YONSEI UNIVERSITY

BIOFLOW *by Orsiro stents*

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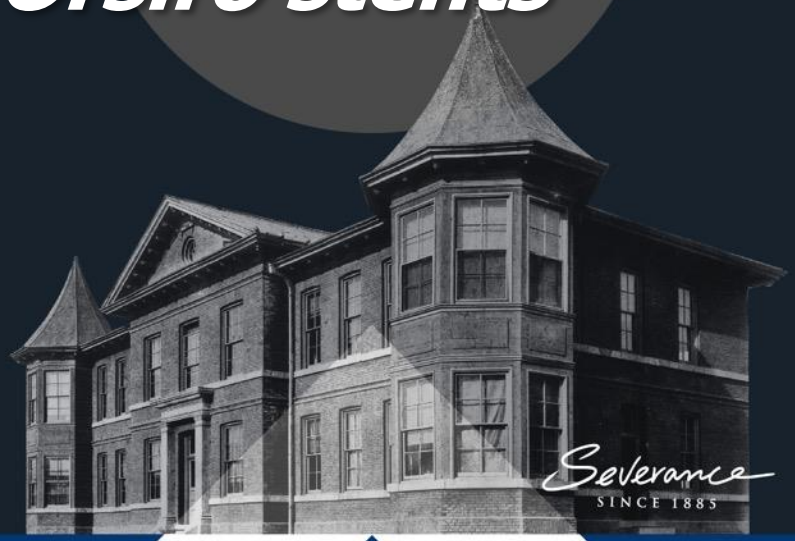


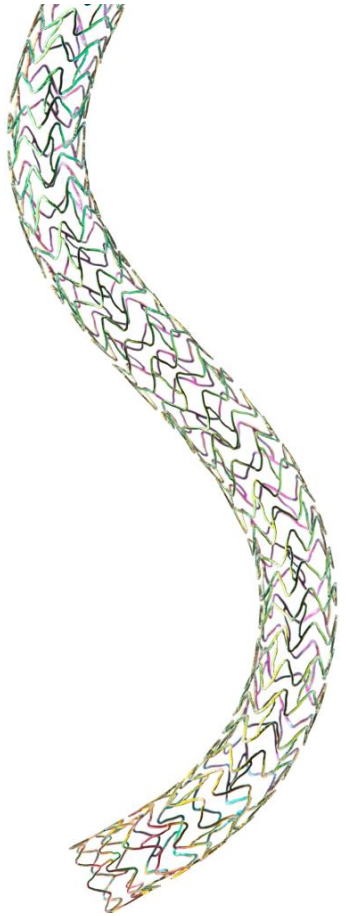
Key Benefits – Orsiro

Clinically proven[1]

- **>32,500** patients enrolled
- **>50,500** patients planned in total
- **>44** studies ongoing
- **>55** studies planned in total

Highly deliverable[1]

Ultrathin 60 µm struts[2]



1 BIOTRONIK data on file; 2. ø 2.25 - 3.0 mm

Key Benefits – Clinically Proven

Clinically proven

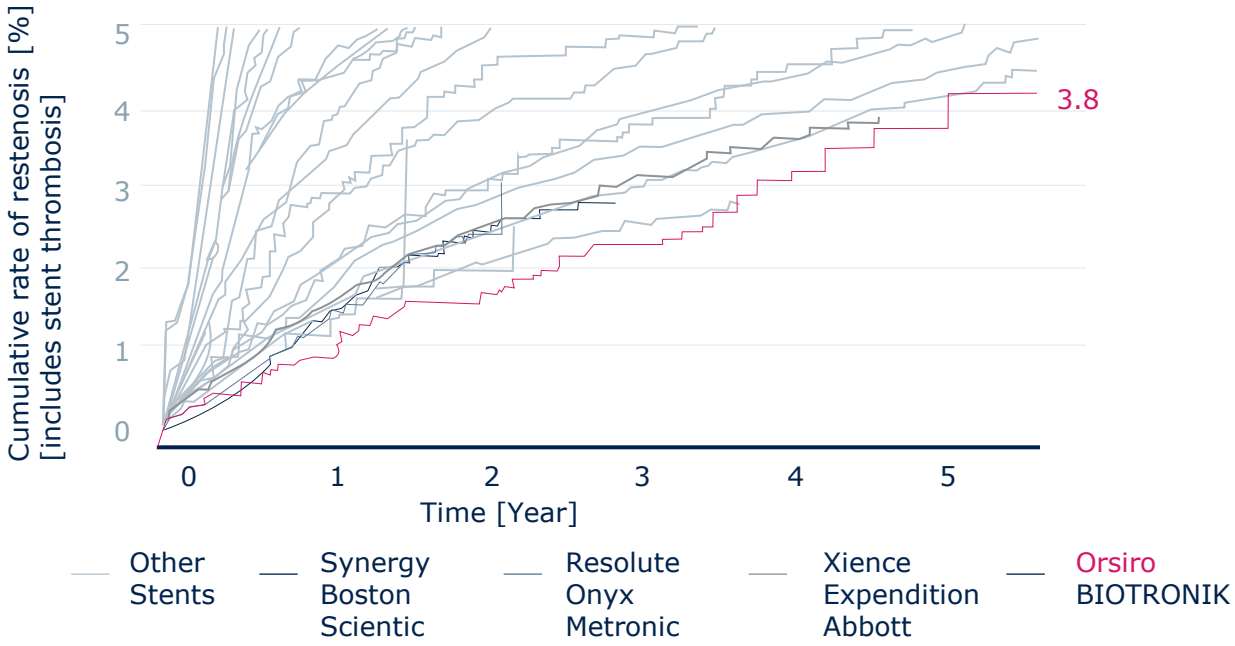
Highly deliverable

Ultrathin strut design

Proven long term clinical outcomes

All stents implanted from 2007 until January 11, 2017 unadjusted (SCAAR)[1,2]

Orsiro showed a lower restenosis rate than all DES out to five years.



* Posterior probability, Bayesian analytical methods were applied

1 Adapted from SCAAR data (August 24th 2016) http://www.ucr.uu.se/swedeheart/99-scaar/forskning-scaar; 2. Compared to other DES included in SCAAR at 5 years

Key Benefits – Highly Deliverable

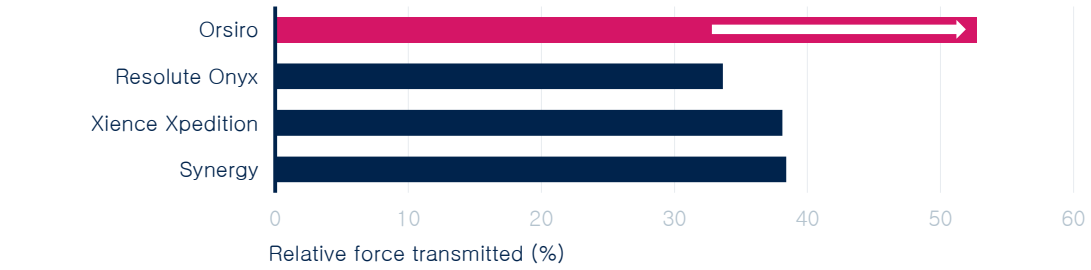
Clinically proven

Highly deliverable

Ultrathin strut design

Designed for challenging cases

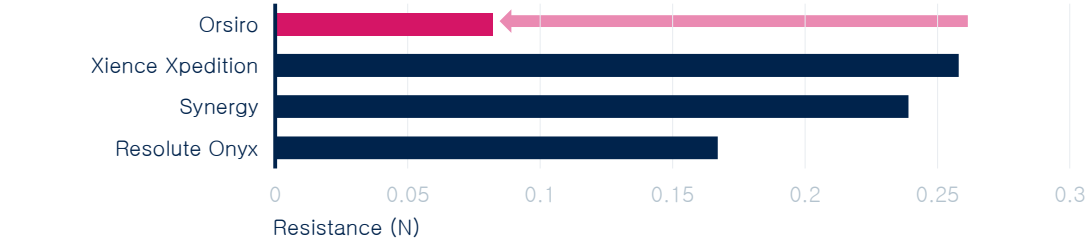
Better push: Transmitting up to 57%[1] more force from hub to tip[2]



57%

Better push

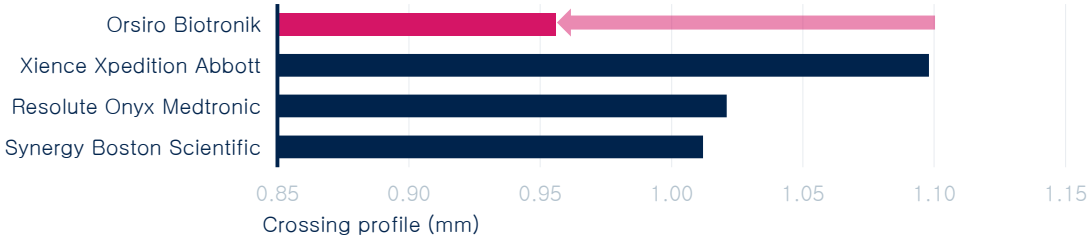
Easier cross: Up to 68% less force[3,4] to successfully cross demanding anatomies



68%

Easier cross

Lower crossing profile: Improved acute performance – up to 13% lower crossing profile [3]



13%

Lower crossing profile

1 Compared to Resolute Onyx; 2. The stent system is advanced through a model, to a point of blockage (simulating a total occlusion). The force at the proximal hub and at the blockage is measured. Pushability is the force transmitted along the length of the catheter. - IIB(P)31/2015 - IIB(P)85/2014-2; 3. Compared to Xience Xpedition; 4 The stent system is advanced through a stenosis model. Crossability is the mean resistance (mean force) registered by the stenosis during the complete passage of the stent delivery system. - IIB(P)31/2015 - IIB(P)85/2014-2

Key Benefits – Ultrathin Strut Design

Clinically proven

Highly deliverable

Ultrathin strut design

Ultrathin 60 µm struts[1]

Strut thickness in perspective[2]

Biosensors **BioMatrix** 316L-BES	Boston **Promus** PtCr-EES	Abbott **Xience** CoCr-EES	Medtronic **Resolute Onyx** CoNi-ZES[3]	Terumo **Ultimaster** CoCr-SES	Boston **Synergy** PtCr-SES	BIOTRONIK **Orsiro** CoCr-SES
						
120 µm	81 µm	81 µm	81 µm[4]	80 µm	74 µm	60 µm[1]

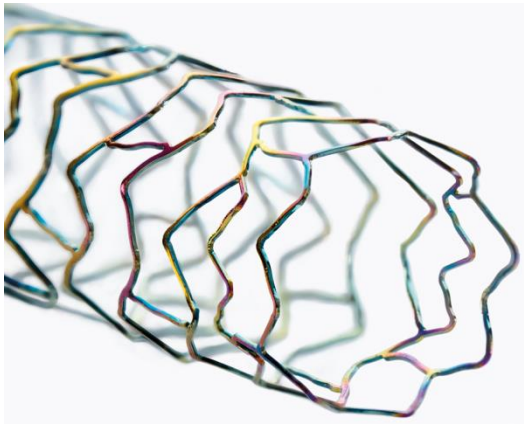
Thinner struts make the difference

Thinner struts create:

- Less disrupted flow[3]
- Less arterial injury[3]

Which leads to:

- Faster re-endothelialization[3]
- Reduced risk of restenosis and thrombosis[3]



1 ø 2.25 - 3.0 mm; 2. GG Stefanini, M Taniwaki, S Windecker, Coronary stents: novel development, Heart doi:10.1136/heartjnl-2012-303522; 3. Foin et al. Impact of stent strut design in metallic stents and biodegradable scaffolds. Int J Cardiol.2014 Dec 20;177(3):800-8

Key Benefits – Ultrathin Strut Design

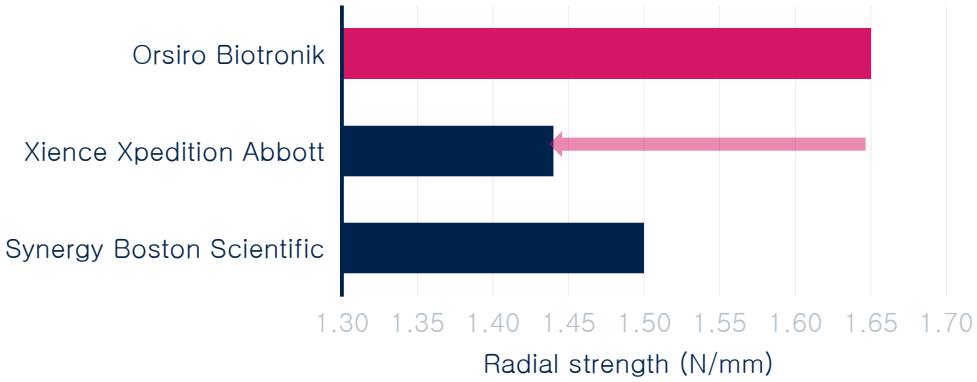
Clinically proven

Highly deliverable

Ultrathin strut design

The thinner the better, as long as radial force can be maintained[1]

Up to 15% more radial strength[2,3] for stronger scaffolding once implanted.

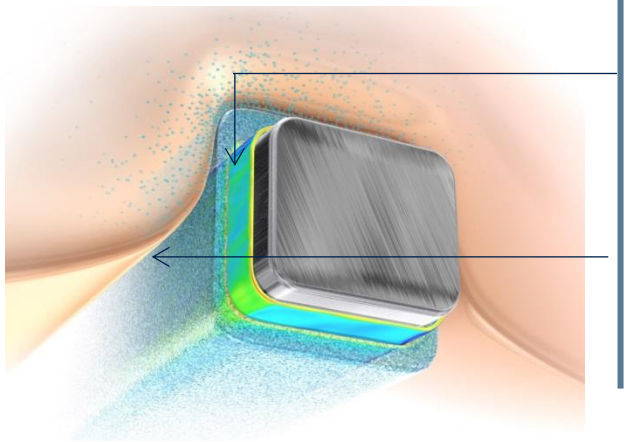


15%

More radial strength

1 The stent system is advanced through a stenosis model. Crossability is the mean resistance (mean force) registered by the stenosis during the complete passage of the stent delivery system. - IIB(P)31/2015 - IIB(P)85/2014-2; 2. Compared to Xience Expedition; 3. Expanded 3.0 mm diameter stents are radially compressed (15% of Ø) along full length. The force required to compress the stent is radial strength. BIOTRONIK data on file.

Orsiro Drug-Eluting Stent with a Bioabsorbable Polymer



The coating structure:

- Passive component **proBIO** encapsulates the stent, reducing interaction between the metal stent and the surrounding tissue
- Active component **BIOlute** consists of the most proven limus family drug and a bioabsorbable polymer matrix (PLLA) which achieves a controlled drug release.

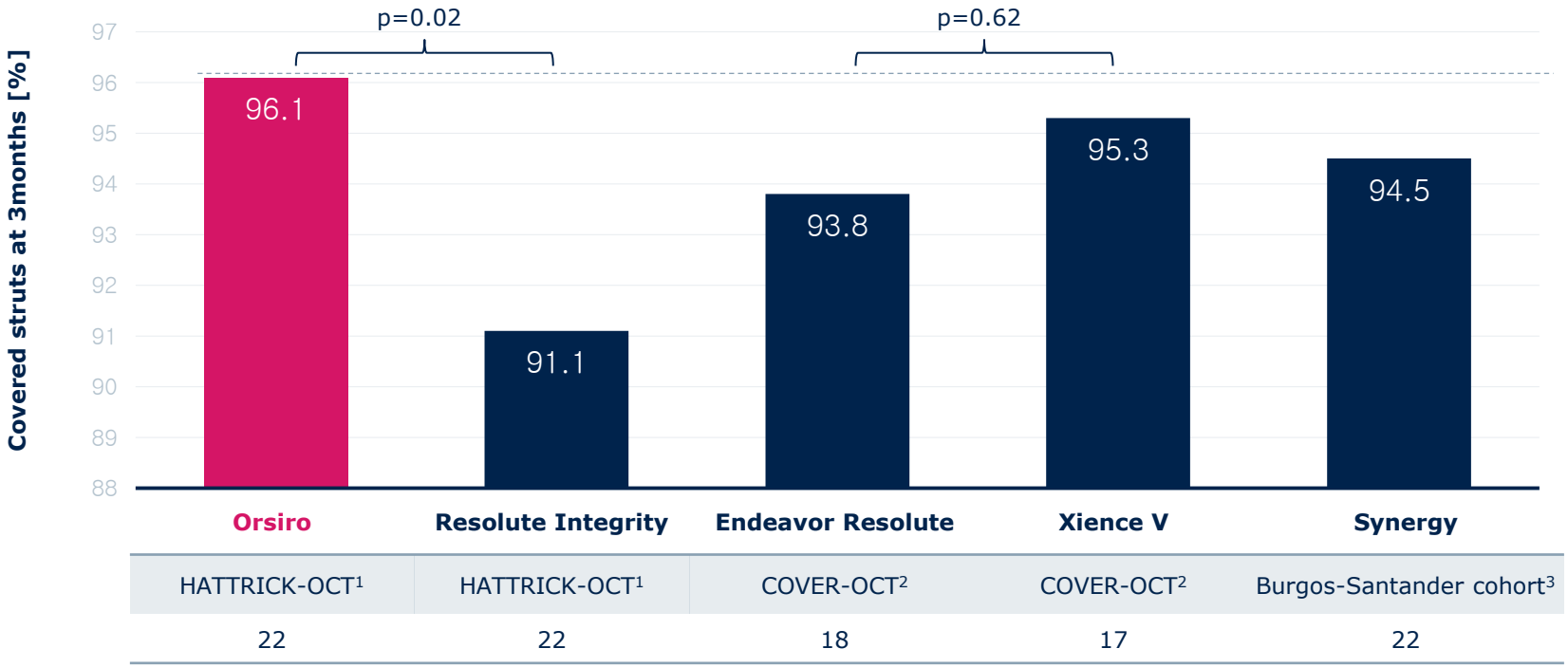
✓ **The BIOlute Coating elutes drug, becomes absorbed and leaves a proBIO coated stent behind.**

Source: Data on file, BIOTRONIK AG.

Based on these features of Orsiro, **re-endothelialization is faster, stable, & more complete.**

Only 3.9% uncovered struts at 3 months in ACS patients[1]

DAPT duration in each individual patient should be guided by an individualized approach based on ischaemic vs. bleeding risk assessment and not by the stent type. -2017 ESC focus update on DAPT in CAD[4]



HATTRICK-OCT[1]	HATTRICK-OCT[1]	COVER-OCT[2]	COVER-OCT[2]	Burgos-Santander cohort[3]
22	22	18	17	22

1 Karjalainen, Pasi P., et al. "Early neointimal coverage and vasodilator response following biodegradable polymer sirolimus-eluting vs. durable polymer zotarolimus-eluting stents in patients with acute coronary syndrome." Circulation Journal 79.2 (2015): 360-367;
2 Kim, Seunghwan, et al. "Comparison of early strut coverage between zotarolimus-and everolimus-eluting stents using optical coherence tomography." American Journal of Cardiology 111.1 (2013): 1-5;
3 de la Torre Hernández, Jose M., et al. "Early healing assessment with optical coherence tomography of everolimus-eluting stents with bioabsorbable polymer (synergy™) at 3 and 6 months after implantation." Catheterization and Cardiovascular Interventions 88.3(2016).;
4 Valgimigli, Marco, et al. "2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS." European Journal of Cardio-Thoracic Surgery 53.1 (2017): 34-78.

BIOFLOW studies, BIOTRONIK Sponsored Studies

BIOFLOW-I	30	2 sites 1 country	FIM	LLL at 9 months	Completed 12 months FU	NCT01214148
BIOFLOW–II	452	24 sites 8 countries	2:1 RCT Orsiro vs Xience	LLL at 9 months	Completed 60 months FU	NCT01356888
BIOFLOW–III	1356	43 sites 14 countries	One arm registry	TLF at 12 months	Completed 60 months FU	NCT01553526
	>7,700	(13)	Satellite registries	12-month TLF	Enrolling	
BIOFLOW-IV	525	46 sites 11 countries	2:1 RCT Orsiro vs Xience	TVF at 12 months	24 months FU available	NCT01939249
BIOFLOW–V	1334	91 sites 13 countries	2:1 RCT Orsiro vs Xience	TVF at 12 months	12 months FU available	NCT02389946
BIOFLOW–VI	440	11 sites 1 country	1:1 RCT Orsiro vs Xience	LLL at 9 months	Enrollment completed	NCT02870985
BIOFLOW-INDIA	120	1 country	Indian single-armed trial	9-month LLL	Completed	NCT01426139
BIOLUX-RCT	210	International	RCT vs. Pantera Lux in ISR	6-month LLL	Enrollment completed	NCT01651390
BIOFLOW-SV	1000	TBD 2 countries	All-comers registry	TLF at 12 months	TBD	TBD
BIOFLOW–DAPT	~2000	TBD	One arm registry	Composite 12 months	TBD	TBD

First-in-man Experience with Orsiro DES in De Novo Coronary Artery Lesions (BIOFLOW-I)

BIOFLOW-I
NCT01214148

Design
Prospective, multi-centre, non-randomized, first in man trial

Objective
To assess the safety and clinical performance of the Orsiro DES in patients with single de novo coronary artery lesions

Coordinating Clinical Investigator
Prof. Martial Hamon,
University Hospital of Caen, France

Principal Investigators
Dr. Rodica Niculescu, MD, PhD, FESC
Dr. Dan Deleanu, MD, FESC

Primary Endpoint
In-stent Late Lumen Loss at 9 months

30 patients enrolled July 2009

↓

Clinical follow-up at 1 month

↓

Clinical & angiographic follow-up at 4 months

↓

Clinical & angiographic follow-up at 9 months

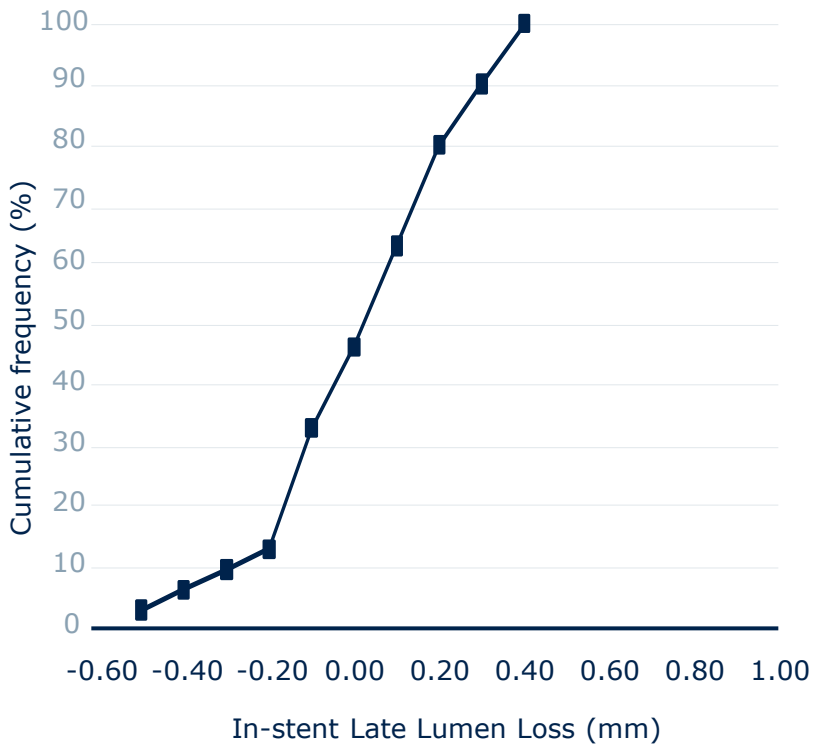
↓

Clinical follow-up at 12, 24 & 36 months

Source: M. Hamon, Late breaking trial presentation, EuroPCR 2011

Primary Endpoint In-stent Late Lumen Loss

BIOFLOW-I



9-month Primary Endpoint	n = 30
In-stent LLL	0.05 ± 0.22 mm

9-month Clinical Results	n	%
Death	0	0.0
Stent thrombosis	0	0.0
MI	0	0.0
TLR (clinically driven)	2	6.7
MACE	2	6.7

Source: M. Hamon, Late breaking trial presentation, EuroPCR 2011

Safety and Clinical Performance of Orsiro DES in the Treatment of Subjects with Single De Novo Coronary Artery Lesions **(Lesion lengths ≤26 mm)**

BIOFLOW-II
NCT01356888

Design

An international, prospective, multi-center, randomized, controlled trial comparing the Orsiro DES to Xience Prime

Objective

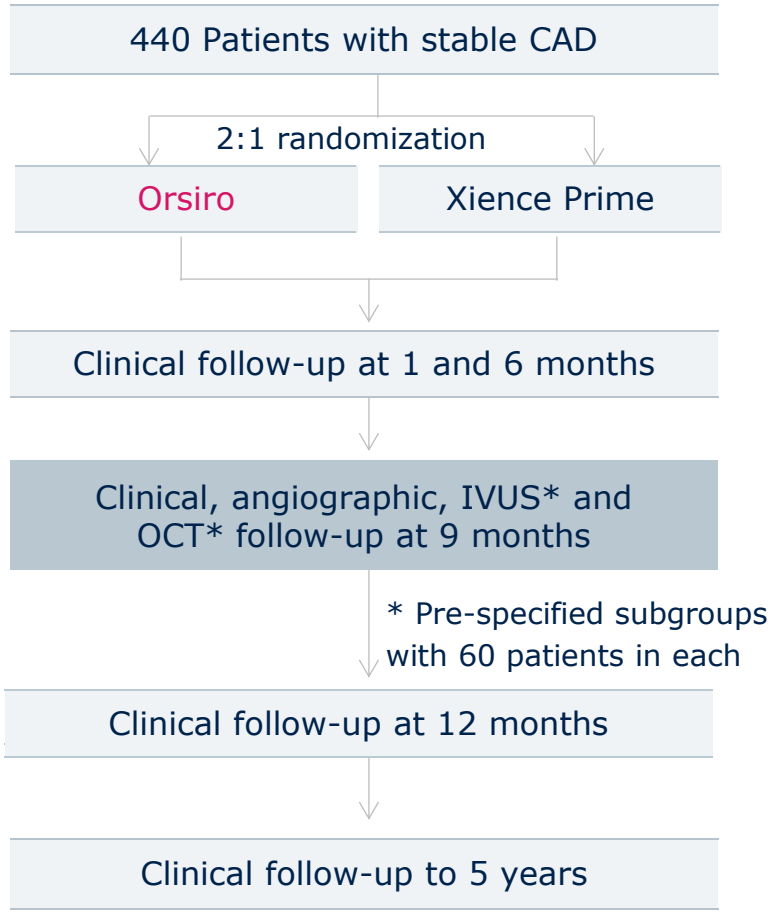
To compare the Orsiro stent with a bioabsorbable polymer to the XIENCE Prime stent with a durable polymer for the treatment of de novo coronary lesions with respect to non-inferiority for in-stent Late Lumen Loss (LLL) at 9 months

Coordinating Clinical Investigators

Prof. Stephan Windecker, Bern, Switzerland
Dr. Thierry Lefèvre, Massy, France

Primary Endpoint

In-stent Late Lumen Loss at 9 months

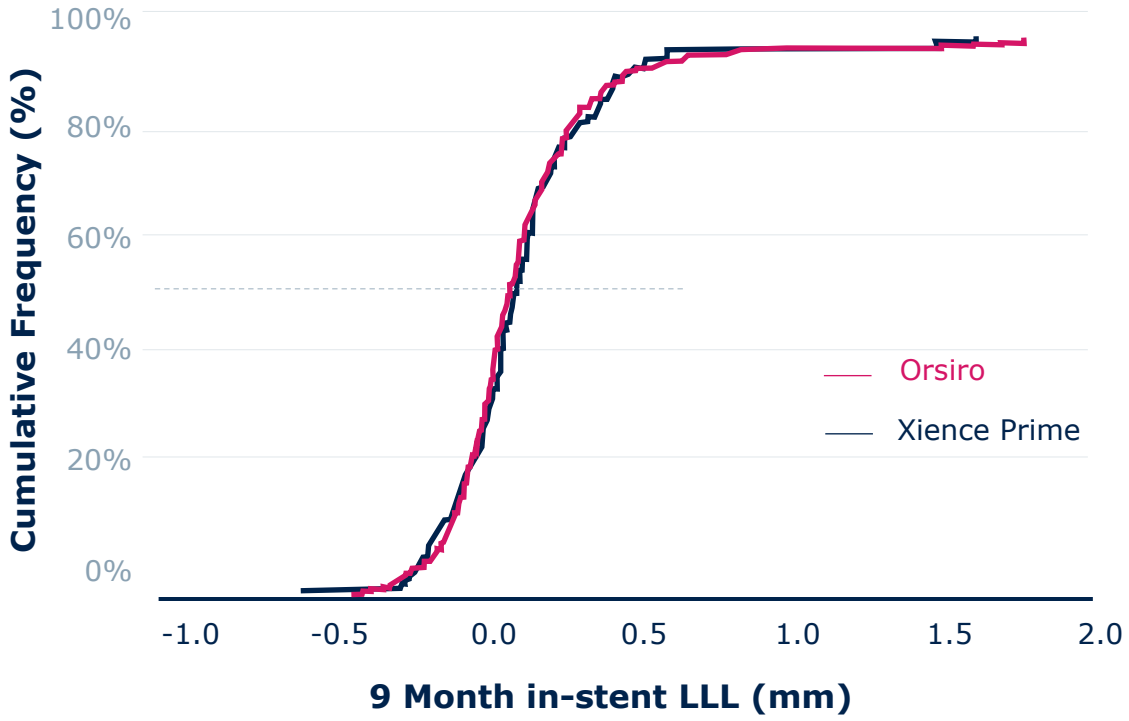


Source: T. Slagboom, Poster, EuroPCR 2015

Primary Angiographic Endpoint
In-stent Late Lumen Loss

BIOFLOW-II

Cumulative frequency of in-stent Late Lumen Loss at 9 months (mm)



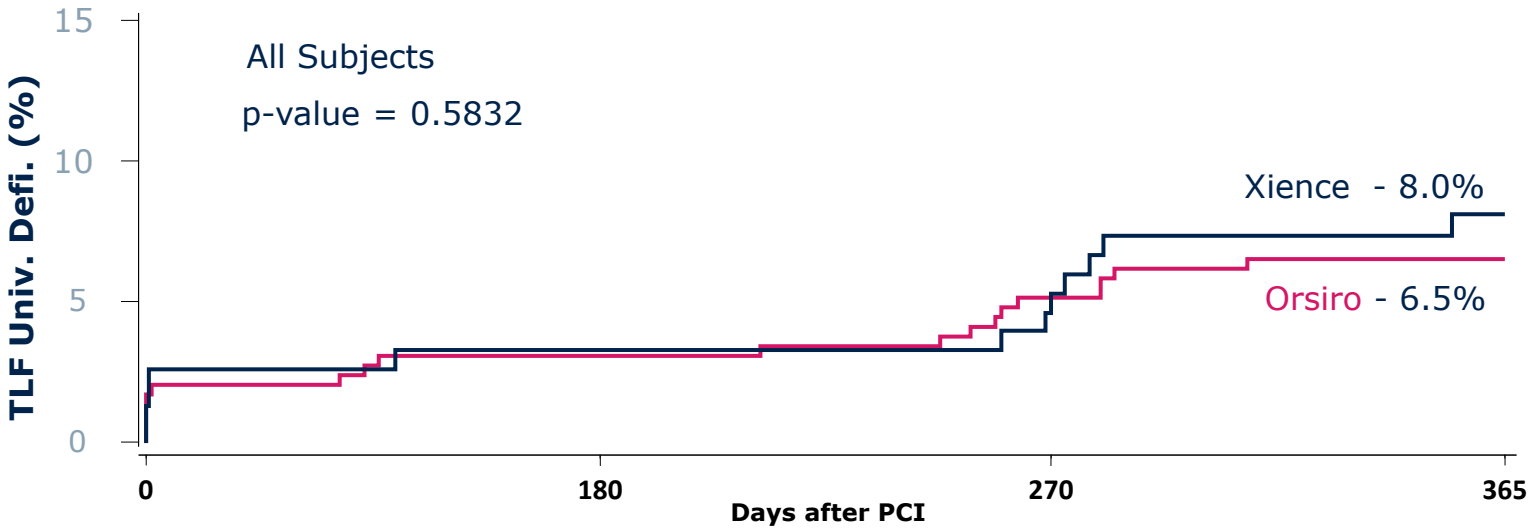
In-stent Late Lumen Loss at 9 months (mm)

Orsiro	Xience Prime	p-value for non-inferiority
0.10 ± 0.32	0.11 ± 0.29	< 0.0001

Sources: Windecker S. et al., Comparison of a Novel Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer verolimus-Eluting Stent Results of the Randomized BIOFLOW-II Trial, Circ Cardiovasc Interv, DOI:10.1161/CIRCINTERVENTIONS.114.001441

Main Secondary Endpoints: TLF Rate at 12 Months

BIOFLOW-II



Target Lesion Failure Composites (%)	Orsiro n = 298	Xience Prime n = 154	p-value
Cardiac Death	0.7	0.7	0.98
Target vessel MI	2.7	2.6	0.95
TLR (Clinically driven)	3.5	4.7	0.54
CABG (Emergent)	0.0	0.0	>0.99

- TLF; a composite of cardiac death, target vessel MI, and clinically driven TLR

Source: S. Windecker, Poster, TCT 2013


JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 10, 2018

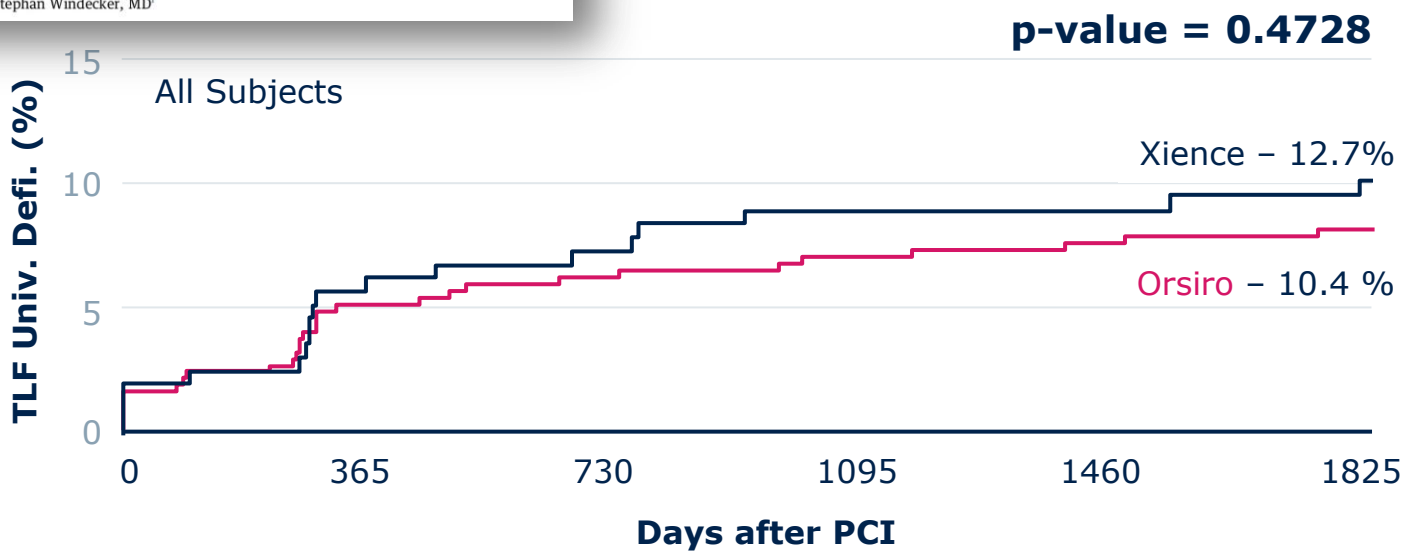
Comparison of a Novel Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent

5-Year Outcomes of the Randomized BIOFLOW-II Trial

Thierry Lefèvre, MD,[a] Michael Haude, MD,[b] Franz-Josef Neumann, MD,[c] Karl Stangl, MD,[d] Carsten Skurk, MD,[e] Ton Slagboom, MD,[f] Manel Sabaté, MD,[g] Javier Goicolea, MD,[h] Paul Barragan, MD,[i] Stéphane Cook, MD,[j] Jean-Christophe Macia, MD,[k] Stephan Windecker, MD[l]

Main Secondary Endpoints: TLF Rate at 60 Months

BIOFLOW-II

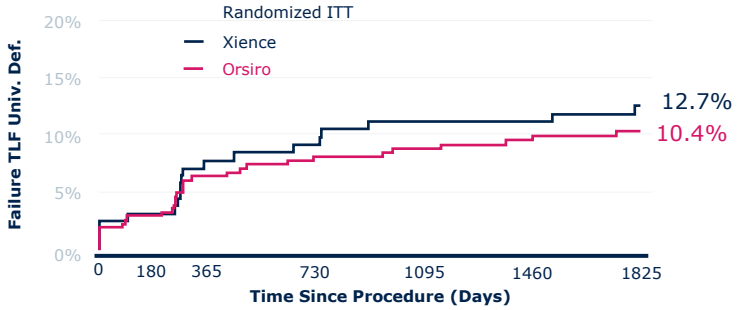


Target Lesion Failure Composites (%)	Orsiro n = 298	Xience Prime n = 154	p-value
Cardiac Death	1.7	2.8	0.5043
Target vessel MI	3.4	3.3	0.9531
TLR (Clinically driven)	6.3	6.7	0.8501
CABG (Emergent)	0.0	0.0	>0.9999

Selected Endpoints at 60 Months

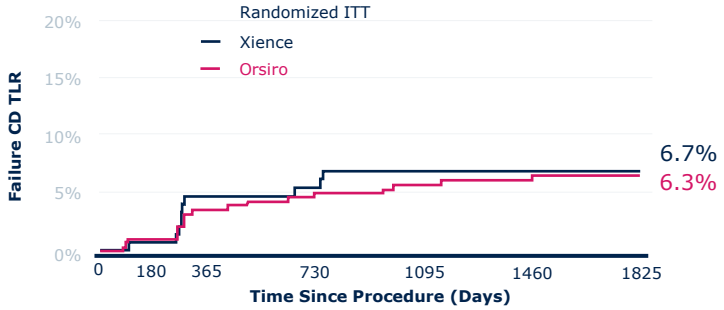
BIOFLOW-II

Target Lesion Failure



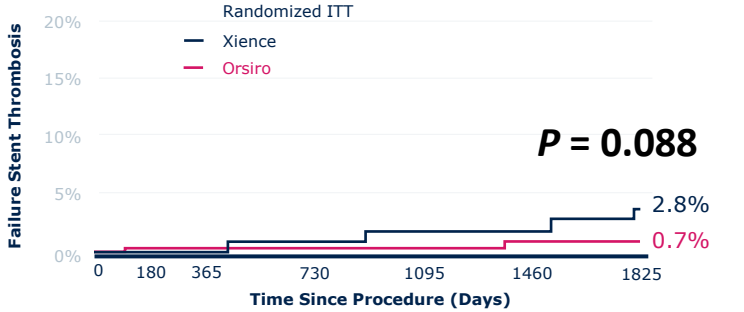
At risk							
Orsiro	298	285	268	261	256	250	138
Xience	154	146	138	134	128	125	63

Target Lesion Revascularization



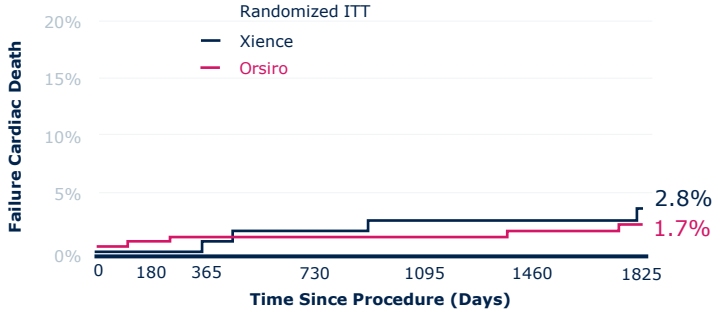
At risk							
Orsiro	298	290	275	269	264	258	144
Xience	154	150	142	138	131	128	65

Stent Thrombosis



At risk							
Orsiro	298	292	284	282	279	273	155
Xience	154	151	149	146	141	138	67

Cardiac Death



At risk							
Orsiro	298	292	284	282	279	273	155
Xience	154	151	149	146	141	138	68

Source: Lefèvre et al. on behalf of BIOFLOW-II investigators, J Am Coll Cardiol Intv 2018;11:995–1002

Main Secondary Endpoints: Stent Thrombosis at 60 Months

BIOFLOW-II

Definite ST

	Orsiro (n = 298)	Xience Prime (n = 154)
Acute (0-48h)	**0 %**	0 %
Subacute (48h-30d)	**0 %**	0 %
Late (>30d)	**0 %**	0 %
Very late (>12m)	**0 %**	0.7 %
Overall	**0 %**	0.7 %

Definite, Probable or Possible ST

	Orsiro (n = 298)	Xience Prime (n = 154)
Acute (0-48h)	**0 %**	0 %
Subacute (48h-30d)	**0 %**	0 %
Late (>30d)	**0 %**	0 %
Very late (>12m)	**0.7 %**	2.8 %
Overall	0.7 %*	2.8 %**

* Two possible stent thrombosis
** Four possible stent thrombosis
Source: T. Slagboom, Poster, EuroPCR 2017

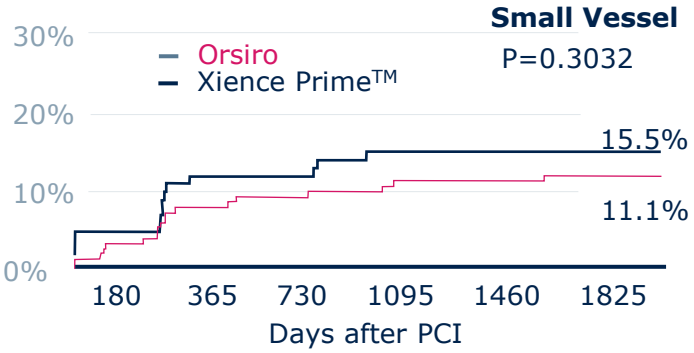
Small Vessel (≤ 2.75mm) Subgroup Analysis

BIOFLOW-II

Small Vessel Subgroup Demographics & Lesion Characteristics

	Orsiro	Xience Prime
	Subjects = 168	**Subjects = 91**
Age (years)	62.9 ± 10.2	65.5 ± 9.0
Hypertension (%)	80.4	76.9
Hyperlipidemia (%)	69.6	68.1
History of MI (%)	33.9	26.4
Diabetes (%)	33.9	28.6
Insulin dependent (%)	29.8	30.8
Non-insulin dependent (%)	70.2	69.2
	Lesions = 195	**Lesions = 109**
Lesion length (mm)	13.93 ± 6.88*	13.08 ± 5.22*
RVD (mm)	2.49 ± 0.37	2.49 ± 0.33
Diameter stenosis (%)	67.55 ± 13.70	65.56 ± 14.47

Small Vessel subgroup TLF at 60 months



Small Vessel subgroup Results at 60 months

Target Lesion Failure Composites (%)	Orsiro n = 168	Xience Prime n = 91	p-value
Cardiac Death	0.6	2.2	0.2652
Target vessel MI	3.7	4.4	0.7380
TLR (Clinically driven)	8.7	8.9	0.9448
CABG (Emergent)	0.0	0.0	> 0.9999

* Analysis only possible for Orsiro n = 191, Xience Prime n = 108

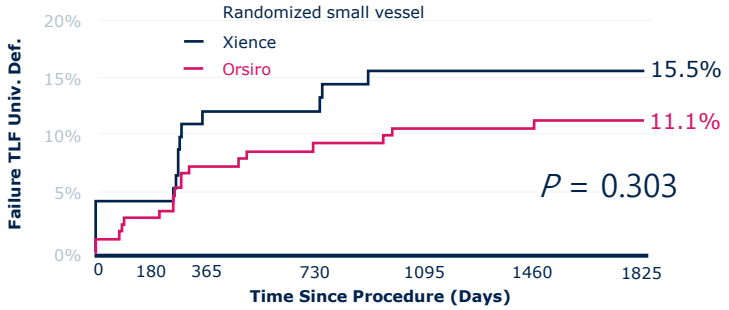
Source : T. Slagboom, Poster, EuroPCR 2015; Sabate M. Oral presentation. EuroPCR, Paris, France, May 2014. Oral Presentation; Ruiz-Salmeron R. Poster presentation. TCT, Washington DC, USA, September 2014.

Small Vessel Subgroup

Selected Endpoints at 60 Months

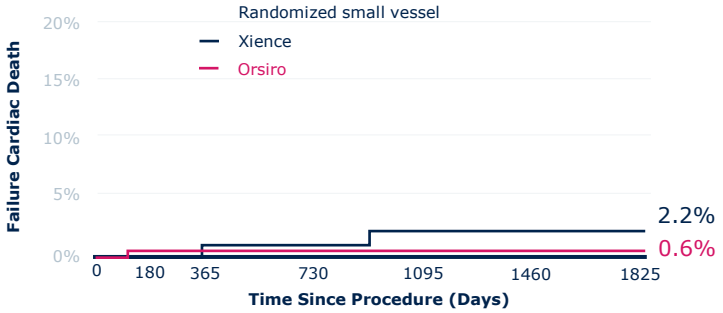
BIOFLOW-II

Target Lesion Failure



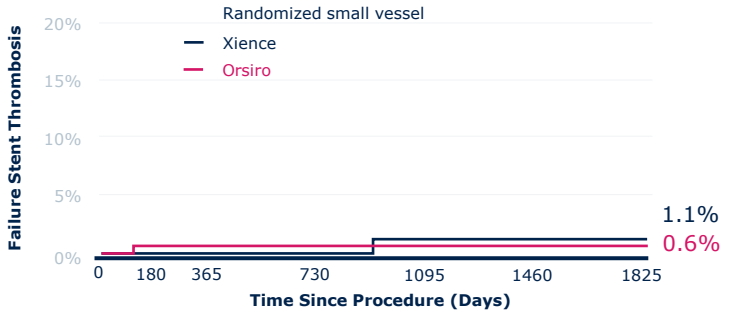
At risk							
Orsiro	168	161	148	143	139	136	70
Xience	91	87	80	78	72	70	36

Cardiac Death



At risk							
Orsiro	168	165	159	157	155	152	84
Xience	91	91	90	88	83	81	40

Stent Thrombosis



At risk							
Orsiro	165	159	157	155	152	84	
Xience	91	90	88	83	81	40	

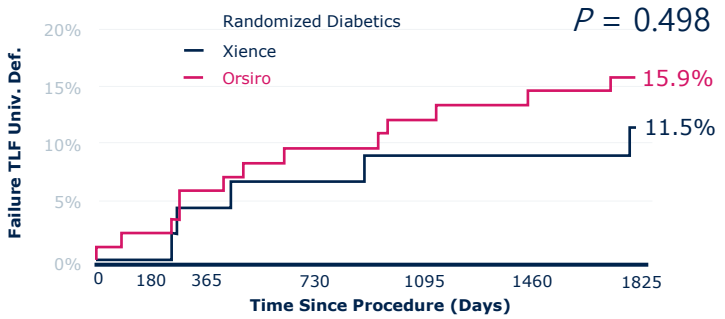
Small vessels subgroup, n	168	91		
Death	6 (3.7)	10 (11.3)	0.33 (0.12-0.90)	0.022
Cardiac death	1 (0.6)	2 (2.2)	0.28 (0.03-3.08)	0.265
MI, univ. def.	8 (4.9)	5 (5.6)	0.86 (0.28-2.63)	0.791
TV MI, univ. def.	6 (3.7)	4 (4.4)	0.81 (0.23-2.86)	0.738
Clinically indicated TLR	14 (8.7)	8 (8.9)	0.97 (0.41-2.32)	0.948
Clinically indicated TVR	25 (15.6)	12 (13.3)	1.16 (0.58-2.31)	0.676
Target lesion failure, univ. def.	18 (11.1)	14 (15.5)	0.69 (0.35-1.40)	0.303
Target vessel failure, univ. def.	27 (16.8)	18 (19.9)	0.80 (0.44-1.46)	0.475
Death or MI, univ. def.	13 (8.0)	14 (15.6)	0.50 (0.23-2.86)	0.066
Stent thrombosis	1 (0.6)	1 (1.1)	0.55 (0.03-8.84)	0.671
Definite	0 (0.0)	0 (0.0)	–	–
Probable	0 (0.0)	0 (0.0)	–	–

- Source: Lefèvre et al. on behalf of BIOFLOW-II investigators, J Am Coll Cardiol Intv 2018;11:995–1002

Diabetic Subgroup Analysis
Selected Endpoints at 60 Months

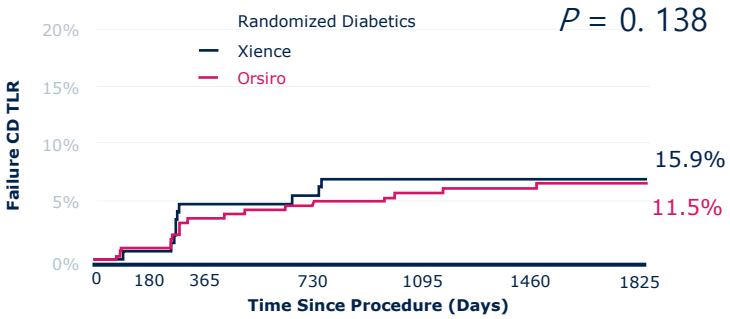
BIOFLOW-II

Target Lesion Failure



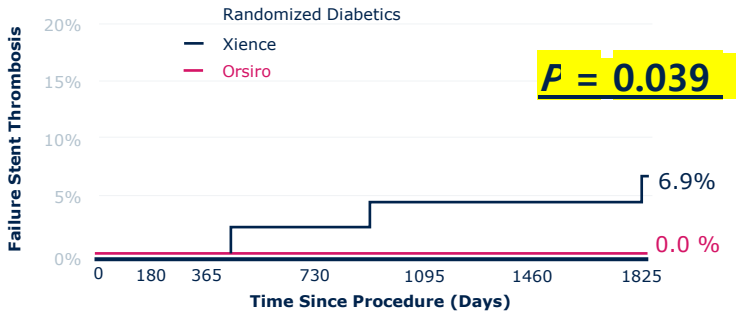
At risk							
Orsiro	84	82	77	74	71	69	42
Xience	44	44	42	41	40	40	21

Target Lesion Revascularization



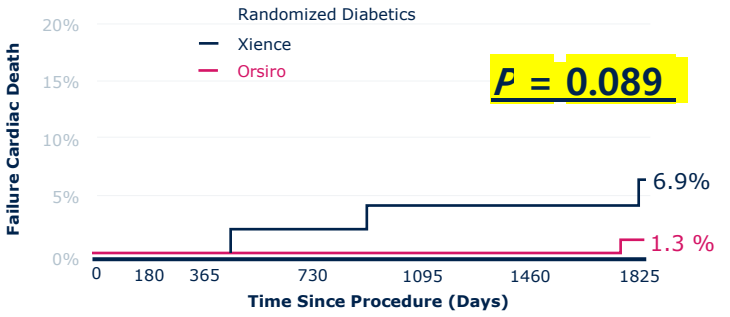
At risk							
Orsiro	298	290	275	269	264	258	144
Xience	154	150	142	138	131	128	65

Stent Thrombosis (any)



At risk							
Orsiro	84	84	82	82	81	79	50
Xience	44	44	44	43	42	42	21

Cardiac Death



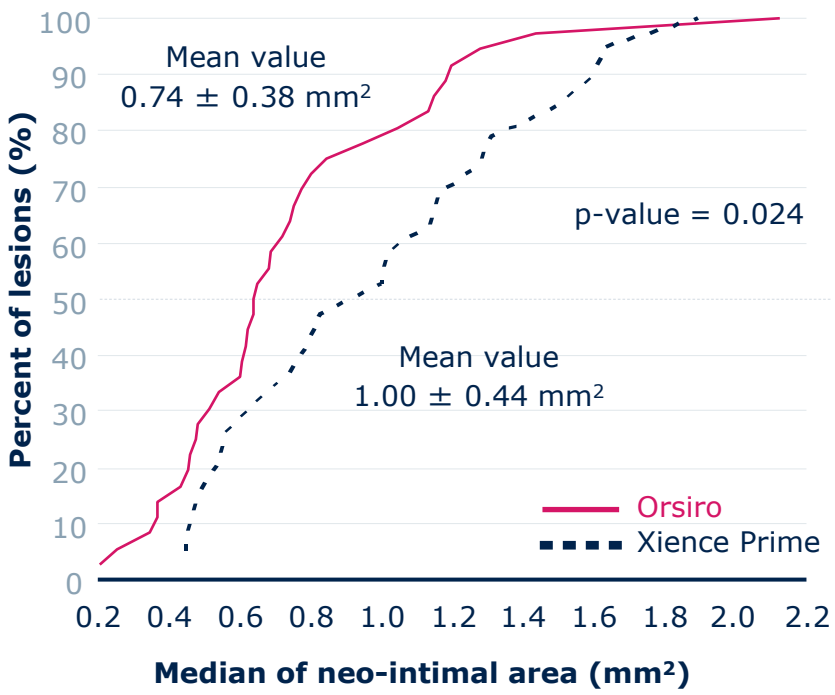
At risk							
Orsiro	84	84	82	82	81	79	50
Xience	44	44	44	43	42	42	21

- Source: Lefèvre et al. on behalf of BIOFLOW-II investigators, J Am Coll Cardiol Intv 2018;11:995–1002

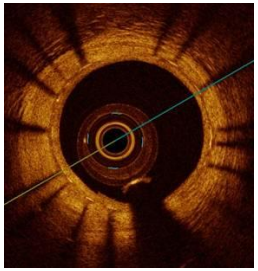
OCT Results at 9 Months

BIOFLOW-II

Neo-intimal area



Apposition and coverage



	Orsiro	Xience Prime	p-value
Well-apposed struts	98.6%	98.8%	0.62
Incomplete Strut Apposition	1.0%	0.6%	0.32
Non-apposed side branch	0.4%	0.6%	0.37
Sum	100%	100%	
Covered Struts	**98.3%**	**97.5%**	**0.042**

Source: S. Windecker, Late breaking trial presentation, EuroPCR 2013

Conclusion

BIOFLOW-II

The 5 years results of this prospective, randomized, study confirms the safety and efficacy of the Orsiro SES, in the whole patient population, as well as in high risk diabetic and small vessel subgroups

Target Lesion Failure	Clinical event rates in the all subjects-, diabetic- and small vessel cohorts were comparable between Orsiro and Xience Prime™ up to 5 years
Stent Thrombosis	No Definite or Probable ST occurred in the whole BIOFLOW-II population or in pre-specified diabetic and small vessel subgroups in the Orsiro arm through 5 years For Xience, one case of very late definite Stent Thrombosis was observed. In diabetic subgroup stent thrombosis rate was significantly lower in Orsiro study arm

Source: Slagboom et al. EuroPCR 2018 Poster Presentation

Registry for an All-comers Patient Population with the Orsiro DES in Daily Clinical Practice

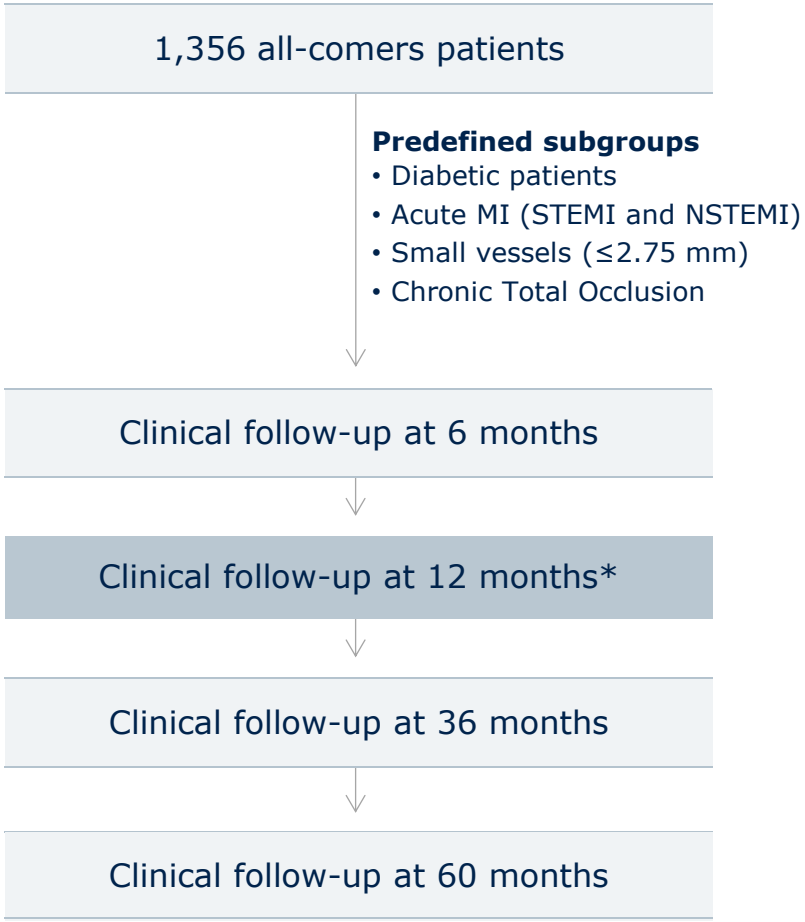
BIOFLOW-III
NCT01553526

Design
An international, prospective, multi-center open-label, registry of the Orsiro DES in daily clinical practice

Objective
Evaluate safety and clinical performance of the Orsiro drug eluting stent with a bioabsorbable polymer in a large patient population in standard clinical care

Coordinating Investigator
Prof. Dr. Johannes Waltenberger, Universitätsklinikum Münster, Germany

Primary Endpoint
Target Lesion Failure (TLF) at 12 months



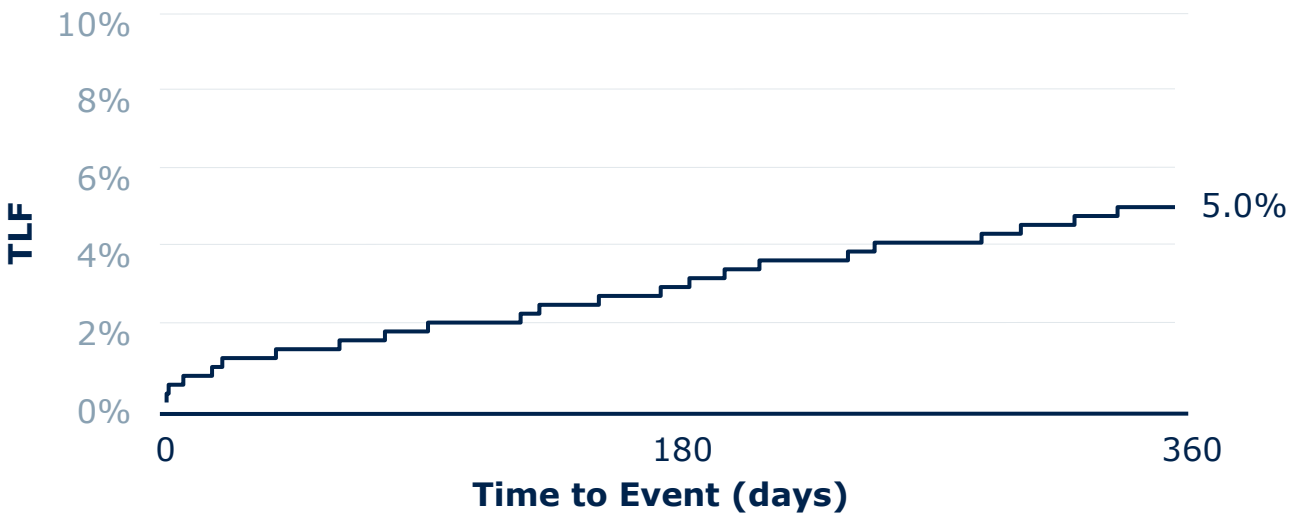
* 97.4 % FUP compliance
Source: Waltenberger et al. EuroIntervention 2015; 10-online publish-ahead-of-print March 2015.

Primary & Major Secondary Endpoint

Results at 12 Months

BIOFLOW-III

TLF at 12 Months – All Subjects



Major Secondary Endpoints

Devices	n = 1,738
Device success	98.8%
Procedures	**n = 1,356**
Procedure success	98.2%

Target Lesion Failure Composites (%)	Orsiro n = 298
Cardiac Death	1.3
Target vessel MI	2.3
TLR (Clinically driven)	3.0
CABG (Emergent)	0.0

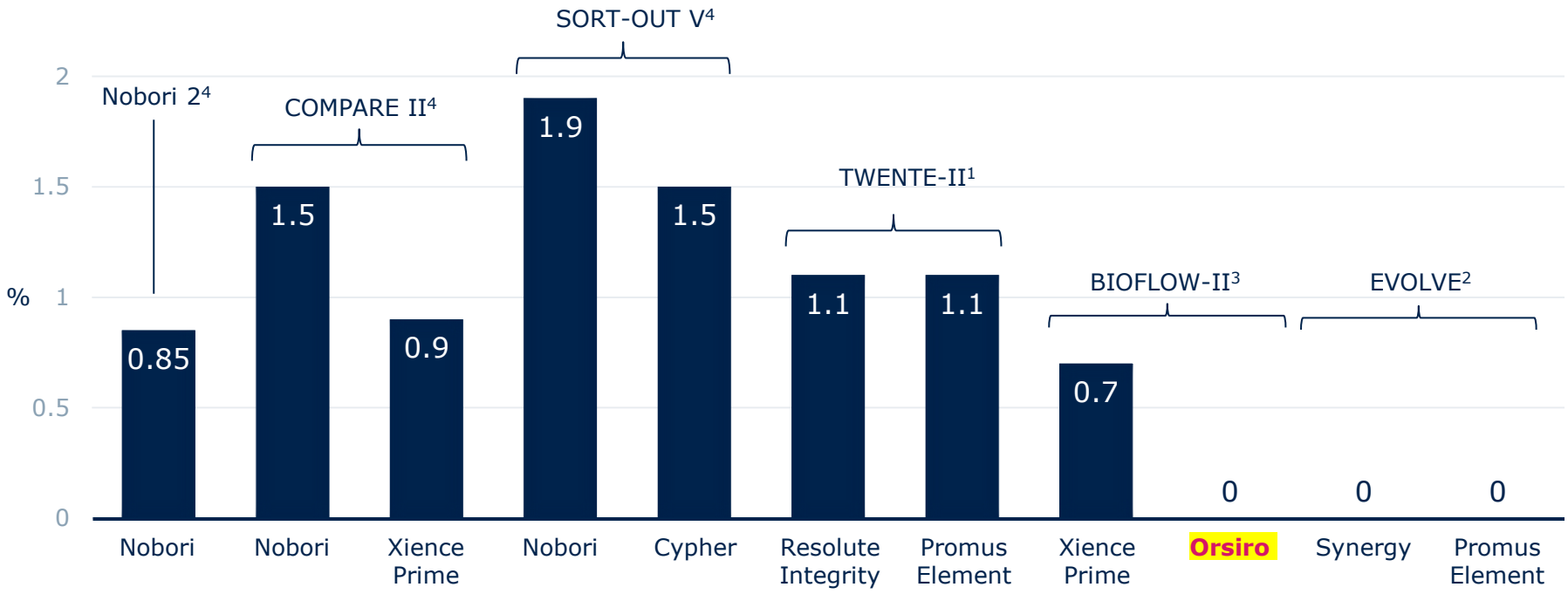
Source: Waltenberger et al. EuroIntervention 2015; 10-online publish-ahead-of-print March 2015.

Stent Thrombosis Results at 60 Months

BIOFLOW-III

Stent Thrombosis out to 5 years for other coronary stents

Definite stent thrombosis*



* Biodegradable polymer biolimus-eluting stents versus durable polymer everolimus-eluting stent in patients with coronary artery disease. G.J. Vlachojannis et. al, JACC: Cardiovascular Interventions, 2017(10):1215-21

1 5-year outcome following randomized treatment of all-comers with zotarolimus-eluting Resolute Integrity and everolimus-eluting PROMUS element coronary stents. P. Zocca et.al, JACC: Cardiovascular Interventions, 2018(11) 462-9

Final five-year outcomes after implantation of biodegradable polymer-coated biolimus-eluting stents versus durable polymer-coated sirolimus-eluting stents. L. Jakobsen, et.al, 2017 13(11):1336-44

2 Final five-year clinical outcomes in the EVOLVE trial: a randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent. I.T. Meredith et.al, EuroIntervention. 2018;13:2047-2050.

3 Comparison of a noverl biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent. T. Lefèvre et.al, JACC

4 Waltenberger et al. on behalf of BIOFLOW-III Investigators, EuroPCR 2018 – Lecture

Comparison of Ultrathin Sirolimus-Eluting Bioresorbable Polymer with Thin Everolimus-Eluting Durable Polymer Stents

BIOFLOW-V

Design

Prospective, multi-center, 2:1 randomized controlled IDE (Investigational Device Exemption) trial.

Objective

Assess the safety and effectiveness of Orsiro in the treatment of patients with up to three de novo or restenotic lesions.

Coordinating Clinical Investigators

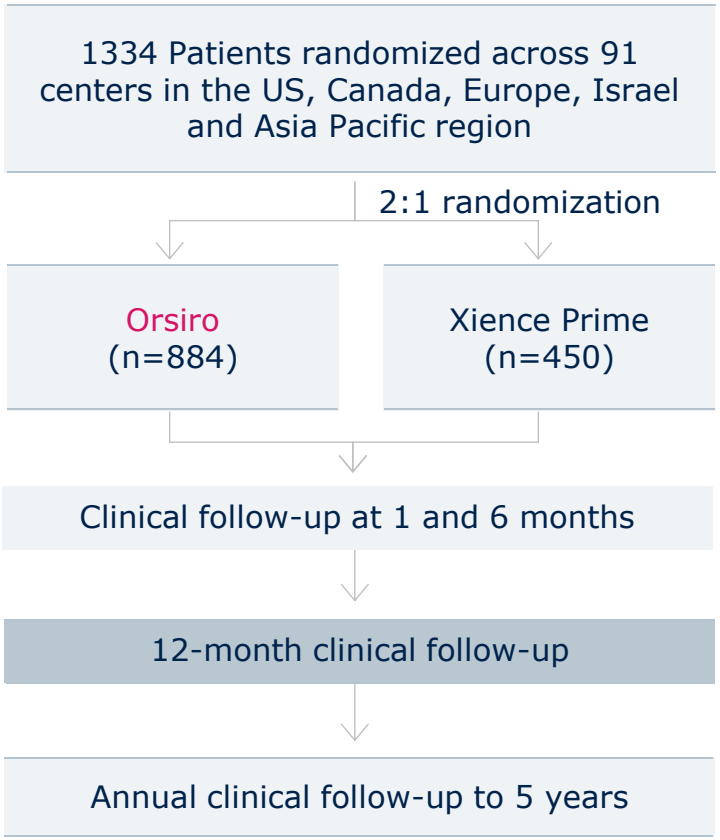
Dr. David E. Kandzari, Piedmont Heart Institute, Atlanta, USA

Dr. Jacques Koolen, Catharina Ziekenhuis, Eindhoven, Netherlands

Primary Endpoint

Target Lesion Failure (TLF) at 12 months, defined as the composite of **cardiovascular death, target vessel-related myocardial infraction (MI), or ischemia-driven TLR**

BIOFLOW-V ITT:



Source: Kandzari D et al, Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a rondomised trial, The Lancet, 2017

BIOFLOW-V

Procedural Results

	Orsiro (n = 884)	Xience (n = 450)	P-Value
Lesion success*	1102/1107 (99.6%)	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

Procedural success was significantly higher with Orsiro, principally driven by a higher rate of in-hospital MI with Xience. Specifically, the peri-procedural MI was higher in the Xience group.

* 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).

Source: Kandzari D, BIOFLOW V Comparison of UltraThin Sirolimus-Eluting Bioresorbable Polymer with Thin Everolimus- Eluting Durable Polymer Stents, Oral presentation ESC 2017

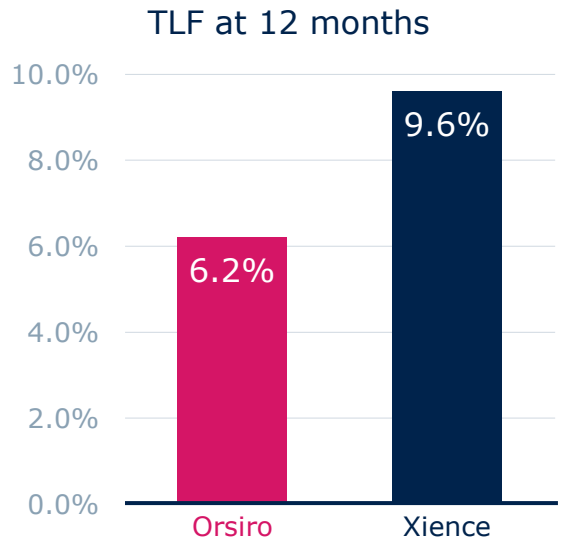
Results: 30-Day Outcomes

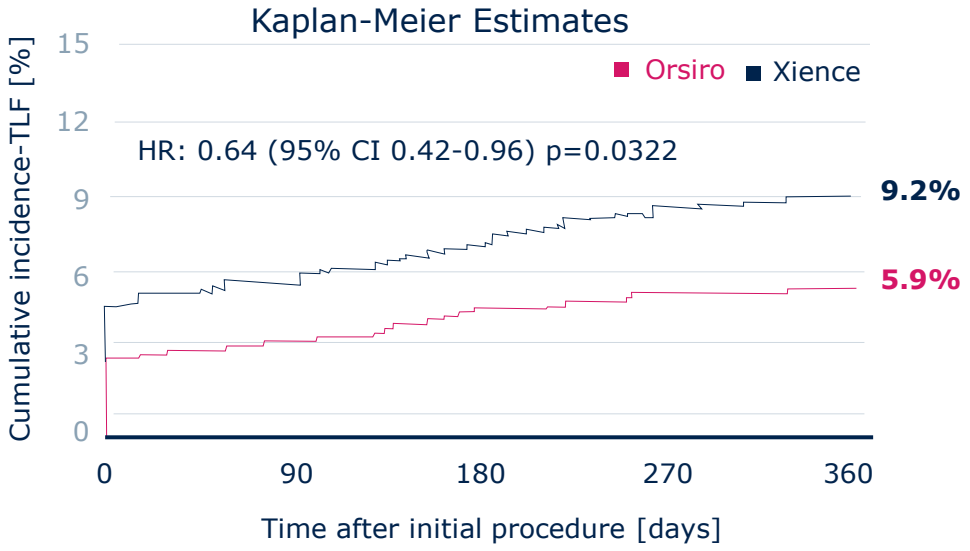
	Orsiro (n = 884)	Xience (n = 450)	P-Value
All-cause death	0.1%	0.2%	1.000
Myocardial Infarction	4.3%	6.9%	0.050
In-Hospital MI	3.9%	6.7%	0.029
TLR	0.5%	0.7%	0.694
Stent Thrombosis	0.3%	0.2%	1.000
TLF	4.2%	7.1%	0.026
TVF	4.3%	7.1%	0.037

Source: Kandzari D, BIOFLOW V Comparison of UltraThin Sirolimus-Eluting Bioresorbable Polymer with Thin Everolimus- Eluting Durable Polymer Stents, Oral presentation ESC 2017

Results: 12-month Outcomes

	Orsiro (n = 884)	Xience (n = 450)	P-Value
Target lesion failure	**52/833 (6.2%)**	**41/427 (9.6%)**	**0.040**
Cardiac death	1/831 (0.1%)	3/425 (0.7%)	0.115
Target-vessel MI	39/831 (4.7%)	35/424 (8.3%)	0.016
Clinically-driven TLR	17/832 (2.0%)	10/422 (2.4%)	0.686





Source: Kandzari D, BIOFLOW V Comparison of UltraThin Sirolimus-Eluting Bioresorbable Polymer with Thin Everolimus- Eluting Durable Polymer Stents, Oral presentation ESC 2017

Results: 12-month Outcomes

	Orsiro (n = 884)	Xience (n = 450)	P-Value
Death from any cause	7/837 (0.8%)	6/428 (1.4%)	0.382
Any MI	**41/832 (4.9%)**	**37/425 (8.7%)**	**0.013**
Q-wave	1/831 (0.1%)	4/422 (1.0%)	0.047
Non-Q-wave	40/831 (4.8%)	34/425 (8.0%)	0.031
Cardiac death or any MI	**42/833 (5.0%)**	**39/427 (9.1%)**	**0.007**
MACE	**59/839 (7.0%)**	**44/429 (10.3%)**	**0.051**
Target-vessel failure	60/834 (7.2%)	45/427 (10.5%)	0.052
Target-vessel myocardial infarction	39/831 (4.7%)	35/424 (8.3%)	0.016
Clinically-driven target-vessel revascularization	27/833 (3·2%)	15/422 (3.6%)	0.7430

Source: Kandzari D et al, Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a rondomised trial, The Lancet, 2017

Results: 12-month Stent Thrombosis

	Orsiro (n = 884)	Xience (n = 450)	P-Value
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**
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

Source: Kandzari D et al, Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial, The Lancet, 2017

ARTICLE IN PRESS

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2018

Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents Versus Thin Durable Polymer Everolimus-Eluting Stents After Myocardial Infarction

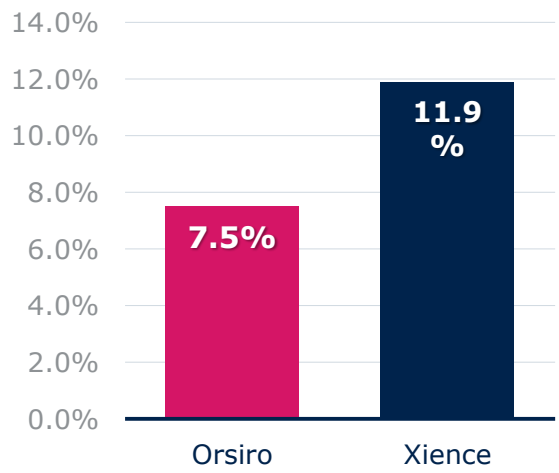
David E. Kandzari, MD,[a] Jacques J. Koolen, MD, PhD,[b] Gheorghe Doros, PhD,[c] Joseph J. Massaro, PhD,[d] Hector M. Garcia-Garcia, MD, PhD,[e] Johan Bennett, MD, PhD,[f] Ariel Roguin, MD, PhD,[g] Elie G. Gharib, MD,[h] Donald E. Cutlip, MD,[i] Ron Waksman, MD,[e] for the BIOFLOW V Investigators

Results: 24-month Outcomes

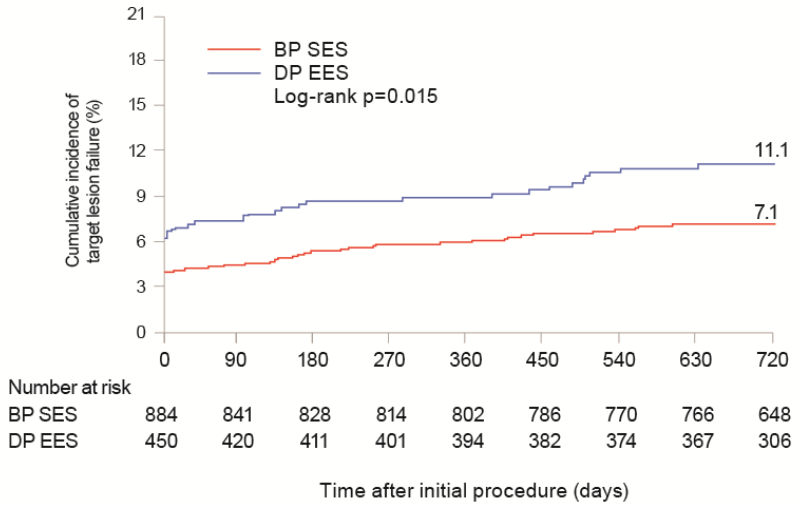
BIOFLOW-V

	Orsiro (n=884)	Xience (n=450)	P-Value
Target lesion failure	**62/823 (7.5%)**	**49/413 (11.9%)**	**0.015**
Cardiac death	5/817 (0.6%)	2/407 (0.7%)	1.0
Target-vessel MI	**43/816 (5.3%)**	**39/410 (9.5%)**	**0.016**
Clinically-driven TLR	**21/816 (2.6%)**	**20/407 (4.9%)**	**0.04**

TLF at 24 months



Kaplan-Meier Estimates

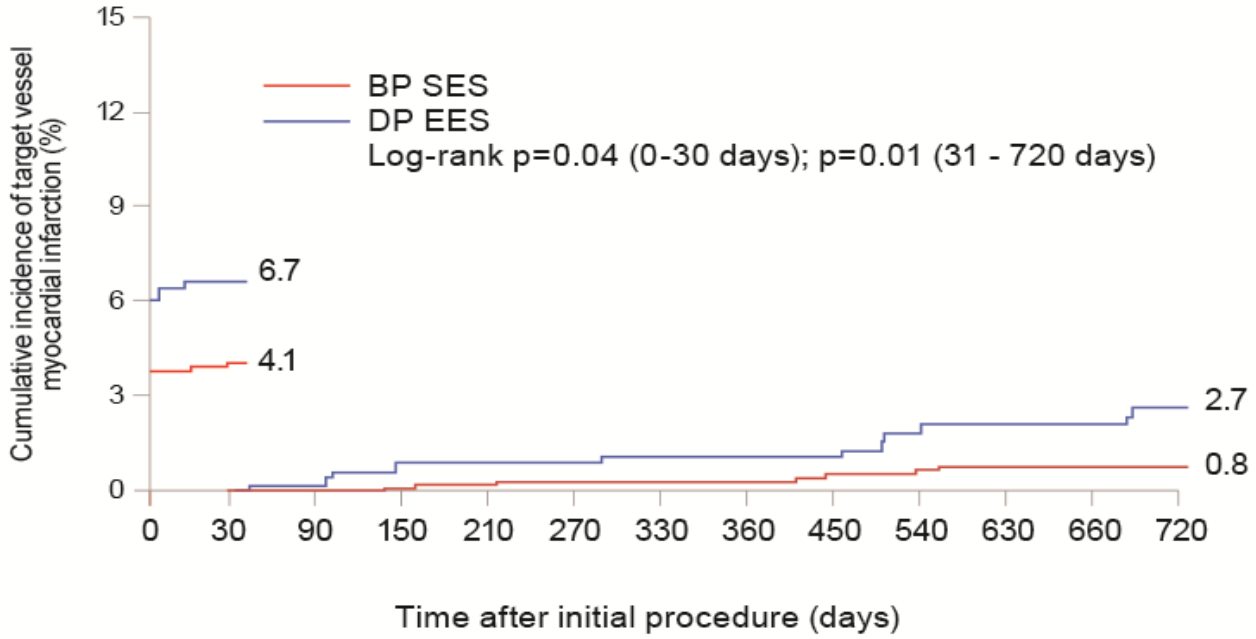


Source: Kandzari D et al , Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin Durable Polymer Everolimus-Eluting Stents: BIOFLOW V 2-Year Results, Journal of the American College of Cardiology, 2018

Results: 24-month Outcomes

BIOFLOW-V

Landmark Analysis **TV-MI 30 days to 24 months**



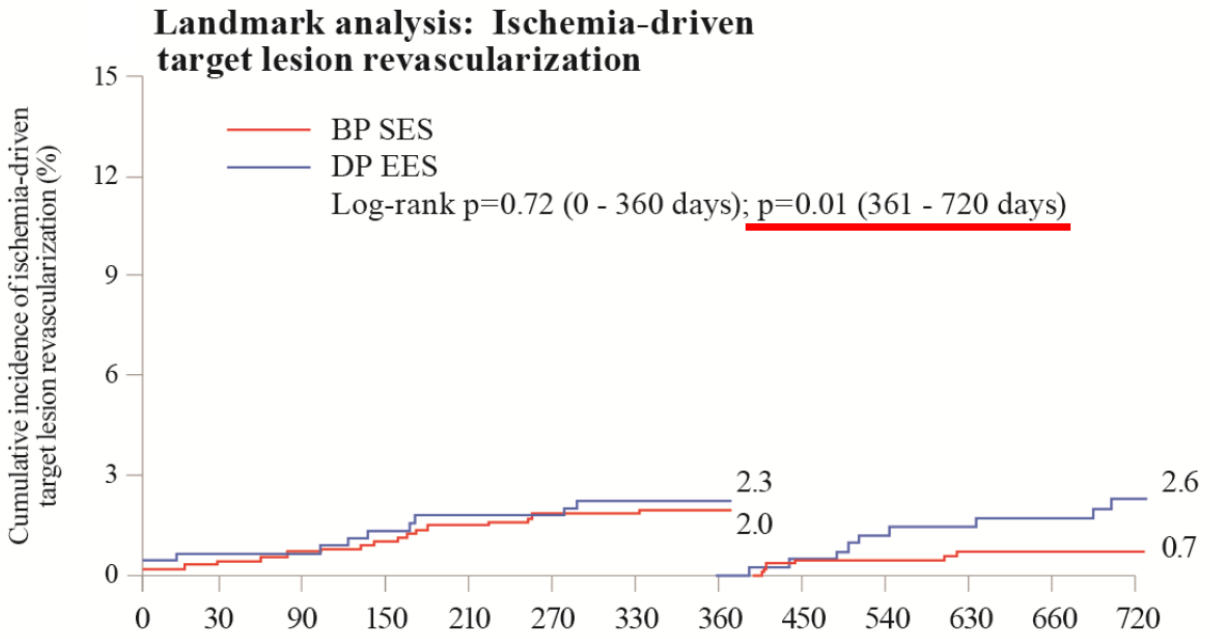
Lower target-vessel related MI (5.3% vs 9.5%, *P*=0.01) at 2 years, both early (≤30 days) and late (31 days to 2 years)

Source: Kandzari D et al , Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin Durable Polymer Everolimus-Eluting Stents: BIOFLOW V 2-Year Results, Journal of the American College of Cardiology, 2018

Results: 24-month Outcomes

BIOFLOW-V

Landmark analysis **Ischemia-Driven Target Lesion Revascularization** to 24 months



Lower ischemia-driven TLR, driven by differences in late (>1 year) TLR (2.6% vs 4.9%, *P*=0.04)

Source: Kandzari D et al , Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin Durable Polymer Everolimus-Eluting Stents: BIOFLOW V 2-Year Results, Journal of the American College of Cardiology, 2018

Results: 24-month Stent Thrombosis

BIOFLOW-V

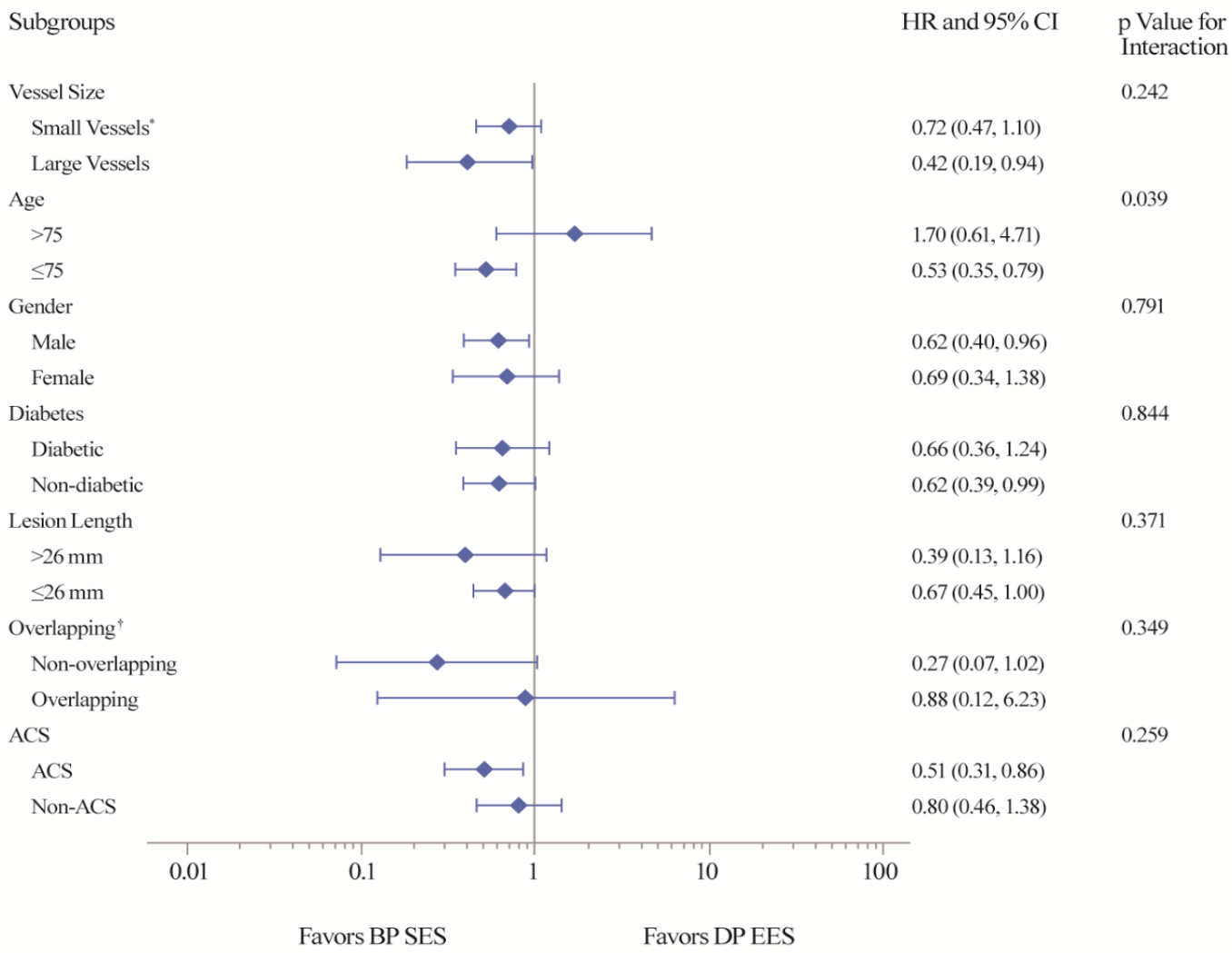
	Orsiro (n=884)	Xience (n=450)	P-Value
Definite	0.5%	1.2%	0.17
Probable	0	0	-
Definite/Probable/Possible	0.7%	1.5%	0.23
Definite/Probable Stent Thrombosis			
Early	0.3%	0.2%	1.00
Late (>30 days and ≤1 year)	0.1%	0.5%	0.26
Very late (> 1 year and ≤2 years)	0	0.5%	0.11
Late/Very Late (>30 days ≤2 years)	**0.1%**	**1.0%**	**0.045**

DAPT adherence at 2 years: 45.6% (368/807) BP SES; 45.1% (181/401) DP EES; P=0.88

Source: Kandzari D et al , Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin Durable Polymer Everolimus-Eluting Stents: BIOFLOW V 2-Year Results, Journal of the American College of Cardiology, 2018

Subgroup Analysis: 24-month TLF

BIOFLOW-V



Source: Kandzari D et al , Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin Durable Polymer Everolimus-Eluting Stents: BIOFLOW V 2-Year Results, Journal of the American College of Cardiology, 2018

Conclusion

BIOFLOW-V

1. Through **2 years in the randomized BIOFLOW V trial**, significant differences in TLF and target vessel MI observed at 1 year were maintained in addition to emergence of other safety and efficacy differences that favor an ultrathin strut BP SES over a contemporary generation thin strut DP EES
   - Lower TLF (7.5% vs 11.9%, *P*=0.015)
   - Lower target vessel related MI (5.3% vs 9.5%, *P*=0.01), both early (≤30 days) and late (31 days to 2 years)

2. **Lower ischemia-driven TLR**, driven by differences in late (>1 year) TLR (2.6% vs 4.9%, *P*=0.04)

3. **Lower late/very late definite and definite/probable ST** (0.1% vs 1.0%, *P*=0.045)

Source: Kandzari D et al , Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin Durable Polymer Everolimus-Eluting Stents: BIOFLOW V 2-Year Results, Journal of the American College of Cardiology, 2018

Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Subgroup Analysis Comparing Ultrathin, Bioresorbable Polymer Sirolimus-Eluting Stents Versus Thin, Durable Polymer Everolimus-Eluting Stents in Acute Coronary Syndrome Patients

BIOFLOW V Acute Coronary Syndromes Subgroup

BIOFLOW-V ACS 1 YEAR

BIOFLOW-V

Design

Prospective, multi-center, 2:1 randomized controlled IDE
(Investigational Device Exemption) trial.

Objective

ACS subgroup analysis of the BIOFLOW V prospective randomized trial

Coordinating Clinical Investigators

David E Kandzari, MD, Ron Waksman, MD et al

Primary Endpoint

Target Lesion Failure (TLF) at 12 months, defined as the composite of cardiovascular death, target vessel-related myocardial infraction (MI), or ischemia-driven TLR

BIOFLOW-V ACS Subgoup:

ACS patients without ST-segment–elevation myocardial infarction (MI; 454 Orsiro and 223 Xience) were identified

Post-hoc analysis

Orsiro (n=454)

Xience Prime (n=223)

Clinical follow-up at 1 and 6 months

12 month follow-up, TLF Primary Endpoint

2,3,4,5-year follow-up

Source: Ron Waksman et al, Subgroup Analysis Comparing Ultrathin, Bioresorbable Polymer Sirolimus-Eluting Stents Versus Thin, Durable Polymer Everolimus-Eluting Stents in Acute Coronary Syndrome Patients, Circ Cardiovasc Interv. 2018

Procedural Results

BIOFLOW-V

	Orsiro	Xience	P-Value
Lesion success*	99.6% (568/570)	99.7% (297/298)	0.967
Device success†	97.5% (556/570)	96.6% (288/298)	0.643
Procedure success‡	**94.7% (428/452)**	**89.7% (200/223)**	**0.023**

Procedural success was significantly higher with Orsiro, principally driven by a higher rate of in-hospital MI with Xience. Specifically, the **peri-procedural MI was higher in the Xience group.**

* 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).

Source: Ron Waksman et al, Subgroup Analysis Comparing Ultrathin, Bioresorbable Polymer Sirolimus-Eluting Stents Versus Thin, Durable Polymer Everolimus-Eluting Stents in Acute Coronary Syndrome Patients, Circ Cardiovasc Interv. 2018

Results: 30-Day Outcomes

BIOFLOW-V

	Orsiro (n=884)	Xience (n=450)	P-Value
All-cause death	0.0% (0/454)	0.5% (1/222)	0.328
Protocol defined myocardial infarction	**3.3% (15/454)**	**7.2% (16/222)**	**0.030**
Stent thrombosis			
Acute (≤ 24 h)	0.2% (1/454)	0.0% (0/222)	1.000
Subacute (> 24 h and ≤ 30 d)	0.2% (1/454)	0.0% (0/222)	1.000
TLF	2.9% (13/454)	7.7% (17/222)	0.008
TVF	3.1% (14/454)	7.7% (17/222)	0.010

Source: Ron Waksman et al, Subgroup Analysis Comparing Ultrathin, Bioresorbable Polymer Sirolimus-Eluting Stents Versus Thin, Durable Polymer Everolimus-Eluting Stents in Acute Coronary Syndrome Patients, Circ Cardiovasc Interv. 2018

Results: 12-month Outcomes

BIOFLOW-V

	Orsiro (n=884)	Xience (n=450)	P-Value
Target lesion failure	5.6% (24/426)	11.0% (23/209)	0.023
Cardiac death	0.0% (0/424)	1.0% (2/208)	0.108

Secondary End Points	BP-SES (N=454 Subjects)	DP-EES (N=223 Subjects)	Difference (95% CI)	*P* Value
Protocol-defined target vessel-MI	3.5% (15/425)	9.7% (20/207)	–6.13% (–11.12% to –2.14%)	0.003
Q-wave type				
Q-wave	0.2% (1/425)	1.0% (2/206)	–0.74% (–3.24% to 0.56%)	0.250
Non-Q-wave	3.3% (14/424)	9.2% (19/207)	–5.88% (–10.77% to –1.99%)	0.004
Timing				
Periprocedural PCI	3.1% (13/424)	7.2% (15/207)	–4.18% (–8.72% to –0.67%)	0.023
Spontaneous	0.5% (2/425)	2.4% (5/206)	–1.96% (–5.10% to –0.10%)	0.041
Magnitude*				
Periprocedural†				
CK-MB or troponin >3×ULN	2.6% (12/454)	6.7% (15/223)	–4.08% (–8.31% to –0.84%)	0.019
CK-MB or troponin >5×ULN	1.3% (6/454)	3.6% (8/223)	–2.27% (–5.67% to 0.07%)	0.080
CK-MB or troponin >10×ULN	0.7% (3/454)	1.3% (3/223)	–0.68% (–3.26% to 0.86%)	0.401

Durable Polymer Everolimus-Eluting Stents in Acute Coronary Syndrome Patients, Circ Cardiovasc Interv. 2018

Conclusion

BIOFLOW-V

1. In the **ACS subgroup population of the BIOFLOW V study**, treatment with BP SES compared with DP EES was associated with a significantly lower rate of 12-month TLF

2. The difference driven by significantly lower peri-procedural MI and spontaneous MI.

3. These findings support treatment with an ultrathin strut BP SES in ACS patients undergoing PCI.

Source: Ron Waksman et al, Subgroup Analysis Comparing Ultrathin, Bioresorbable Polymer Sirolimus-Eluting Stents Versus Thin, Durable Polymer Everolimus-Eluting Stents in Acute Coronary Syndrome Patients, Circ Cardiovasc Interv. 2018

BIOTRONIK-Safety and Clinical PerFormance of the Drug ELuting Orsiro Stent in the Treatment of Subjects With De novo Coronary Artery Lesions – VI: BIOFLOW-IV

BIOFLOW-VI
NCT02870985

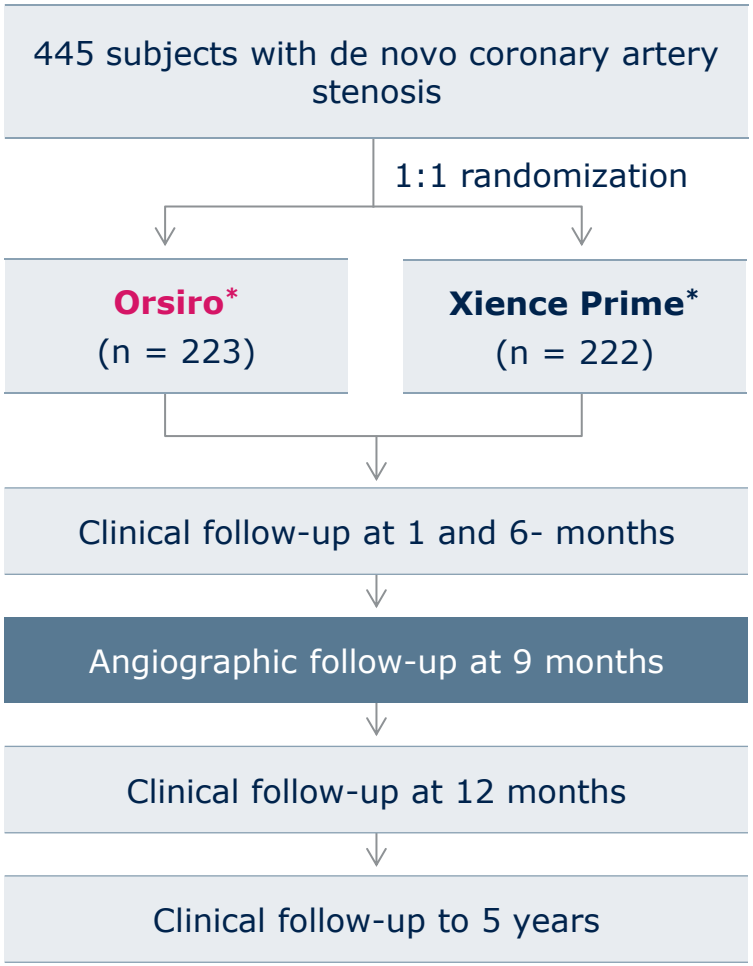
Design
Prospective, multi-centre, non-inferiority, 1:1 randomized-controlled trial

Objective
Evaluate the efficacy and safety of the Orsiro drug eluting stent in the treatment of coronary artery disease

Coordinating Investigator
Prof. Yuejin Yang, FuWai Hospital, National Center For Cardiovascular Disease, Beijing, China

Primary Endpoint
In-stent Late Lumen Loss (LLL) at 9 months (assessed by QCA)

Independent Corelab Assessment
MedStar Health Research Institute, Washington DC, USA

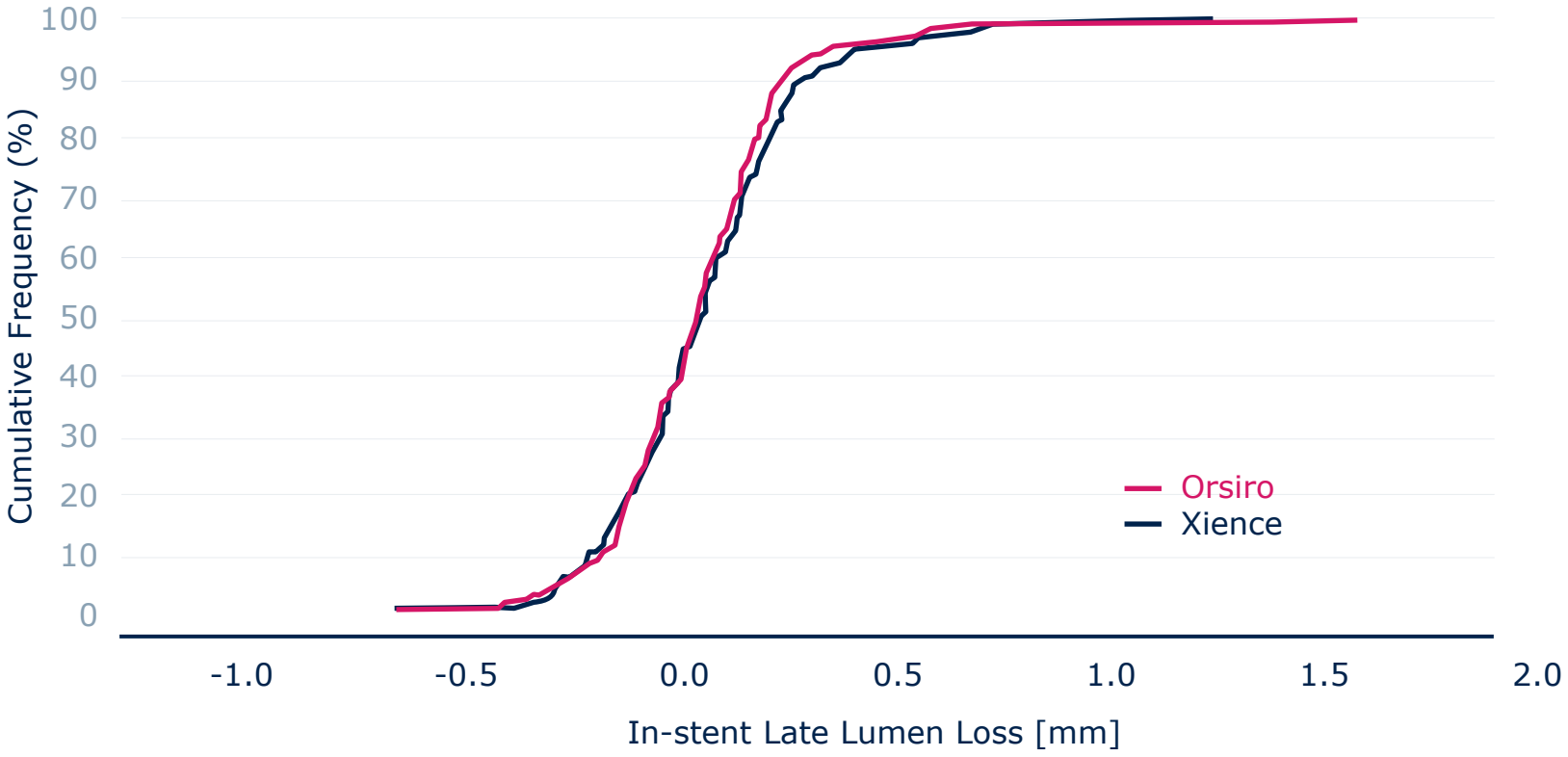


Y. Yang et al. BIOFLOW-IV Oral Presentation, CIT 2018 - Late Breaking Clinical Trials & First Report Investigations, Su Zhou, Mar. 23, 2018
* 3 withdrawal of consent in Orsiro group, 2 withdrawal of consent in Xience group; did not receive device treatment

Primary Endpoint
In-stent LLL at 9 Months (Lesion Level)

BIOFLOW-VI

Orsiro: 0.05 ± 0.21; 95% CI 0.03; 0.08
Xience: 0.07 ± 0.22; 95% CI 0.04; 0.10
p for non-inferiority < 0.0001



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BIOFLOW-VI

Target Lesion Failure at 12 Months

TLF and composites	Orsiro	Xience	p-value
Target Lesion Failure (%)	2.3 (5/218)	1.8 (4/220)	0.7505
Cardiac Death (%)	0.5 (1/218)	0.0 (0/220)	0.4977
Target Vessel MI (%)	1.8 (4/218)	0.9 (2/220)	0.4472
Clinically-driven TLR (%)	0.0 (0/217)	0.9 (2/220)	0.4989
CABG (%)	0.0 (0/217)	0.5 (1/220)	1.0000

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Secondary Clinical Outcomes at 12 Months

Endpoints	Orsiro	Xience	p-value
Target Vessel Failure (%)	2.3 (5/218)	2.3 (5/220)	1.0000
Cardiac Death (%)	0.5 (1/218)	0.0 (0/220)	0.4977
Any MI (%)	2.3 (5/217)	0.9 (2/220)	0.2823
Clinically- driven TVR (%)	0.0 (0/217)	1.8 (4/220)	0.1233

Endpoints	Orsiro	Xience	p-value
Stent thrombosis (def/prob) (%)	0 (0/217)	0 (0/217)	Not applicable

Y. Yang et al. BIOFLOW-IV Oral Presentation,
CIT 2018 - Late Breaking Clinical Trials & First Report Investigations, Su Zhou, Mar. 23, 2018

Conclusion

The BIOFLOW-VI study confirms the safety and efficacy of the Orsiro device compared with Xience in Chinese patients:

1. The non-inferiority of Orsiro confirmed with regards to In-stent LLL at 9 months ($p<0.0001$), which is comparable to BIOFLOW II results

2. Target Lesion Failure rates are low at 12 months in both arms with no statistically significant differences between the individual composites, which are also comparable with other clinical trials in Western and Asian populations

3. No definite / probable stent thrombosis reported up to 12 months

Y. Yang et al. BIOFLOW-IV Oral Presentation,
CIT 2018 - Late Breaking Clinical Trials & First Report Investigations, Su Zhou, Mar. 23, 2018

Take-Home Message

From BIOFLOW studies, **Orsiro stents** have shown …

- … the improved clinical and angiographic outcomes with unique novel advantageous characteristics.
- … the balanced efficacy and safety through many stepwise studies.

  → **Expanding the indication and implication, especially for high-risked patients and lesions.**

- The recent long-term results of Bioflow studies confirmed the safety and efficacy of the Orsiro SES, in the whole patient population, as well as in high risk subgroups

With the Love of God, Free Humankind from Disease and Suffering

Severance

Thank you for your attention!