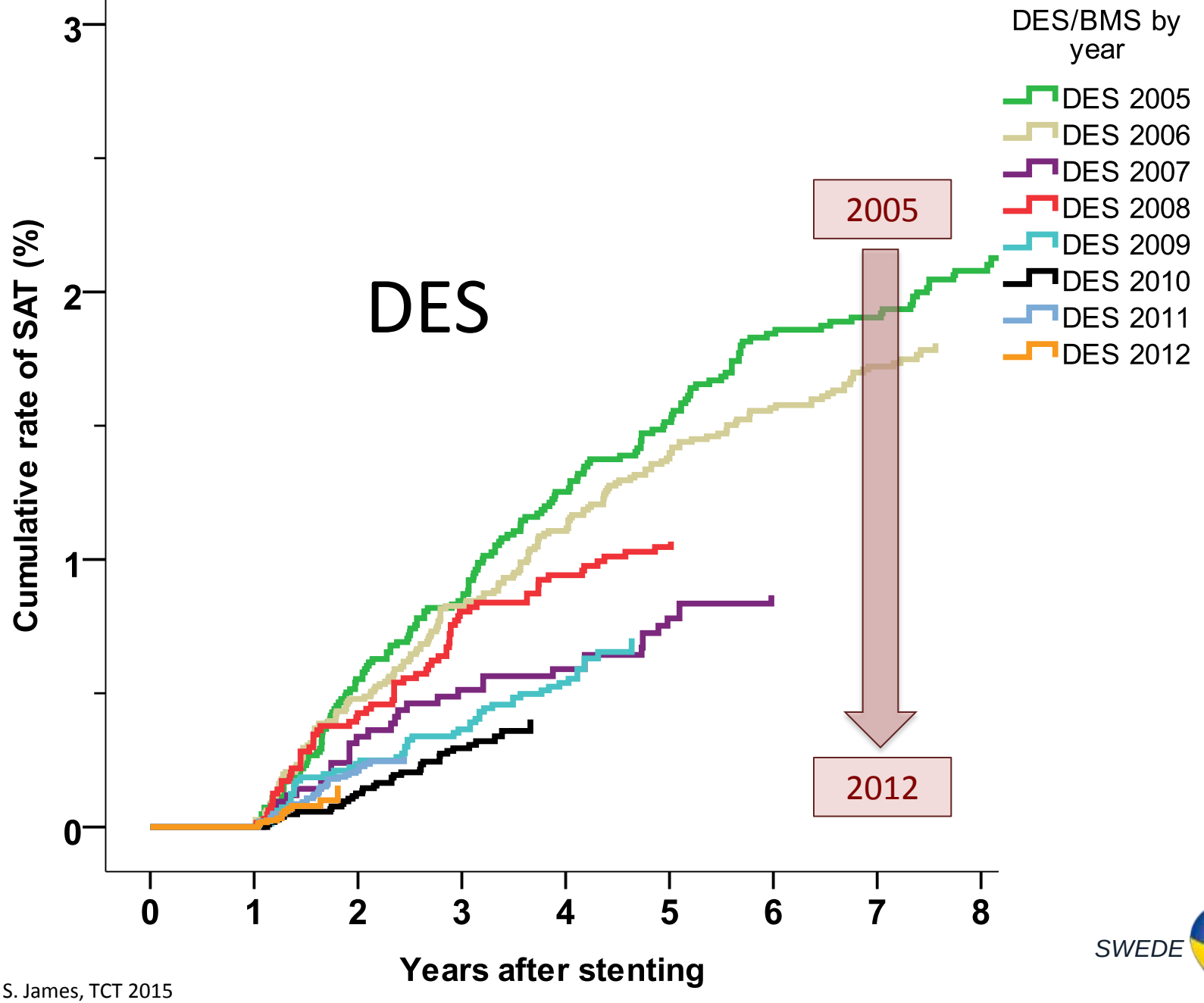
SCAAR Cumulative ST Risk for DES



S. James, TCT 2015

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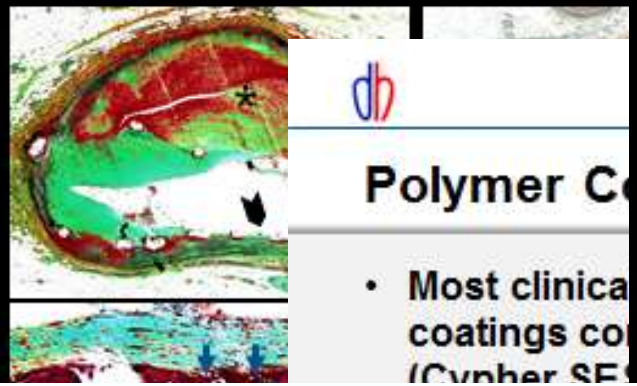
Delayed Arterial Healing Af



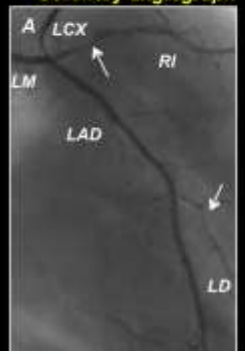
Polymer C

- Most clinica
coatings co
(Cypher SE

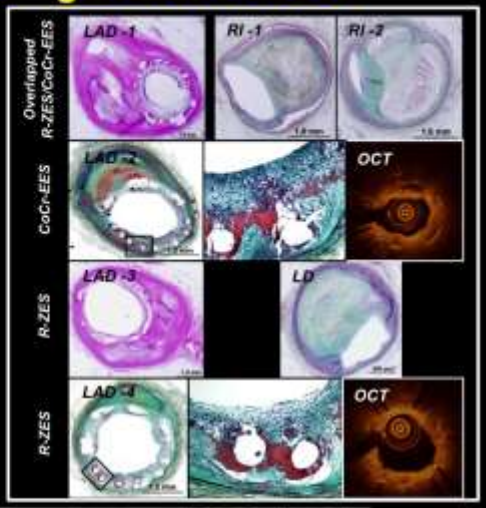
Hypersensitivity Reaction in 2nd generation DES

A 55-year old male who presented with unstable angina secondary to diffuse disease in the LAD; four stents were implanted (3 Resolute zotarolimus-eluting stents (R-ZES) and a single cobalt-chromium everolimus-eluting stent (CoCr-EES). At 238-days following implantation of the 4 stents the patient died suddenly.

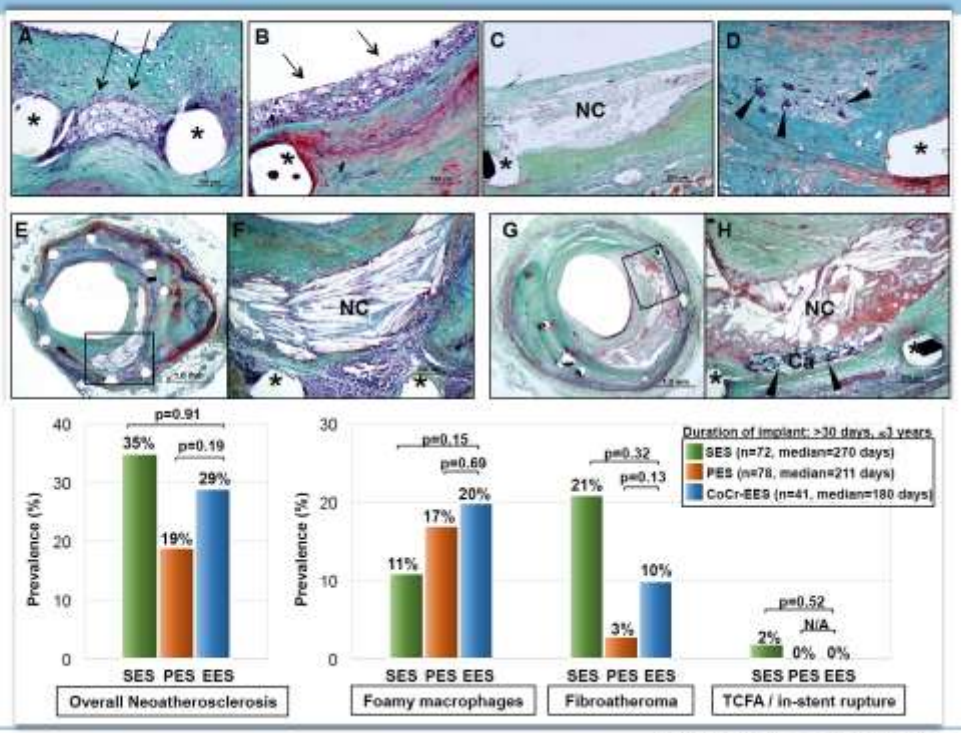
Coronary angiograph



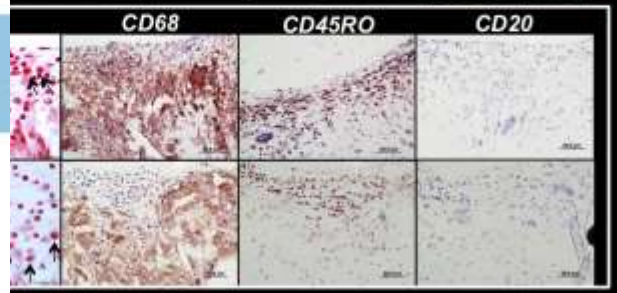
Radiograph



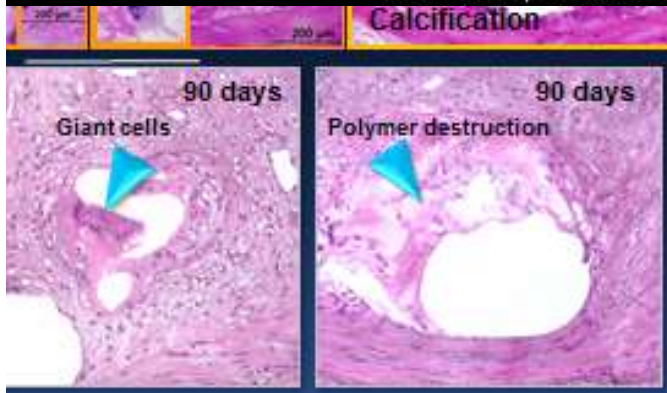
Neoatherosclerosis: Prevalence



Otsuka, Byrne et al. | Eur Heart J 2015



Otsuka et al. | Circulation 2015

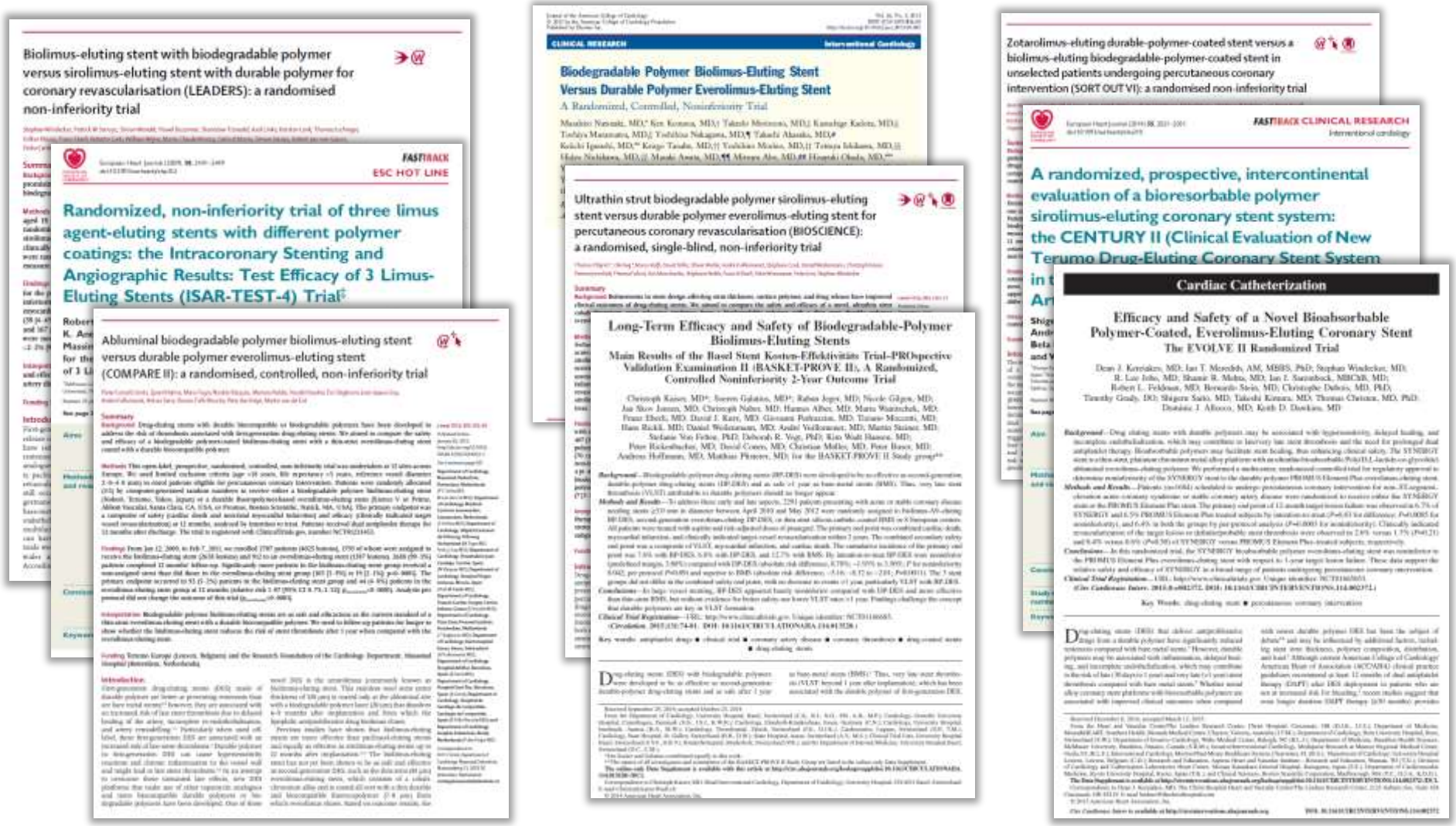


sponse to durable polymer
ys a central role in DAH

Evolution of DES

- Newer generation durable polymer DES (DP DES) significantly improve safety and efficacy outcomes compared with both BMS and early generation DP DES
  - Represent the current standard of care for PCI in all patient and lesion subsets
- Newer generation DP DES in higher risk patients remains associated with higher clinical failure
- Permanent polymer coatings of newer generation DES have been associated with chronic inflammation, hypersensitivity, and neoatherosclerosis translating to late restenosis and thrombosis
  - SPIRIT III, COMPARE: 2-3% annualized TLF rate
  - ISAR TEST 4: 2-fold progression of neointimal hyperplasia with EES
- Biodegradable polymer DES (BP DES) were designed to overcome limitations of DP DES and represent a safe and effective alternative to unselected PCI patients

Comparable 1 Year Outcomes for BP DES and PP DES



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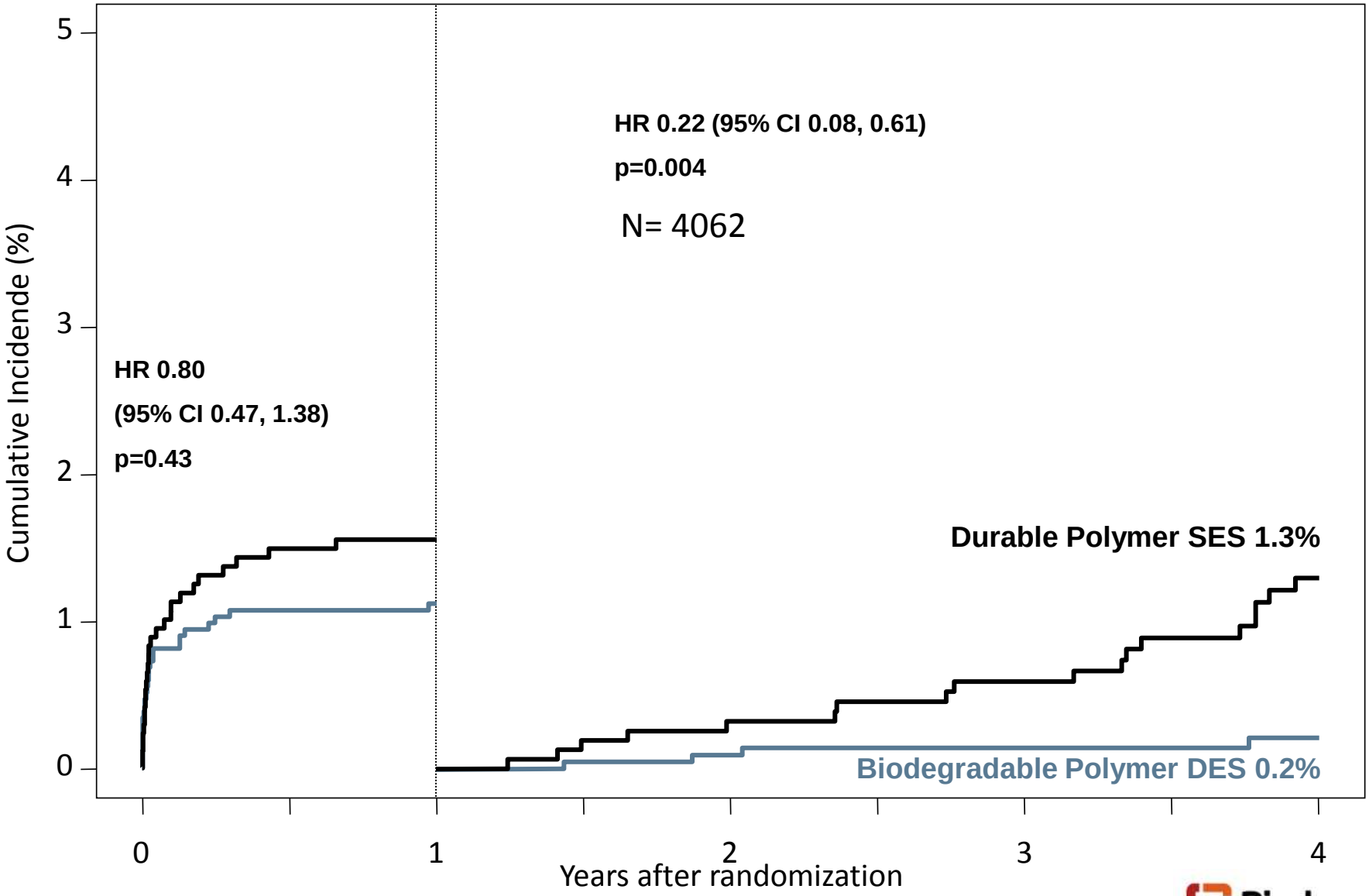
Definite Stent Thrombosis

Pooled Analysis of ISAR TEST 3, ISAR TEST 4 and LEADERS Trials



Stefanini, Byrne et al, Eur Heart J 2012

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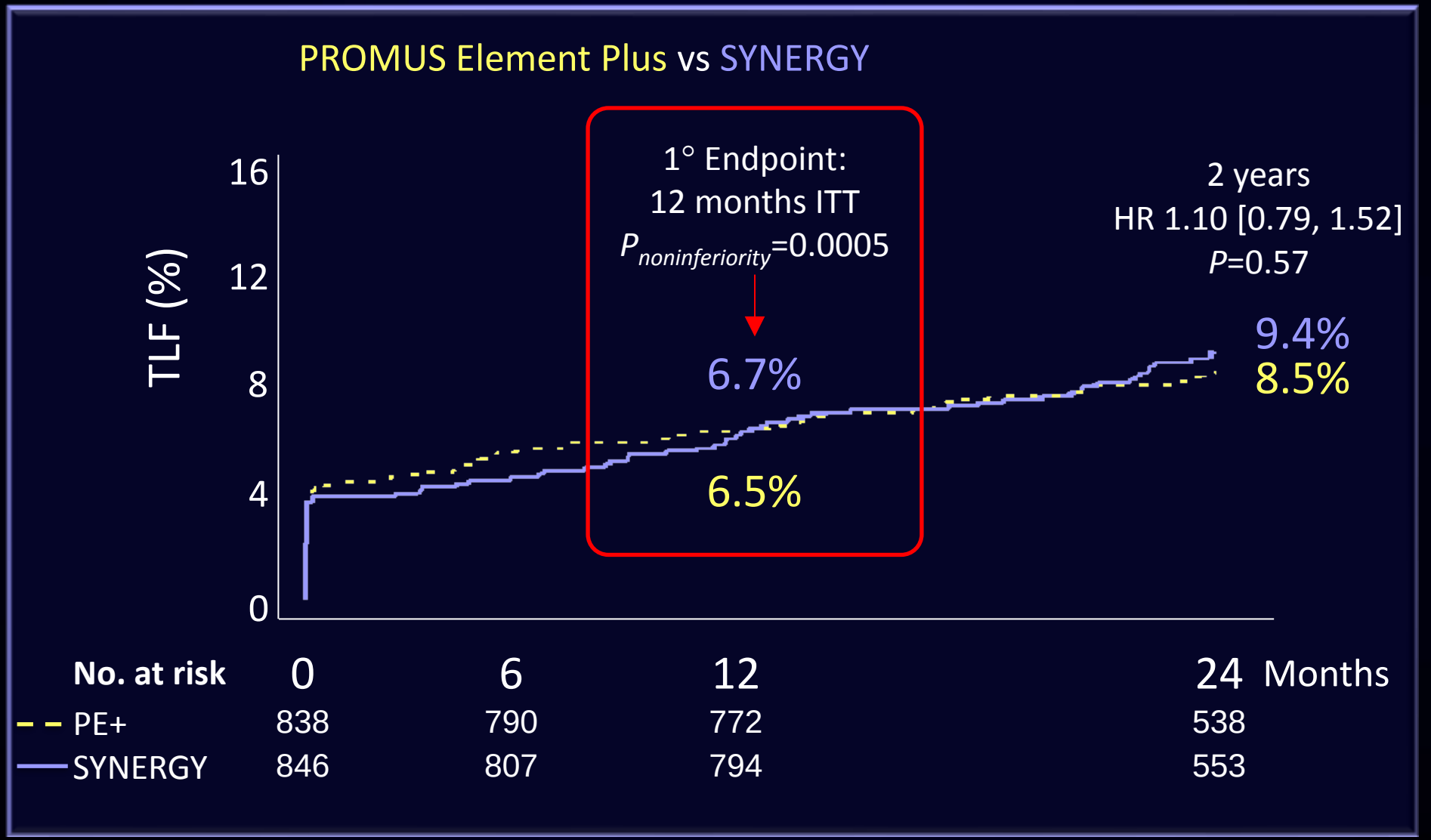
EVOLVE II TLF at 1 and 2 years

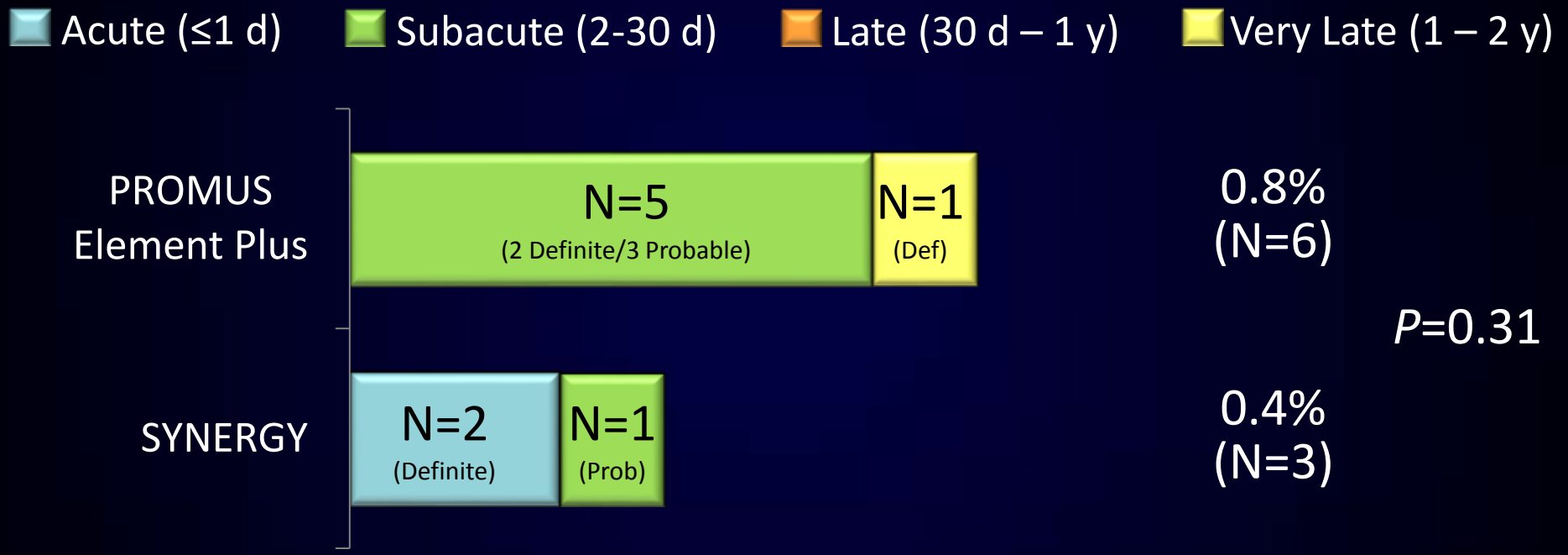


Kereiakes ACC 2016

ITT Population; Patients who did not receive a study stent were censored at 1 year; KM Event Rates; log-rank *P* values

Stent Thrombosis at 2 years

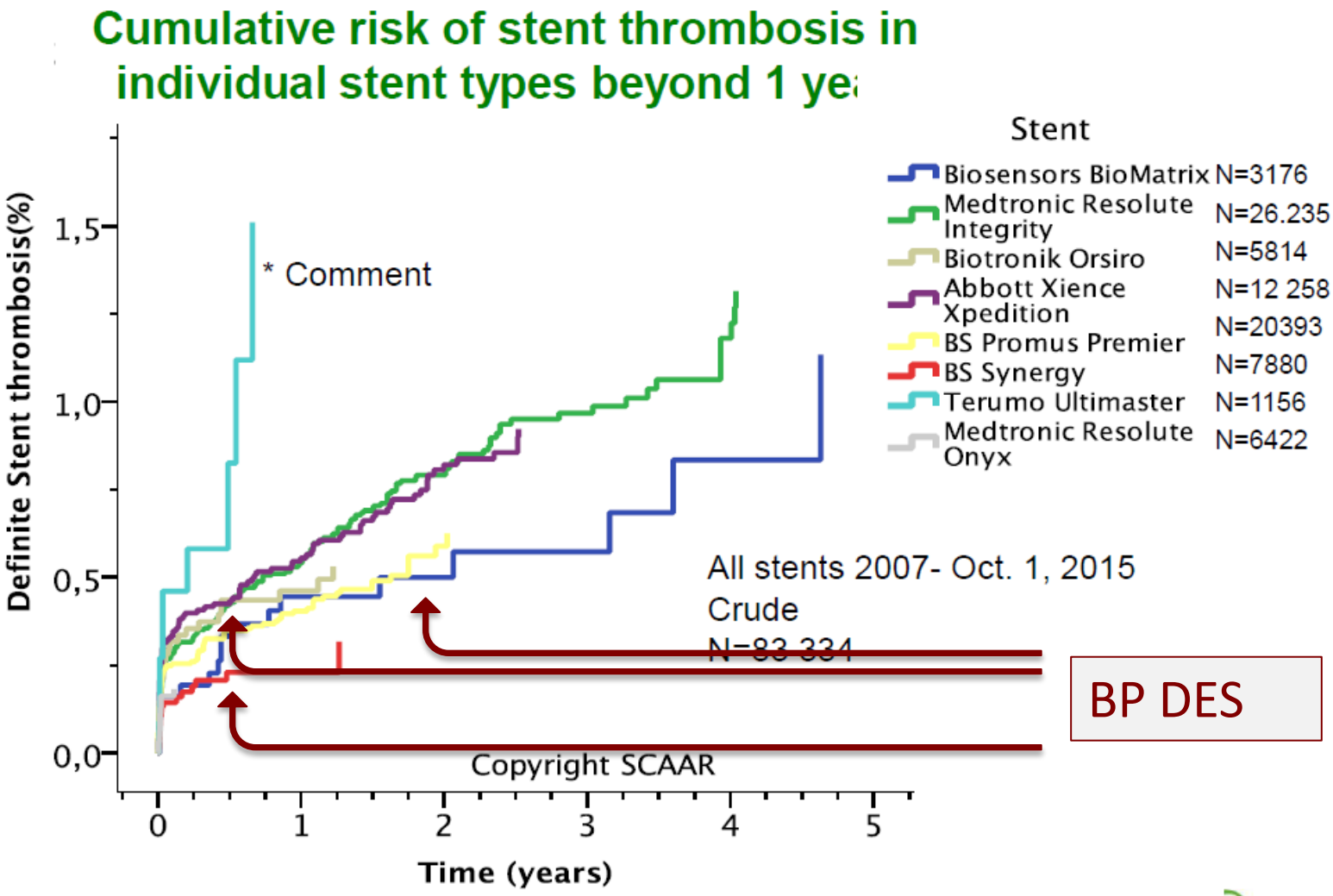
Definite/Probable : ITT Population



No definite ST in the SYNERGY arm after 24 hours

Kereiakes ACC 2016

SCAAR Registry Definite ST for Contemporary DES



*The risk of Stent trombosis is based on the Kaplan Meier Estimat. For the Ultimaster stent only 9 stent thromboses was reported in 1156 stents. Eight of these in one hospital.

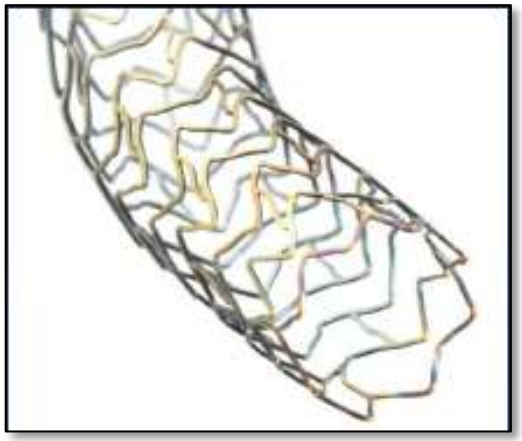
S. James, TCT 2015

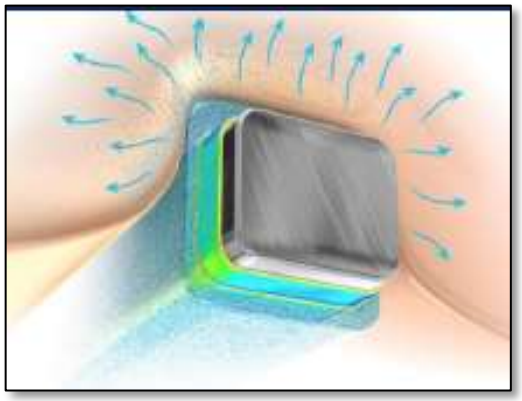
BIOTRONIK Osiro Clinical Trial Program

Stent platform: PRO-Kinetic Energy
- Cobalt Chromium, L-605
- 60µm struts, double helix design

Active coating: BIOlute (Conformal)
- PLLA* bioabsorbable polymer matrix
- Sirolimus (Drug load is 1.4µg/mm$^{2)}$

Passive coating: PROBIO
- Silicon carbide** layer that encapsulates the stent surface, reducing ion release and prevent corrosive process





* Poly-L-lactide
** aSiC:H amorphous silicon carbide

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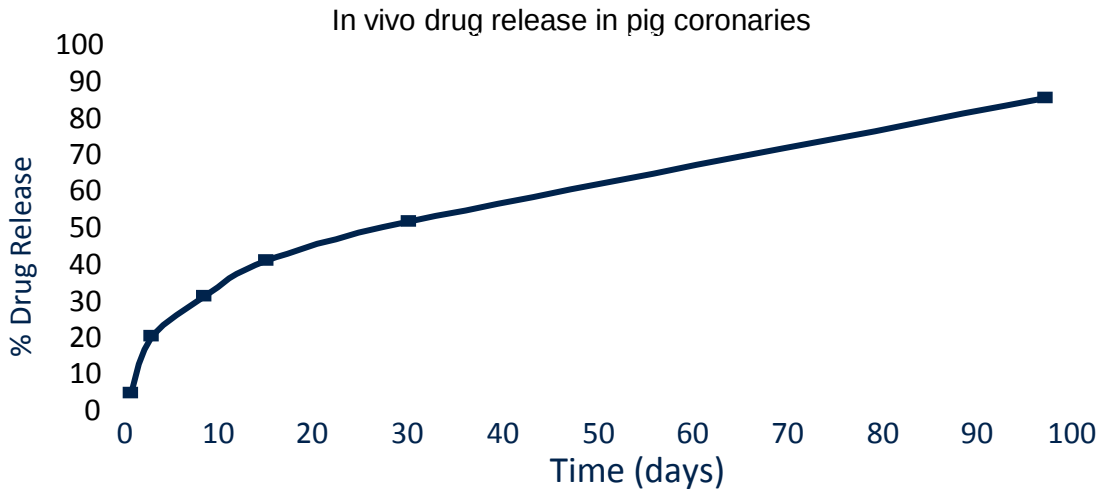
BIOTRONIK Osiro BP DES

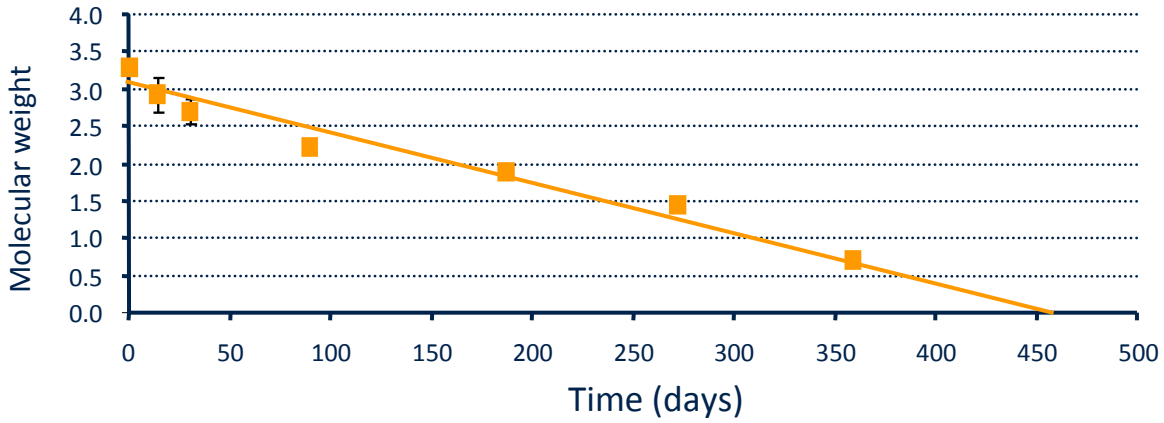
Sirolimus Elution as Measured on Orsiro DES

- ≈50% of the drug is eluted over 30 days
- In vivo studies show Sirolimus release in 90-100 days
- Drug load is 1.4 µg/mm²



Degradation Profile of Orsiro's BIOlute Polymer Coating

- BIOlute degrades over time, leaving BMS for best long-term clinical outcome
- Durable polymers can lead to chronic inflammatory responses



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BIOTRONIK Osiro BP DES

Durable Polymer Coated Stent		Bioabsorbable Polymer Coated Stent		Bioabsorbable Scaffold
Abbott/Boston	Medtronic	Boston	BIOTRONIK	Abbott
Xience/Promus[1] CoCr/PtCr-EES	**Resolute**[1] CoNi-ZES	**Synergy**[1] PtCr-EES	**Orsiro**[1*] CoCr-SES	**Absorb**[2] PLLA-EES

Strut thickness

81 µm	91 µm	74 µm	60 µm	150 µm

Polymer coating

Circumferential 7-8 µm/side	Circumferential 6 µm/side	Abluminal 4 µm	Circumferential 4-7µm/side	Circumferential 3 µm/side

Sources: 1: GG Stefanini, M Taniwaki, S Windecker, Coronary stents: novel development, Heart doi:10.1136/heartjnl-2012-303522; 2: IT Meredith, Scientific symposium, TCT 2013

Osiro Clinical Trial Program

	BIOFLOW-I	BIOFLOW-II	BIOFLOW-III	BIOFLOW-IV	BIOSCIENCE
Study type	• Prospective • Multi-center • Non-randomized • Single-arm	• Prospective • Multi-center • **Randomized** (2:1 vs Xience Prime)	• Prospective • Multi-center • Non-randomized • Single-arm • Open label	• Prospective • Multi-center • **Randomized** (2:1 vs Xience Prime/Expedition)	• Prospective • Multi-center • **Randomized** (1:1 vs Xience Prime)
Primary Endpoint	Late lumen loss at 9 months	Late lumen loss at 9 months	Target lesion failure at 12 months	Target vessel failure at 12 months	Target lesion failure at 12 months
Number of subjects enrolled	30	452 (Orsiro: 298, Xience Prime: 154)	1,356	555 planned (Orsiro: 370, Xience: 185)	2,060
Lesion criteria	• Single, *de novo* lesion • Native artery • ≥50% and ≤100%	• 1 or 2 *de novo* lesions • Separate arteries • ≥50% and ≤100% • ≤ 26 mm • RVD ≥ 2.25 mm and ≤ 4.0 mm	All-comers	• 1 or 2 *de novo* lesions • Separate arteries • ≥50% and ≤100% • ≤ 26 mm • RVD ≥ 2.5 mm and ≤ 3.75 mm	All-comers
Follow-up	• 1 month and 1,2, 3 yrs: clinical • 4 and 9 months: clinical and angio • 4 and 9 months: IVUS (15 pts)	• 1, 6, 12 mos and 2-5 yrs: clinical • 9 months: angio • 9 months: OCT and IVUS (60 pts)	• 6, 12 mos and 3,5 yrs: clinical	• 1, 6, 12 mos and 2-5 yrs: clinical	• 1, 6, 12 mos and 2-5 yrs: clinical
Status (enrollment period)	Primary endpoint complete (Enrollment July 2009)	Primary endpoint complete (Enroll July ’11–Mar ‘12)	Primary endpoint complete (Enroll Aug ’11 - Mar ‘12)	Expected completion Q12015	Primary endpoint complete (Aug ’11 - Mar 12)

Total Orsiro pts in these studies = 3,117

Total Xience pts in these studies = 1,395

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BIOFLOW-II

- Multi-center RCT comparing Orsiro and Xience Prime
- Primary endpoint: LLL at 9 mos. Secondary endpoint: TLF
- OCT and IVUS imaging results

Results

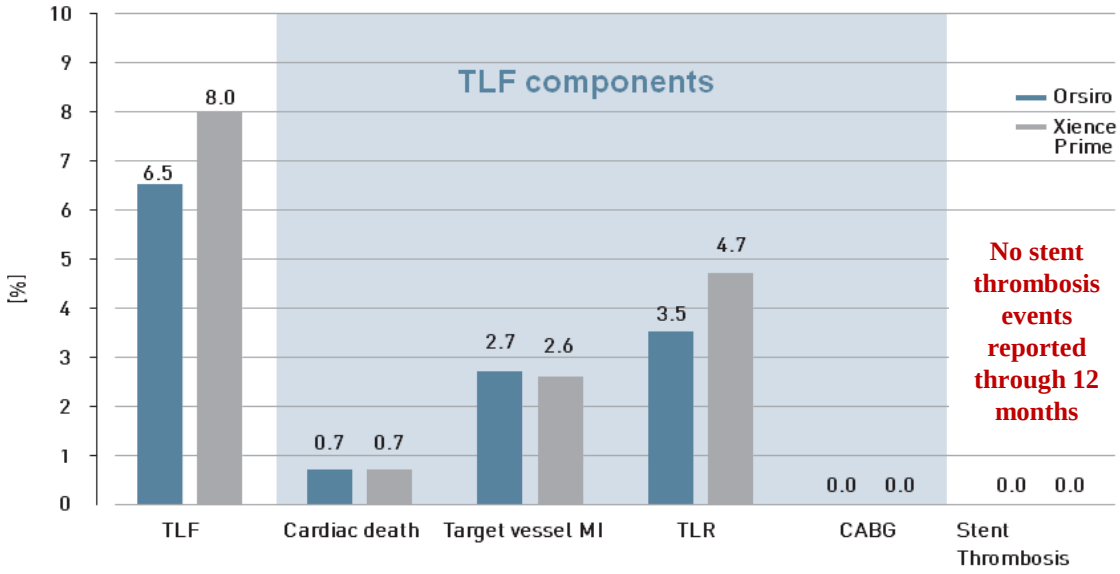
In-Stent Late Loss at 9 Months (mm)

Orsiro	p-value*	Xience Prime
0.10 ± 0.32	<0.001	0.11 ± 0.29

Secondary clinical endpoint results

TLF rate and stent thrombosis out to 12 month follow-up

No significant p-value



Strut Coverage

Orsiro	Xience Prime	p-value
36 lesions 8388 struts	19 lesions 3991 struts	
98.3%	97.5%	0.042

Windecker TCT 2013; Circ Cardiovasc Intervent 2015

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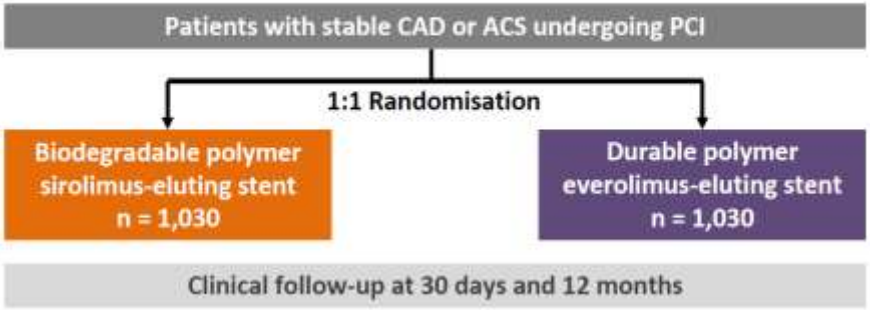
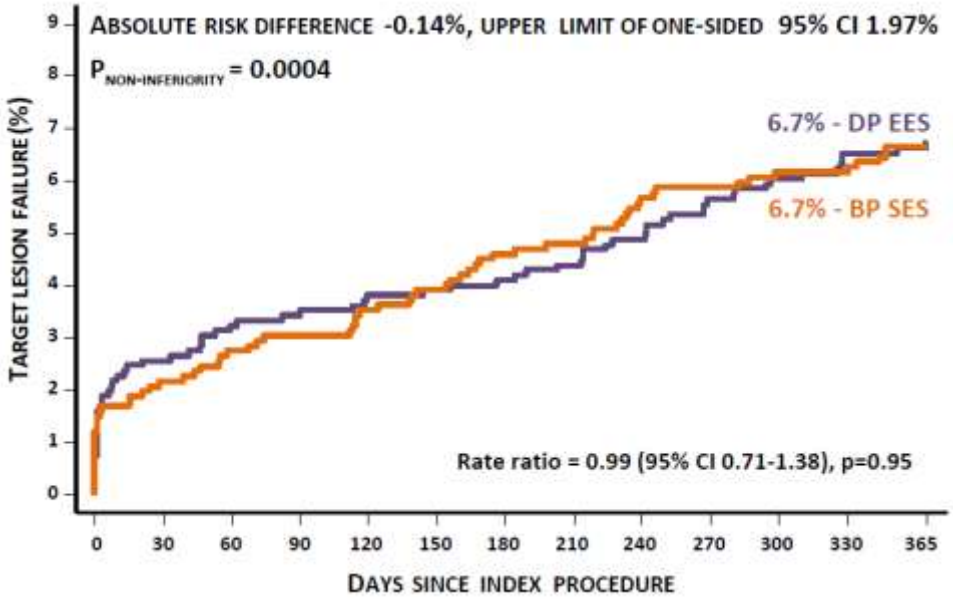
BIOSCIENCE

- Prospective, multi-center, “more comers” trial comparing Orsiro to Xience Prime
- Primary endpoint: Target Lesion Failure (TLF) at 12 mos.

TRIAL DESIGN



Selected Baseline Pt Characteristics	Orsiro (n=1063)	Xience Prime (n=1056)
Diabetes mellitus	257 (24%)	229 (22%)
Hypertension	728 (69%)	706 (67%)
STEMI	211 (20%)	196 (19%)



Pilgrim, Windecker, et al. Lancet 2014

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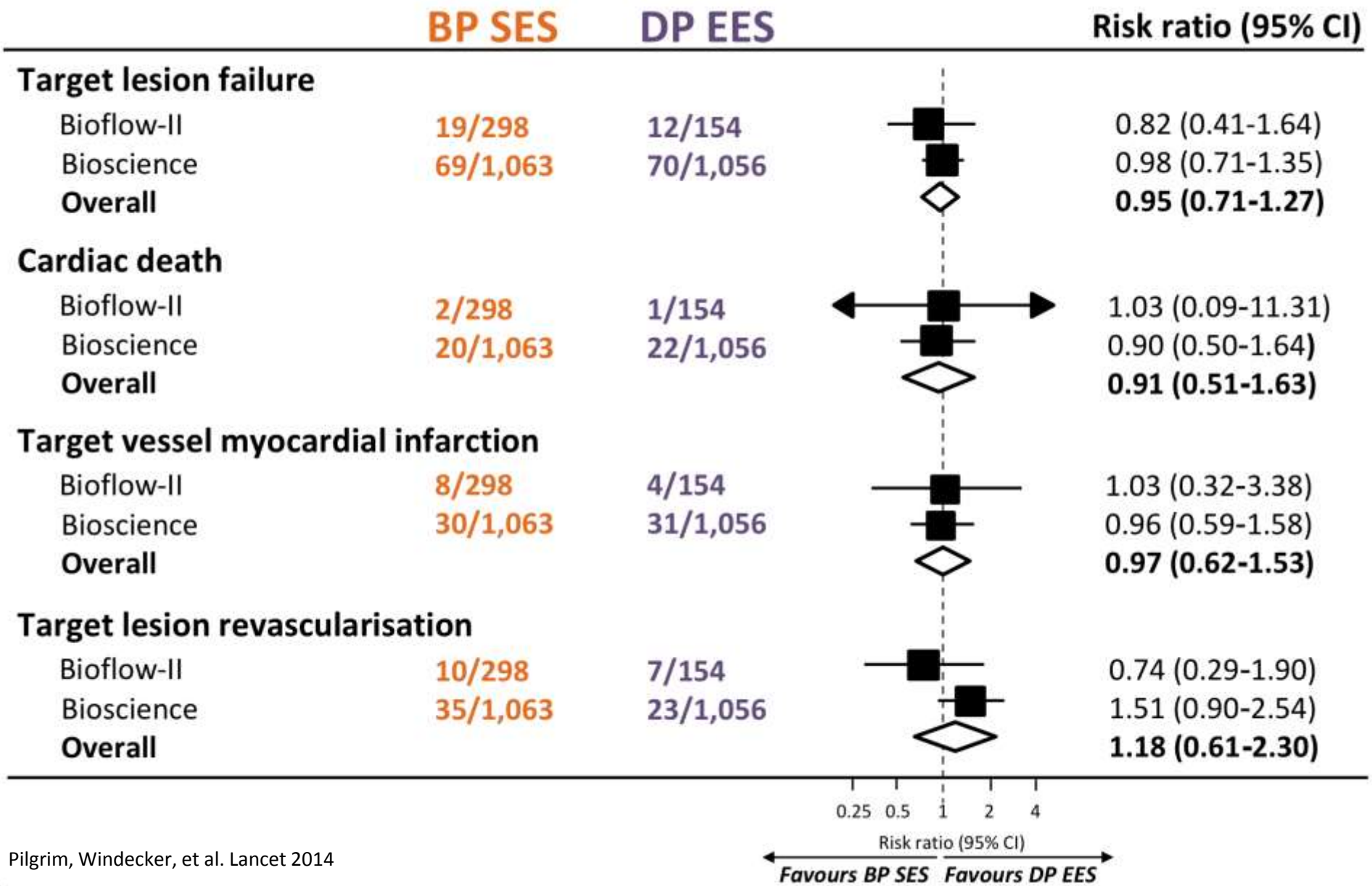
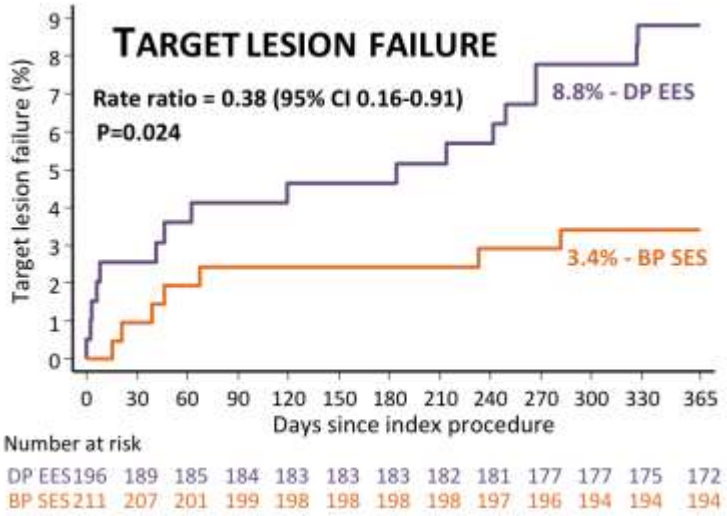
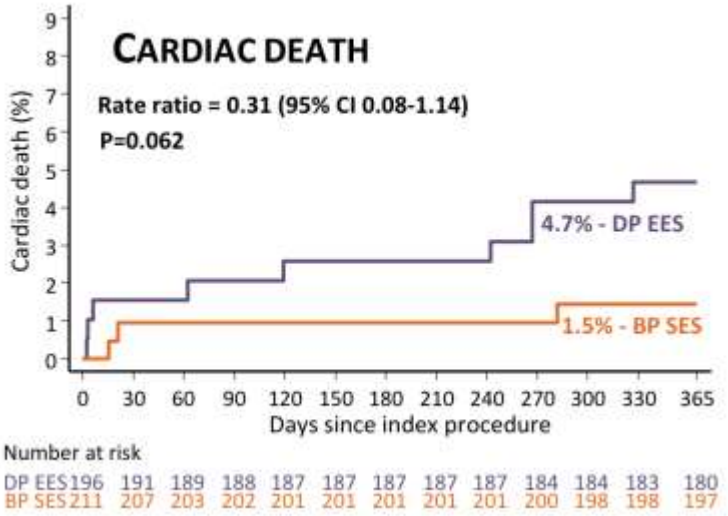
Pooled Analysis of BIOFLOW II and BIOSCIENCE Trials

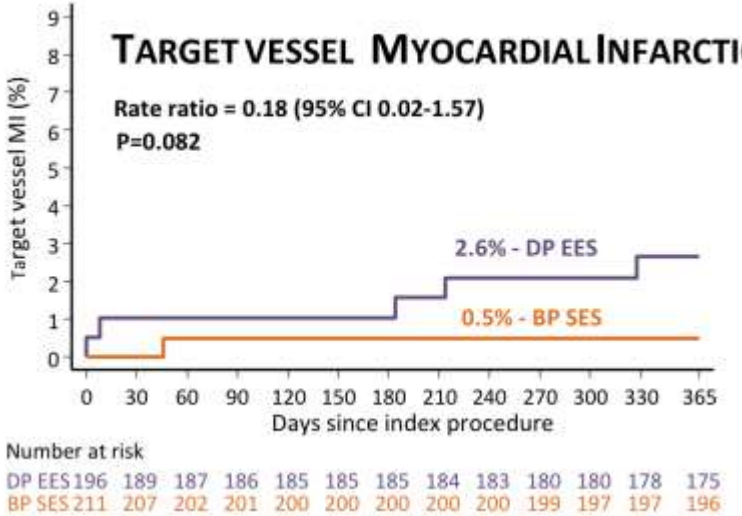


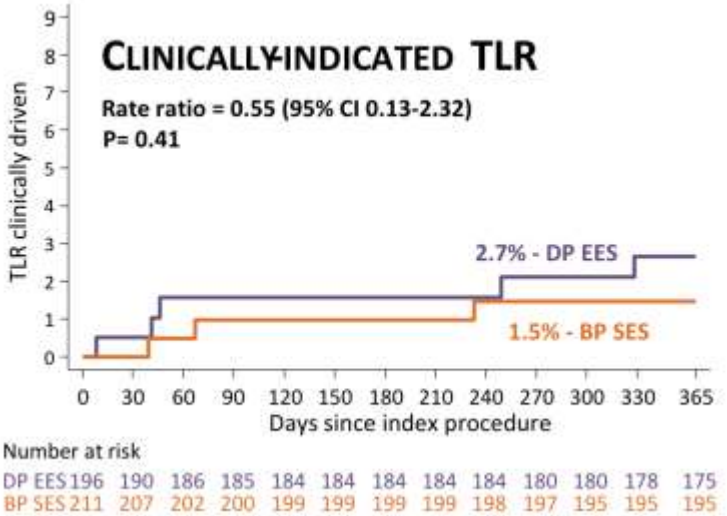
Pilgrim, Windecker, et al. Lancet 2014

BIOSCIENCE STEMI Subgroup Analysis









Pilgrim, Windecker, et al. Lancet 2014; Eurointervntion 2016

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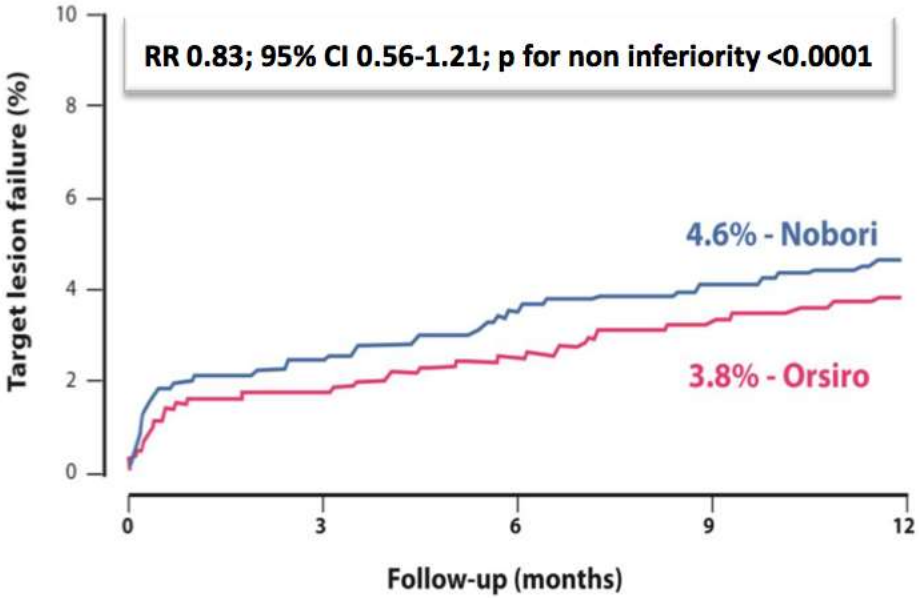
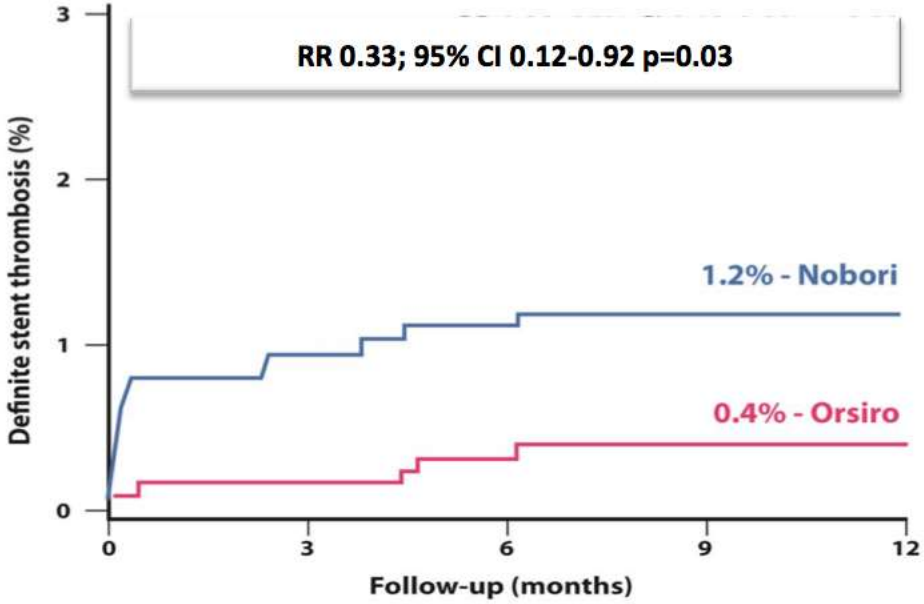
SORT OUT VII

N= 2,525

TARGET LESION FAILURE



DEFINITE STENT THROMBOSIS



Jensen EuroPCR 2015; Am Heart J 2015

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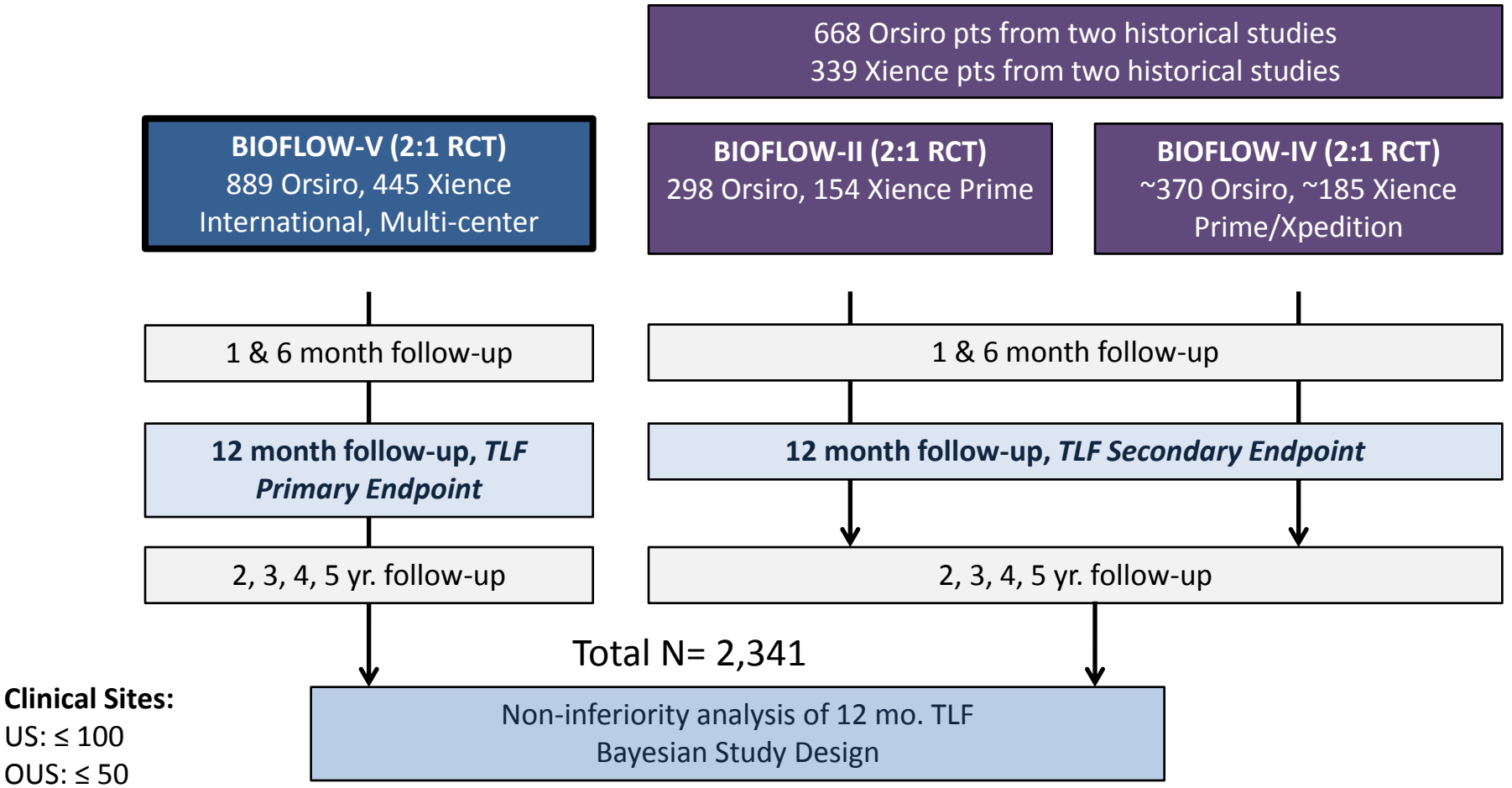
BIOFLOW-V Study Design



Clinical Sites:
US: ≤ 100
OUS: ≤ 50

Enrollment began April 2015, completed April 2016

PIs: D Kandzari, J. Koolen

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Forthcoming Osiro DES Trials

BIOFLOW V *US/Europe*	N=2,341; Osiro vs Xience	Enrollment complete April 2016
BIOFLOW IV *Japan*	N=555; Osiro vs Xience	TCT 2016
BIOFLOW VI *China*	N=440; Osiro vs Xience	Currently enrolling
BIORESORT *Netherlands/Twente*	N=3,530; Osiro vs Synergy vs Resolute	TCT 2016

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Opportunities For Improvement

- We are realizing the best outcomes with DES than ever before reported
- But….evolution is inherent to interventional cardiology
- As newer DES are introduced, adoption will be driven more by intuition than scientific evidence as the opportunity to refine outcomes is increasingly difficult
- Still, opportunities remain to develop novel drug, polymer and stent delivery systems with selected attributes of each that confer incremental clinical and performance benefits above existing technologies
- Rather than focus on device approval through non-inferiority alone, bioresorbable polymer DES technologies enable us to address existing challenges, test strategy or a new advantage, and demonstrate value that informs dilemmas in existing practice