From Durable to Biodegradable: Expectations from Nobori, Ultimaster

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Background

- Permanent polymer coatings on drug-eluting stents surface have been identified as triggers of adverse events following PCI.

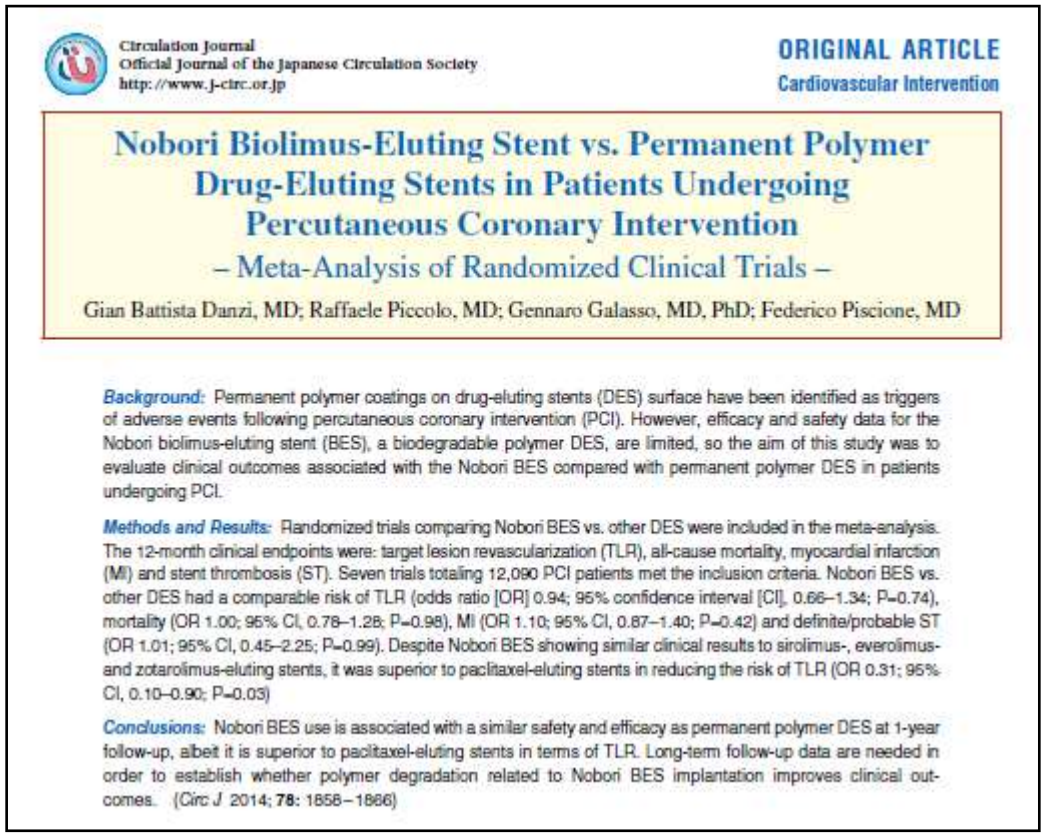
- Efficacy and safety data for the Nobori biolimus-eluting stent (BES), a biodegradable polymer DES, are limited.

Aim of this study

- Evaluate clinical outcomes associated with the Nobori BES compared with permanent polymer DES in patients undergoing PCI.

Disclosures

- There is no conflict of interest for any of the authors. No funding was received for the writing of this manuscript.



Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Cardiovascular Intervention

Nobori Biolimus-Eluting Stent vs. Permanent Polymer Drug-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention

– Meta-Analysis of Randomized Clinical Trials –

Gian Battista Danzi, MD; Raffaele Piccolo, MD; Gennaro Galasso, MD, PhD; Federico Piscione, MD

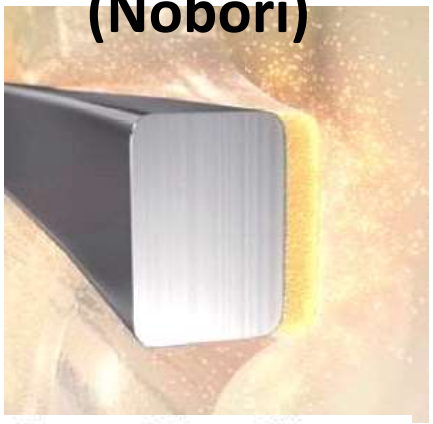
Background: Permanent polymer coatings on drug-eluting stents (DES) surface have been identified as triggers of adverse events following percutaneous coronary intervention (PCI). However, efficacy and safety data for the Nobori biolimus-eluting stent (BES), a biodegradable polymer DES, are limited, so the aim of this study was to evaluate clinical outcomes associated with the Nobori BES compared with permanent polymer DES in patients undergoing PCI.

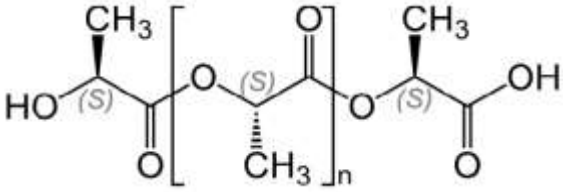
Methods and Results: Randomized trials comparing Nobori BES vs. other DES were included in the meta-analysis. The 12-month clinical endpoints were: target lesion revascularization (TLR), all-cause mortality, myocardial infarction (MI) and stent thrombosis (ST). Seven trials totaling 12,090 PCI patients met the inclusion criteria. Nobori BES vs. other DES had a comparable risk of TLR (odds ratio [OR] 0.94; 95% confidence interval [CI], 0.66–1.34; P=0.74), mortality (OR 1.00; 95% CI, 0.78–1.28; P=0.98), MI (OR 1.10; 95% CI, 0.87–1.40; P=0.42) and definite/probable ST (OR 1.01; 95% CI, 0.45–2.25; P=0.99). Despite Nobori BES showing similar clinical results to sirolimus-, everolimus- and zotarolimus-eluting stents, it was superior to paclitaxel-eluting stents in reducing the risk of TLR (OR 0.31; 95% CI, 0.10–0.90; P=0.03)

Conclusions: Nobori BES use is associated with a similar safety and efficacy as permanent polymer DES at 1-year follow-up, albeit it is superior to paclitaxel-eluting stents in terms of TLR. Long-term follow-up data are needed in order to establish whether polymer degradation related to Nobori BES implantation improves clinical outcomes. (*Circ J* 2014; **78:** 1858–1866)

Chemical structure of each polymer

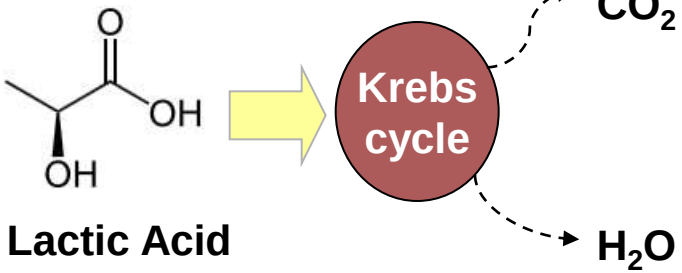
Biodegradable Polymer (Nobori)





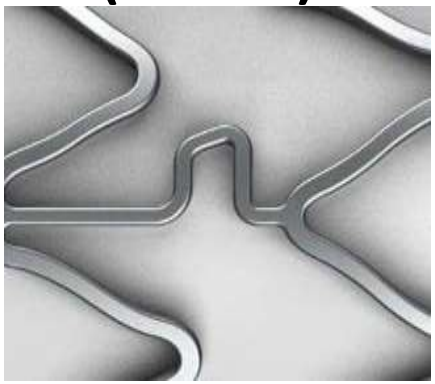
Poly Lactic Acid

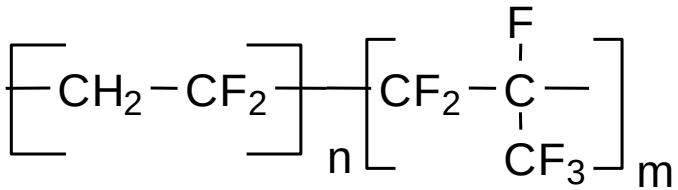
hydrolysis



Lactic Acid

Durable Polymer (Xience)

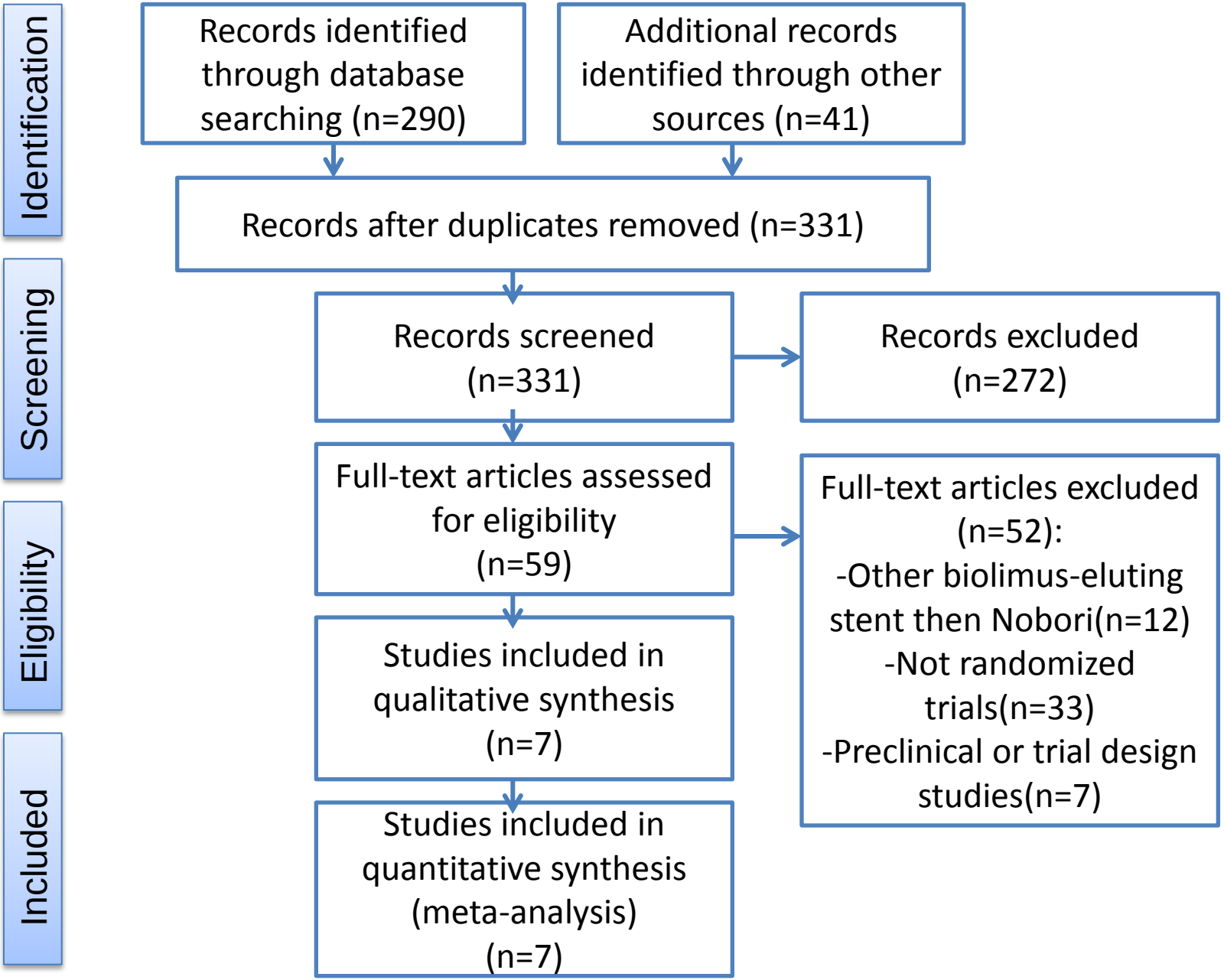




VDF **HFP**

VDF = vinylidene fluoride
HFP = hexafluoropropylene

Flow chart of trial selection



Main Characteristics of RCTs Included in the Meta-Analysis of the Nobori BES vs. Permanent Polymer DES in Patients Undergoing PCI

Trial	Study design (no. of patients)	Primary endpoint	Follow-up
COMPARE 2	BES(n=1,795) vs. EES(n=912)	12-month cardiac death, MI, and clinically-driven TVR	12-month
NEXT	BES(n=1,617)vs.EES(n=1,618)	12-month any TLR, and 3-year death or MI	12-month
NOBORI 1 Phase 1	BES(n=85)vs.PES(n=35)	9-month in-stent late loss	12-month
NOBORI 1 Phase 2	BES(n=153) vs. PES(n=90)	9-month in-stent late loss	9-month
NOBORI JAPAN	BES(n=198) vs. SES(n=137)	9-month cardiac death, MI, TVR	9-month
SORT OUT 5	BES(n=1,229) vs. SES(n=1,239)	9-month cardiac death, MI, definite ST, and clinically-driven TVR	12-month
SORT OUT 6	BES(n=1,497) vs. ZES(n=1,502)	12-month cardiac death, MI, TLR	12-month

Main Characteristics of Patients Enrolled in RCTs of the Nobori BES vs. Permanent polymer DES in PCI Included in Meta-Analysis

Trial	Age (mean years)	Male (%)	Diabetes (%)	ACS (%)	Reference vessel diameter (mm)	Lesion length (mm)	Type B2/C lesion (%)
COMPARE 2	63	74	22	58	2.9	17.2	63
NEXT	69	77	46	16	2.6	19.4	NA
NOBORI 1 Phase 1	64	67	20	25*	2.7	11	61
NOBORI 1 Phase 2	63	73	29	28*	2.7	10.6	48
NOBORI JAPAN	67	72	39	14*	2.68	12.7	65
SORT OUT 5	65	75	15	49	3.2	18	54
SORT OUT 6	66	76	18	51	3.1	N/A	60

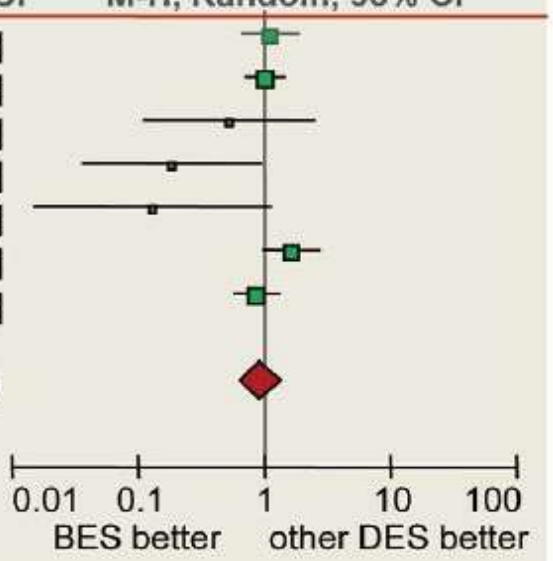
*Only patients with unstable angina were enrolled.

Odds ratio of TLR

Study	BES Events	BES Total	other DES Events	other DES Total	Weight	Odds Ratio M-H, Random, 95% CI
COMPARE II	48	1795	22	912	19.8%	1.11 [0.67, 1.85]
NEXT	67	1617	66	1618	25.4%	1.02 [0.72, 1.44]
NOBORI I Phase 1	4	85	3	35	4.5%	0.53 [0.11, 2.49]
NOBORI I Phase 2	2	153	6	90	4.2%	0.19 [0.04, 0.94]
NOBORI JAPAN	1	190	5	128	2.5%	0.13 [0.02, 1.13]
SORT OUT V	40	1229	25	1239	20.0%	1.63 [0.98, 2.71]
SORT OUT VI	46	1497	53	1502	23.5%	0.87 [0.58, 1.30]
Total (95% CI)		**6566**		**5524**	**100.0%**	**0.94 [0.66, 1.34]**
Total events	208		180			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 12.51$, df = 6 (P = 0.05); $I^2 = 52\%$

Test for overall effect: Z = 0.34 (P = 0.74)

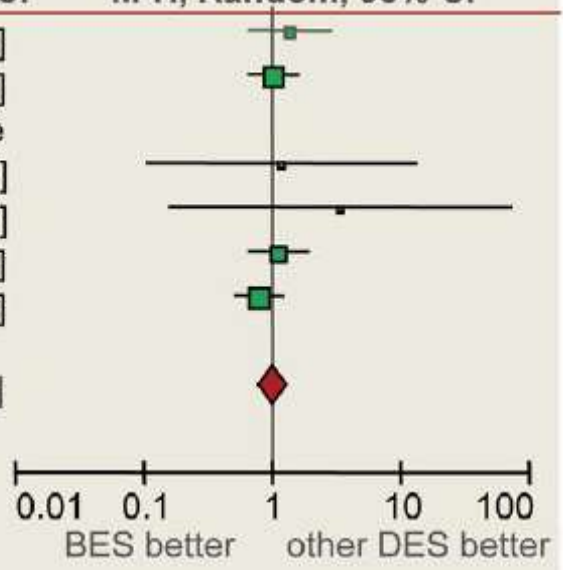


Odds ratio of all-cause mortality

Study	BES Events	BES Total	other DES Events	other DES Total	Weight	Odds Ratio M-H, Random, 95% CI
COMPARE II	27	1795	10	912	11.4%	1.38 [0.66, 2.86]
NEXT	41	1617	40	1618	31.1%	1.03 [0.66, 1.60]
NOBORI I Phase 1	0	85	0	35		Not estimable
NOBORI I Phase 2	2	153	1	90	1.0%	1.18 [0.11, 13.19]
NOBORI JAPAN	2	190	0	128	0.7%	3.41 [0.16, 71.59]
SORT OUT V	30	1229	27	1239	21.9%	1.12 [0.66, 1.90]
SORT OUT VI	40	1497	50	1502	34.0%	0.80 [0.52, 1.22]
Total (95% CI)		**6566**		**5524**	**100.0%**	**1.00 [0.78, 1.28]**
Total events	142		128			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.69$, df = 5 (P = 0.75); $I^2 = 0\%$

Test for overall effect: Z = 0.02 (P = 0.98)

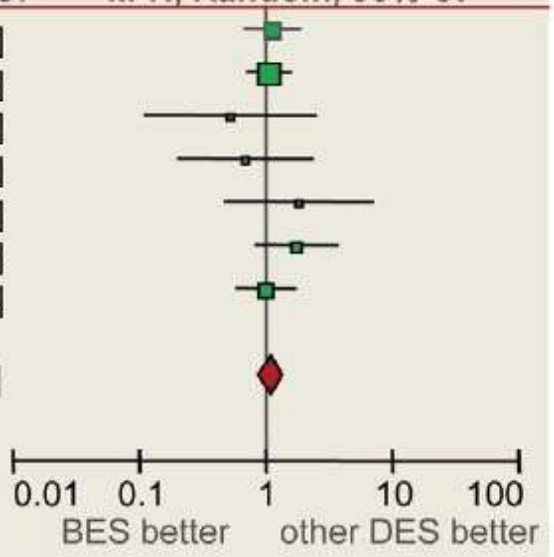


Odds ratio of MI

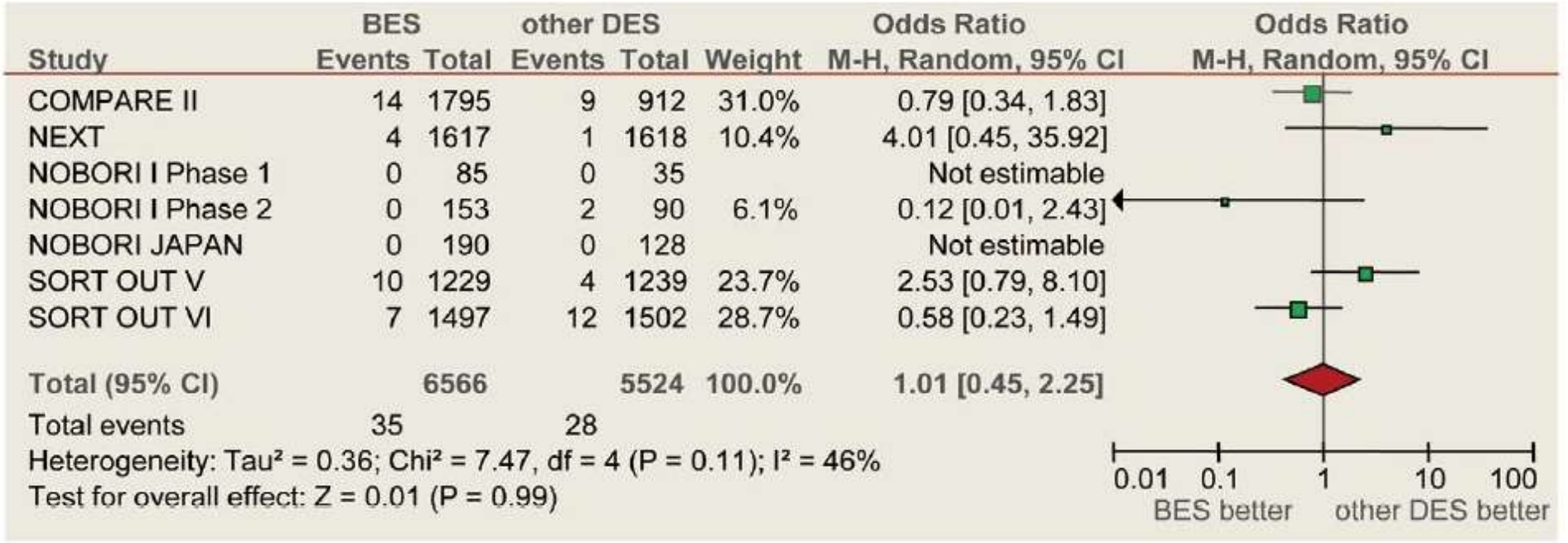
Study	BES Events	BES Total	other DES Events	other DES Total	Weight	Odds Ratio M-H, Random, 95% CI
COMPARE II	51	1795	23	912	22.9%	1.13 [0.69, 1.86]
NEXT	53	1617	50	1618	37.0%	1.06 [0.72, 1.57]
NOBORI I Phase 1	4	85	3	35	2.4%	0.53 [0.11, 2.49]
NOBORI I Phase 2	6	153	5	90	3.9%	0.69 [0.21, 2.34]
NOBORI JAPAN	8	190	3	128	3.2%	1.83 [0.48, 7.04]
SORT OUT V	19	1229	11	1239	10.2%	1.75 [0.83, 3.70]
SORT OUT VI	28	1497	28	1502	20.4%	1.00 [0.59, 1.70]
Total (95% CI)		**6566**		**5524**	**100.0%**	**1.10 [0.87, 1.40]**
Total events	169		123			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.62$, df = 6 (P = 0.73); $I^2 = 0\%$

Test for overall effect: Z = 0.81 (P = 0.42)



Odds ratio of definite/probable stent thrombosis



Study	BES Events	BES Total	other DES Events	other DES Total	Weight	Odds Ratio M-H, Random, 95% CI
COMPARE II	14	1795	9	912	31.0%	0.79 [0.34, 1.83]
NEXT	4	1617	1	1618	10.4%	4.01 [0.45, 35.92]
NOBORI I Phase 1	0	85	0	35		Not estimable
NOBORI I Phase 2	0	153	2	90	6.1%	0.12 [0.01, 2.43]
NOBORI JAPAN	0	190	0	128		Not estimable
SORT OUT V	10	1229	4	1239	23.7%	2.53 [0.79, 8.10]
SORT OUT VI	7	1497	12	1502	28.7%	0.58 [0.23, 1.49]
Total (95% CI)		**6566**		**5524**	**100.0%**	**1.01 [0.45, 2.25]**
Total events	35		28			

Heterogeneity: Tau² = 0.36; Chi² = 7.47, df = 4 (P = 0.11); I² = 46%

Test for overall effect: Z = 0.01 (P = 0.99)

Conclusions

- The results demonstrate the 1-year equivalence of the Nobori stent and permanent polymer DES in terms of safety and efficacy.

- Nobori use is associated with a reduction in the risk of TLR compared to PES.

Discussions

- The absence of a permanent polymer from the DES platform seems to mitigate late reduction in anti-restenotic efficacy.

- Long-term (5 years) data are required to establish whether polymer degradation improves clinical outcome

Five-Year Clinical Outcome of the Nobori DES in the Treatment of Patients With CAD

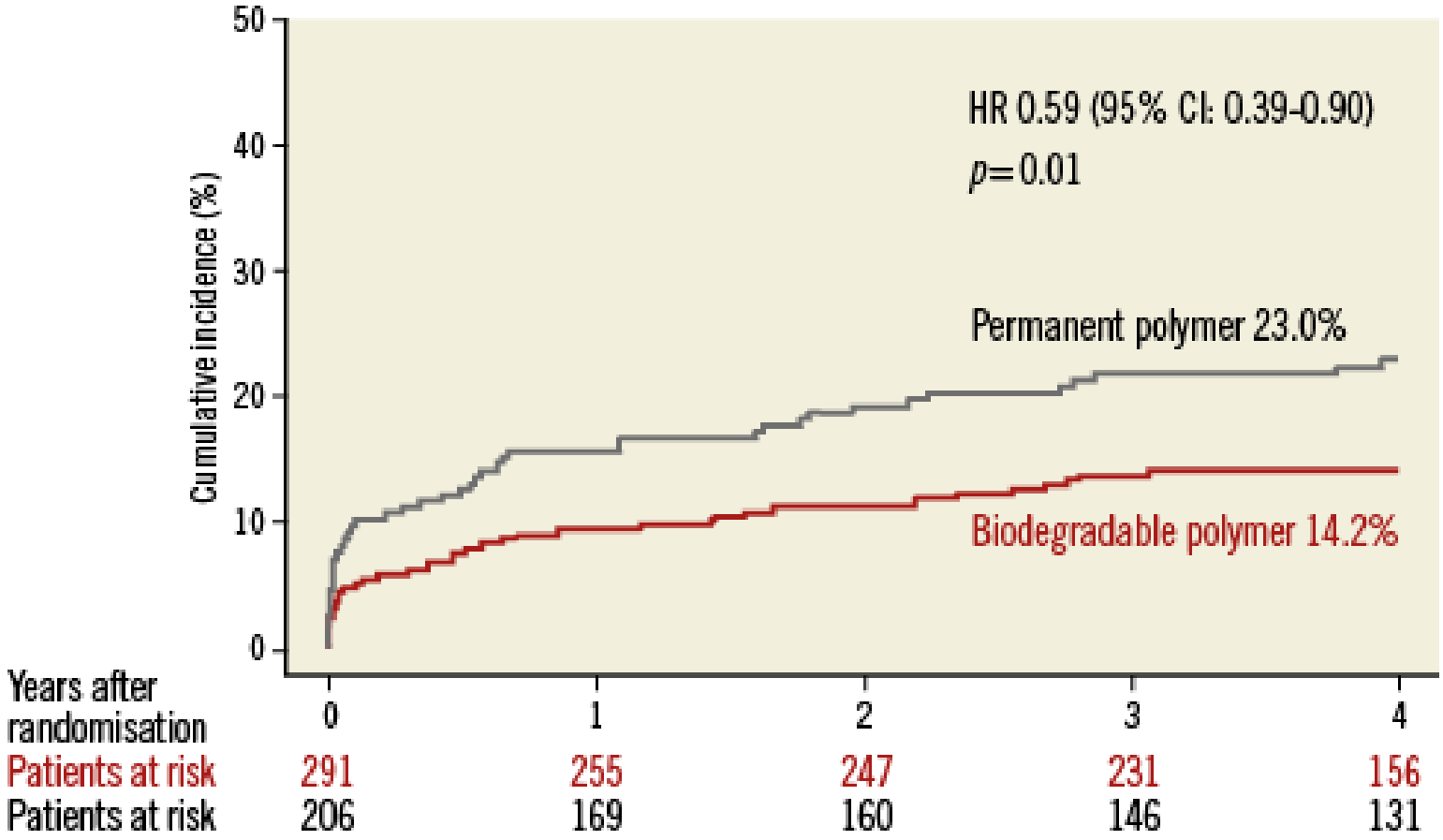
Final follow-up of the NOBORI 1 trial: 363 patients randomized to biodegradable-polymer Nobori or Taxus Express/Liberté.

5-Year Follow-up	Nobori (n = 238)	Taxus (n = 125)	*P* Value
TLR	6.3%	16.0%	.005
Stent Thrombosis	0	3.2%	.014
Composite Events	27.3%	27.2%	1.00

The Nobori group also had a lower rate of Q-wave MI (*P* = .02) and a trend toward less MI compared with the Taxus group.

Conclusion: Compared with a first-generation DES, the biodegradable-polymer Nobori DES reduces TLR and stent thrombosis over 5 years.

Chevalier B, et al. *EuroIntervention*. 2014;Epub ahead of print.



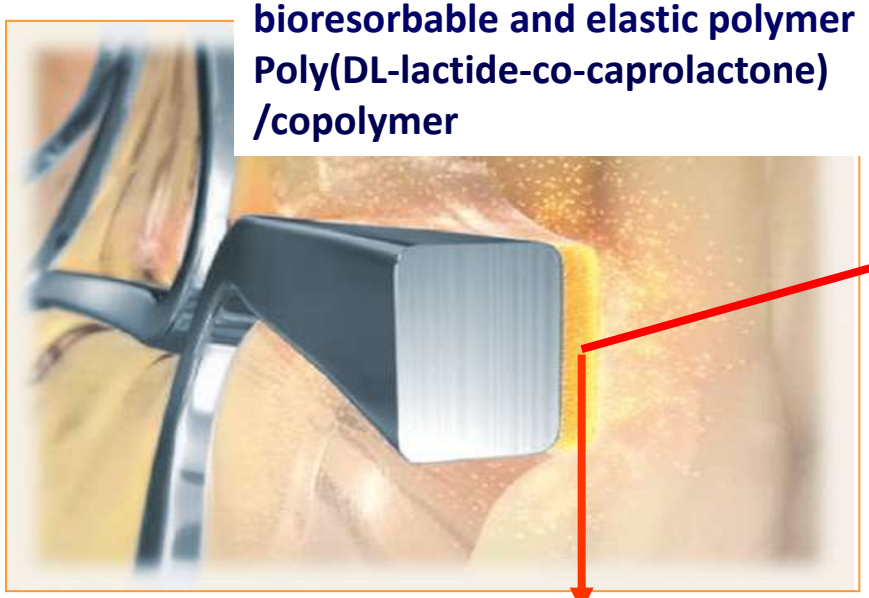
De Waha A, EuroIntervention 2015;10:1425-1431

Long-term outcomes of biodegradable versus durable polymer drug-eluting stents in patients with acute ST-segment elevation myocardial infarction: a pooled analysis of individual patient data from three randomised trials

Ultimaster DES
A new abluminal bioabsorbable coated stent with gradient coating

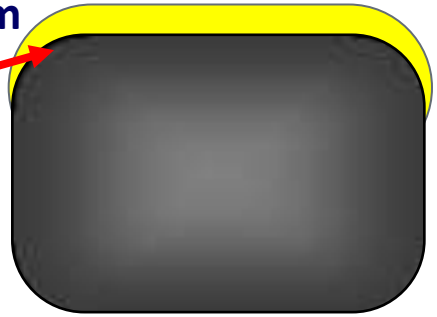
Bioresorbable polymer
Abluminal coating

Abluminal Coating with bioresorbable and elastic polymer Poly(DL-lactide-co-caprolactone) /copolymer

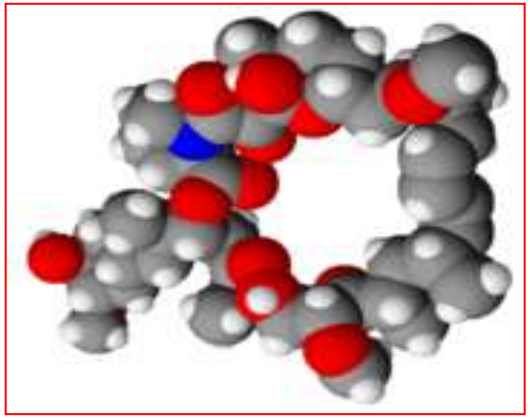


Bio-reabsortion in 3-4 Months

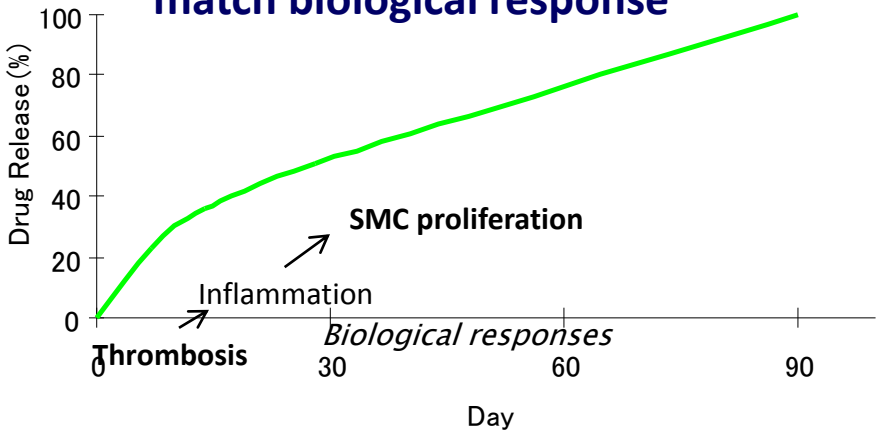
Thickness=15 µm



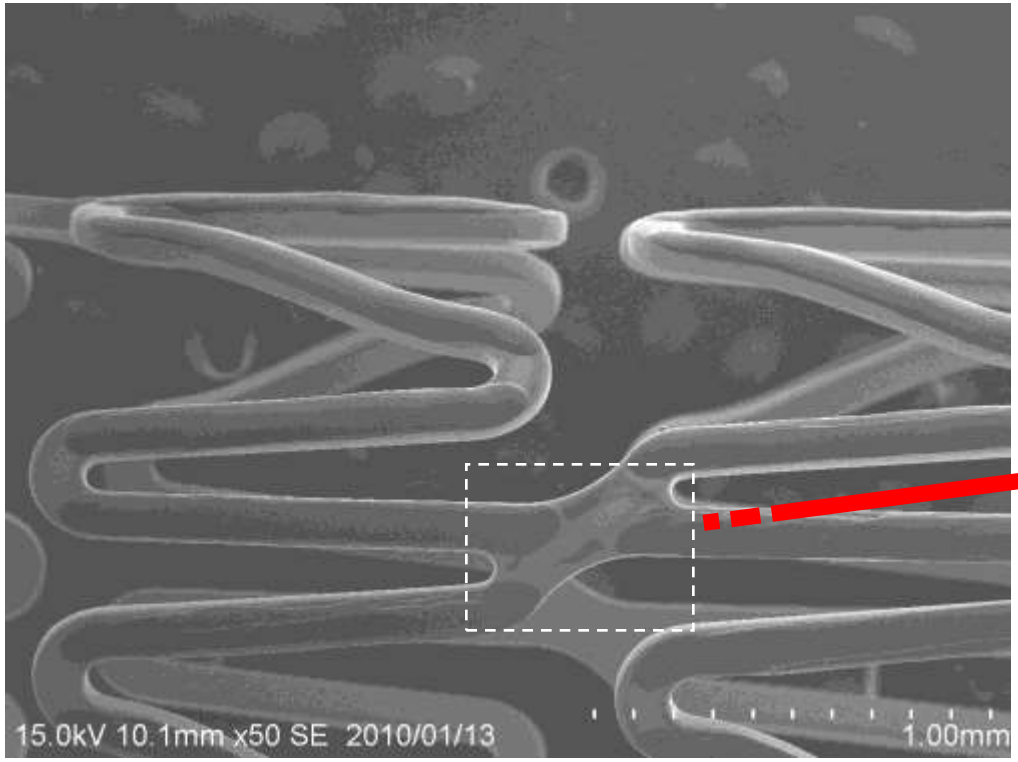
Sirolimus
3.9 µg/mm stent



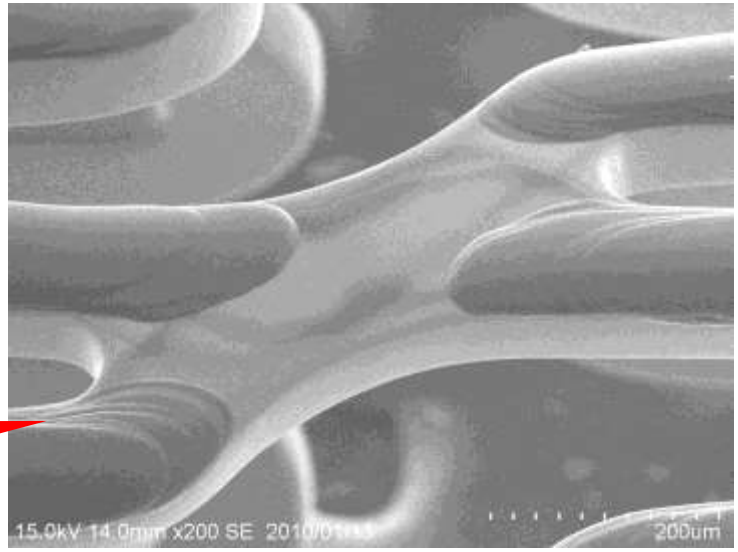
Optimal drug release kinetics to match biological response



State of the Art
Gradient Coating Technology



X 50



X 200

Ultimaster DES
Design - Feature and Benefits

Feature	Benefit
Thin Struts, CoCr	Less injury, higher flexibility, good visibility
Bioresorbable polymer, short degradation time	Shorter dual antiplatelet therapy, no polymer fatigue and inflammation
Abluminal coating	Targeted drug release, low drug loss in circulation, faster endothelialization
Gradient coating	Reduced potential of polymer cracking and webbing on stent expansion
Drug Sirolimus	Proven efficacy, wide therapeutic window, lower dose, still highly effective

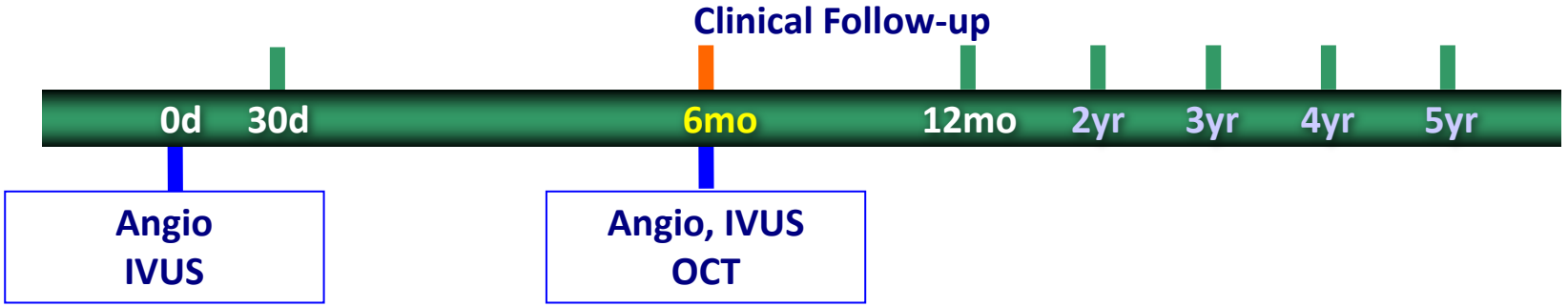
CENTURY - study design

Prospective, multicentre, single arm clinical trial
Hypothesis: superiority vs. historical control of Kaname bare metal stent platform for late loss at 6m

Ultimaster
n = 105

PI: W. Wijns
8 sites in Europe

Historical control
Kaname
n = 282



Primary endpoint In-Stent Late Loss at 6 months

Main secondary endpoints: TLF, Death&MI, ST, at 6 and 12m and yearly to 5 years
Angio/IVUS: late loss, BAR, neointima volume and volume obstruction…
OCT – strut coverage, neointima thickness

CENTURY Study
Patient population

- Main Inclusion Criteria
  - Up to two *de-novo* lesions located in two epicardial vessels
  - Target lesion length <25 mm, RVD: 2.5-4.0 mm
- Main Exclusion Criteria
  - Intolerance to common PCI associated medications, or limus like drugs
  - Left main CAD
  - CTO, ostial, bifurcation, SVG lesions
  - Prior PCI with stenting (within 1 month before enrolment)
  - Planned major surgery within 6 m post procedure
  - STEMI <72h before procedure

Historical control: Patient level data of KARE study. Inclusion and exclusion criteria were comparable between two trials, except only single lesion in KARE study and up to two lesions in two epicardial vessels in CENTURY study

CENTURY Study
Baseline patient characteristics

Baseline characteristics	**CENTURY** Ultimaster DES N=105	**KARE** Kaname BMS Historical control N=282	P-value
Age, Mean±SD	60.6±8.4	64.9±11.5	<0.001
Gender, Male, %	76.2	73.0	0.60
Smoking, current, %	29.5	27.0	0.70
History of Diabetes Mellitus, %	23.8	22.7	0.89
Dyslipidemia requiring treatment, %	85.6	67.7	<0.001
Hypertension requiring treatment, %	81.6	70.2	0.06
Family history of CAD, %	58.8	32.2	<0.001
History of revascularization, %	19.1	22.7	0.42
History of MI, %	48.6	33.3	0.007

Baseline Angiographic data

Mean±SD	CENTURY Ultimaster DES N=105 patients N=113 lesions	KARE Kaname CoCr N=282 patients N=284 lesions	P-value
QCA Baseline, before			
Lesion Length (mm)	**13.4±5.9**	**11.6±4.8**	**0.005**
Diameter stenosis, %	**57.7±11.5**	**58.8±11.0**	**0.344**
Minimum limen diameter, mm	**1.14±0.4**	**1.10±0.4**	**0.483**
Reference Diameter, (mm)	**2.72±0.50**	**2.69±0.52**	**0.497**
QCA Baseline, post PCI			
Diameter stenosis post (%)	**10.8±6.2**	**11.0±5.3**	**0.950**
Minimum limen diameter, mm	**2.57±0.4**	**2.51±0.4**	**0.186**

Success endpoints

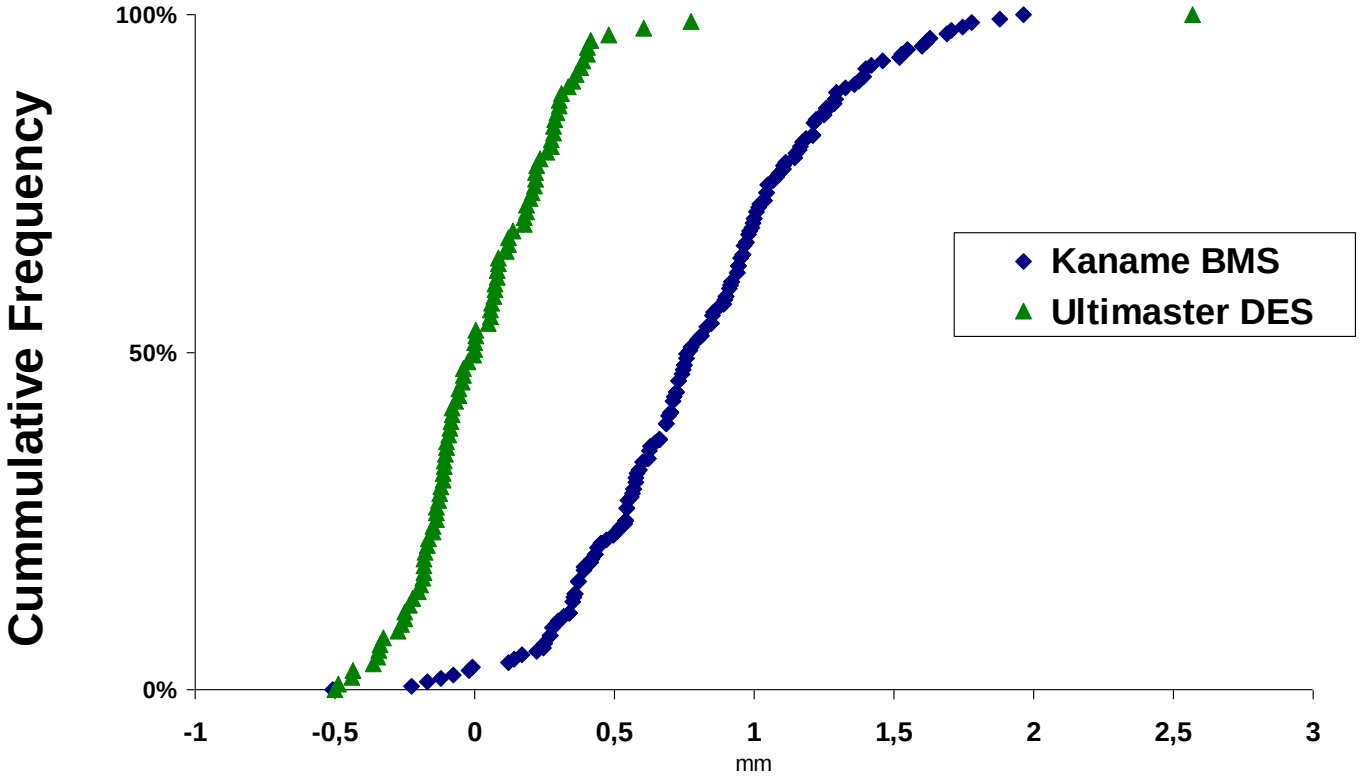
	Ultimaster DES N=105 Patients N=112 LESIONS	Historical Control BMS N=249 Patients N=250 Lesions
Unit = stent		
Delivery success	**100%**	**99.3%**
Unit=Lesion		
Device success	**100%**	**99.3%**
Lesion success	**100%**	**100%**
Unit=Patient		
Procedure success	**97.1%**	**99.3%**

P= NS for all parameters

Delivery success: achievement of successful delivery of study stent to the target lesion, expansion of the study stent and withdrawal of the delivery catheter.
Device success: achievement of a residual diameter stenosis of < 50% by QCA or < 30% by visual estimate, using the assigned device only.
Lesion success: attainment of residual diameter stenosis of < 50% by QCA or < 30% by visual estimate, using any percutaneous method.
Procedure success defined as achievement of a final diameter stenosis of < 50% by QCA or < 30% by visual estimate, using any percutaneous method, without death, MI or revascularization during the hospital stay.

Barbato E. PCR 2013

Late loss at 6 months
Frequency distribution

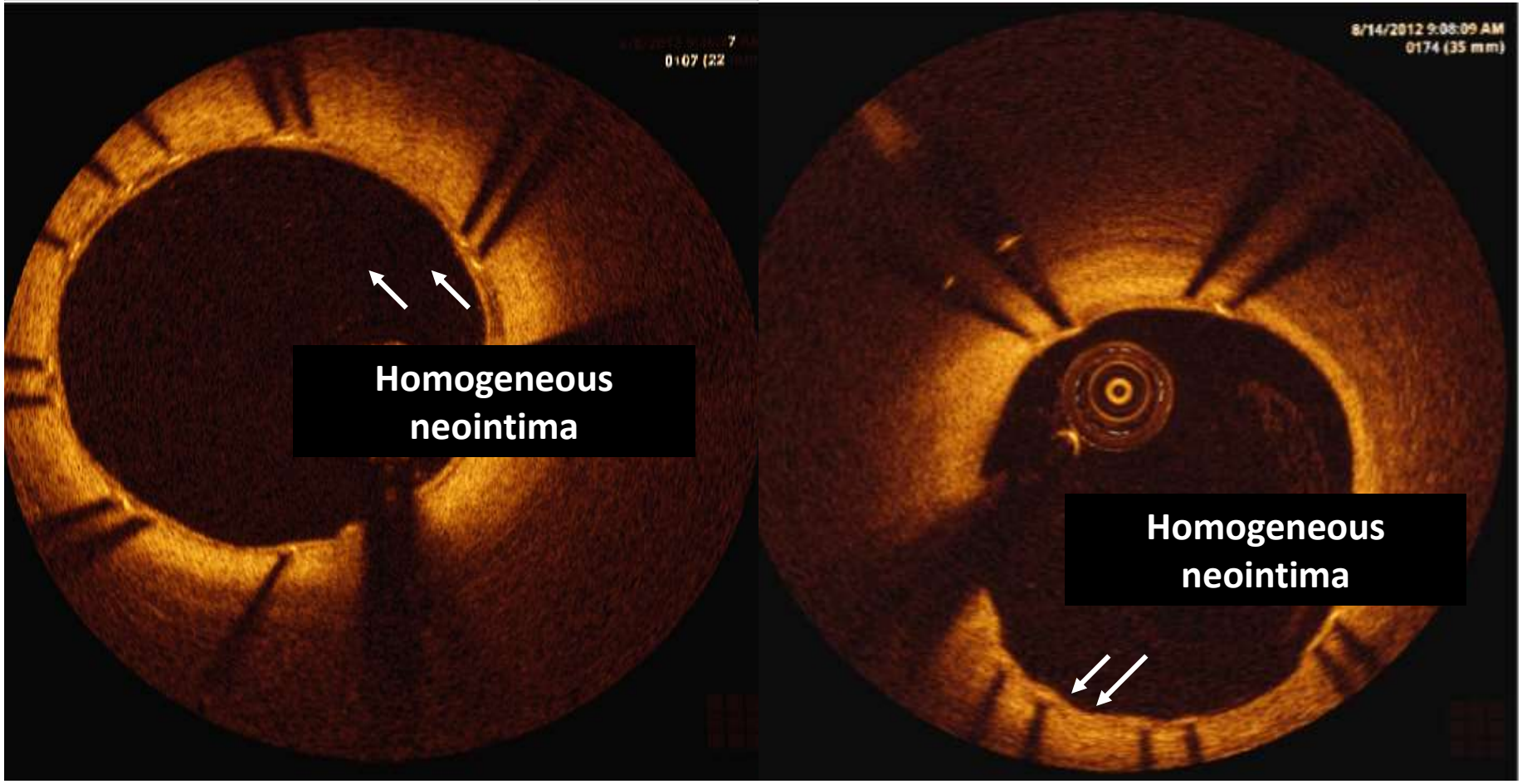


Angiographic and IVUS results at 6 months

Mean ± SD	CENTURY Ultimaster DES N=112 Lesions	KARE Kaname BMS Historical control N=284 Lesions	P-value
QCA 6-Month Follow-up			
% Diameter Stenosis	**12.1 ± 11.2**	**33.8 ± 15.5**	**<0.0001**
Minimum lumen diameter, mm	**2.52±0.52**	**1.77±0.54**	**<0.0001**
Late loss in-segment, (mm)	**0.00 ± 0.37**	**0.50 ± 0.43**	**<0.0001**
Restenosis, % - segment	**2.8**	**19.0**	**<0.0001**
Restenosis, (%) - stent	**0.9**	**17.0**	**<0.0001**
IVUS at 6 months			
Neo-Intima Volume (mm^3)	**1.33 ± 1.92**	**33.1 ± 17.9**	**<0.0001**
Stent Volume Obstruction (%)	**1.02 ± 1.62**	**24.98 ± 11.26**	**<0.0001**

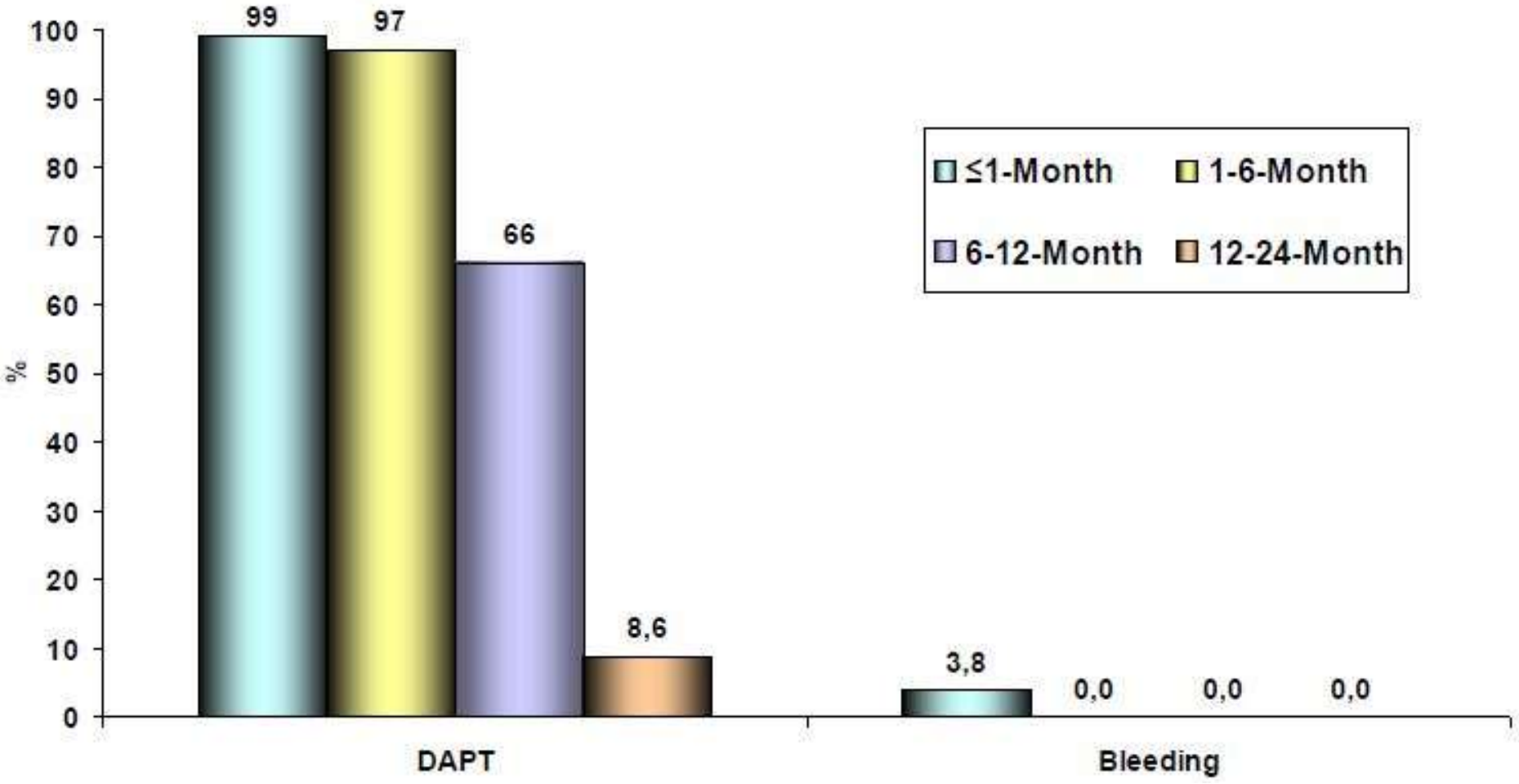
OCT Representative Images – 6 months

Mean strut coverage (mm)	0.08±0.04	Malapposed struts, %	**1.66**
% Covered Struts at 6 months	96.2±5.4	Malapposition volume, mm^3	**1.86 ± 6.58**

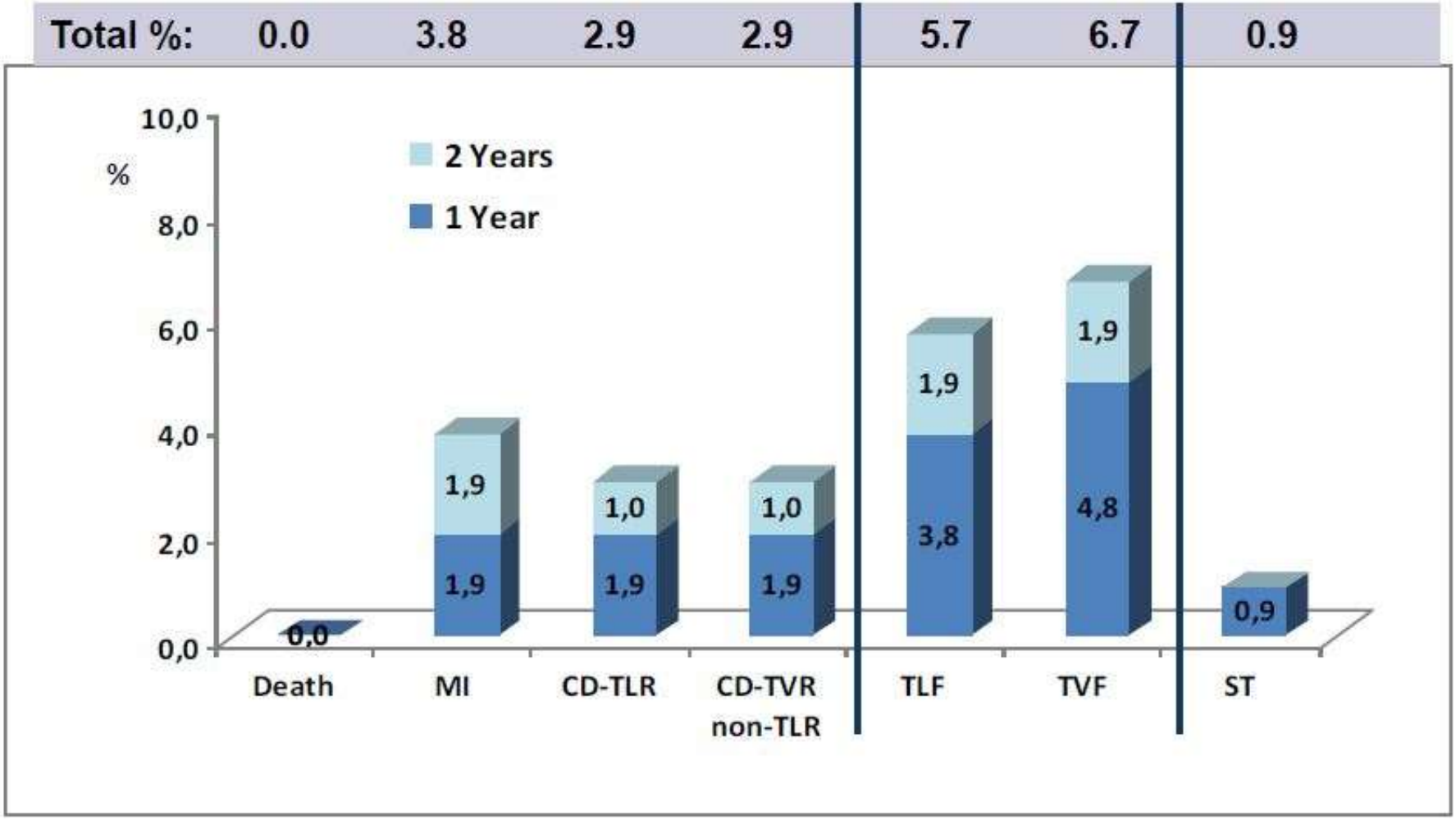


Courtesy H. Garcia Garcia

Dual antiplatelet therapy and Bleeding up to 2-Year



Clinical outcomes at 1 year and 2 years



ST= 1 acute stent thrombosis due to a long untreated dissection

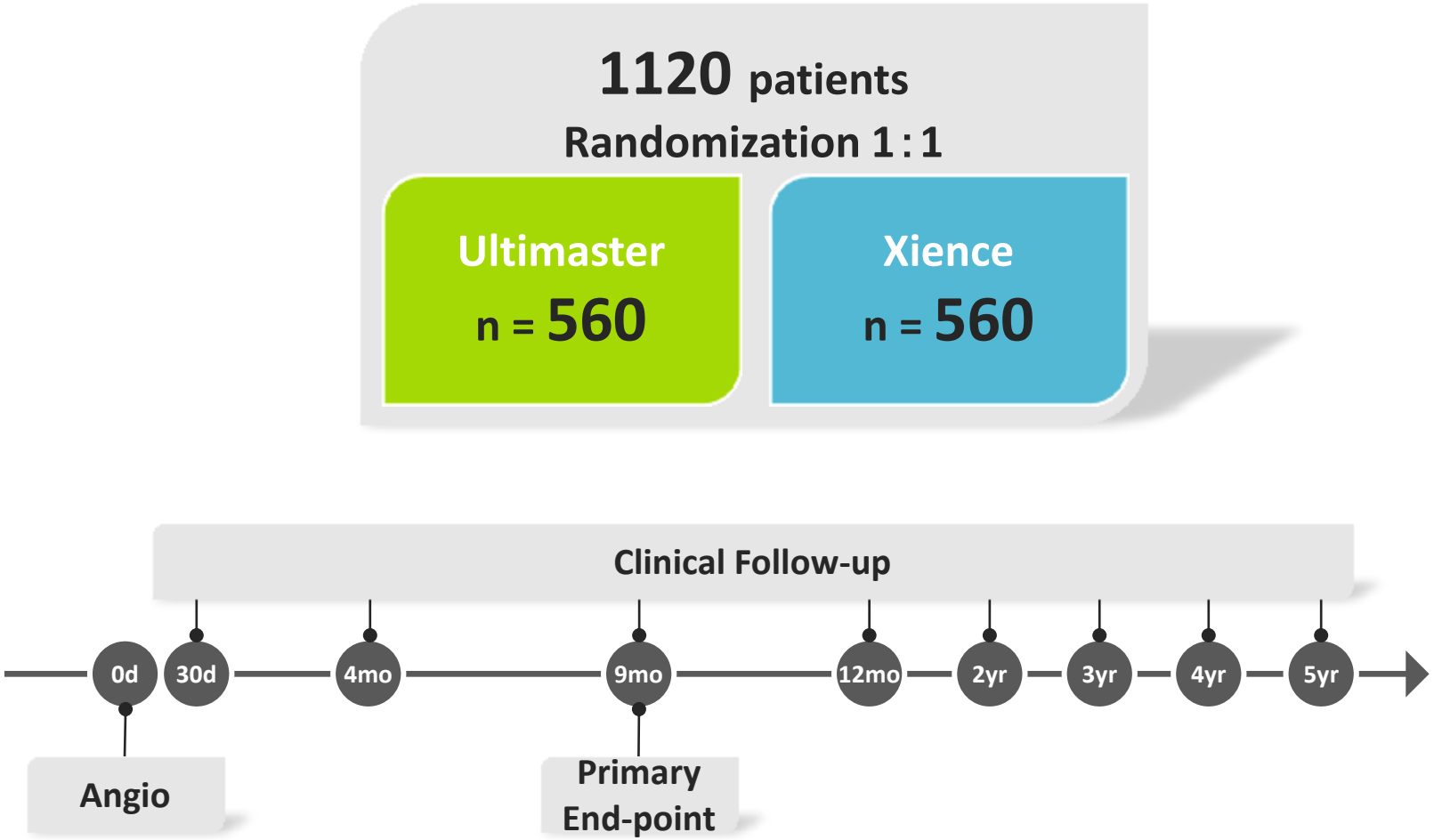
CENTURY Study

Conclusion

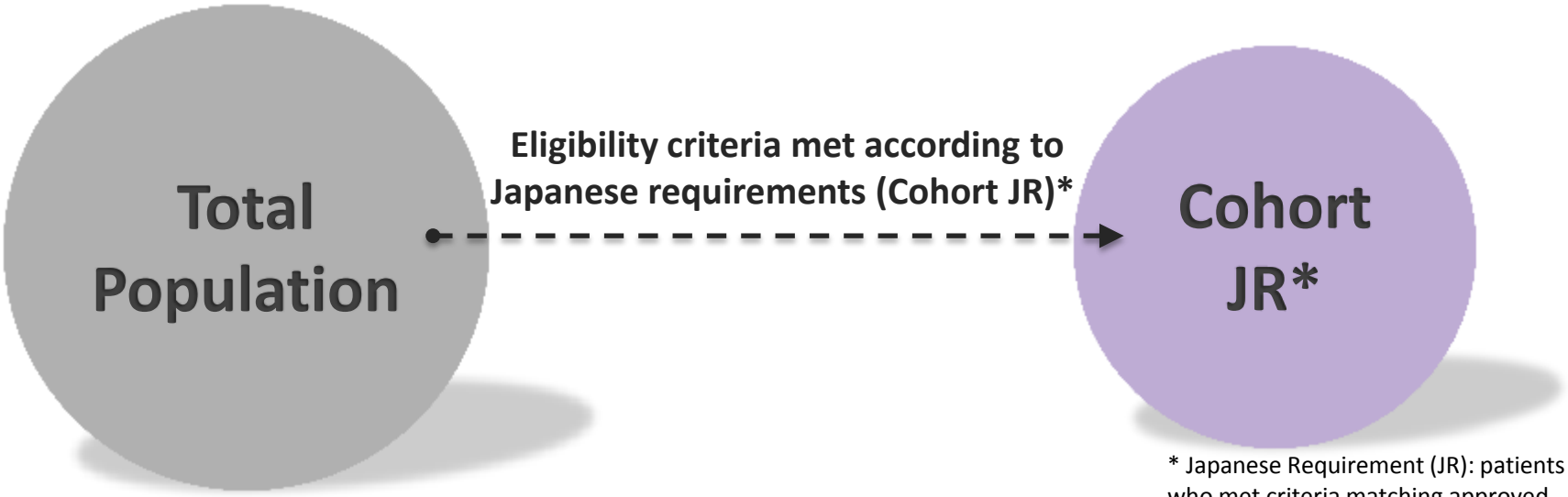
- Ultimaster DES showed superior efficacy versus bare metal stent (historical control) by reducing late loss at 6 months by 95%
- The rate of adverse events up to 2 year was low

CENTURY II

CENTURY II – Study Design



CENTURY II – Study Design

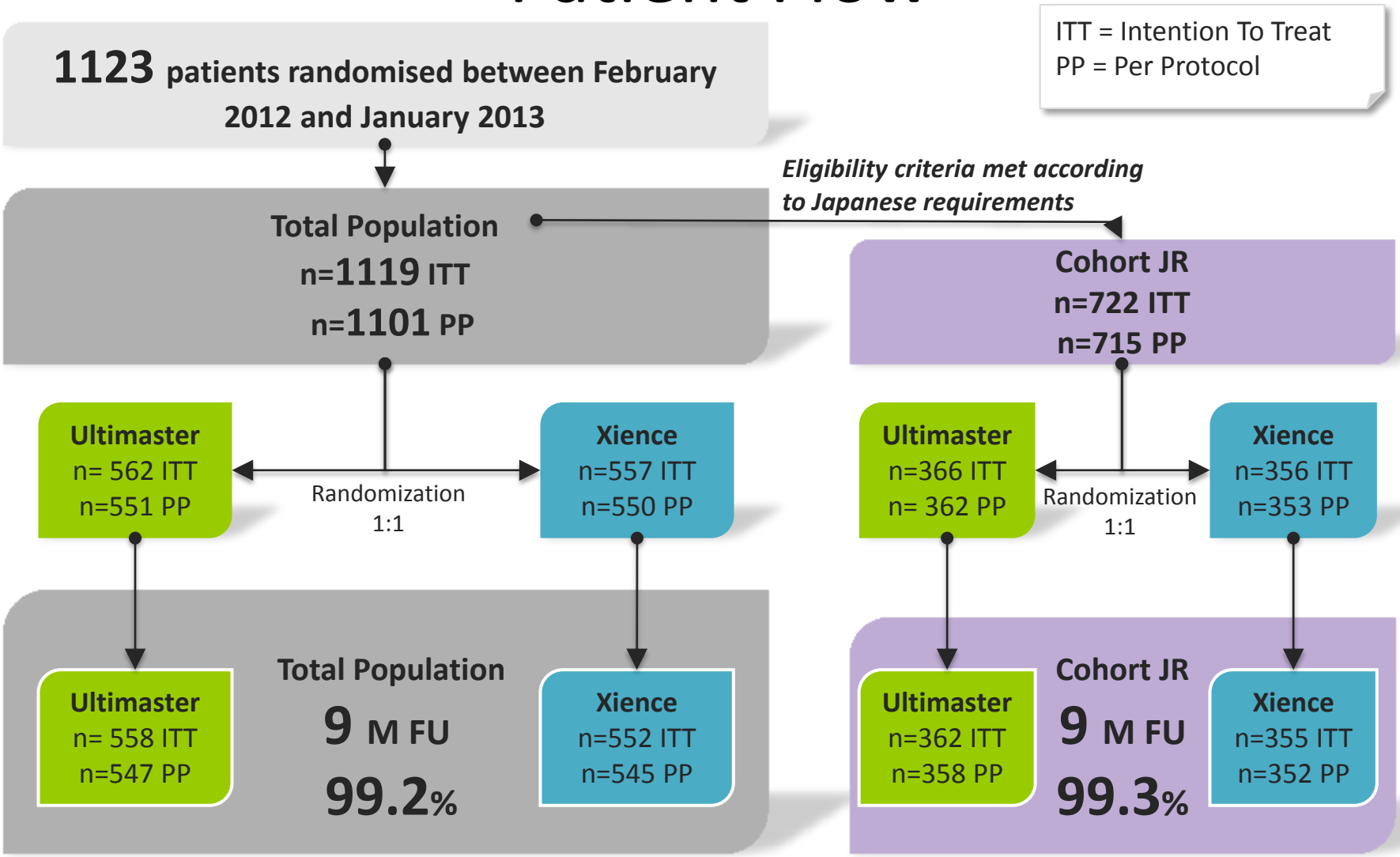


* Japanese Requirement (JR): patients who met criteria matching approved indications for DES in Japan

Cohorts balanced for major risk factors:

- Diabetes
- Multivessel disease ▶ "Multivessel disease refers to the coronary anatomy with presence of lesions with >50% diameter stenosis based on visual estimate".
- High risk Acute Coronary Syndrome (N)STEMI/Unstable angina with increased cardiac enzymes

CENTURY II – Study Design and Patient Flow



Patient eligibility

Inclusion criteria

- Age ≥ 18 years (≥20 years Japan)
- Suitable for treatment with DES
- RVD matching stents 2.5-4.0 mm
- Diameter stenosis >50%
- Eligible for DAPT

Main exclusion criteria - general

- EF<25%
- Renal failure
- Cardiogenic shock
- Planned staged procedure

Additional exclusion criteria

Cohort JR

- AMI < 48h
- Target lesion located in left-main trunk
- Bifurcation lesion that needs stenting of main and side branch
- Ostial lesions
- Lesion in venous or arterial graft
- Previous (<1month) PCI with stenting
- Previous stenting in target lesion

Sample size calculation

Assumptions

	Cohort JR	Total Population
TLF event free rate	94%	90%
Non-inferiority margin	5.5%	
Power	90%	
Type I error (one-sided)	0.05	

Sample Size

- Based on the results of SPIRIT III (TVF rate of 7.2% in simple patient population) estimated TLF free rate for Ultimaster in CENTURY II trial was set at 90%
- Considering 1:1 sampling ratio (Ultimaster : Xience) and 10% drop out rate, a sample size was calculated at 560 patients in each group for the TP (total of 1120 patients).
- In agreement with Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the TLF event free rate for Ultimaster in Cohort JR was estimated at 94% implying that 345 patients should be included in each group (total of 690 patients).

Baseline Clinical characteristics

Total Population	Ultimaster (N = 551 pts)	Xience (N = 550 pts)	P
Age, N	65 ± 11	65 ± 11	0.61
Gender, Males (%)	78.58	82.36	0.11
Diabetes (%)	31.94	30.91	0.71
IDDM (%)	16.48	14.71	0.65
Hypertension (%)	73.31	67.82	0.05
Dyslipidemia (%)	70.30	69.56	0.79
High risk ACS (%)	22.50	24.73	0.39
NSTEMI (%)	17.24	19.09	0.43
STEMI (%)	5.26	5.64	0.79
History of CAD (%)	30.75	32.06	0.66
Current smoker (%)	22.16	23.89	0.50
Previous PCI (%)	37.21	35.04	0.45
Previous CABG (%)	4.54	3.65	0.46
Previous MI (%)	28.31	27.64	0.80

Baseline Clinical characteristics

Cohort JR	Ultimaster (N = 362 pts)	Xience (N = 353 pts)	P
Age, N	65 ± 11	66 ± 10	0.65
Gender, Males (%)	74.59	80.74	0.05
Diabetes (%)	35.91	33.71	0.54
IDDM (%)	16.92	10.92	0.17
Hypertension (%)	76.39	69.52	0.04
Dyslipidemia (%)	69.83	72.57	0.42
High risk ACS (%)	12.43*	11.05*	0.57
NSTEMI (%)	10.50	10.20	0.90
STEMI (%)	1.93	0.85	0.22
History of CAD (%)	30.61	30.35	0.94
Current smoker (%)	19.03	21.26	0.46
Previous PCI (%)	32.32	30.68	0.64
Previous CABG (%)	3.04	2.27	0.53
Previous MI (%)	23.20	19.83	0.27

*Acute MI >48h before procedure

Baseline lesion characteristics

Total Population	Ultimaster (N = 711)	Xience (N = 716)	P
Lesions treated (mean±SD)	**1.29 ± 0.57**	**1.30 ± 0.57**	**0.62**
ACC/AHA classification (%)			
A	4.35	3.91	
B1	13.64	15.20	0.13
B2	48.33	52.97	
C	33.67	27.93	
Calcification (%)			
None/mild	78.52	82.34	0.70
Moderate/severe	21.48	17.66	
Thrombus present (%)	**3.92**	**4.05**	**0.90**
Bifurcation (%)	**13.78**	**14.39**	**0.74**
Syntax Score (mean±SD)	9.3 ± 7.0	9.3 ± 6.4	0.36

Baseline lesion characteristics

Cohort JR	Ultimaster (N = 417)	Xience (N = 397)	P
Lesions treated (mean±SD)	**1.15 ± 0.37**	**1.12 ± 0.33**	**0.33**
ACC/AHA classification (%)			
A	5.24	4.31	
B1	14.29	15.99	0.31
B2	49.52	54.57	
C	30.95	25.13	
Calcification (%)			
None/mild	80.95	83.25	0.75
Moderate/severe	19.05	16.75	
Thrombus present (%)	**2.62**	**0.76**	**0.04**
Bifurcation (%)	**14.87**	**15.62**	**0.77**
Syntax Score (mean±SD)	8.3 ± 5.9	8.3 ± 5.8	0.78

Baseline procedural characteristics

Total Population	Ultimaster (N = 551)	Xience (N = 550)	P
Access site (%)			
Femoral	26.68	25.64	
Radial	71.69	73.09	0.55
Brachial	1.63	1.27	
Pre-dilation (%)	**77.36**	**77.37**	**0.99**
Post-dilation (%)	**53.53**	**54.71**	**0.66**
N° of stents implanted/pt (mean ±SD)	**1.51 ± 0.78**	**1.55 ± 0.86**	**0.94**
N° of stents implanted/lesion (mean ±SD)	**1.18 ± 0.43**	**1.20 ± 0.44**	**0.32**
Delivery success (%)	**99.05**	**99.53**	**0.23**
Procedure success (%)	**98.00**	**98.18**	**0.83**

Baseline procedural characteristics

Cohort JR	Ultimaster (N = 362)	Xience (N = 353)	P
Access site (%)			
Femoral	22.38	22.38	
Radial	75.14	75.64	0.79
Brachial	2.49	1.98	
Pre-dilation (%)	**82.49**	**80.35**	**0.43**
Post-dilation (%)	**58.99**	**56.93**	**0.55**
N° of stents implanted/pt (mean ±SD)	**1.36 ± 0.62**	**1.32 ± 0.63**	**0.20**
N° of stents implanted/lesion (mean ±SD)	**1.18 ± 0.43**	**1.17 ± 0.42**	**0.90**
Delivery success (%)	**99.40**	**99.57**	**0.70**
Procedure success (%)	**98.34**	**98.30**	**0.96**

Primary endpoint

Freedom from TLF @ 9 months

Per protocol population	Total population 1101 patients			
	Ultimaster n=551	Xience n=550	Difference [95% CI]	p
Freedom from TLF	95.64%	95.09%	0.55% [-2.07%;3.18%]	<0.0001
Intention to treat population	**Total Population 1119 patients**			
	Ultimaster n=562	Xience n=557	Difference [95% CI]	p
Freedom from TLF	95.37%	94.97%	0.40% [-2.22%;3.02%]	0.0001

Primary endpoint

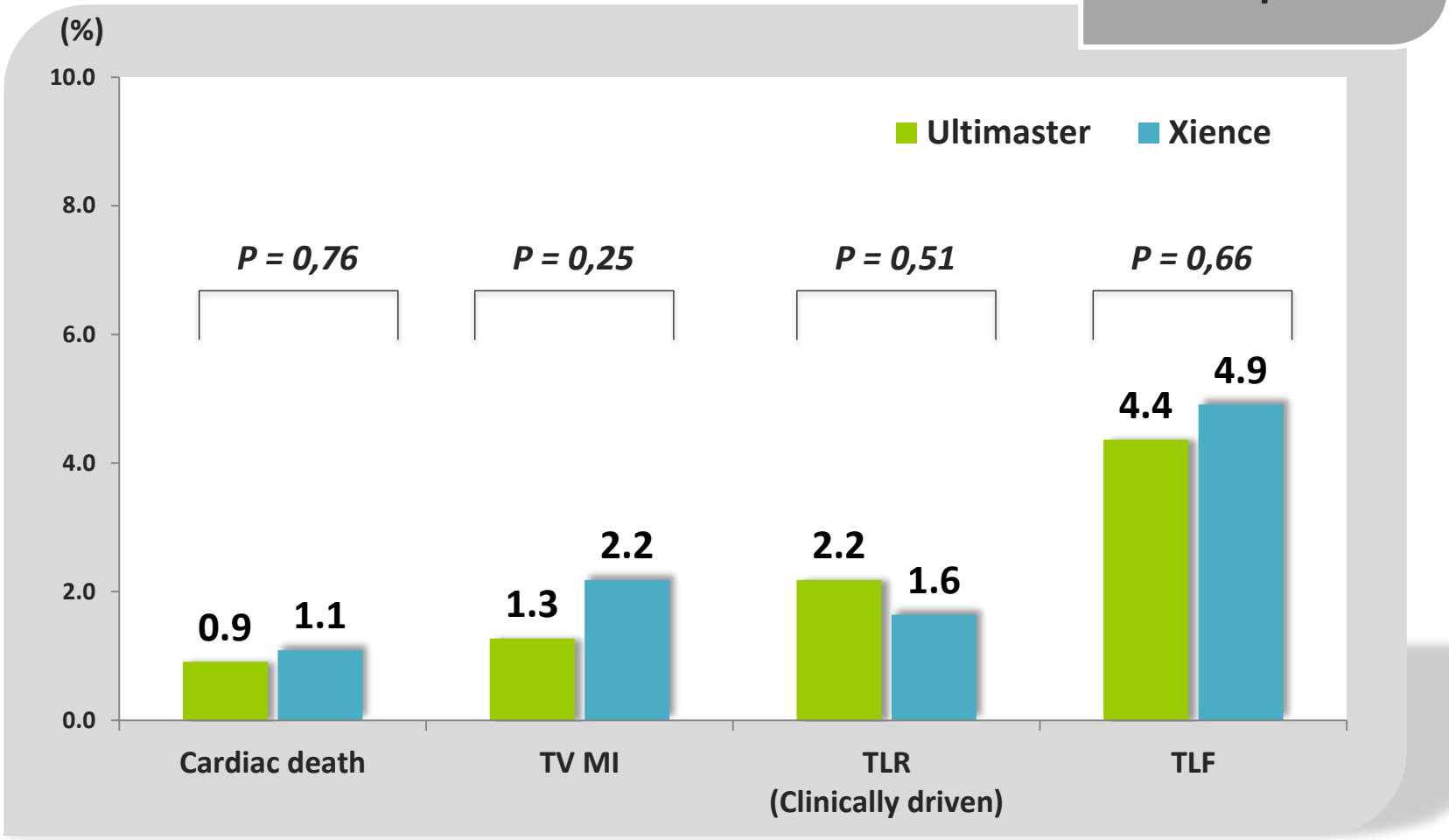
Freedom from TLF @ 9 months

Per protocol population	Cohort JR 715 patients			
	Ultimaster n=**362**	**Xience** n=**353**	**Difference** [**95**% CI]	p
Freedom from TLF	**95.86**%	**94.62**%	**1.24**% [-2.10%;4.58%]	0.0005
Intention to treat population	**Cohort JR 722 patients**			
	Ultimaster n=**366**	**Xience** n=**356**	**Difference** [**95**% CI]	p
Freedom from TLF	**95.90**%	**94.66**%	**1.24**% [-2.08%;4.55%]	0.0004

Target Lesion Failure

Clinical Outcome @ 9 months

Total Population



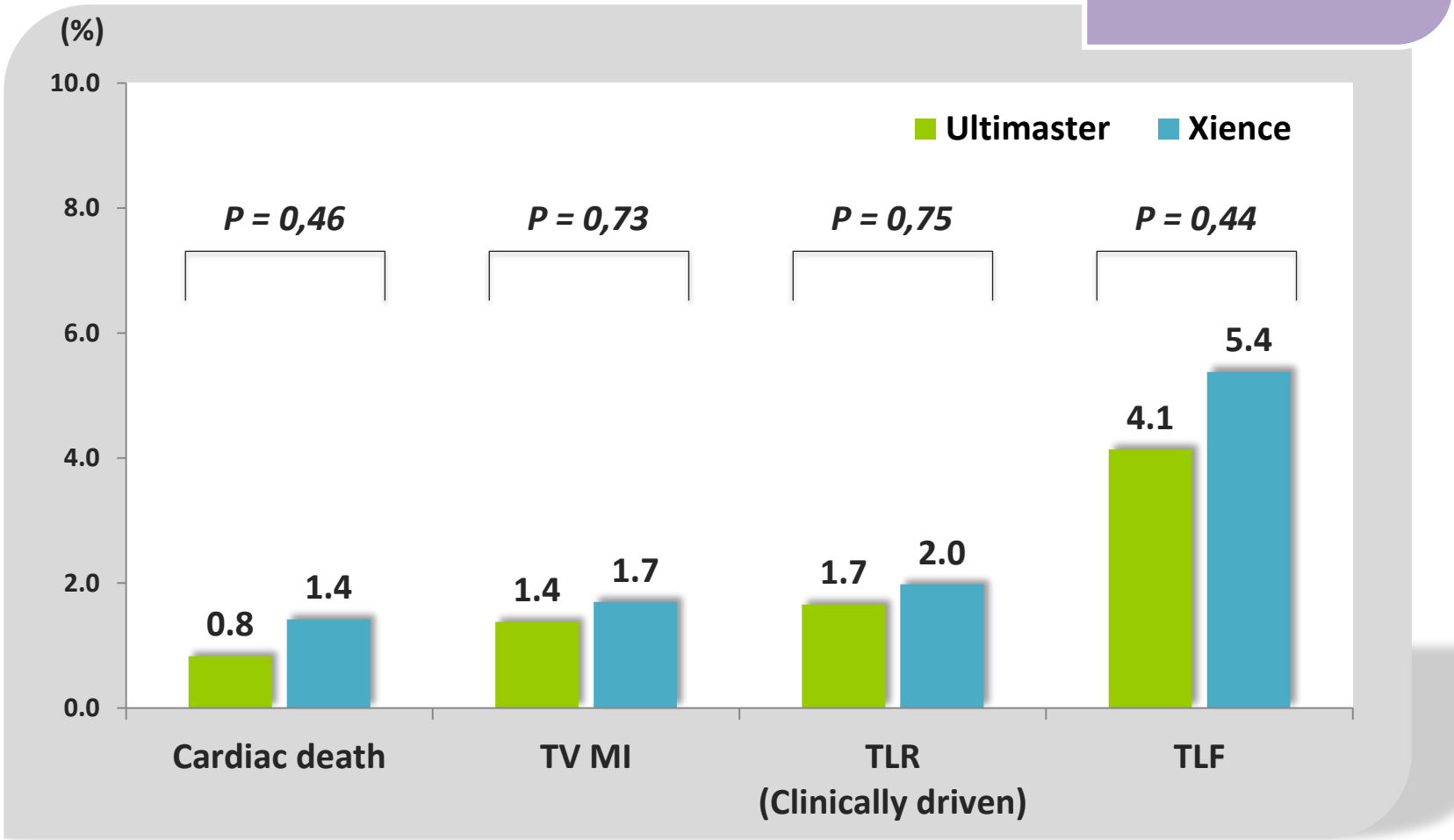
9 months = 284 days

TLF = composite of cardiac death, target vessel MI and clinically driven TLR

Target Lesion Failure

Clinical Outcome @ 9 months

Cohort JR



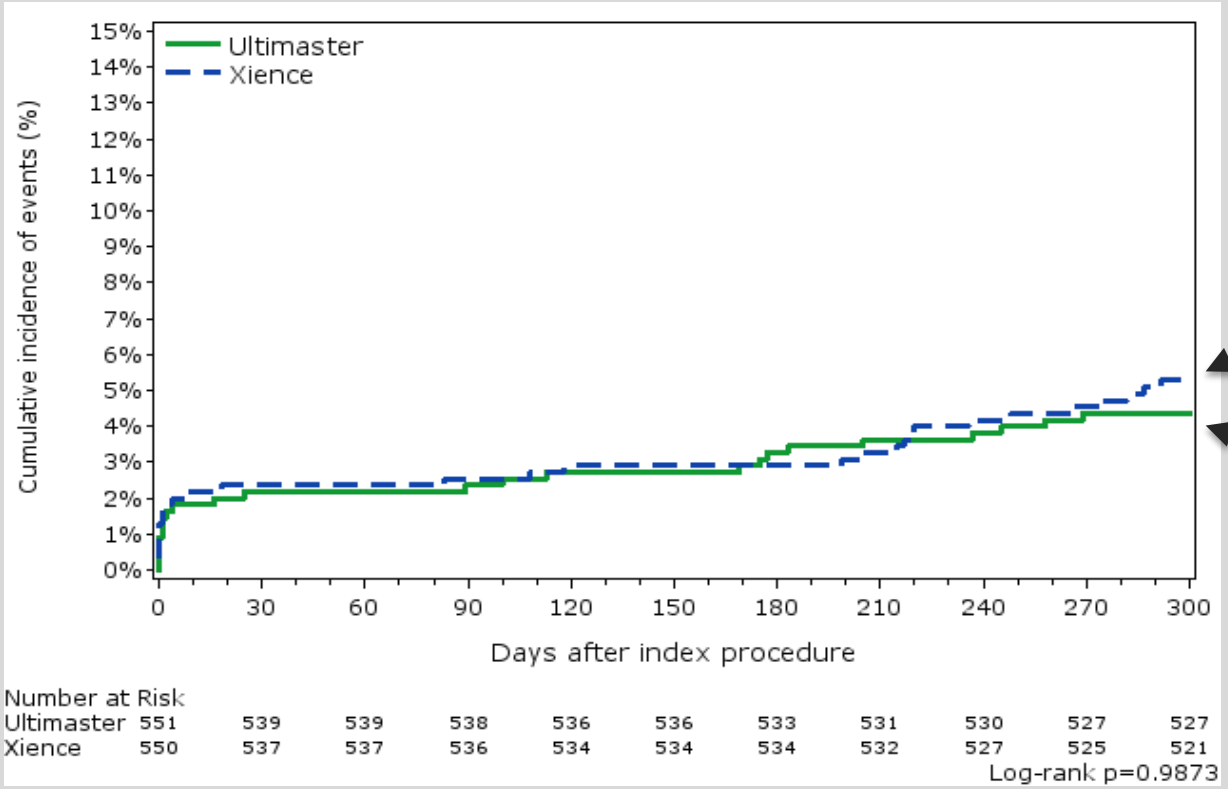
9 months = 284 days

TLF = composite of cardiac death, target vessel MI and clinically driven TLR

Target Lesion Failure

Cumulative frequency of the events

Total Population



Xience
5.27%
[3.69% ; 7.50%]

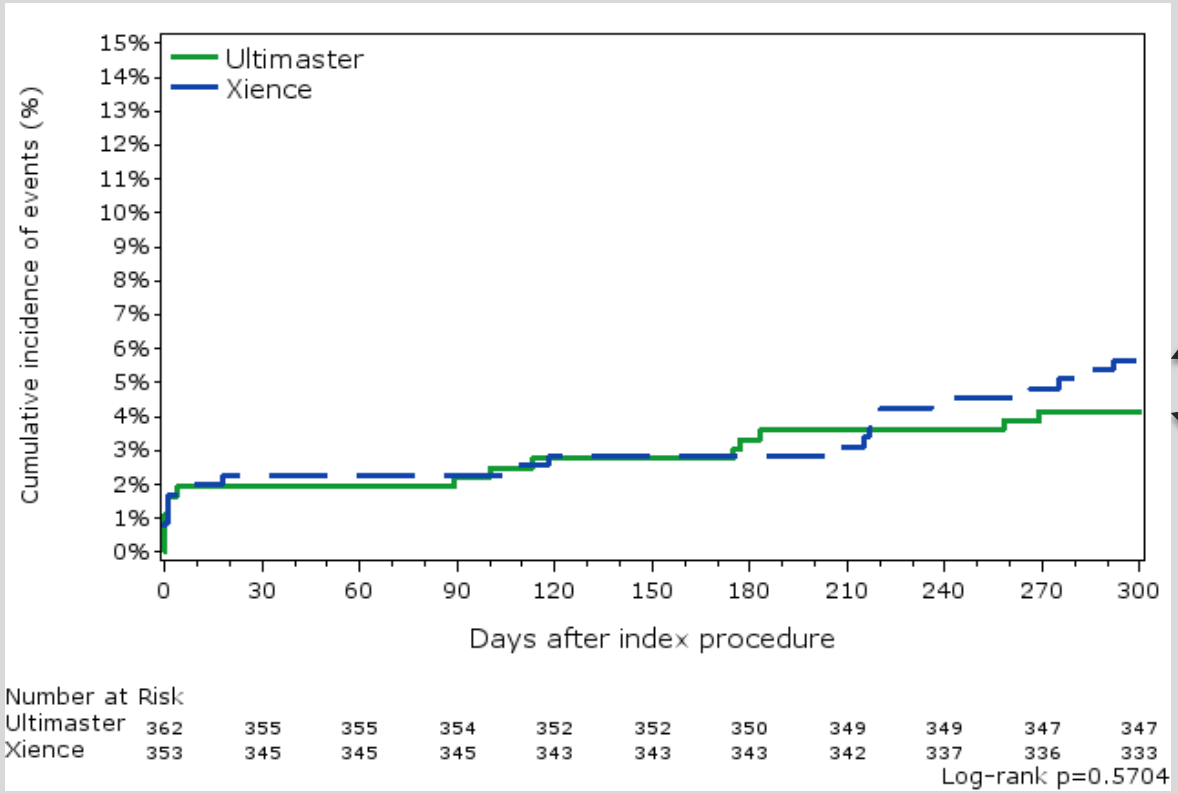
Ultimaster
4.36%
[2.94% ; 6.43%]

Data up to 300 days

Target Lesion Failure

Cumulative frequency of the events

Cohort JR



Xience
5.67%
[3.69% ; 8.64%]

Ultimaster
4.14%
[2.52% ; 6.78%]

Data up to 300 days

Stent Thrombosis Through 9 Months

Total Population

(%)	Ultimaster	Xience
Overall	**0.91**	**0.91***
Definite	0.91	0.91
Probable	0.00	0.00
Possible	0.00	0.00
Acute (0-48h)	0.00	0.00
Subacute (48h-30d)	0.54	0.36
Late (>30d-9m)	0.36	0.54

P=NS

**** 1 patient had 2 definite ST at 83 and 94 days in 2 separate lesions treated at baseline***

Stent Thrombosis Through 9 Months

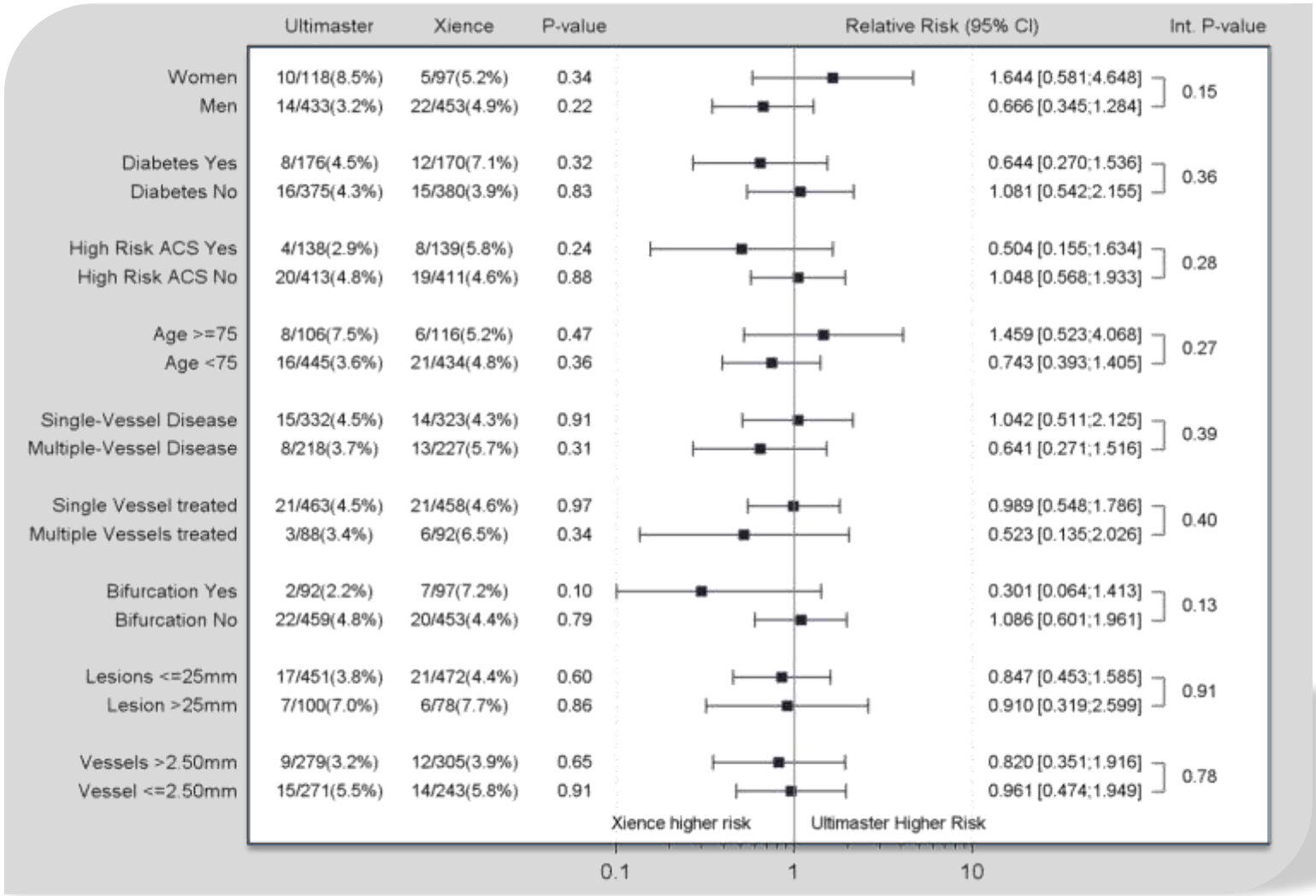
Cohort JR

(%)	Ultimaster	Xience
Overall	**0.28**	**0.57**
Definite	0.28	0.57
Probable	0.00	0.00
Possible	0.00	0.00
Acute (0-48h)	0.00	0.00
Subacute (48h-30d)	0.28	0.28
Late (>30d-9m)	0.00	0.28

P=NS

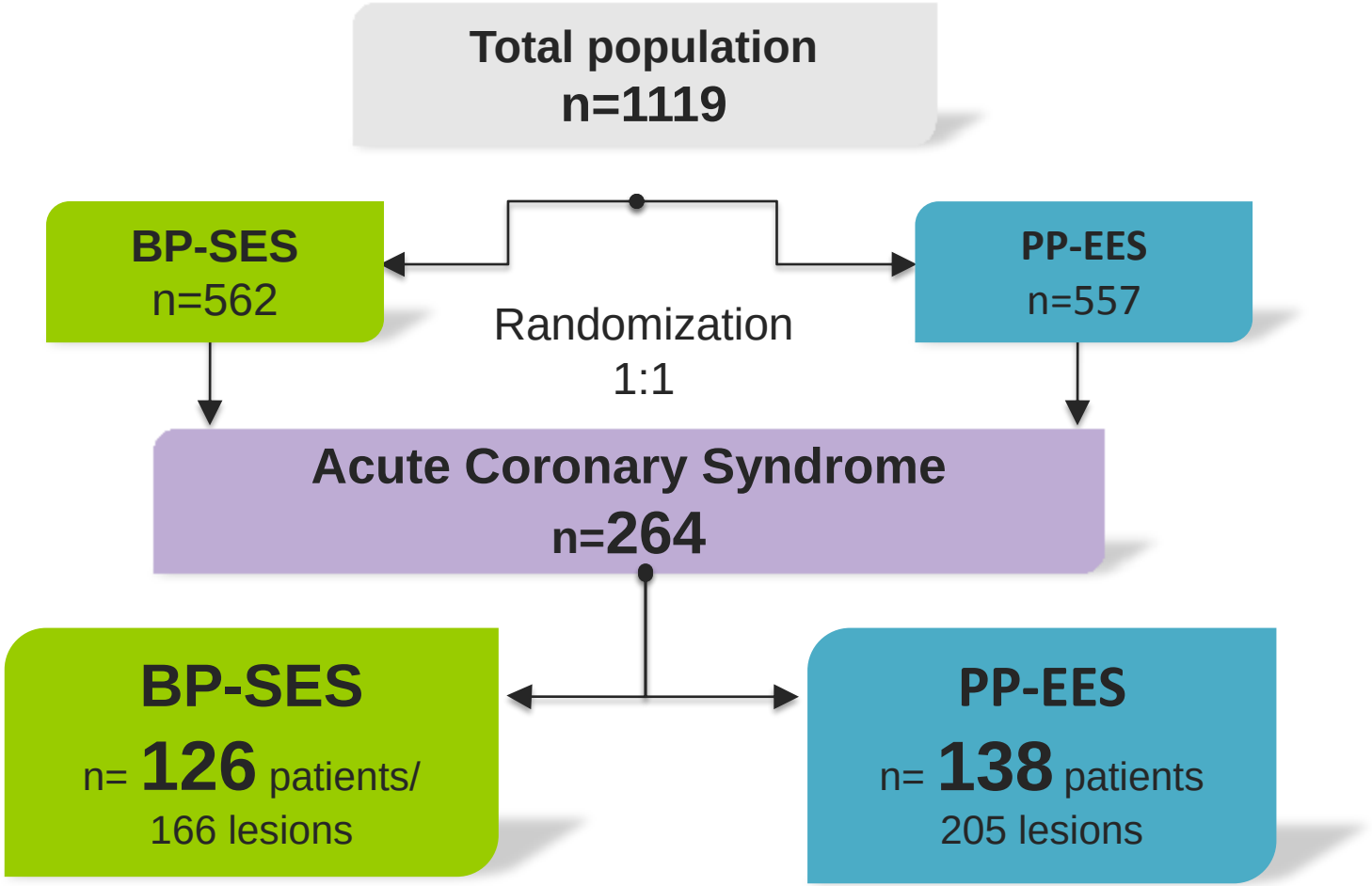
Century II – Subgroup analyses

TLF at 9 months



CENTURY II
Subgroup analysis

CENTURY II – High risk ACS



Baseline patient characteristics

	BP-SES (n=126)	PP-EES (n=138)	P-value
Age (mean ± SD)	63.1 ± 11.4	64.3 ± 11.4	0.45
Gender – male	79.4%	84.8%	0.25
DM	25.4%	21.7%	0.48
IDDM	21.9%	13.3%	0.38
Hypertension	58.9%	57.3%	0.79
Current Smoker	39.0%	34.3%	0.43
Previous MI	31.8%	34.8%	0.60
STEMI	23.0%	23.2%	0.97
NSTEMI	77.0%	76.8%	0.97
Previous PCI	21.4%	21.7%	0.95
Previous CABG	0.8%	2.9%	0.21

Baseline lesion characteristics

	BP-SES (n=159)	PP-EES (n=195)	P-value
ACC/AHA classification			0.49
A	5.0%	3.6%	
B1	13.8%	16.9%	
B2	47.8%	51.8%	
C	33.3%	27.7%	
Ostial	3.1%	6.7%	0.13
Calcification			0.98
None/mild	86.2%	88.7%	
Moderate	9.4%	8.2%	
Severe	4.4%	3.1%	
Thrombus present	10.1%	11.8%	0.61
Bifurcation	10.2%	9.8%	0.88

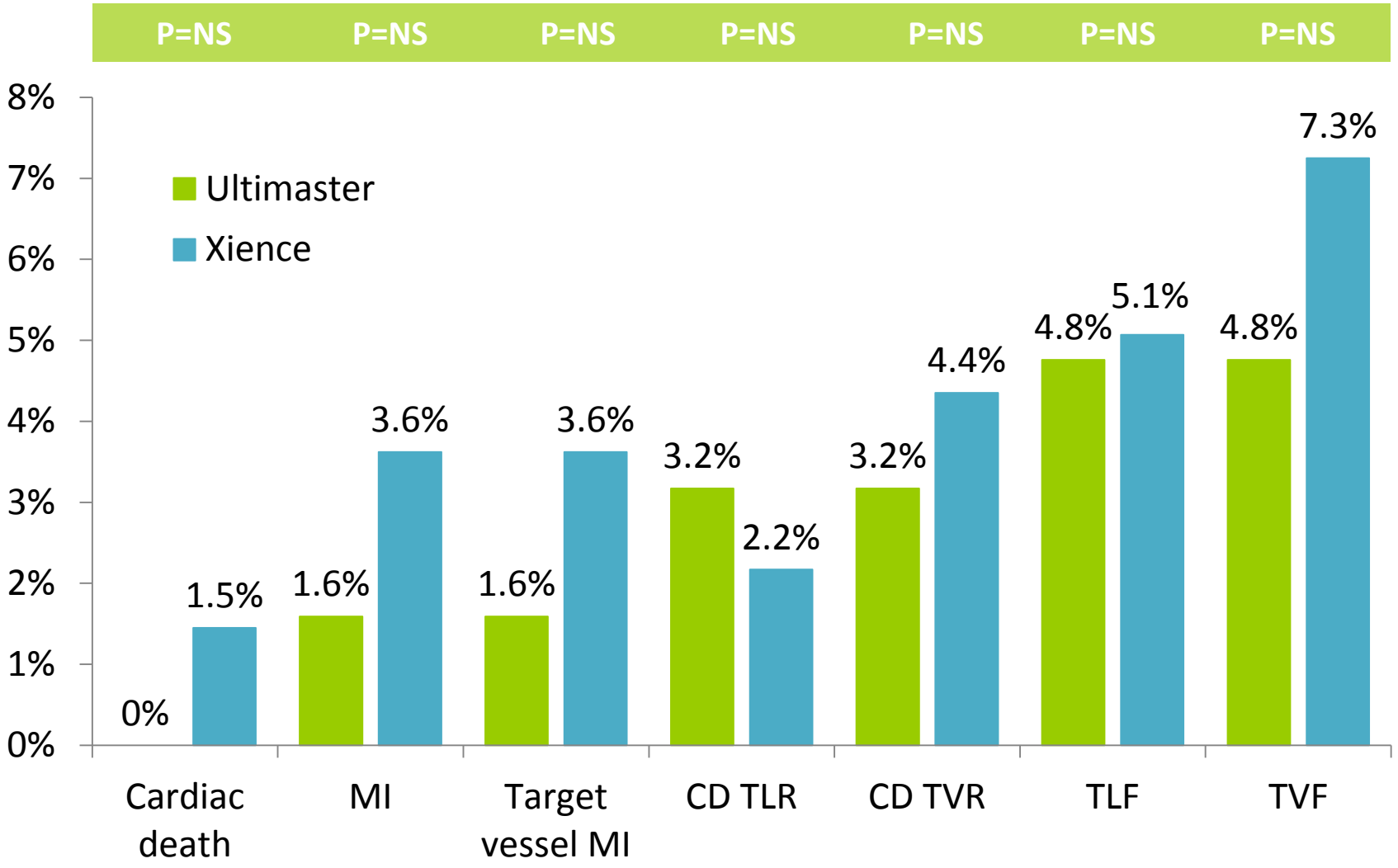
Baseline procedure characteristics

	BP-SES (n=126)	PP-EES (n=138)	P-value
Access site Femoral Radial	 27.0% 73.0%	 28.3% 71.7%	0.82
Pre-dilation	71.7%	68.3%	0.48
Post-dilation	42.2%	43.1%	0.86
N° of stents implanted/pt (mean ±SD)	1.55 ± 0.77	1.75 ± 1.00	0.24
N° of stents implanted/lesion (mean ±SD)	1.17 ± 0.44	1.19 ± 0.44	0.61

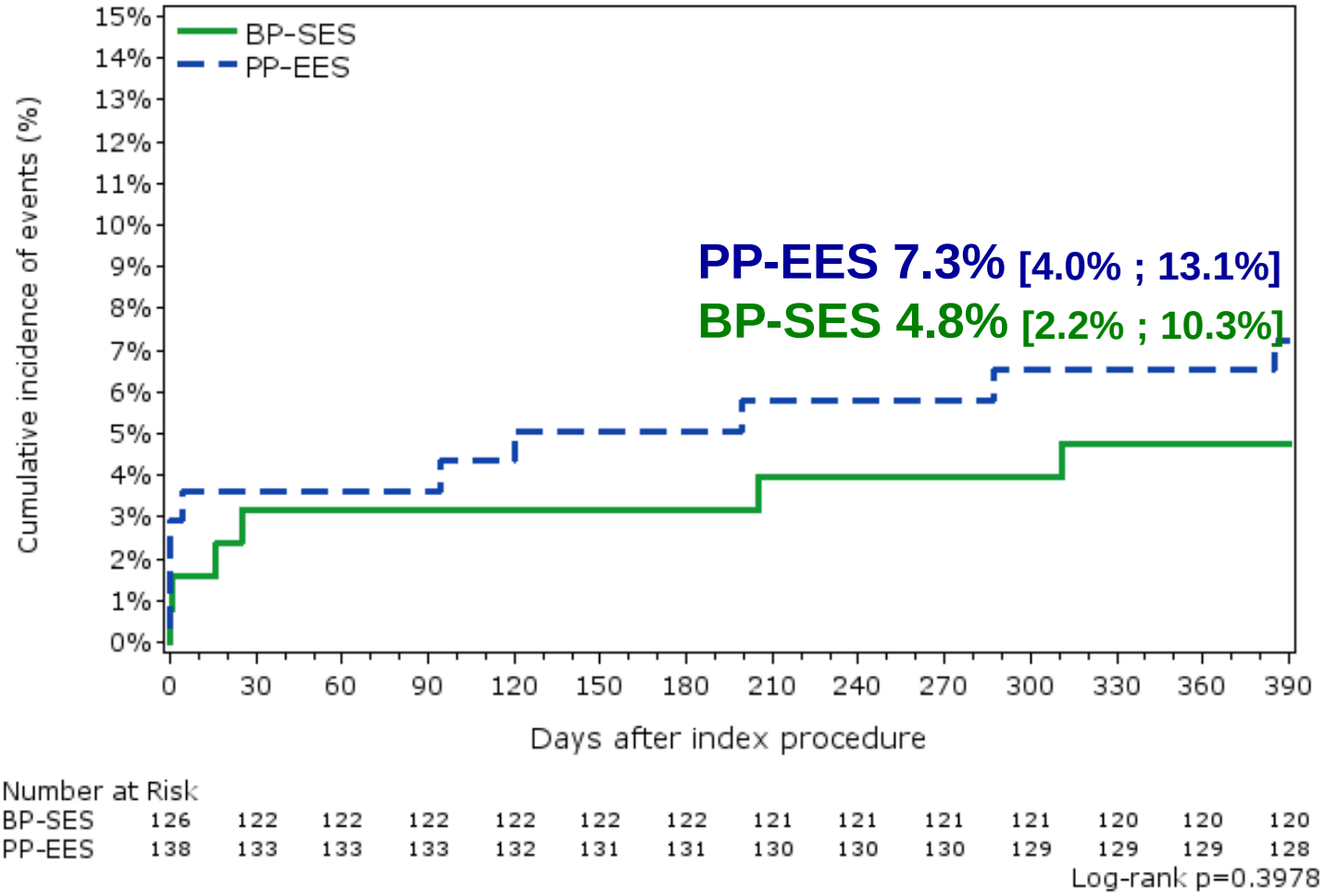
Baseline QCA lesion characteristics

	BP-SES (n=159)	PP-EES (n=195)	P-value
Lesion length, pre- (mm)	18.14 ± 11.13	15.48 ± 8.15	0.10
RVD, pre- (mm)	2.68 ± 0.56	2.62 ± 0.62	0.29
MLD, pre- (mm)	0.75 ± 0.40	0.71 ± 0.44	0.52
Diameter stenosis, pre- (%)	72.1 ± 13.4	72.5 ± 15.5	0.64
MLD, post- (mm) in-stent in-segment	 2.53 ± 0.46 2.19 ± 0.60	 2.49 ± 0.49 2.11 ± 0.63	 0.41 0.26
Diameter stenosis, post- (%) in-stent in-segment	 12.6 ± 6.30 23.4 ± 11.7	 12.4 ± 6.50 24.3 ± 11.9	 0.74 0.33
Acute gain (mm) in-stent in-segment	 1.78 ± 0.50 1.44 ± 0.59	 1.79 ± 0.56 1.40 ± 0.69	 0.91 0.42

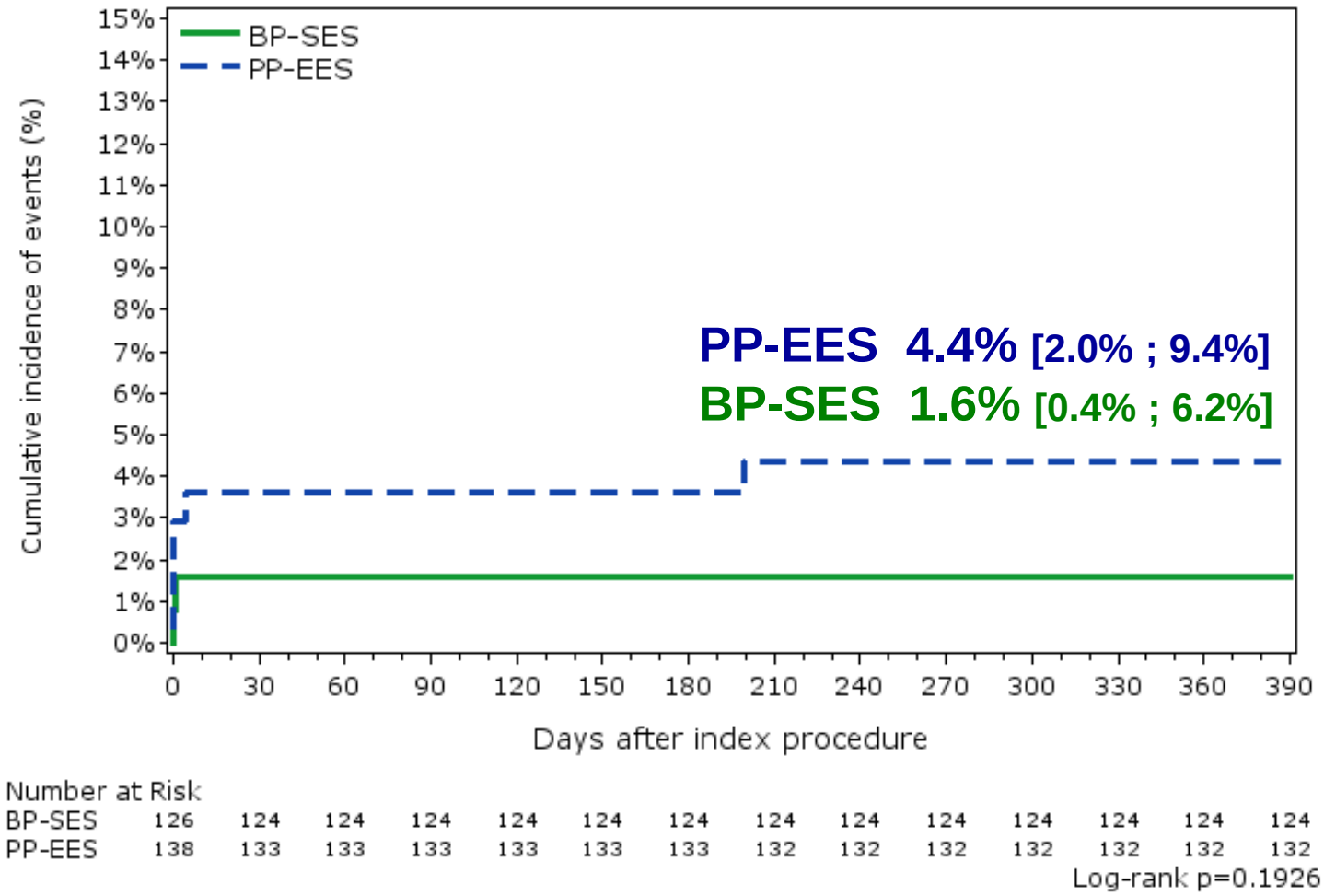
Clinical outcomes at 12 months



Target Vessel Failure



Cardiac death or MI



Stent thrombosis at 12 months

	BP-SES (n=126)	PP-EES (n=138)	P-value
Stent thrombosis (n)	1.6% (2)	0.7% (1)*	0.51
Definite (n)	1.6% (2)	0.7% (1)	0.51
Definite/Probable (n)	1.6% (2)	0.7% (1)	0.51
Timing of ST			
Acute (n)	0% (0)	0% (0)	1
Subacute (n)	1.6% (2)	0.7% (1)	0.51
Late (n)	0% (0)	0% (0)	1

***the patient had 3 vessels of stent thrombosis**

CENTURY II – High risk ACS

Conclusions

- Short and mid-term safety and efficacy of new Ultimaster BP-SES were favorable and similar to the PP-EES in patients with high risk ACS.
- Larger study and long-term follow-up are necessary to provide further unambiguous assessment of the potential clinical benefits of DES with a bioresorbable polymer in this sub-group.

CENTURY II: Summary of Results

- Baseline patient and lesion characteristics were similar in both study arms.
- Radial access was used in >70% of cases, without difference between treatment arms.
- There were no significant differences in clinical outcomes between the two stent arms at 12-months .
- There were 2 patients with subacute stent thrombosis in BP-SES and 1 patient with 3 vessels of stent thrombosis in PP-EES arm, resulting in low and similar ST rates (1.6% vs 0.7%, p=0.51).
- Incidence of MI was numerically lower in BP-SES.

CENTURY II: Conclusion

- CENTURY II study reached its primary endpoint
- The Ultimaster stent with bioresorbable polymer was found to be as safe and as effective as Xience stent with permanent polymer in this relatively complex patient population
- Both stents showed excellent performance and low rate of adverse events

ESC/EACTS 2014 DES RECOMMENDATION

5 out of 8 DES with highest level of recommendation are DES with bioresorbable polymer

Table 10 **CE-approved new-generation DES recommended for clinical use based on randomized trials with a primary clinical endpoint (in alphabetical order)**

DES	Stent platform	Polymer coating	Drug	References
Based on durable polymer coatings				
Promus element	Platinum–chrome	PBMA and PVDF-HFP	Everolimus	664,665
Resolute	Cobalt–chrome	PBMA, PHMA, PVP, and PVA	Zotarolimus	655,665,666
Xience	Cobalt–chrome	PBMA and PVDF-HFP	Everolimus	247, 654,667
Based on biodegradable polymer coatings				
Biomatrix	Stainless steel	PDLLA	Biolimus A9	248, 668
Nobori	Stainless steel	PDLLA	Biolimus A9	656,658,669
Yukon Choice PC	Stainless steel	PDLLA	Sirolimus	657
Orsiro	Cobalt-chrome	PLLA	Sirolimus	961
Ultimaster	Cobalt–chrome	PDLLA and PCL	Sirolimus	960

CE = Conformité Européenne; DES = drug-eluting stent; PBMA = poly n-butyl methacrylate; PDLLA = poly(d,l)-lactic acid; PHMA = polyhexyl methacrylate; PLLA = poly-L-lactic acid; PVA = polyvinyl acetate; PVDF-HFP = poly(vinylidene fluoride-cohexafluoropropylene).

From Durable to Biodegradable:
Expectations from Nobori, Ultimaster

Thank You !