From the first generation to the second generation of biodegradable polymer DES

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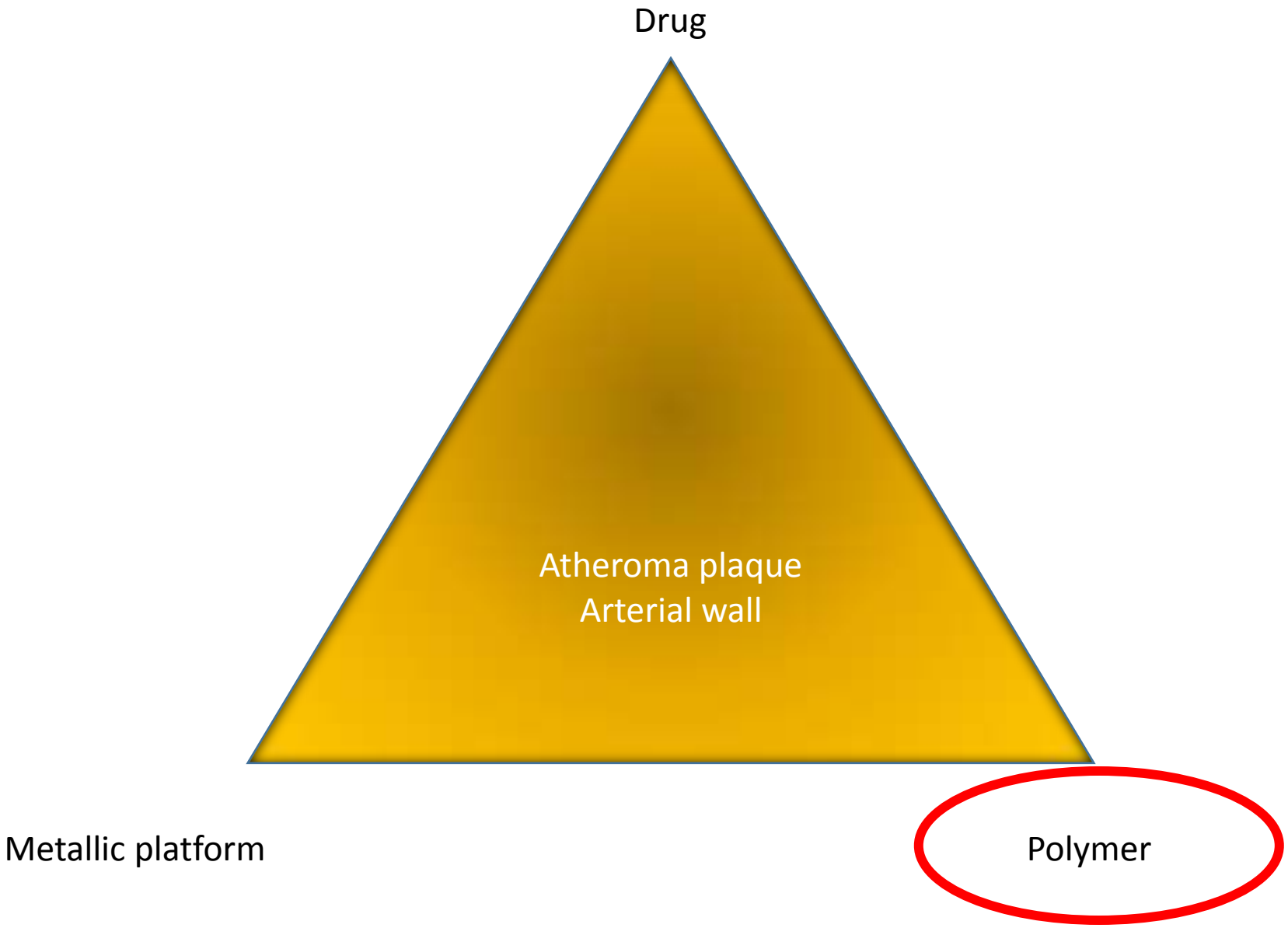
In the last five years , I received research grants or speaker fees or I am/was consultant for: Abbott Vascular, Asahi, Astra Zeneca, AVI, Boston Scientific, Biotronik, Colibri, Cook, Cordis, Daichi-Sankyo, Eli-Lilly, Iroko, Medtronic, Terumo. I am currently minor shareholder & general mamager of CERC (CRO)


Drug
Atheroma plaque
Arterial wall
Metallic platform
Polymer

First generation DES: Polymer limitations

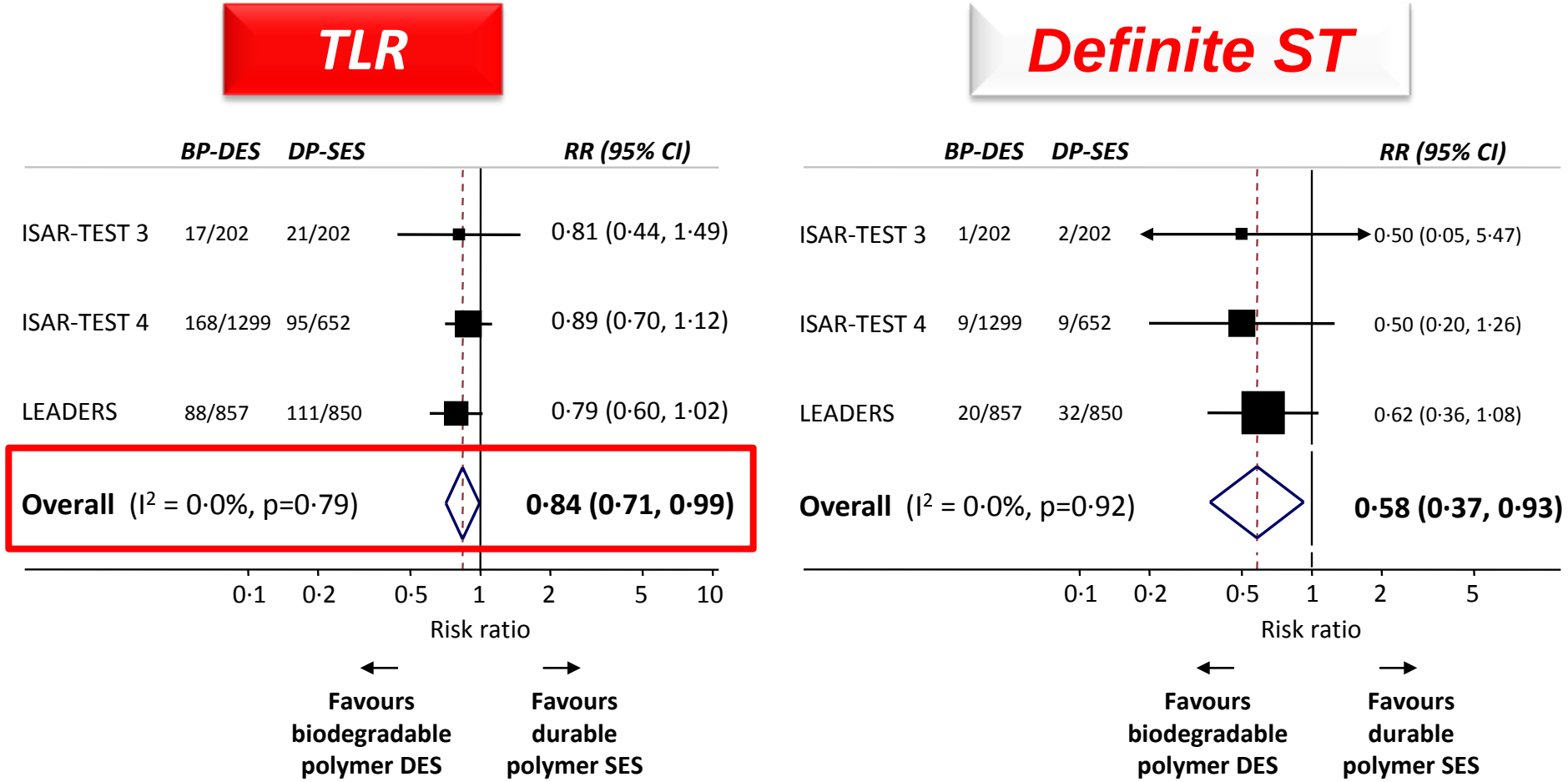
- Fragile: uneven drug distribution
  - Focal restenosis
- Unconsistent drug kinetic release
  - Diffuse restenosis
- Systemic diffusion/prolonged elution
  - Delayed endothelialisation
- Chronic inflammation
- Hypersensitivity
  - LST/VLST

Less polymer!

- Neutral durable polymer
  - Thin layer (Xience*, Resolute*) 0.13 /0.22
- Biobasorbable polymer
  - Abluminal layer (Nobori*, Biomatrix*) 0.13

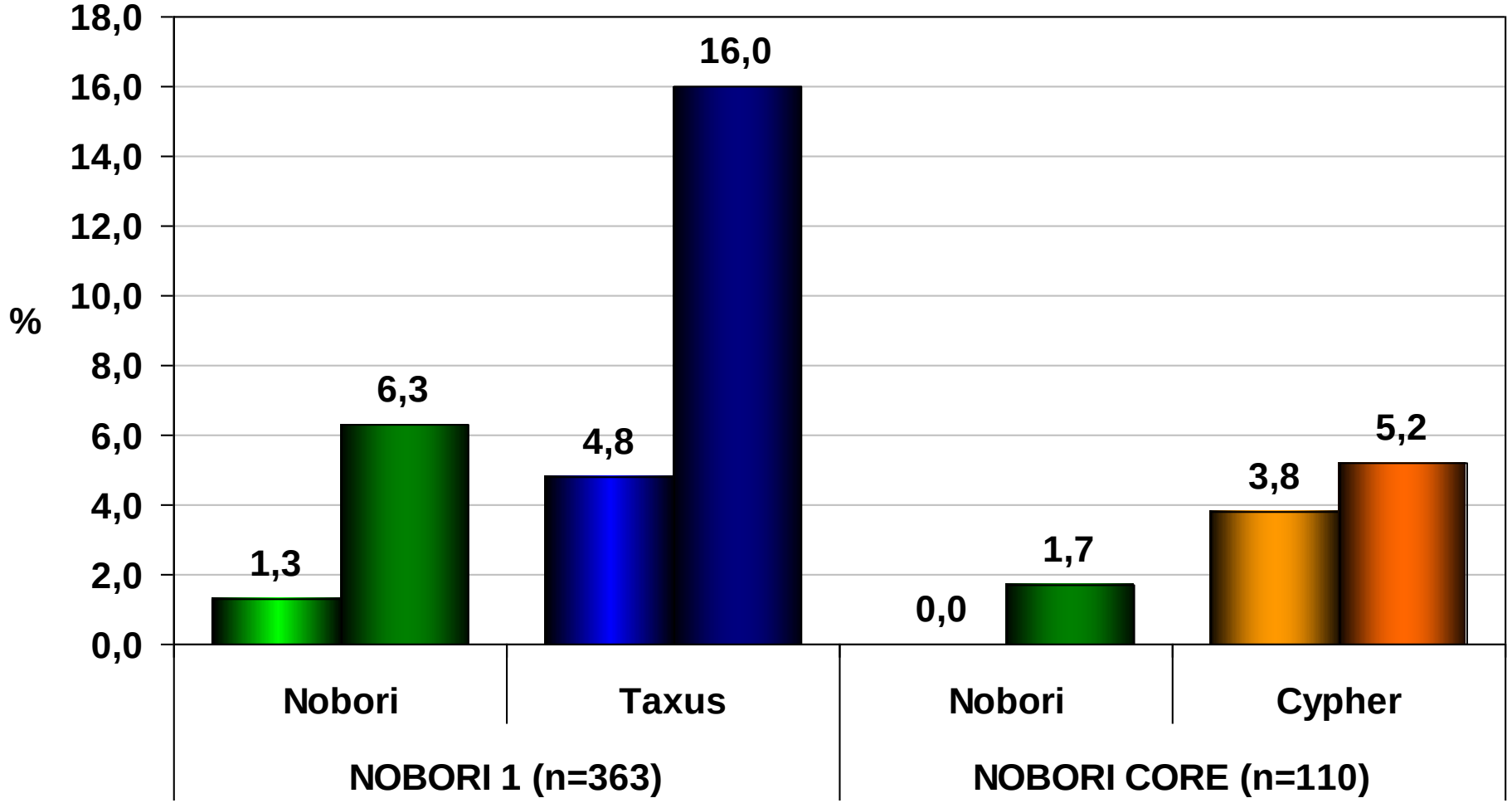
Bioabsorbable polymer eluting stent vs 1st generation DES

Efficacy and Safety with Biodegradable Polymer DES versus Durable Polymer Sirolimus-Eluting Stent During Long-Term Follow-up

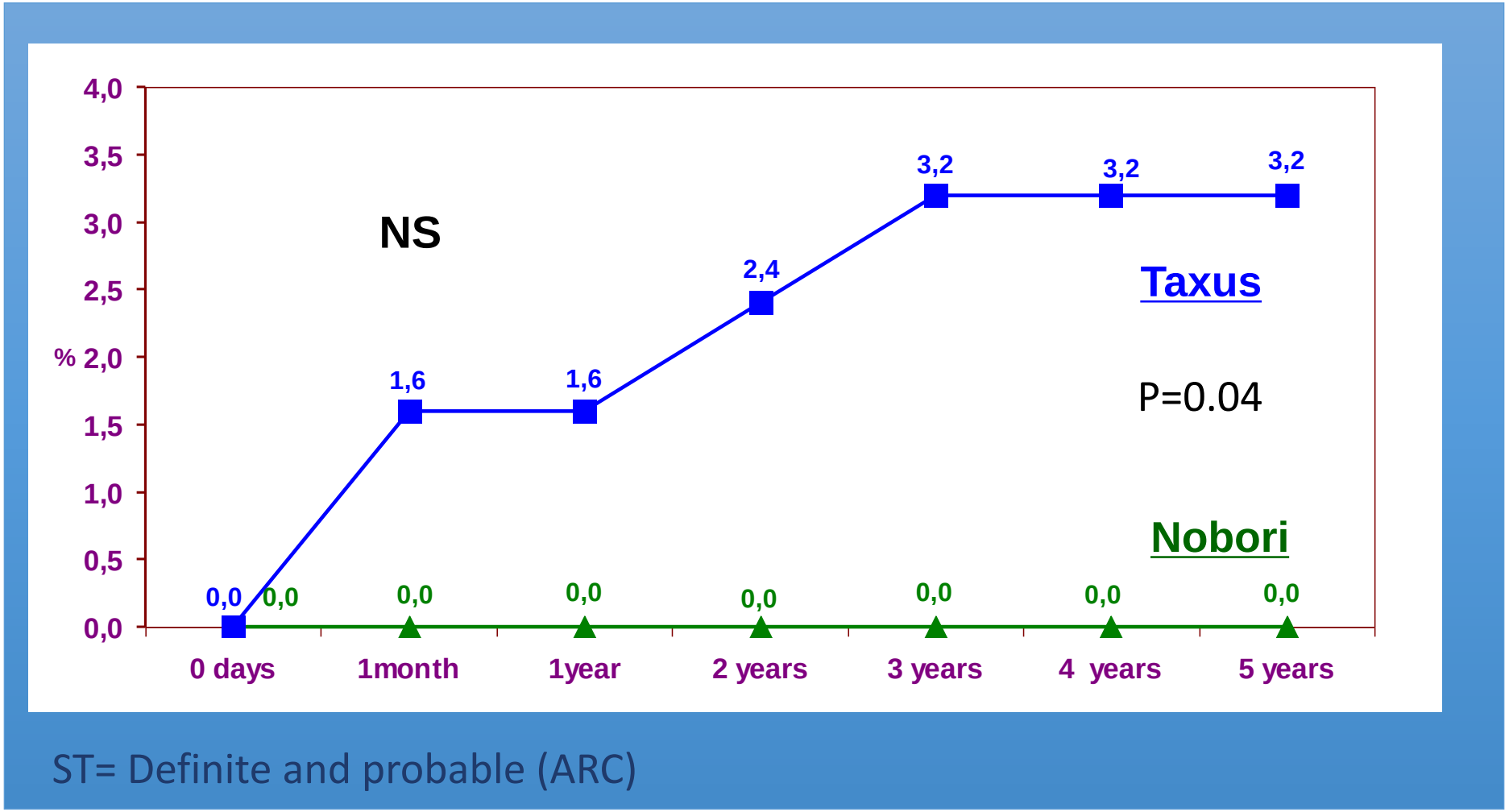


Stefanini G et al. *Lancet* 2011

Nobori DES Efficacy
TLR at 5-Year in NOBORI Pivotal Trials

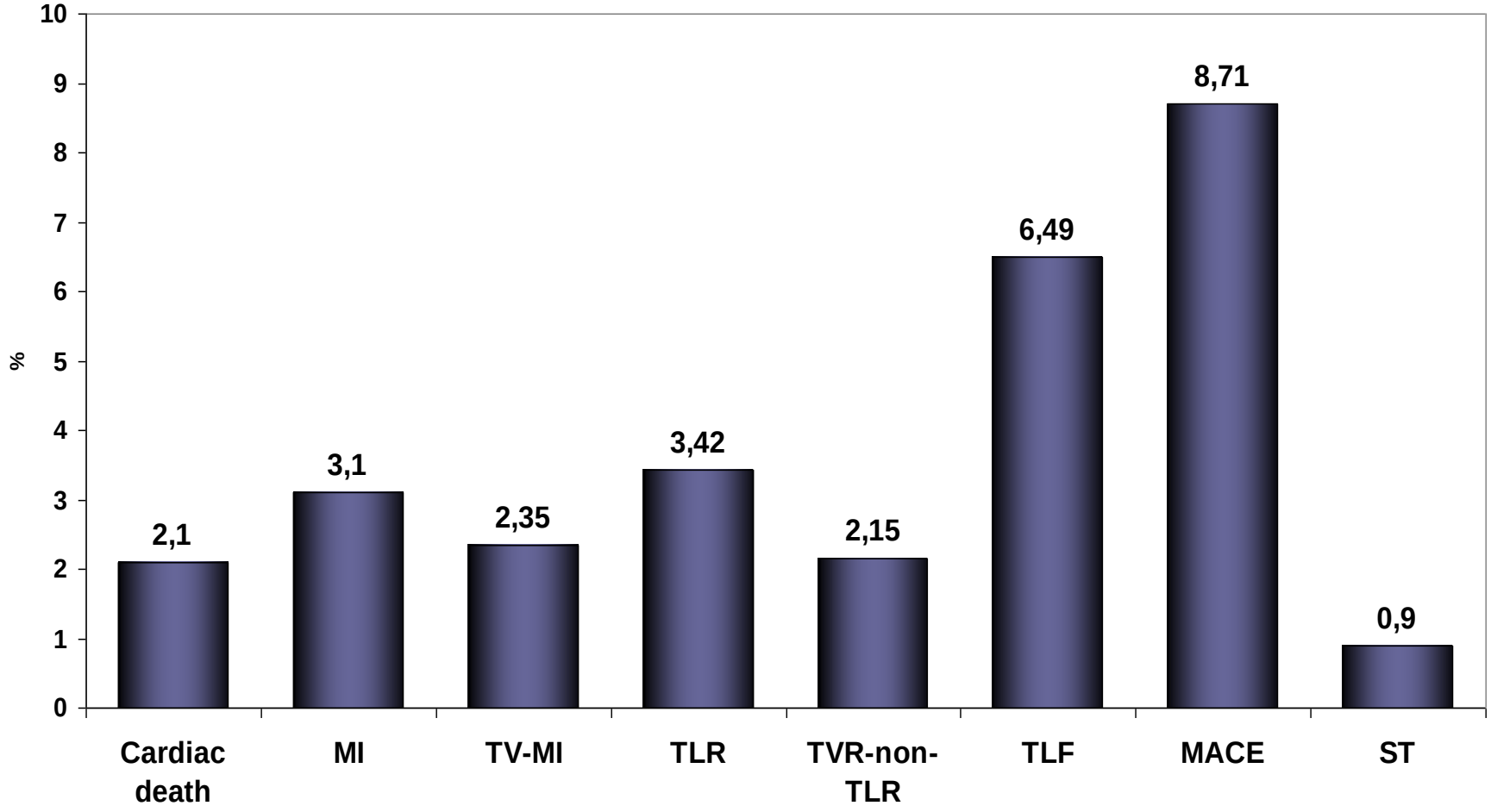


Long term safety
NOBORI 1 – Stent Thrombosis @ 5 Years



ST= Definite and probable (ARC)

NOBORI II – 3-Year Results

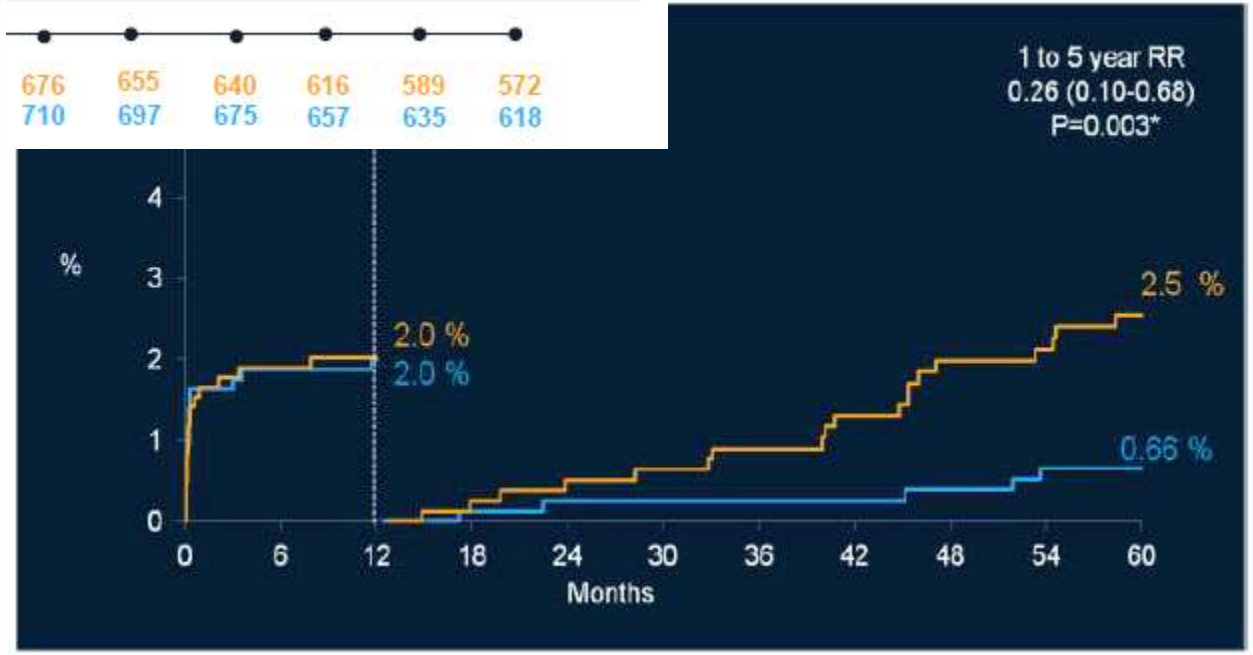


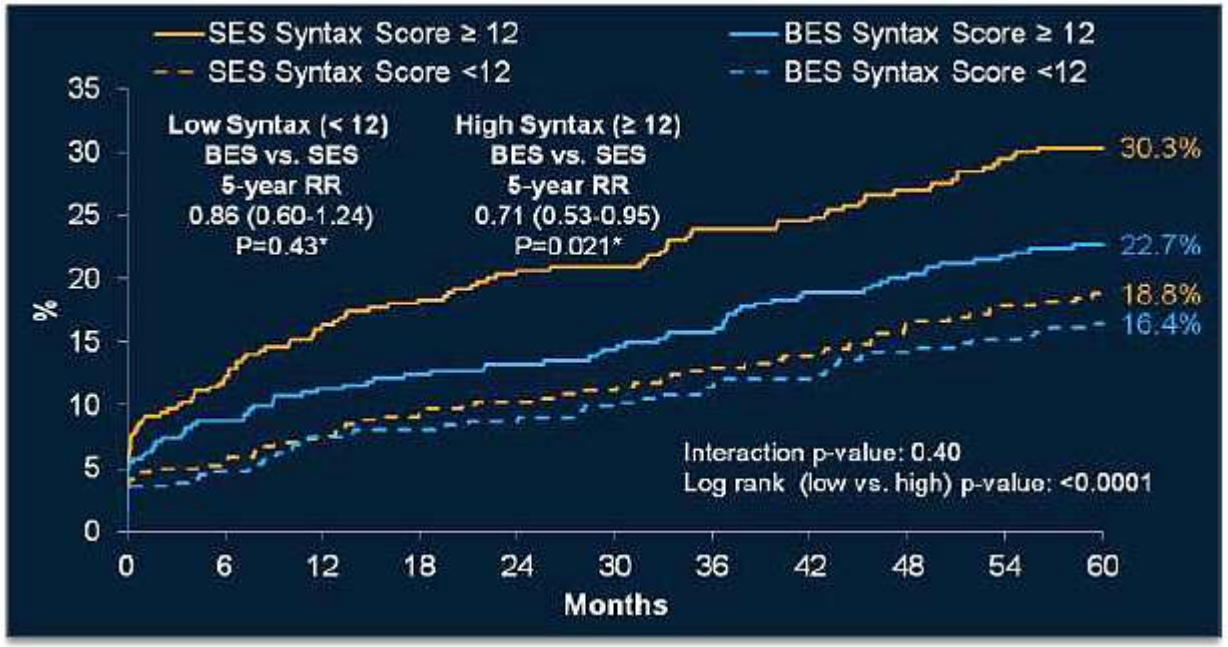
LEADERS

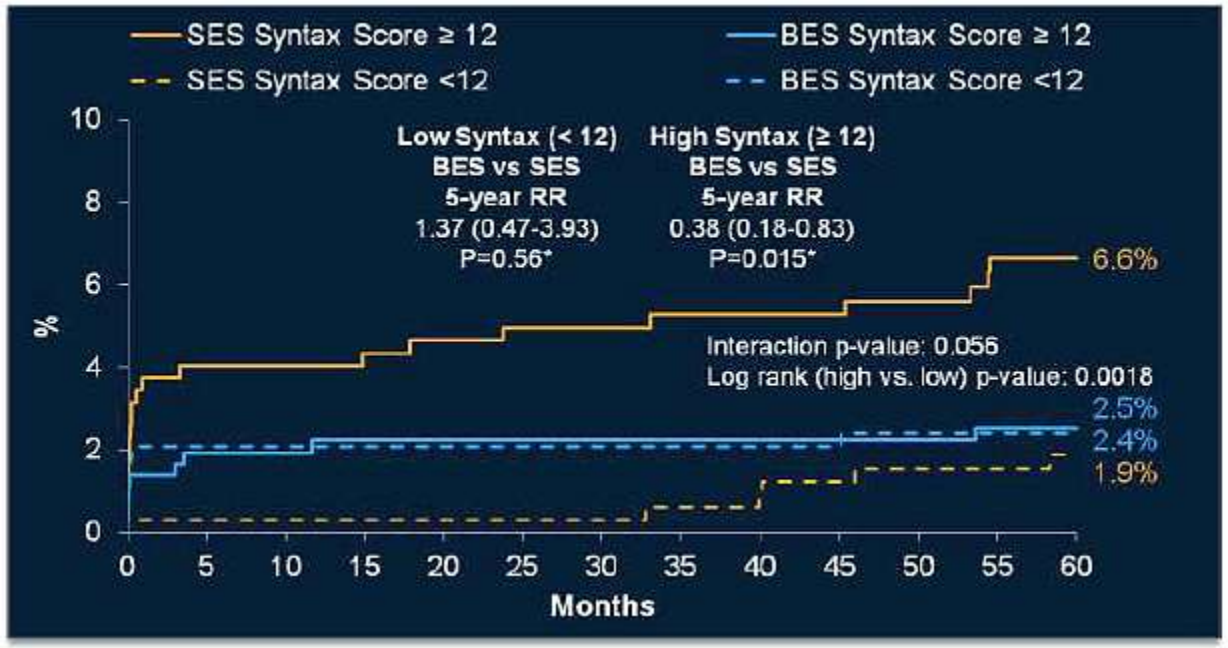
MACE

TVR

ST



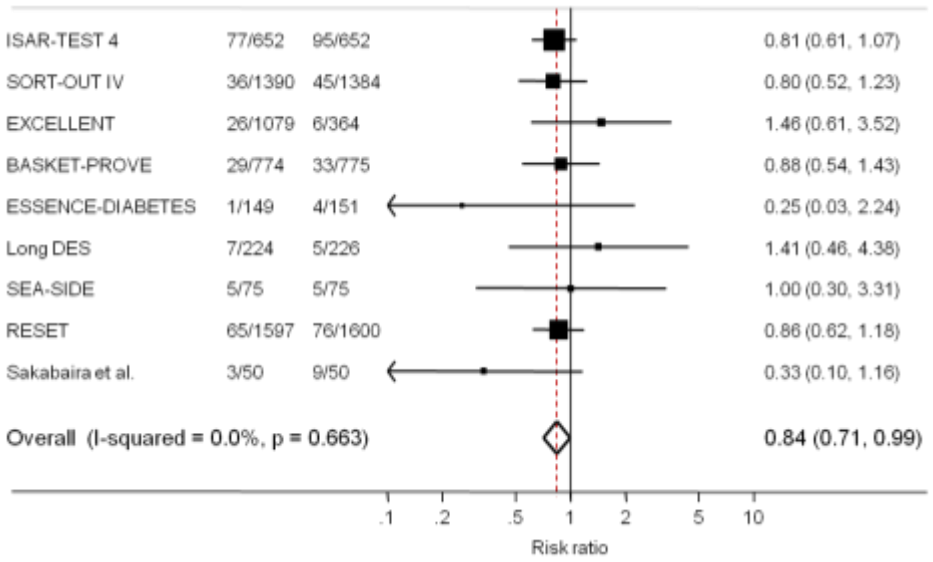

SES Syntax Score ≥ 12
SES Syntax Score <12
BES Syntax Score ≥ 12
BES Syntax Score <12
Low Syntax (< 12)
BES vs. SES
5-year RR
0.86 (0.60-1.24)
P=0.43*
High Syntax (≥ 12)
BES vs. SES
5-year RR
0.71 (0.53-0.95)
P=0.021*
30.3%
22.7%
18.8%
16.4%
Interaction p-value: 0.40
Log rank (low vs. high) p-value: <0.0001
%
Months


SES Syntax Score ≥ 12
SES Syntax Score <12
BES Syntax Score ≥ 12
BES Syntax Score <12
Low Syntax (< 12)
BES vs SES
5-year RR
1.37 (0.47-3.93)
P=0.56*
High Syntax (≥ 12)
BES vs SES
5-year RR
0.38 (0.18-0.83)
P=0.015*
6.6%
Interaction p-value: 0.056
Log rank (high vs. low) p-value: 0.0018
2.5%
2.4%
1.9%
%
Months

Bioabsorbable polymer eluting stent vs 2nd generation of durable polymer DES

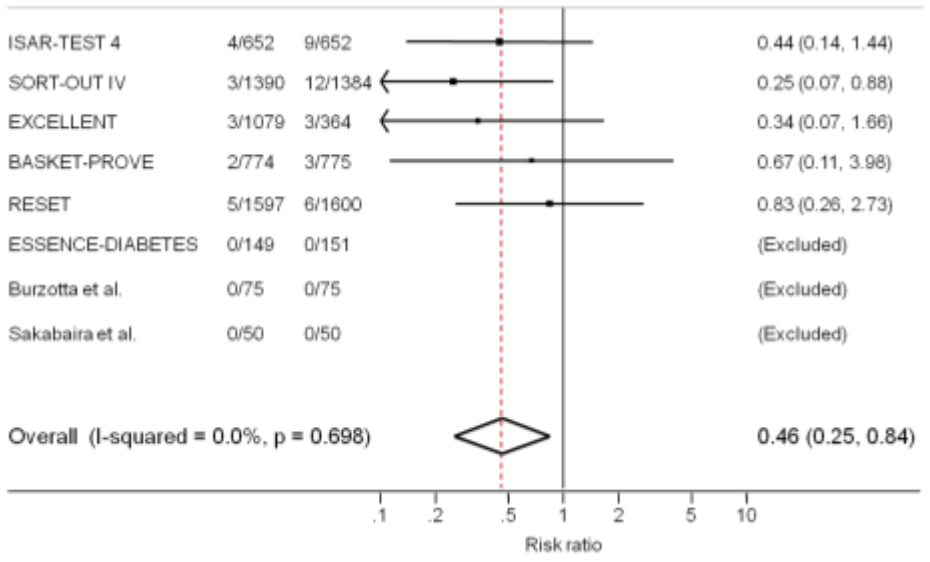
Everolimus-Eluting Versus Sirolimus-Eluting Durable Polymer Stents

Target Lesion Revasc



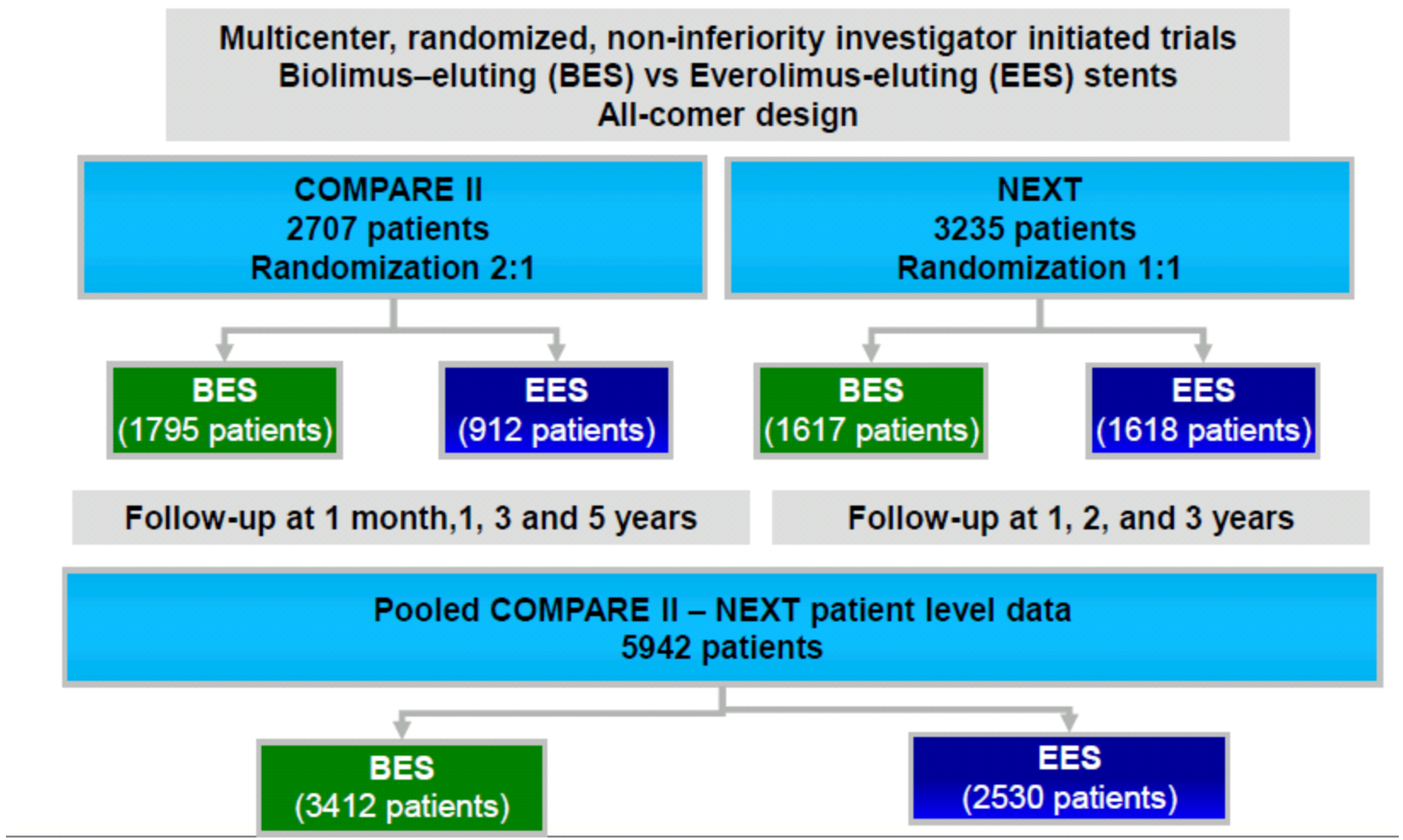
Favors EES ***Favors SES***

Definite ST

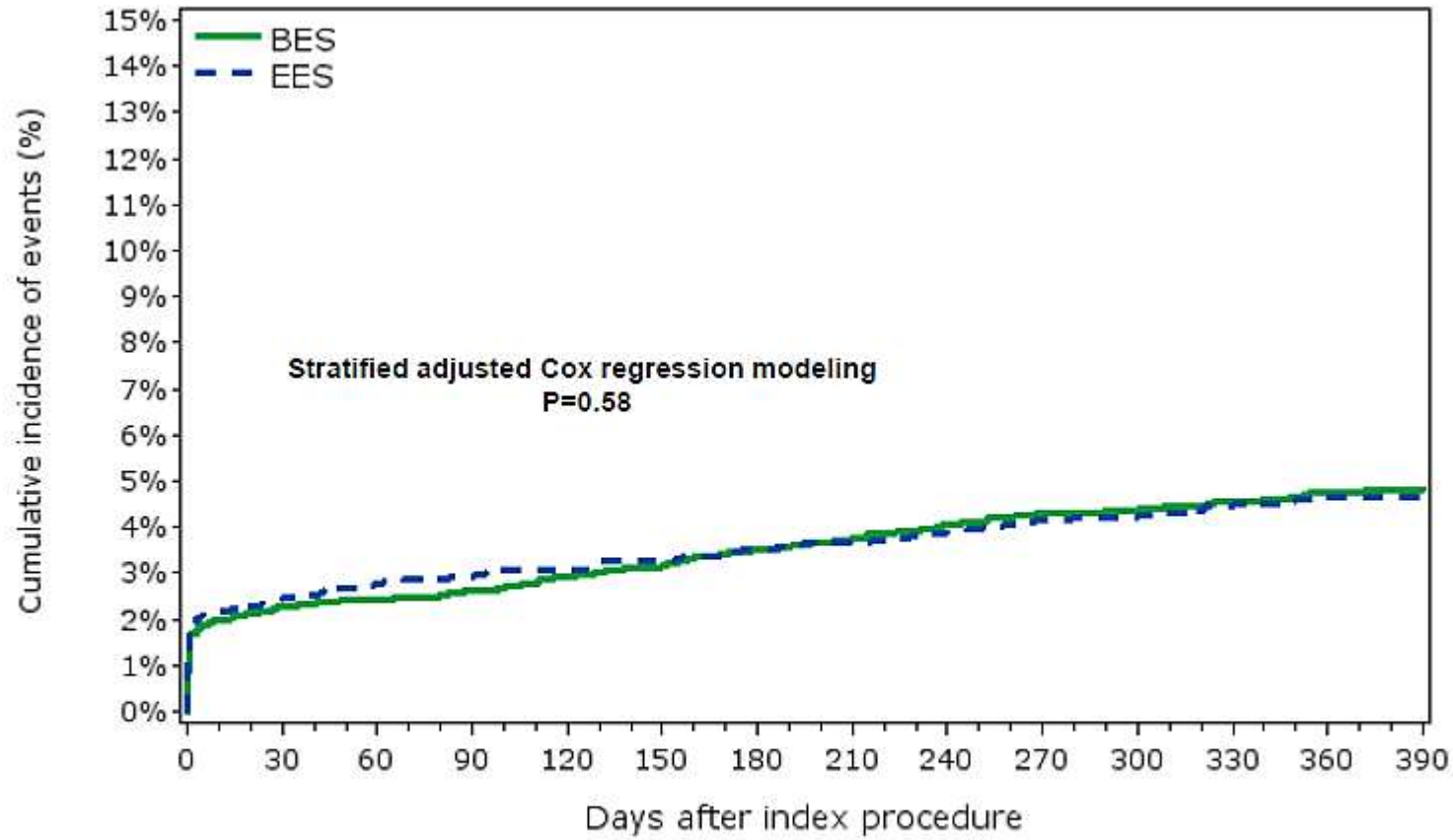


Favors EES ***Favors SES***

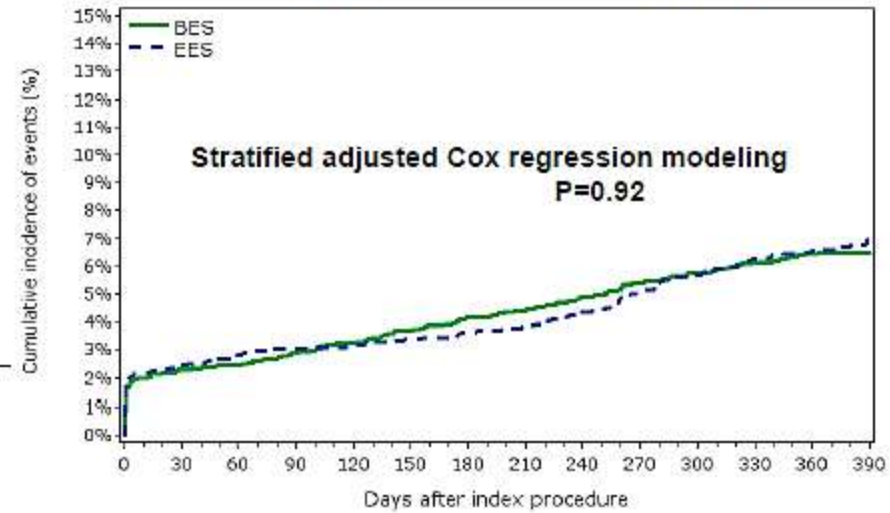
Meta-Analysis N = 11,167


Multicenter, randomized, non-inferiority investigator initiated trials
Biolimus–eluting (BES) vs Everolimus-eluting (EES) stents
All-comer design
COMPARE II
2707 patients
Randomization 2:1
NEXT
3235 patients
Randomization 1:1
BES
(1795 patients)
EES
(912 patients)
BES
(1617 patients)
EES
(1618 patients)
Follow-up at 1 month,1, 3 and 5 years
Follow-up at 1, 2, and 3 years
Pooled COMPARE II – NEXT patient level data
5942 patients
BES
(3412 patients)
EES
(2530 patients)

Death & MI @ 1 year



Target Vessel Failure (TVF)

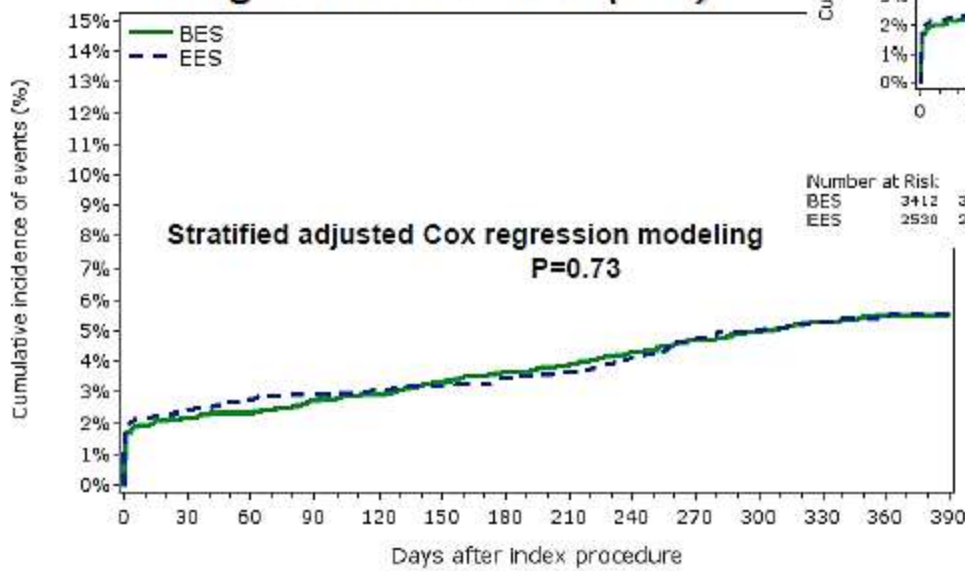


Number at Risk:

BES	3412	3322	3308	3291	3277	3262	3243	3230	3208	3183	3160	3146	3129	1695
EES	2530	2463	2446	2440	2431	2421	2412	2404	2387	2353	2331	2313	2301	863

Log-rank p=0.6394

Target Lesion Failure (TLF)



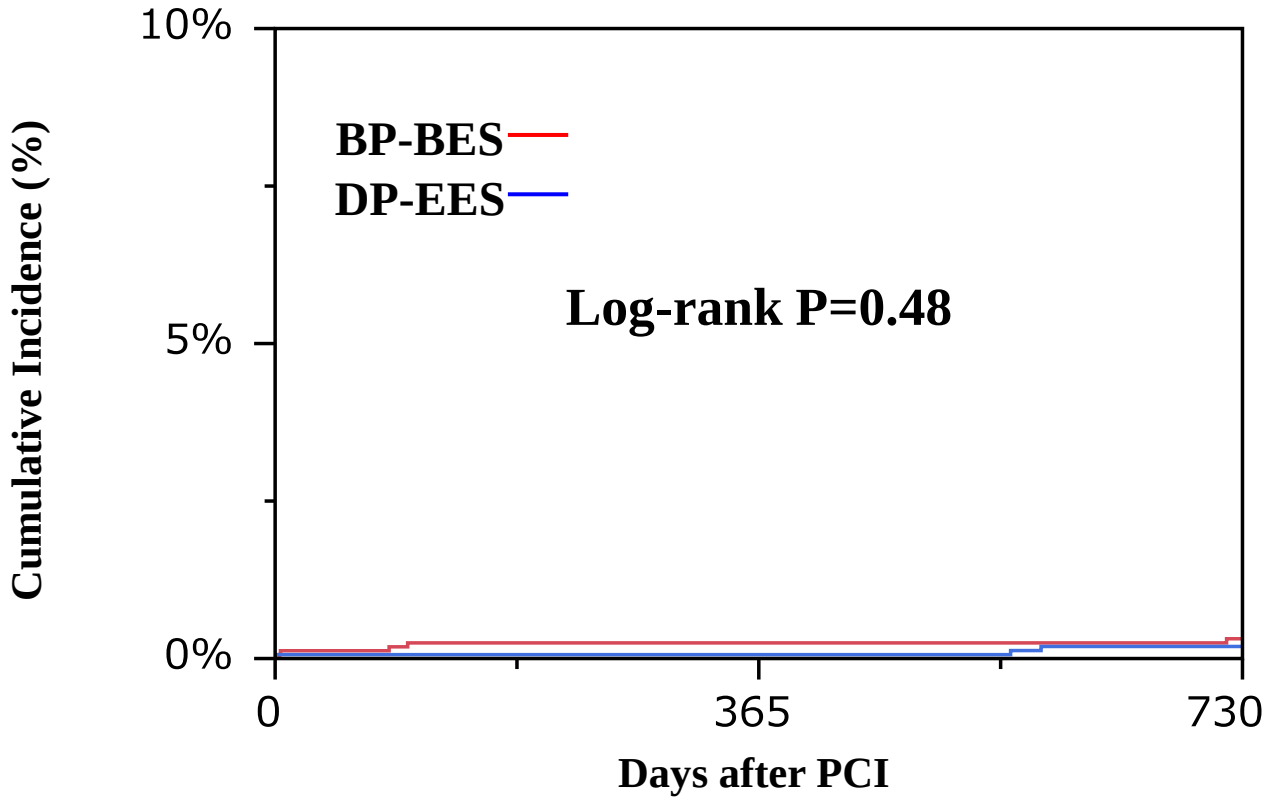
Number at Risk:

BES	3412	3324	3311	3297	3287	3274	3260	3248	3228	3207	3194	3174	3161	1706
EES	2530	2463	2447	2442	2433	2425	2415	2407	2391	2362	2347	2335	2326	870

Log-rank p=0.8798

Definite Stent Thrombosis

NEXT



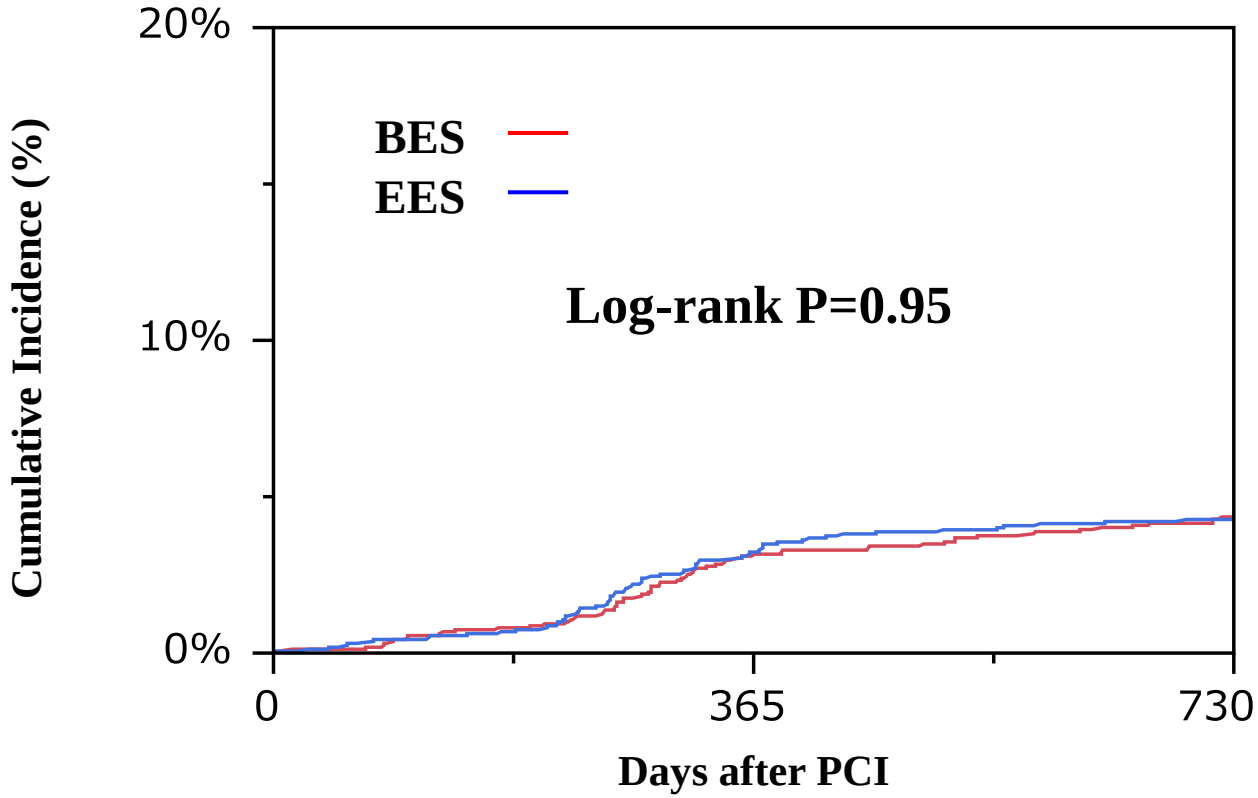
BP-BES:0.31%

DP-EES:0.19%

Interval	0 day	30 days	365 days	730 days
BP-BES group				
N of patients with at least 1 event		2	4	5
N of patients at risk	1617	1612	1569	1508
Cumulative Incidence		0.12%	0.25%	0.31%
DP-EES group				
N of patients with at least 1 event		1	1	3
N of patients at risk	1618	1616	1573	1512
Cumulative Incidence		0.06%	0.06%	0.19%

Clinically-Driven TLR

NEXT



BP-BES:4.4%

DP-EES:4.3%

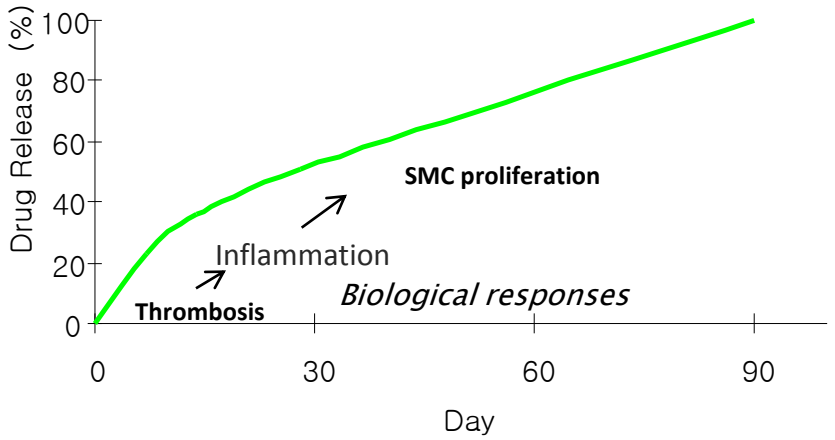
Interval	0 day	30 days	365 days	730 days
BES group				
N of patients with at least 1 event		2	50	68
N of patients at risk	1617	1612	1506	1417
Cumulative Incidence		0.1%	3.2%	4.4%
EES group				
N of patients with at least 1 event		2	51	67
N of patients at risk	1618	1614	1503	1424
Cumulative Incidence		0.1%	3.2%	4.3%

The new generation of bioabsorbable polymer eluting stents

ULTIMASTER design – POLYMER

ULTIMASTER - Poly(DLLA-CL)

- Full bioresorption in 3-4 months
- Improved elasticity by adding caprolactone (CL)
- Providing optimal drug release kinetics



Animal data with stent explantation at any time point: N=36

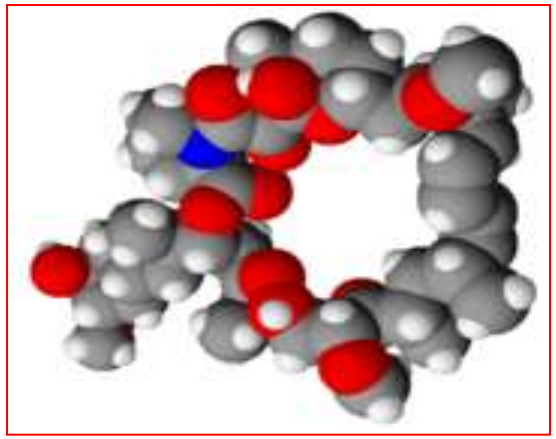
ULTIMASTER design – COATING

- ✓ ***Abluminal coating – provides possibility for decreasing drug and polymer dose, and targets drug release to vessel wall, minimizing release of drug in systemic circulation***

ULTIMASTER – abluminal coating

ULTIMASTER design - DRUG

ULTIMASTER – DRUG SIROLIMUS
Limus drug
Long experience in DES
High efficacy
Wide therapeutic window



3.9 µg / mm stent length

(½ of drug dose of Cypher)

(¼ of drug dose of Nobori)

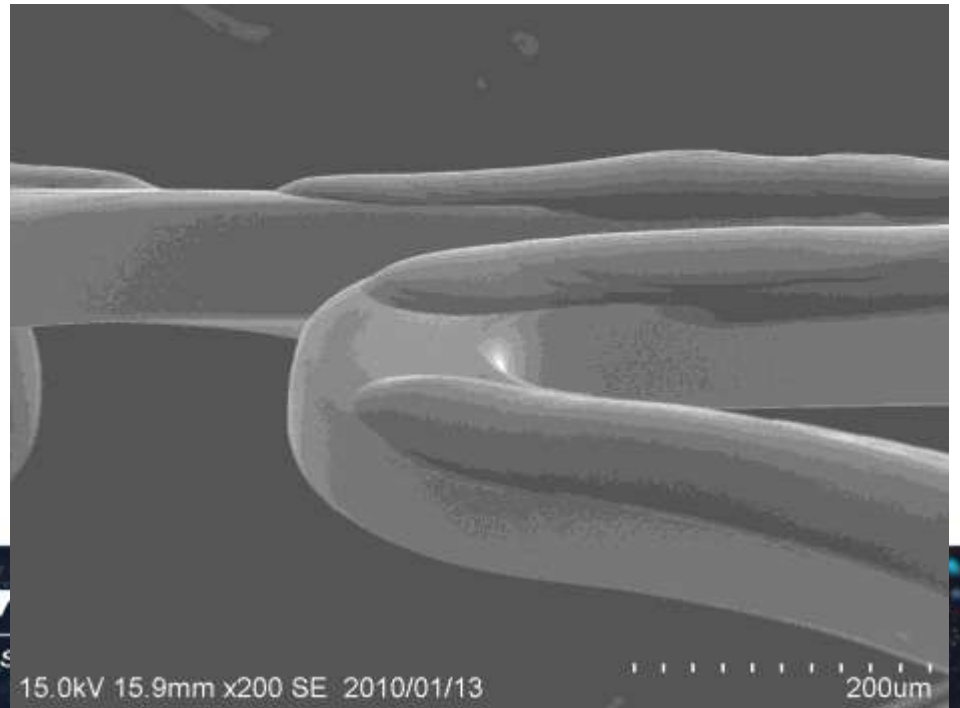
ULTIMASTER design – GRADIENT COATING

✓ *Stent expansion related to the risk of coating cracks and delamination*

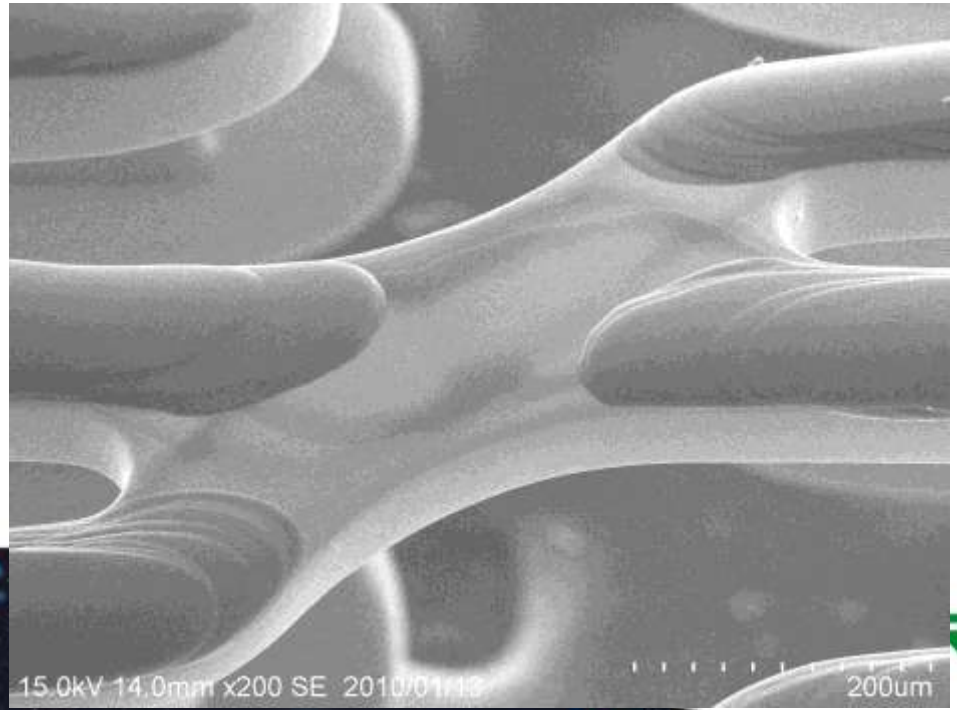
ULTIMASTER

argon plasma treatment of the platform before coating to ensure smoothness of the surface

“gradient coating” technique



highest pressure links - without coating



Ultimaster Clinical program – CENTURY
Primary endpoint

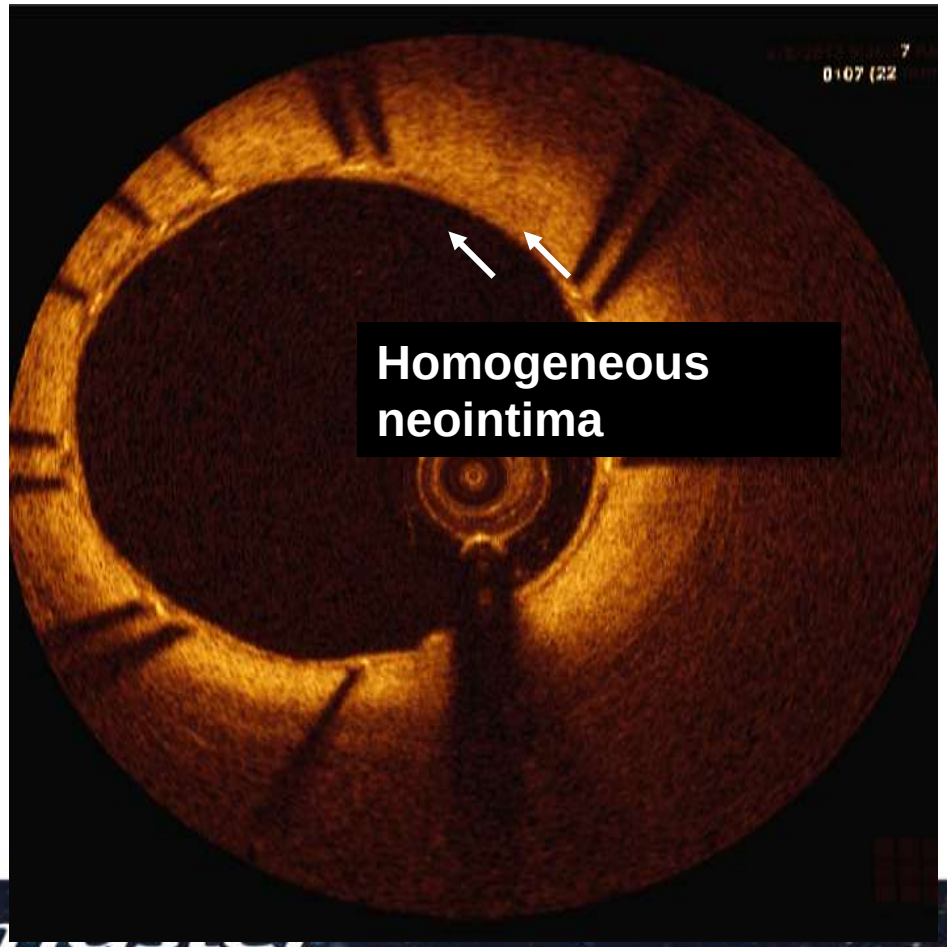
Based upon estimated Kaname Late Loss
0.90±0.50 mm
0.40 mm improvement considered as clinically significant
Late loss of 0.50 mm (0.90-0.40 mm) is considered upper limit for CENTURY study

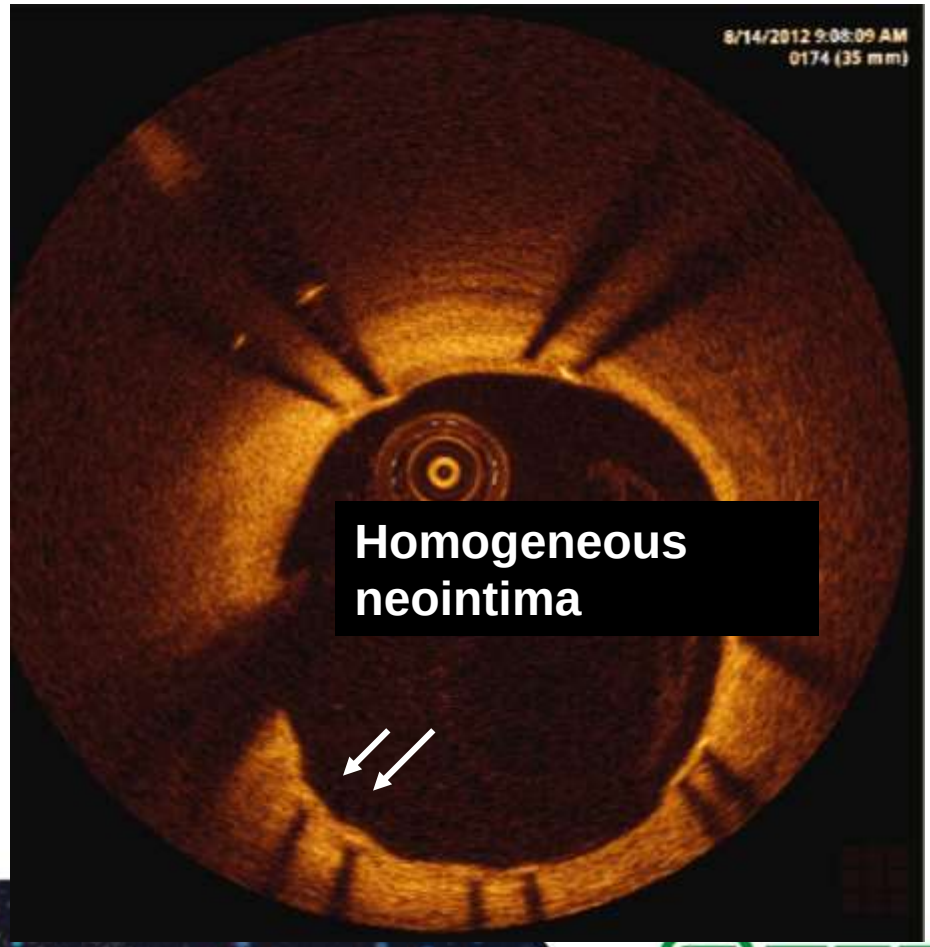
Late Loss result
Kaname : 0.75±0.43 mm
Ultimaster : 0.04±0.35 mm

Result:
Ultimaster = SUPERIOR p<0.0001

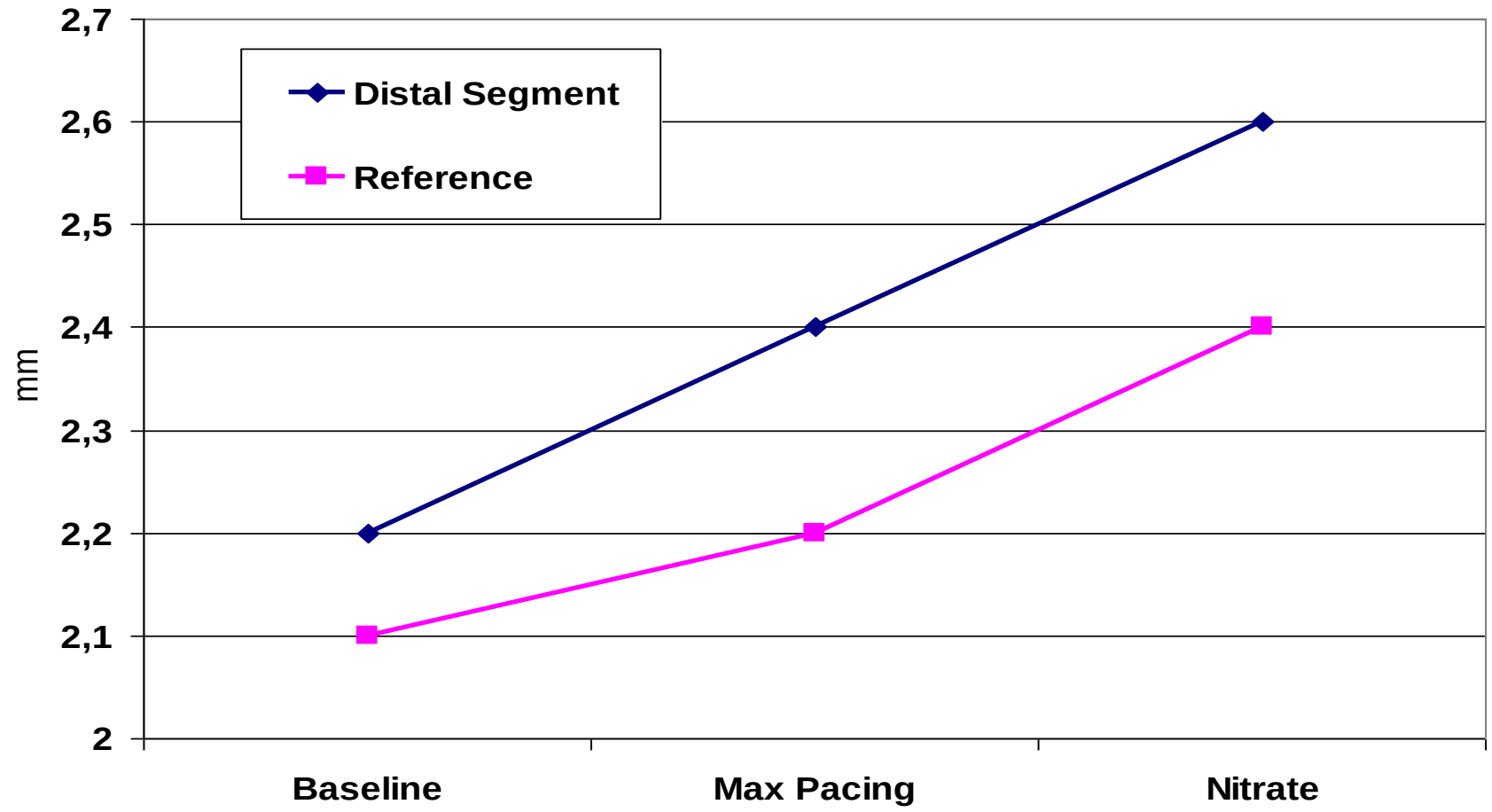
Ultimaster Clinical program – CENTURY
OCT assessment

✓ **96.2±5.4** % of covered stent struts at 6 months

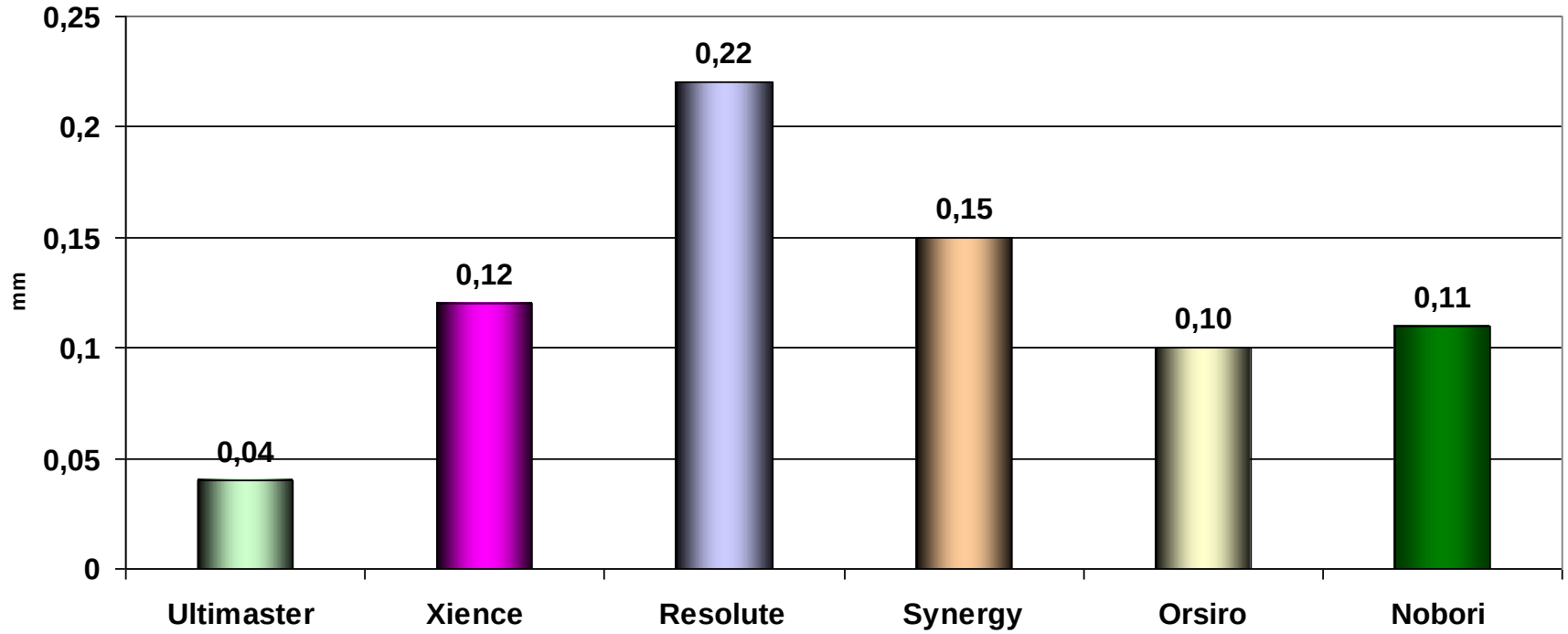




Endothelial function fully preserved at 6 months



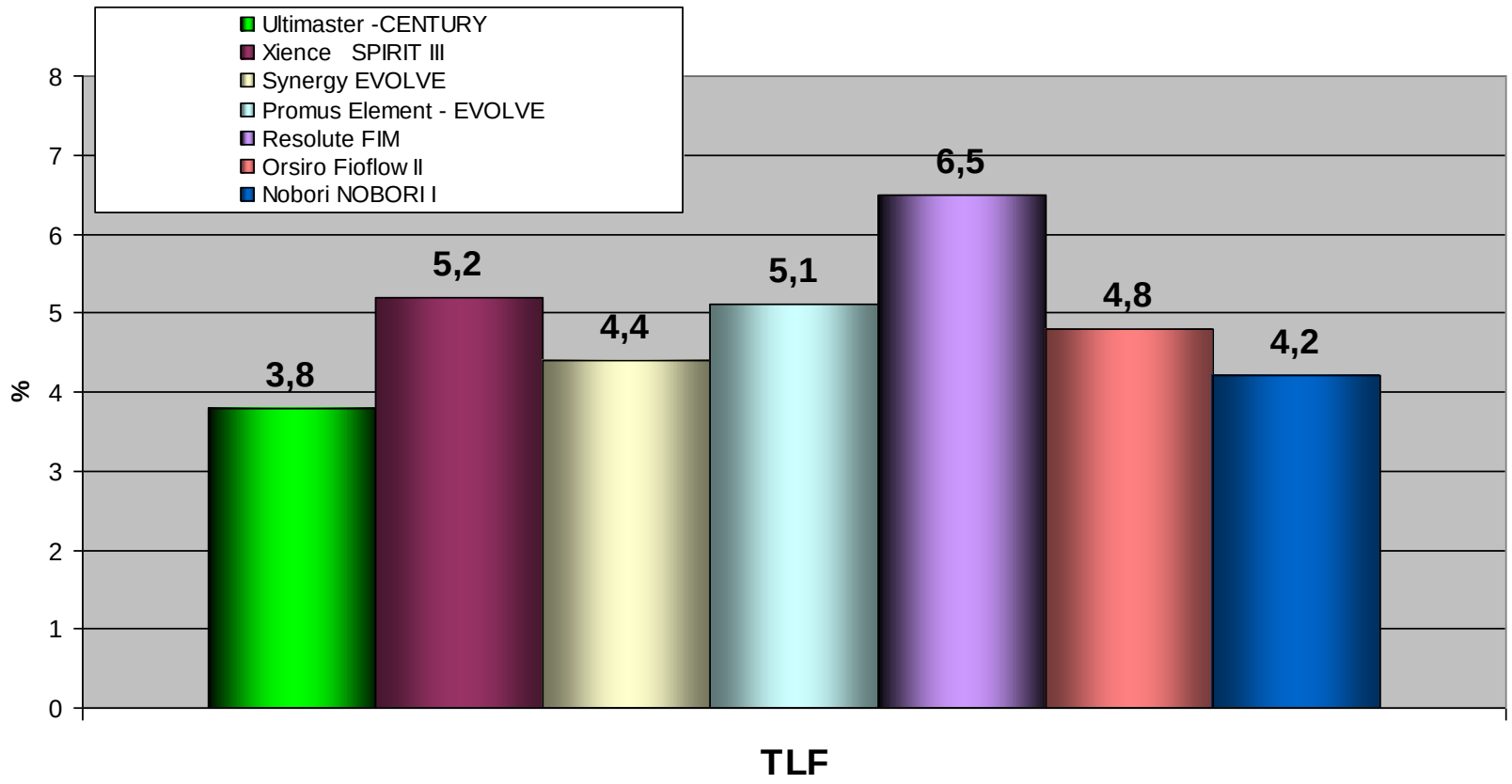
Late Loss



Ultimaster, Xience and Synergy= 6m Resolute, Orsiro and Nobori = 9m

Barbato E. PCR2013; Serruys P et al.EuroInterv.2005; Meredith I et al. JACC Cardiov. Interv. 2009; Meredith I et al. EuroInterv. 2013 Windecker S. PCR2013; Chevalier B et al. Circulation CV Intervention; 2012

Ultimaster vs other new generation DES
Clinical Outcomes at 1 Year



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Ultimaster Clinical Program

STUDY	DESIGN	# OF PATIENTS	STATUS
TCD-10023PK Pharmacokinetics	Single-arm	20	Completed
CENTURY	Single-arm	105	Ongoing PE reached
CENTURY II	Randomized	1123	Ongoing PCR-LBT
MASTER	Randomized	500	Ongoing
DISCOVERY1TO3	Single arm	60	Ongoing

ULTIMASTER design - PLATFORM

ULTIMASTER - platform

New CoCr platform (Kaname)

Thin-struts (80 µm)

High flexibility

Open cell design

Uniform scaffolding

Vessel conformability

Mr H.
72 y.o

Risk factors

2 Diabetes.

Clinical presentation

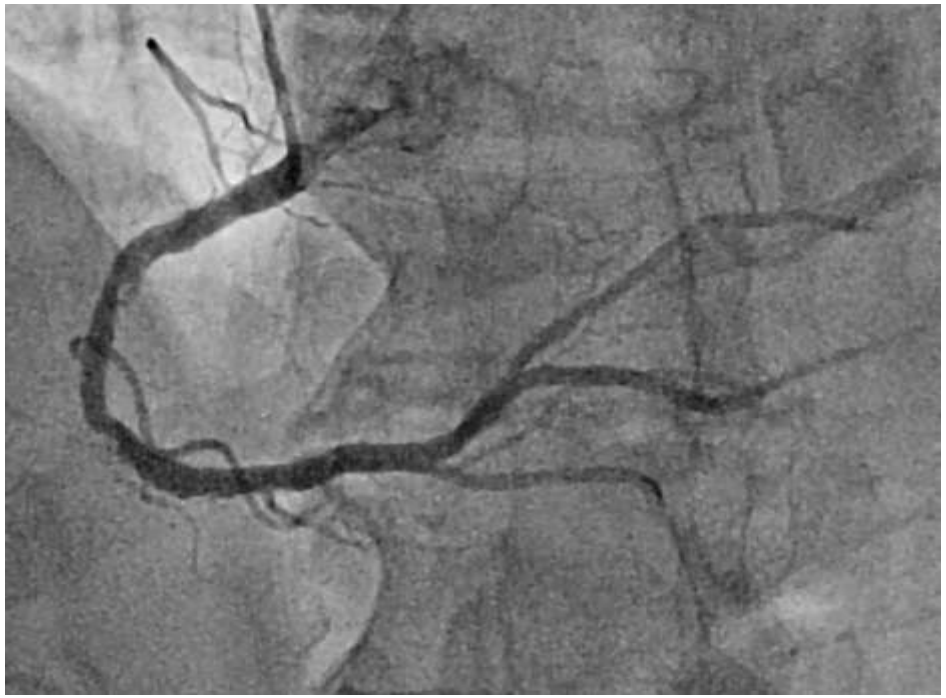
Patient referred for angina pectoris

LVEF 60%

Coronary angiography

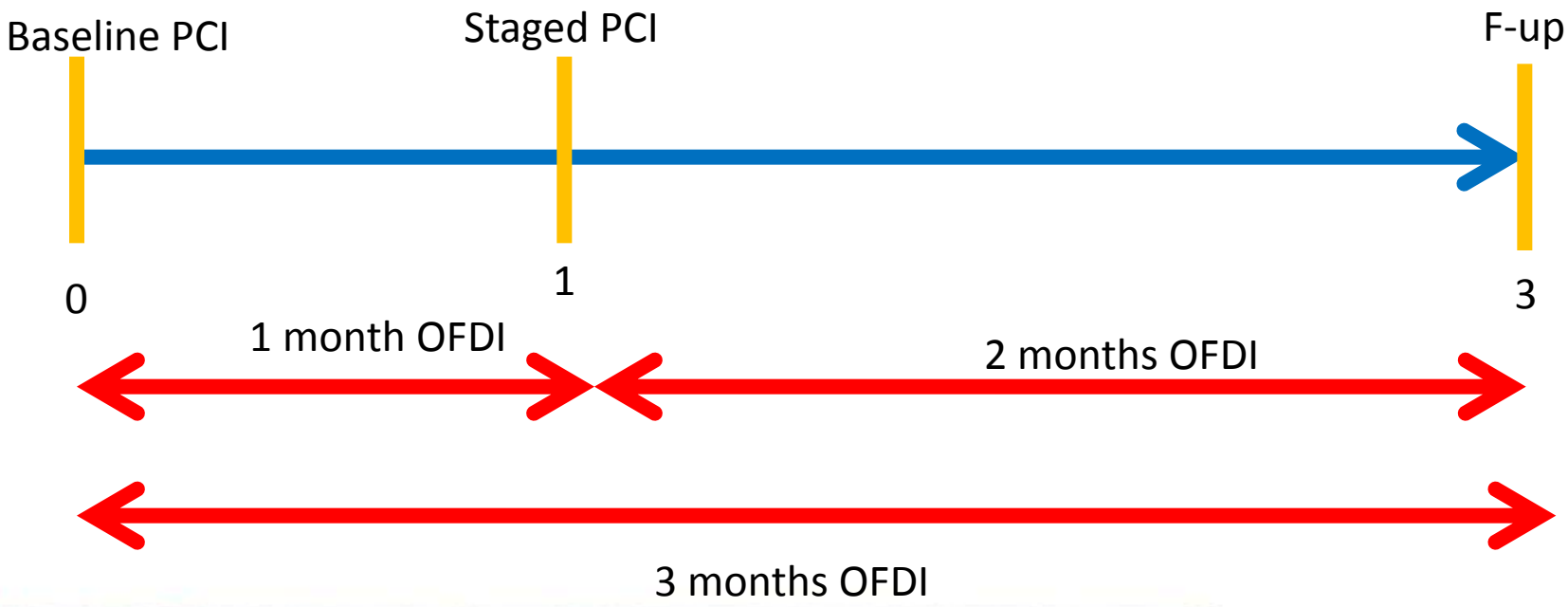
Cx sub occlusive stenosis

RCA stenosis



Patients with MVD

Staged PCI on non target vessel(s)@ 1month



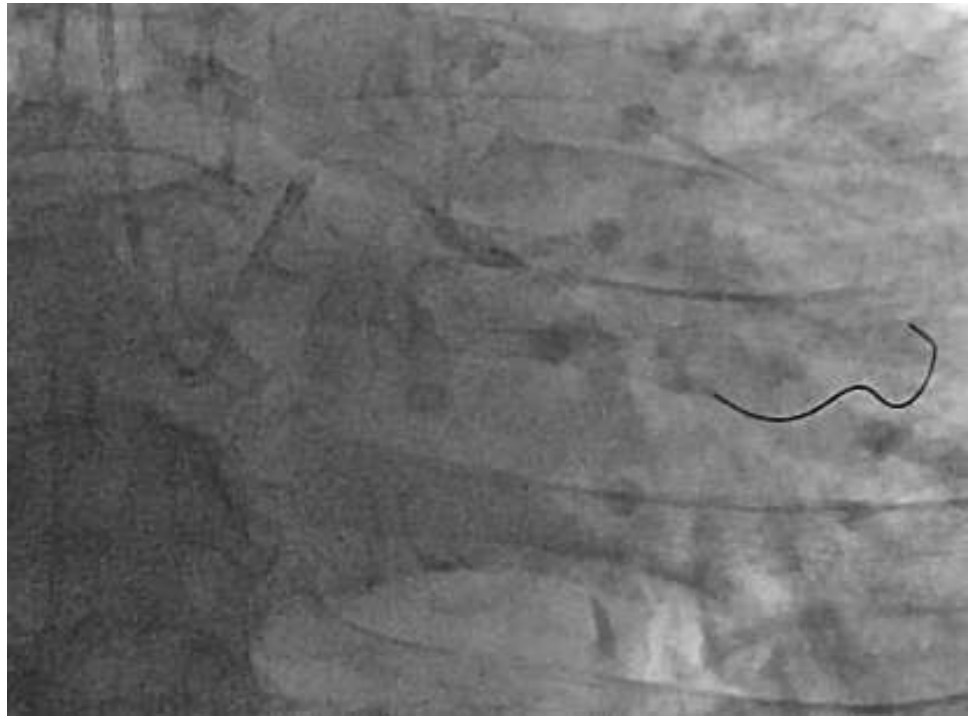
Step by step

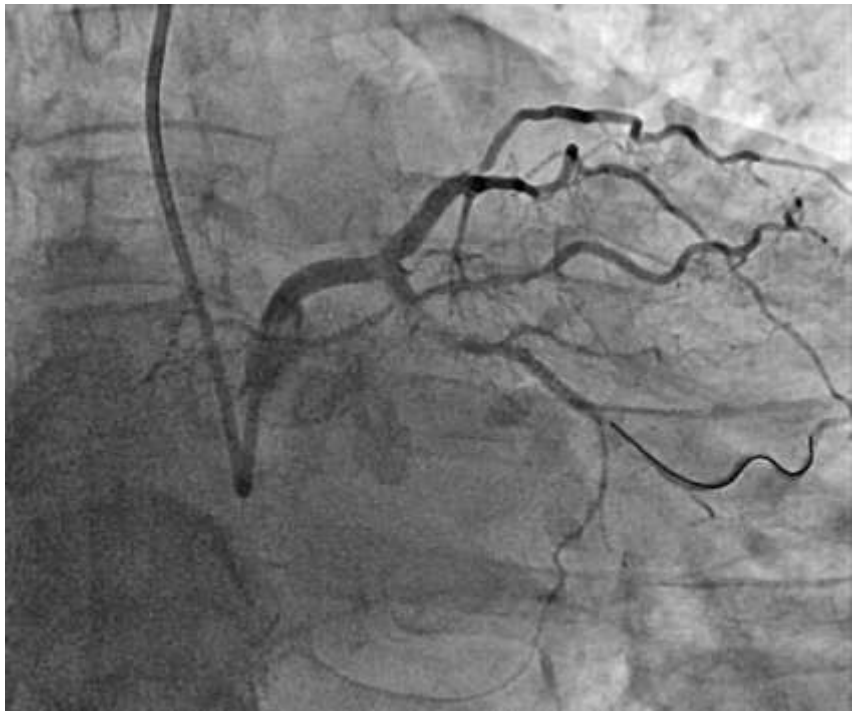
Fielder pass the lesion with Finecross

Step by step

Finecross and 1.2 balloon did not pass the lesion

- Anchoring balloon in the first Mg

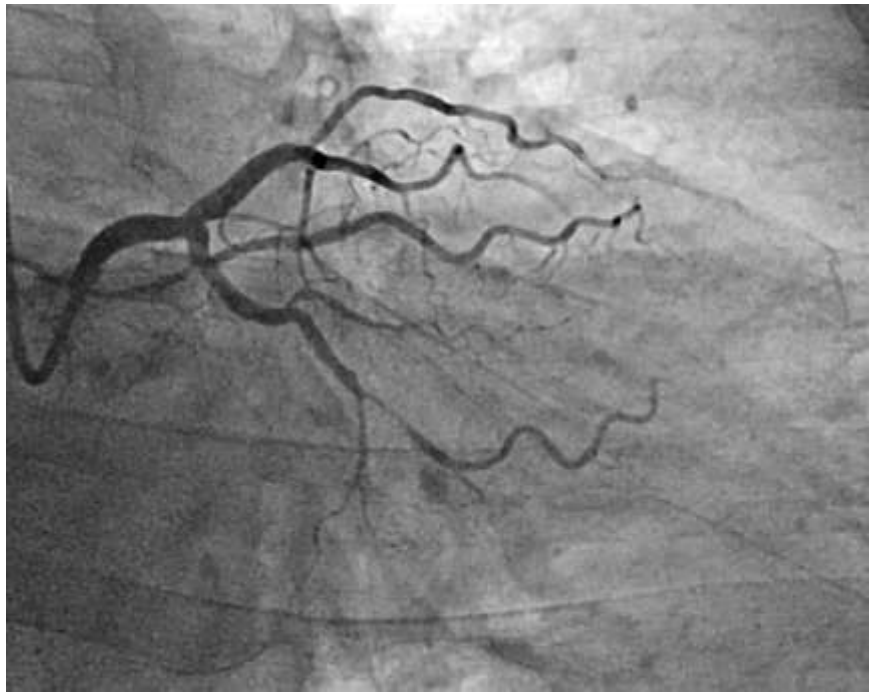


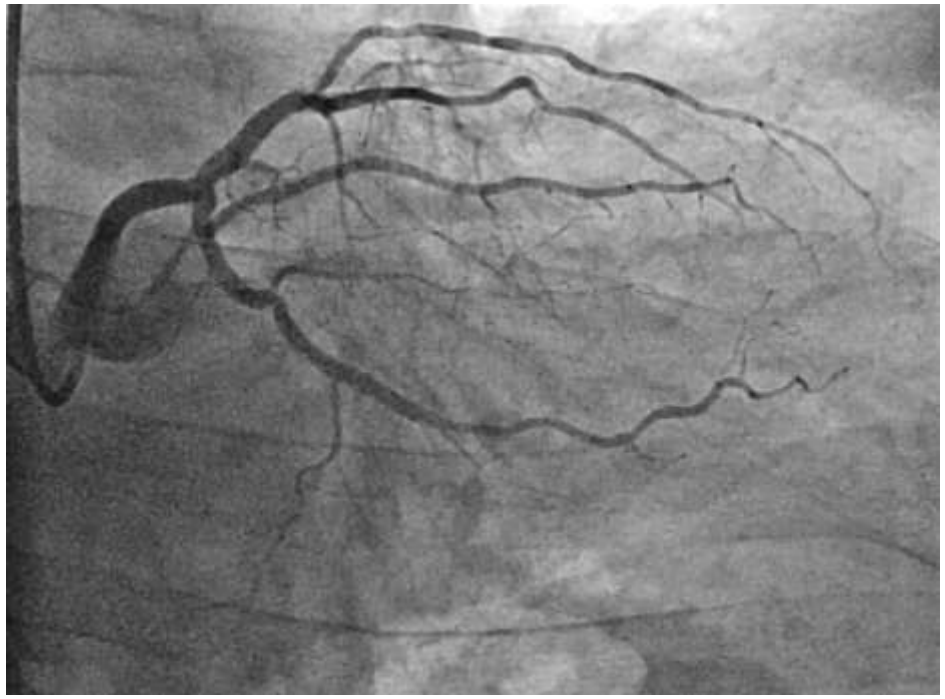


Step by step

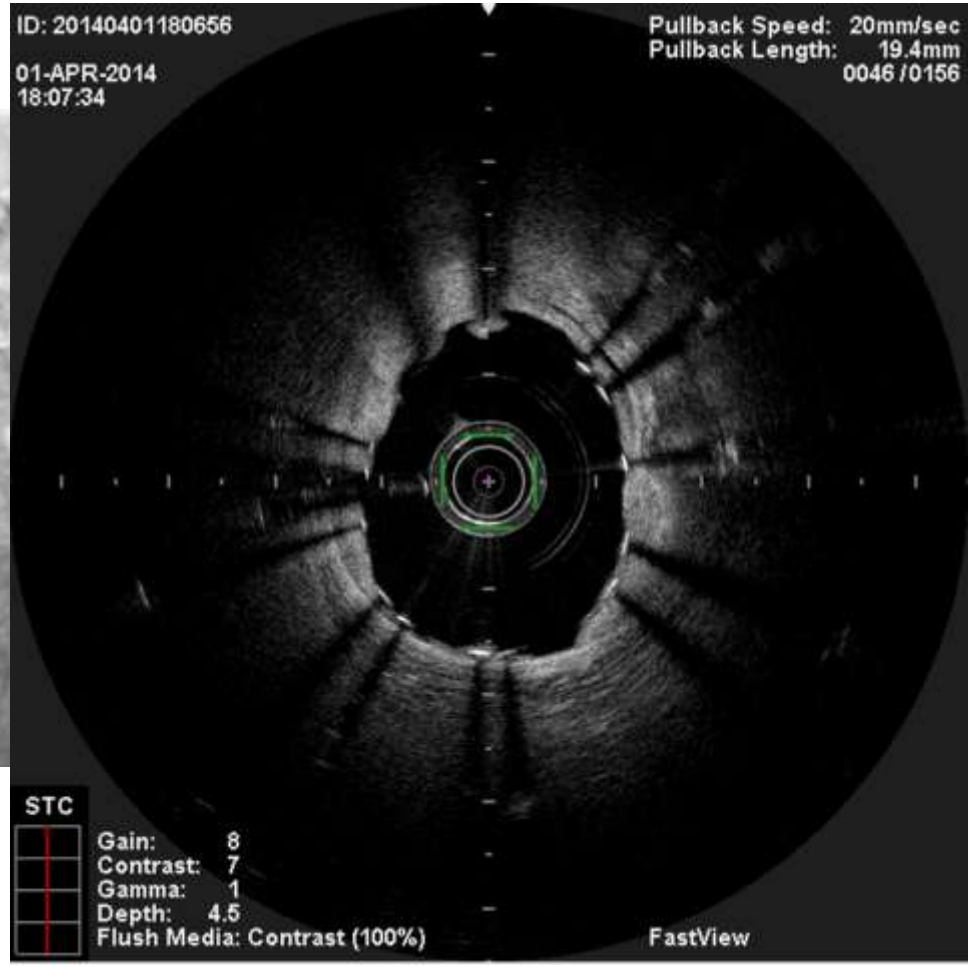
- Lesion treated by Ultimaster stent
- 2.5 X 15 mm
- After predilatation with 2.5mm balloon
- Distal lesion become visible in 2d Mg

Second lesion was crossed(through the first stent)with a balloon 2.5mm
and a second Ultimaster stent 2.5 X 15 mm

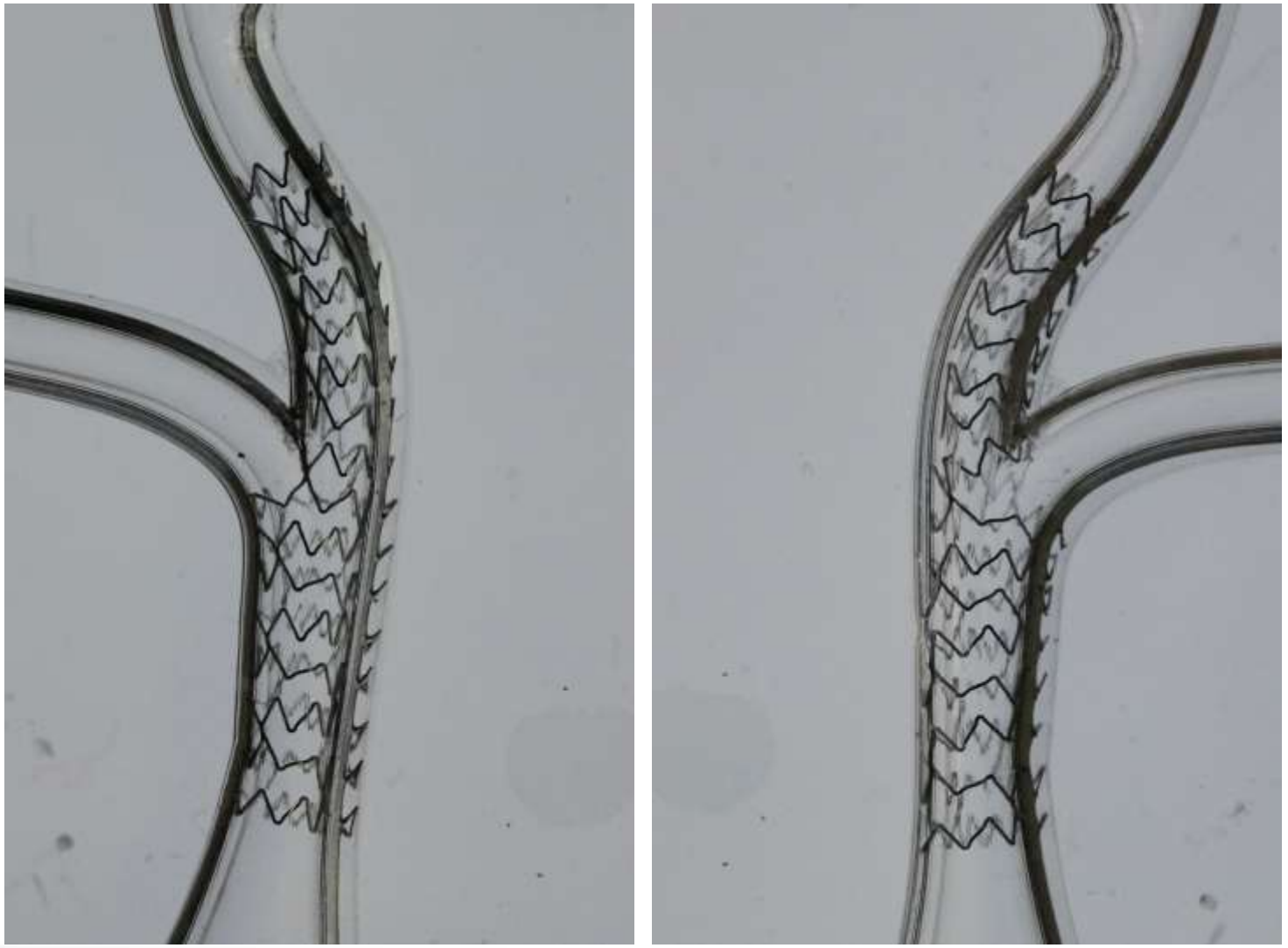




Final Cx Result (proximal stent)



Bench test on fractal bifurcation model



Conclusions

- Long term safety/efficacy profile of bioabsorbable polymer biolimus eluting stent is excellent
- Second generation bioabsorbable polymer DES « Ultimaster » combines specific features and early promising results
- Results of the pivotal CENTURY II trial will be presented at Hot Line during EuroPCR 2014