

Stent Technology: Past, Present and Future

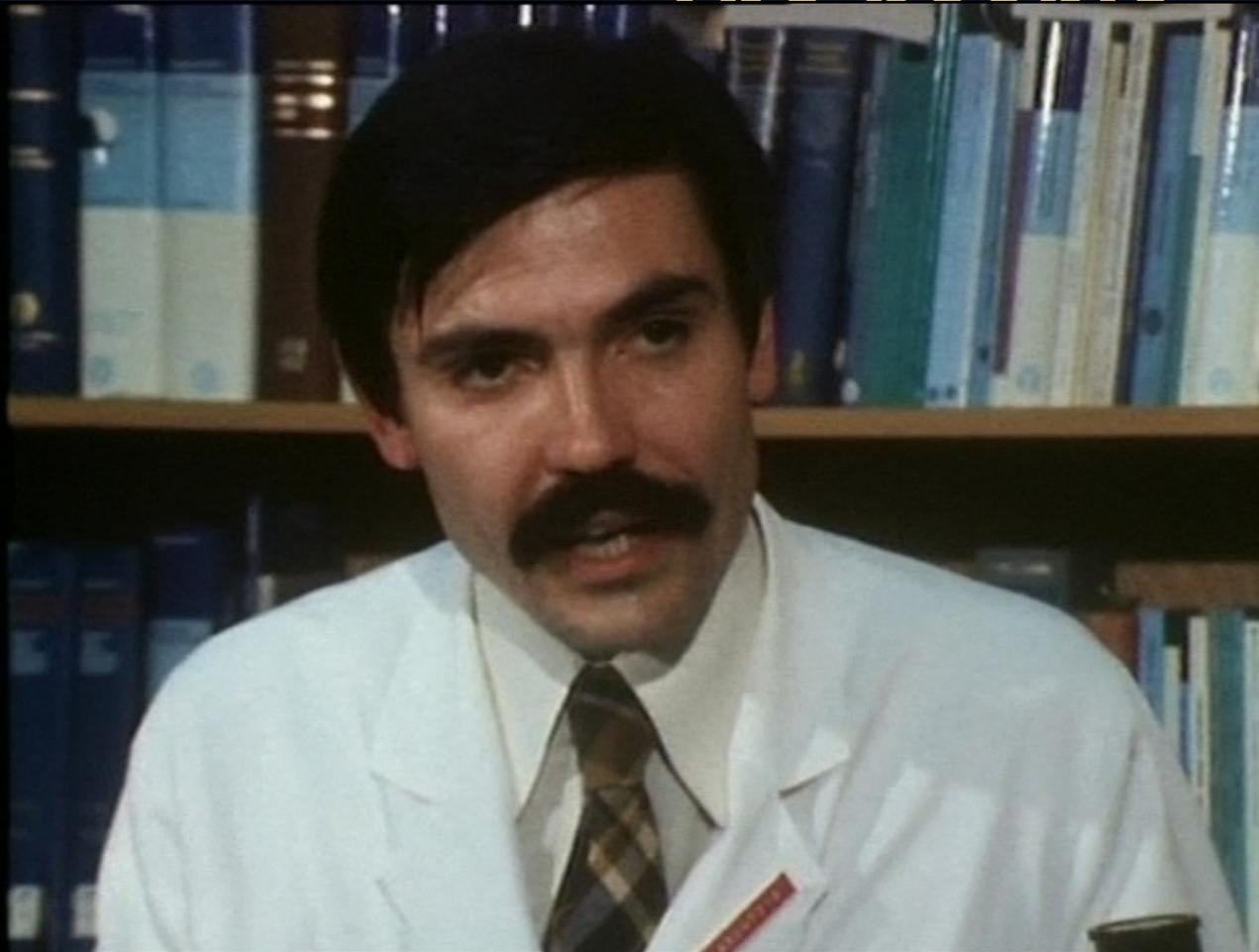
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Cardiovascular Research Foundation

Disclosures

- Principal investigator of DES pivotal trials for Abbott, Medtronic and Medinol, uncompensated
- Consultant to Reva

The First PTCA; September 16, 1977, Zurich

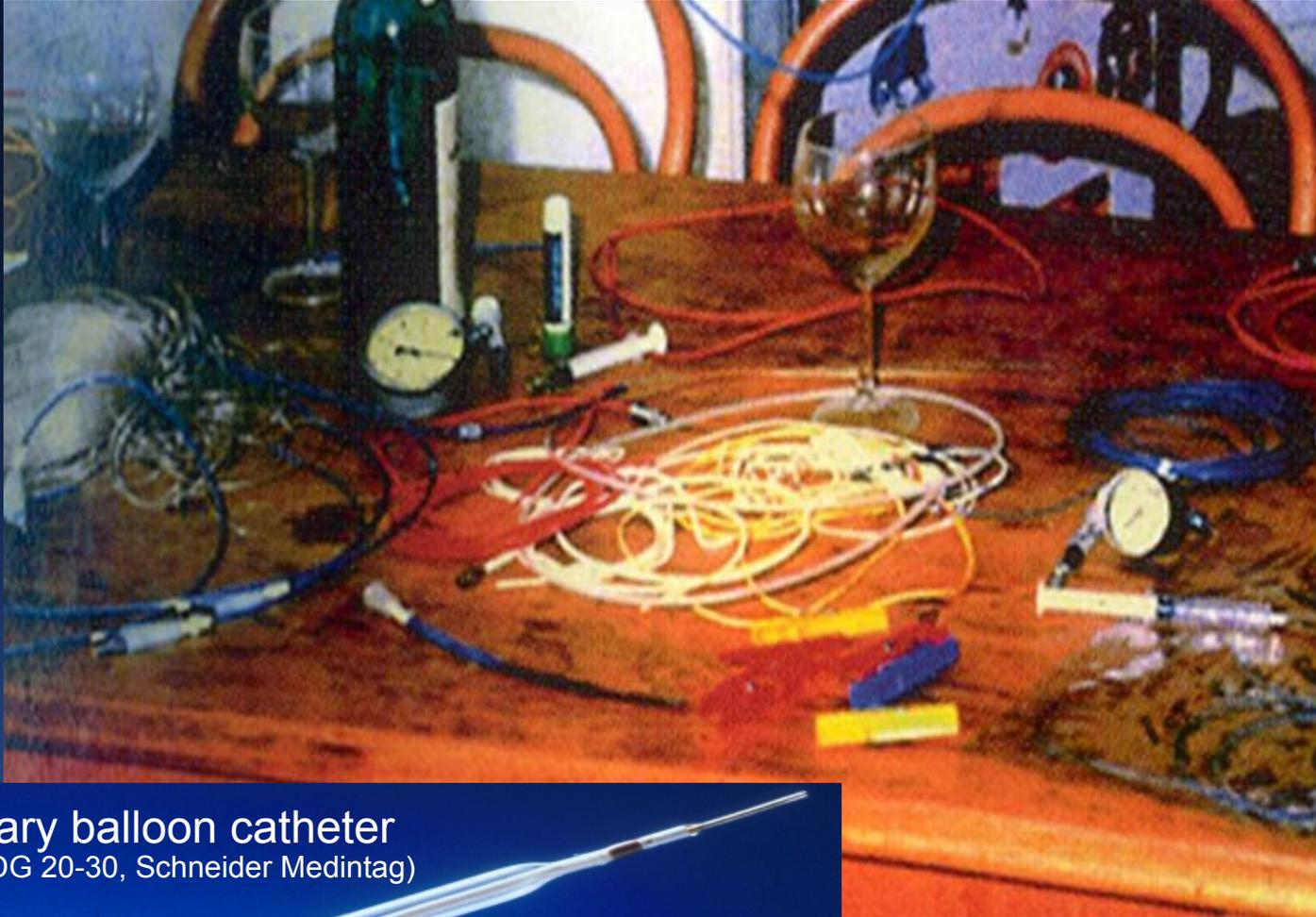


Andreas Grüentzig



Adolph Bachmann

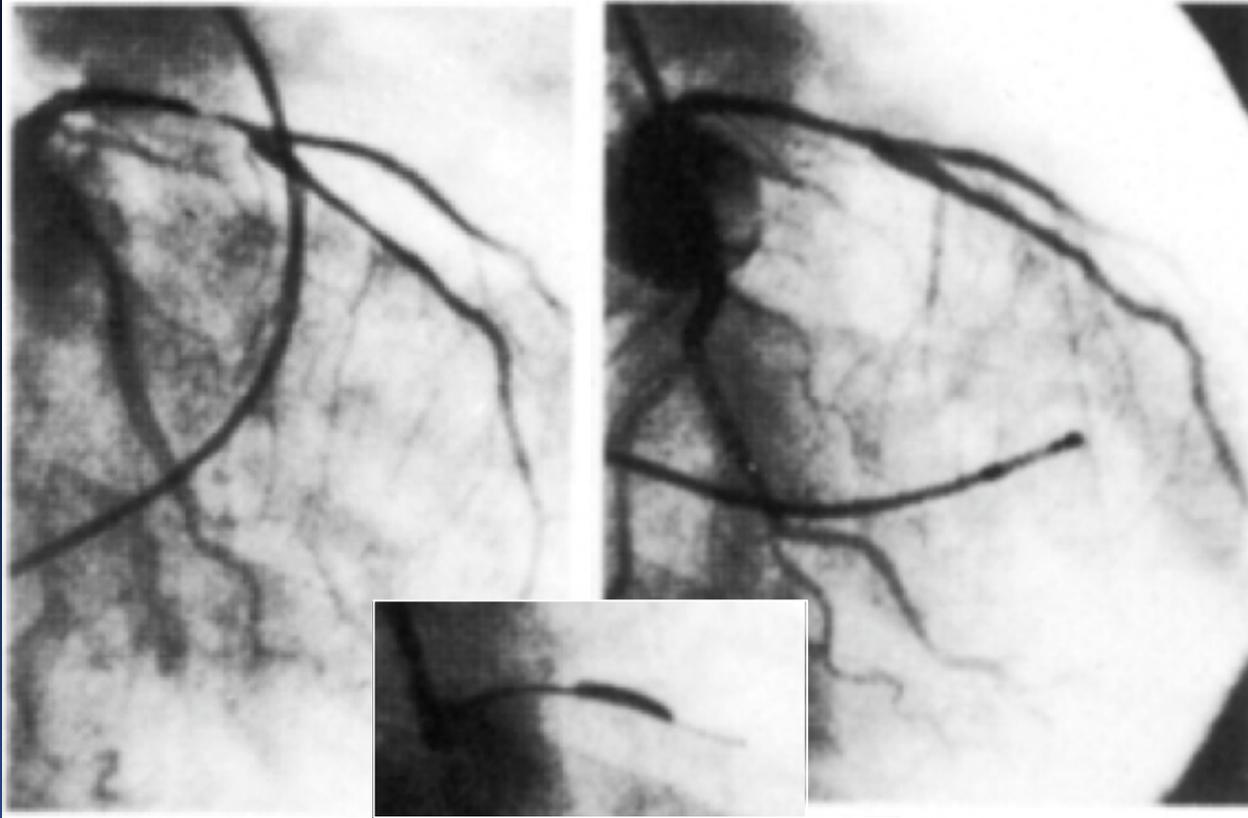
The First PTCA; September 16, 1977, Zurich



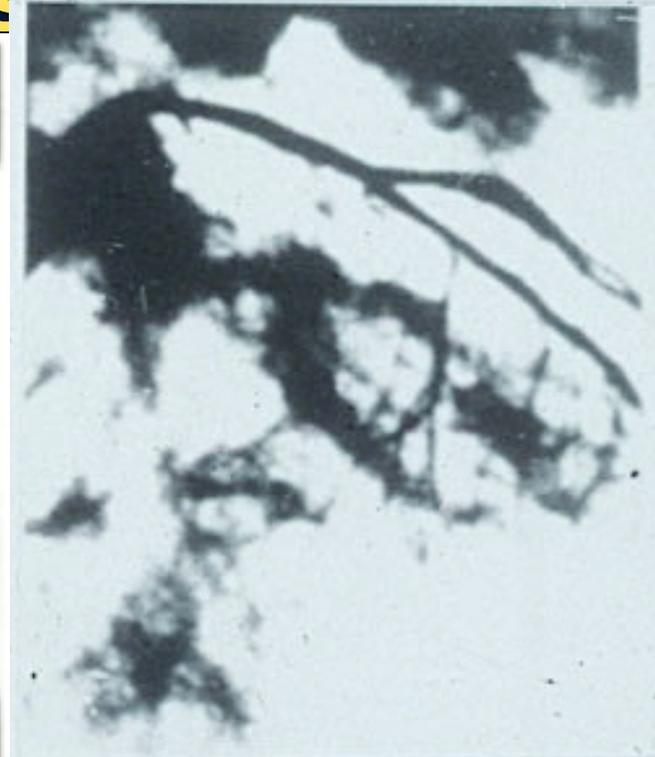
First coronary balloon catheter
(Grüntzig Dilaca DG 20-30, Schneider Medintag)

The First PTCA; September 16, 1977, Zurich

Acute and Late Results

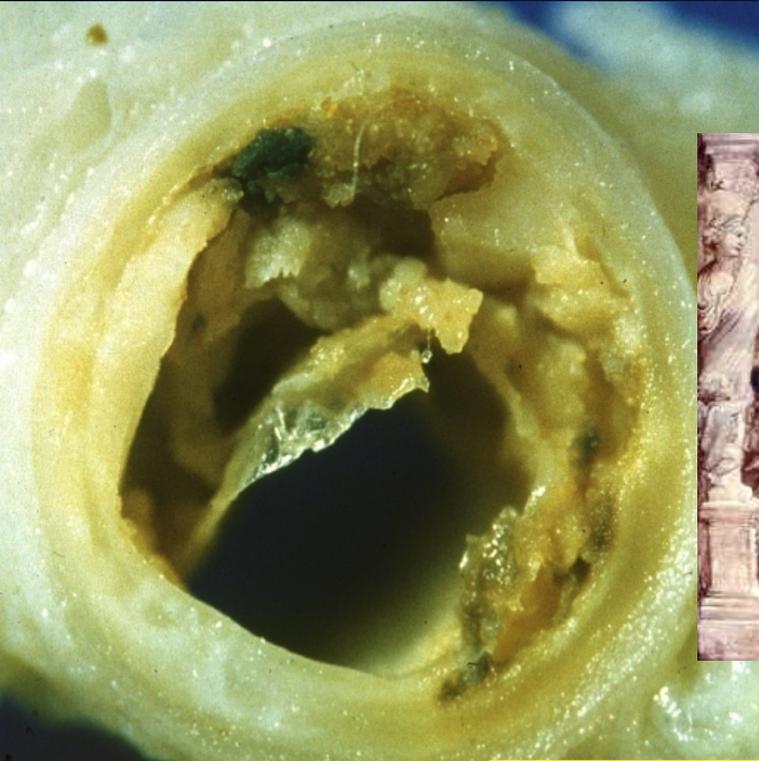


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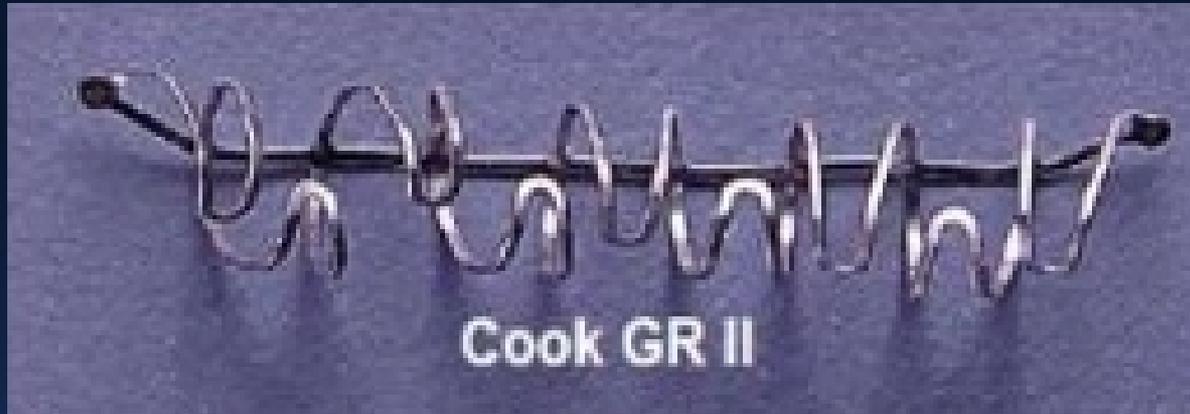
9 - 16 - 87

Acute Closure was the Achilles' Heel of PTCA!



Acute closure after PTCA
5-10%

To Treat and Prevent Acute Closure, Bare Metal Stents were Developed



Restenosis was the Achilles' Heel of Bare Metal Stents!

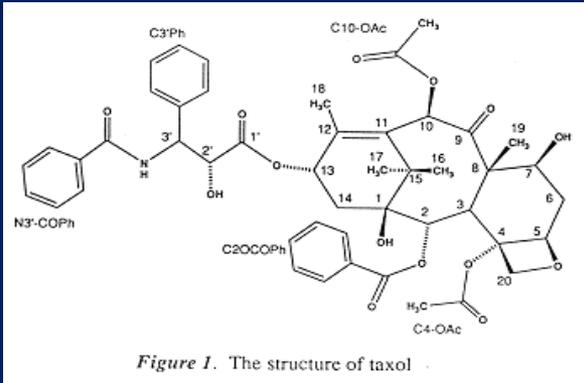


Restenosis after BMS
20-50%

Drug-eluting Stents: 1st Generation

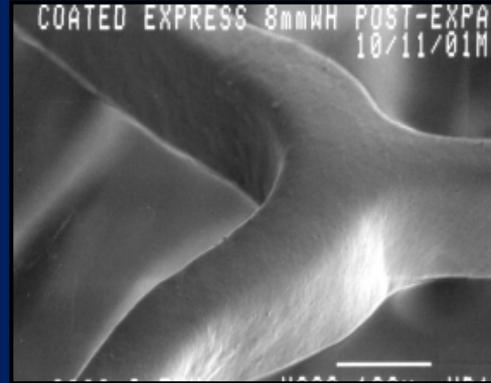
TAXUS

Drug



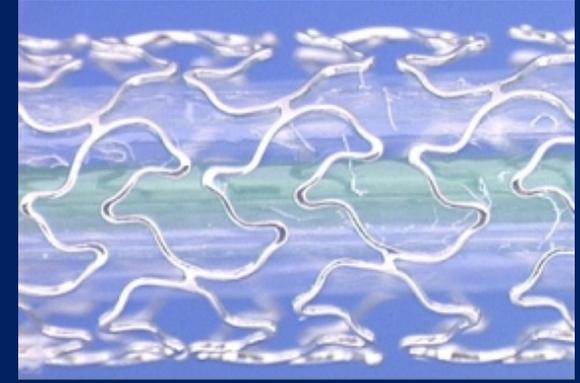
Paclitaxel

Polymer



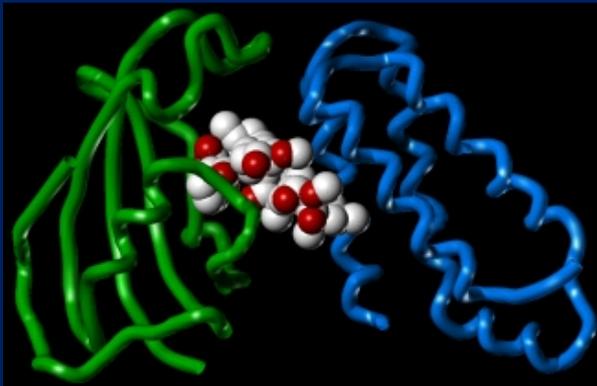
Polyolefin derivative

Stent

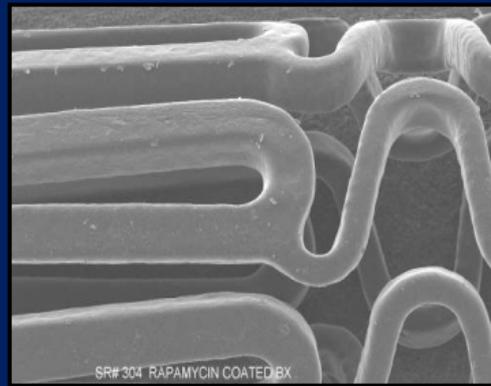


Liberté

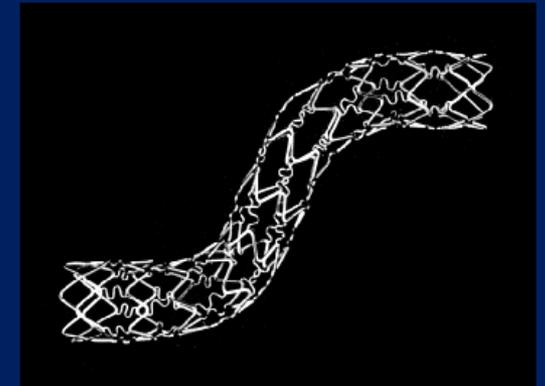
Cypher



Sirolimus

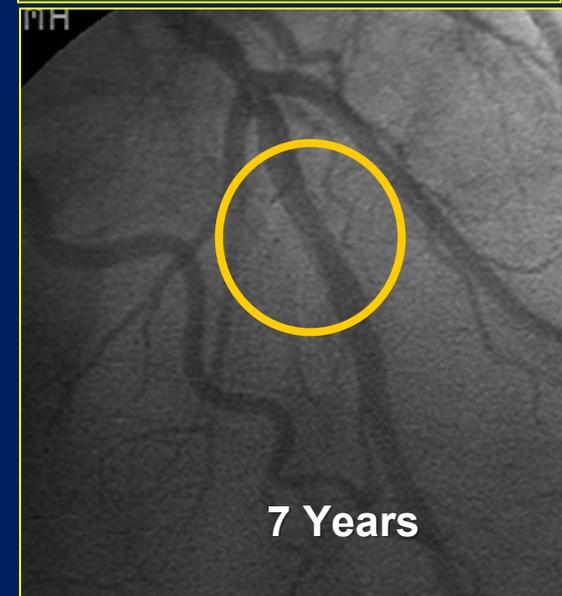
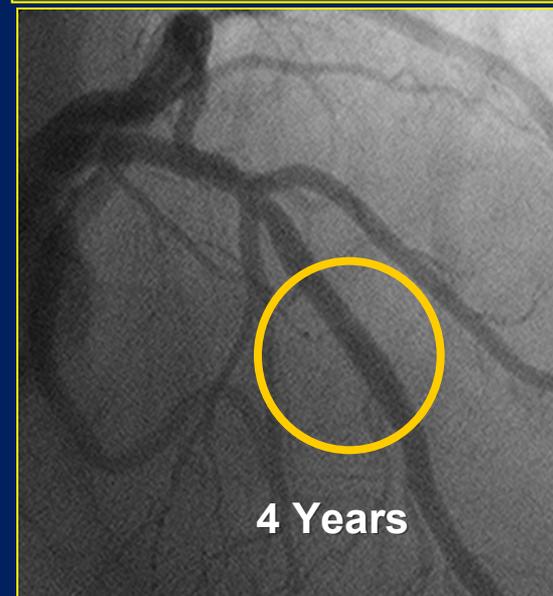
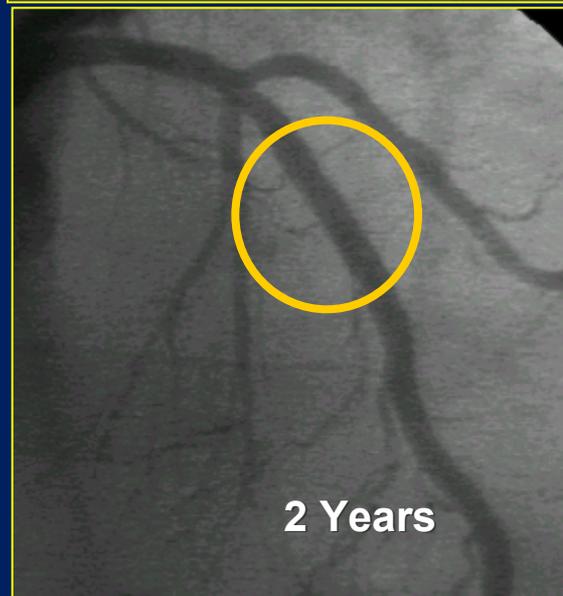
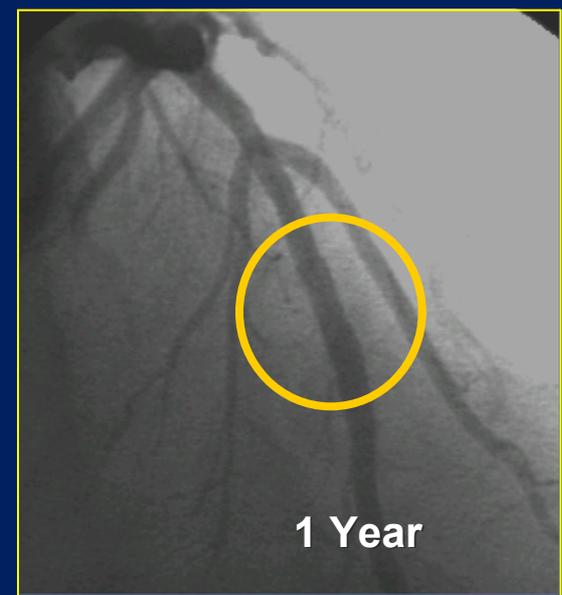
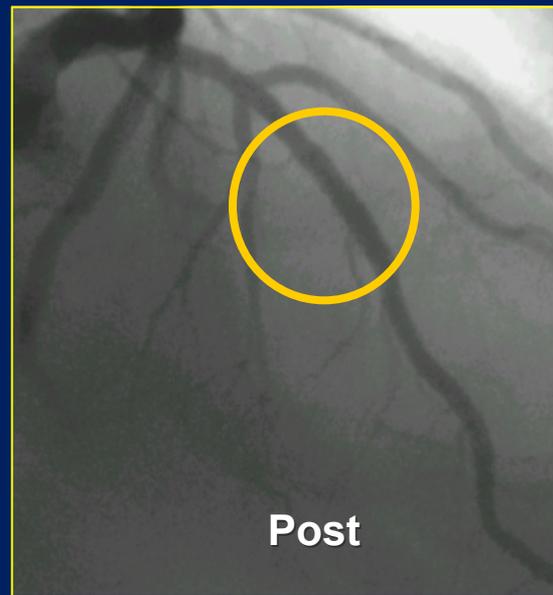
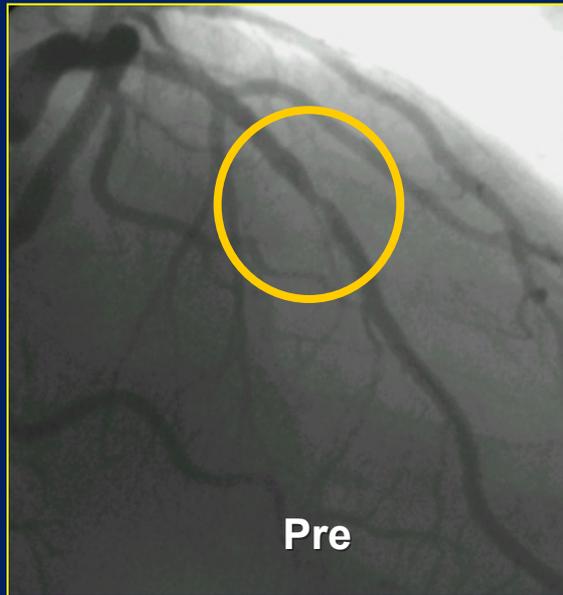


PEVA + PBMA blend



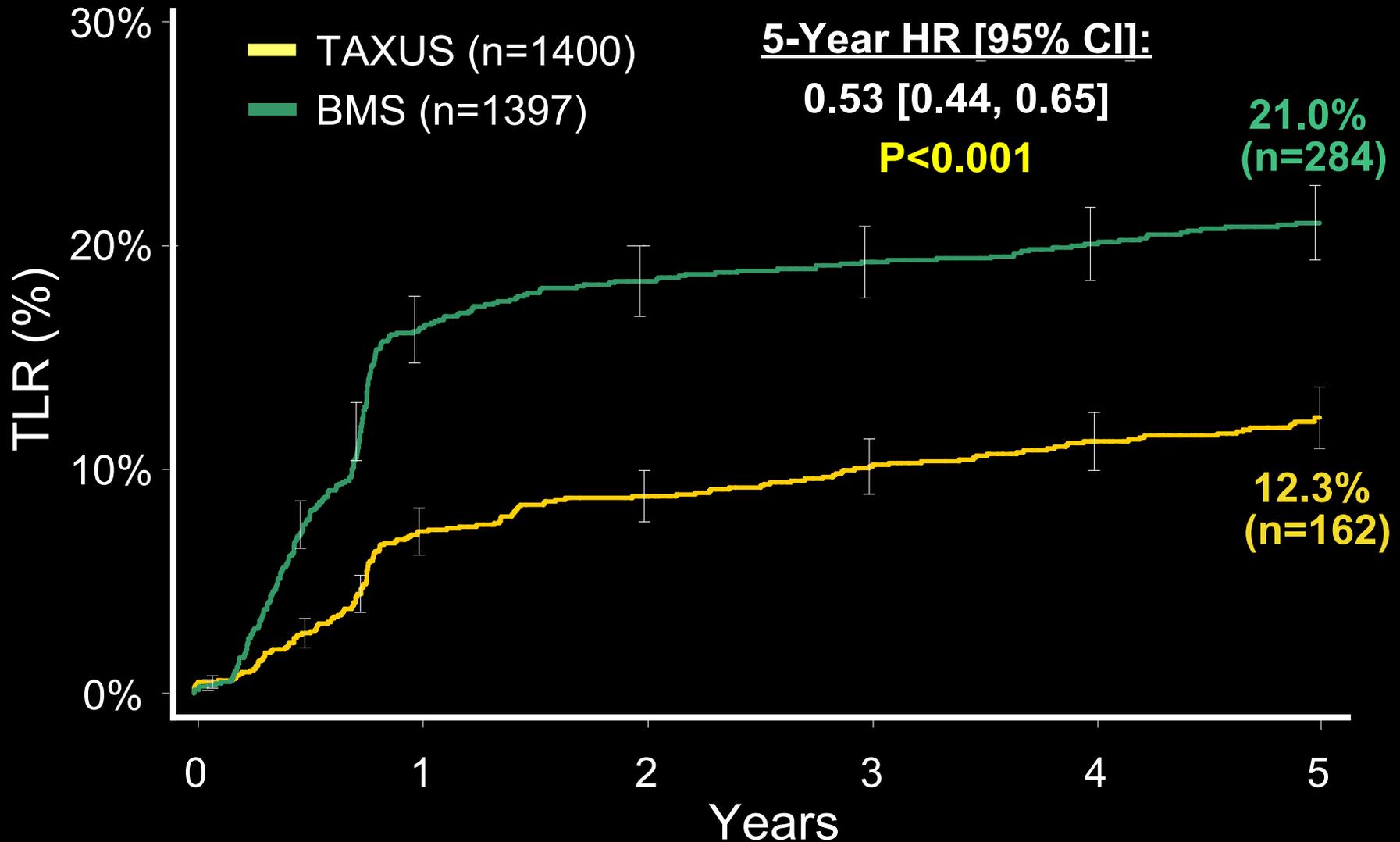
BX Velocity

Sirolimus-eluting stent: 7 year F/U

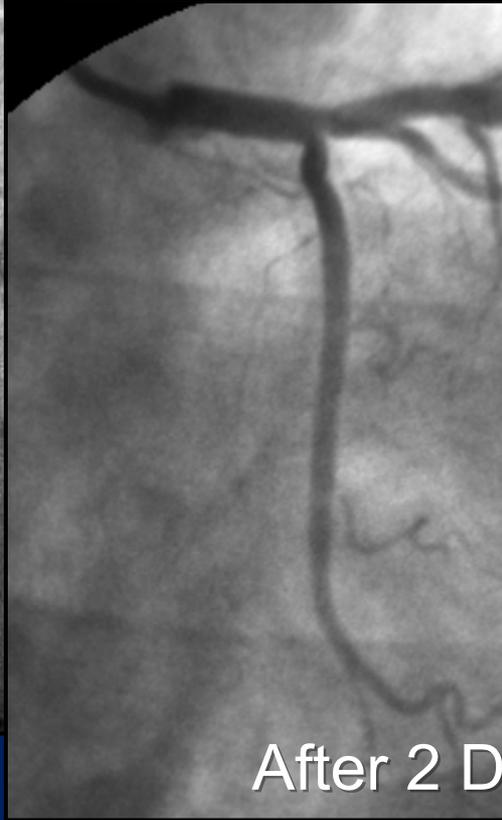




Target Lesion Revascularization at 5 Years TAXUS I, II-SR, IV & V

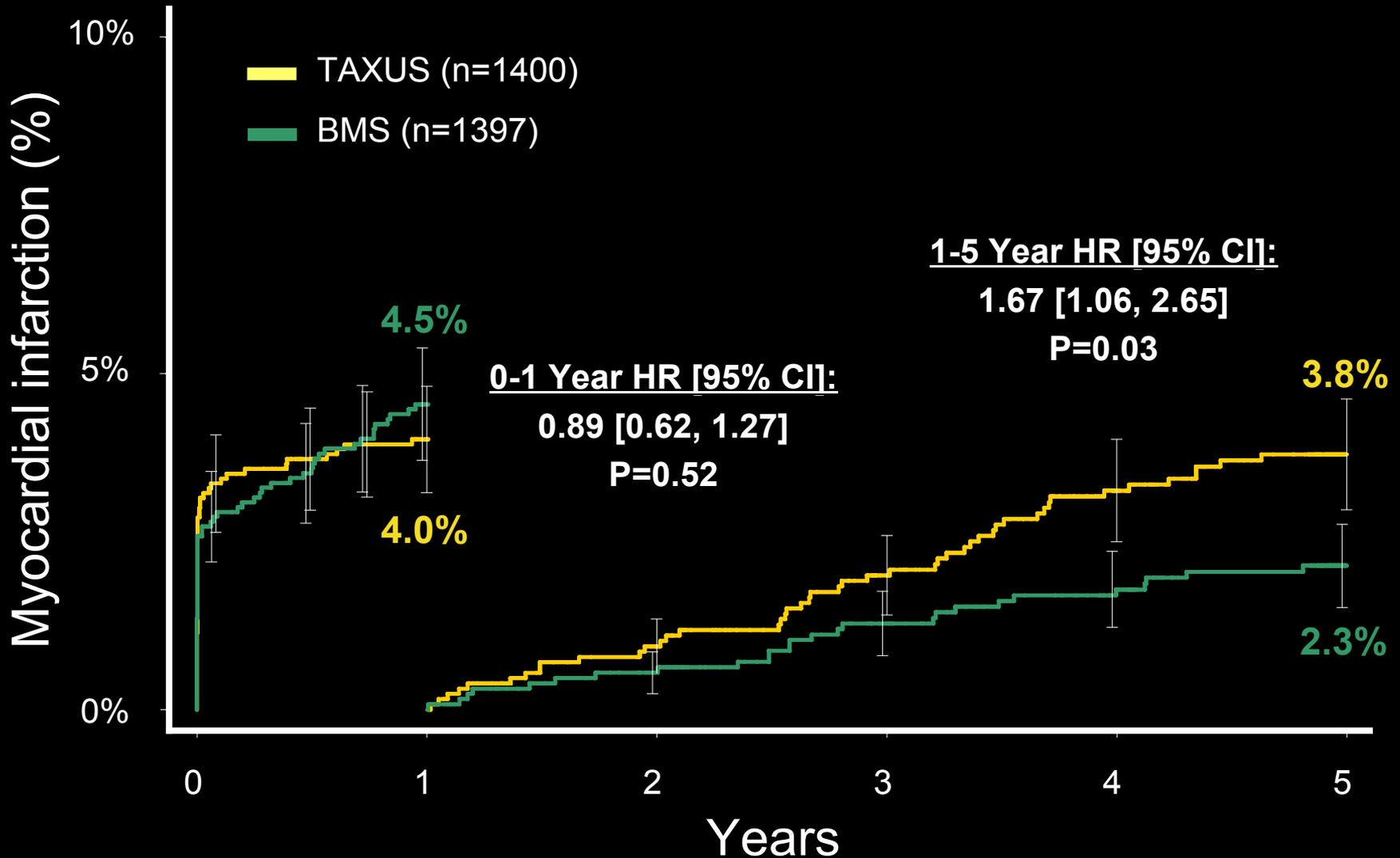


Very Late (>1 year) Drug-eluting Stent Thrombosis



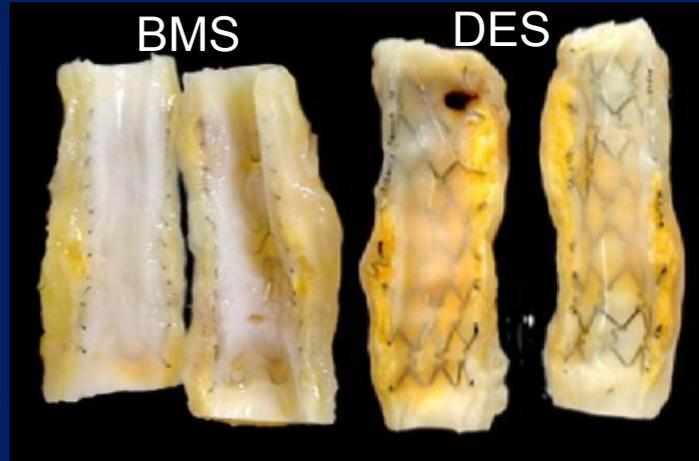
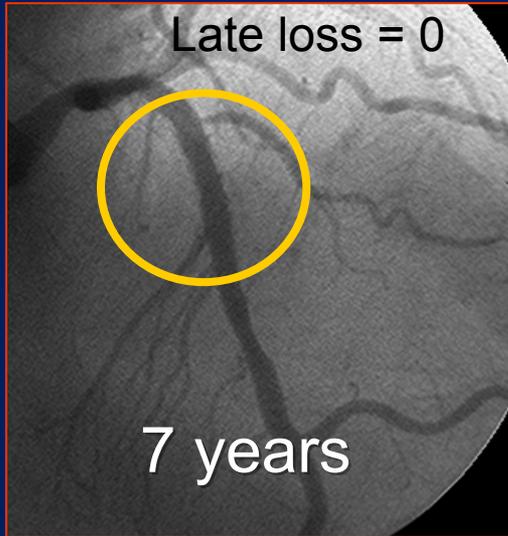


Myocardial Infarction: Landmark Analysis TAXUS I, II-SR, IV & V (n=2,797)



1st Gen Drug-Eluting Stents

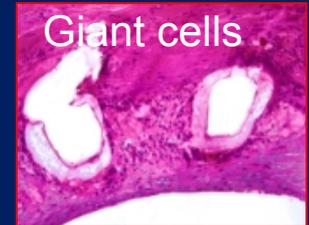
The good, the bad, and the ugly!



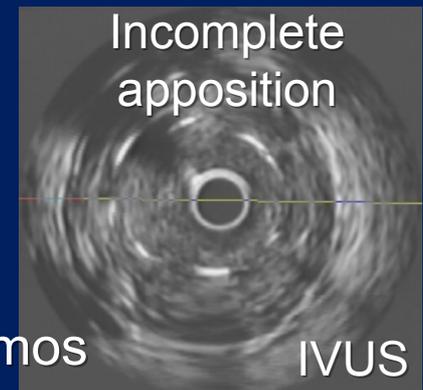
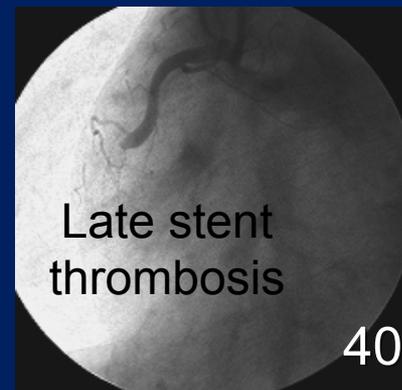
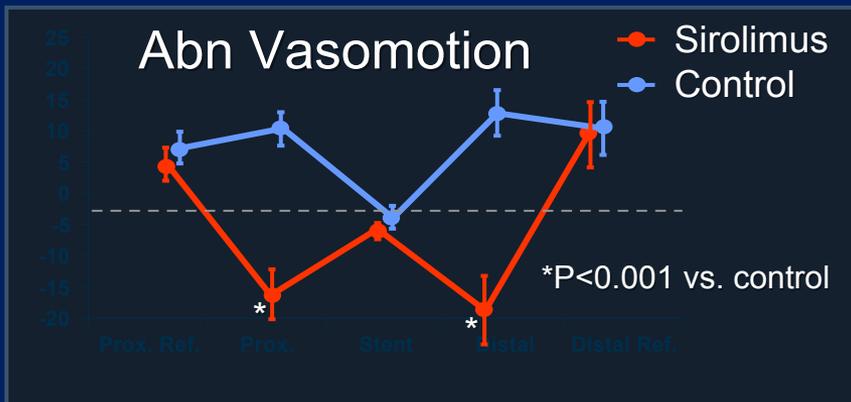
Delayed Healing!



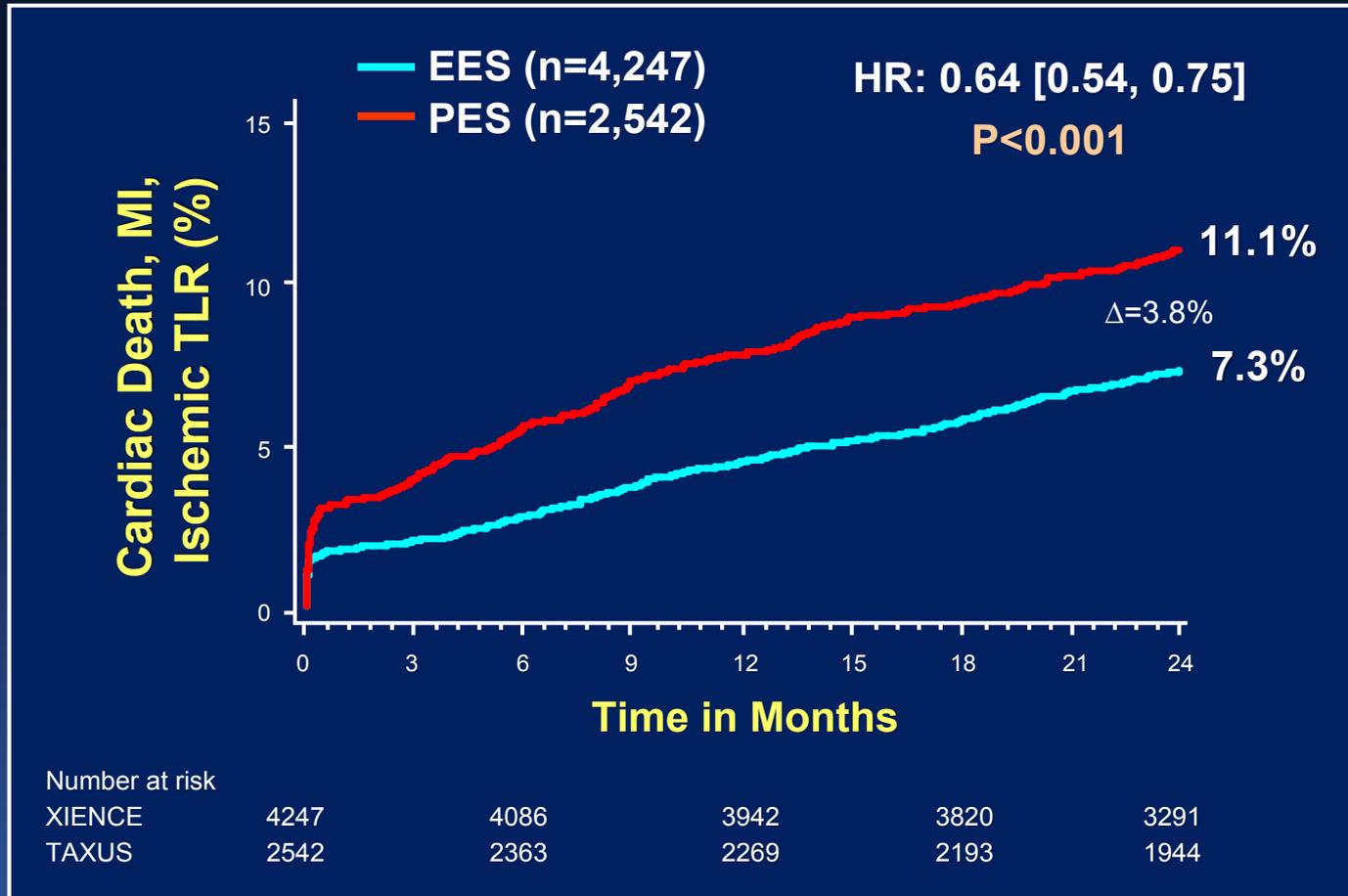
Angioscopy



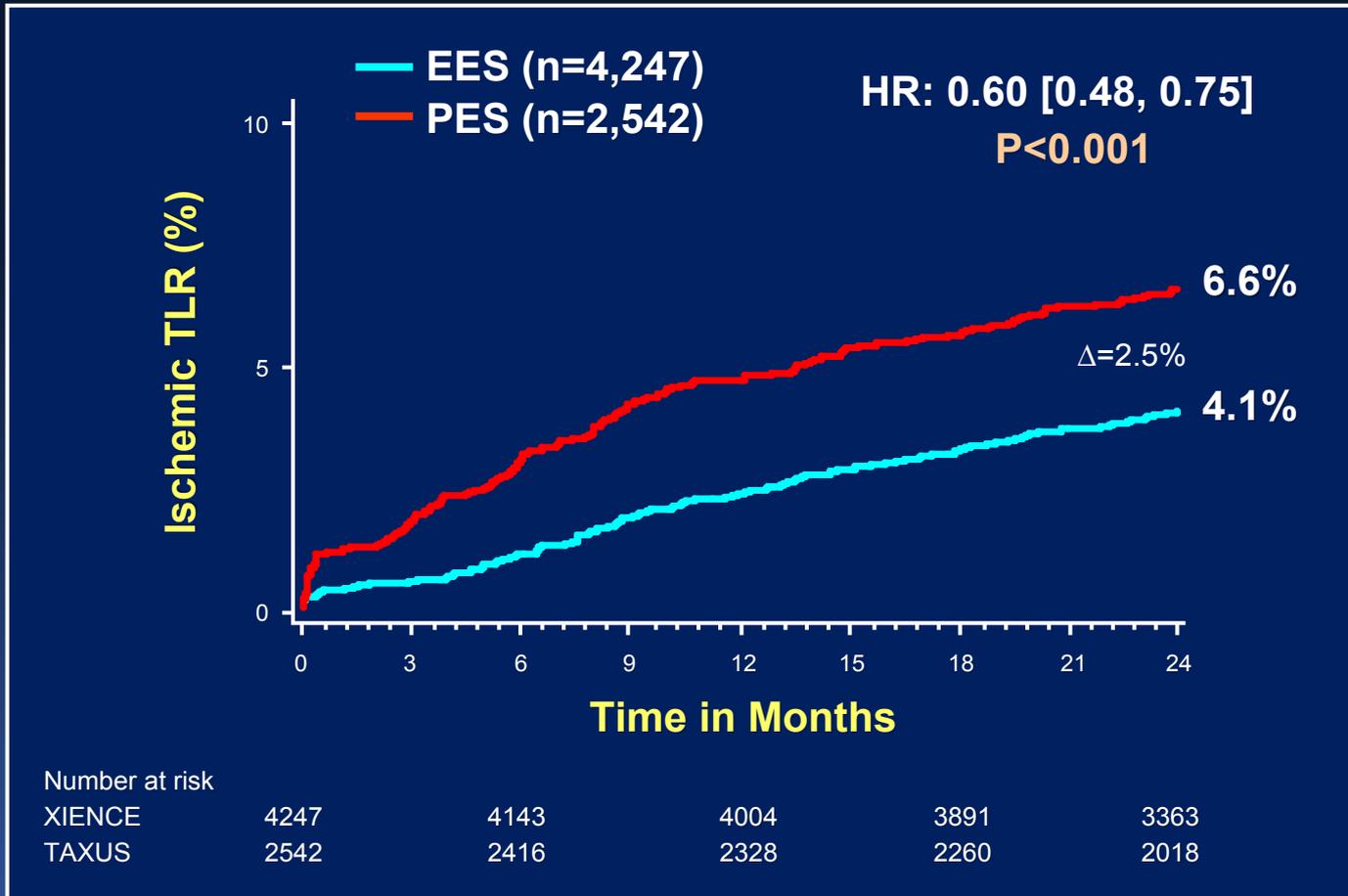
Inflammation



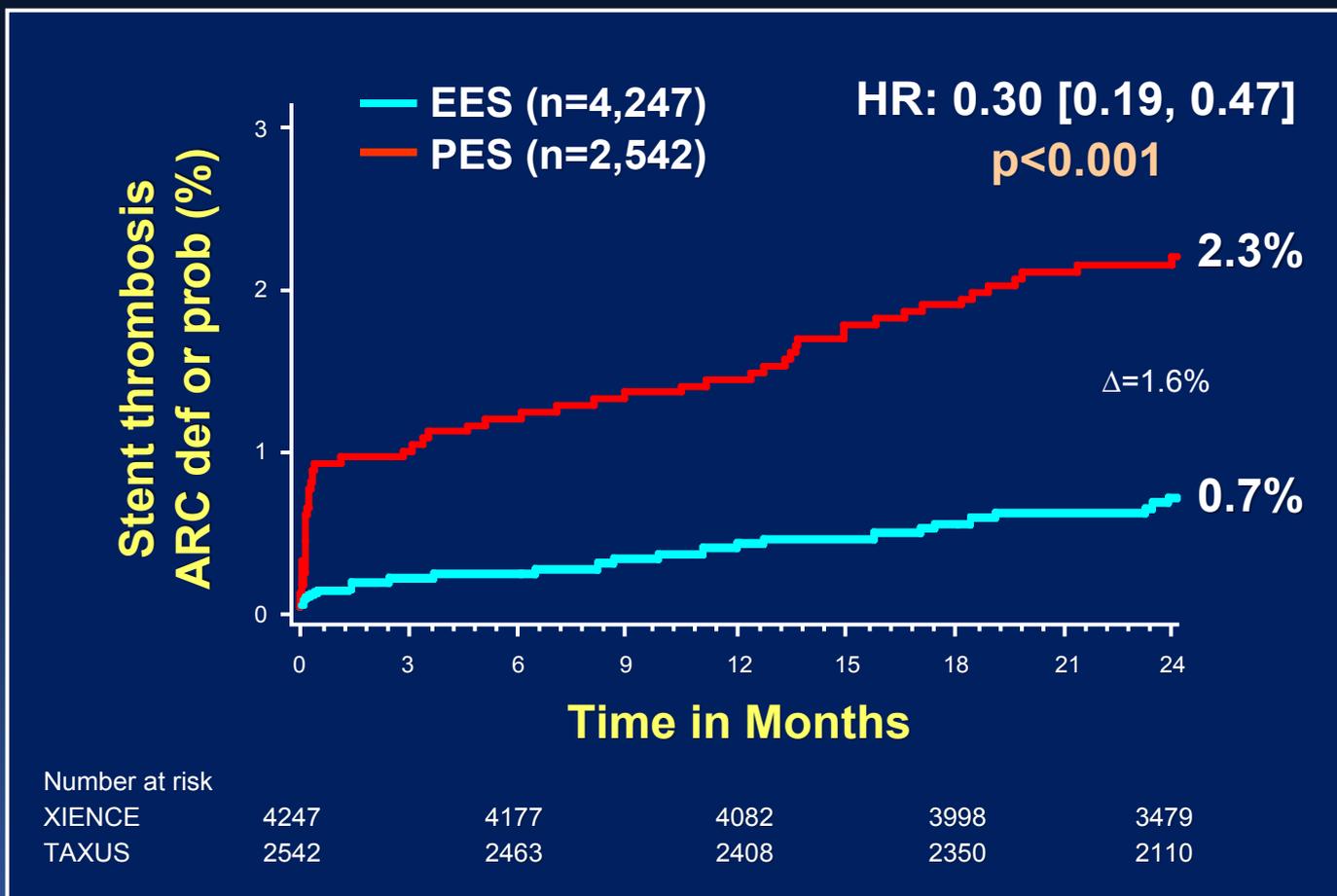
SPIRIT II, III, IV and COMPARE trials Pooled database analysis (n=6,789) MACE (Cardiac Death, MI, ID-TLR)



SPIRIT II, III, IV and COMPARE trials Pooled database analysis (n=6,789) Ischemic TLR



SPIRIT II, III, IV and COMPARE trials Pooled database analysis (n=6,789) Stent thrombosis (ARC definite/probable)



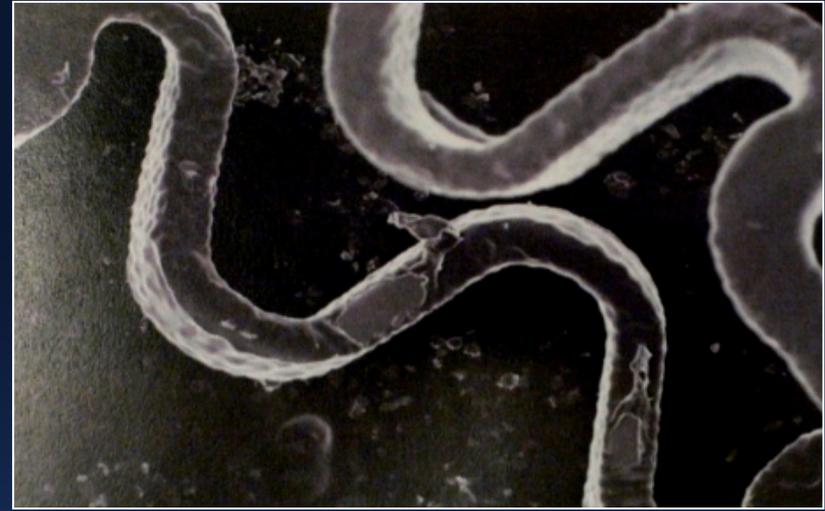
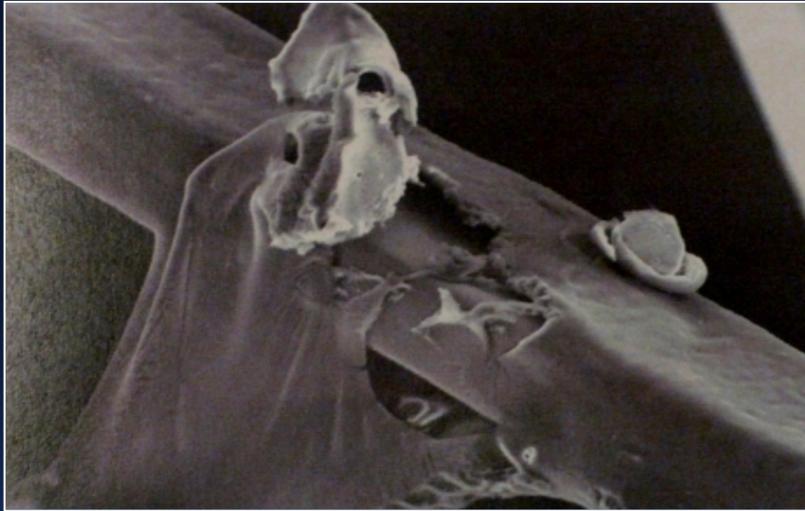
2019: Why do we Need Better Stents?

- To further eliminate early and late stent thrombosis and restenosis
- To reduce dependency on long-term DAPT
- To improve lifelong prognosis after DES

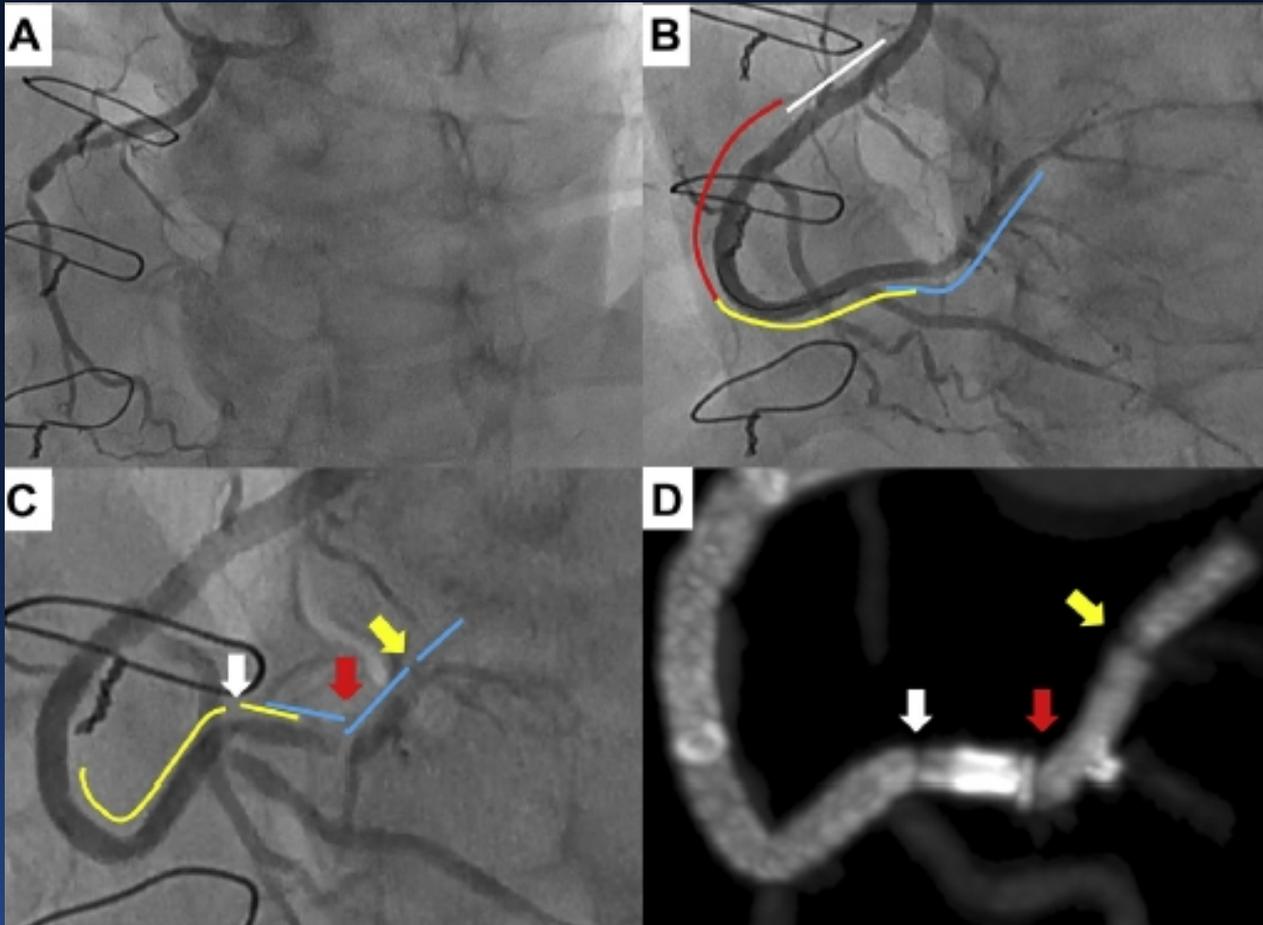
Principal Causes of Adverse Events with Current DES

- Early and late inflammatory and hypersensitivity reactions to the drug or polymer
- Polymer irregularities that result in inconsistent drug delivery or serve as a nidus for thrombus
- Mechanical issues: Strut fracture >> longitudinal deformation
- Very late issues with a permanent metallic implant (vessel straightening and loss of cyclic strain, loss of vasomotion and adaptive vascular remodeling, neoatherosclerosis)

Polymer Integrity Issues in FDA Approved DES



Late Fractures After EES



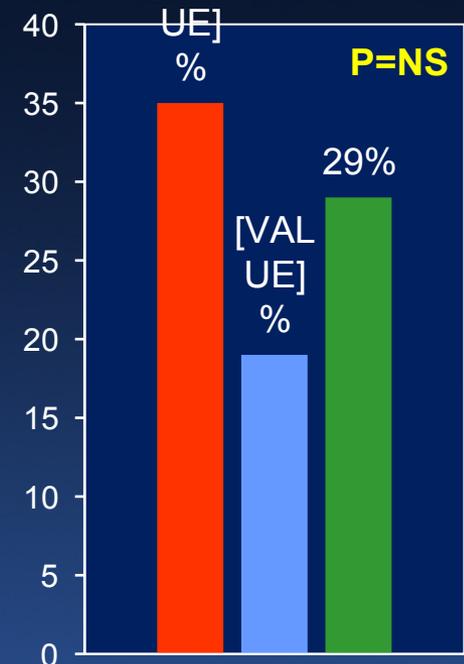
3 strut fractures
6 months after
placement of
4 overlapping
Pt-Cr-EES

Strut fractures occur in 2-3% of CoCr-EES and PtCr-EES within 6-9 months, and are associated with restenosis and stent thrombosis

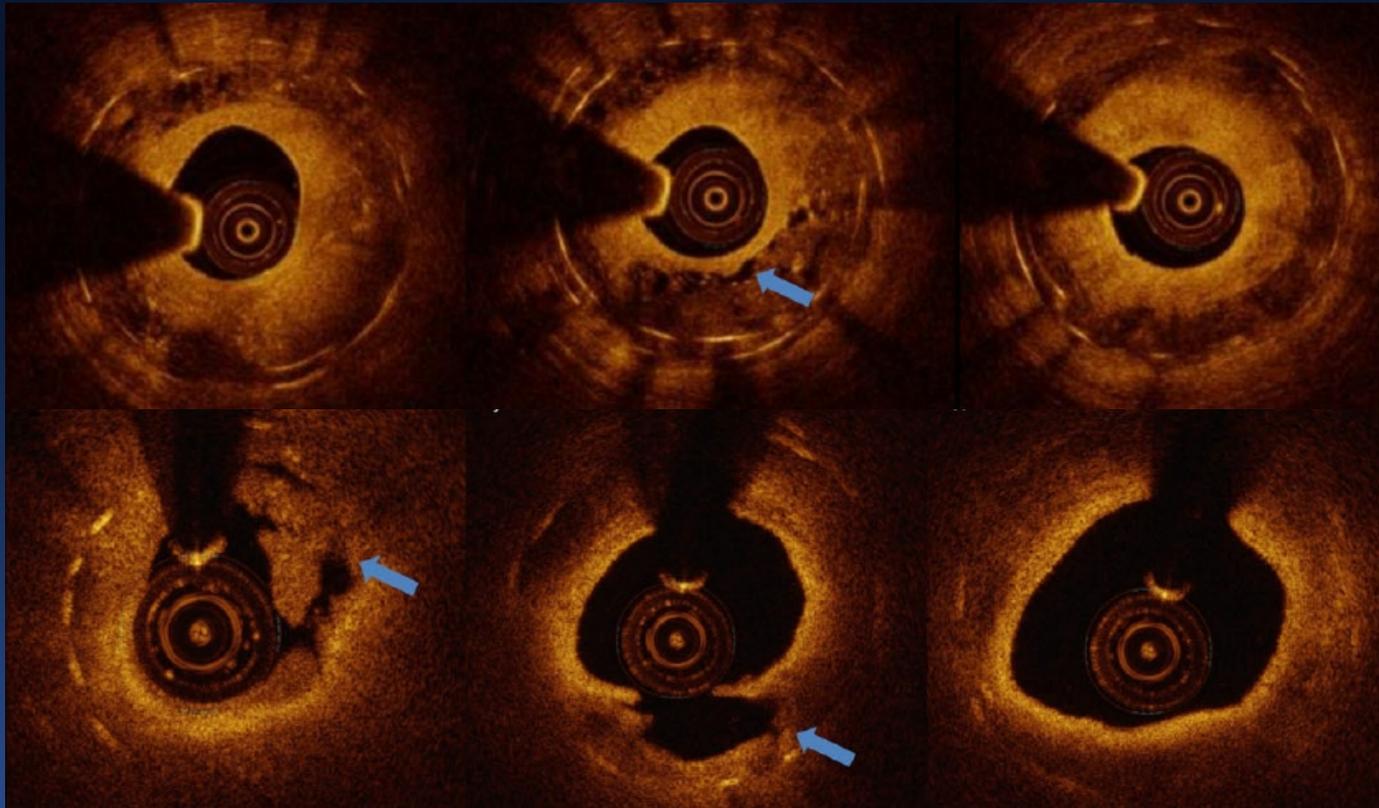
Neoatherosclerosis may be the common final denominator in many cases of late DES failure, and is not decreasing in prevalence

Autopsy series

SEVAL PES EES



Neoatherosclerosis



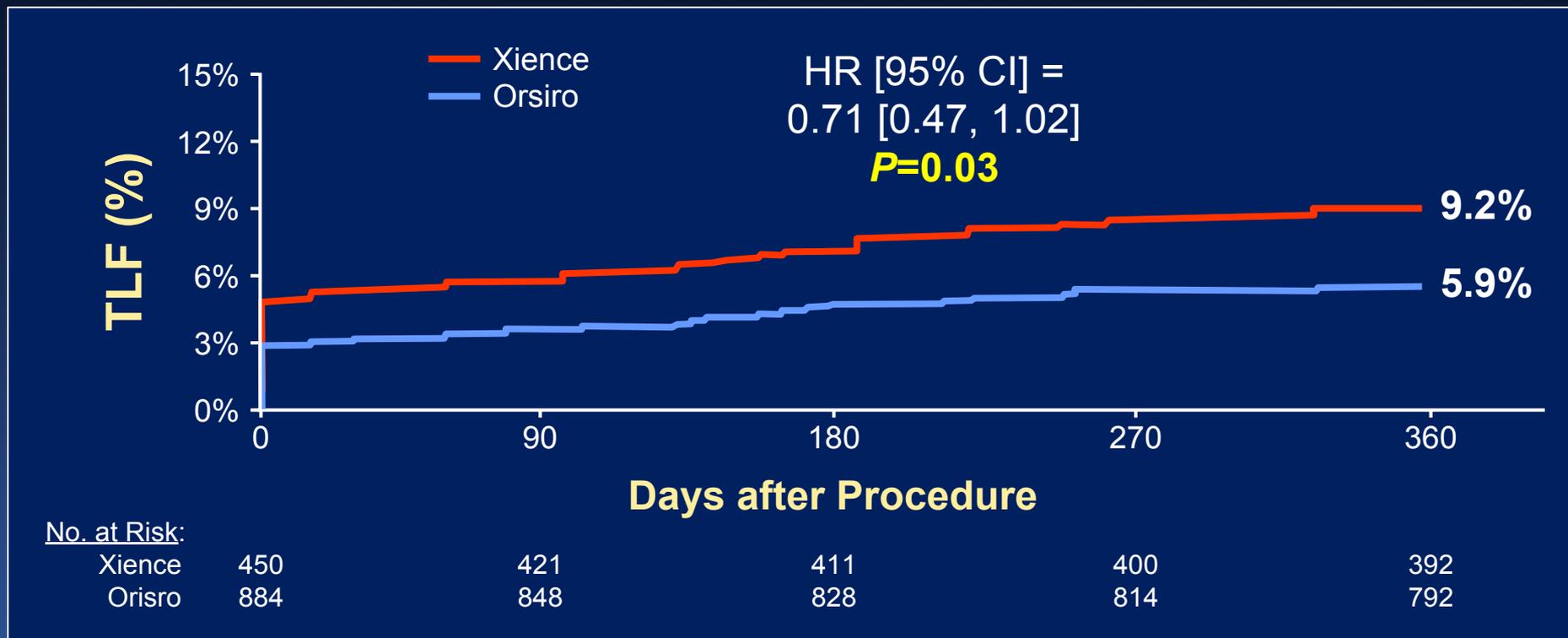
To Further Improve DES Outcomes

- **Make the stent struts thinner**
 - **Bioabsorbable polymers**
 - **Eliminate the polymer**
 - **Eliminate the stent**

BIOFLOW V RCT (n=1,334)

Orsiro 60 um CoCr bioabsorbable PLLA-based SES vs.
Xience 82 um CoCr durable fluoropolymer-based EES

Primary Endpoint: Target Lesion Failure at 1 Year
(2:1 randomization, powered for noninferiority)

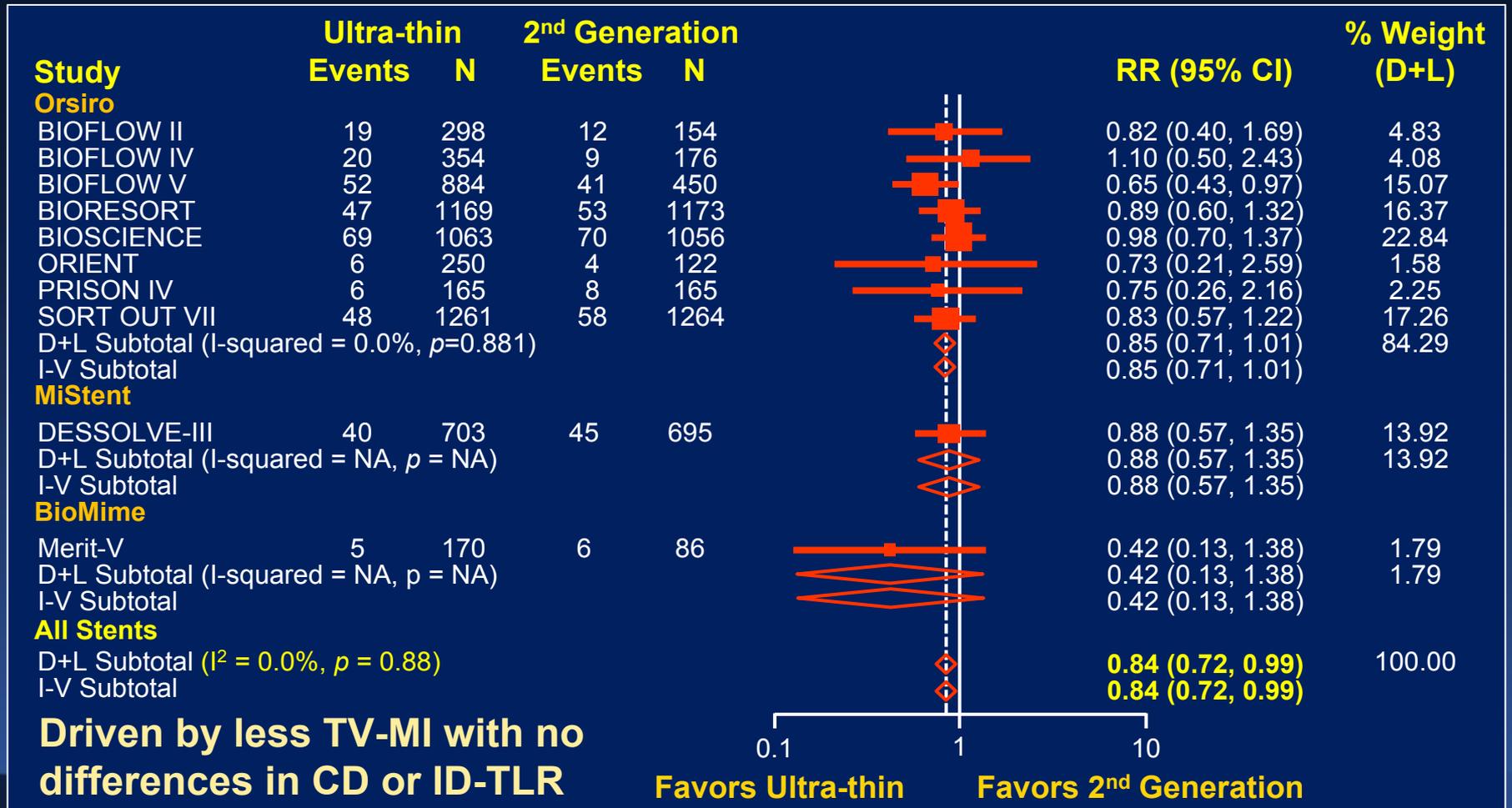


Ultra-thin (<70 μm) vs. Thicker Strut 2nd Gen DES

10 RCTs, 11,658 pts, 3 ultra-thin strut DES:

Orsiro (60 μm), MiStent (64 μm) and BioMime (65 μm)

1-Year Target Lesion Failure



Driven by less TV-MI with no differences in CD or ID-TLR

Favors Ultra-thin

Favors 2nd Generation

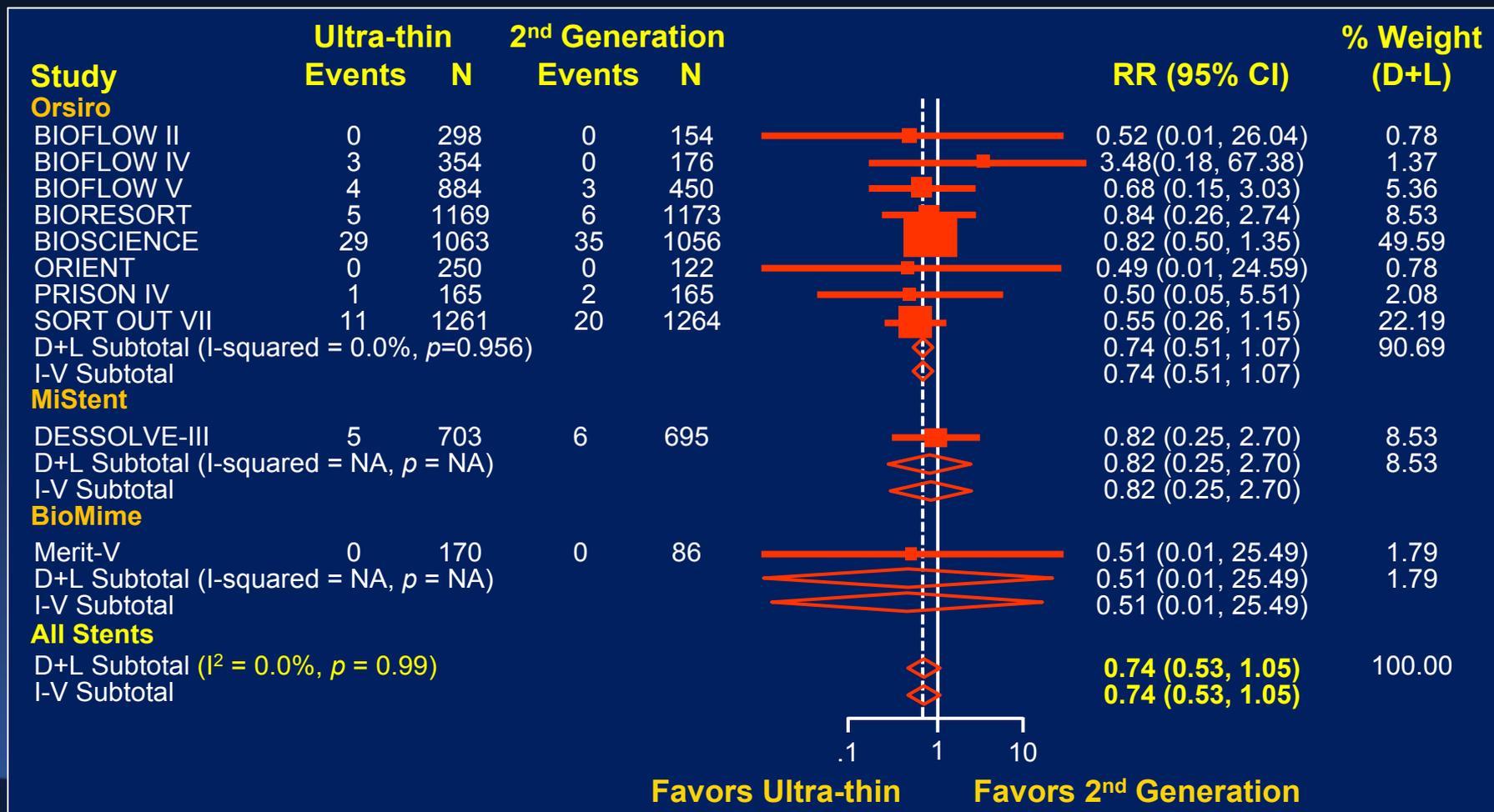
Bangalore S and Stone GW, submitted

Ultra-thin (<70 μm) vs. Thicker Strut 2nd Gen DES

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1-Year Stent Thrombosis (def/prob)

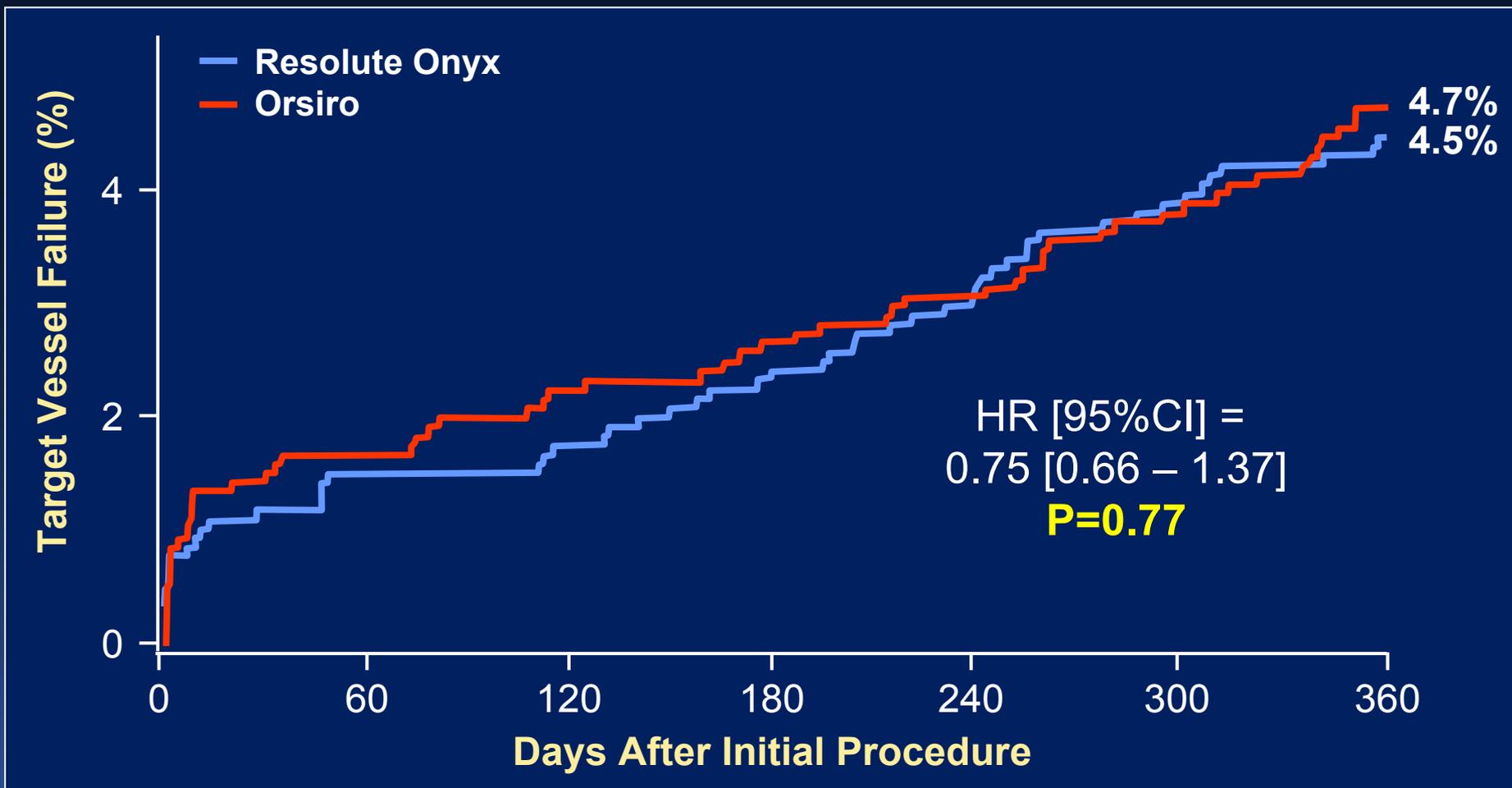


Favors Ultra-thin

Favors 2nd Generation

BIONYX RCT: Orsiro vs. Onyx (n=2,488)

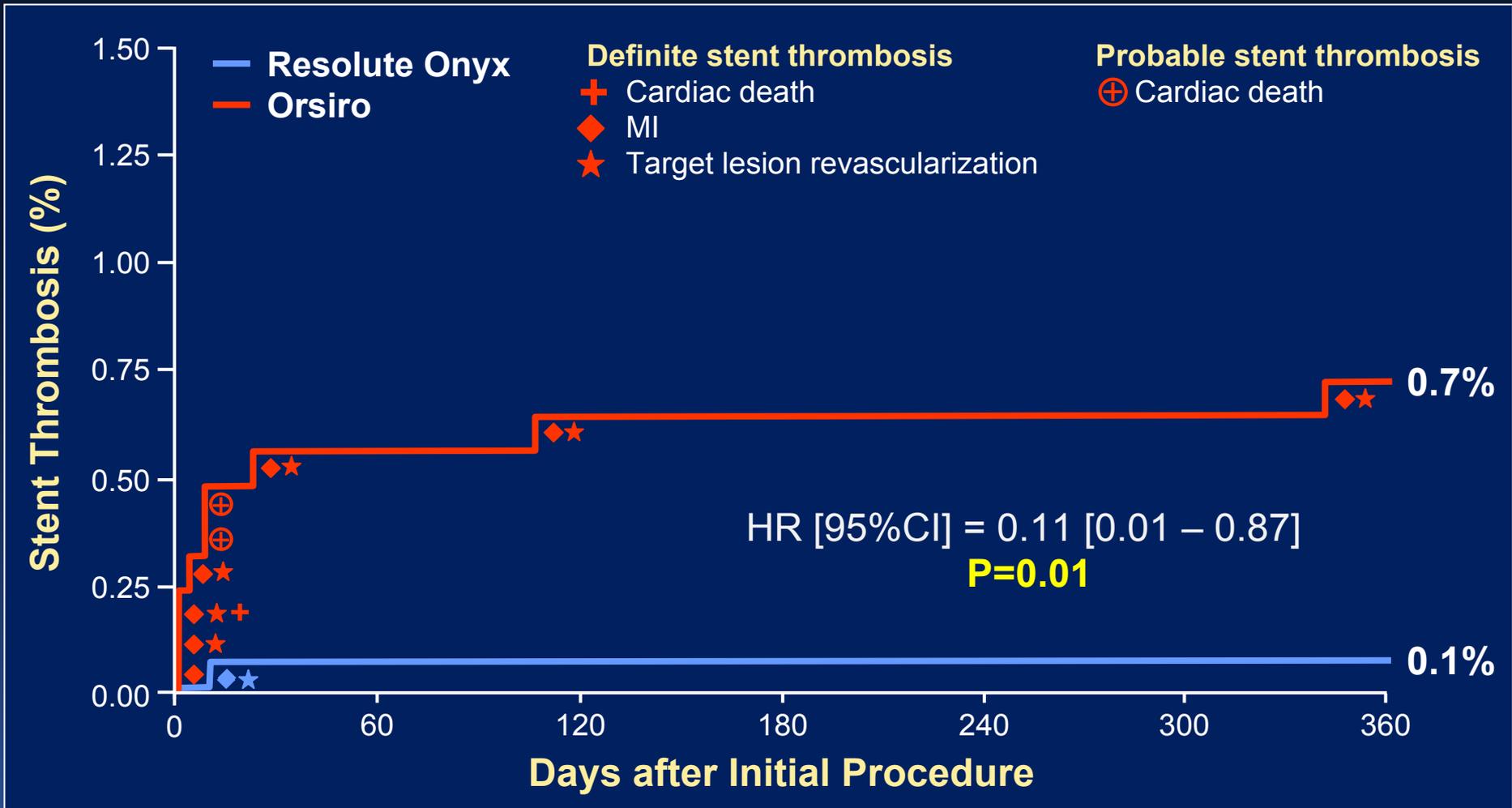
Primary endpoint: 1-year TVF (cardiac death, TV-MI or CD-TVR)



1-year TLF: 3.9% (Orsiro) vs. 3.6% (Onyx); **P=0.68**

BIONYX RCT: Orsiro vs. Onyx (n=2,488)

Definite or probable stent thrombosis

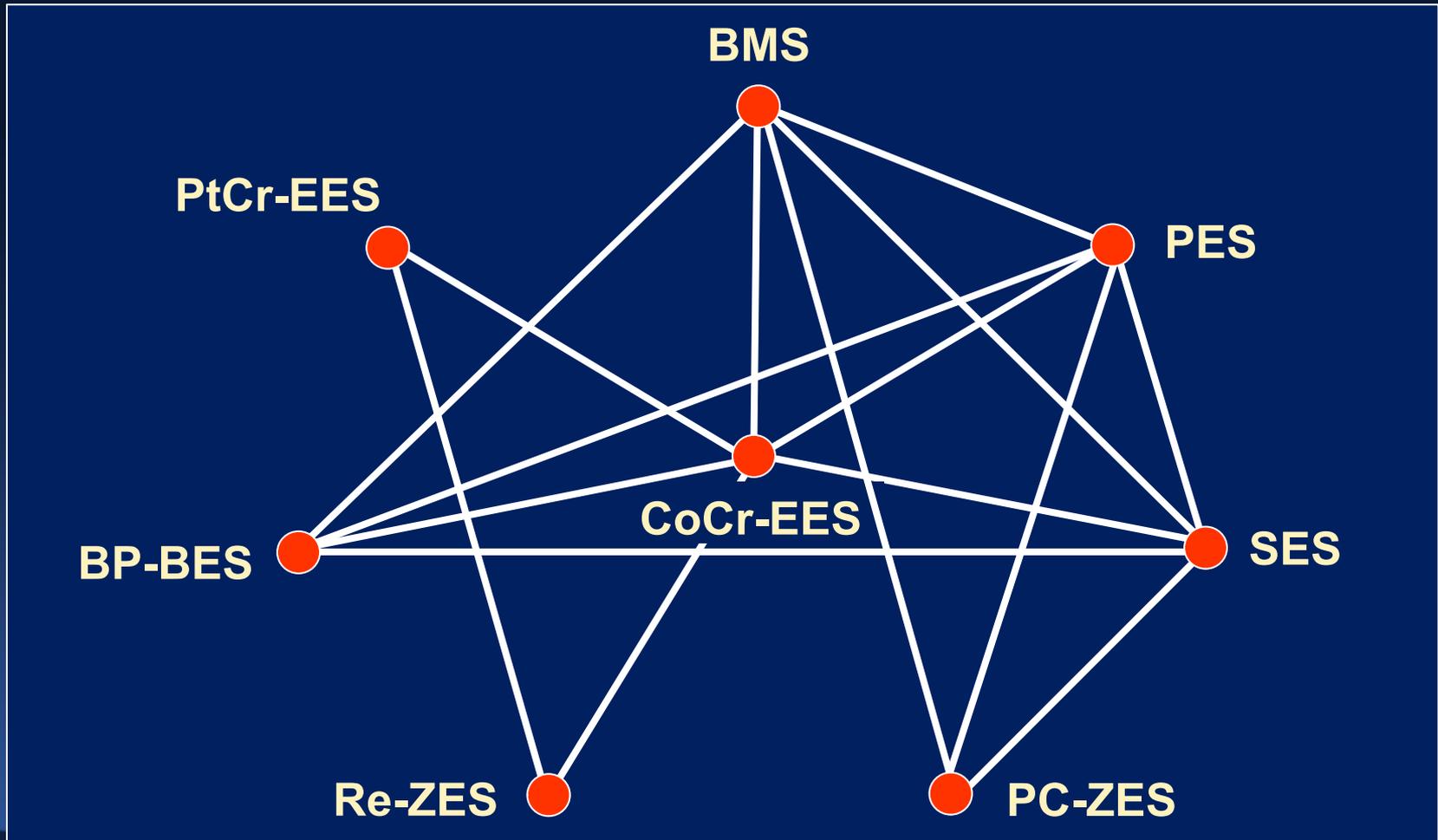


1-year definite ST: 0.1% vs. 0.6%, HR 0.14 [0.02 – 1.16], **P=0.03**

Bioabsorbable Polymer-based DES

Meta-analysis of 89 RCTs, 84,590 pts

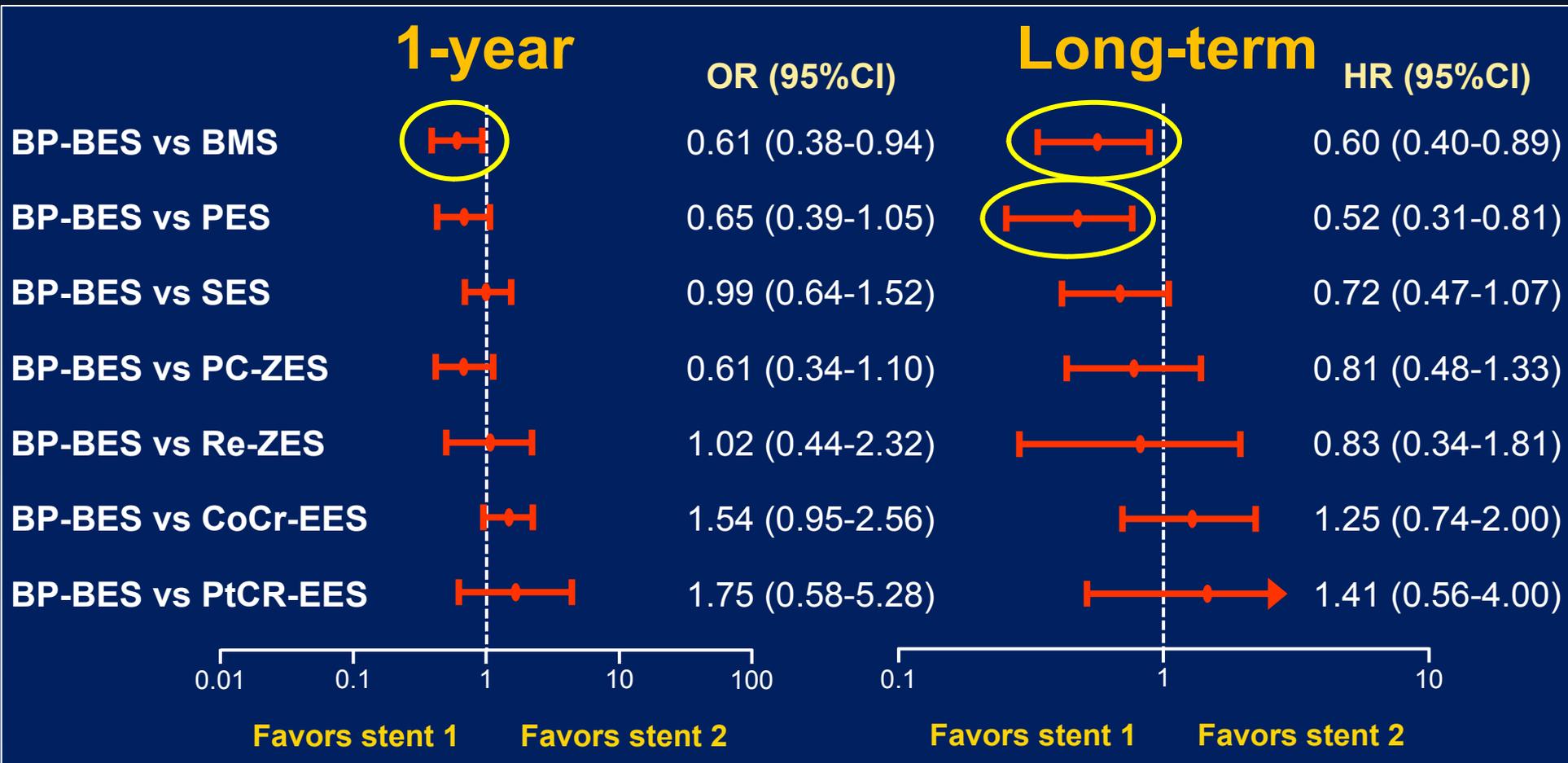
Evidence Network



Bioabsorbable Polymer-based DES

Meta-analysis of 89 RCTs, 84,590 pts

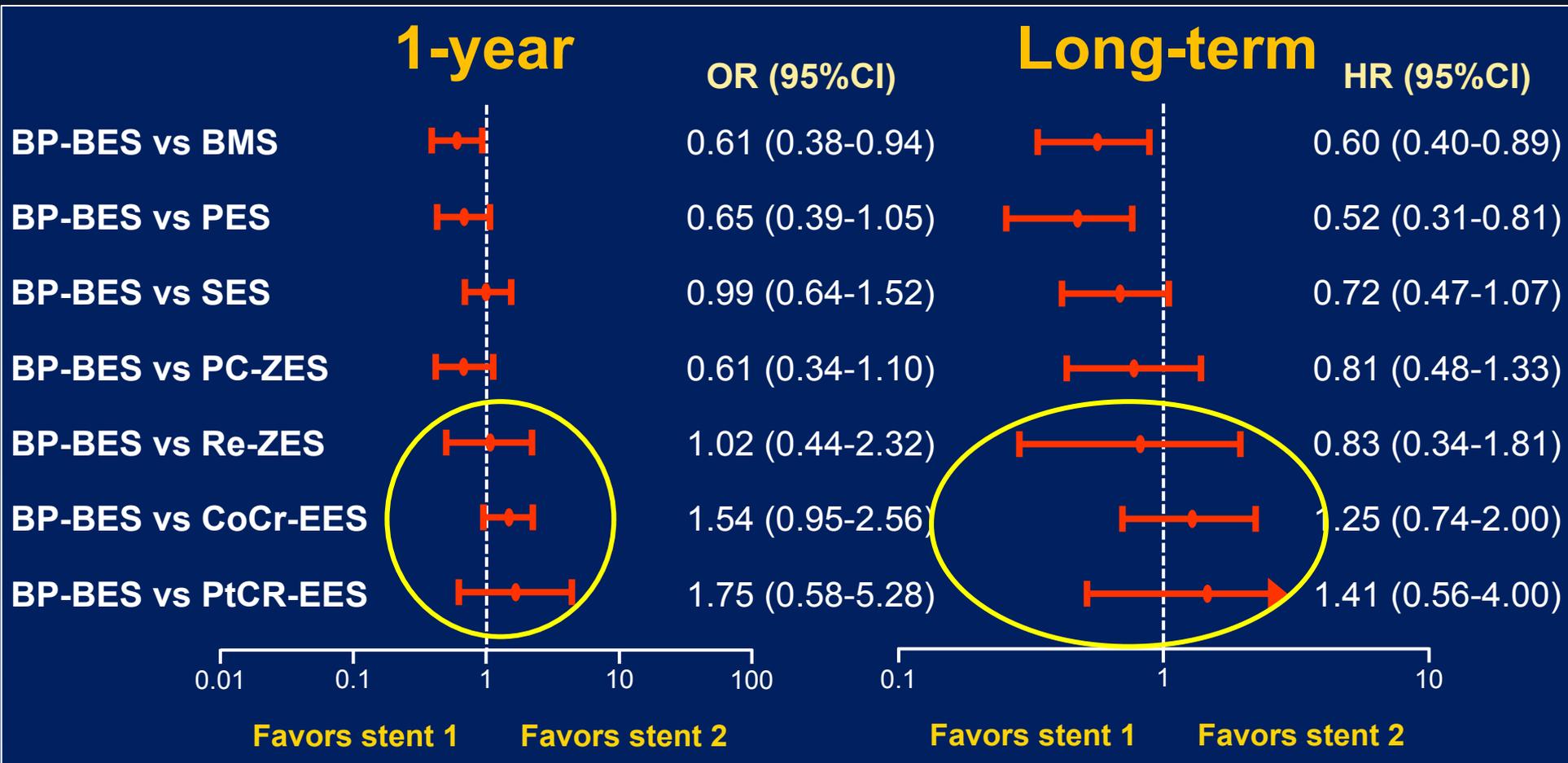
Stent Thrombosis



Bioabsorbable Polymer-based DES

Meta-analysis of 89 RCTs, 84,590 pts

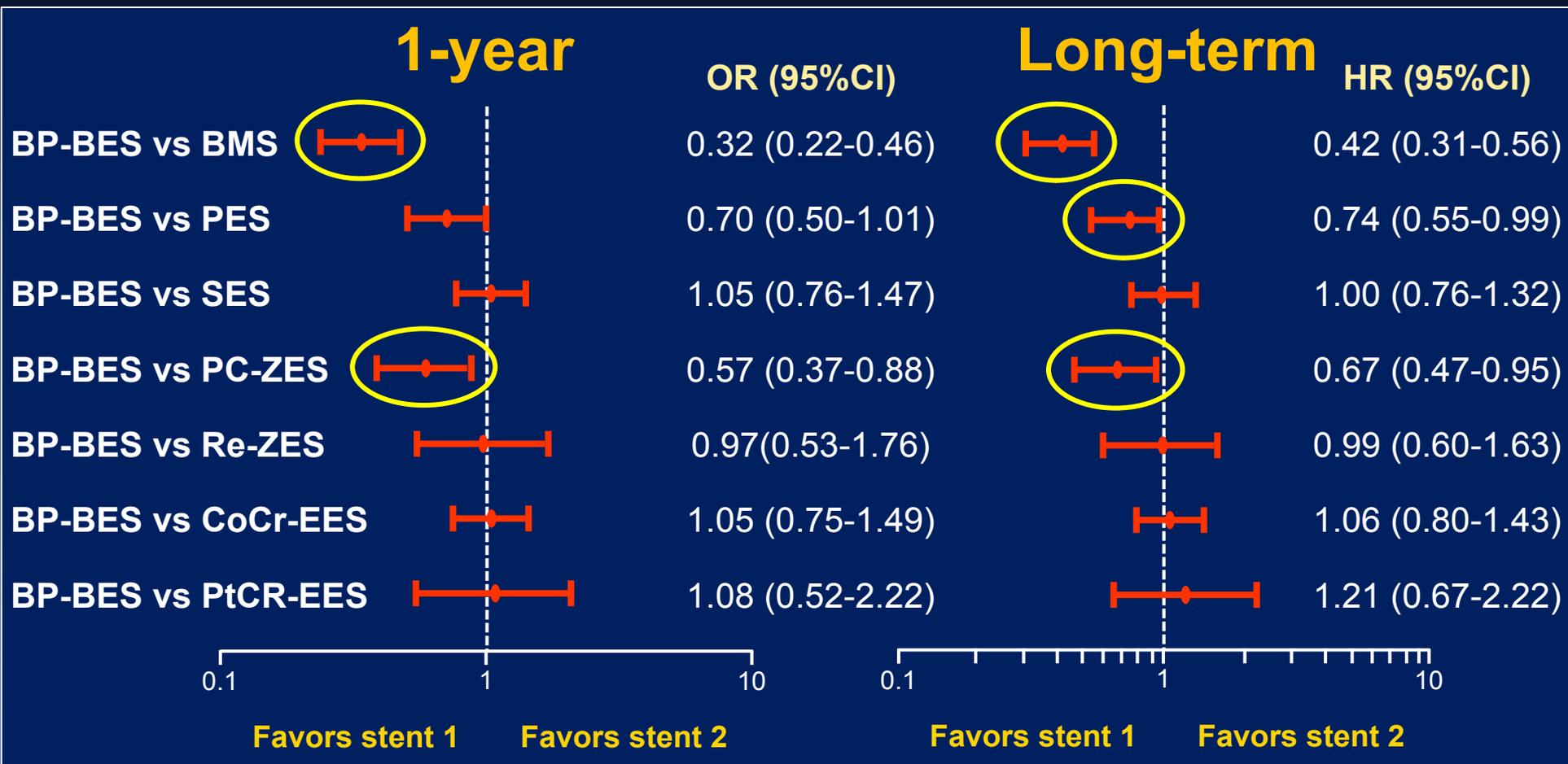
Stent Thrombosis



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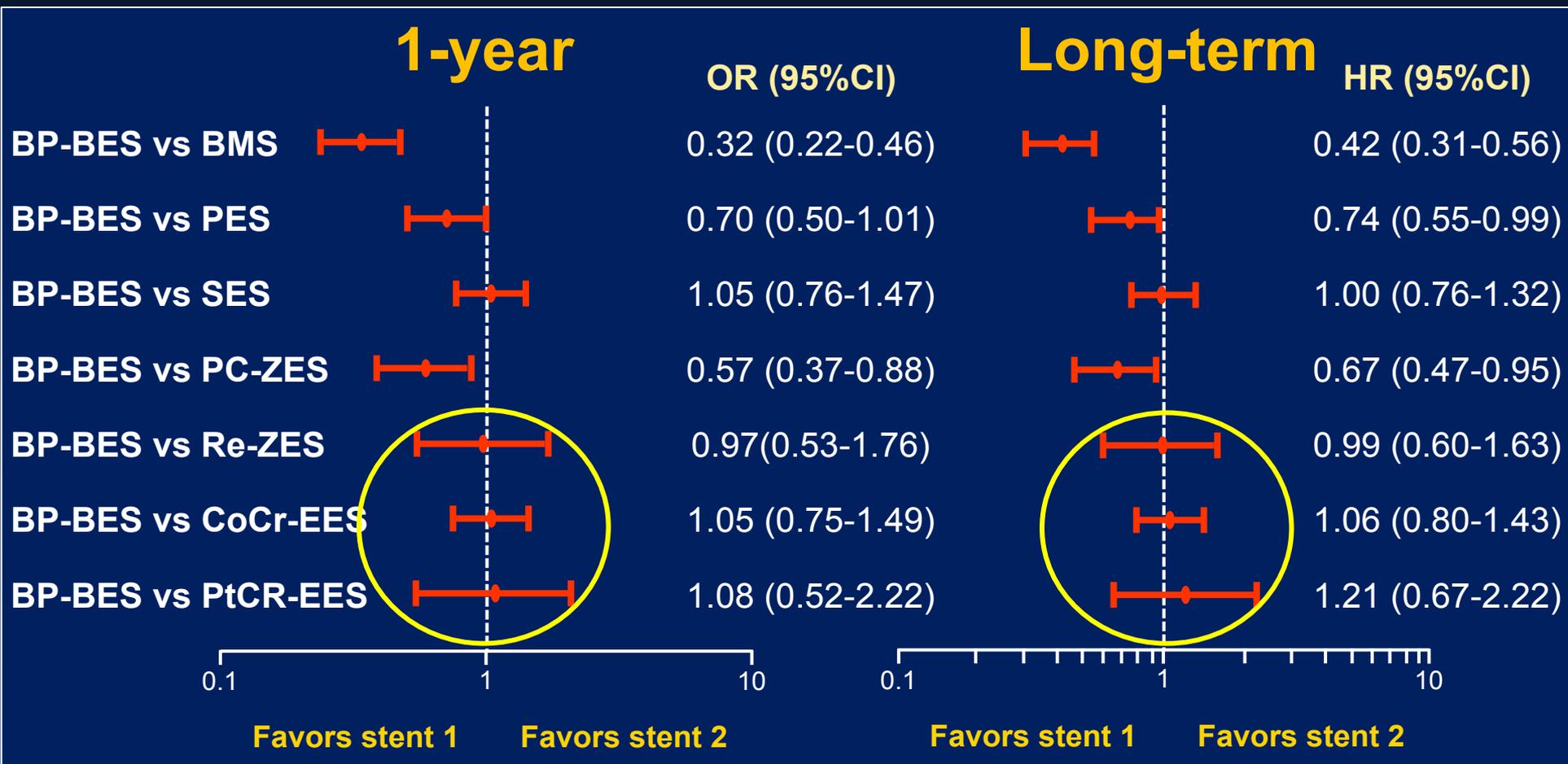
Target Vessel Revascularization



Bioabsorbable Polymer-based DES

Meta-analysis of 89 RCTs, 84,590 pts

Target Vessel Revascularization



SYNERGY Stent

Platinum Chromium Platform

- **74 μm** (0.0029 in) strut thickness

- ↑ Visibility
- ↑ Strength
- ↑ **Flexibility**
- ↑ **Conformability**
- ↓ Recoil

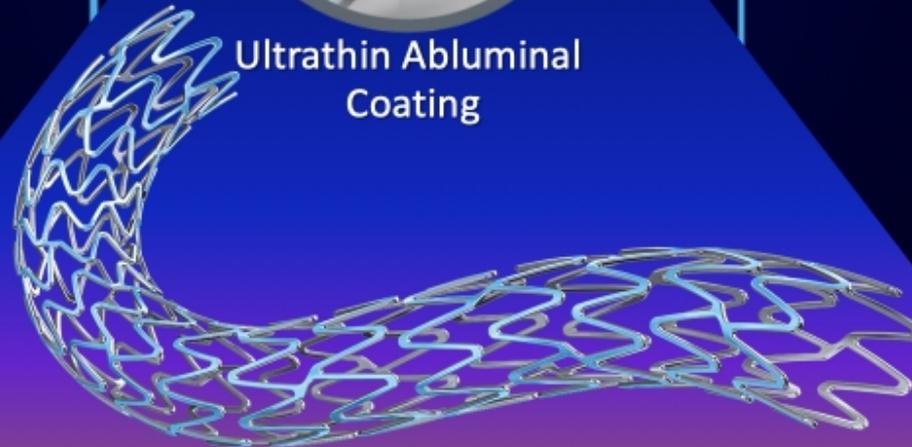
Everolimus-Eluting

- 100 $\mu\text{g}/\text{cm}^2$
- 3 month release time

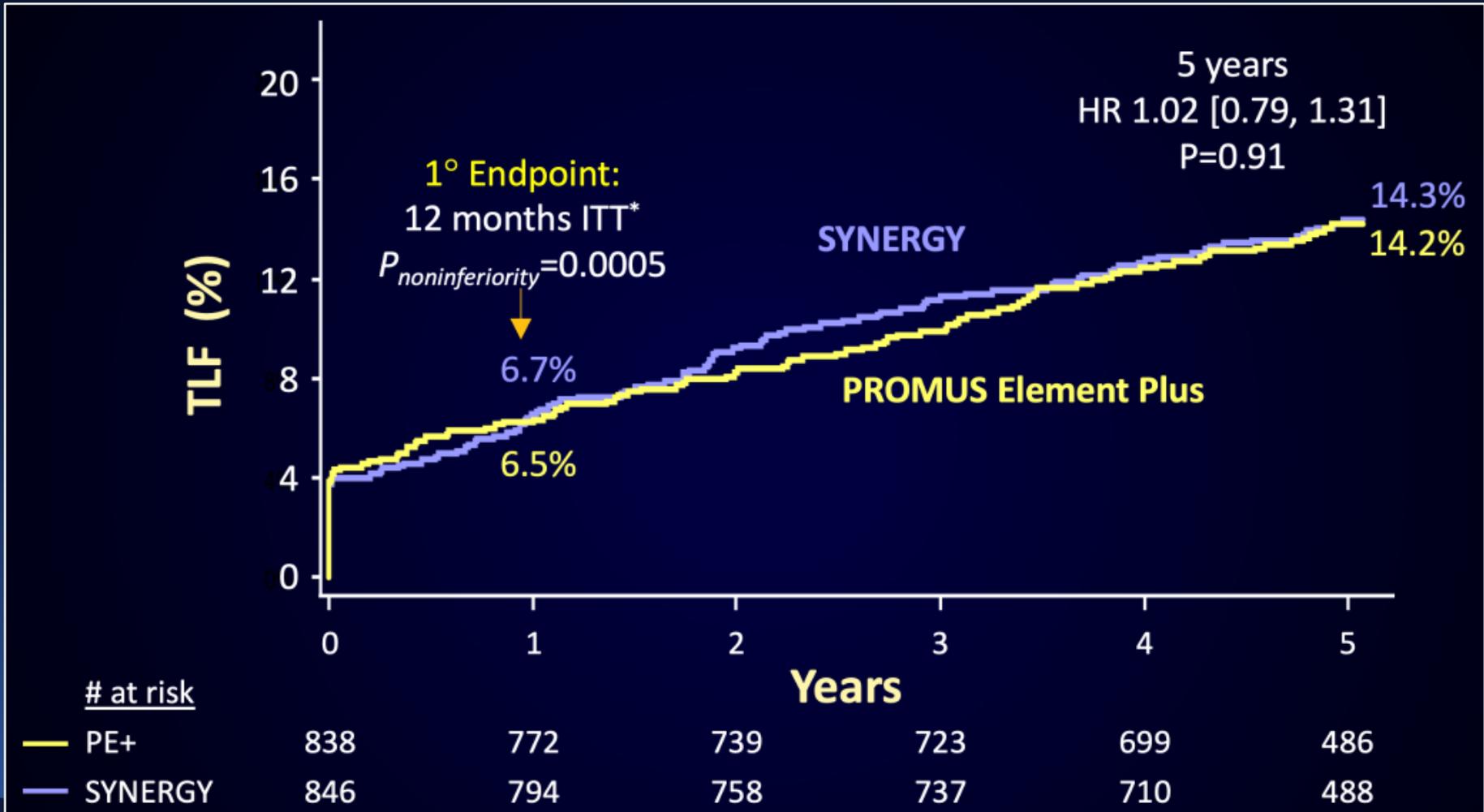


Bioabsorbable Polymer Coating

- **Abluminal Only**
- Ultrathin **PLGA** – **4 μm thick**
- 85:15 ratio
- **<4 month absorption time**



EVOLVE II: SYNERGY vs. Promus Element Plus (n=1684) - TLF at 5 Years

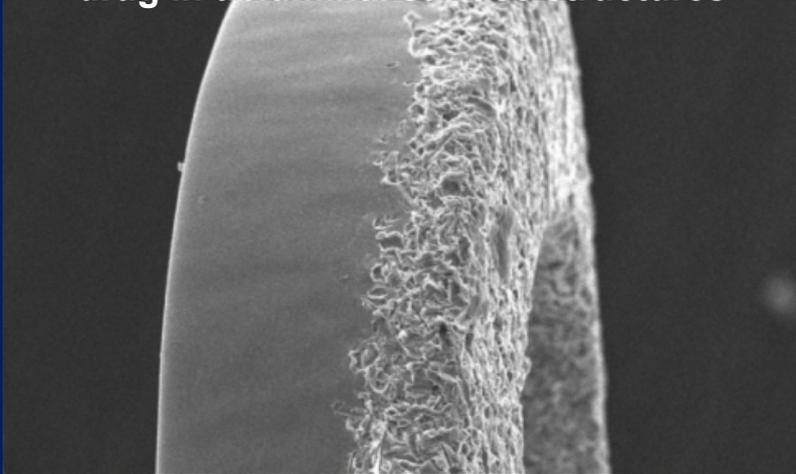


Polymer-Free Metallic Stents

- Once the drug is eluted, a BMS is left behind
- Potential advantages
 - More uniform drug delivery
 - No adverse polymer reactions
 - Potentially more rapid healing and shorter mandatory duration of DAPT
- Potential disadvantages
 - Difficult to control drug dose and elution rate
 - Some polymers are thromboresistant and may promote healing

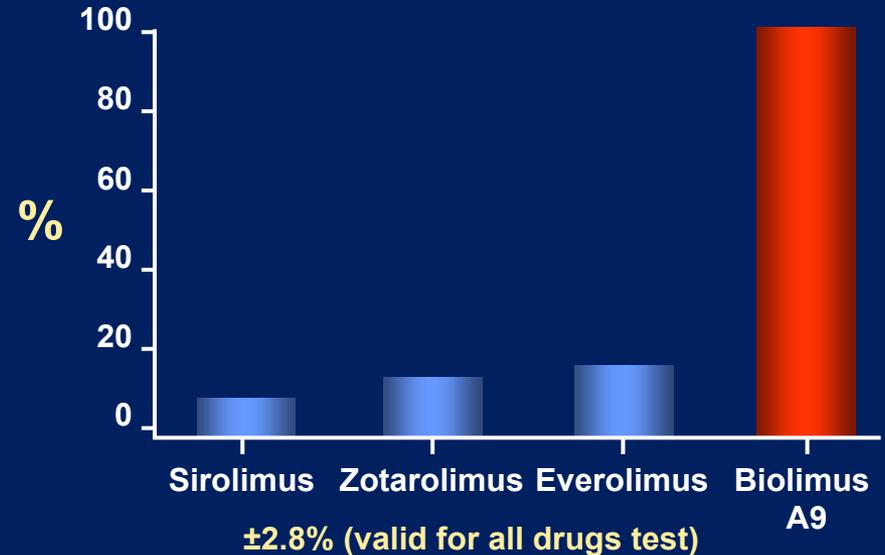
BioFreedom Drug Coated Stent (DCS)

120 um thick stainless steel stent
Selectively micro-structured surface holds
drug in abluminal surface structures



12 mo in-stent LL ~0.17 mm (n=31)

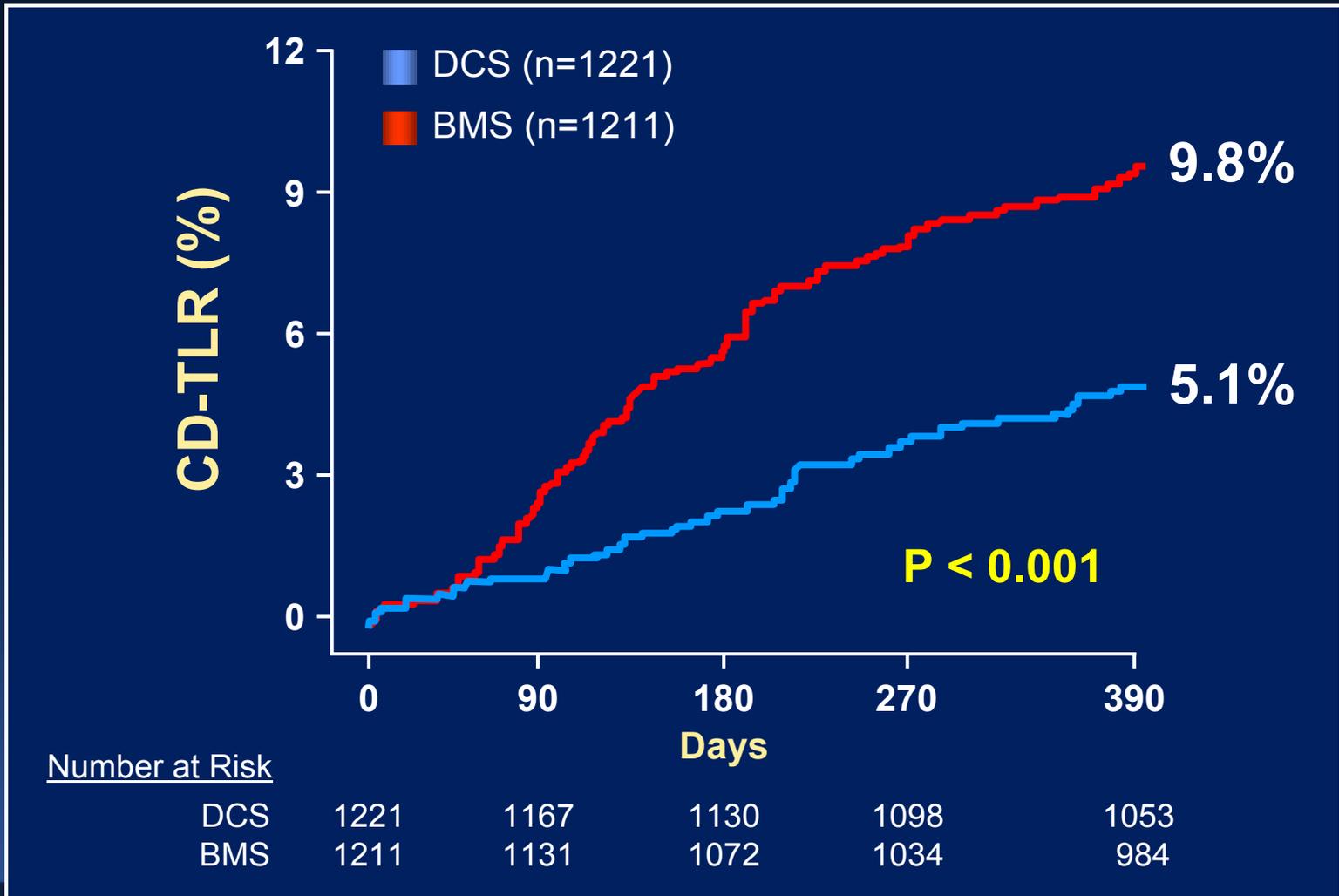
Biolimus A9 is 10x more
lipophilic than sirolimus¹



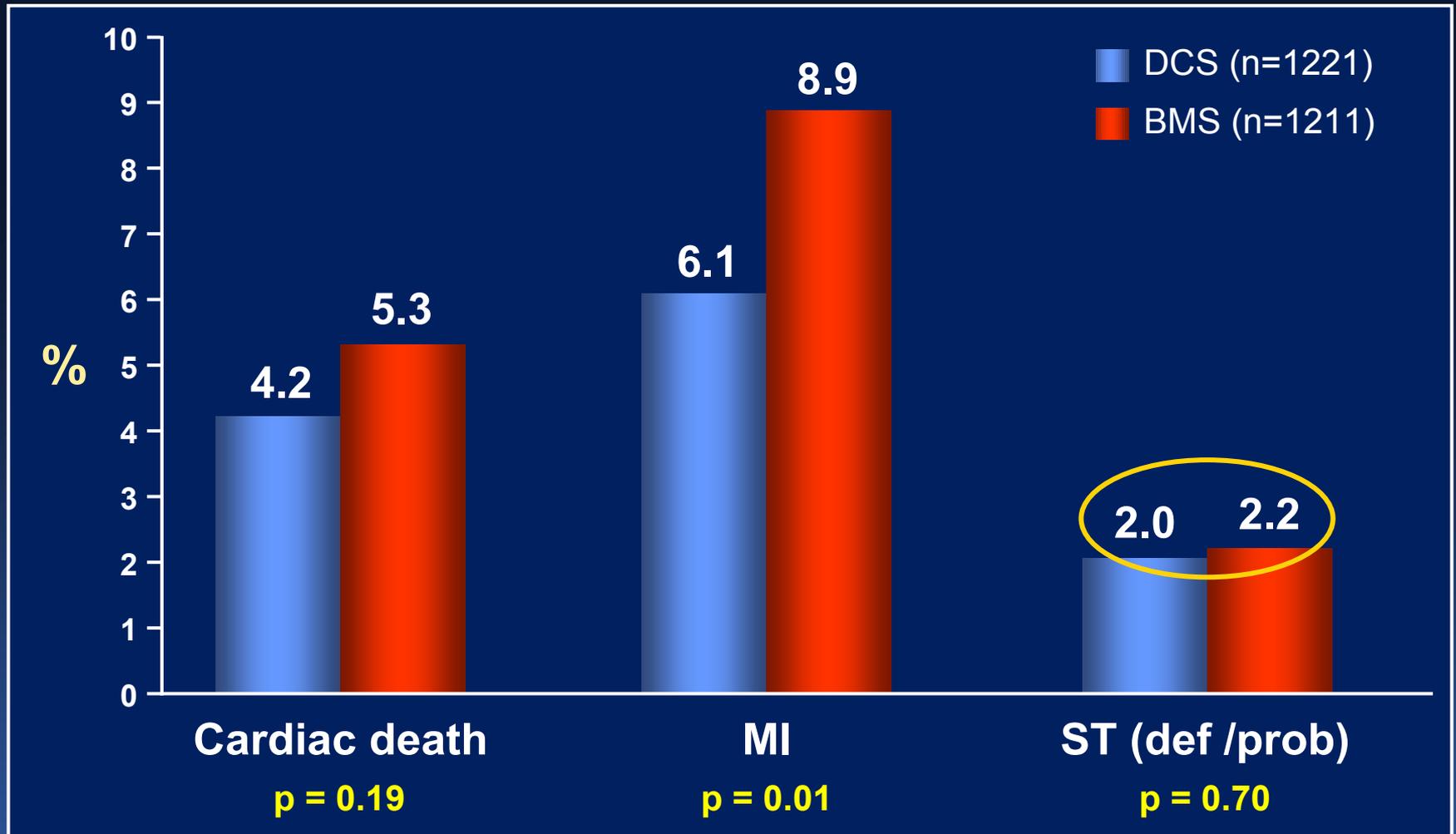
Potential Advantages:

- Rapid drug transfer to vessel wall (98% within one month²)
- Avoid possible polymer-related adverse effects
- Safe to shorten DAPT?

Leaders Free: Primary Efficacy Endpoint (Clinically-Driven TLR)



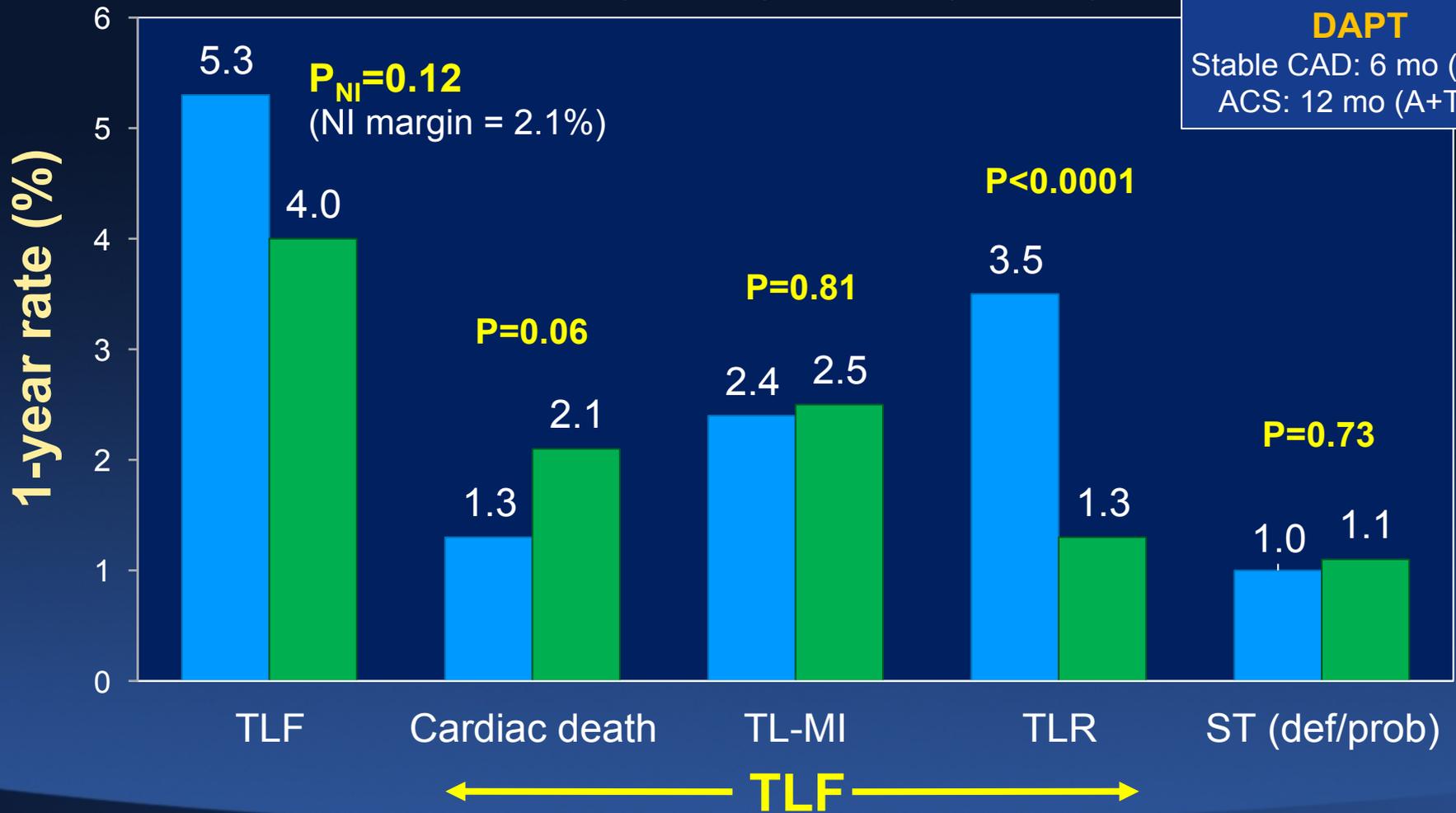
Leaders Free: Components of the Safety Endpoint (1-year)



SORT OUT IX RCT: Biofreedom (120 um SS polymer-free BES) **vs. Orsiro** (60 um CoCr PLLA-based SES) (n=3,151)

■ Biofreedom (n=1572) ■ Orsiro (n=1579)

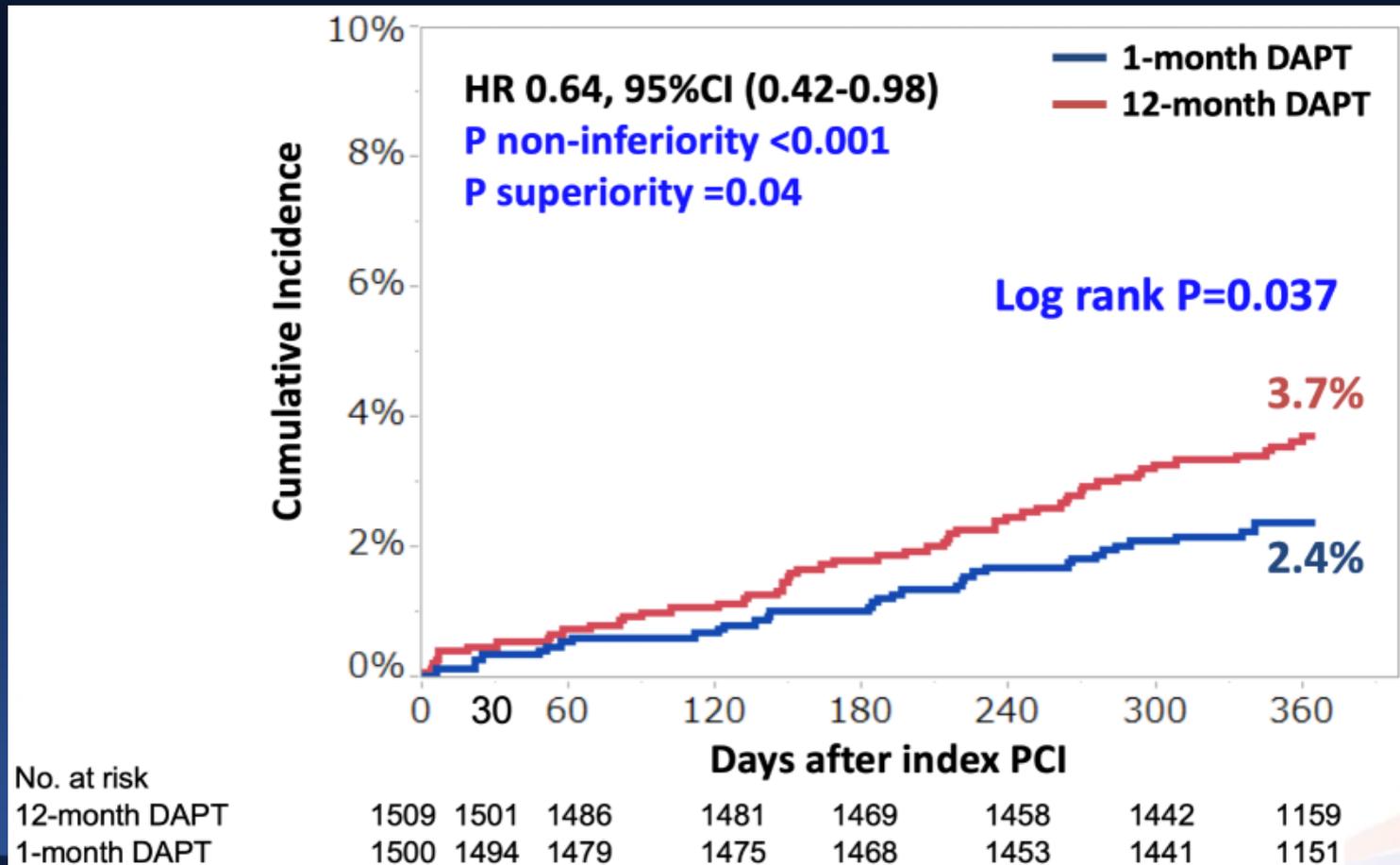
All-comers
DAPT
 Stable CAD: 6 mo (A+C)
 ACS: 12 mo (A+T/P)



STOPDAPT-2

3,045 pts (few excl, but no OAC) rand to DAPT for 1 mo followed by C alone vs. A+C x12 mo after Xience at 90 Japanese centers.

38% ACS, mean SS 8, IV imaging in 98%. **1° EP NACE***

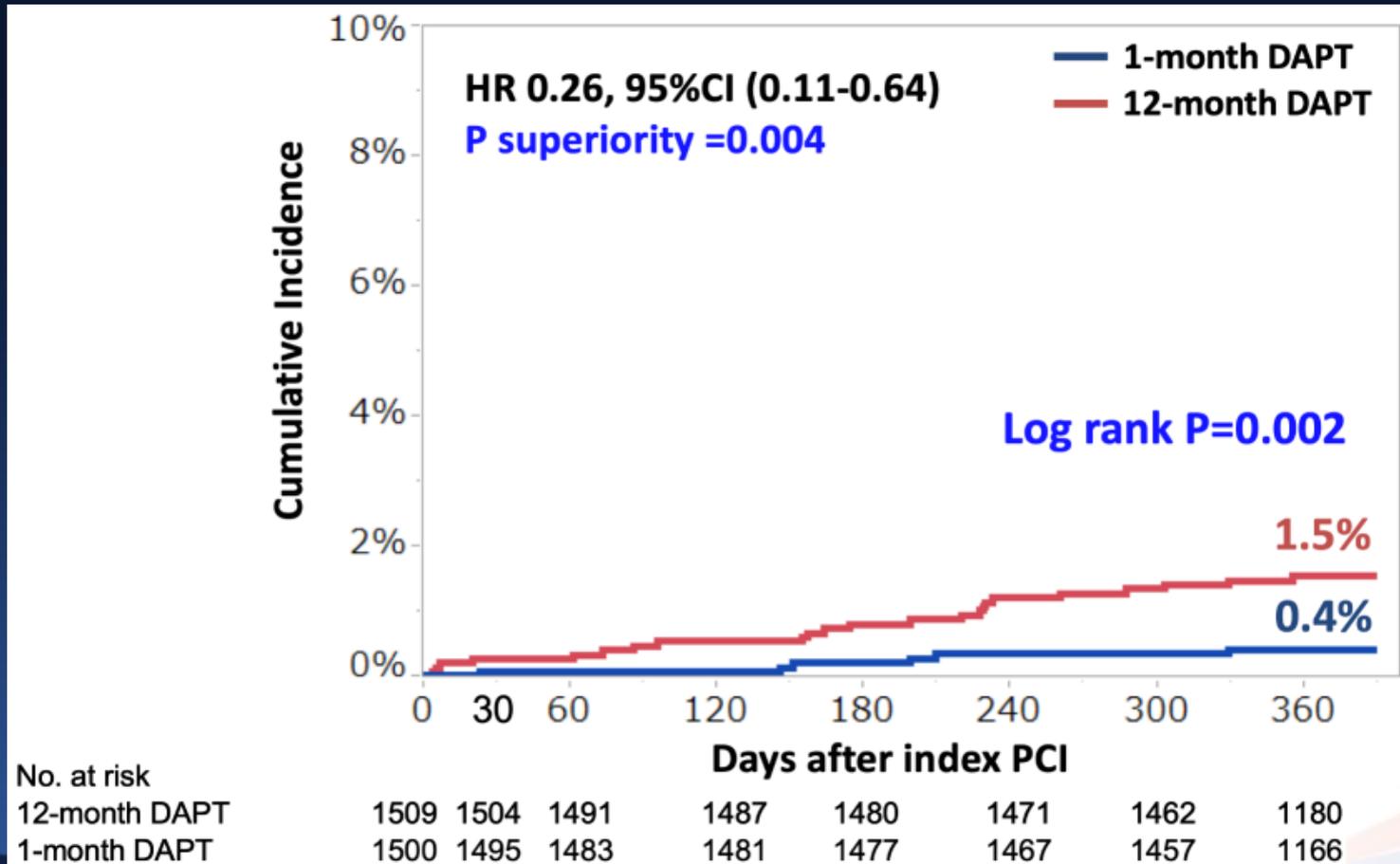


*CV death, MI, ST, stroke, or TIMI major/minor bleeding

Kimura T. ACC 2019

STOPDAPT-2

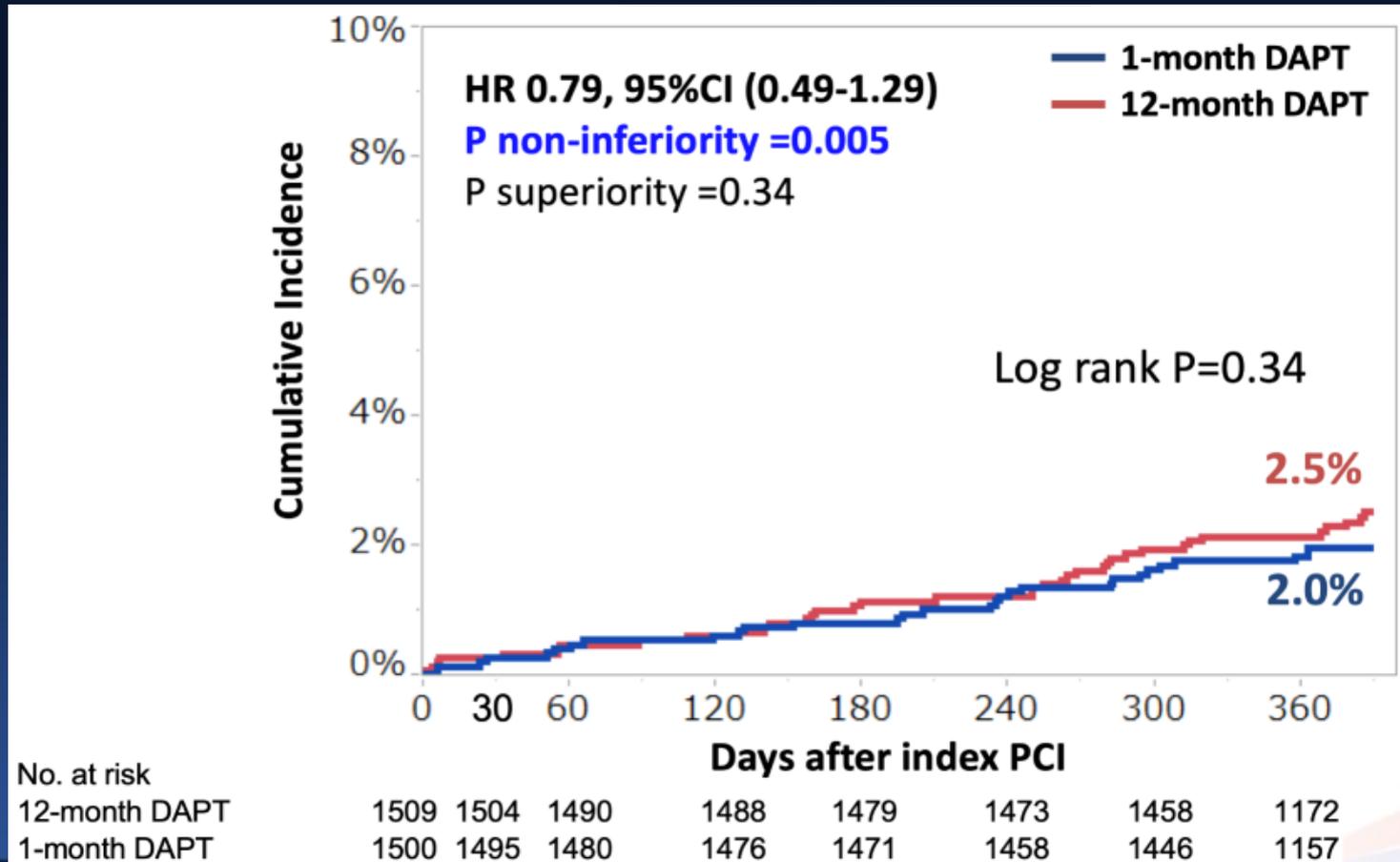
3,045 pts (few excl, but no OAC) rand to DAPT for 1 mo followed by C alone vs. A+C x12 mo after Xience at 90 Japanese centers. 38% ACS, mean SS 8, IV imaging in 98%. **2° EP TIMI Bleeding**



STOPDAPT-2

3,045 pts (few excl, but no OAC) rand to DAPT for 1 mo followed by C alone vs. A+C x12 mo after Xience at 90 Japanese centers.

38% ACS, mean SS 8, IV imaging in 98%. **2° EP MACE***



Short-DAPT Programs in HBR Pts with Contemporary Polymer-based DES

| Study | Device | DAPT Duration | N | Design |
|---|---------------|----------------------------------|------|-------------------------------------|
| EVOLVE Short DAPT NCT02605447 | Synergy | 3 months | 2000 | Registry |
| POEM NCT03112707 | Synergy | 1 month | 1023 | Registry |
| XIENCE 90 NCT03218787 | Xience | 3 months | 2000 | Registry |
| STOP-DAPT2 NCT02619760 | Xience | 1 month | 3045 | Randomized (1 vs 12 mo DAPT) |
| MASTER-DAPT NCT03023020 | Ultimaster | 1 month | 4300 | Randomized (1 vs 12 mo DAPT) |
| SENIOR NCT02099617 | Synergy | 1 month (SIHD) 6 months (ACS) | 1200 | Randomized (Synergy vs. BMS) |
| Onyx ONE NCT03344653 | Onyx Resolute | 1 month | 2000 | Randomized (Onyx vs. BioFreedom) |

**TCT
2019**

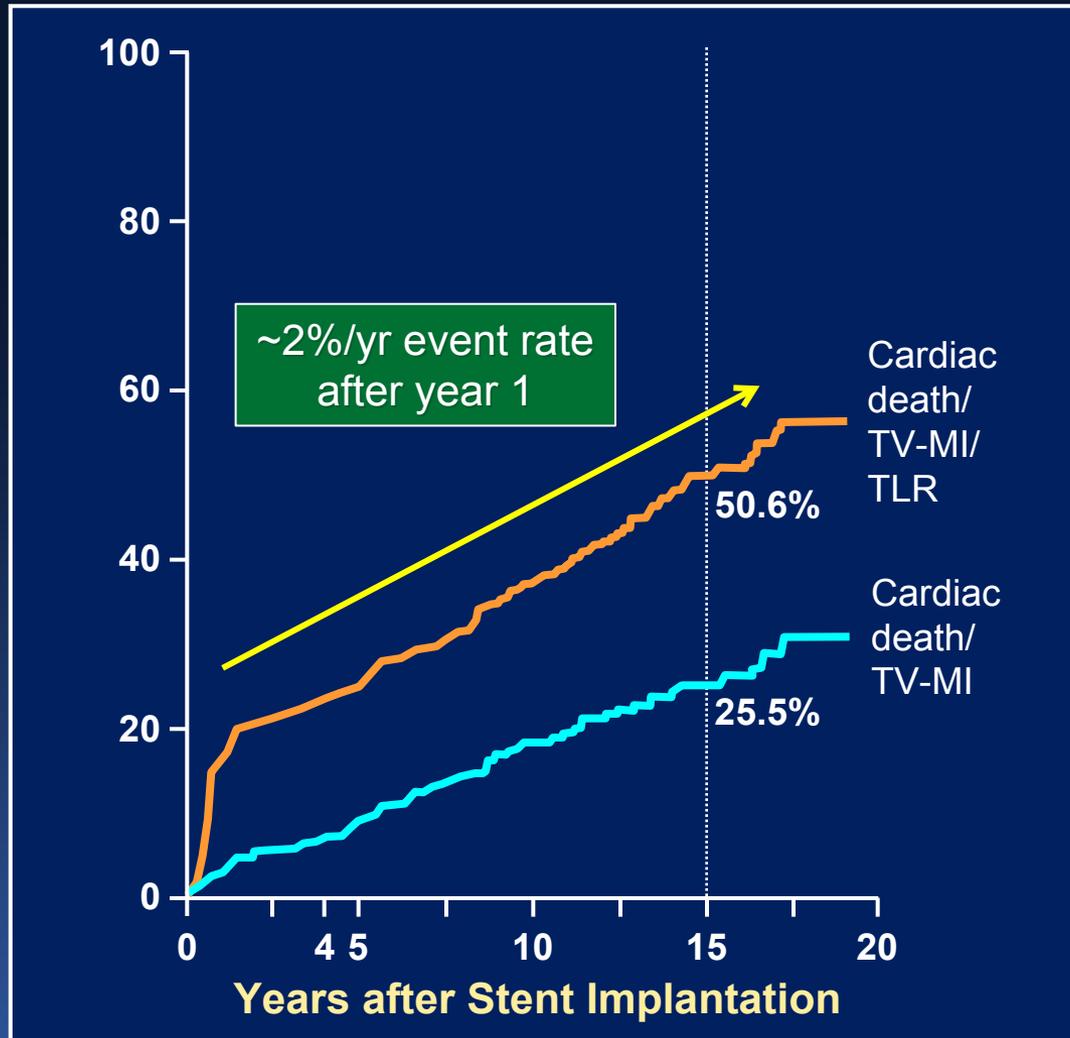
Rationale for Bioresorbable Scaffolds

Metallic DES result in...

- Ongoing risk of very late events (lifelong)
- Suboptimal outcome in special situations:
 - STEMI and NSTEMI (high stent thrombosis rates)
 - Bifurcations (jailed side branches)
 - Diffuse disease (full metal jacket)
 - Treatment of in-stent restenosis (layer on layer)
- Permanent implant not desirable for many pts

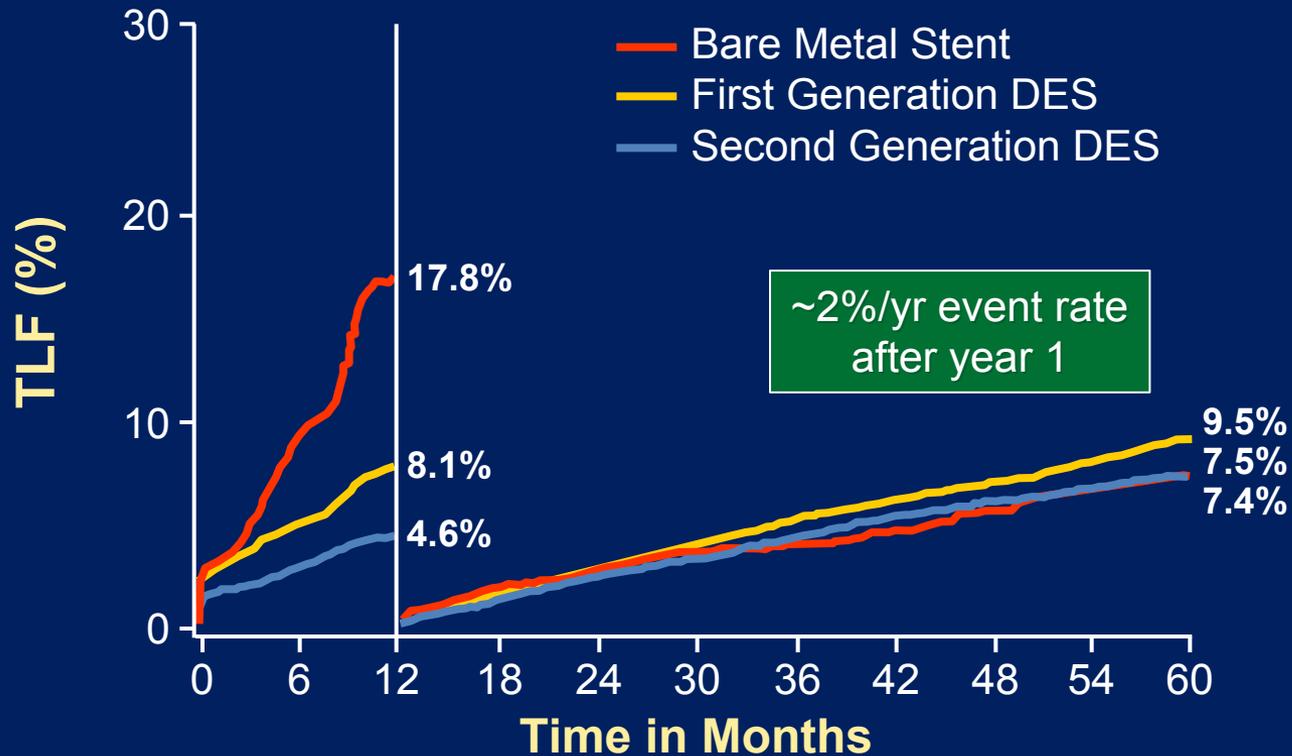
15-year Follow-up After BMS (1990-1993)

N=405



17 RCTs, 21,830 patients

TLF Between 0-1 and 1-5 Years by Stent Type (Landmark Analysis)

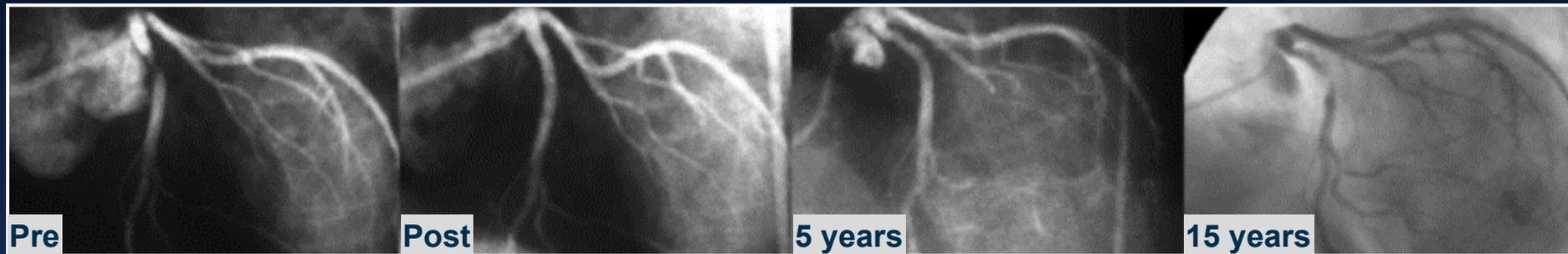


| | No. at risk | | | | | | | | | | |
|-----------------------|-------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Bare Metal Stent | 1,830 | 1,636 | 1,468 | 1,425 | 1,401 | 1,365 | 1,340 | 1,314 | 1,272 | 1,223 | 480 |
| First Generation DES | 4,591 | 4,296 | 4,124 | 4,022 | 3,929 | 3,828 | 3,477 | 3,172 | 2,860 | 2,465 | 1,474 |
| Second Generation DES | 9,955 | 9,606 | 9,334 | 9,149 | 8,962 | 8,799 | 8,160 | 5,125 | 4,559 | 3,852 | 2,366 |

Why do we Need a New Approach for Coronary Artery Disease?

Very late adverse events after metallic stents

In-stent restenosis (at 15 years)



Stent thrombosis (at 17 years)





Absorb BVS

**Fully
Bioresorbable**

PLLA Backbone

- Semi-crystalline
- Circumferential sinusoidal rings connected by linear links
- Strut thickness 150 μm
- Platinum markers in each end ring

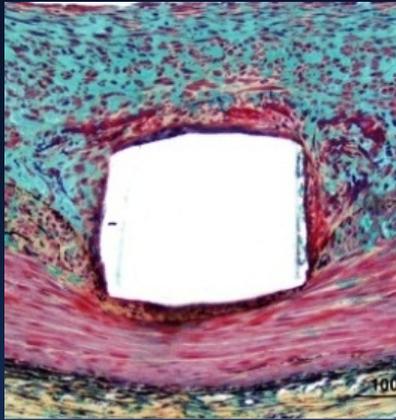
Everolimus/PDLLA (1:1) matrix coating

- 7 μm
- Conformal coating
- Controlled drug release similar to Xience CoCr-EES

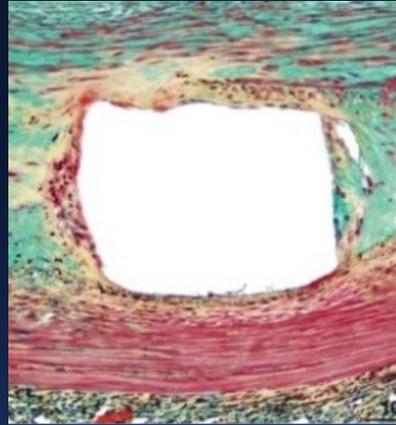


Full Bioresorption of Absorb Within ~3 Years

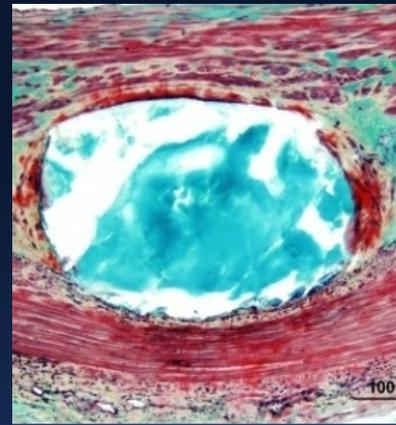
Porcine Histology



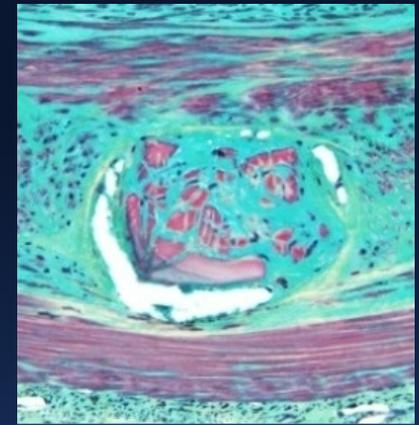
1 month



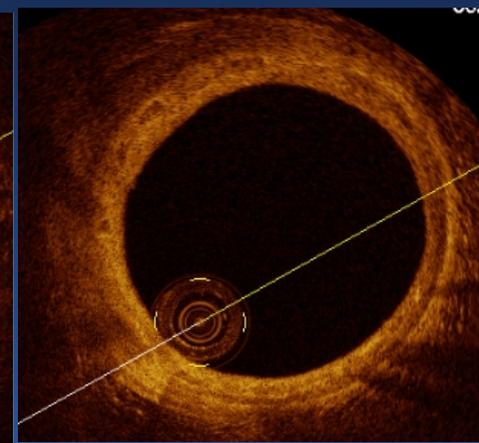
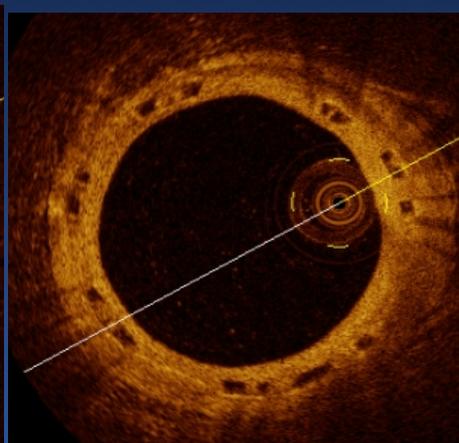
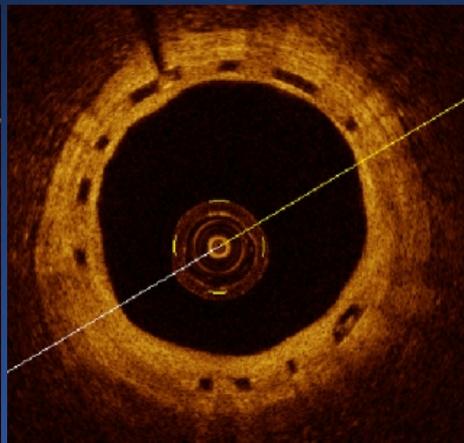
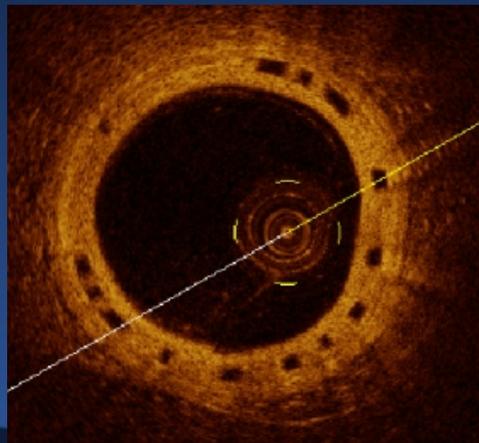
12 months



24 months



36 months

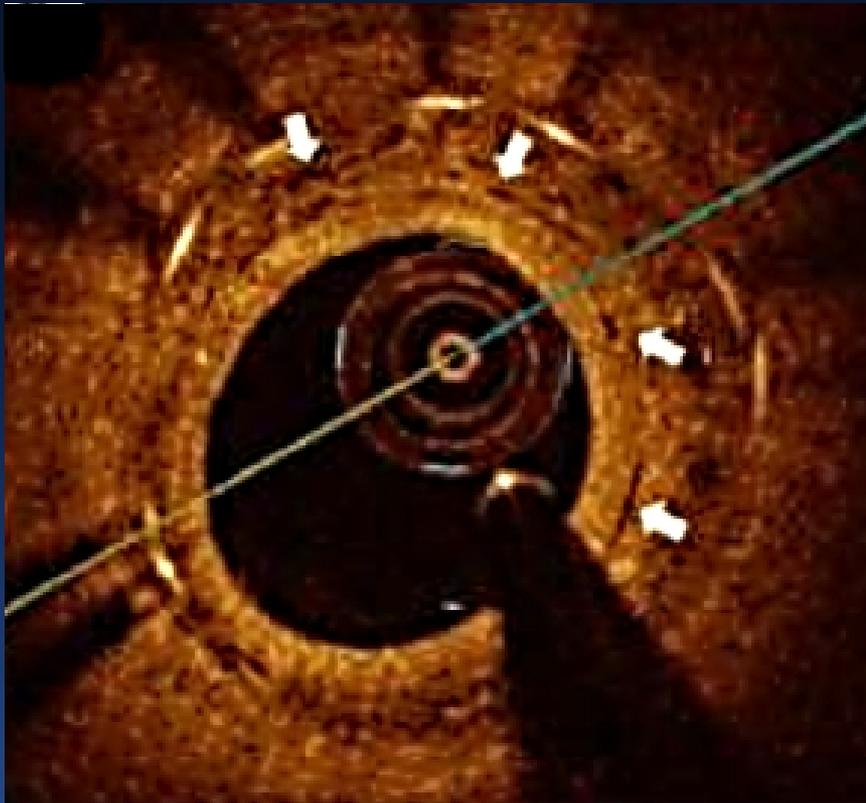


Human OCT

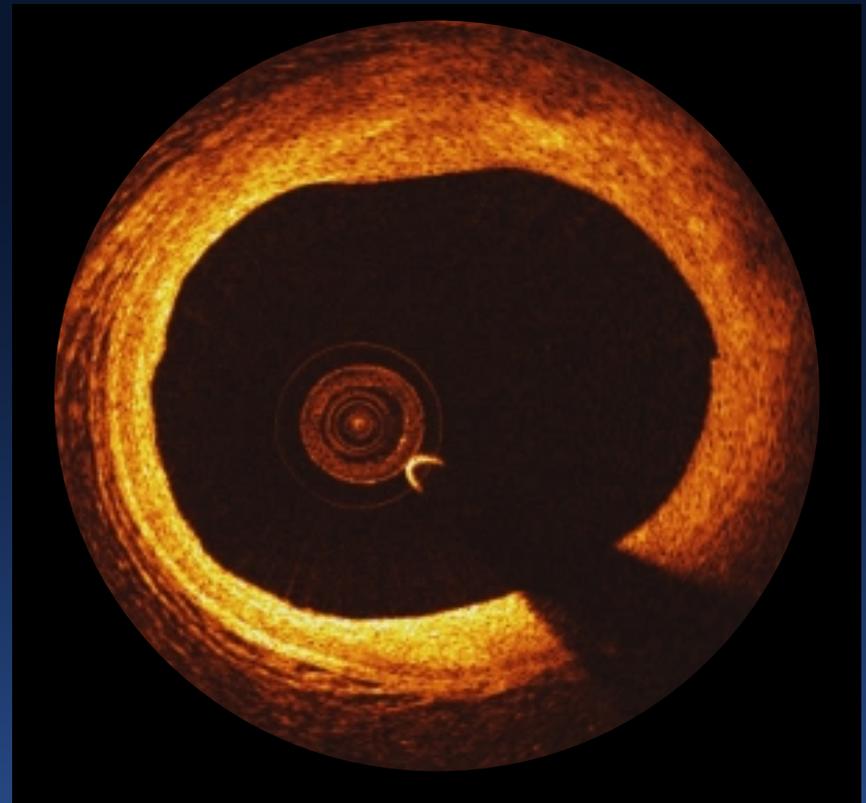


Metallic DES vs. Absorb BVS

Representative Human images at 5 Years



Metallic DES¹



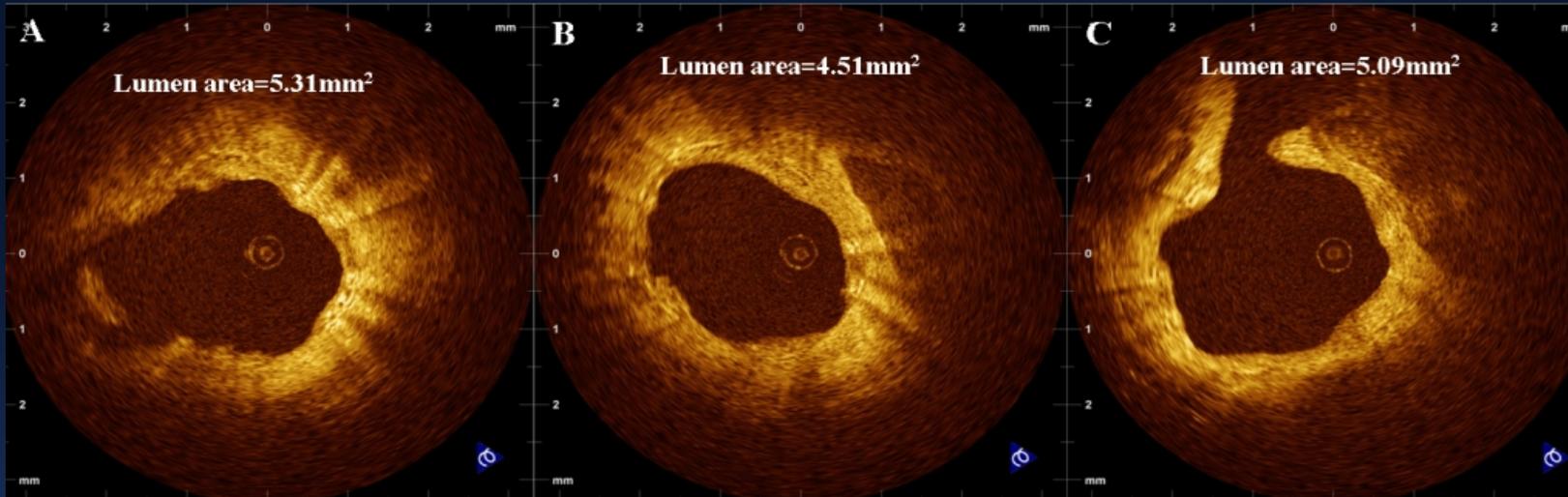
Absorb-Treated Artery²



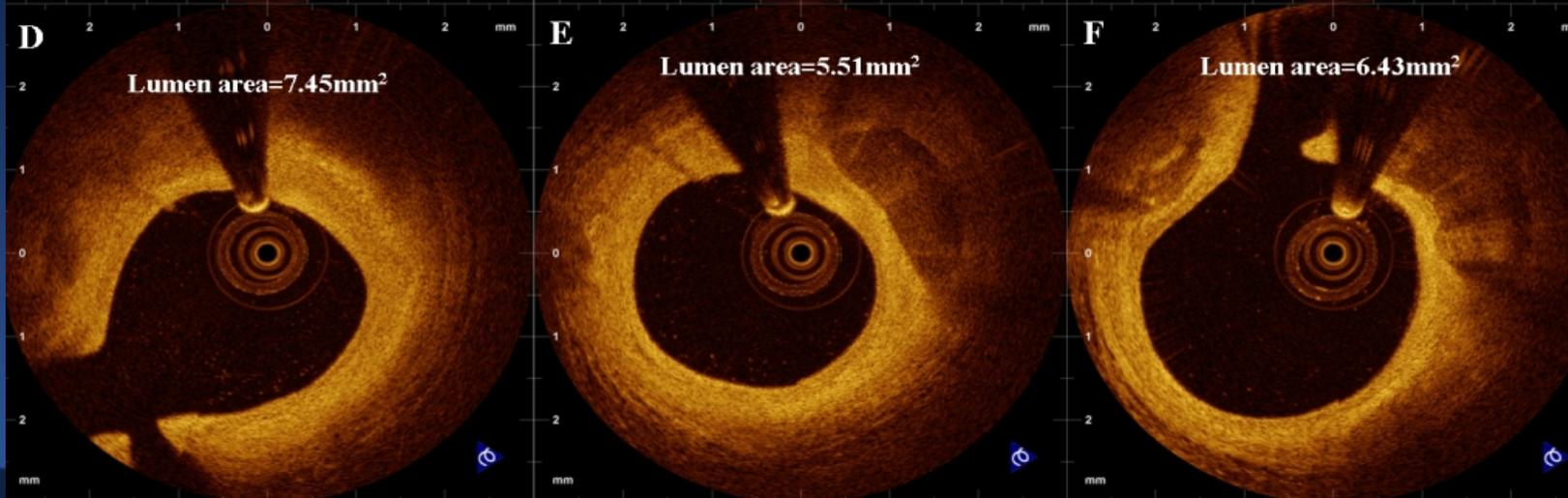
Treatment with BVS

Substantial lumen enlargement due to plaque regression and adaptive remodeling

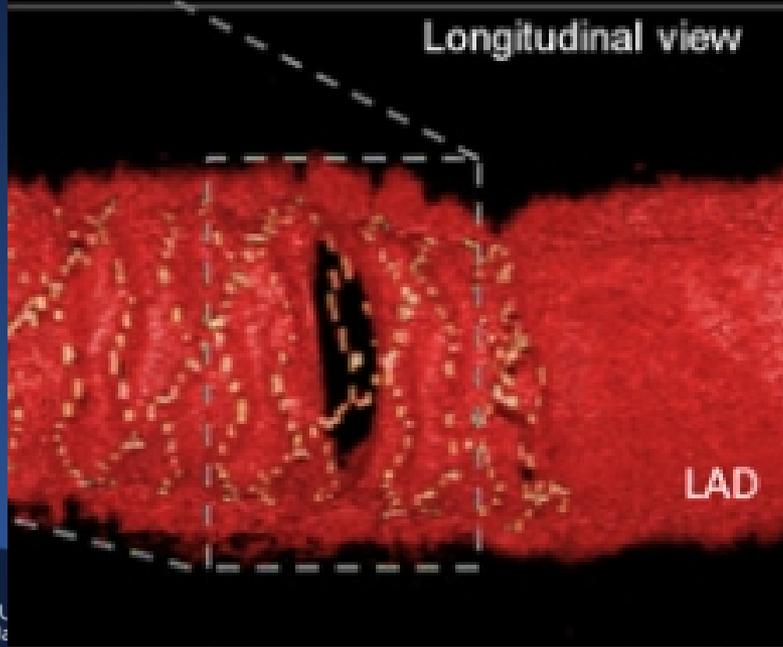
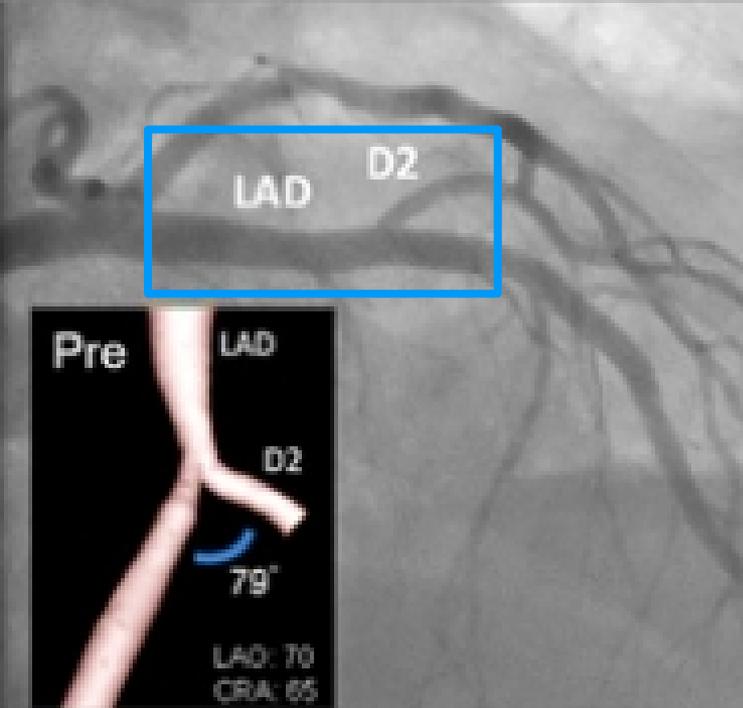
6 months



5 years



Jailed Side Branches with Metallic Stents Never go away!



Unjailing Side Branches with Absorb BVS

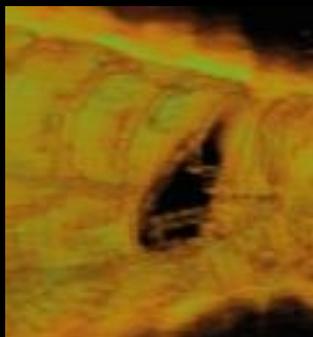
Post-procedure

1 Year

3 Years

5 Years

Longitudinal



Single cut plane

Compartments: 3,
area free from struts:
0.91 mm²



Unjailing Side Branches with Absorb BVS

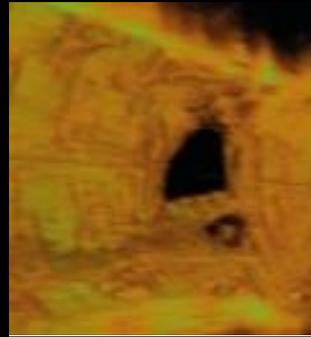
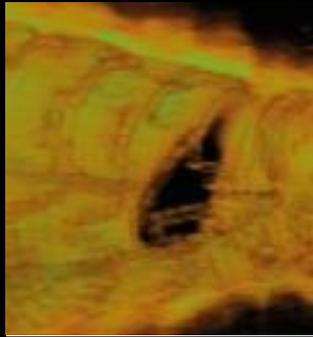
Post-procedure

1 Year

3 Years

5 Years

Longitudinal



Single cut plane



Unjailing Side Branches with Absorb BVS

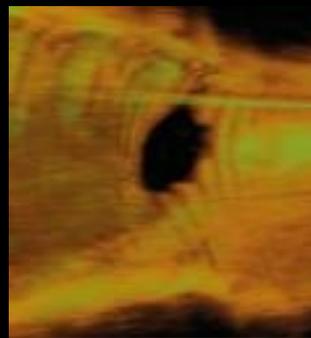
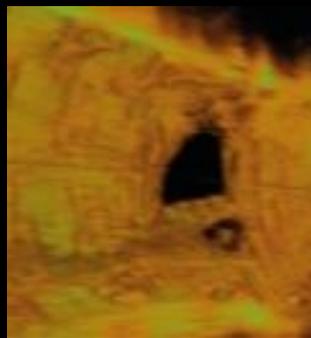
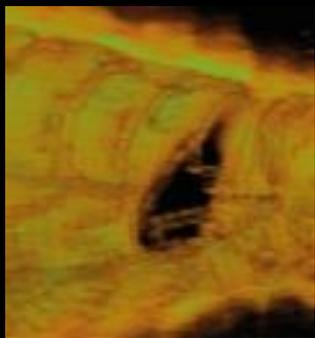
Post-procedure

1 Year

3 Years

5 Years

Longitudinal



Single cut plane



Unjailing Side Branches with Absorb BVS

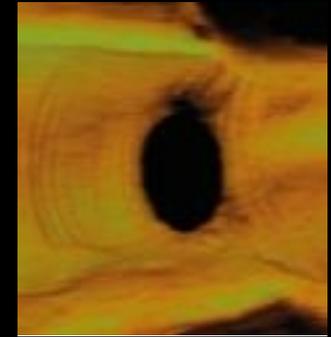
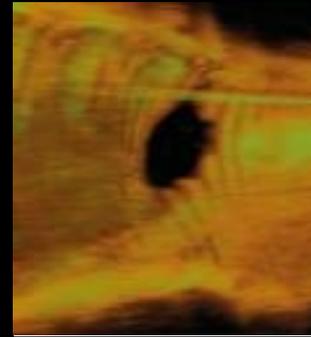
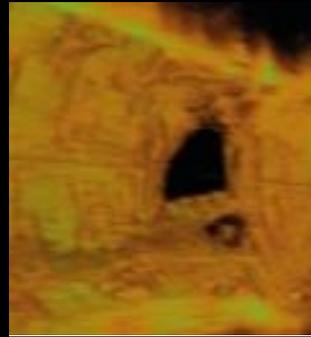
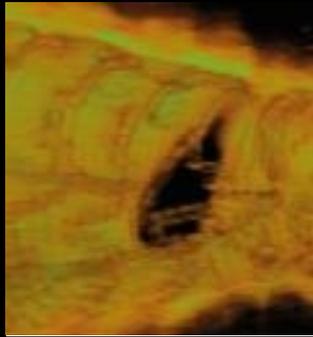
Post-procedure

1 Year

3 Years

5 Years

Longitudinal



Single cut plane

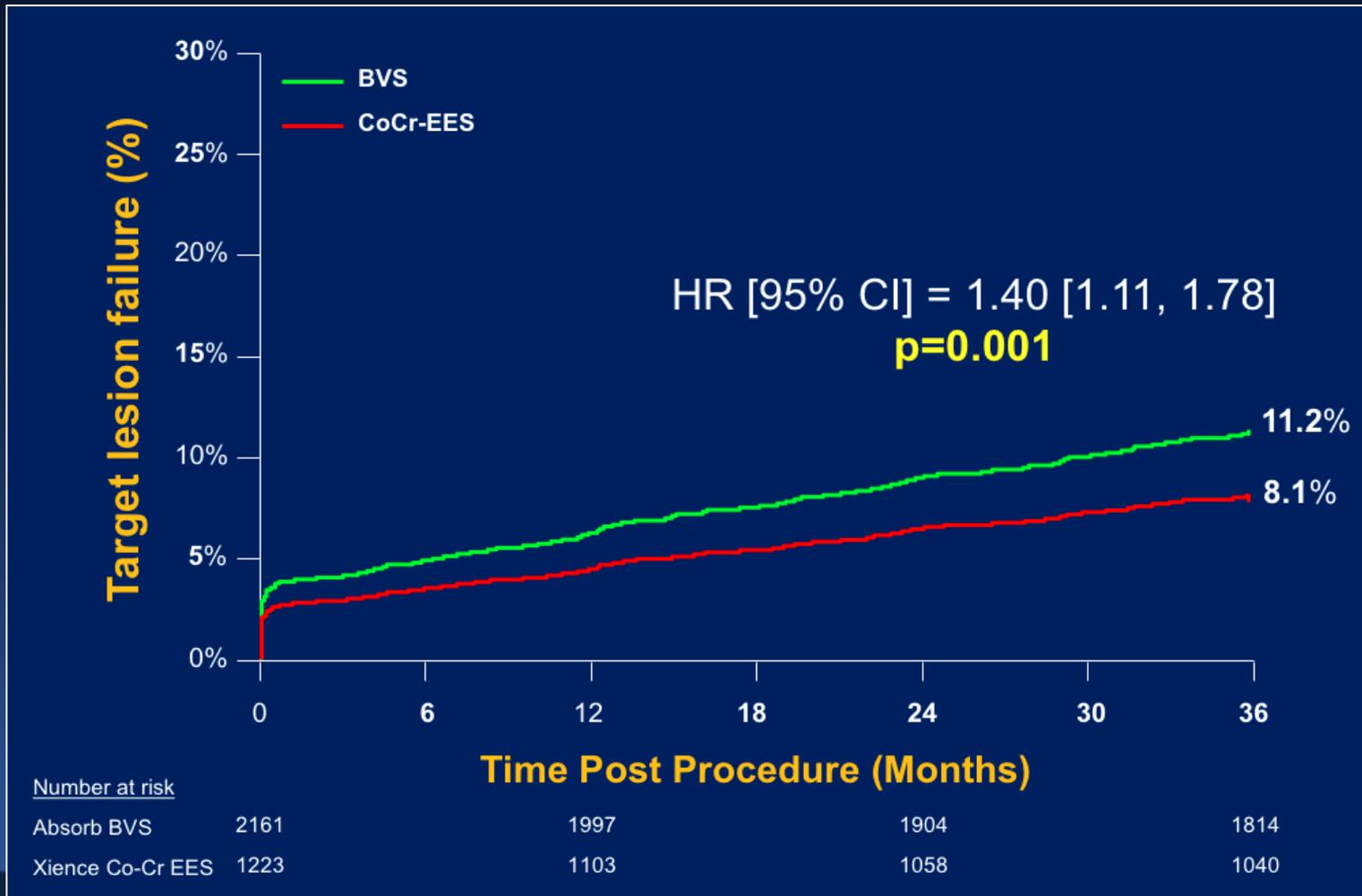




ABSORB: 3-year Outcomes

Meta-analysis of 4 BVS vs. EES RCTs (n=3,389 pts)

3-Year TLF

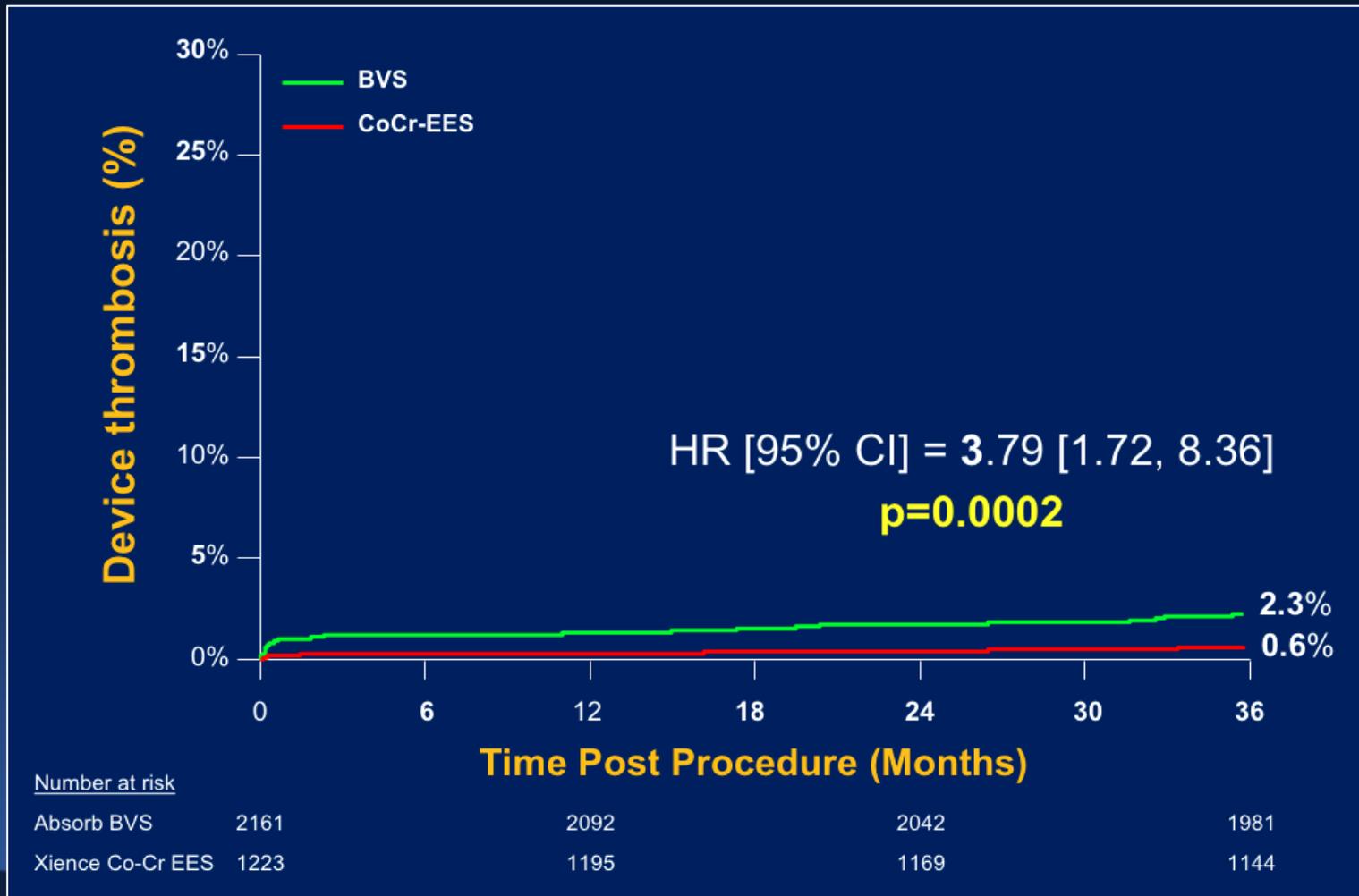




ABSORB: 3-year Outcomes

Meta-analysis of 4 BVS vs. EES RCTs (n=3,389 pts)

3-Year Device Thrombosis

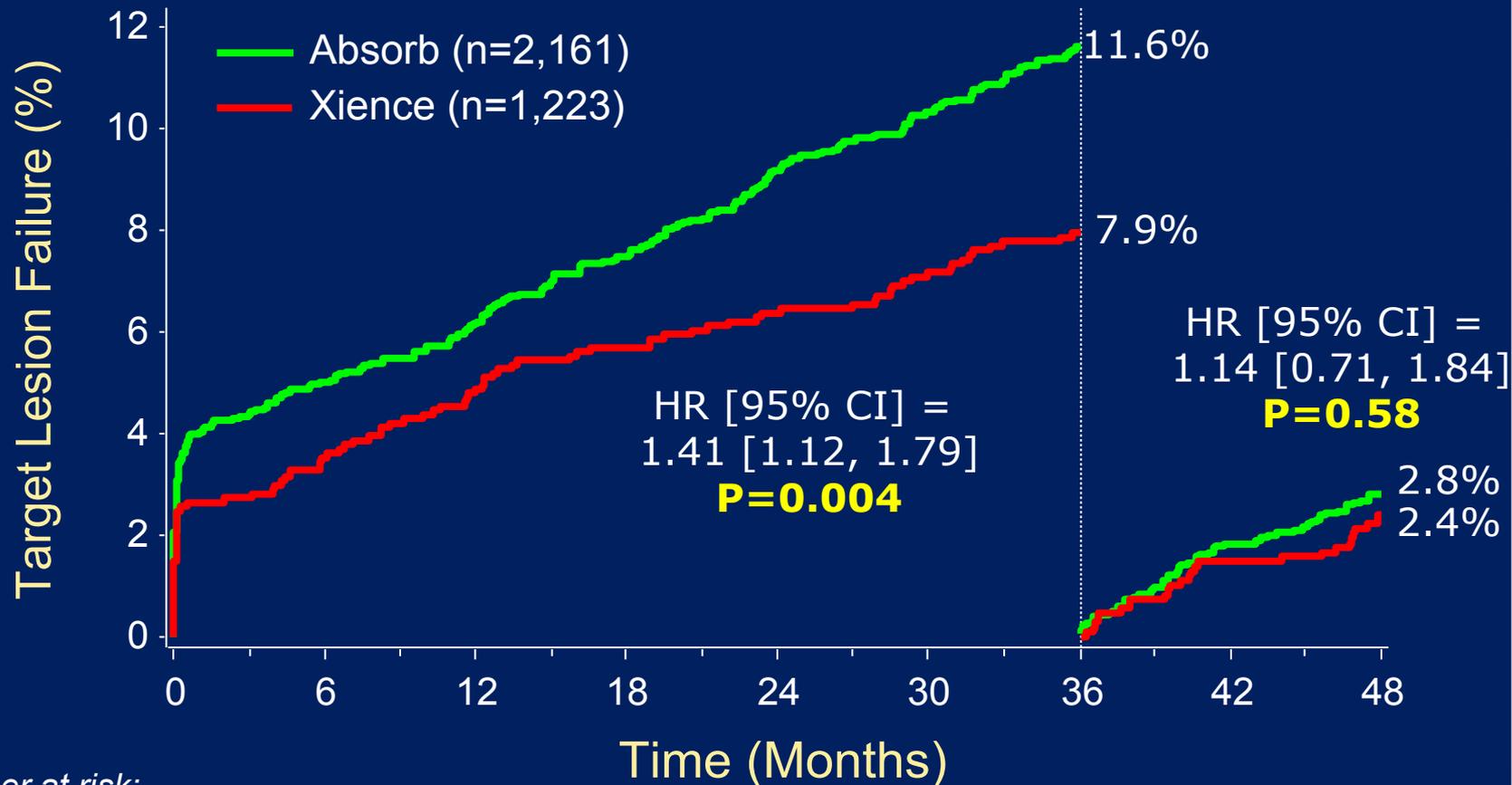




ABSORB: 4-year Outcomes

Meta-analysis of 4 BVS vs. EES RCTs (n=3,389 pts)

4-Year TLF (Landmark)



Number at risk:

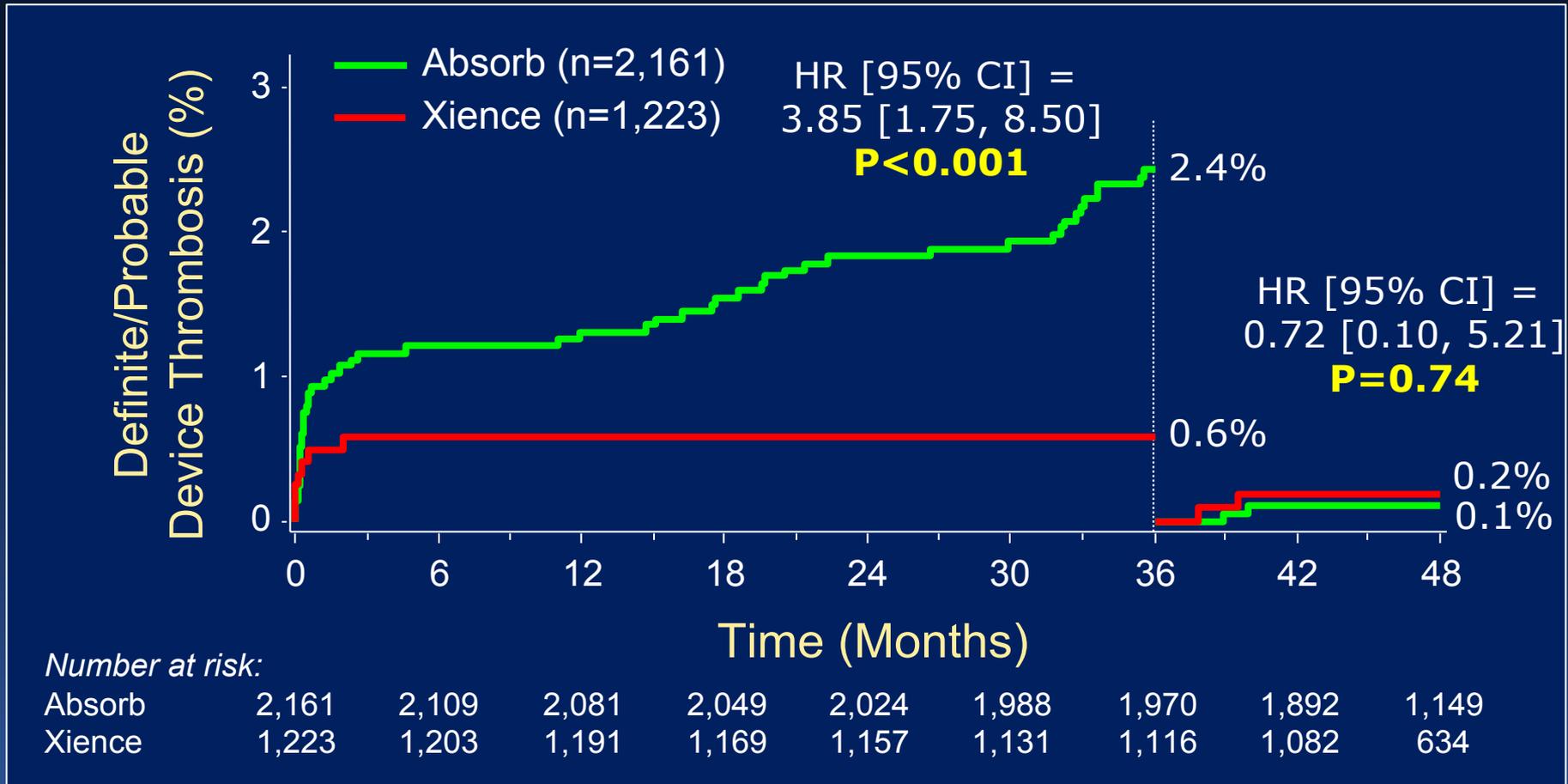
| | | | | | | | | | |
|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Absorb | 2,161 | 2,032 | 1,987 | 1,935 | 1,887 | 1,833 | 1,970 | 1,866 | 1,123 |
| Xience | 1,223 | 1,169 | 1,144 | 1,115 | 1,096 | 1,064 | 1,116 | 1,072 | 626 |



ABSORB: 4-year Outcomes

Meta-analysis of 4 BVS vs. EES RCTs (n=3,389 pts)

4-Year Device Thrombosis (Landmark)



How to Improve BRS Outcomes Prior to Their Complete Bioresorption

Improve the Technique

PSP

Imaging

Prolonged DAPT

Improve the Device

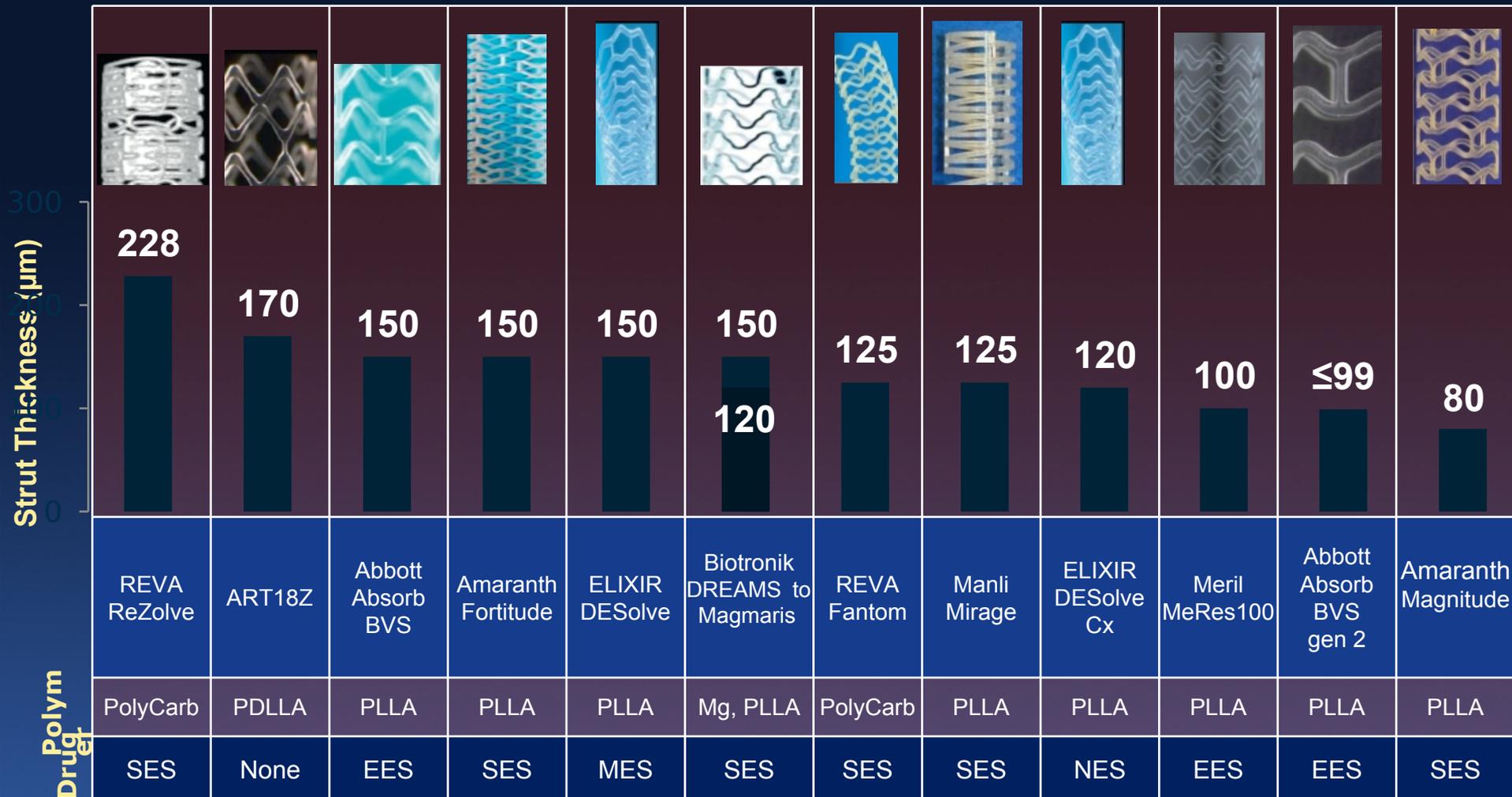
Thinner struts

Improved mechanical properties

Bioresorbable Scaffolds: **Rapidly thinning**

1st Generation BRS

2nd Generation BRS



SES = sirolimus-eluting scaffold, EES = everolimus-eluting scaffold
 MES = myolimus-eluting scaffold, NES = novolimus-eluting scaffold

Conclusions: The Evolution of PCI



It has been an exciting ride with many twists and turns – **but the best is yet to come!**