DES Thrombosis and Restenosis:

Still Problematic in Current Real-World with Updated DES?

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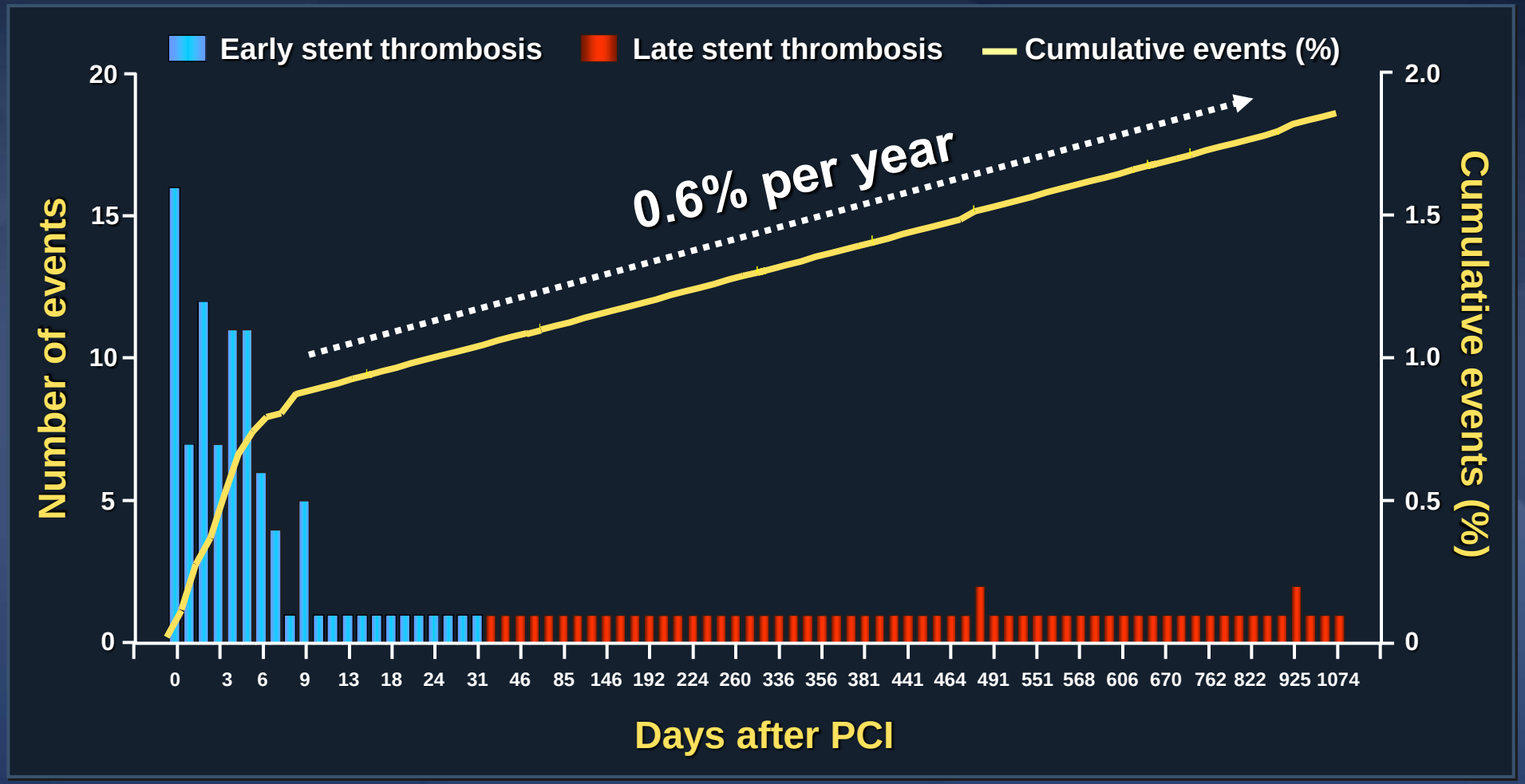
Risk of Stent Thrombosis after 1st Generation DES

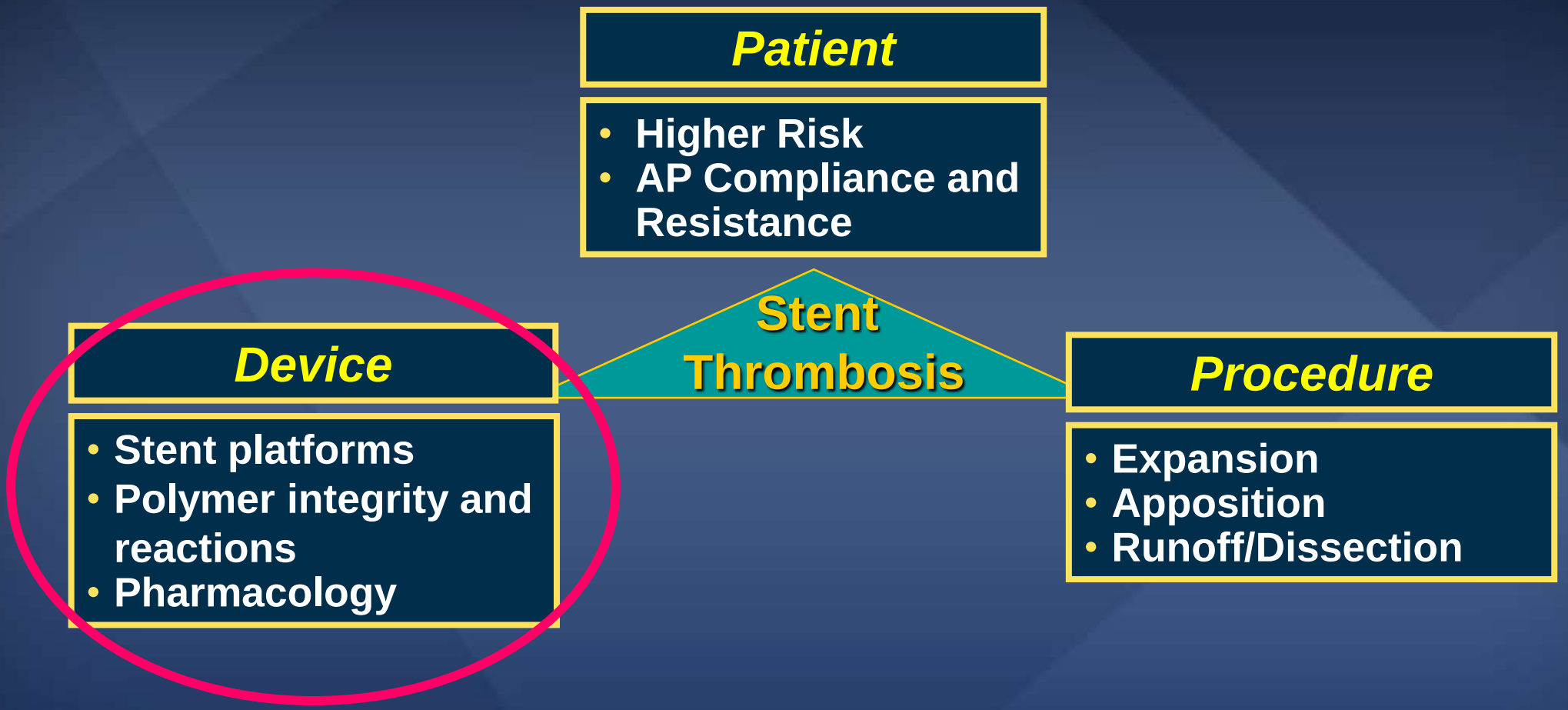
SES (n=3823) or PES (n=4323) at 2 academic centers



Daemen J, et al, *Lancet* 2007;369:667–78

Stent Thrombosis

Patient, Device, Procedure



Evolution of DES Technology

First Gen

Durable Polymer Stents

	Cypher	TAXUS Express	TAXUS Liberte
Strut Thickness	140 µm	132 µm	96 µm
Coat Thickness	7µm / side	16µm/side	14µm/side

Bioabsorbable Polymer Stents

	Biomatrix	Nobori
Strut Thickness	120 µm	125 µm
Coat Thickness	10 µm	20 µm

Second Gen

	Resolute Integrity	Xience Xpedition	Promus PREMIER
Strut Thickness	89 µm	81 µm	81 µm
Coat Thickness	6µm / side	8µm / side	8µm / side

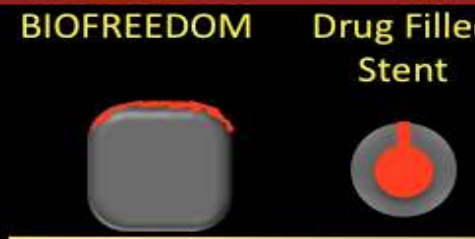
	Firehawk	Synergy	Ultimaster
Strut Thickness	86µm	74µm	80µm
Coat Thickness	10 µm	4 µm	14 µm

First Generation Future Technologies

Fully Bioresorbable Stents

	BVS	ELIXIR DESolve	DREAMS II
Strut Thickness	150 µm	150 µm	150 µm
Coat Thickness	3 µm / side	<3 µm / side	8 µm / side

Polymer Free Stents



	BIOFREEDOM	Drug Filled Stent
Strut Thickness	112	86
Coat Thickness	NA	NA

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EDITORIAL COMMENT

Percutaneous Coronary Intervention

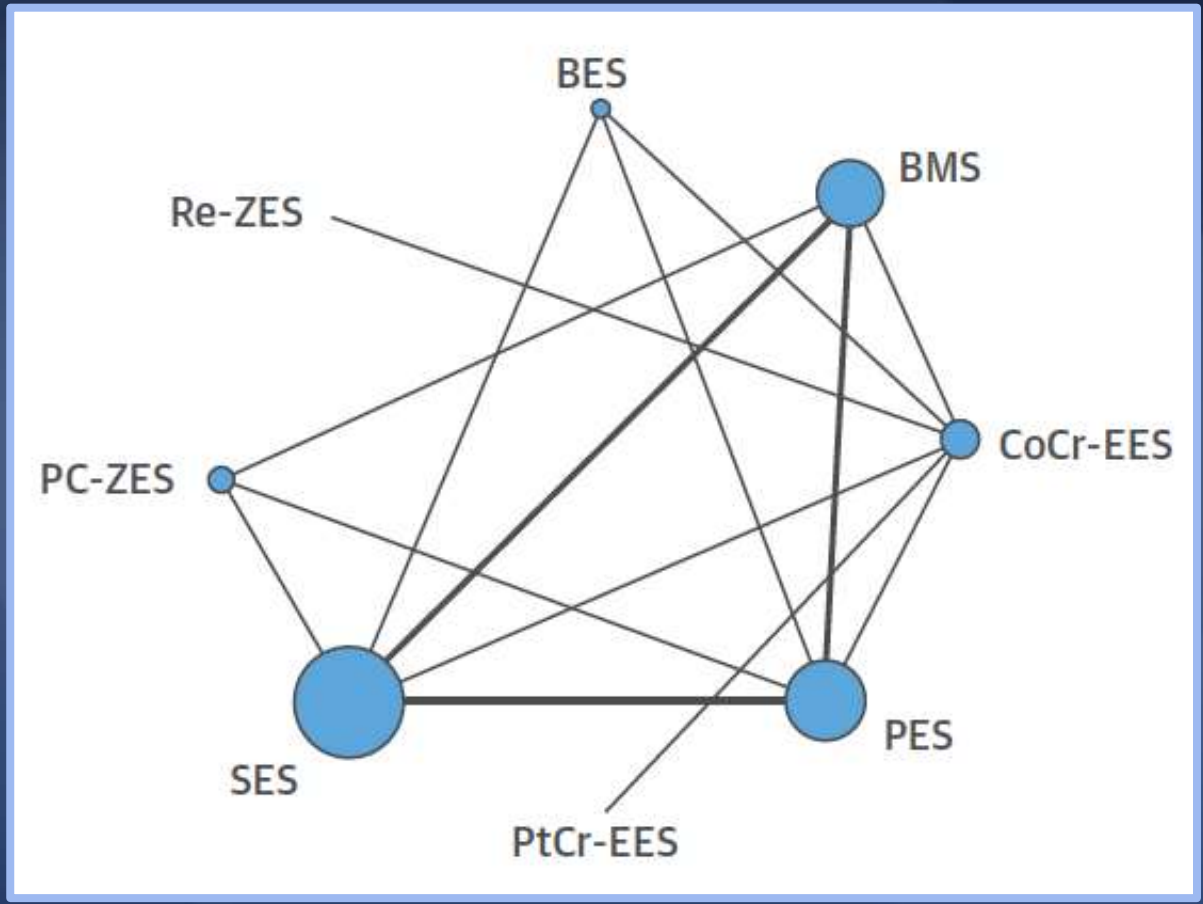
Finally Mature Enough*

Stéphane Rinfret, MD, SM,† Suzanne J. Baron, MD, MSc,‡ David J. Cohen, MD, MSc‡

1. Stent Thrombosis
2. In-Stent Restenosis

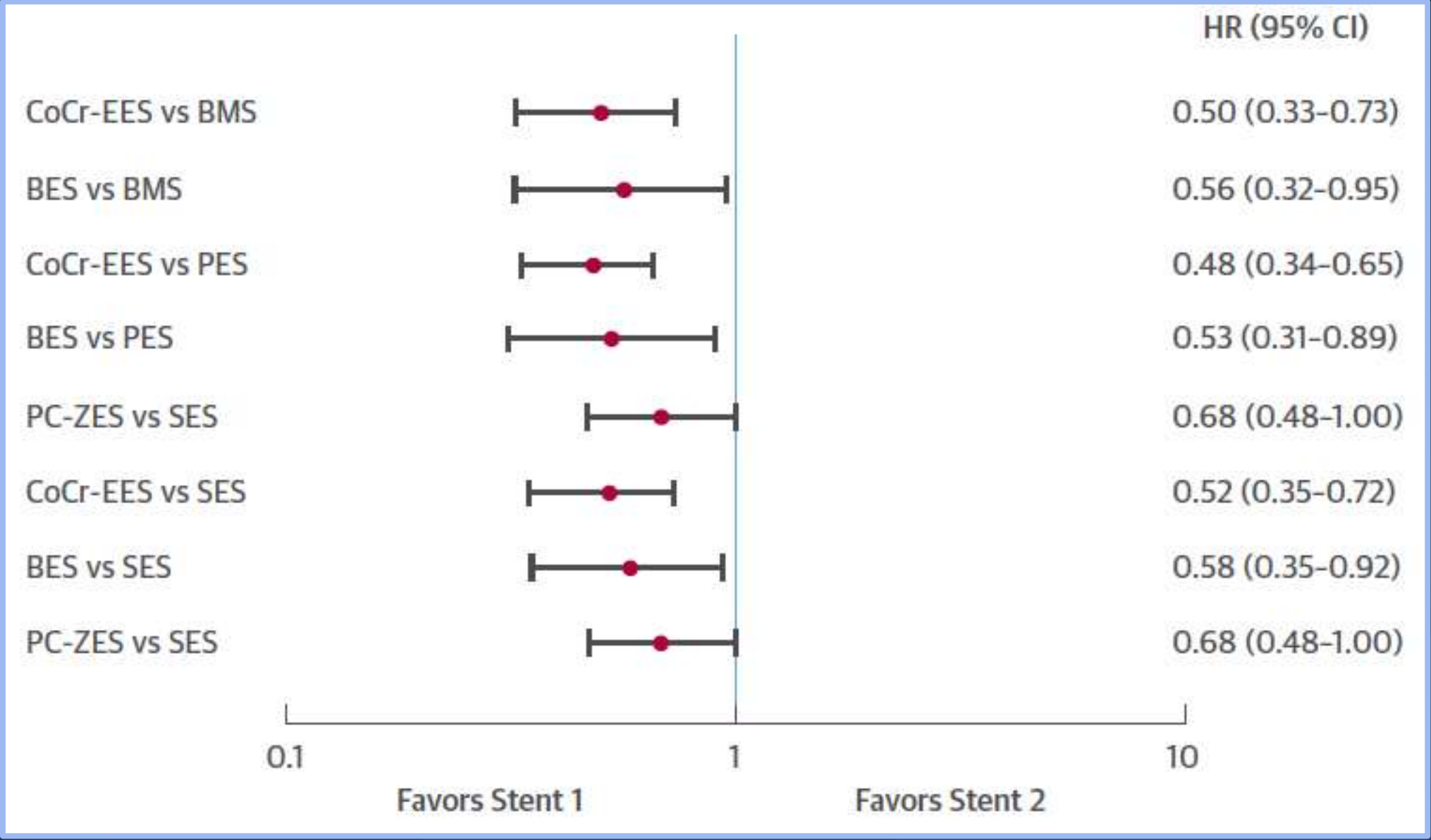
Updated Network Meta-Analysis including RCT with at least 3 year FU

51 RCTs; 52,158 patients, median 3.8 years



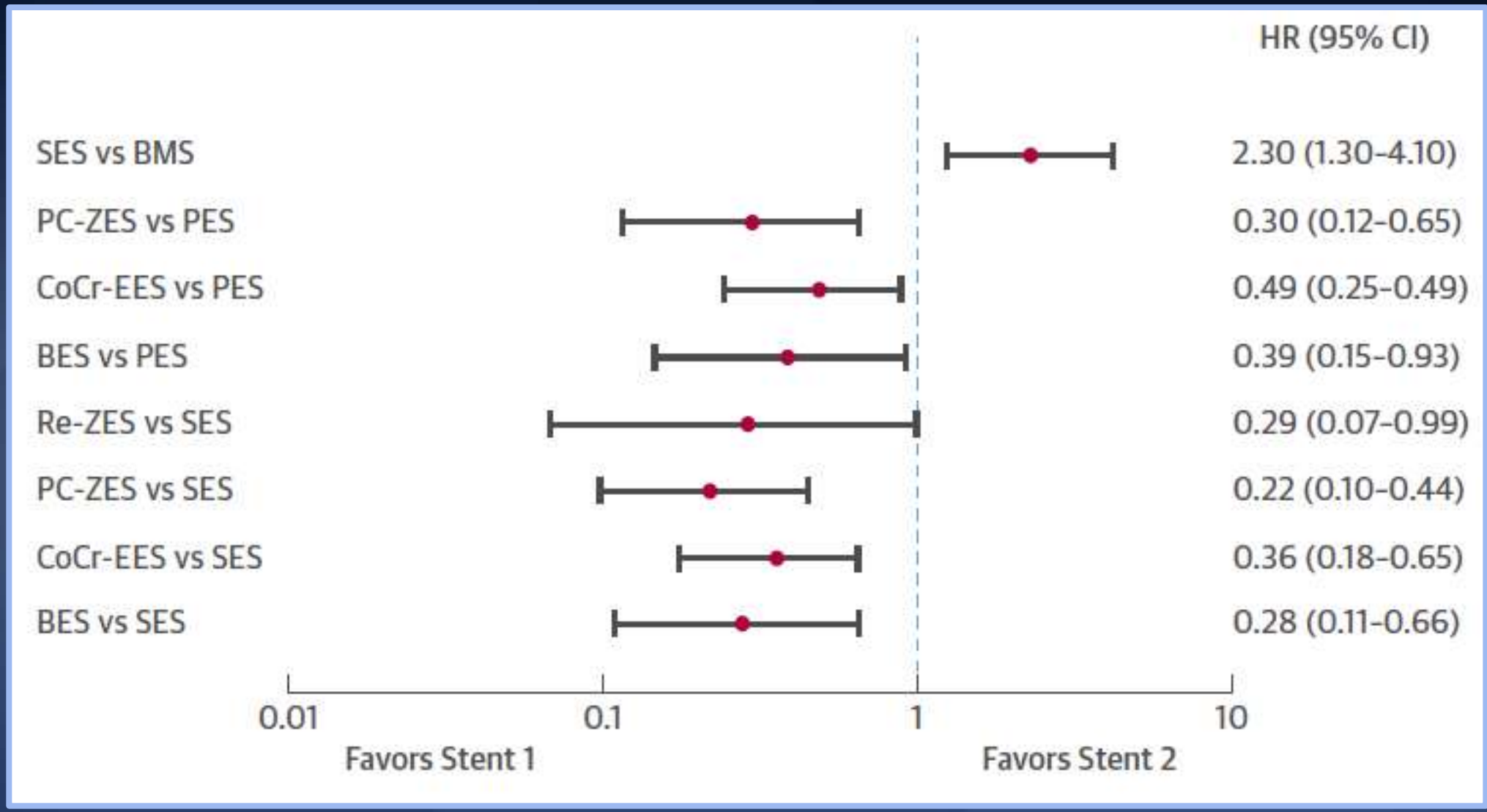
Palmerini et al. J AmColl Cardiol 2015;65:2496–507

Definite or Probable ST



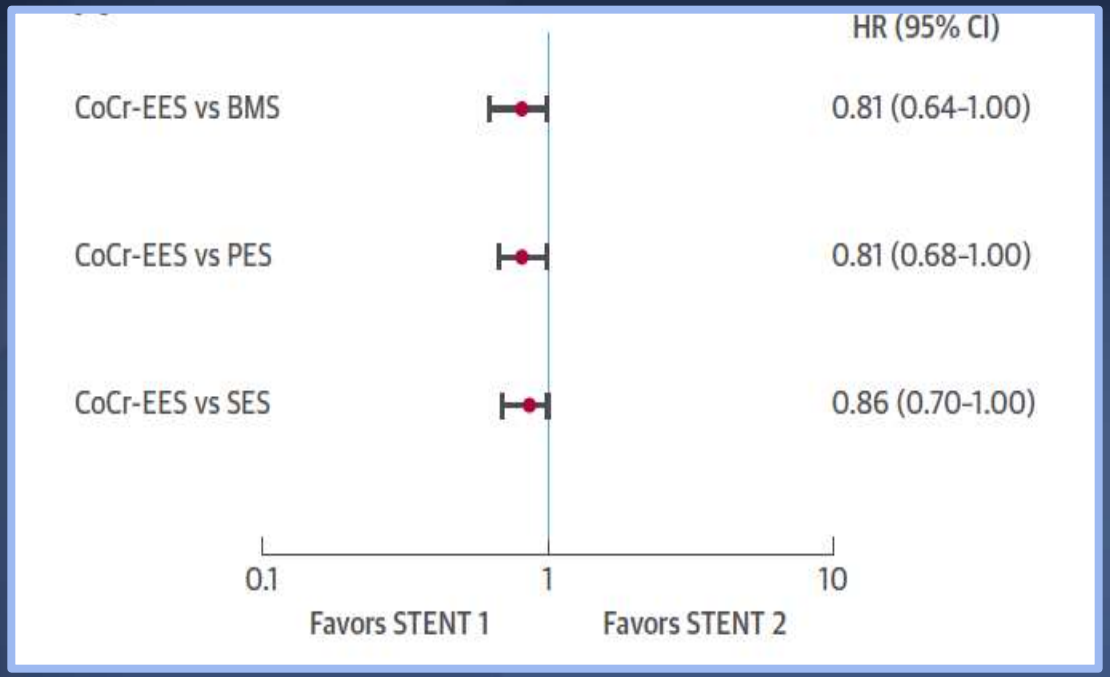
Palmerini et al. J AmColl Cardiol 2015;65:2496–507

Very Late Definite or Probable ST

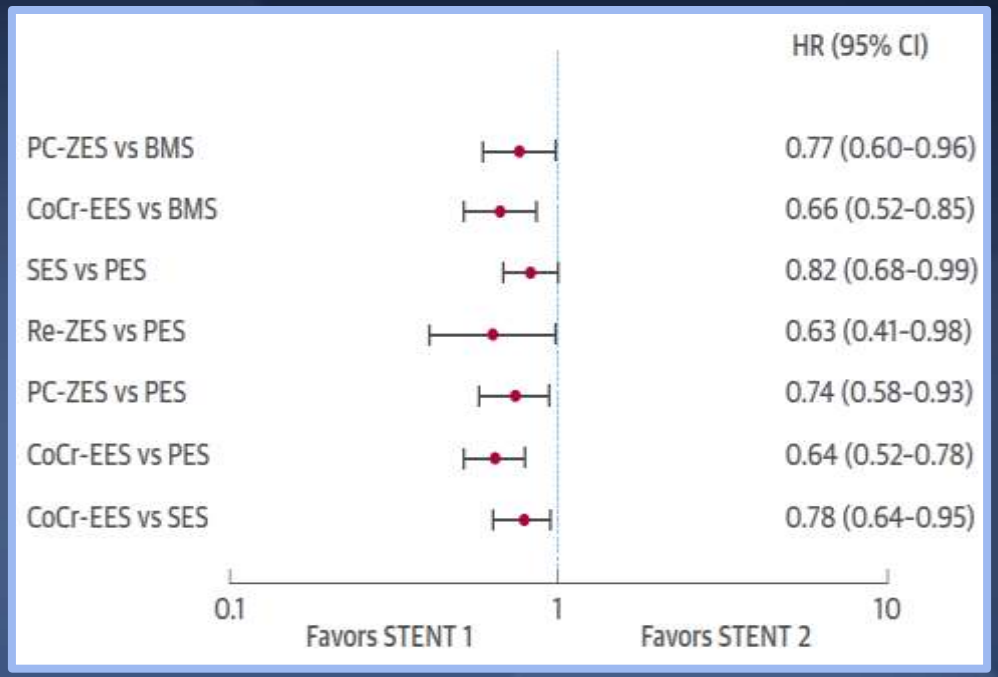


Palmerini et al. J AmColl Cardiol 2015;65:2496–507

Death



MI



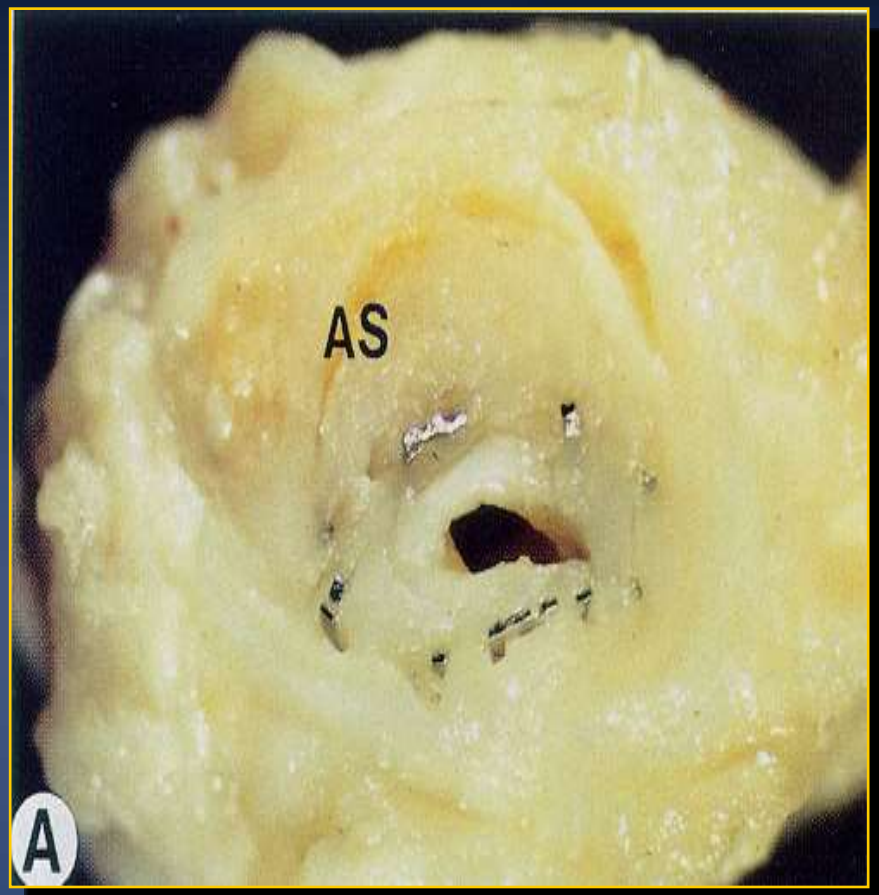
Palmerini et al. J AmColl Cardiol 2015;65:2496–507

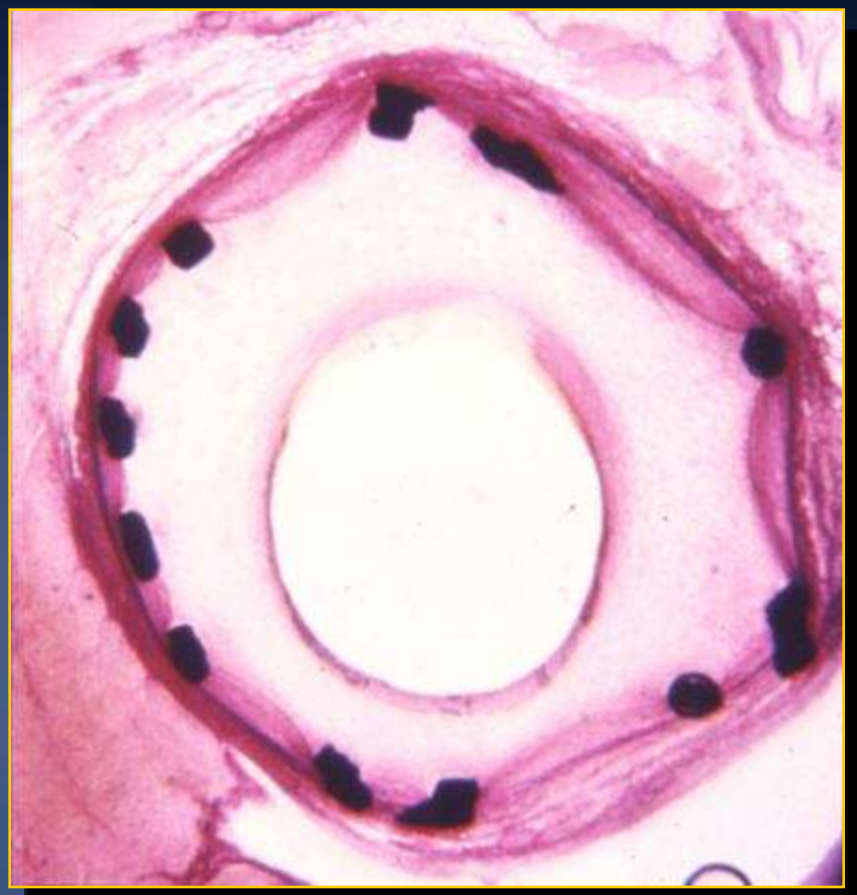
Updated DES; Enhanced Safety Outcomes

- Second-generation DES have been developed with novel materials and delivery systems (i.e., changes in stent alloy, architecture, thickness, polymer characteristics, drug type, dose, and release kinetics)

  ➔ *more rapid and complete endothelialization*
- Second-generation DES showed better safety outcomes (ST, death, or MI) than first-generation DES or BMS during long-term FU.

Pathology of Restenosis





In-Stent Restenosis = Intimal Hyperplasia

Mechanisms of DES Restenosis

- ***Biological factors***
  - Drug resistance
  - Hypersensitivity
- ***Mechanical factors***
  - Non uniform stent strut distribution
  - Stent fractures
  - Polymer peeling
  - Non uniform drug deposition
- ***Technical factors***
  - Incomplete stent expansion
  - Stent gaps or “misses” (uncovered lesion segments)
  - Barotrauma to unstented segments

Old vs. Newer DES

New anti-proliferative drugs
Biodegradable polymer
Thinner struts
Better strut coverage

→ *Expected to reduce* ***neoatherosclerosis*** *…*

	73 **SES**	85 **PES**	46 **EES**	P vs. SES	P vs. PES
Median F/U	9 months	7 months	7 months		
Uncovered strut, %	18.0 (0-51.4)	18.7 (7.1-44.4)	2.6 (0-7.1)	<0.001	<0.001
Fibrin deposition,%	29.9 (12.1–59.9)	51.1 (36.9–72.9)	8.5 (0-28.2)	0.001	<0.001
Inflammatory score	1.0 (0.3–2.0)	1.0 (0.1–1.4)	0.26 (0-0.6)	<0.001	0.006
Neoatherosclerosis	**25 (35%)**	**15 (19%)**	**12 (29%)**	**0.91**	**0.19**

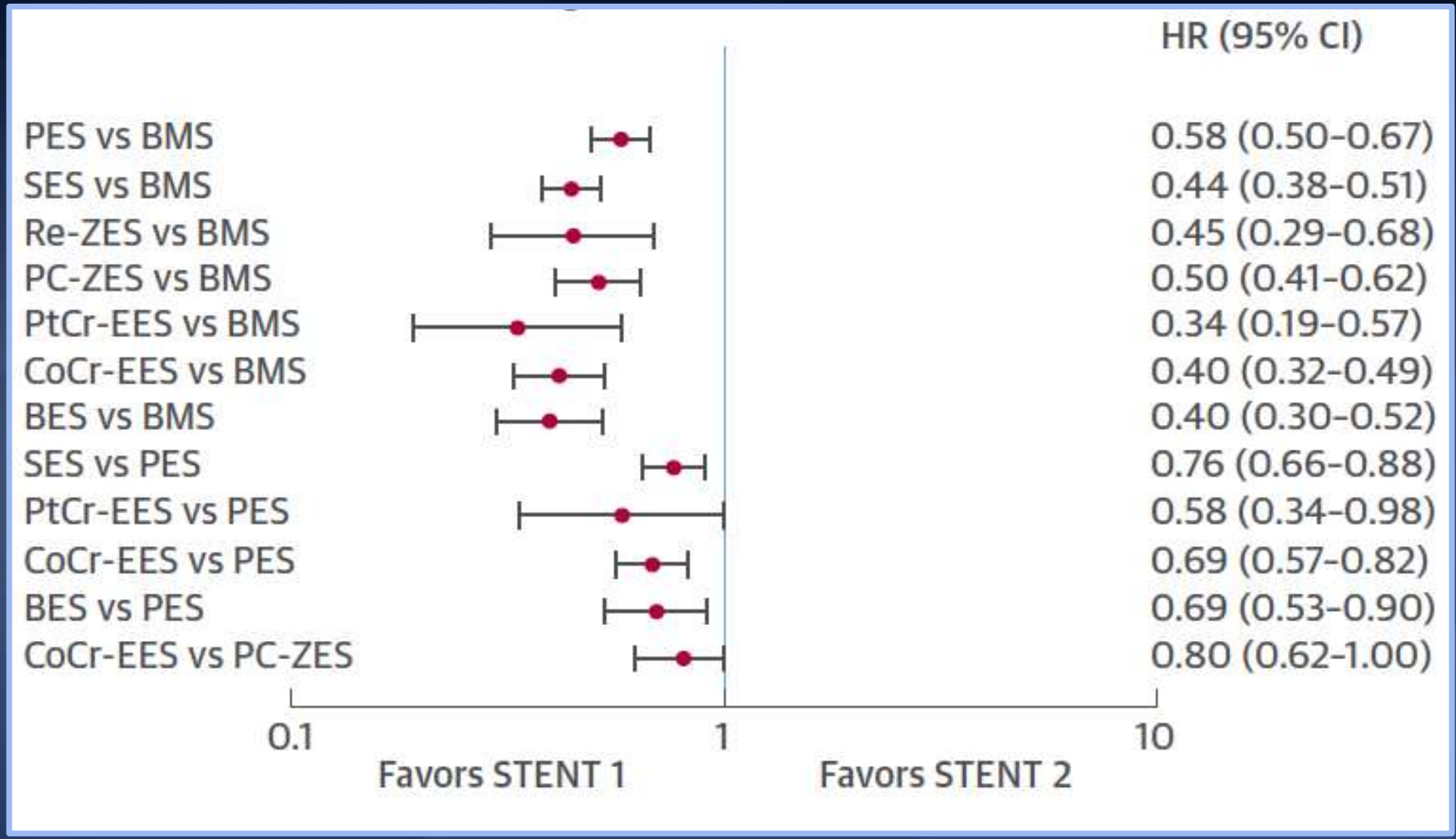
Otsuka, Virmani et al. Circulation 2014;129:211-23

Angiographic Follow-Up In Contemporary DES Studies

- Routine angiographic follow-up is allowed to asses the efficacy performance of early DES.
- But, routine angiographic surveillance can bias results!! ➔ Oculostenotic reflex

- In contemporary DES practice, clinical restenosis measured as TLR or TVR is a mostly adapted clinical outcome instead of invasive angiographic restenosis.

Target Vessel Revascularization



Palmerini et al. J AmColl Cardiol 2015;65:2496–507

Updated DES; Enhanced Efficacy Outcomes

- Second-generation DES have been developed with novel materials and delivery systems.

- By a meta-analysis of 51 comparative trials, second-generation DES showed better efficacy outcomes than either first-generation DES or BMS after a median 4-year FU.

IRIS-DES Registry

Design

- DESIGN: An unrestricted, multicenter, prospective cohort
- OBJECTIVE: To compare the safety and efficacy of the second- or newer-generation DES and the first-generation DES in everyday clinical practice,
- PRINCIPAL INVESTIGATOR
  Seung-Jung Park, MD, PhD, Asan Medical Center, Seoul, Korea

Evaluation of Effectiveness and Safety of the First, Second, and Newer Drug-Eluting Stents in Routine Clinical Practice;

IRIS-DES Registry

Consecutive PCI patients receiving New DES without a mixture of other DES

Prospective Enrollment

DESSIAN Registry	K-XIENCE Registry	IRIS-PRIME Registry	IRIS-NOBORI Registry	IRIS-BIOMATRIX Registry	IRIS-ELEMENT Registry	IRIS-GENOUS-STEMI Registry	IRIS-INTEGRITY Registry
Patents with CYPHER (N=3,000)	Patents with XIENCE (N=3,000)	Patents with XIENCE PRIME (N=2,000)	Patents with NOBORI (N=2,000)	Patents with BIOMATRIX (N=1,000)	Patents with PROMUS ELEMENT (N=3,000)	STEMI with GENOUS (N=1,000)	Patents with RESOLUTE INTEGRITY (N=1000)

Clinical follow-up at 1-, 6-, and 12-months, and annually up to 5 years

Outcomes After Unrestricted Use of Everolimus-Eluting and Sirolimus-Eluting Stents in Routine Clinical Practice

A Multicenter, Prospective Cohort Study

Duk-Woo Park, MD; Young-Hak Kim, MD; Hae-Geun Song, MD; Jung-Min Ahn, MD; Won-Jang Kim, MD; Jong-Young Lee, MD; Soo-Jin Kang, MD; Seung-Whan Lee, MD; Cheol Whan Lee, MD; Seong-Wook Park, MD; Sung-Cheol Yun, PhD; Sung Ho Her, MD; Seung Ho Hur, MD; Jin Sik Park, MD; Myeong-Kon Kim, MD; Yun Seok Choi, MD; Hyun Sook Kim, MD; Jang-Hyun Cho, MD; Sang Gon Lee, MD; Yong Whi Park, MD; Myung-Ho Jeong, MD; Bong Ki Lee, MD; Nae-Hee Lee, MD; Do-Sun Lim, MD; Junghan Yoon, MD; Ki Bae Seung, MD; Won-Yong Shin, MD; Seung-Woon Rha, MD; Kee-Sik Kim, MD; Seung-Jea Tahk, MD; Byoung Eun Park, MD; Taehoon Ahn, MD; Joo-Young Yang, MD; Yong Seok Jeong, MD; Jay-Hyun Rhew, MD; Seung-Jung Park, MD; for the IRIS-DES Investigators*

Background—It remains unclear whether there are differences in the safety and efficacy outcomes between everolimus-eluting stents (EES) and sirolimus-eluting stents (SES) in contemporary practice.

Methods and Results—We prospectively enrolled 6166 consecutive patients who received EES (3081 patients) and SES (3085 patients) between April 2008, and June 2010, using data from the Interventional Cardiology Research In-Cooperation Society-Drug-Eluting Stents Registry. The primary end point was a composite of death, nonfatal myocardial infarction (MI), or target-vessel revascularization (TVR). At 2 years of follow-up, the 2 study groups did not differ significantly in crude risk of the primary end point (12.1% for EES versus 12.4% for SES; HR, 0.97; 95% CI, 0.84–1.12, P=0.66). After adjustment for differences in baseline risk factors, the adjusted risk for the primary end point remained similar for the 2 stent types (HR, 0.96; 95% CI, 0.82–1.12, P=0.60). There were also no differences between the stent groups in the adjusted risks of the individual component of death (HR, 0.93; 95% CI, 0.67–1.30, P=0.68), MI (HR, 0.97; 95% CI, 0.79–1.18, P=0.74), and TVR (HR, 1.10; 95% CI, 0.82–1.49, P=0.51). The adjusted risk of stent thrombosis also was similar (HR, 1.16; 95% CI, 0.47–2.84, P=0.75).

Conclusions—In contemporary practice of percutaneous coronary intervention procedures, the unrestricted use of EES and SES showed similar rates of safety and efficacy outcomes with regard to death, MI, sent thrombosis, and TVR. Future longer-term follow-up is needed to better define the relative benefits of these drug-eluting stents.

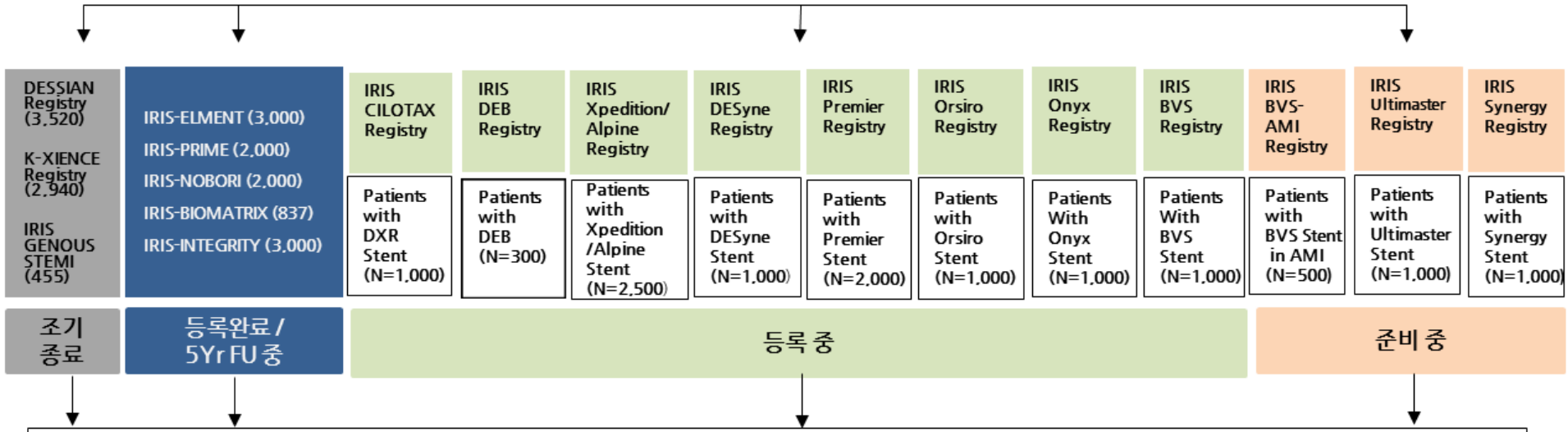
Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01070420. ***(Circ Cardiovasc Interv*. 2012;5:365-371.)**

Evaluation of Effectiveness and Safety of the First, Second, and New Drug-Eluting Stents in Routine Clinical Practice;

IRIS-DES Registry

Consecutive PCI patients receiving New DES without a mixture of other DES

Prospective Enrollment



Clinical follow-up at 1-, 6-, and 12-months, and annually up to 5 years

***Primary end point: Composite of Death, MI, and TVR at 12-months**

Comparative Effectiveness Research of Various DES

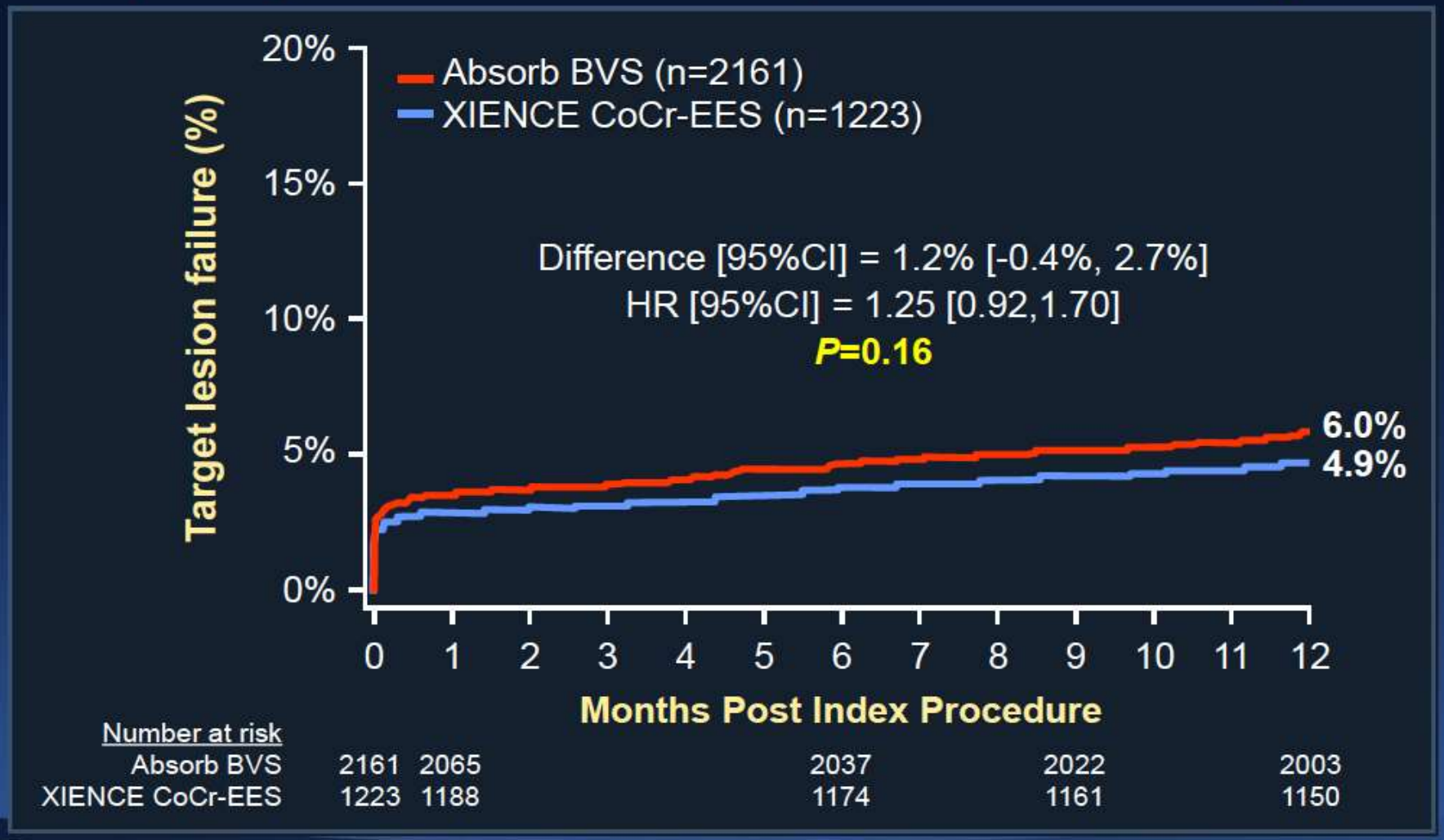
- Enrollment and at least 2-year clinical follow-up was completed for Cypher, Xience, Genous, Promus element, Xience prime, Nobori, Biomatrix, and Resolute intergrity.

- Results are expected in the summer of 2016.

ABSORB 1-Year Meta-analysis

ABSORB II, ABSORB III, ABSORB Japan, ABSORB China

DoCE (TLF): Cardiac Death, MI or ID-TLR (pooled)

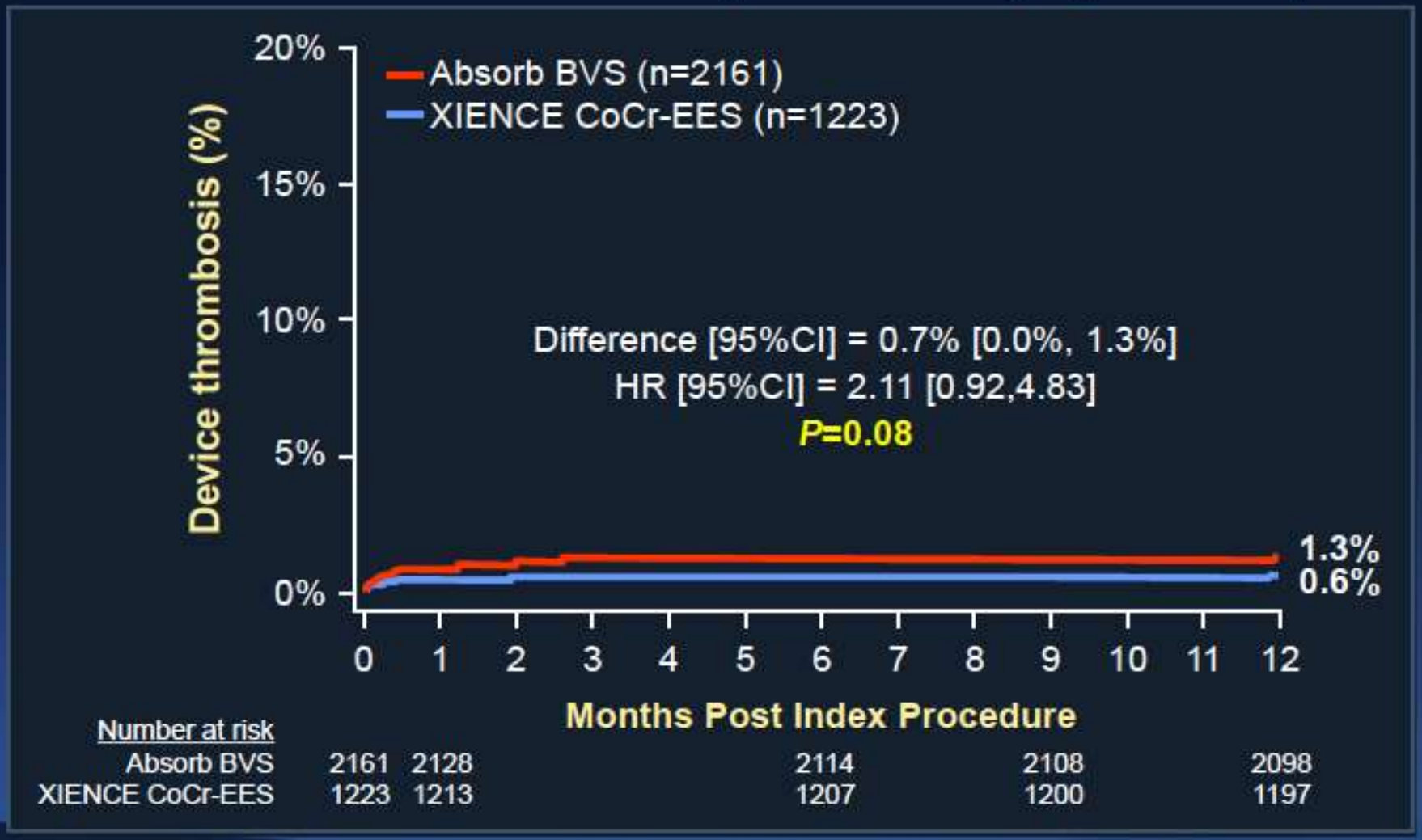


Lancet 2016;387:1277-89.

ABSORB 1-Year Meta-analysis

ABSORB II, ABSORB III, ABSORB Japan, ABSORB China

Device Thrombosis (Def/Prob) (pooled)



Lancet 2016;387:1277-89.

Study-level Meta-Analysis of 6 RCT

ABSORB Series and EVERBIO II and TROFI II

A Target lesion revascularisation

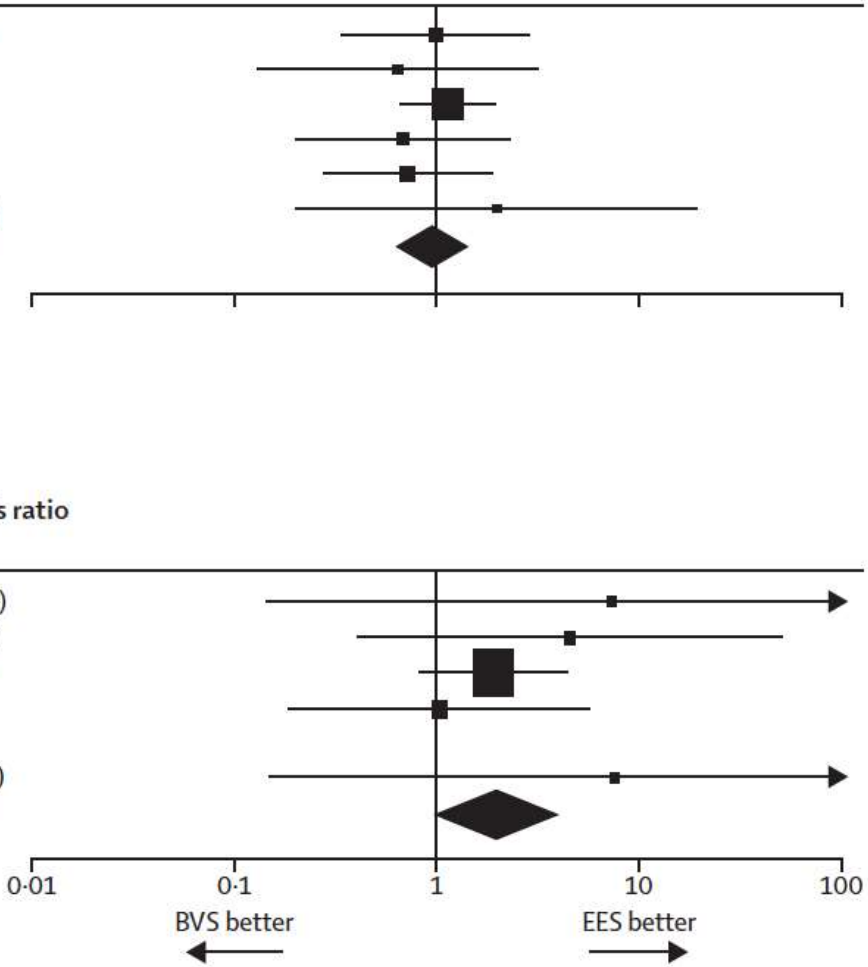
	BVS Events	BVS Total	EES Events	EES Total	Weight (%)	Fixed-effects odds ratio (95% CI)
ABSORB China	7	238	7	237	13·2	1·00 (0·34–2·88)
ABSORB II	4	335	3	166	5·9	0·64 (0·13–3·12)
ABSORB III	42	1313	19	677	51·6	1·14 (0·67–1·95)
ABSORB Japan	7	265	5	133	10·1	0·68 (0·20–2·31)
EVERBIO II	8	78	11	80	16·3	0·72 (0·28–1·87)
TROFI II	2	95	1	96	2·9	1·98 (0·20–19·29)
Overall	**70**	**2324**	**46**	**1389**	**100**	**0·97 (0·66–1·43)**

Heterogeneity: χ^2=1·69, df=5; p=0·89; I^2=0%
Test for overall effect: Z=0·16; p=0·87
Random-effects odds ratio 0·97 (95% CI 0·66–1·43)

B Definite or probable stent thrombosis

	BVS Events	BVS Total	EES Events	EES Total	Weight (%)	Fixed-effects odds ratio (95% CI)
ABSORB China	1	238	0	232	3·1	7·21 (0·14–363·23)
ABSORB II	3	335	0	166	8·2	4·49 (0·04–49·92)
ABSORB III	20	1301	5	675	69·1	1·89 (0·82–4·34)
ABSORB Japan	4	262	2	133	16·5	1·02 (0·18–5·58)
EVERBIO II	0	78	0	80		Not estimable
TROFI II	1	95	0	96	3·1	7·47 (0·15–376·35)
Overall	**29**	**2309**	**7**	**1382**	**100**	**1·99 (1·00–3·98)**

Heterogeneity: χ^2=1·90, df=4; p=0·75; I^2=0%
Test for overall effect: Z=1·96; p=0·05
Random-effects odds ratio 1·99 (95% CI 1·00–3·98)



Lancet 2016; 387: 537–44

BVS Registry

A Propensity-Matched Cohort (N=1,810) of the GHOST-EU and XIENCE V USA

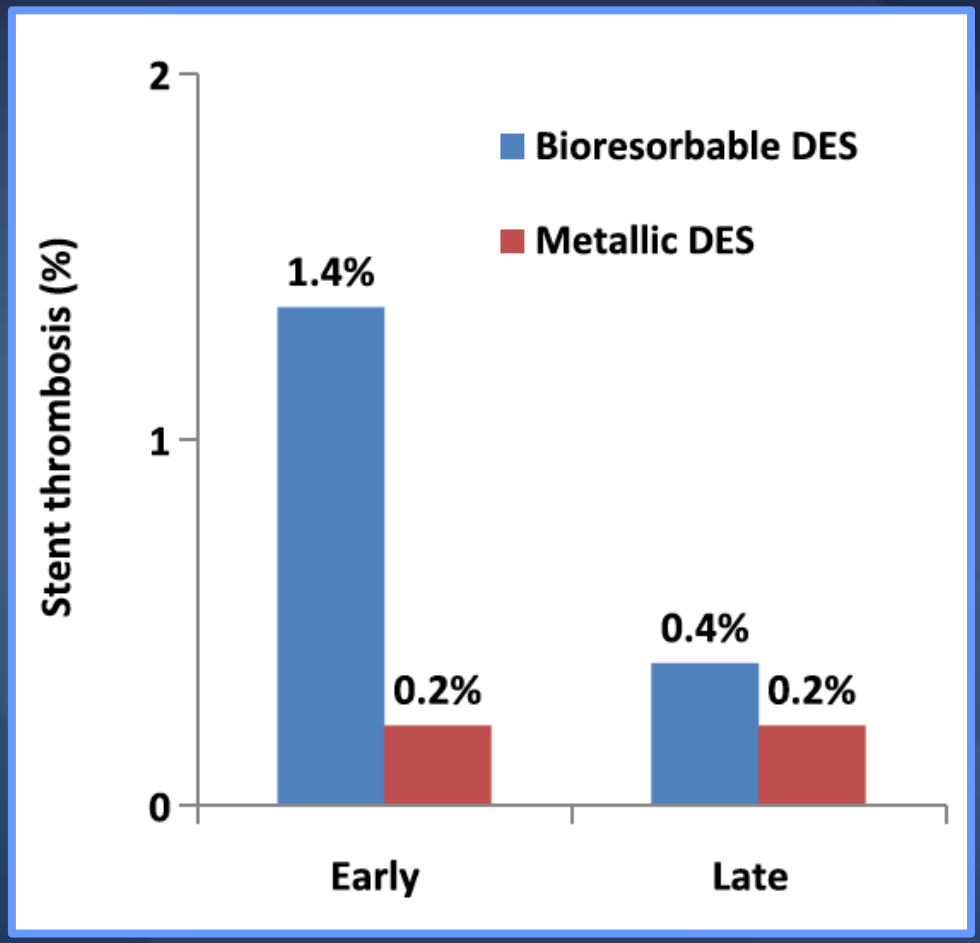
	BVS (%)	EES (%)	HR (95% CI)	P
Device-oriented composite outcome	5.8	7.6	0.75 (0.52 to 1.08)	0.12
CV death	0.7	1.9	0.36 (0.14 to 0.92)	0.025
MI	2.4	4.0	0.61 (0.36 to 1.05)	0.07
TLR	4.6	3.5	1.35 (0.84 to 2.17)	0.22
Definite or probable ST	1.8	1.1	1.62 (0.73 to 3.57)	0.23

J Am Coll Cardiol Intv 2016;9:440–9

Bioresorbable Drug-Eluting Stents

An Immature Technology in Need of Mature Application*

Robert A. Byrne, MB, BCh, PhD, Adnan Kastrati, MD



JACC Intv 2015; 016;8:190-200

Current 1st generation BVS

- Efficacy Issues in BVS
  - Inferior midterm angiographic performance
  - Similar rates of composite patient-oriented and device-oriented adverse events
- Safety Issues in BVS
  - Increased peri-procedural MI
  - Increased early risk of stent thrombosis
  - Data on long-term FU and optimal duration of DAPT is not yet available.

Current Status and Future Evolution of DES

- Current DES with durable and bioresorbable polymers have improved safety and efficacy outcomes compared to earlier DES and BMS.
- Polymer-free DES is also promising and will further reduce the risk of ST and long-term DAPT requirement.
- More studies are needed to determine whether BVS can lower the risk of late events and provide additional clinical advantage beyond contemporary metallic DES.

Last Message; Current PCI with DES

- We now have reached a major milestone in the maturation of PCI as a treatment for CAD.
- Regardless of where the technology goes, “When technology stops continued innovation”, “The Knowledge will also stops”
- As the technologies are getting better and better, we can provide a better opportunity for optimal patient care in the long run.