Contemporary DES Thrombosis and Restenosis: Mechanisms, Incidence, and Treatment

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

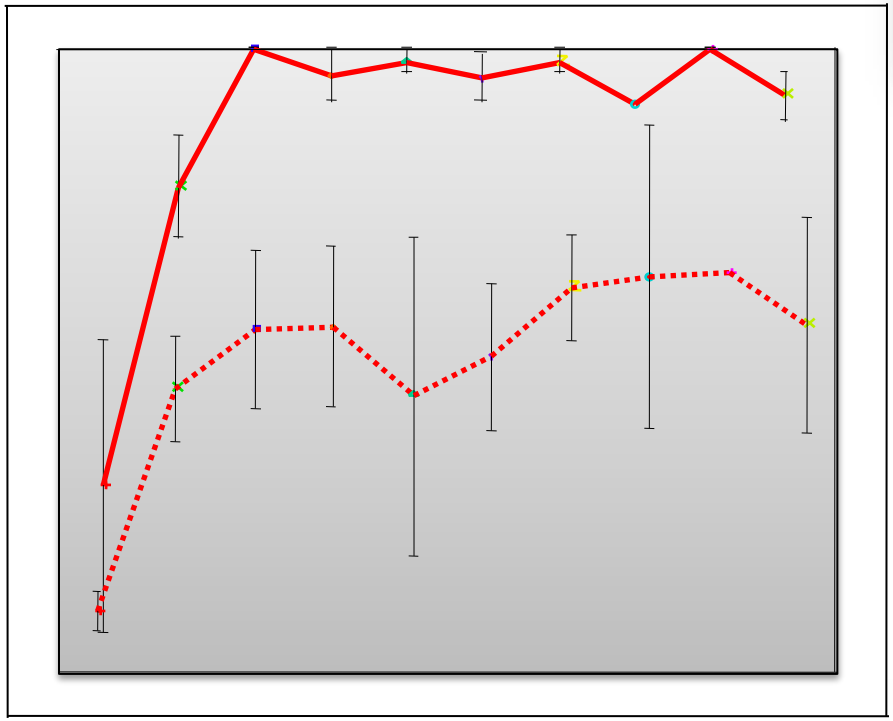
Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott Vascular, Medtronic
• Scientific Advisory Board	• Medtronic, Abbott Vascular
• Executive Physician Council	• Boston Scientific Corp

Mechanisms

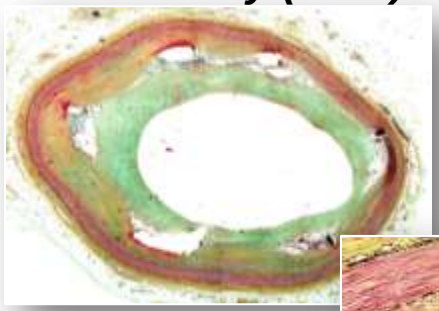
Principal Causes of Adverse Events with Current DES

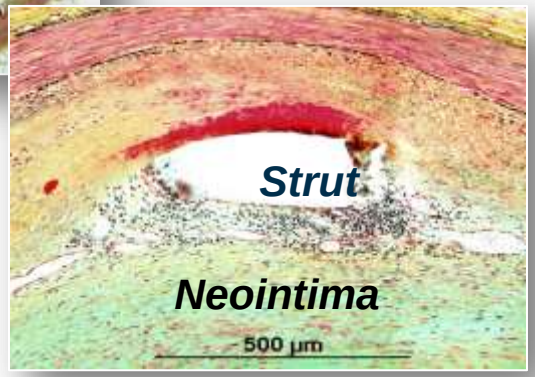
- Early and late inflammatory and hypersensitivity reactions to the drug or polymer (dose related?)
- Polymer irregularities that result in inconsistent drug delivery or serve as a nidus for thrombus
- Mechanical issues: Strut fracture >> longitudinal deformation; thick struts.
- Very late issues with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

Delayed Arterial Healing in 1st Generation DES

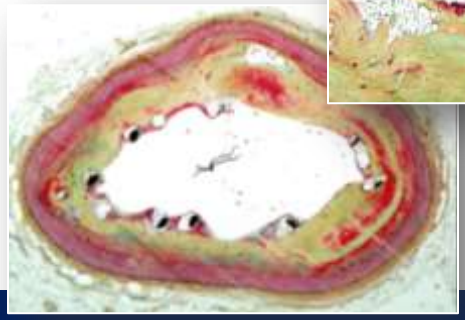


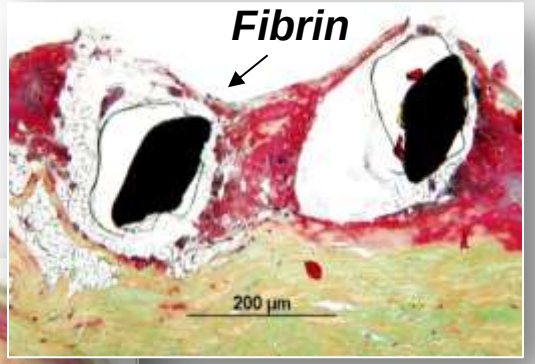
BxVelocity (BMS)





Cypher (DES)





Joner M et al. J Am Coll Cardiol. 2006;48(1):193-202.

Hypersensitivity Reaction to SES

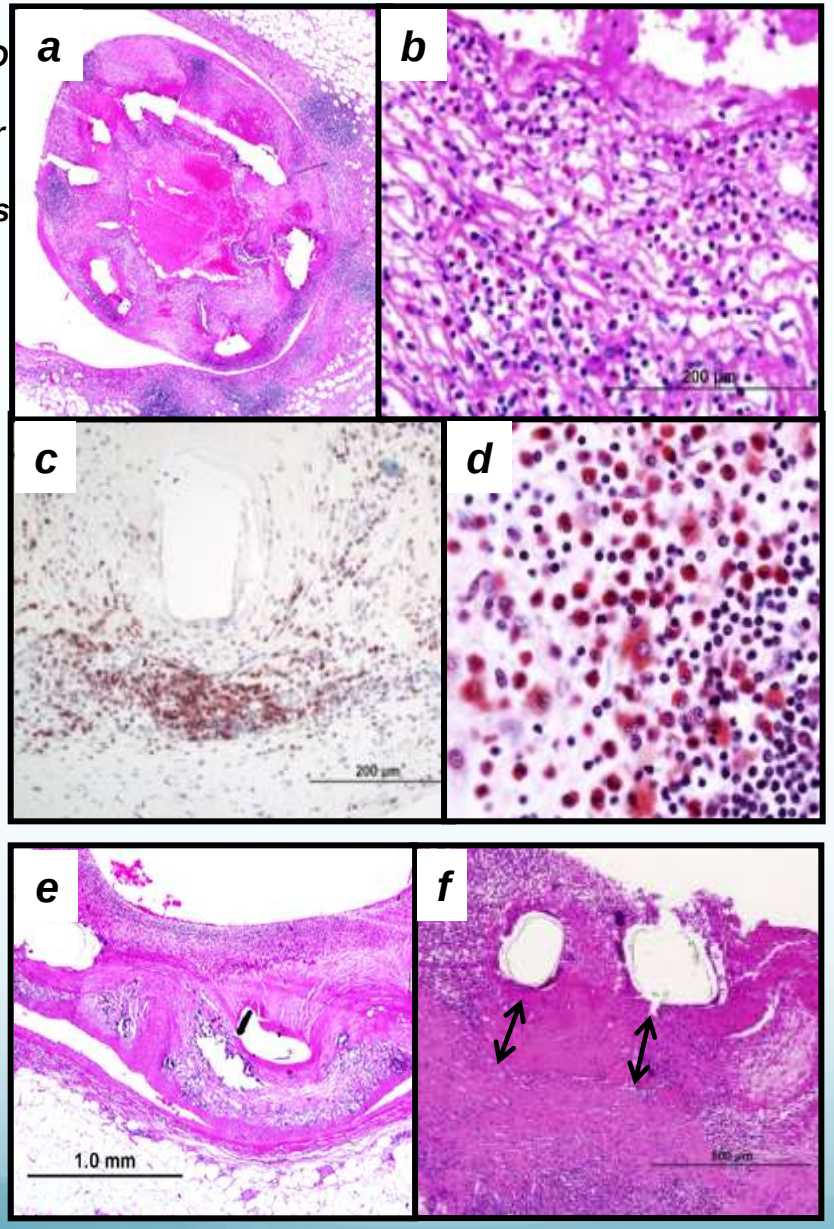
40F with 2 SES in LAD and RCA, died suddenly 4 days after surgical removal of melanoma. DAPT was discontinued 5 days before surgery.

(a)-(d)

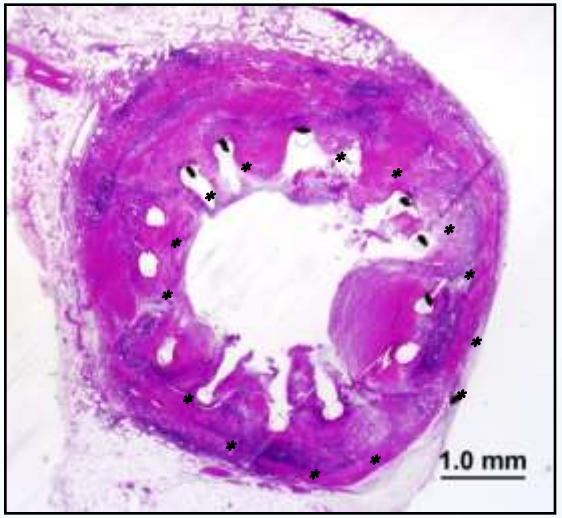
LAD: SES 17months

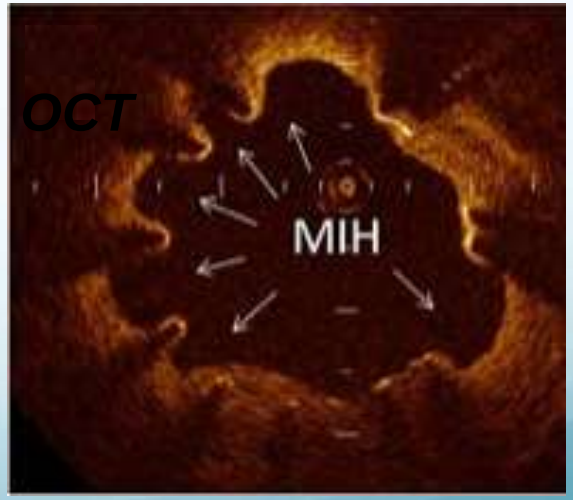
(e), (f)

RCA: SES 17months



39F SES in LMCA for 5 yrs.
The patient recently stopped taking medication due to lack of insurance.





MIH = Multiple interstrut hollow

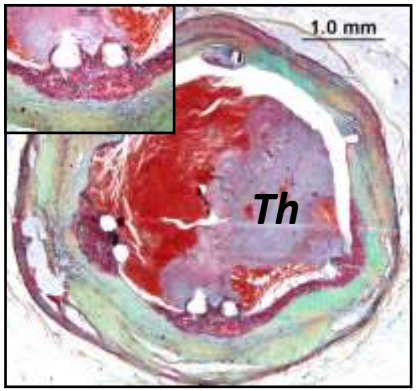
Nakazawa G, et al. JACC 2011;57:390-398

OCT: Tada T. AHA2011

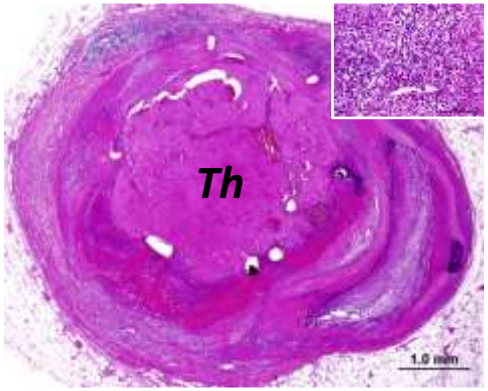
Pathology of 1st-Generation DES: High Efficacy, Incomplete Healing

- *Thick struts*
- *Thick, durable coating (~15 µm)*
- *High drug dose*
- *High polymer load*

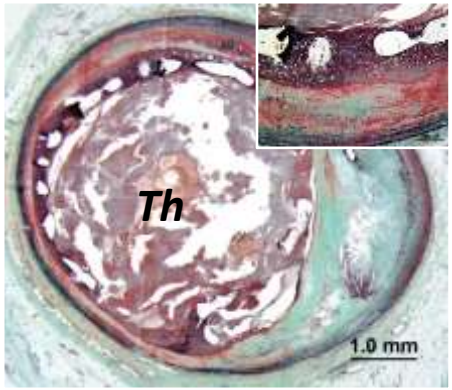
- ✓ *Uncovered struts*
- ✓ *Hypersensitivity*
- ✓ *Malapposition*
- ✓ *Late stent thrombosis*
- ✓ *Neoatherosclerosis*



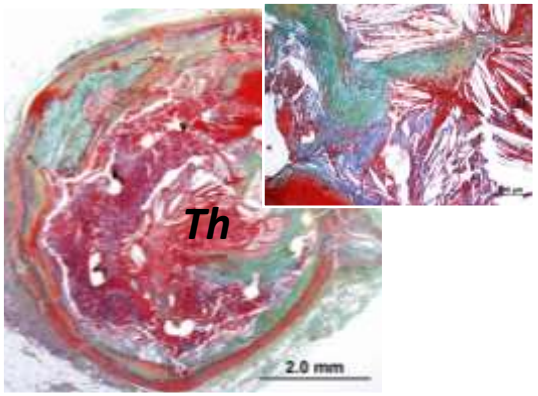
Uncovered struts



Hypersensitivity reaction

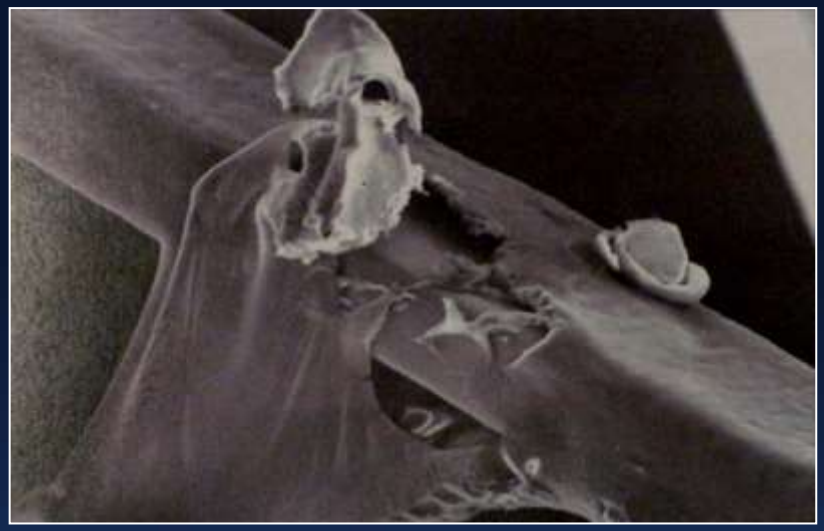


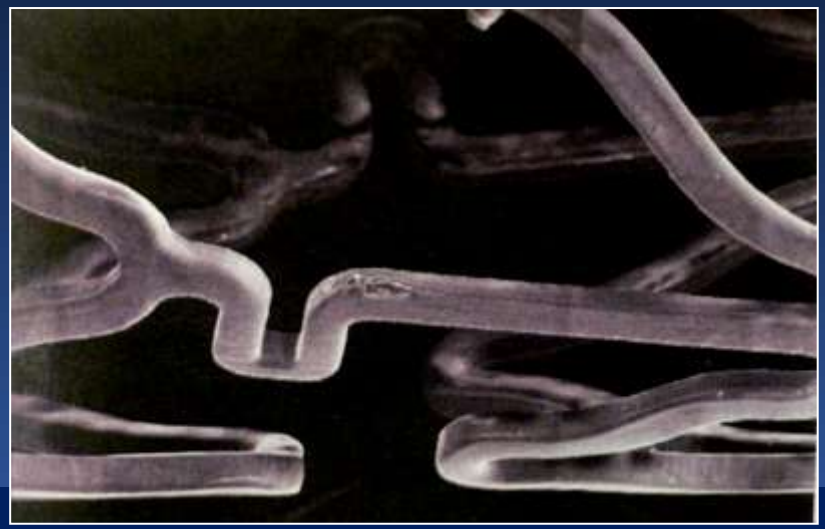
Malapposition from excessive fibrin deposition



Neoatherosclerosis

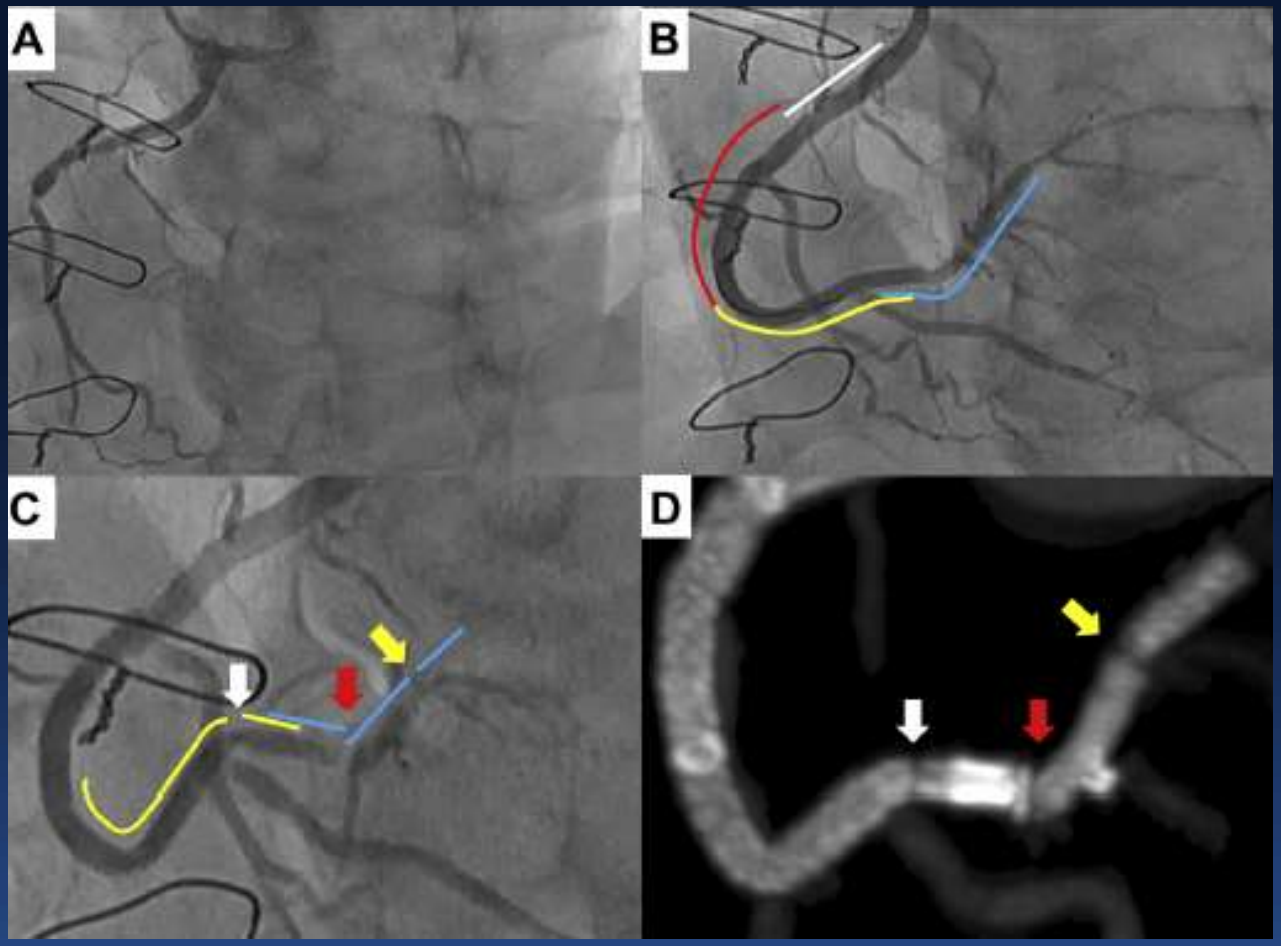
Polymer Integrity Issues in FDA Approved DES





c/o Renu Virmani

Late Fractures After EES

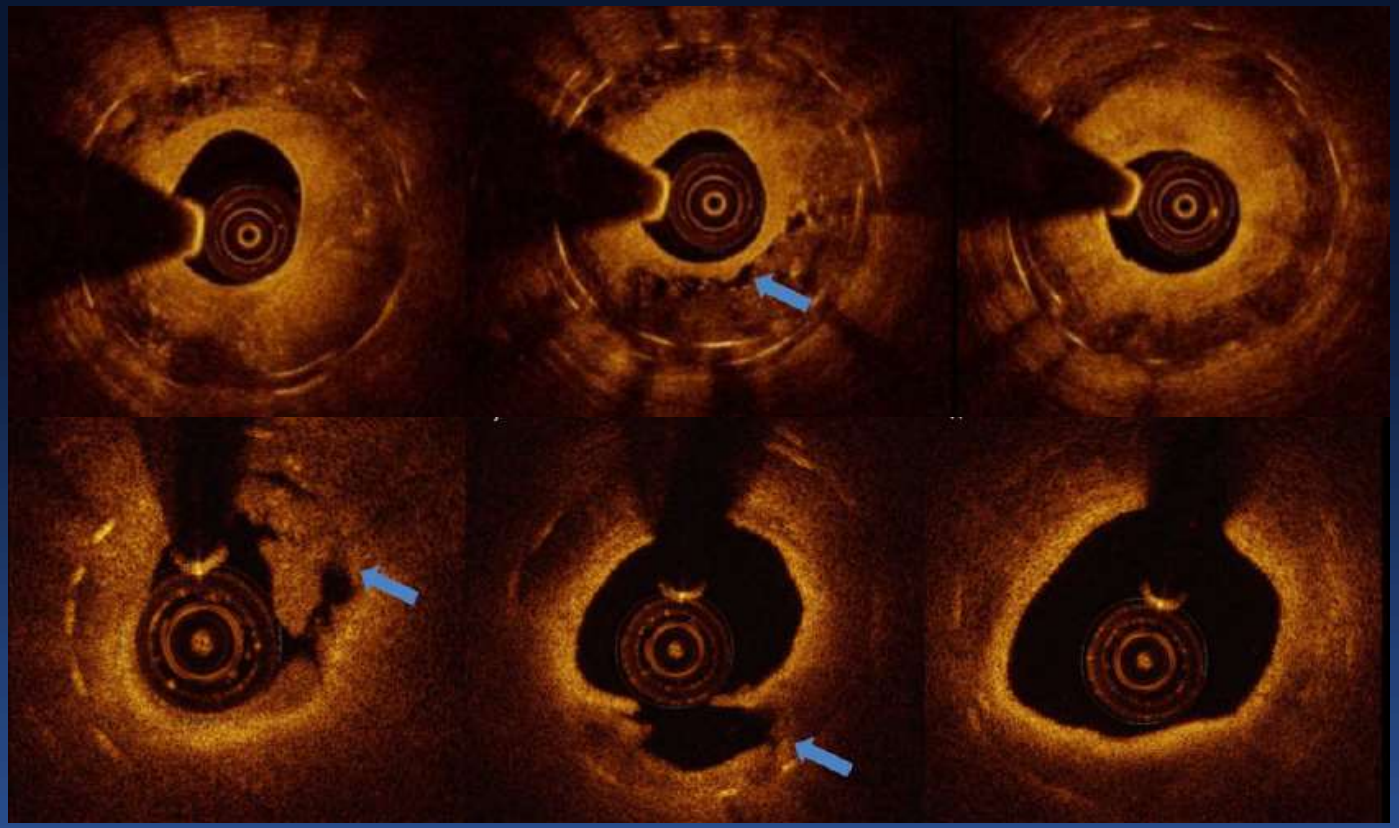


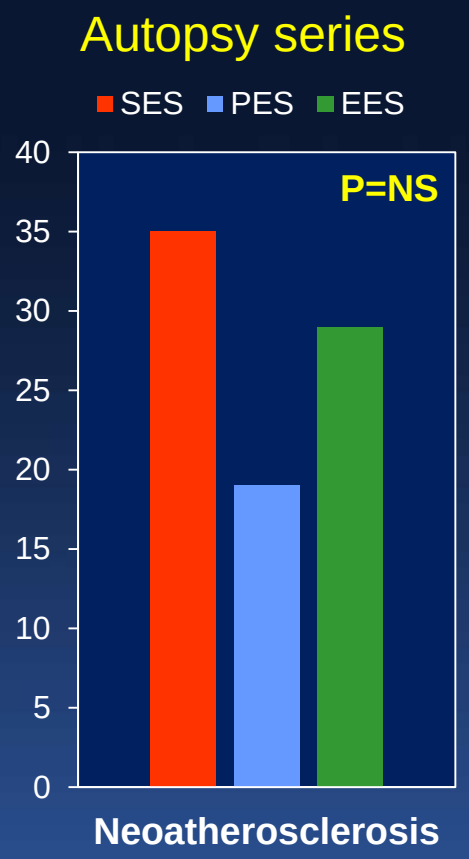
3 strut fractures 6 months after placement of 4 overlapping Pt-Cr-EES

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

Kuramitsu S et al. Circ CV Interv. 2012;5:663-671
Kuramitsu S et al. JACC Intv 2015;8:1180–8

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

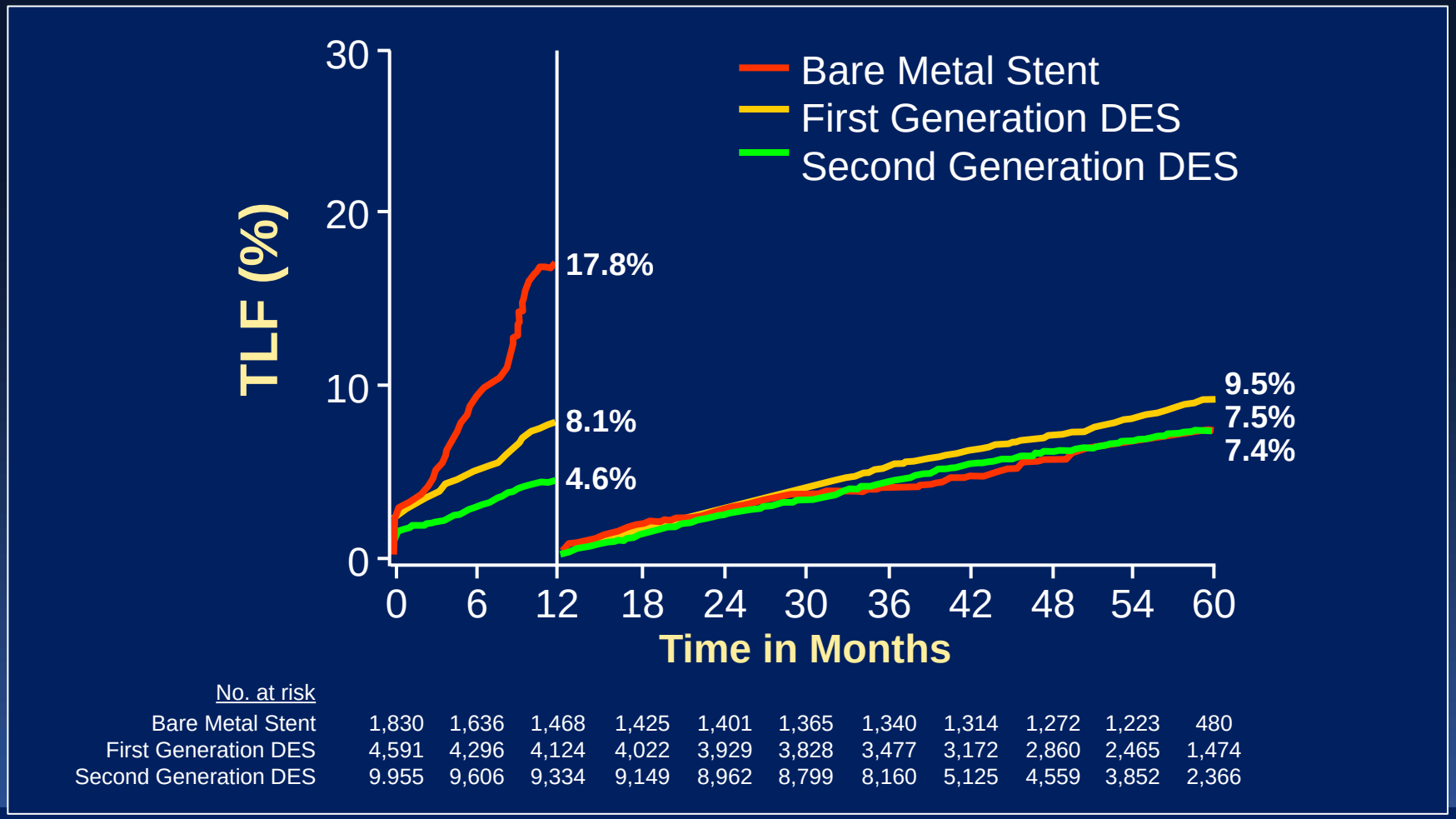




Otsuka F et al. Eur Heart J 2015;36:2147–59

Incidence

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

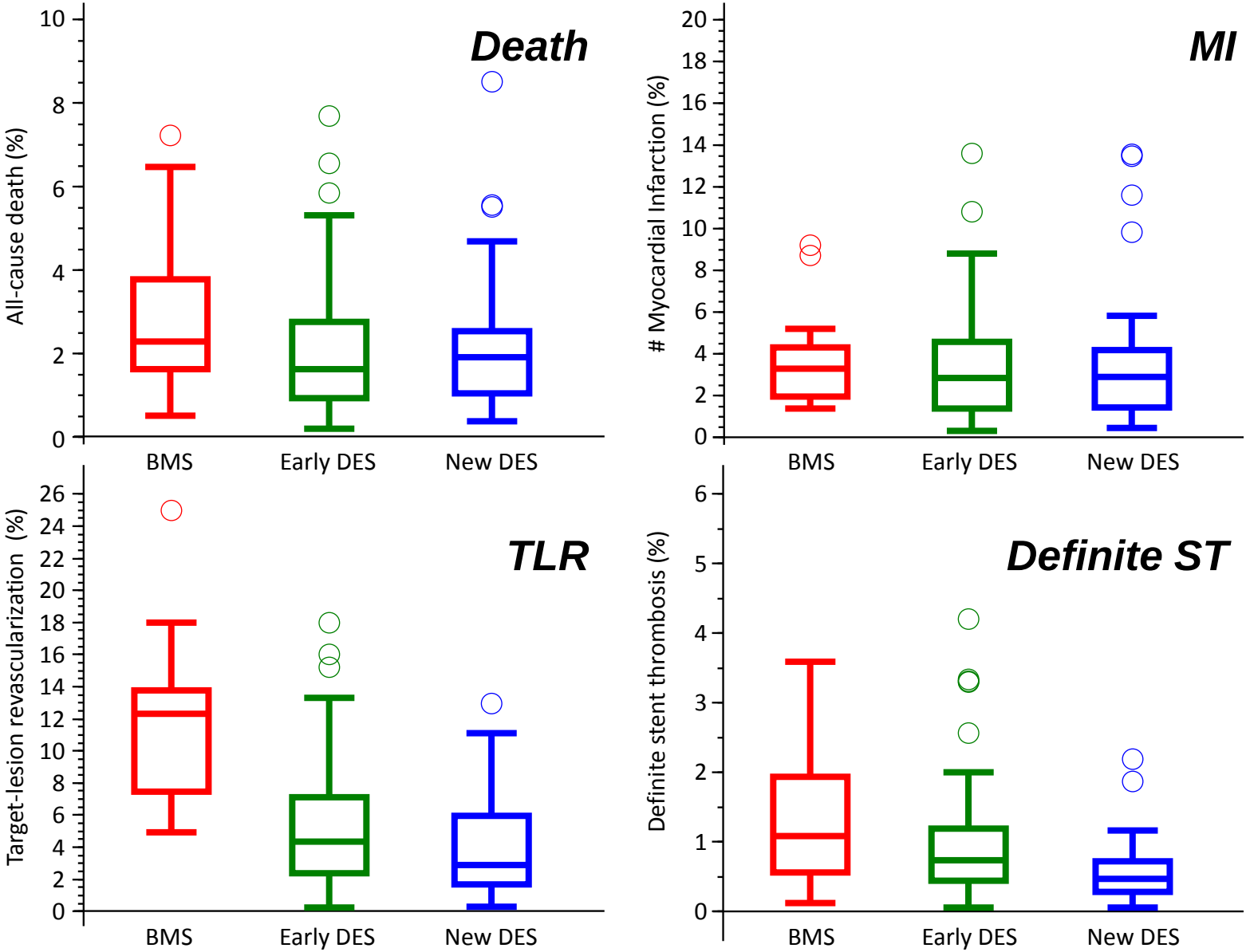


No. at risk											
Bare Metal Stent	1,830	1,636	1,468	1,425	1,401	1,365	1,340	1,314	1,272	1,223	480
First Generation DES	4,591	4,296	4,124	4,022	3,929	3,828	3,477	3,172	2,860	2,465	1,474
Second Generation DES	9.955	9,606	9,334	9,149	8,962	8,799	8,160	5,125	4,559	3,852	2,366

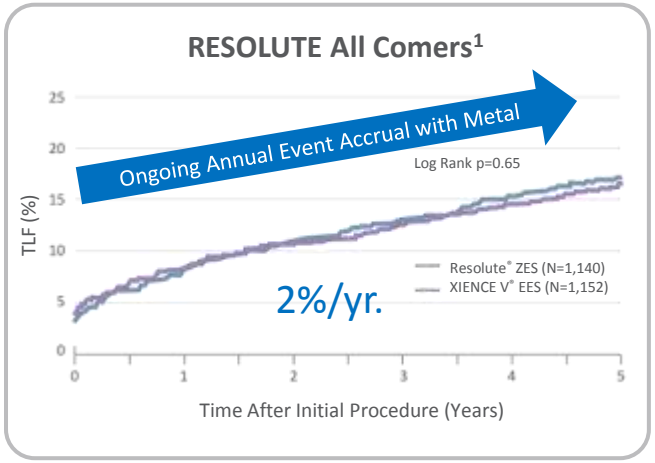
Madhaven M et al. TCT 2016.

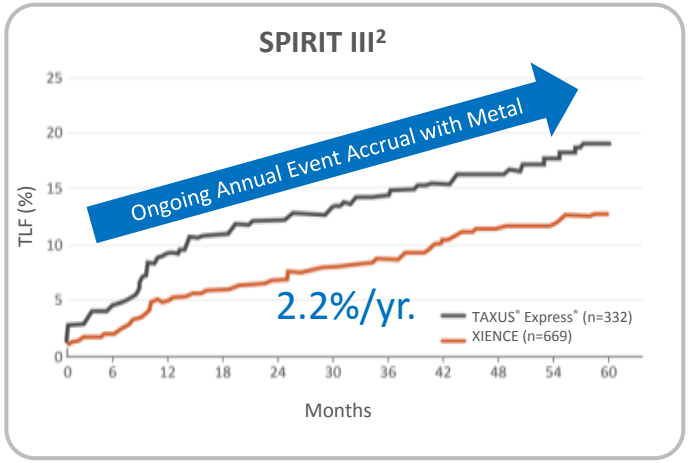
Impact of Stent Iterations on Safety & Efficacy

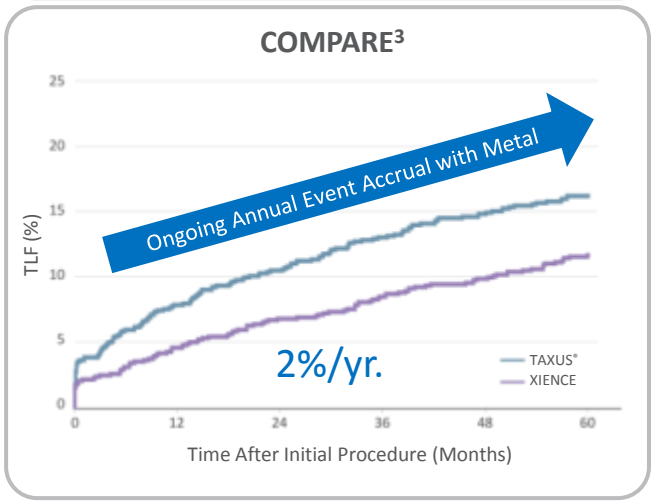
ESC-EAPCI Stent Task Force | *Eur Heart J* 2015

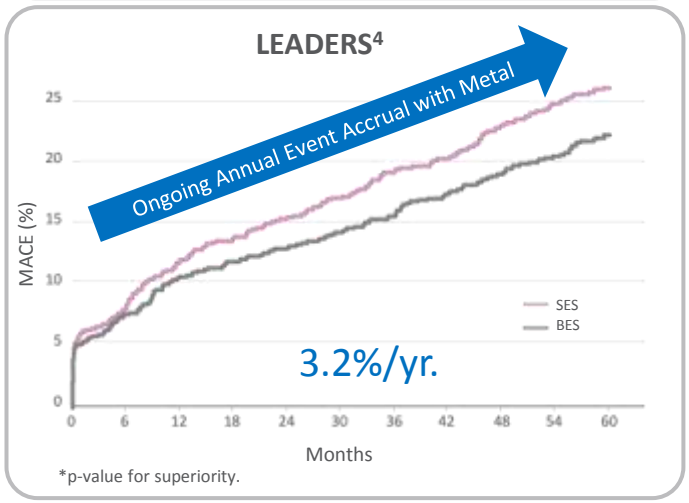


Limitations of Permanent DES Implants









1. Windecker S. RESOLUTE All Comers 5-Year. EuroPCR 2014. 2. Gada H et al. SPIRIT III 5-year. JACC Cardiovasc Interv. 2013;6:1263-1266.
3. Smits P. COMPARE 5-Year. TCT 2013. 4. Serruys PW. LEADERS 5-Year. TCT 2012.

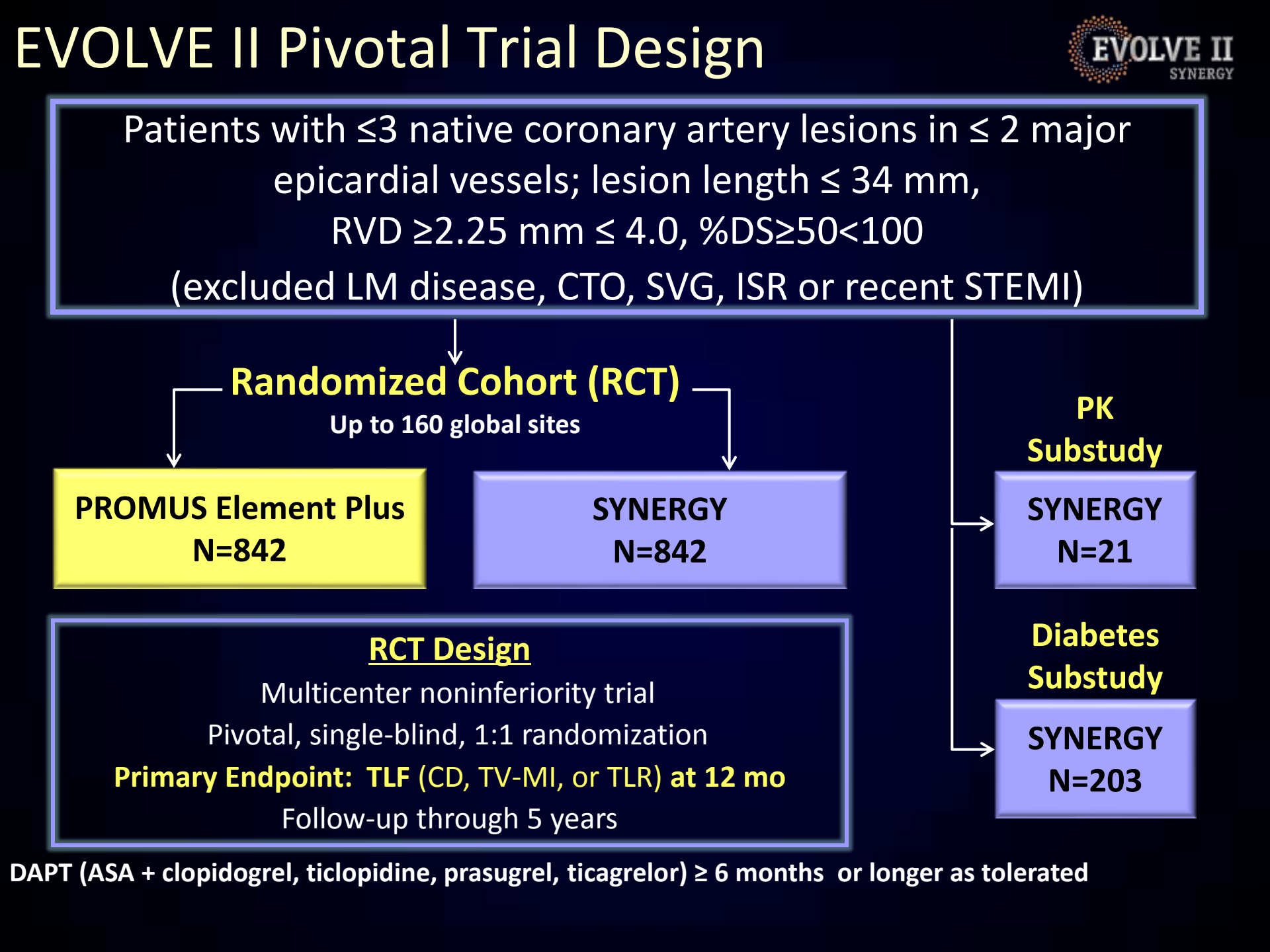
Contemporary DES : Strut Thickness/Coating

	Durable Polymer Coated		Bioabsorbable Polymer Coated					
	Xience CoCr-EES	Resolute	Biomatrix	Nobori	SYNERGY	BioMime	MiStent	Orsiro
	Promus PtCr-EES	CoNi-ZES	316L-BES	316L-BES	PtCr-EES	CoCr-SES	CoCr-SES	CoCr-SES
								
Strut thickness	81µm 0.0032”	89µm 0.0035”	120µm 0.0046”	125µm 0.0047”	74µm 0.0029”	65µm 0.0026”	64µm 0.0025”	61µm 0.0024”
Polymer	PVDF	BioLINX	PLA	PLA	PLGA	PLLA + PLGA	PLGA	PLLA Probio*
Distribution / thickness	Conformal 7-8µm / side	Conformal 6µm / side	Abluminal 10µm	Abluminal 20µm	Abluminal 4µm	Conformal 2µ / 2µ	Conformal 5µm / 15µm	Conformal 3.5µm / 7.5µm

*silicon carbide

Slide c/o Boston Scientific Corporation

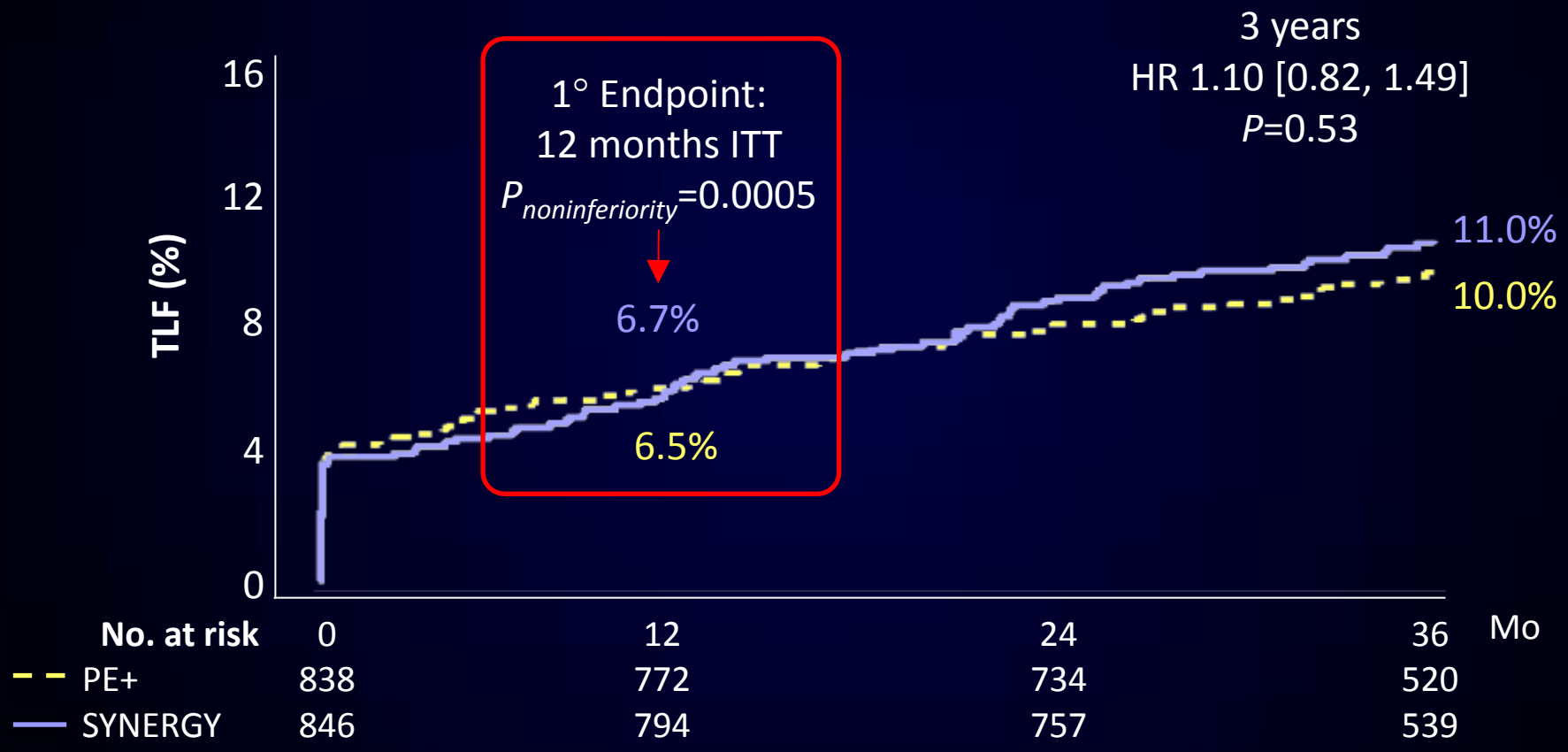
EVOLVE II Pivotal Trial Design



DAPT (ASA + clopidogrel, ticlopidine, prasugrel, ticagrelor) ≥ 6 months or longer as tolerated

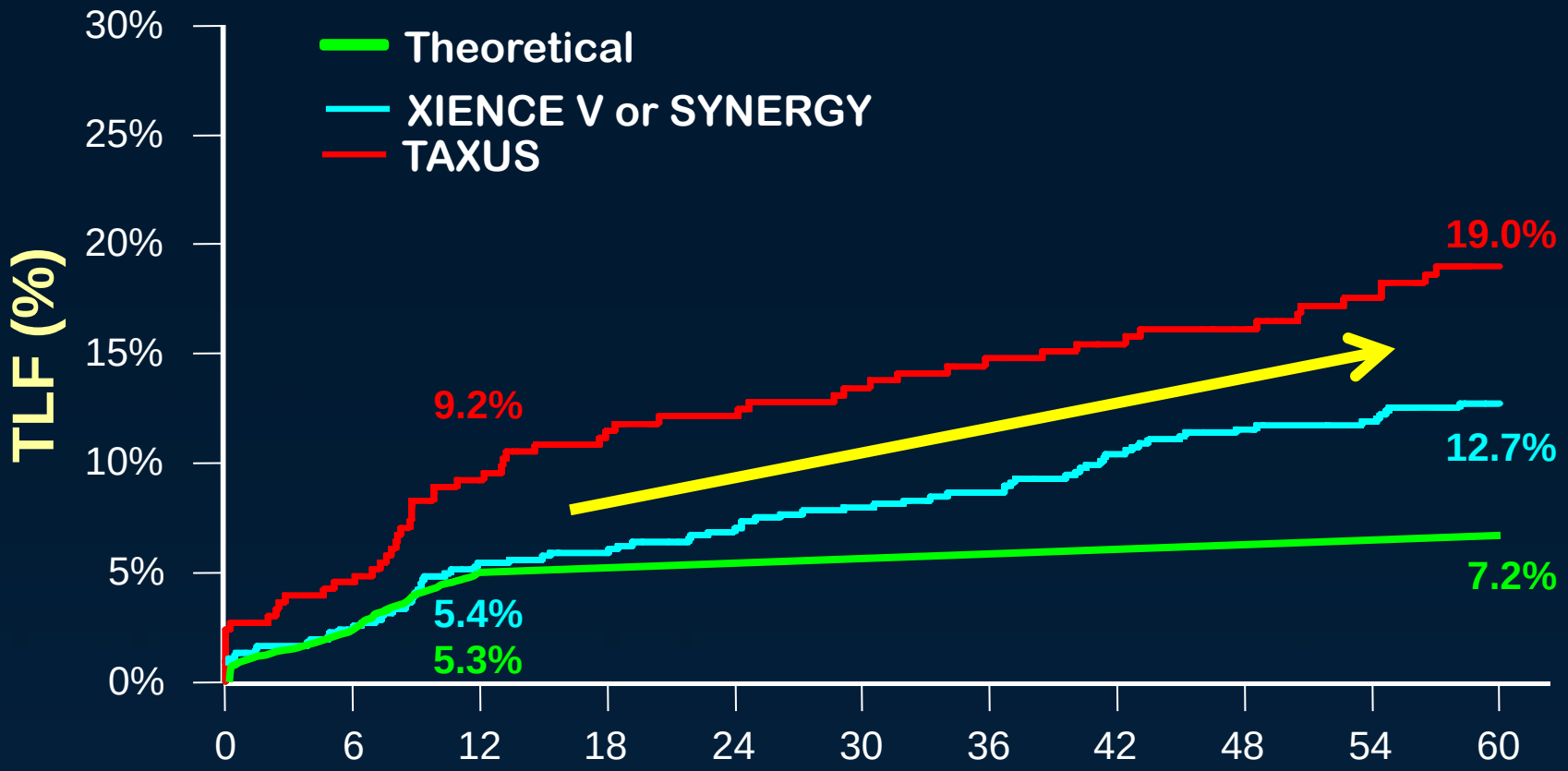
EVOLVE II TLF at 3 years

PROMUS Element Plus vs. SYNERGY



ITT; Patients who did not receive a study stent were censored at 1 year; KM Event Rate; log-rank *P* values

From TAXUS to XIENCE to Ideal



Number at risk

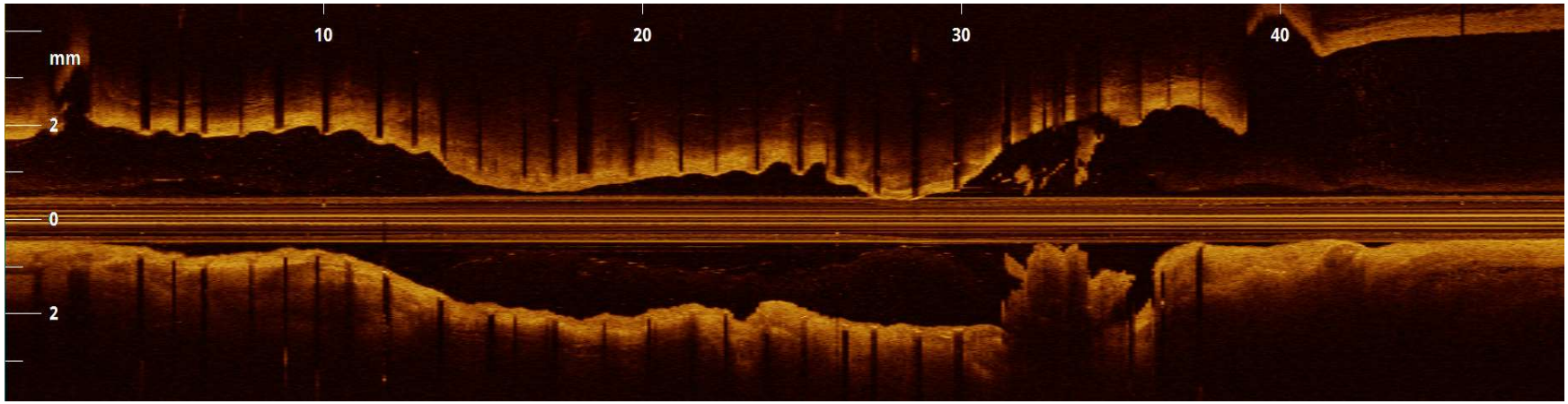
XIENCE V	669	646	616	601	582	571	565	548	537	529	521
TAXUS	332	310	288	274	269	262	255	248	243	231	223

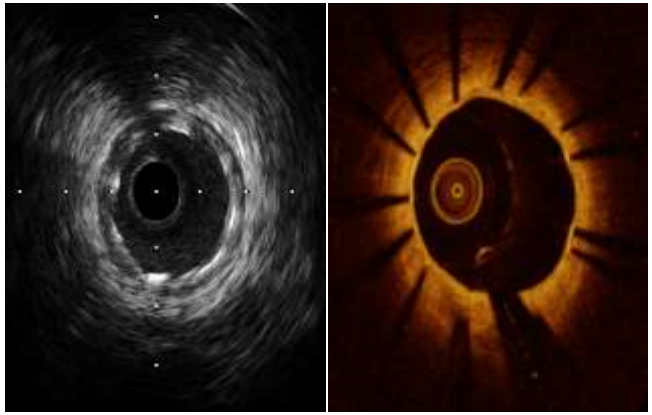
TLF = cardiac death, target vessel MI, or ischemic-driven TLR

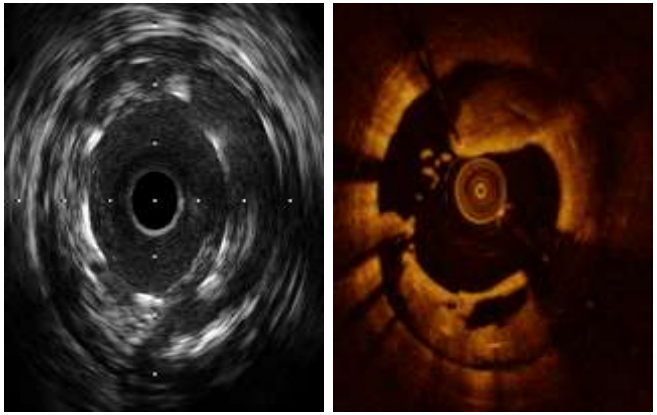
Spirit III: Gada H et al. J Am Coll Cardiol Intv 2013;6:1263–6

Treatment

State-of-the-Art Review: Intravascular Imaging and Physiology to Evaluate Stent Thrombosis and Restenosis



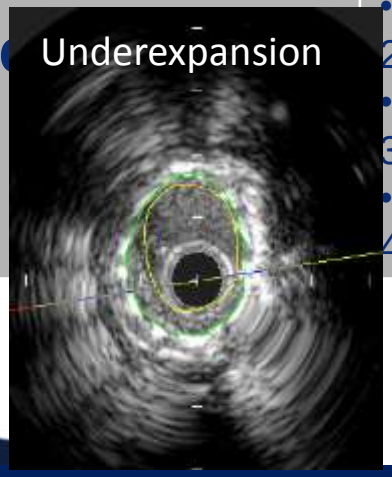


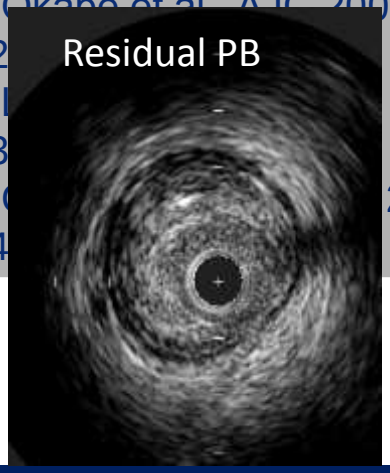


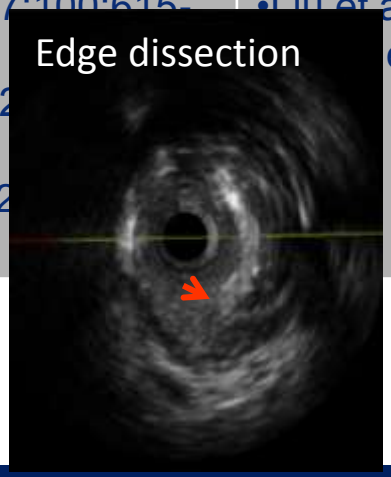
IVUS Mechanisms of DES Failure

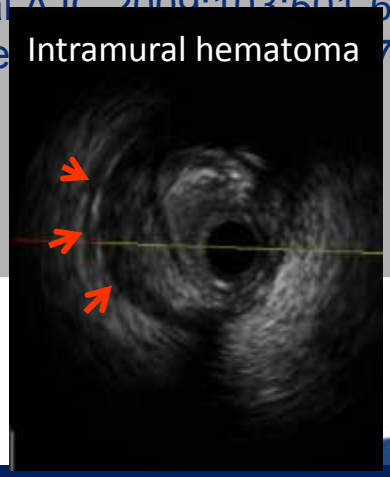
Patient, Device and Procedure–related Multi-factors within 1 year

	Early Thrombosis	Restenosis
Small MSA (Underexpansion)	•Fujii et al. JACC 2005;45:995-8 •Okabe et al., AJC 2007;100:615-20 •Liu et al. JACC Interv 2009;2:428-34 •Choi et al. Circ Interv 2011;4:239-47	•Sonoda et al. JACC 2004;43:1959-63 •Hong et al. EHJ 2006;27:1305-10 •Doi et al. JACC Interv. 2009;2:1269-75 •Fujii et al. Circulation 2004;109:1085-8 •Kang et al. Circ Interv 2011;4:9-14 •Song et al. CCI in press
Inflow/outflow trac	•Fujii et al. JACC 2005;45:995-8	•Sakurai et al. AJC 2005;96:1251-3

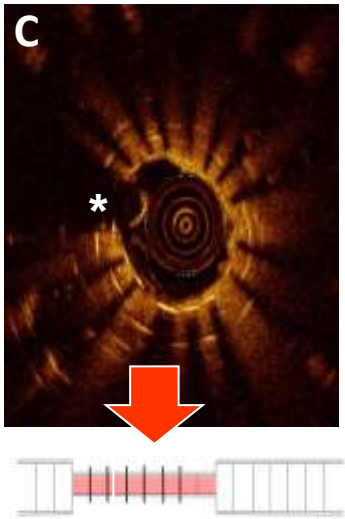


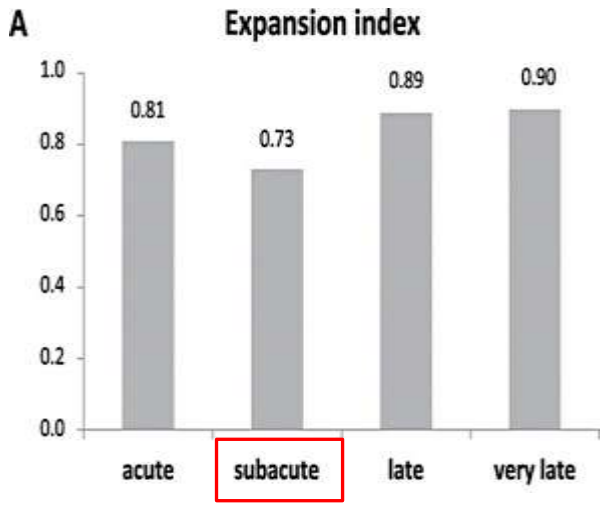


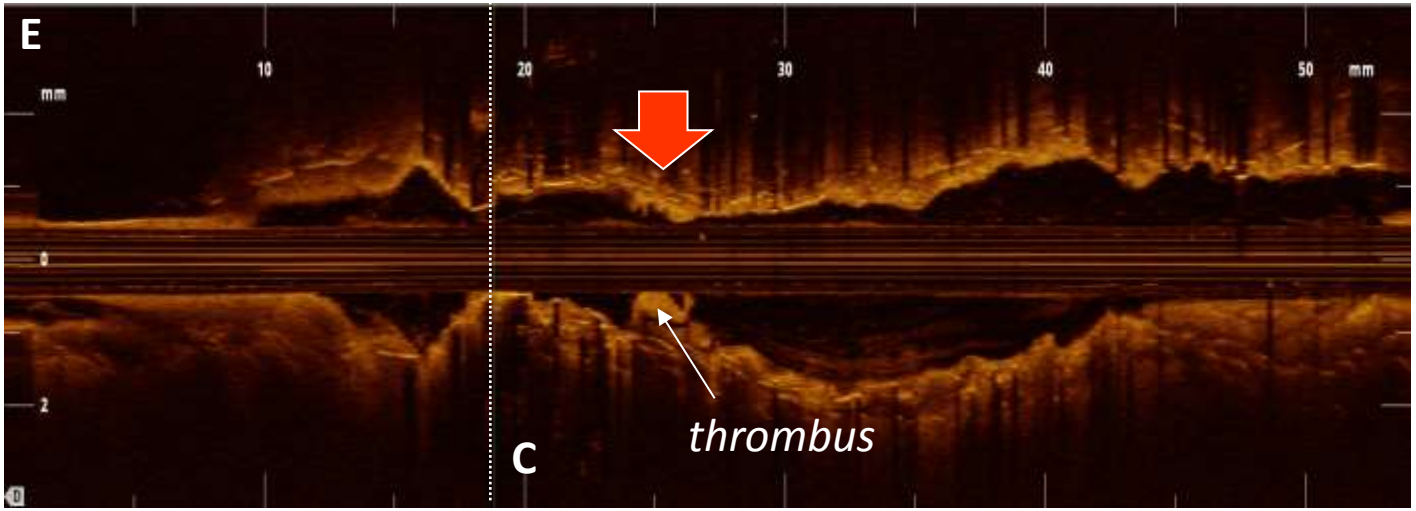




UNDEREXPANSION (<0.8 STENT EXPANSION) IN 44% OF STENT THROMBOSIS



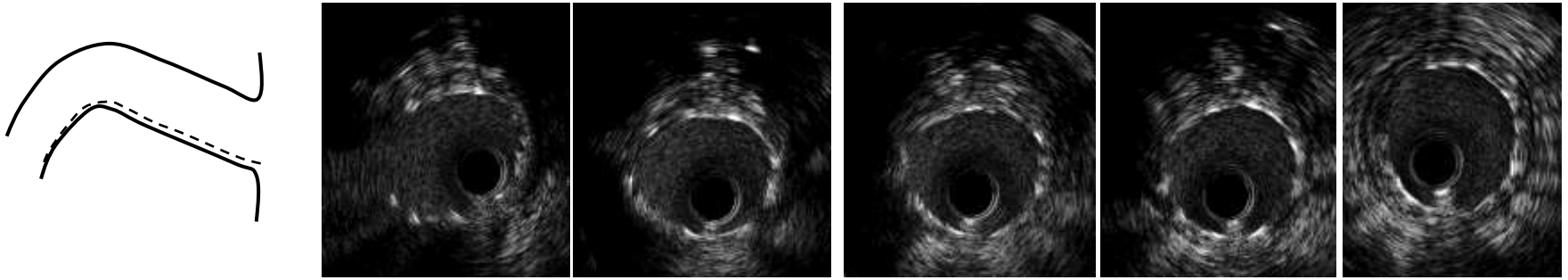




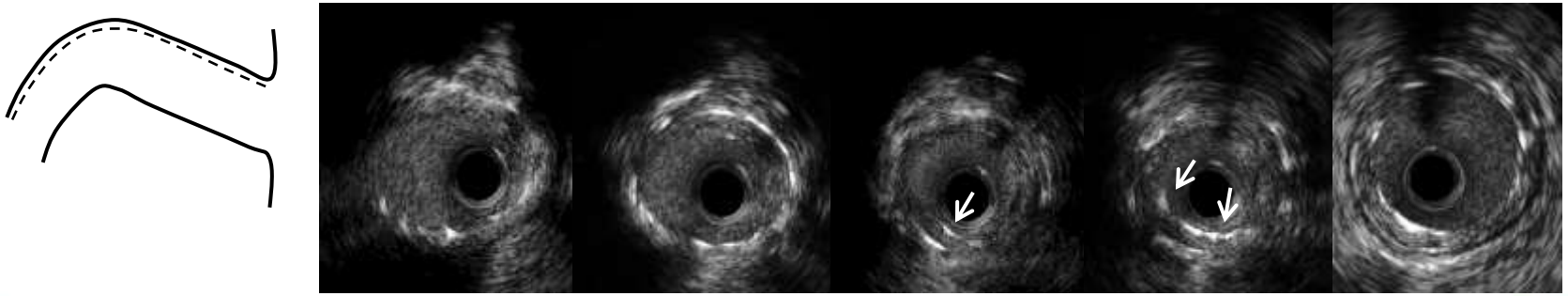
Fracture/Deformation of EES Relates to Restenosis

- 177 EES in 136 patients with follow-up IVUS (1.3yrs)
- 17 pts (9.6 %) with 15 TLR, angio visible fracture (29%)
- Fracture site: **36% smaller stent area** than adjacent site

Baseline



Follow-up



Inaba S et al. *Eurointervention*, 2014; 9: 1301-8.

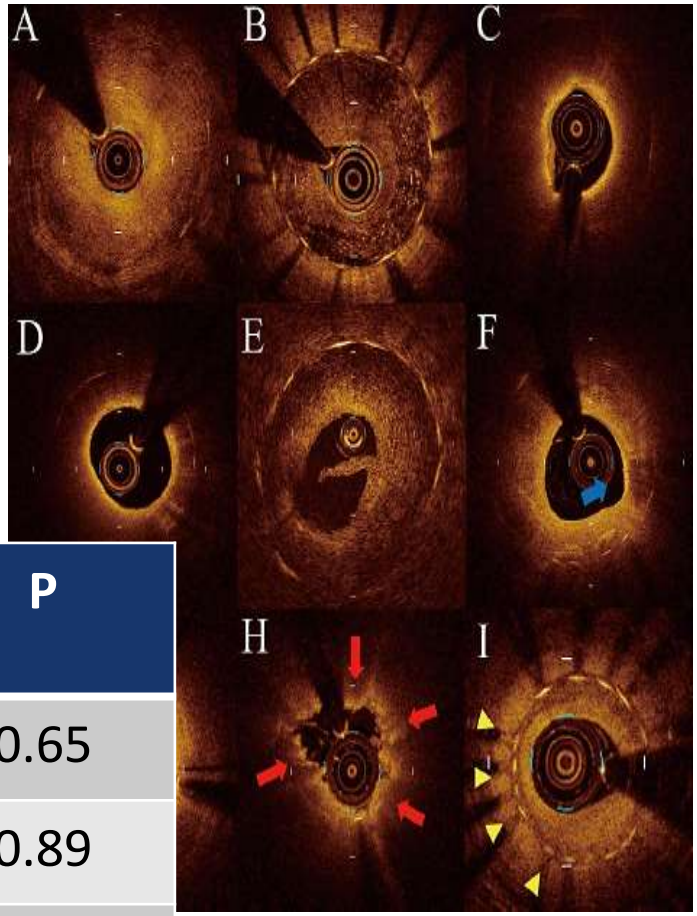
Circ J 2017; 81: 450–457
doi:10.1253/circj.CJ-16-1069

ORIGINAL ARTICLE
Cardiovascular Intervention

Difference of Tissue Characteristics Between Early and Late Restenosis After Second-Generation Drug-Eluting Stents Implantation

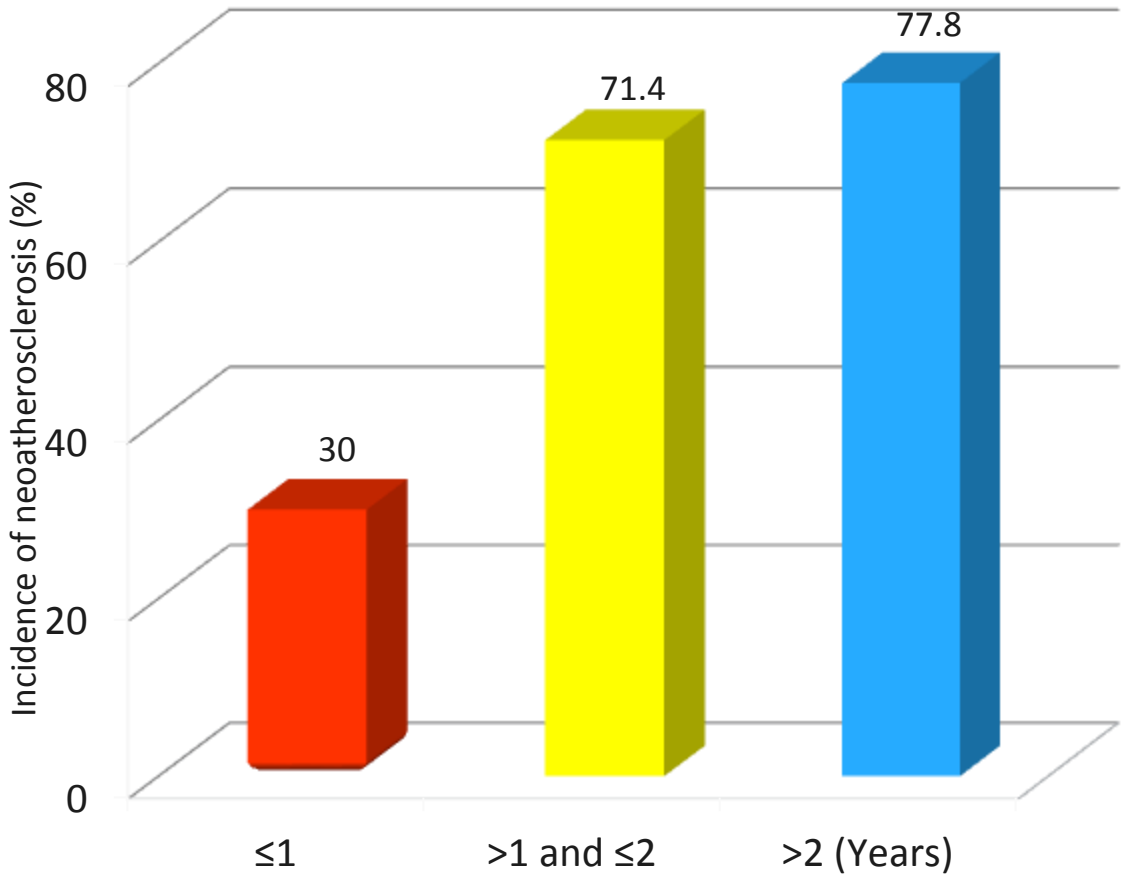
– An Optical Coherence Tomography Study –

Hiroyuki Jinnouchi, MD; Shoichi Kuramitsu, MD; Tomohiro Shinozaki; Yusuke Tomoi, MD;



	Early-ISR (n=30)	Late-ISR (n=23)	P
LUMEN AREA, MM^2	1.5±1.0	1.3±0.7	0.65
NIH AREA, MM^2	4.2±2.1	4.1±1.7	0.89
HOMOGENEOUS INTIMA	8(26.7)	1(4.4)	0.02
LIPID-LADEN	9(30.0)	16(69.6)	<0.01
NEOATHEROSCLEROSIS	9(30.0)	17(73.9)	<0.01

INCIDENCE OF NEOATHEROSCLEROSIS IN DIFFERENT PHASES OF ISR AFTER IMPLANTATION OF SECOND-GENERATION DES



Circulation

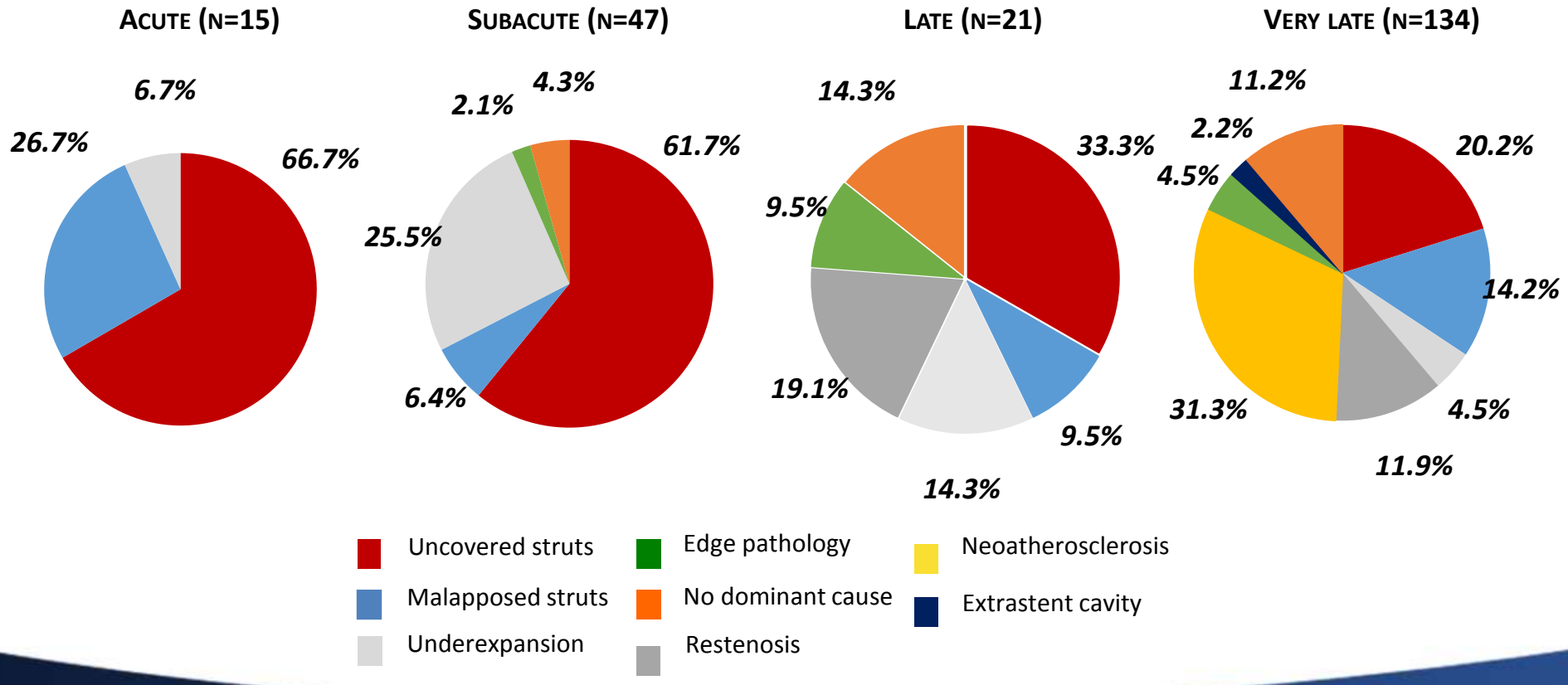
American Heart Association

Circulation. published online July 18, 2017;

217 pts with ST

Optical Coherence Tomography Findings in Patients with Coronary Stent Thrombosis: A Report of the PREvention of Late Stent Thrombosis by an Interdisciplinary Global European Effort (PRESTIGE) Consortium

Tom Adriaenssens, Michael Joner, Thea Godschalk, Nikesh Malik, Fernando Alfonso, Erion Xhepa, Dries De Cock, Kenichi Komukai, Tomohisa Tada, Javier Cuesta, Vasile Sirbu, Laurent J. Feldman, Franz-Josef Neumann, Alison H. Goodall, Ton Heestermans, Ian Buysschaert, Ota Hlinomaz, Ann Belmans, Walter Desmet, Jurrien M. ten Berg, Anthony H. Gershlick, Steffen Massberg, Adnan Kastrati, Giulio Guagliumi and Robert Byrne
on behalf of the PREvention of Late Stent Thrombosis by an Interdisciplinary Global European Effort (PRESTIGE) Investigators



Treatment

Underexpansion - upsize, focal high pressure dilation
rotational atherectomy to remove stent strut
?Lithroplasty

Edge Restenosis - new DES

In-stent hyperplasia, Focal - adequate expansion first
- DEB vs POBA

In-stent hyperplasia, Diffuse - adequate expansion first
- DES-BP?

Address adequacy of DAPT