

DES Evolution

Bioresorbable Polymer DES as a Standard in Trials and Clinical Practice

David E. Kandzari, MD, FACC, FSCAI

Chief Scientific Officer
Director, Interventional Cardiology

Piedmont Heart Institute
Atlanta, Georgia
david.kandzari@piedmont.org

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

<u>Affiliation/Financial Relationship</u>	<u>Company</u>
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

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?*

Stent delivery system

Evolution of DES Randomized Trials

Trial	N	Primary Endpoint	Comparison	Outcome
ENDEAVOR				9.9 EES vs 9.9
SPIRIT II				17.2 vs 17.2
SPIRIT IV				9.9 vs 9.9
ZEST ⁴				vs. 9.9 vs. 9.9
LEADERS ⁵				15.7 vs 15.7
COMPARE ⁶	1800	Non-inferiority D/M/TVR at 12	vs TAXUS Liberté	2-Year TVF: 9.0 EES vs 13.7 PES, P=0.002
RESOLUTE ⁷	2300	Non-inferiority TLF at 12 months	or Resolute vs Xience	2-year TLF: 11.2 ZES vs 10.7 EES, P=0.74

“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.”

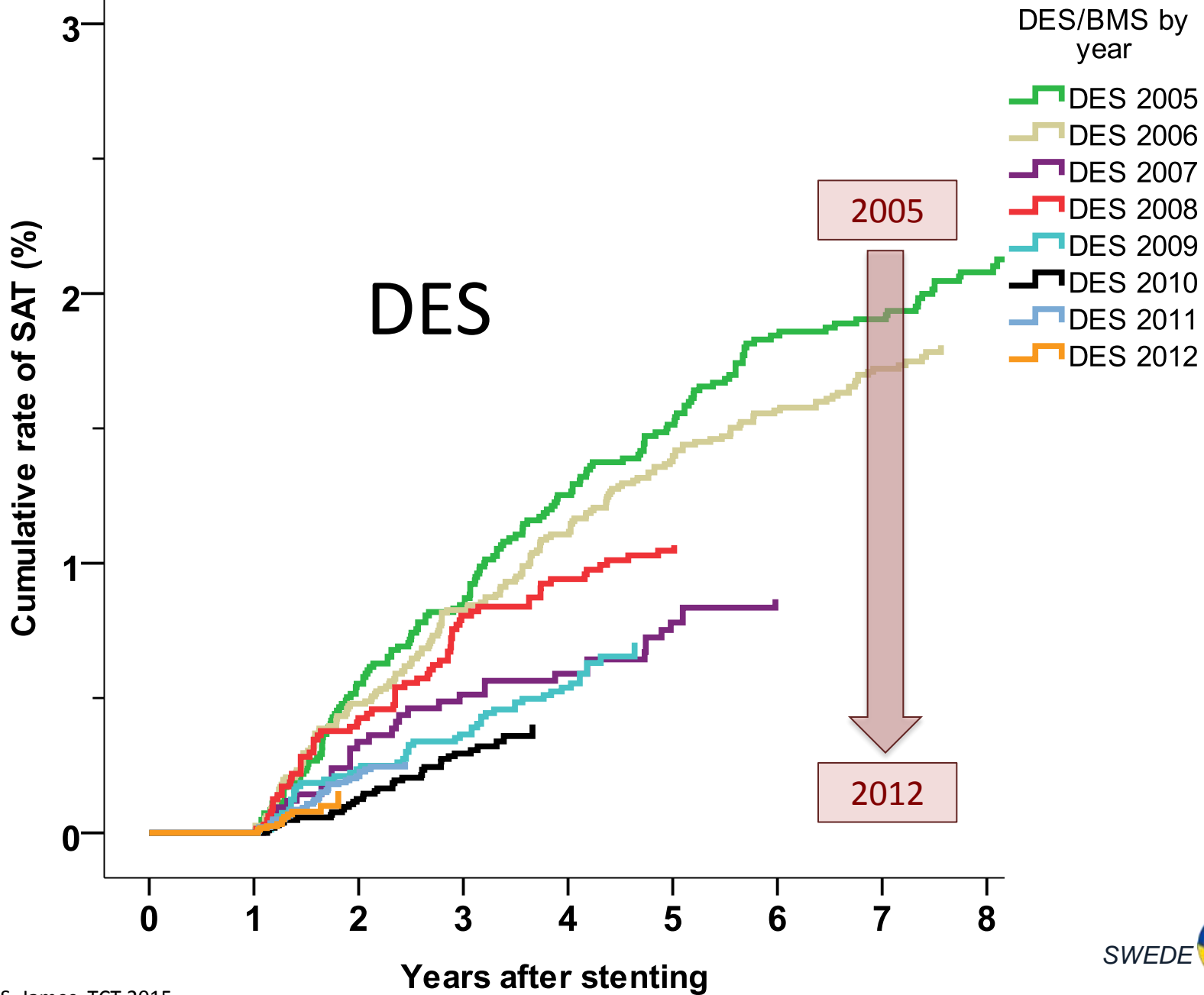
Byrne, R. A. et al. J Am Coll Cardiol 2011;58:1325-1331

Meta-Analyses, Network Meta-Analyses...

RCT remain standard for regulatory approval

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

SCAAR Cumulative ST Risk for DES



Delayed Arterial Healing After

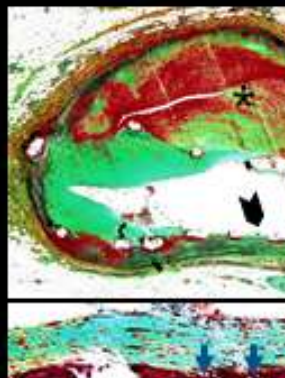
Hypersensitivity Reaction in 2nd generation DES

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

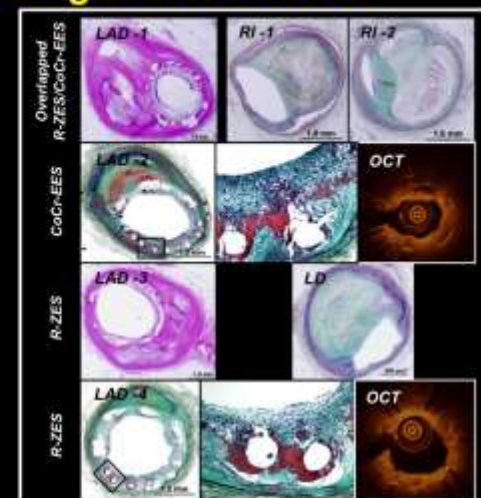


Radiograph

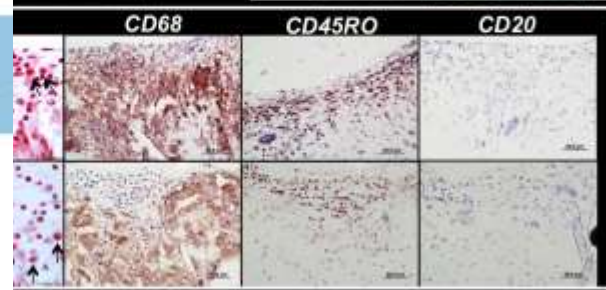


Polymer Coatings

- Most clinical polymer coatings consist of polyethylene terephthalate (Cypher SE)

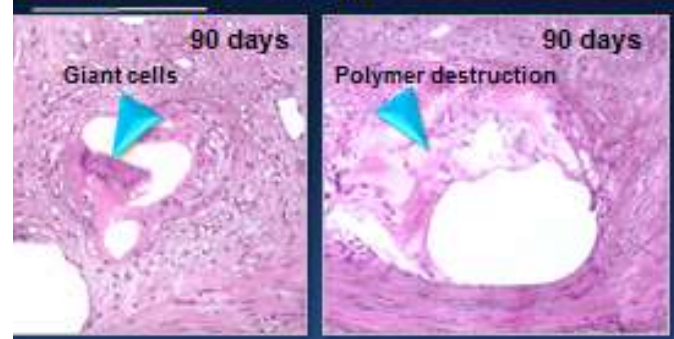


Neoatherosclerosis: Prevalence

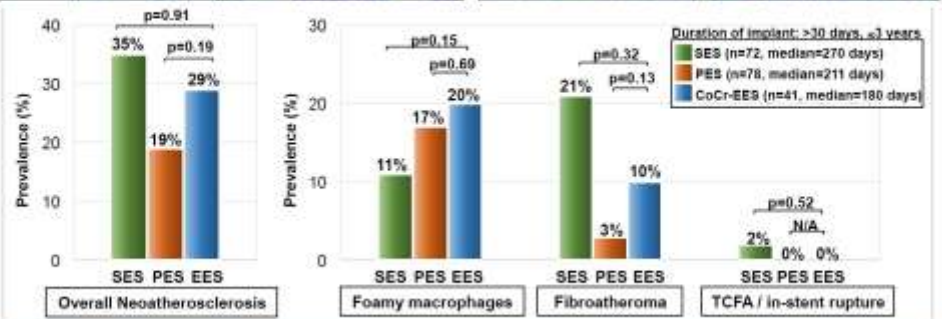
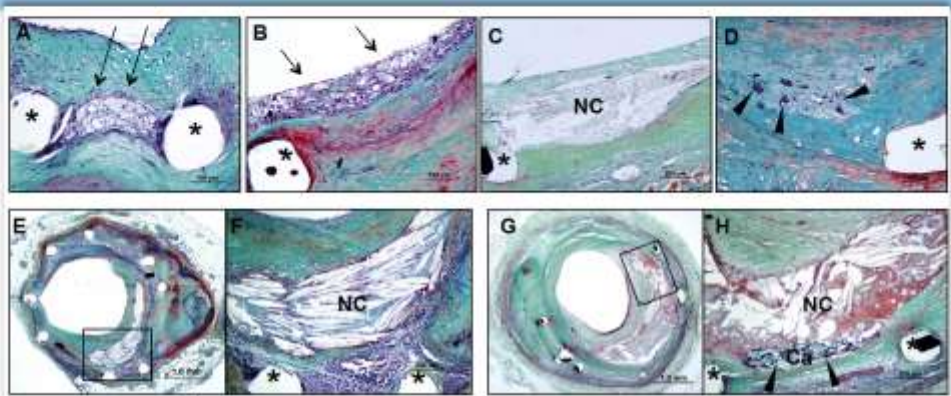


Otsuka et al. | Circulation 2015

Calcification



Response to durable polymer coatings has 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

Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial

Stephan Windecker, Frank D. Seino, David Woodhouse, David Brown, Benjamin Bruchmann, and others. *Lancet* 2014; 384: 1240-1249

FASTTRACK ESC HOT LINE

Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial[†]

Abdominal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE III): a randomised, controlled, non-inferiority trial

Paul Costantino, Benjamin Marquis, Marko Vukobratovic, Marko Vukobratovic, Dragoljub Kostic, and others. *Lancet* 2014; 384: 1240-1249

FASTTRACK ESC HOT LINE

Long-Term Efficacy and Safety of Biodegradable-Polymer Biolimus-Eluting Stents

Main Results of the Basel Stent Kosten-Effektivitäts-Trial-PROspective Validation Examination II (BASKET-PROVE II), A Randomized, Controlled Noninferiority 2-Year Outcome Trial

Christoph Kaiser, MD; Lorenz Gattolisi, MD; Rainer Jeger, MD; Nicole Gilgen, MD; Jan René Jansen, MD; Christoph Naber, MD; Hannes Albers, MD; Maria Wenzel, MD; Frank Eberle, MD; Daniel J. Ryan, MD; Giovanni Palmazzoni, MD; Tobiaso Mazzoni, MD; Hans Raskel, MD; Daniel Widmer, MD; Andrei Wolfensberger, MD; Martin Strasser, MD; Stefan Van Felten, PhD; Deborah R. Weir, PhD; Rüdiger Wachtmann, MD; Peter Hackenbroich, MD; David Costantini, MD; Christian Müller, MD; Peter Buser, MD; Andrei Hoffmann, MD; Matthias Pfisterer, MD. *JAMA* 2014; 311: 1000-1010

FASTTRACK ESC HOT LINE

Ultra-thin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial

Thomas Danchin, MD; Marco Hoffmann, MD; Frank Witzke, MD; Johannes W. J. Meuwissen, MD; Christoph Hahn, MD; Thomas Danchin, MD; Marco Hoffmann, MD; Frank Witzke, MD; Johannes W. J. Meuwissen, MD; Christoph Hahn, MD. *Lancet* 2014; 384: 1240-1249

FASTTRACK ESC HOT LINE

Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent

A Randomized, Controlled, Noninferiority Trial

Masahito Nishiida, MD; Ken Kurokawa, MD; Takashi Nakamura, MD; Kanagabe Keietsu, MD; Tadayuki Matsumoto, MD; Yoshitaka Nakagawa, MD; Takashi Akashi, MD; Kokiichi Iguchi, MD; Koichi Taniuchi, MD; Yoshitaka Matsui, MD; Tetsuya Nakano, MD; Hideaki Nakahara, MD; Masaki Asano, MD; Masaru Aoki, MD; Hiroyuki Okada, MD. *JAMA* 2014; 311: 1000-1010

FASTTRACK ESC HOT LINE

Long-Term Efficacy and Safety of Biodegradable-Polymer Biolimus-Eluting Stents

Main Results of the Basel Stent Kosten-Effektivitäts-Trial-PROspective Validation Examination II (BASKET-PROVE II), A Randomized, Controlled Noninferiority 2-Year Outcome Trial

Christoph Kaiser, MD; Lorenz Gattolisi, MD; Rainer Jeger, MD; Nicole Gilgen, MD; Jan René Jansen, MD; Christoph Naber, MD; Hannes Albers, MD; Maria Wenzel, MD; Frank Eberle, MD; Daniel J. Ryan, MD; Giovanni Palmazzoni, MD; Tobiaso Mazzoni, MD; Hans Raskel, MD; Daniel Widmer, MD; Andrei Wolfensberger, MD; Martin Strasser, MD; Stefan Van Felten, PhD; Deborah R. Weir, PhD; Rüdiger Wachtmann, MD; Peter Hackenbroich, MD; David Costantini, MD; Christian Müller, MD; Peter Buser, MD; Andrei Hoffmann, MD; Matthias Pfisterer, MD. *JAMA* 2014; 311: 1000-1010

FASTTRACK ESC HOT LINE

Ultra-thin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial

Thomas Danchin, MD; Marco Hoffmann, MD; Frank Witzke, MD; Johannes W. J. Meuwissen, MD; Christoph Hahn, MD; Thomas Danchin, MD; Marco Hoffmann, MD; Frank Witzke, MD; Johannes W. J. Meuwissen, MD; Christoph Hahn, MD. *Lancet* 2014; 384: 1240-1249

FASTTRACK ESC HOT LINE

Long-Term Efficacy and Safety of Biodegradable-Polymer Biolimus-Eluting Stents

Main Results of the Basel Stent Kosten-Effektivitäts-Trial-PROspective Validation Examination II (BASKET-PROVE II), A Randomized, Controlled Noninferiority 2-Year Outcome Trial

Christoph Kaiser, MD; Lorenz Gattolisi, MD; Rainer Jeger, MD; Nicole Gilgen, MD; Jan René Jansen, MD; Christoph Naber, MD; Hannes Albers, MD; Maria Wenzel, MD; Frank Eberle, MD; Daniel J. Ryan, MD; Giovanni Palmazzoni, MD; Tobiaso Mazzoni, MD; Hans Raskel, MD; Daniel Widmer, MD; Andrei Wolfensberger, MD; Martin Strasser, MD; Stefan Van Felten, PhD; Deborah R. Weir, PhD; Rüdiger Wachtmann, MD; Peter Hackenbroich, MD; David Costantini, MD; Christian Müller, MD; Peter Buser, MD; Andrei Hoffmann, MD; Matthias Pfisterer, MD. *JAMA* 2014; 311: 1000-1010

FASTTRACK ESC HOT LINE

Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial

European Heart Journal 2014; 35: 2011-2021

FASTTRACK CLINICAL RESEARCH

A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: the CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System

Cardiac Catheterization

Efficacy and Safety of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent: The EVOLVE II Randomized Trial

Dean J. Kereiakes, MD; Ian T. Meredith, AM, MBBS, PhD; Stephan Windecker, MD; R. Lee Jolly, MD; Shamir R. Mehta, MD; Ian T. Saric, MD; Mihail G. Mihalek, MD; Robert L. Feldman, MD; Bernardo Stein, MD; Christopher Dubois, MD, PhD; Timothy Gearty, MD; Shigeru Saito, MD; Takashi Komura, MD; Thomas Chakraborty, MD, PhD; Dorian J. Alfonso, MD; Keith D. Thoreson, MD. *JAMA* 2014; 311: 1000-1010

FASTTRACK ESC HOT LINE

Ultra-thin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial

Thomas Danchin, MD; Marco Hoffmann, MD; Frank Witzke, MD; Johannes W. J. Meuwissen, MD; Christoph Hahn, MD; Thomas Danchin, MD; Marco Hoffmann, MD; Frank Witzke, MD; Johannes W. J. Meuwissen, MD; Christoph Hahn, MD. *Lancet* 2014; 384: 1240-1249

FASTTRACK ESC HOT LINE

Ultra-thin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial

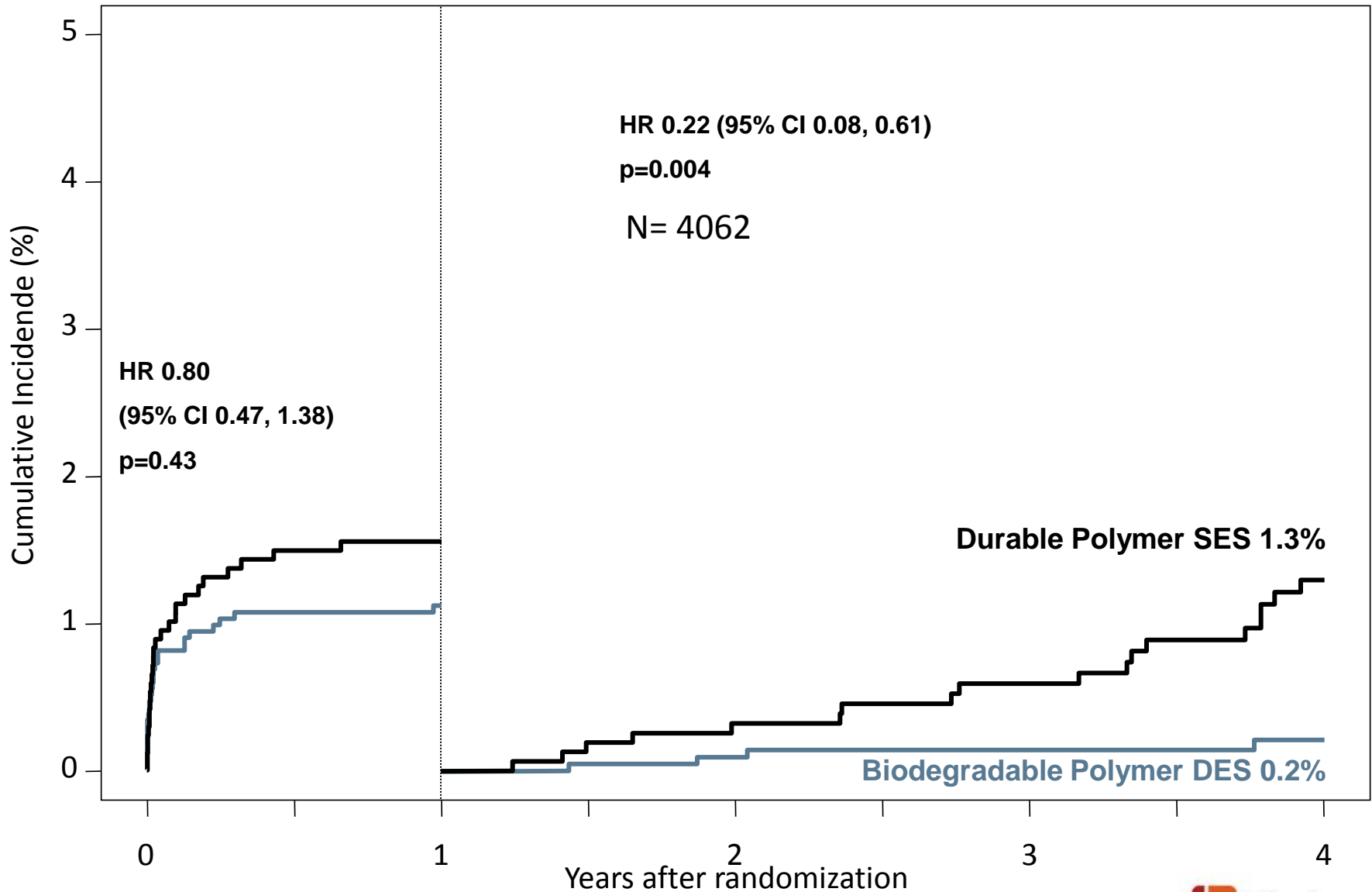
Thomas Danchin, MD; Marco Hoffmann, MD; Frank Witzke, MD; Johannes W. J. Meuwissen, MD; Christoph Hahn, MD; Thomas Danchin, MD; Marco Hoffmann, MD; Frank Witzke, MD; Johannes W. J. Meuwissen, MD; Christoph Hahn, MD. *Lancet* 2014; 384: 1240-1249

FASTTRACK ESC HOT LINE

FASTTRACK ESC HOT LINE

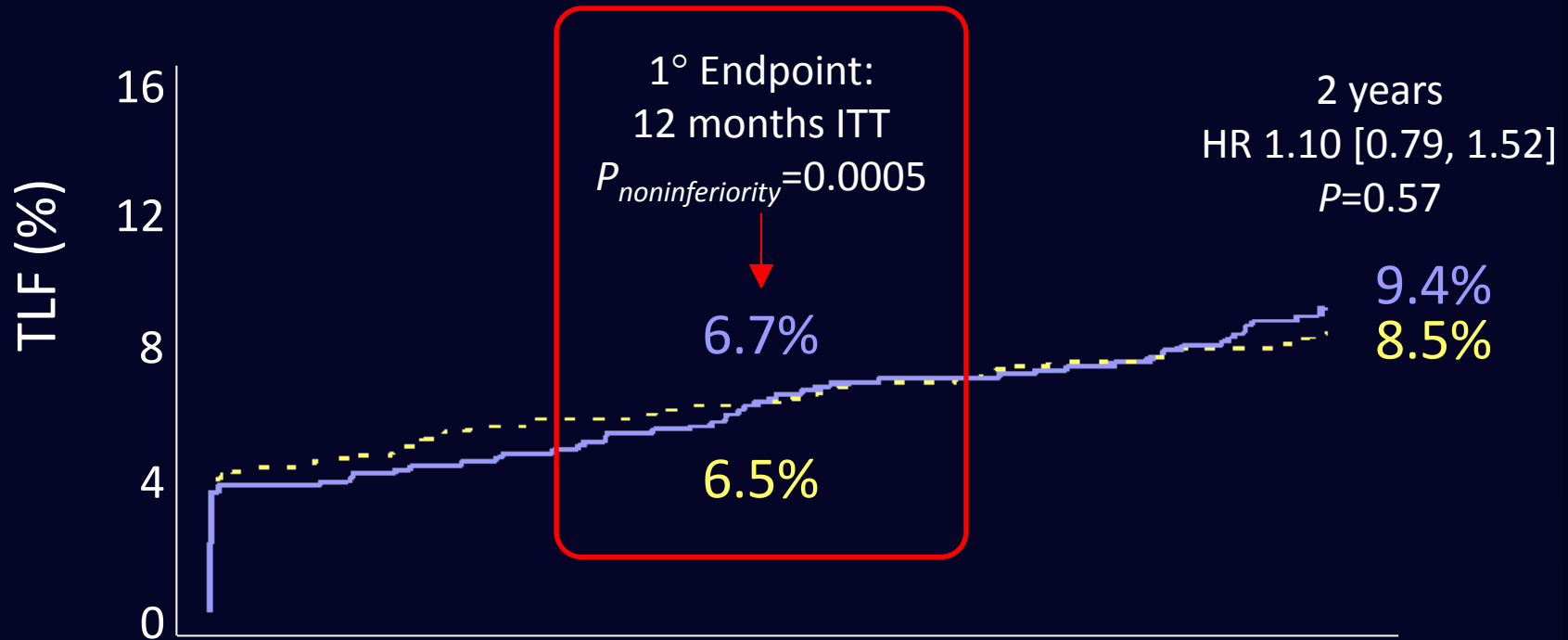
Definite Stent Thrombosis

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



EVOLVE II TLF at 1 and 2 years

PROMUS Element Plus vs SYNERGY

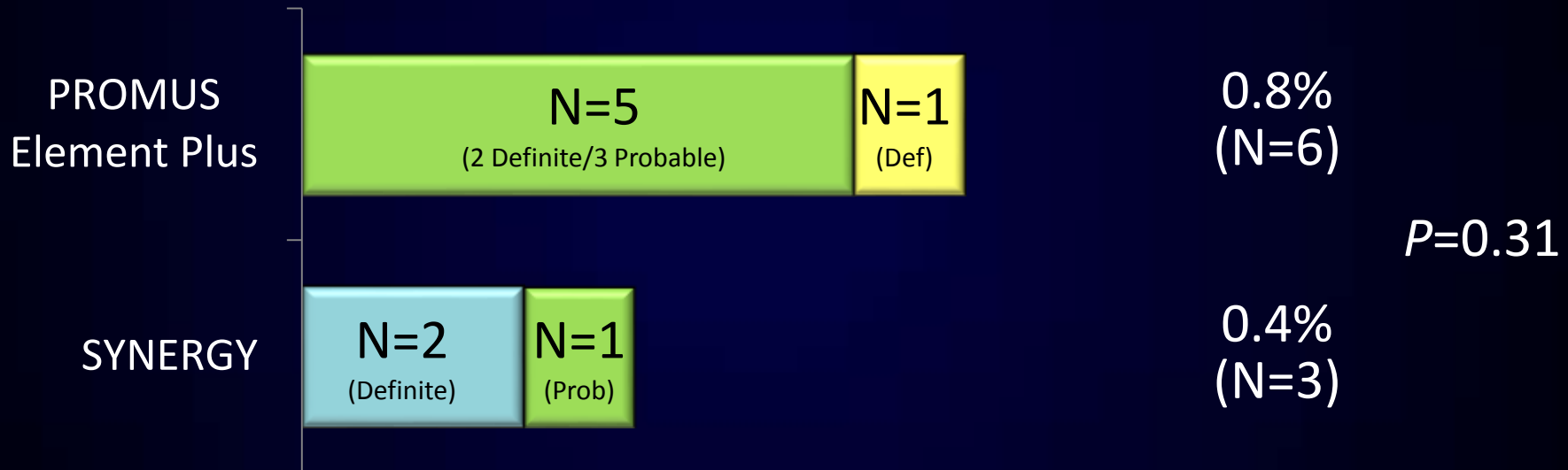


No. at risk	0	6	12	24 Months
— PE+	838	790	772	538
— SYNERGY	846	807	794	553

Stent Thrombosis at 2 years

Definite/Probable : ITT Population

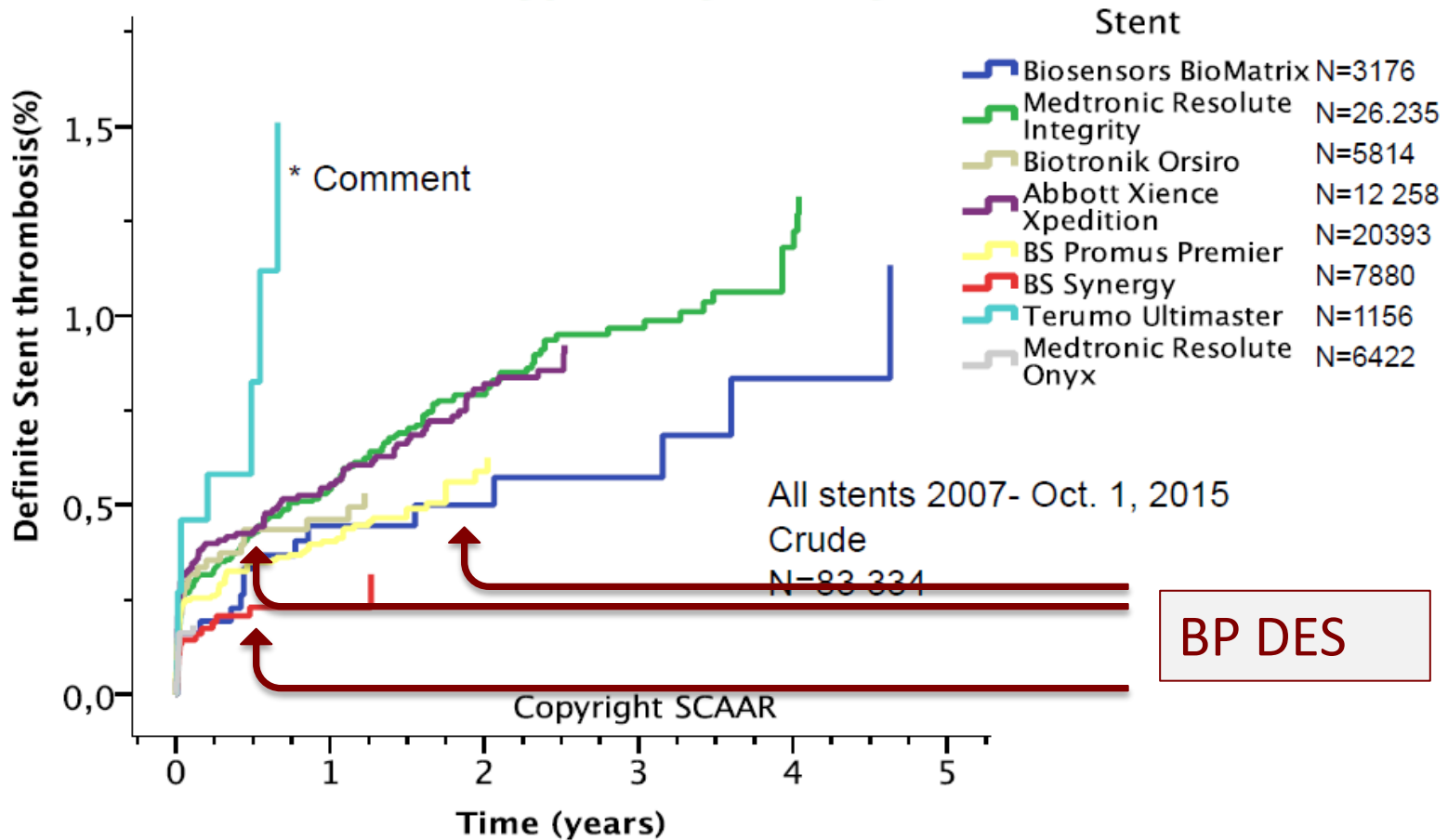
■ Acute (≤ 1 d)
 ■ Subacute (2-30 d)
 ■ Late (30 d – 1 y)
 ■ Very Late (1 – 2 y)



No definite ST in the SYNERGY arm after 24 hours

SCAAR Registry Definite ST for Contemporary DES

Cumulative risk of stent thrombosis in individual stent types beyond 1 year



*The risk of Stent thrombosis 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.



BIOTRONIK Osiro Clinical Trial Program

Stent platform: PRO-Kinetic Energy

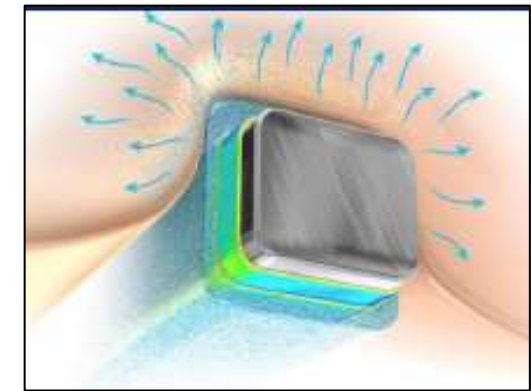
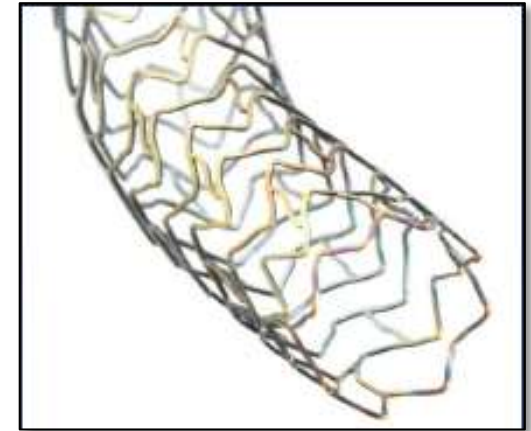
- Cobalt Chromium, L-605
- 60 μ m struts, double helix design

Active coating: BIOlute (Conformal)

- PLLA* bioabsorbable polymer matrix
- Sirolimus (Drug load is 1.4 μ g/mm²)

Passive coating: PROBIO

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



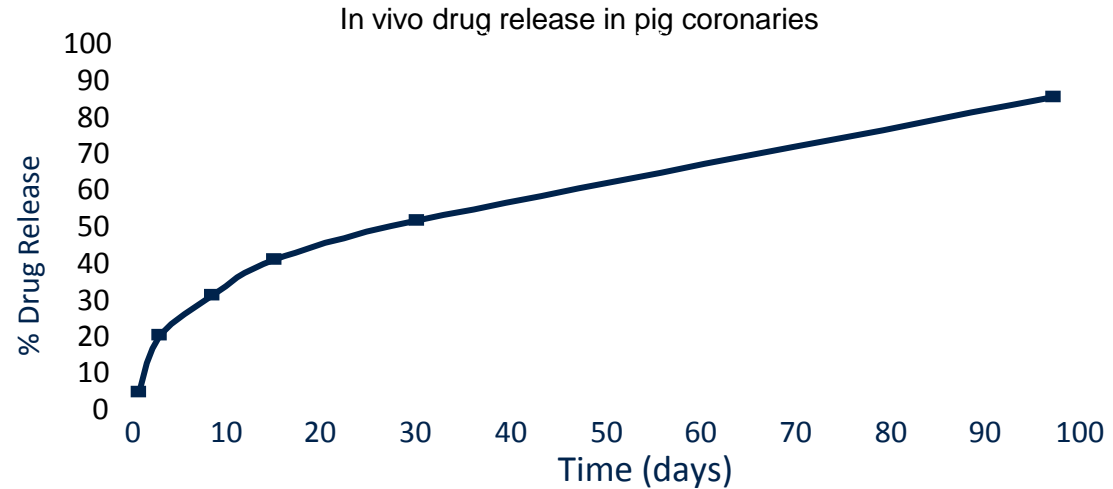
* Poly-L-lactide

** aSiC:H amorphous silicon carbide

BIOTRONIK Osiro BP DES

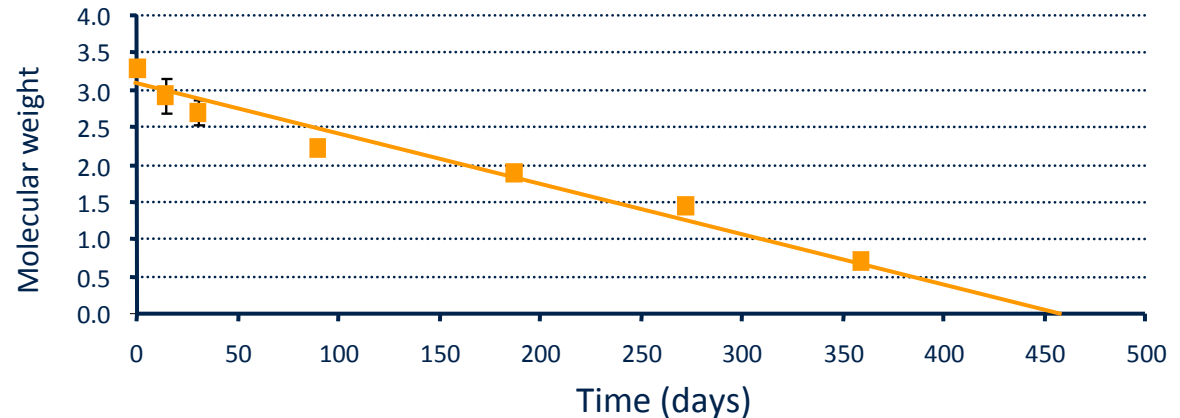
Sirolimus Elution as Measured on Orsiro DES

- ~50% of the drug is eluted over 30 days
- In vivo studies show Sirolimus release in 90-100 days
- Drug load is 1.4 $\mu\text{g}/\text{mm}^2$








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



BIOTRONIK Orsiro BP DES

Durable Polymer Coated Stent		Bioabsorbable Polymer Coated Stent		Bioabsorbable Scaffold
Abbott/Boston	Medtronic	Boston	BIOTRONIK	Abbott
Xience/Promus¹ CoCr/PtCr-EES	Resolute¹ CoNi-ZES	Synergy¹ PtCr-EES	Orsiro^{1*} CoCr-SES	Absorb² 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	<ul style="list-style-type: none"> Prospective Multi-center Non-randomized Single-arm 	<ul style="list-style-type: none"> Prospective Multi-center Randomized (2:1 vs Xience Prime) 	<ul style="list-style-type: none"> Prospective Multi-center Non-randomized Single-arm Open label 	<ul style="list-style-type: none"> Prospective Multi-center Randomized (2:1 vs Xience Prime/Expedition) 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Single, <i>de novo</i> lesion Native artery ≥50% and ≤100% 	<ul style="list-style-type: none"> 1 or 2 <i>de novo</i> lesions Separate arteries ≥50% and ≤100% ≤ 26 mm RVD ≥ 2.25 mm and ≤ 4.0 mm 	All-comers	<ul style="list-style-type: none"> 1 or 2 <i>de novo</i> lesions Separate arteries ≥50% and ≤100% ≤ 26 mm RVD ≥ 2.5 mm and ≤ 3.75 mm 	All-comers
Follow-up	<ul style="list-style-type: none"> 1 month and 1,2, 3 yrs: clinical 4 and 9 months: clinical and angio 4 and 9 months: IVUS (15 pts) 	<ul style="list-style-type: none"> 1, 6, 12 mos and 2-5 yrs: clinical 9 months: angio 9 months: OCT and IVUS (60 pts) 	<ul style="list-style-type: none"> 6, 12 mos and 3,5 yrs: clinical 	<ul style="list-style-type: none"> 1, 6, 12 mos and 2-5 yrs: clinical 	<ul style="list-style-type: none"> 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

BIOFLOW-II

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

In-Stent Late Loss at 9 Months (mm)

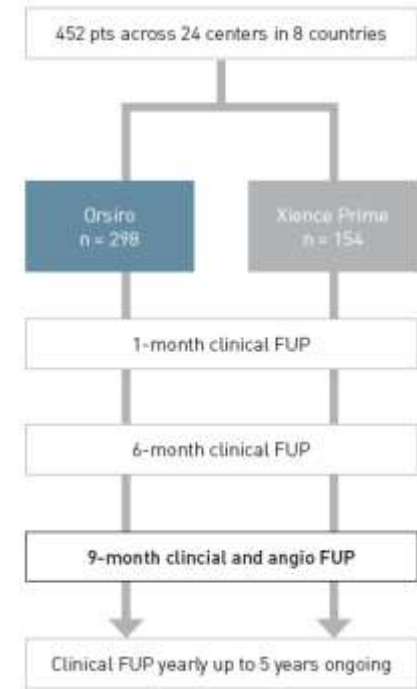
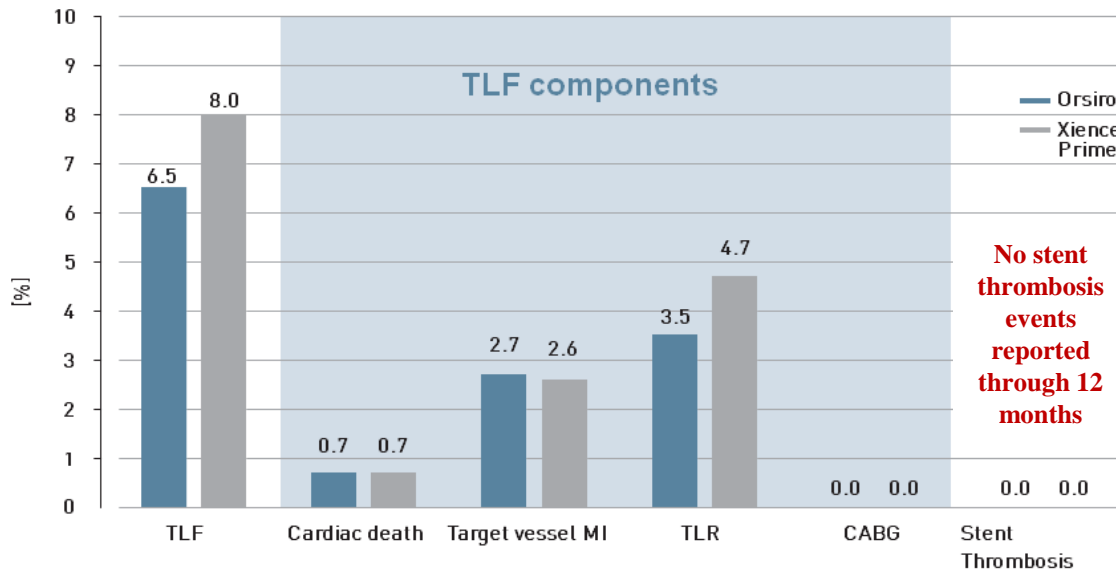
Results

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

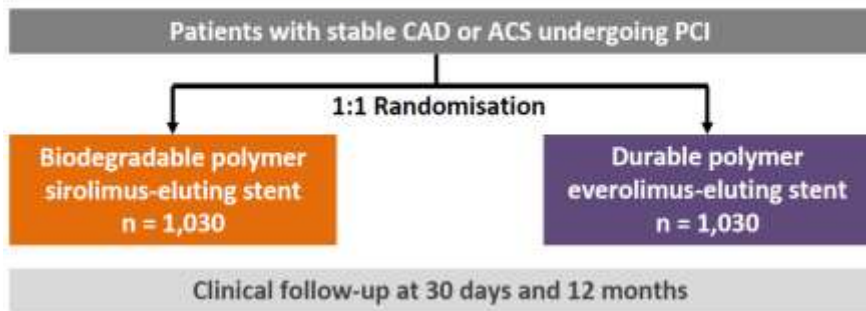


Strut Coverage

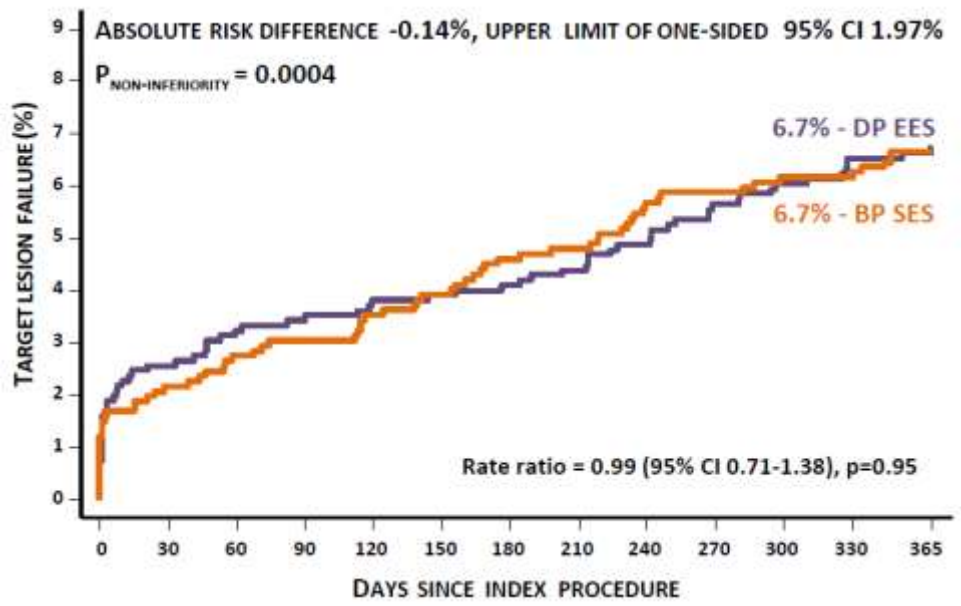
Orsiro	Xience Prime	p-value
36 lesions 8388 struts	19 lesions 3991 struts	
98.3%	97.5%	0.042

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

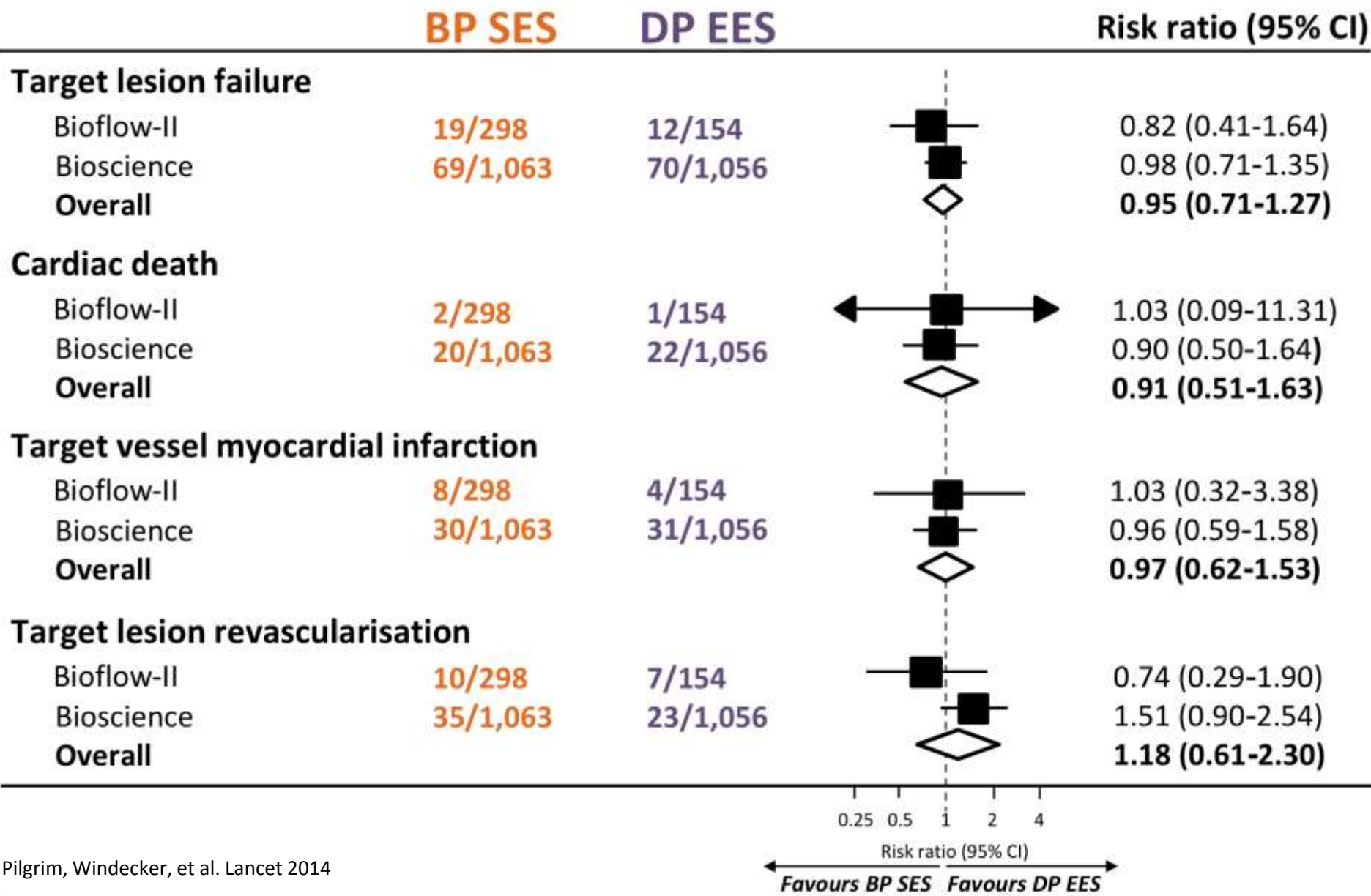
TRIAL DESIGN



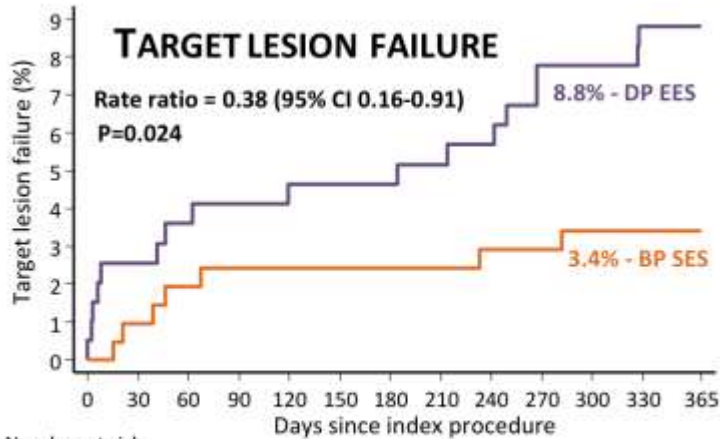
Selected Baseline Pt Characteristics	Orsiro (n=1063)	Xience Prime (n=1056)
Diabetes mellitus	257 (24%)	229 (22%)
Hypertension	728 (69%)	706 (67%)
STEMI	211 (20%)	196 (19%)



Pooled Analysis of BIOFLOW II and BIOSCIENCE Trials

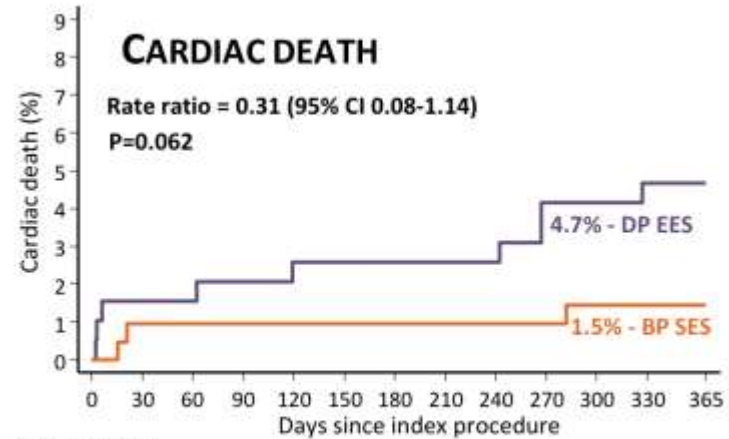


BIOSCIENCE STEMI Subgroup Analysis



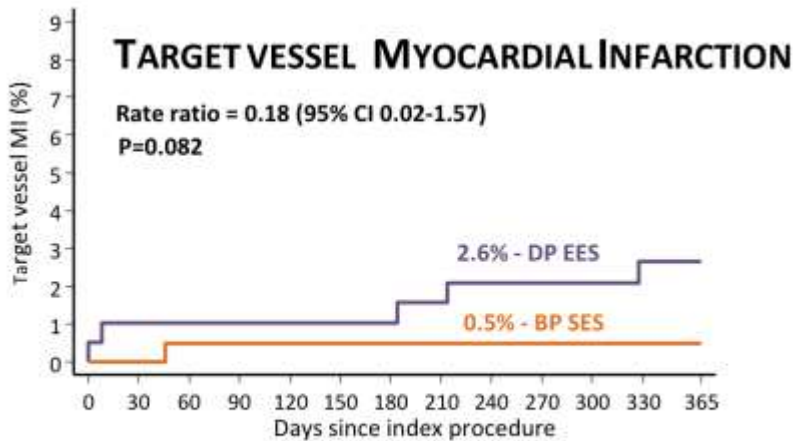
Number at risk

DP EES	196	189	185	184	183	183	183	182	181	177	177	175	172
BP SES	211	207	201	199	198	198	198	198	197	196	194	194	194



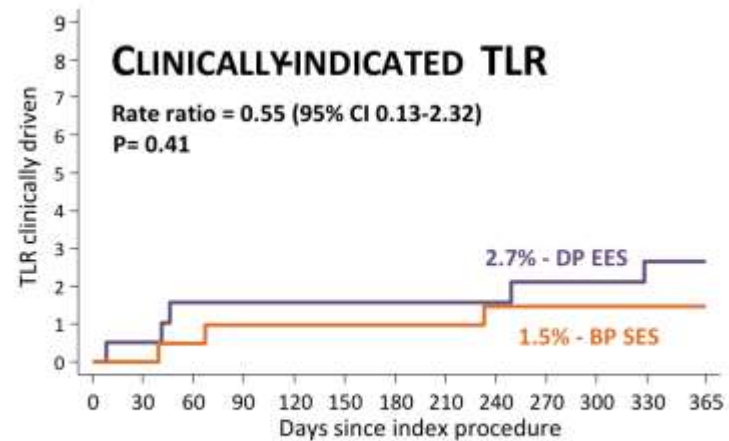
Number at risk

DP EES	196	191	189	188	187	187	187	187	187	187	184	184	183	180
BP SES	211	207	203	202	201	201	201	201	201	201	200	198	198	197



Number at risk

DP EES	196	189	187	186	185	185	185	184	183	180	180	178	175
BP SES	211	207	202	201	200	200	200	200	200	199	197	197	196



Number at risk

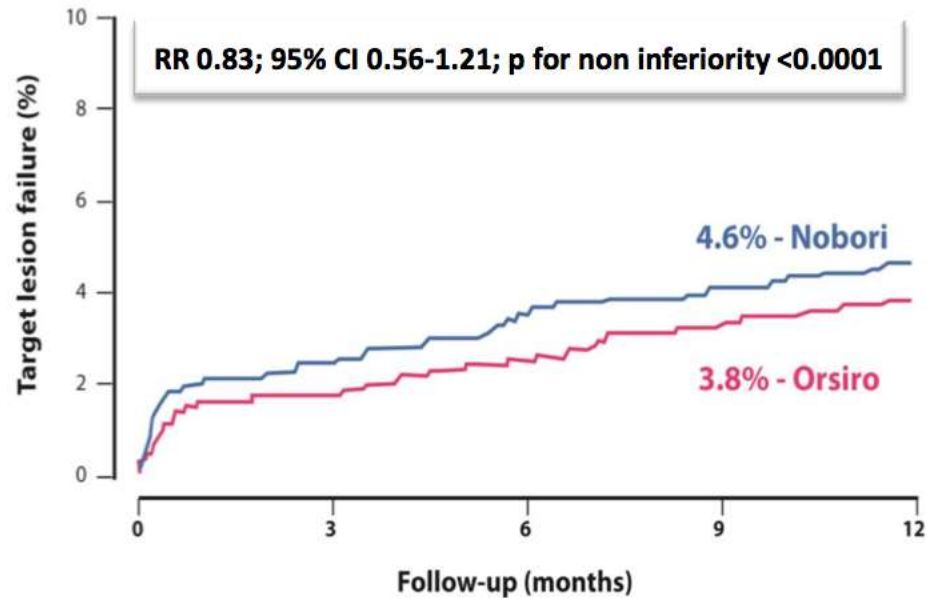
DP EES	196	190	186	185	184	184	184	184	184	184	180	180	178	175
BP SES	211	207	202	200	199	199	199	199	199	198	197	195	195	195

SORT OUT VII

N= 2,525

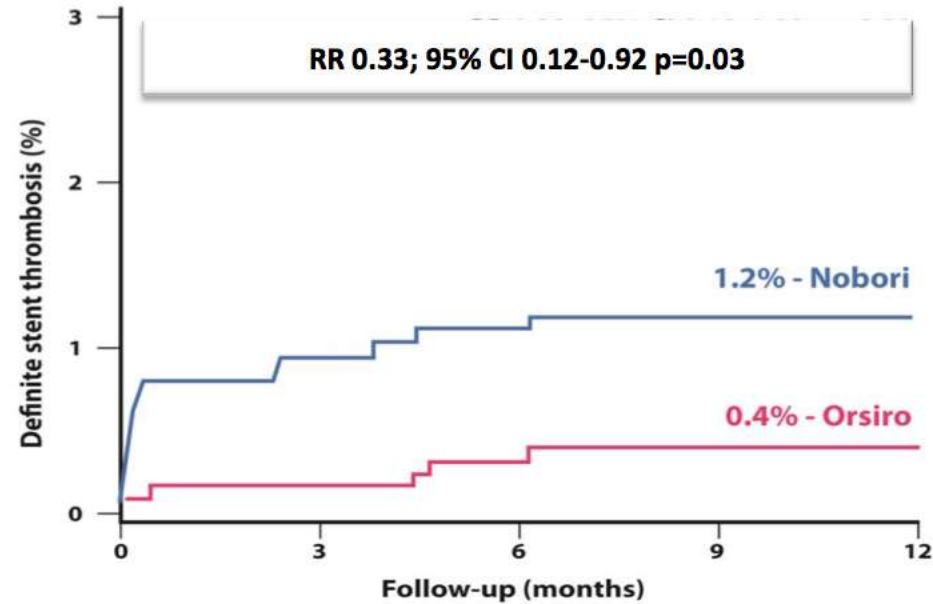
TARGET LESION FAILURE

RR 0.83; 95% CI 0.56-1.21; p for non inferiority <0.0001

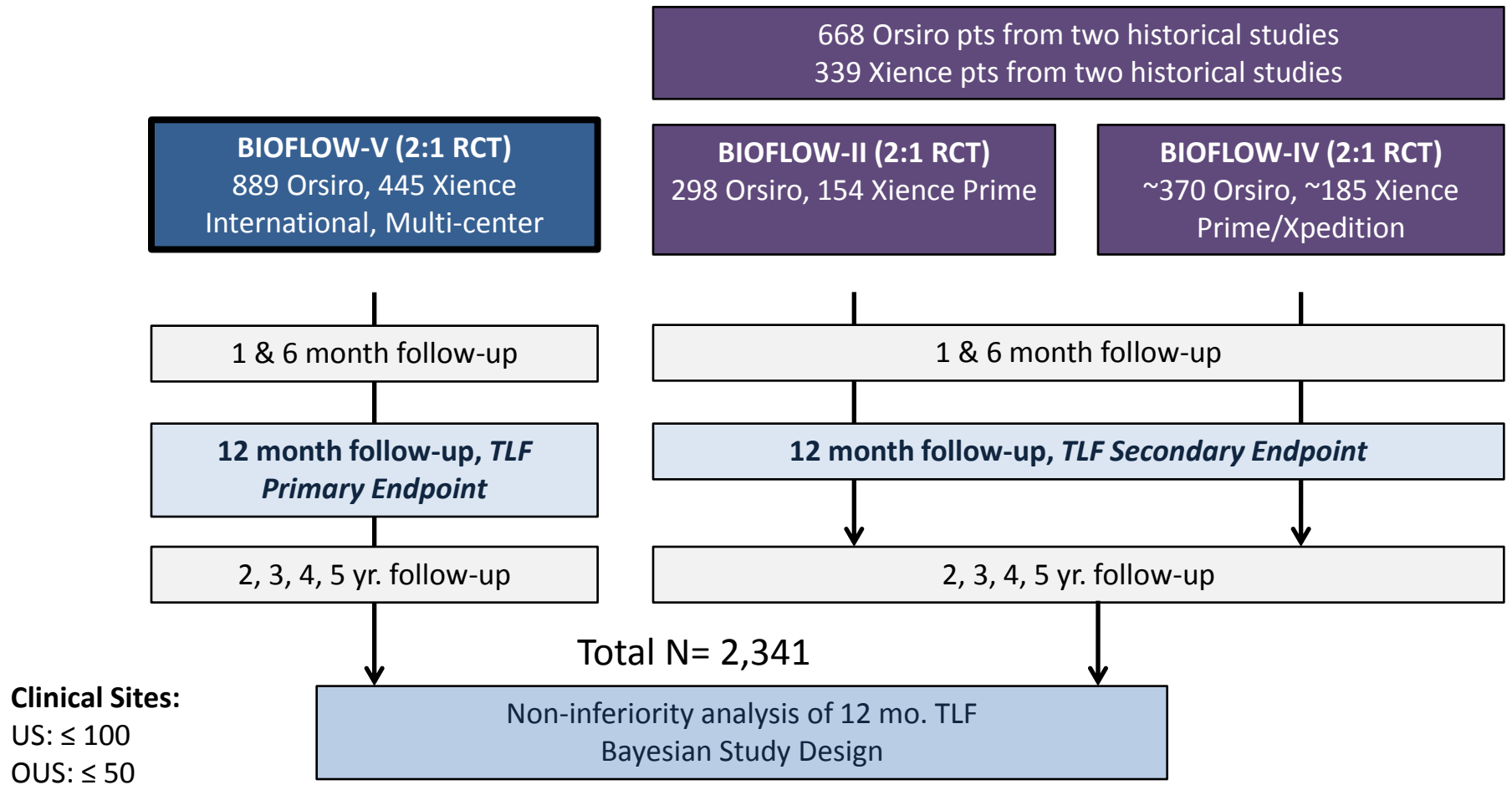


DEFINITE STENT THROMBOSIS

RR 0.33; 95% CI 0.12-0.92 p=0.03



BIOFLOW-V Study Design



Enrollment began April 2015, completed April 2016

Forthcoming Osiro DES Trials

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

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