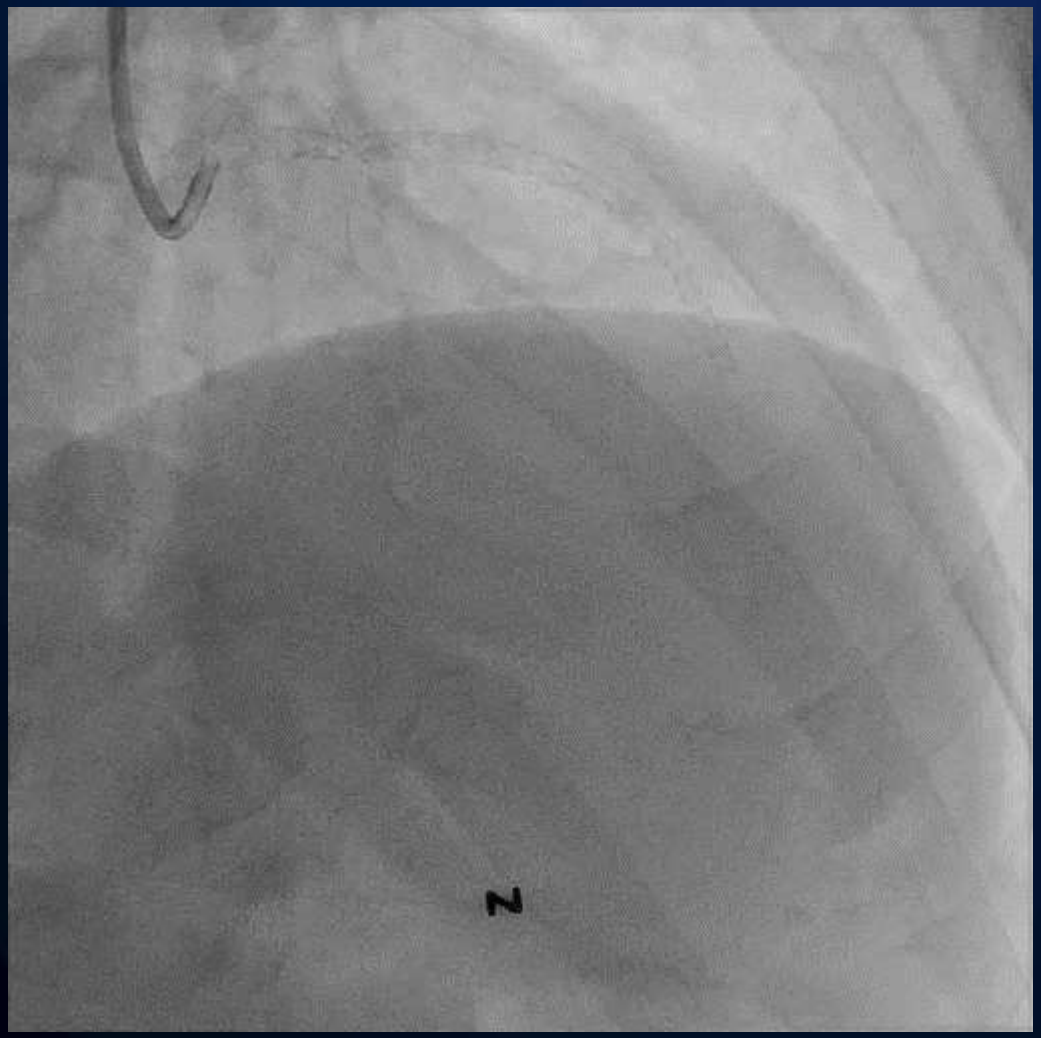
Stent Thrombosis Risk of Drug-Eluting Stents

Si-Hyuck Kang
Seoul National University Bundang Hospital

Very late ST

(11Y after Cypher implantation)



M/58

11YA STEMI, anterior wall

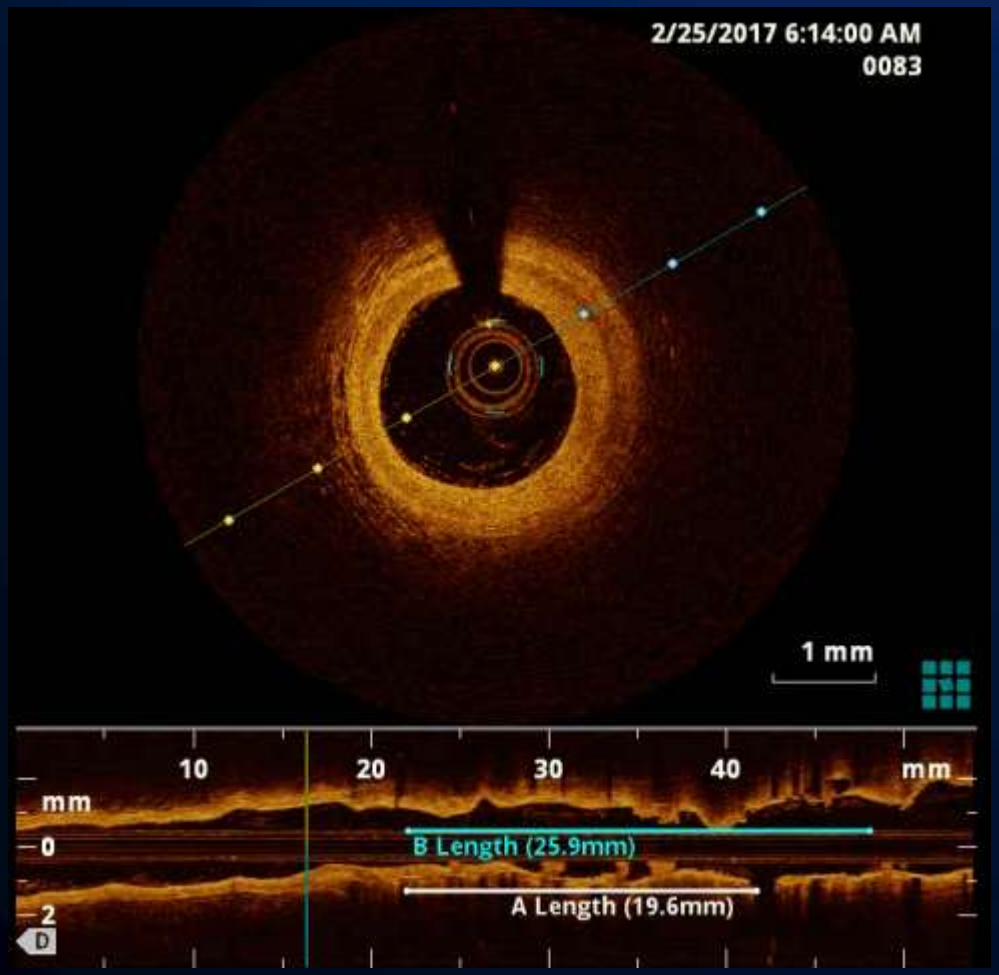
PCI with Cypher

Diabetes, on insulin

Current smoker

Presentation with STEMI

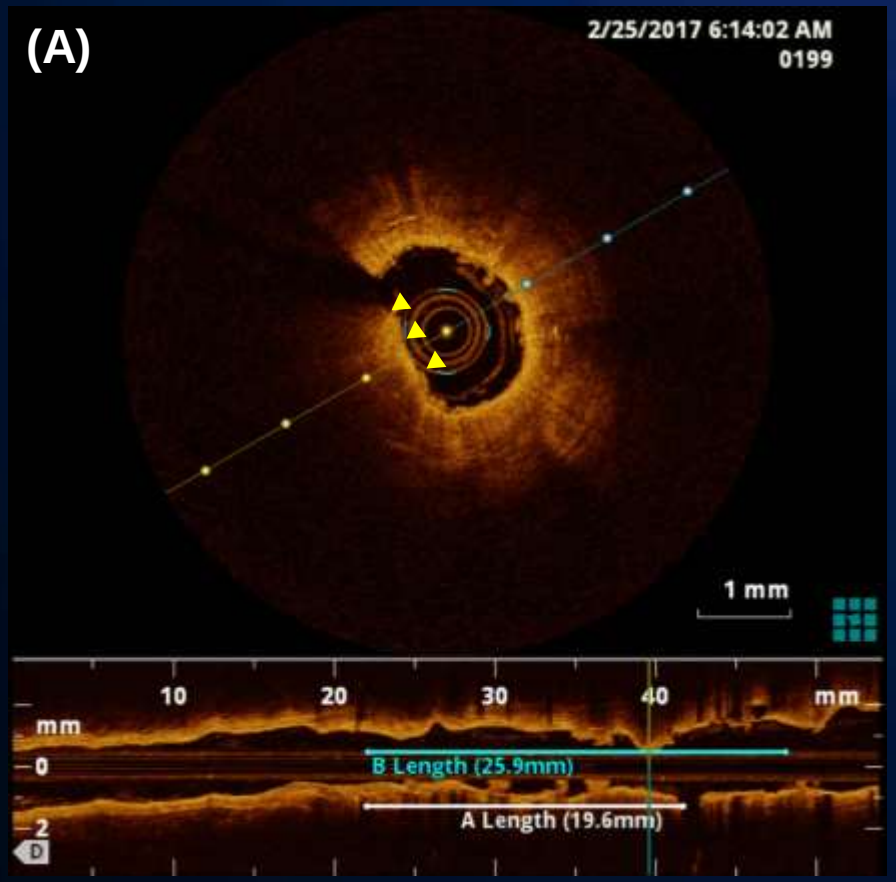
Very late ST (11Y)
OCT findings



- Intraluminal thrombi
- Neoatherosclerosis
- Ectatic change associated with thrombus formation

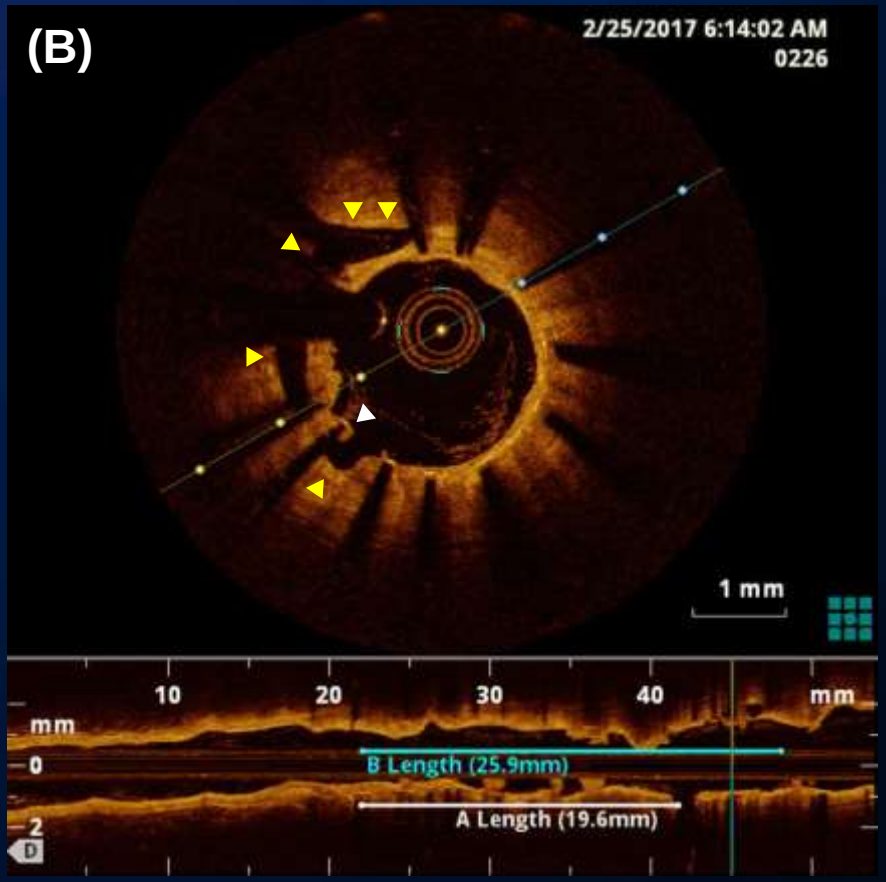
Very late ST (11Y)

OCT findings



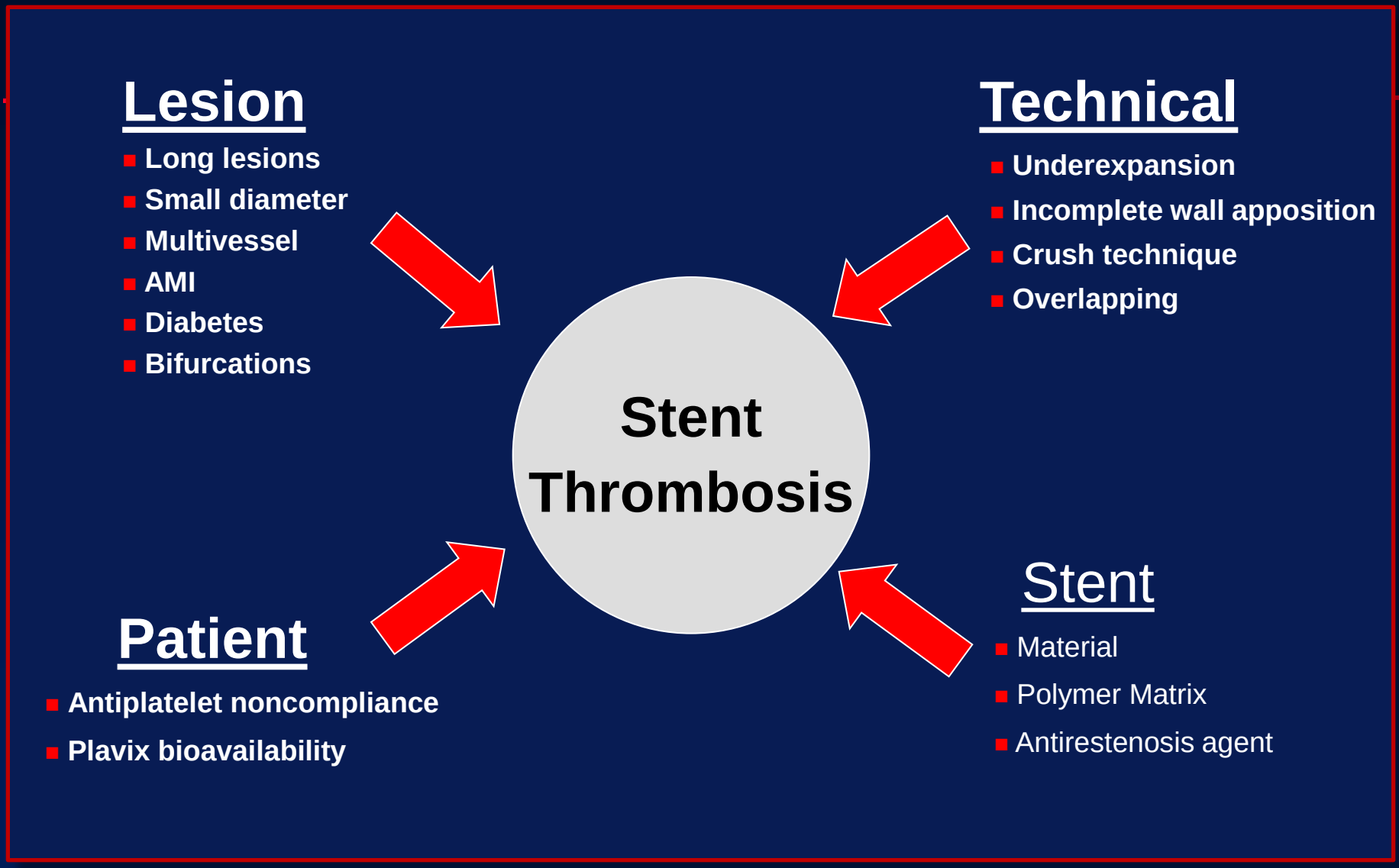
Neoatherosclerosis

Intraluminal thrombosis



Ectatic change associated with thrombus formation

Stent Thrombosis: a Multifactorial Problem



Courtesy of Popma, J

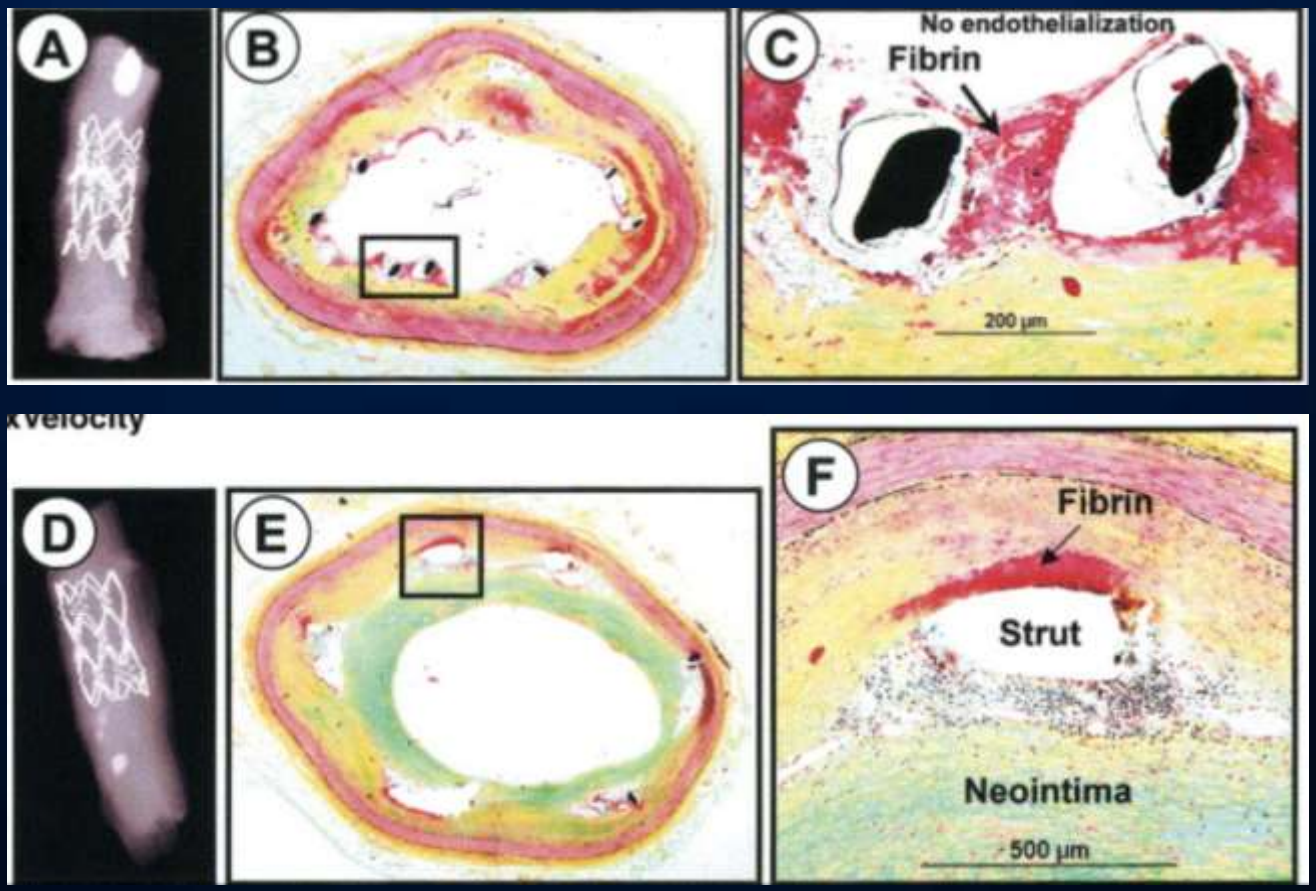
Adapted and modified from: Kereiakes D., et. al., Rev Cardiovasc Med. 2004;5(1):9-15.

Polymer and late stent thrombosis

- DES ➔ delayed vessel wall healing
  ➔ abnormal vascular response ➔ potential for ST
- Polymer in DES ➔ Thrombogenic nidus

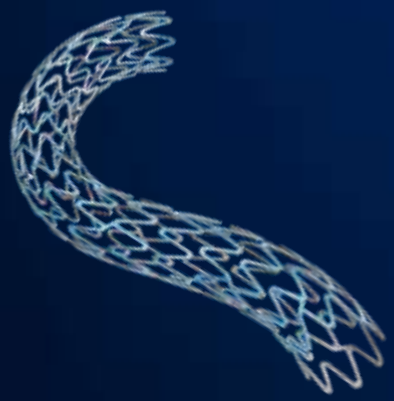
DES

BMS



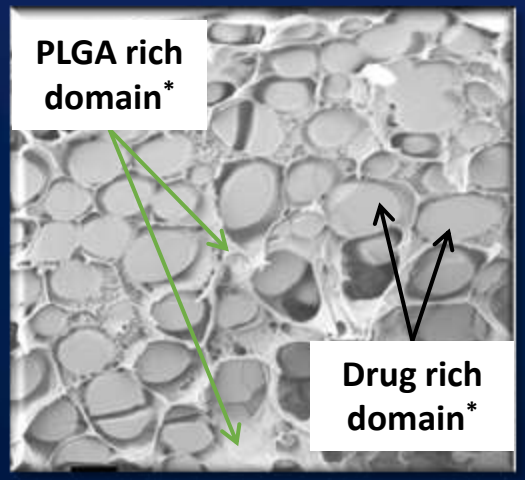
Joner et at. JACC 2006

The SYNERGY Stent



Platinum Chromium Platform

- 74µm (0.0029in) strut thickness
- ↑ Visibility
- ↑ Strength
- ↑ Flexibility
- ↑ Conformability
- ↓ Recoil



Everolimus-Eluting

- 100µg/cm^2
- 3 month release time
- 45% / 55% mix of drug and polymer

Ultrathin Abluminal Coating

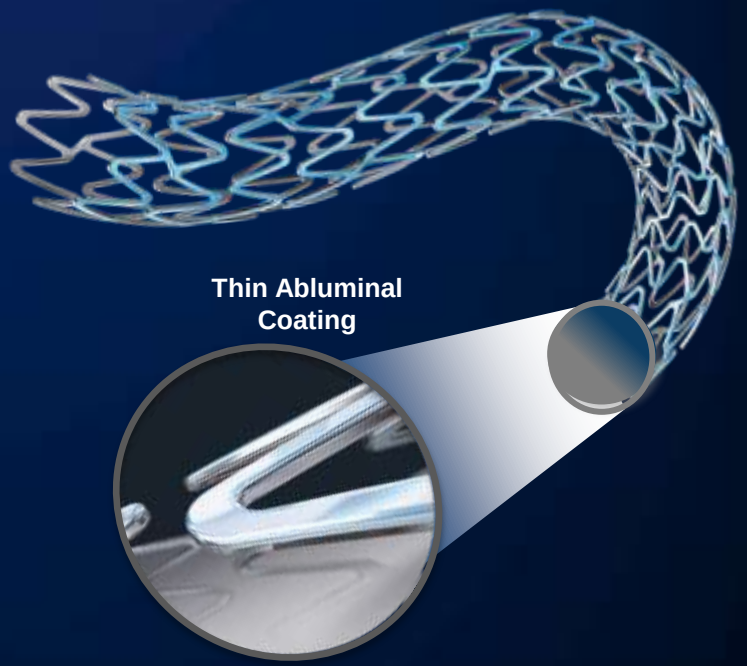
Bioabsorbable Polymer Coating (PLGA)

- Abluminal
- 4µm thick
- 85:15 ratio
- <4 month absorption time

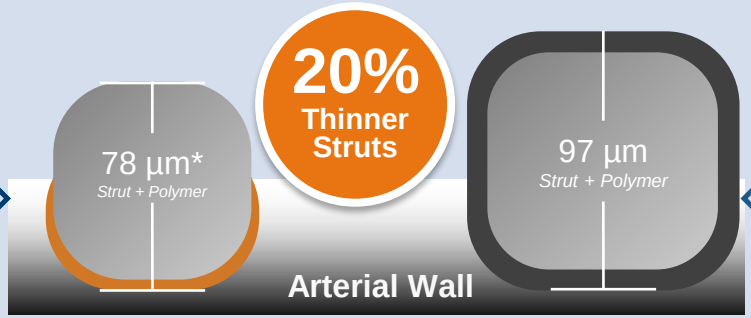
Adapted from Boston Scientific

Synchrony™ Bioabsorbable Coating

- Polymer is gone when no longer needed, shortly after completion of drug elution at 3 months
- Applied to the abluminal side of the stent, designed for optimal healing
- Providing ***Suppression*** of neointimal growth at the arterial wall & ***Promotion*** of healing inside the lumen



SYNERGY Stent
Abluminal PLGA Bioabsorbable Polymer



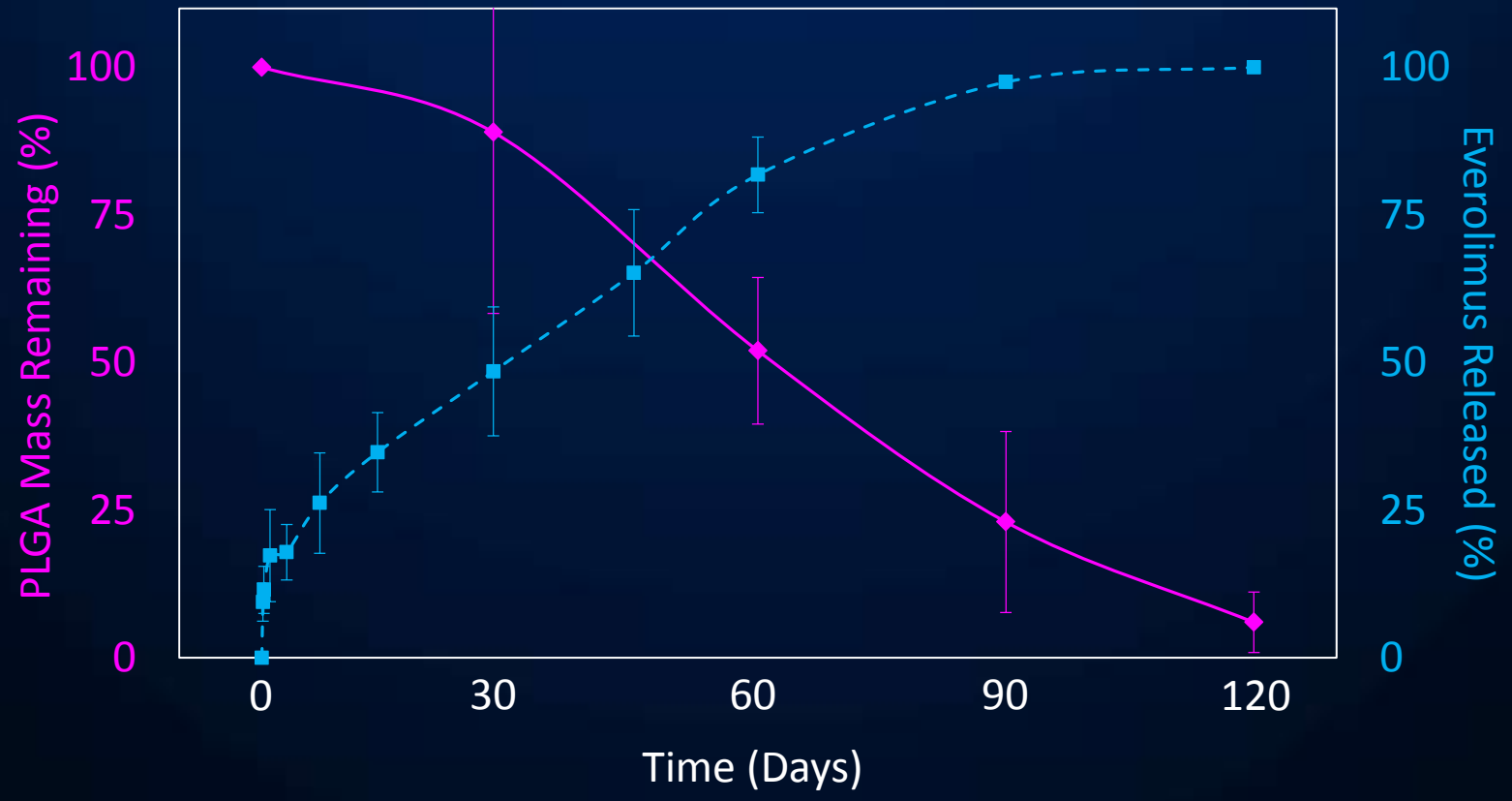
Promus PREMIER™
Conformal Permanent Polymer

Adapted from Boston Scientific

The SYNERGY Stent

Synchronous Drug Release & Polymer Absorption

Kinetics of Drug Release and Polymer Absorption in a Preclinical Porcine Model



Bennett and Dubois. *Biologics: Targets and Therapy.* 2013; 7: 149-159

Bioabsorbable Polymer in Perspective

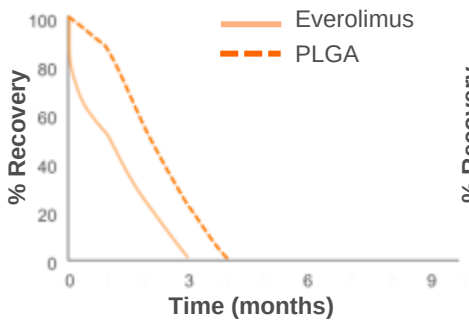
Relative Polymer and Drug Absorption Profiles

The SYNERGY Stent's polymer is absorbed shortly after drug elution ends at 3 months

Bioabsorbable Polymer-Coated Stents

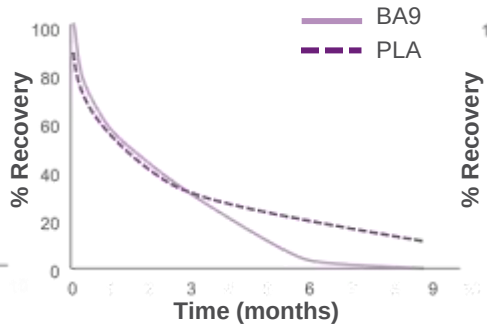
SYNERGY™[1] Stent

Polymer Coating: PLGA
Absorption Time:
3-4 mo



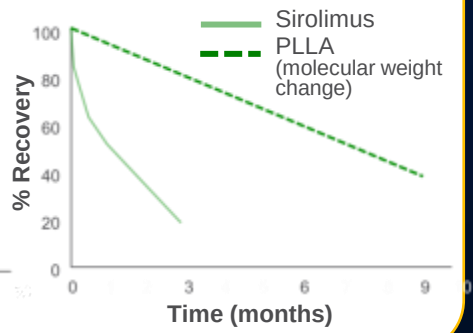
Nobori™[2] and BioMatrix Flex™[3] Stents

Polymer Coating: PLA
Absorption Time:
>9 mo



Orsiro™[4] Stent

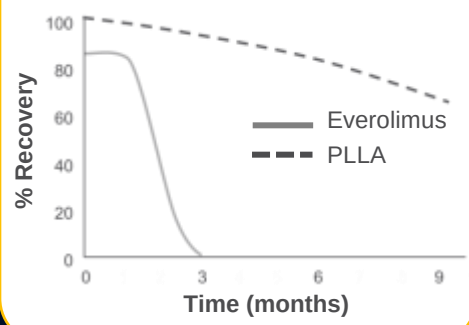
Polymer Coating: PLLA
Absorption Time:
>12 mo



Bioabsorbable Scaffold

Absorb™ BVS[3]

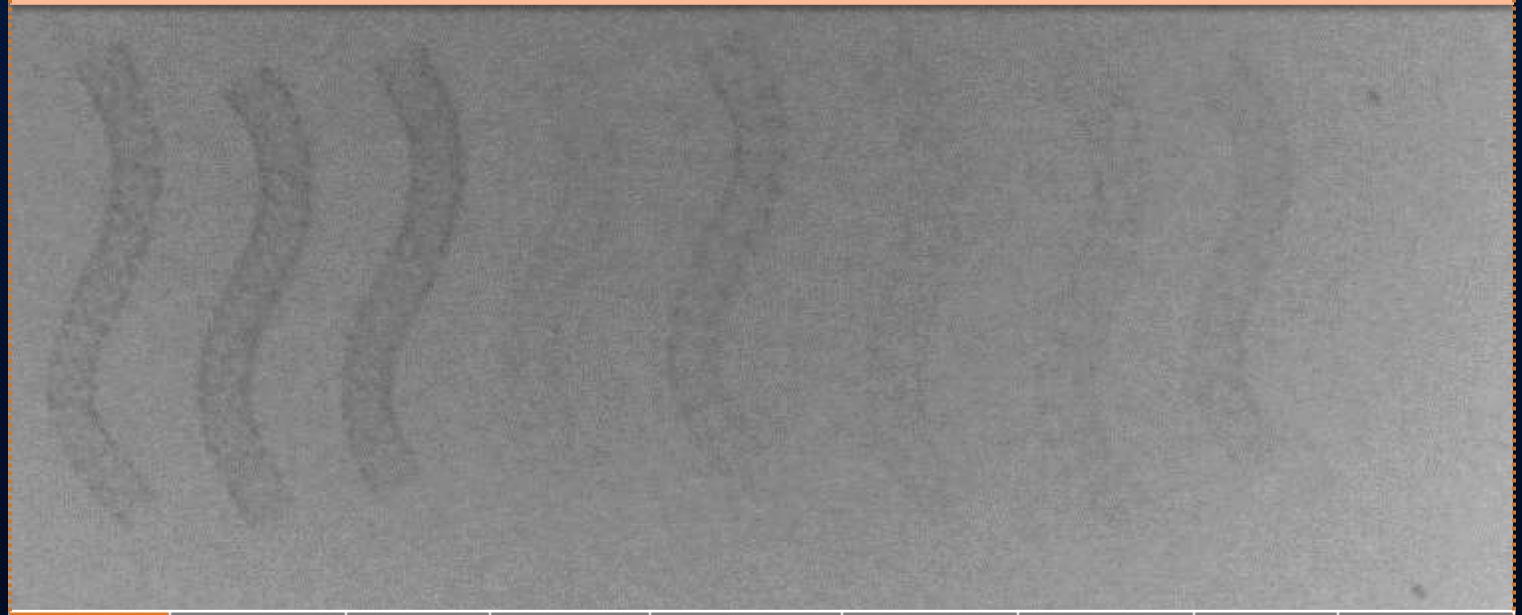
Polymer Scaffold: PLLA
Polymer Coating: PDLLA
Absorption Time:
>2 yrs



[1] Boston Scientific data on file. [2] *World J Cardiol* 2011 March 26; 3(3): 84-92. [3]Garg, S, *J Am Coll Cardiol*. 2010;56 (10s1):S43-S78. doi:10.1016. [4] Presented by Stephan Windecker, MD, TCT2012.

PtCr Alloy: Visibility

Even with thin struts the high density of Platinum Chromium allows for greater visibility*

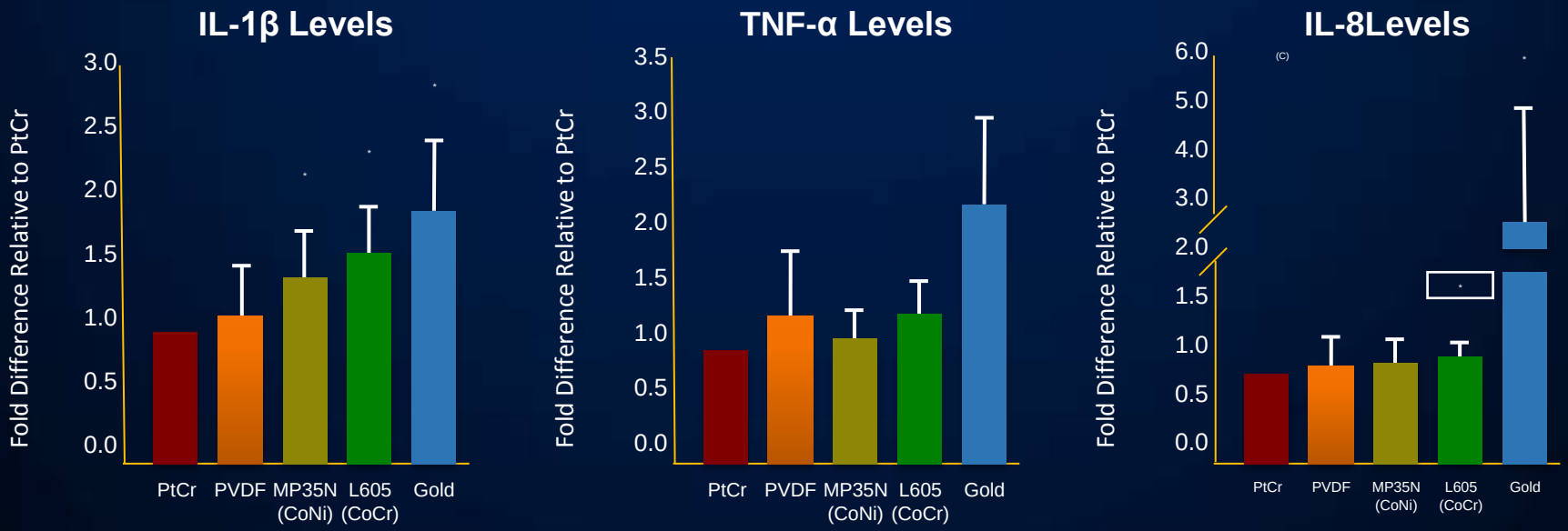


	SYNERGY Stent	Promus PREMIER™ Stent	PROMUS Element ™ Stent	**Resolute Integrity™ Stent**	**XIENCE™ Xpedition Stent**	**BioMatrix™ Stent**	**Nobori™ Stent**	**Orsiro™ Stent**	**ABSORB™ BVS Stent**
Alloy	PtCr	PtCr	PtCr	CoNi	CoCr	Stainless Steel	Stainless Steel	CoCr	PLLA Polymer
Strut Thickness	74 µm**	81 µm	81 µm	89 µm	81 µm	120 µm	120 µm	60 µm	150 µm

Based on 2.5mm stents. Under 6.0mm copper phantom to simulate body mass.

Stent surfaces and inflammatory cytokines

PtCr displayed higher degrees of endothelial surface coverage compared with PVDF-HFP surfaces.

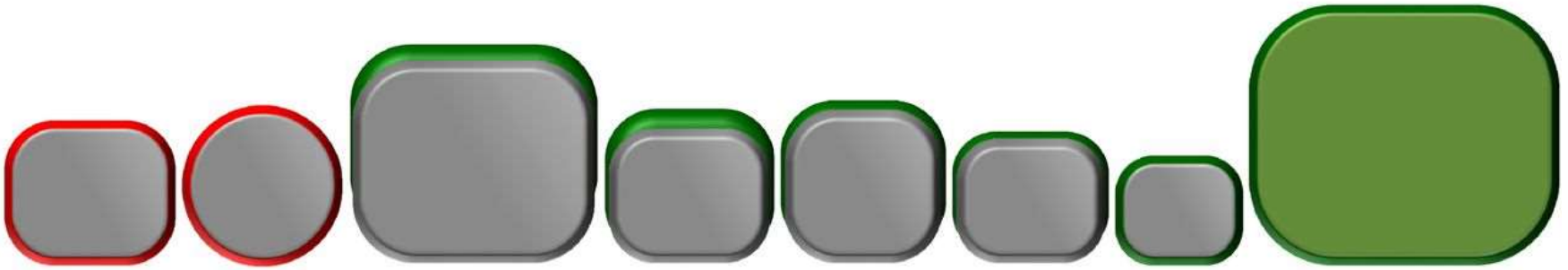


PtCr Surface Elicits Lowest Cytokine Response
Gold > L605 > MP35N > PtCr

Eppihimer et al. Circ CVI 2013

Thin Struts

Durable polymer-coated stent		Biodegradable polymer-coated stent					Bioresorbable drug-eluting stent
Abbott/ Boston	Medtronic	Biosensors	Terumo	Translumina	Boston	Biotronik	Abbott
Xience/ Promus	Resolute	BioMatrix	Ultimaster	Yukon Choice PC	Synergy	Orsiro	ABSORB
CoCr/PtCr-EES	CoNi-ZES	316L-BES	CoCr-SES	316L-SES	PtCr-EES	CoCr-SES	PLLA-EES



Strut thickness

81 µm	91 µm	120 µm	80 µm	87 µm	74 µm	60 µm	150 µm

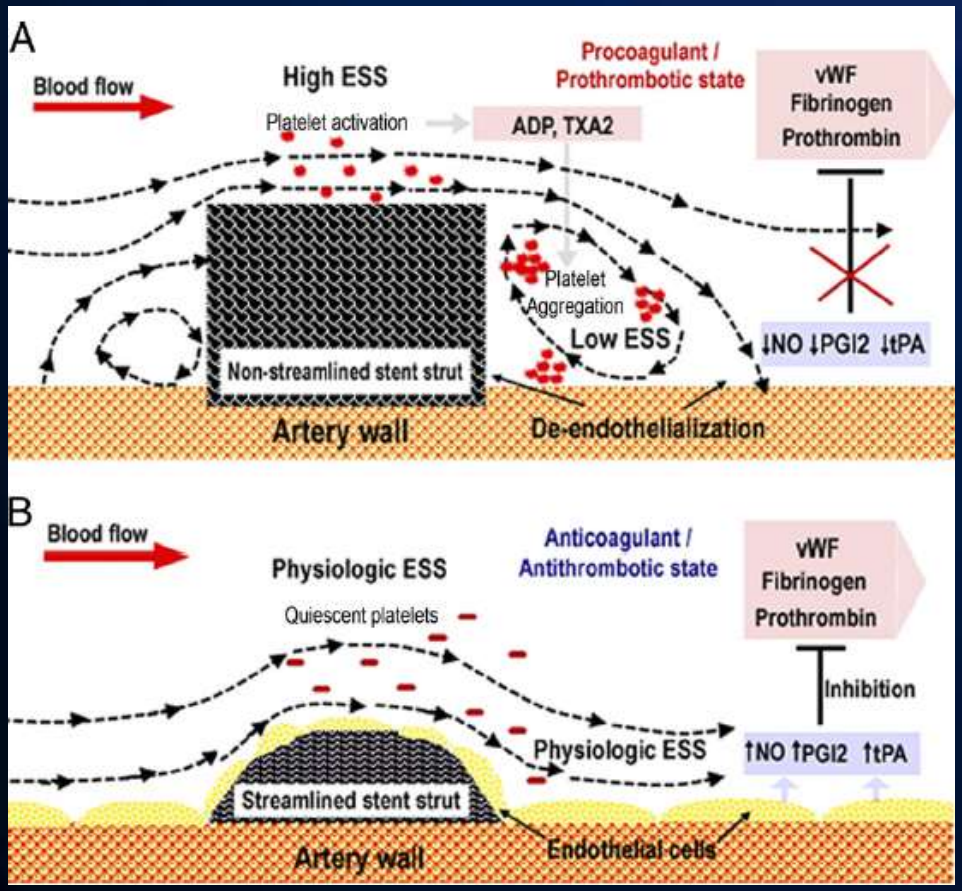
Polymer coating

Circumferential	Abluminal	Circumferential

Byrne et al. Eur Heart J 2015

Shear Stress Impacts ST Risk

Strut Design and Stent Thrombogenicity



Thick, rectangular struts promote stent thrombogenicity.

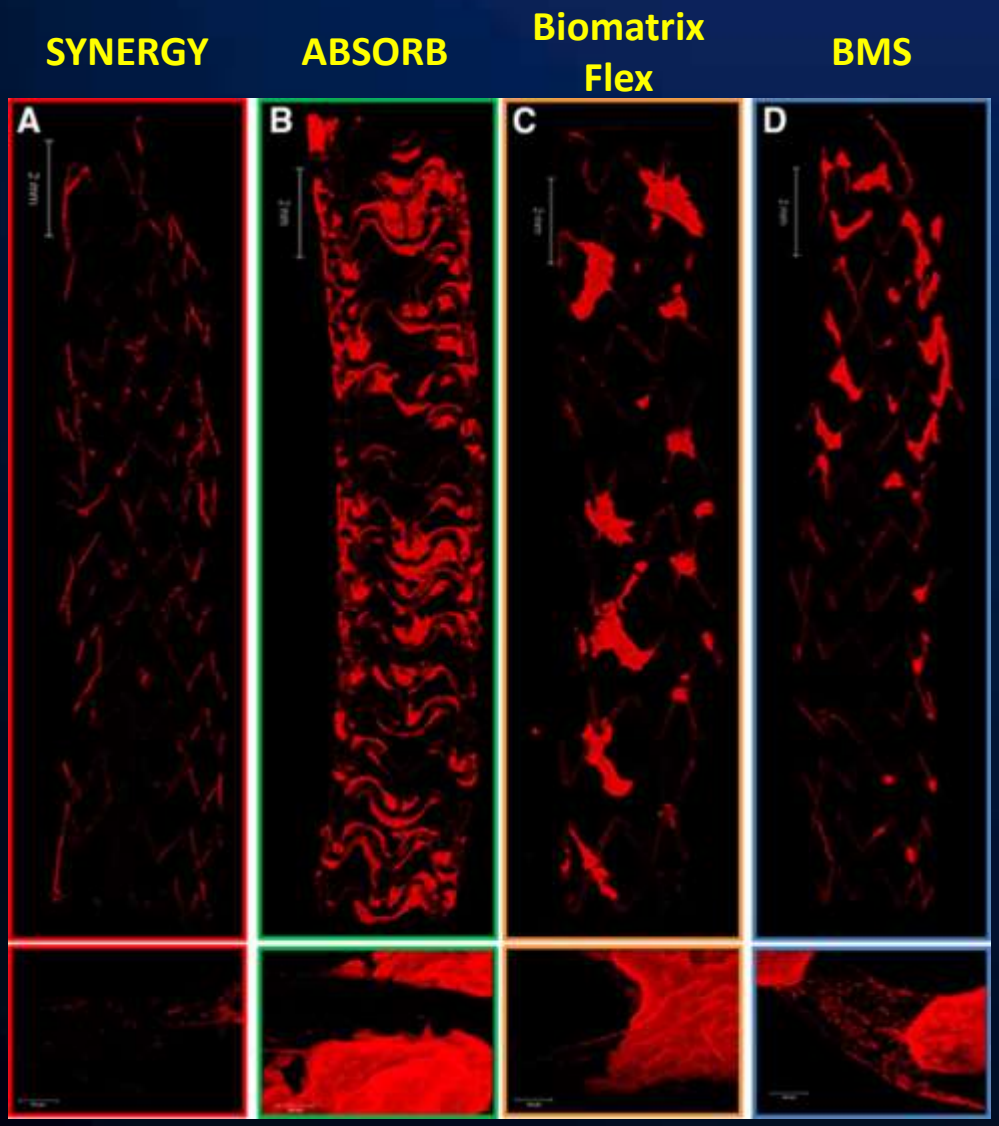
- High ESS (on top of struts)
  → platelet activatation
  → ADP release
- Low ESS (downstream of the strut) → activated platelets ↑
  re-endothelialization ↓
  natural anticoagulant production ↓

Thin, circular struts retain physiologic ESS, which favors platelet quiescence on top of struts and enhances re-endothelialization and production of antithrombotic factors downstream of struts

Koskinas et al. JACC 2012

Acute thrombogenicity

Porcine ex-vivo AV shunt model

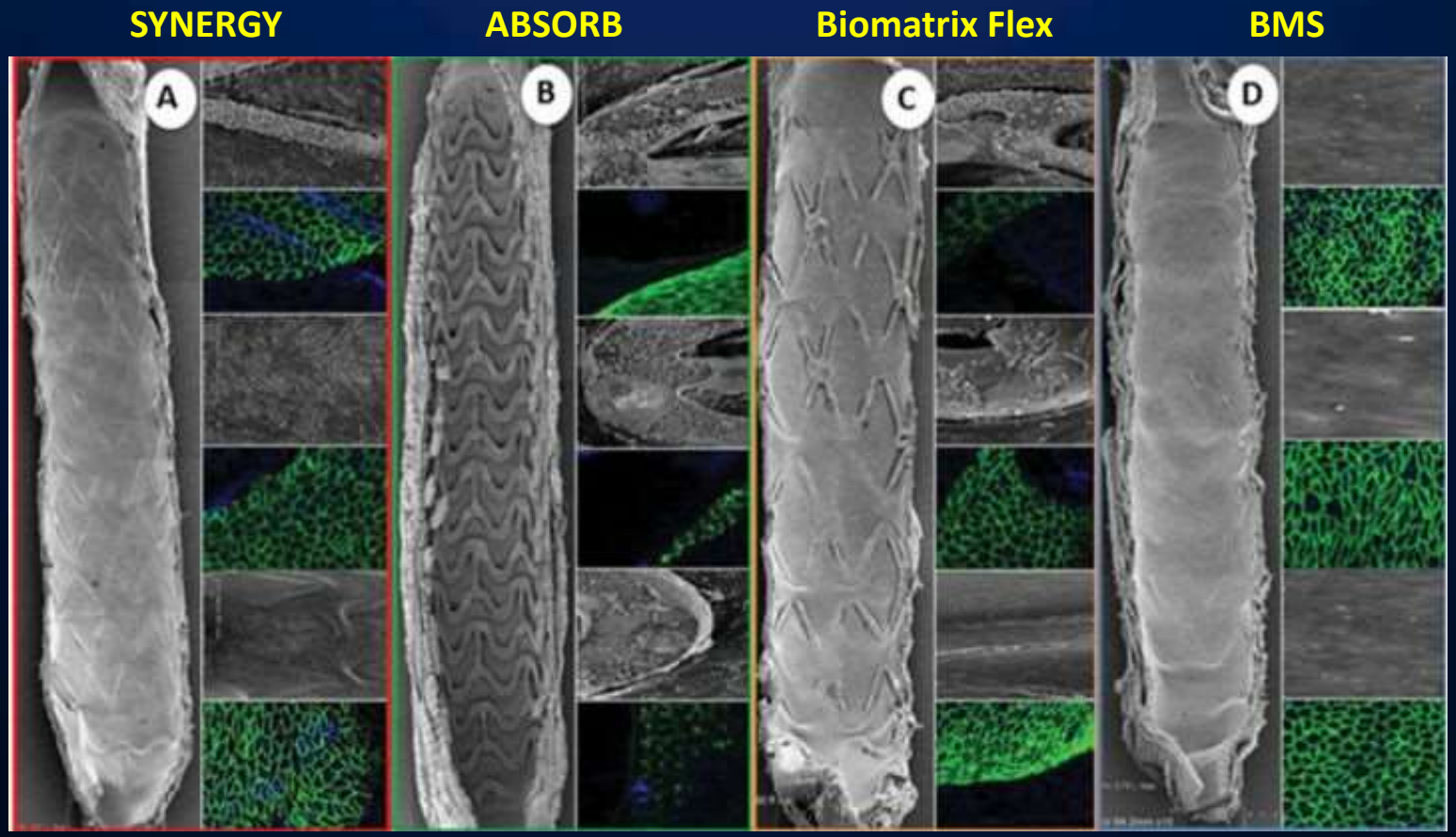


"Thin strut EES revealed significantly less platelet aggregation and inflammatory cell adhesion in a porcine AV shunt model as compared with bEES, BES, and BMS."

Koppara et al. Circ CVI 2014

Re-endothelialization

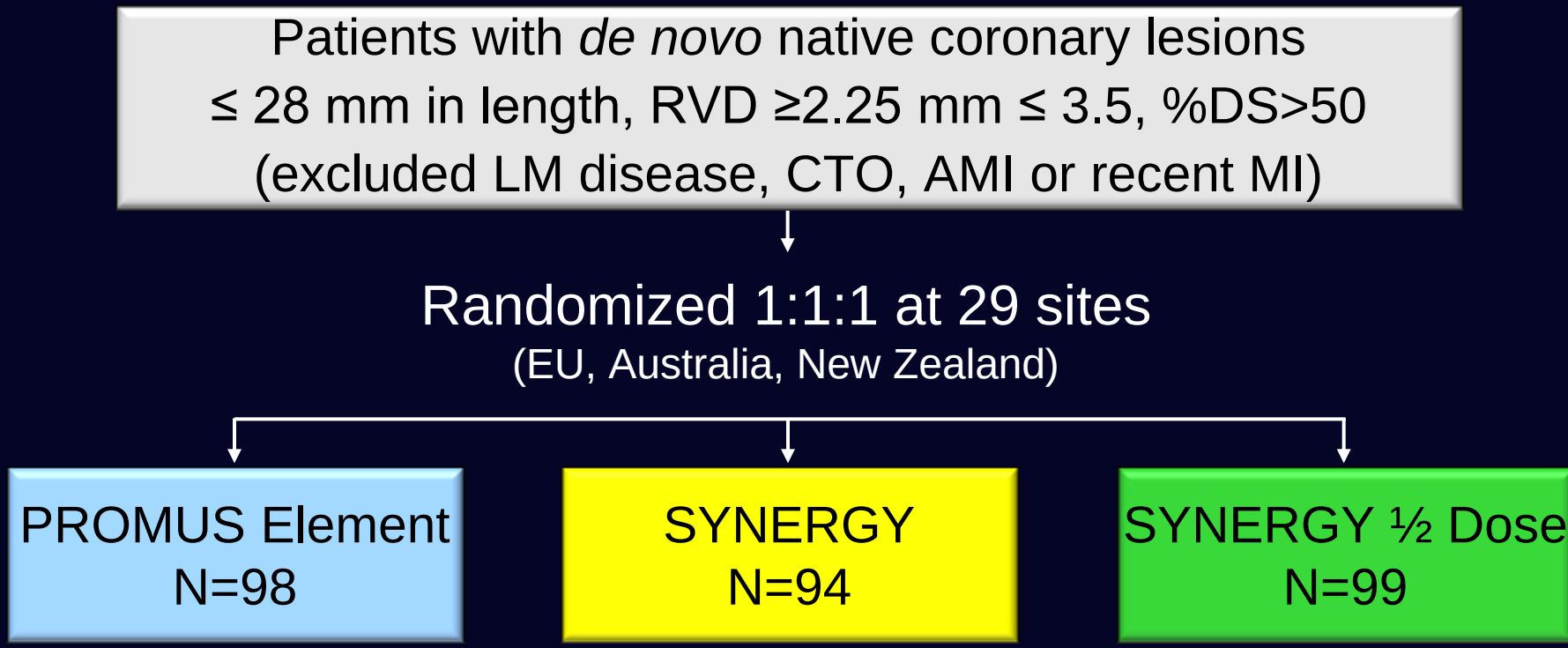
Rabbit model (iliofemoral artery) at 28 days



"Re-endothelialization after arterial denudation and stent implantation was significantly greater in thin-strut EES as compared with bEES…"

Koppara et al. Circ CVI 2014

EVOLVE Study Design



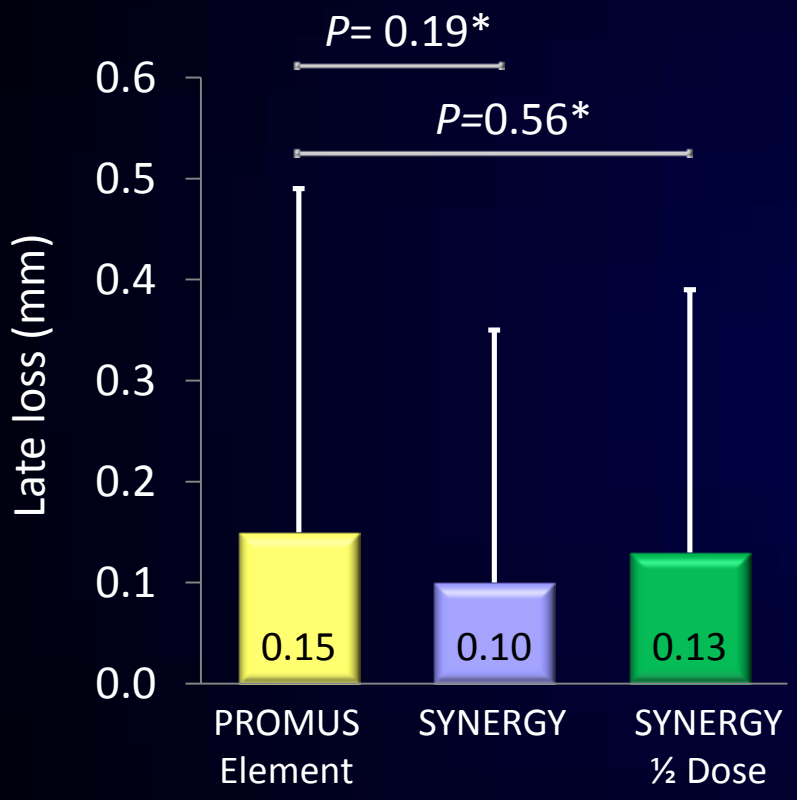
Single-blind, noninferiority design

Primary Clinical Endpoint: TLF (TV-CD, TV-MI, or TLR) at 30 days

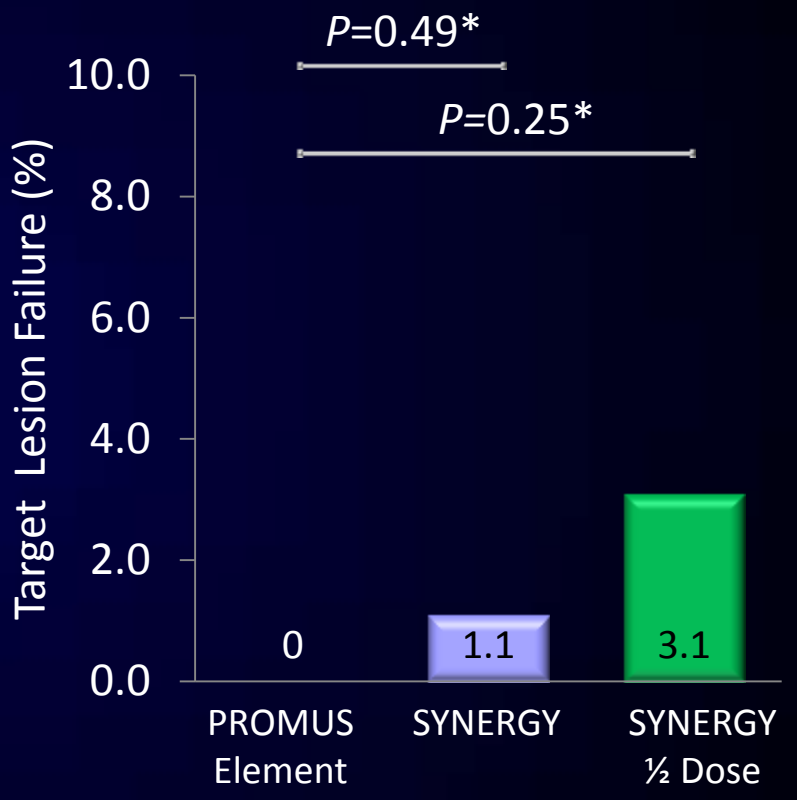
Primary Angiographic Endpoint: In-stent late loss at 6 months

EVOLVE Primary Endpoint

Late Loss at 6 Months



TLF at 30 days



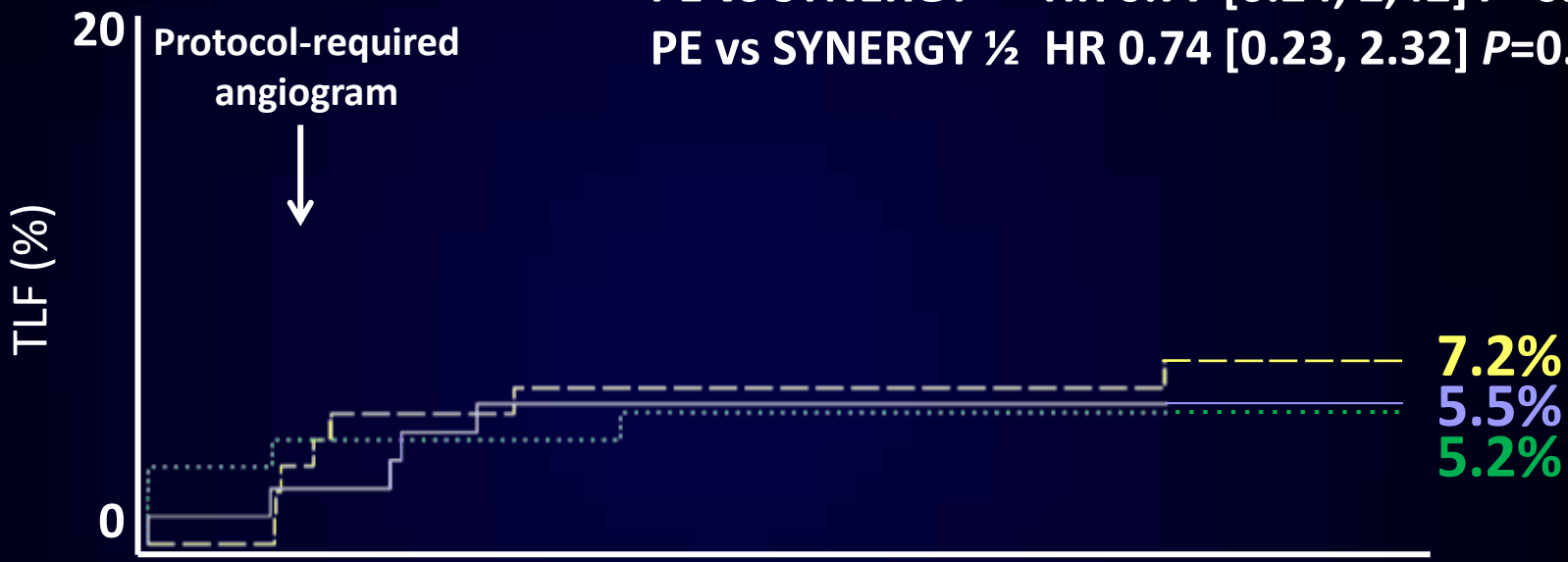
Noninferiority was proven because the upper 95.2% confidence bound of the difference in 6-month late loss is <0.20 for both SYNERGY stents ($P_{noninferiority}$<0.001)

Intent-to-treat; Mean + Standard Deviation; **P* values for superiority comparison

Meredith et al. *JACC* 2012; 59 (15): 1362-70

Target Lesion Failure
5-year Follow-up

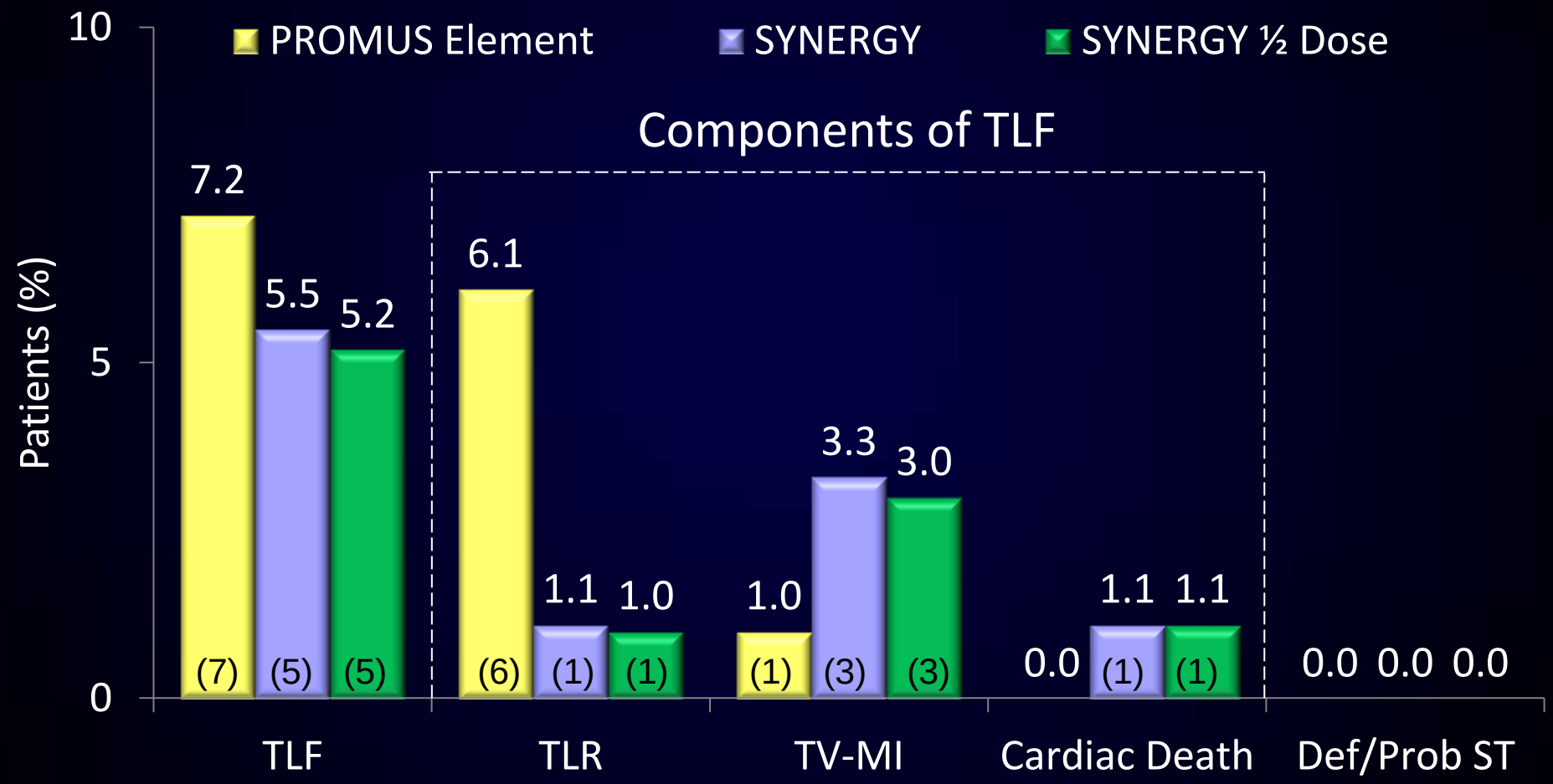
PE vs SYNERGY **HR 0.77 [0.24, 2,42] *P*=0.65**
PE vs SYNERGY ½ **HR 0.74 [0.23, 2.32] *P*=0.60**



Numbers at risk	0	1	2	3	4	5 Years
PE	98	98	93	92	92	67
SYNERGY	92	90	86	83	82	61
SYNERGY ½ Dose	99	92	90	88	88	65

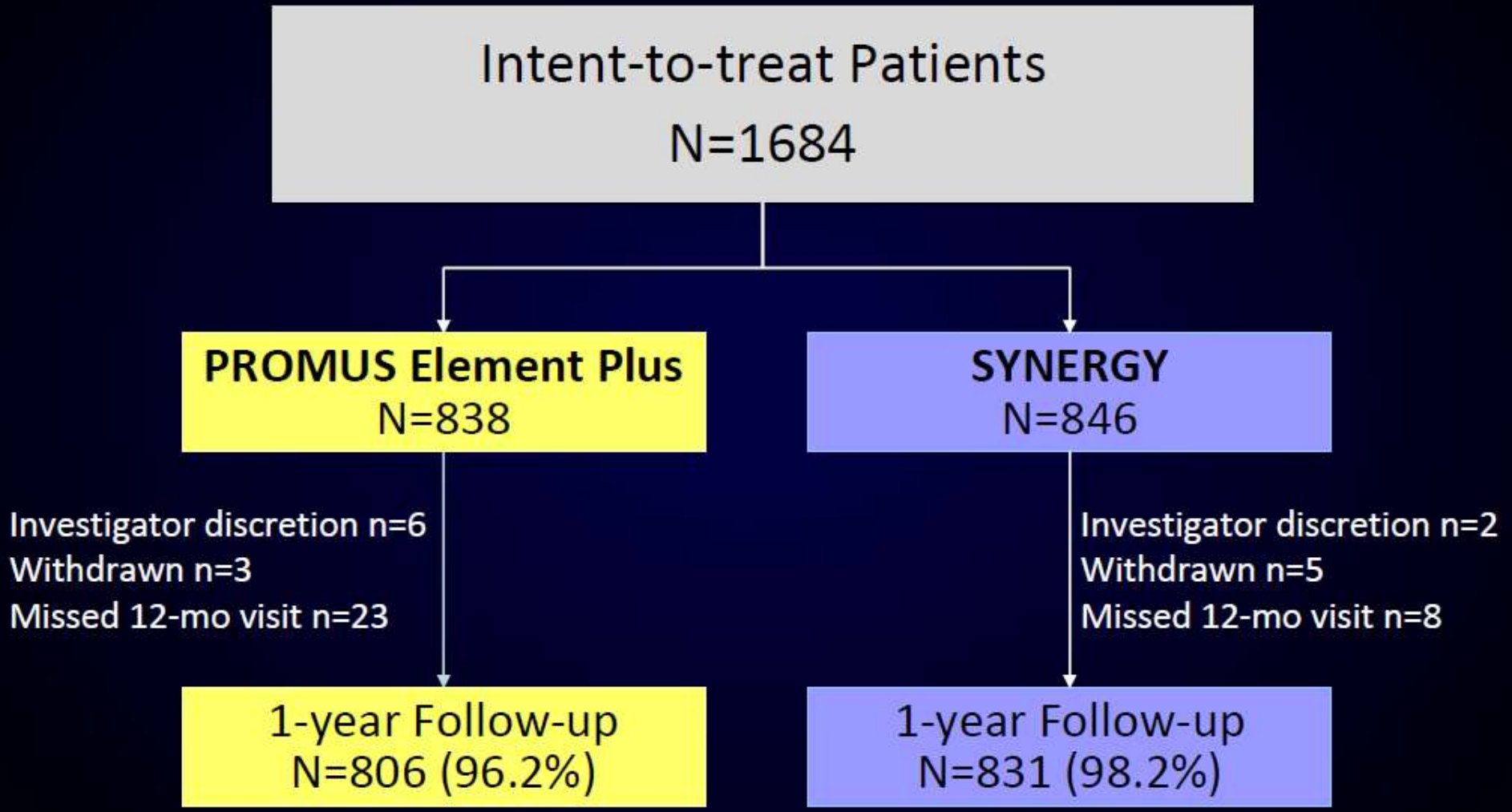
Safety Population; KM Event Rate; log-rank *P* values

5-Year Clinical Outcomes



Number of Events (N)
Safety Population; KM Event Rates; All *P* values are >0.05

EVOLVE II Patient Disposition



Baseline Clinical Characteristics

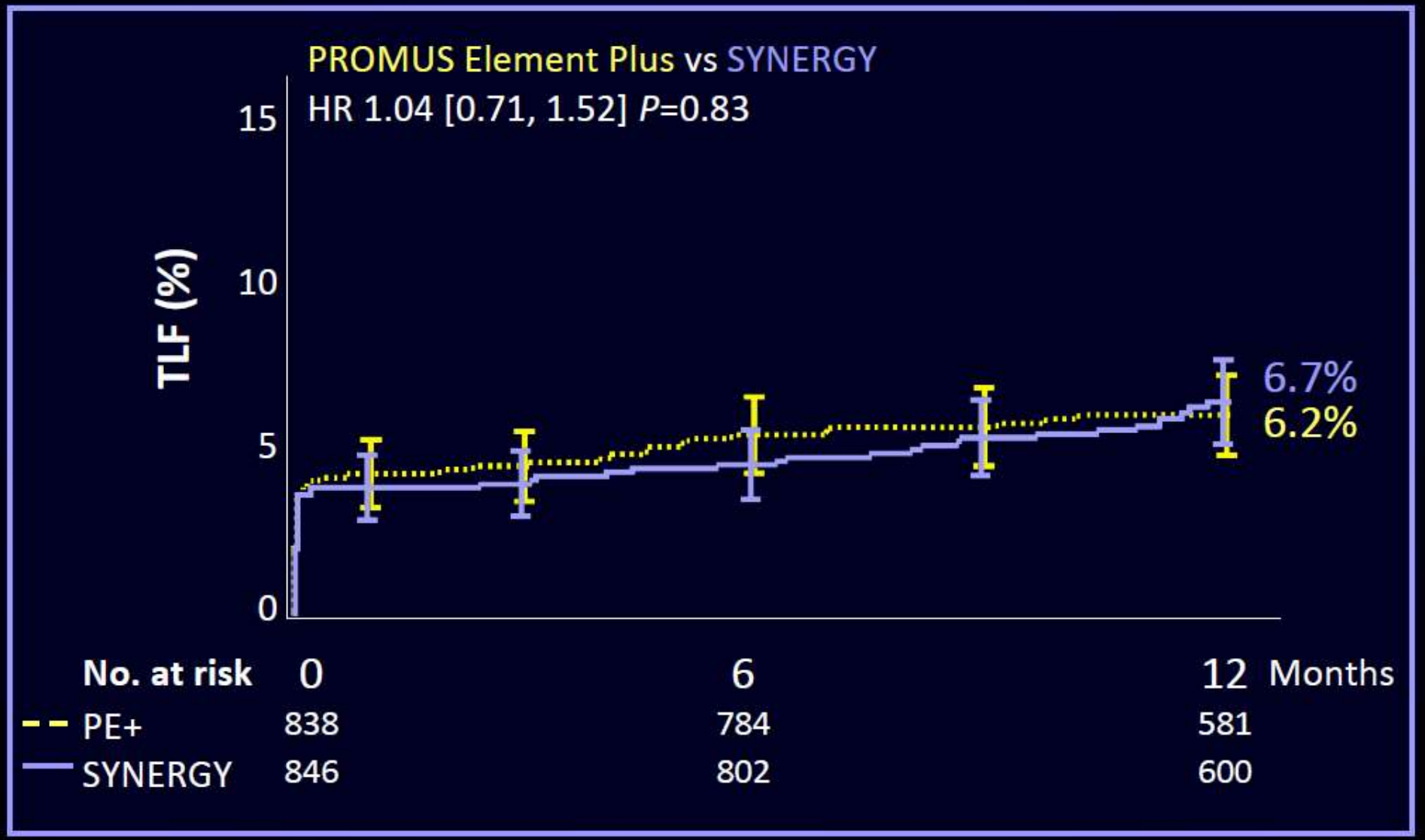
EVOLVE II SYNERGY

Per Patient	PROMUS Element Plus n=838 patients	SYNERGY n=846 patients	*P* value
Male	**72.7%**	**70.6%**	0.34
Age (yr) ± SD	**63.9 ± 10.5**	**63.5 ± 10.4**	0.40
Caucasian	79.2%	77.4%	0.37
Smoking, Ever	62.8%	61.7%	0.63
Current Smoker	22.4%	21.8%	0.76
Diabetes*	**30.8%**	**31.1%**	0.89
Treated with Insulin	10.9%	12.3%	0.36
Hyperlipidemia*	74.5%	74.0%	0.82
Hypertension*	75.1%	77.3%	0.29
Previous PCI	37.3%	35.8%	0.52
Previous CABG	6.1%	4.6%	0.18
History of CHF	9.0%	8.3%	0.63
Unstable Angina	**34.8%**	**33.9%**	0.69
MI	**29.2%**	**25.9%**	0.12

Intent-to-treat; *medically-treated; *P* values from Student's t test or Chi-square test; SD=standard deviation

EVOLVE II Primary Endpoint:

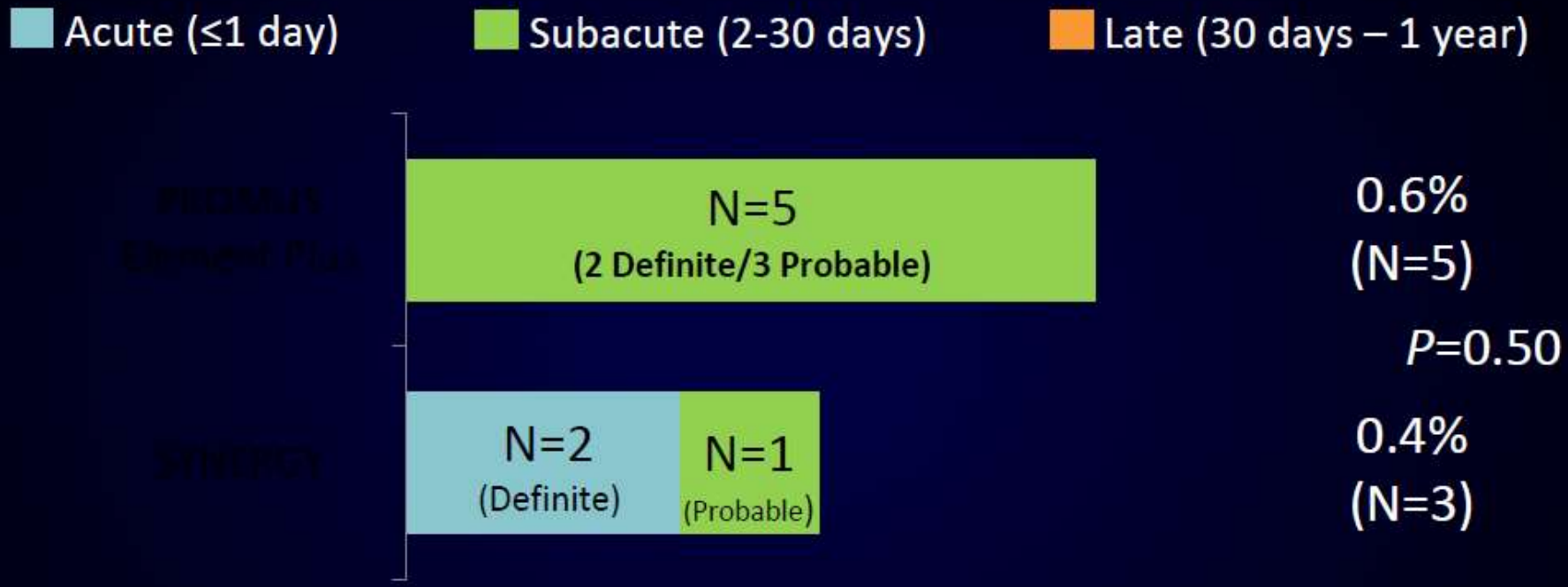
12-month TLF (ITT)



ITT; KM Event Rate; log-rank *P* values

Stent Thrombosis through 12-months

Definite/Probable, ITT Population



No definite/probable stent thrombosis in the SYNERGY arm after Day 6

JACC: CARDIOVASCULAR INTERVENTIONS

PUBLISHED BY ELSEVIER

VOL. 9, NO. 12, 2016
ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcin.2016.03.038

CLINICAL RESEARCH

CORONARY

Stent Thrombosis With Drug-Eluting Stents and Bioresorbable Scaffolds

Evidence From a Network Meta-Analysis of 147 Trials

Si-Hyuck Kang, MD,[a] In-Ho Chae, MD, PhD,[a] Jin-Joo Park, MD, PhD,[a] Hak Seung Lee, MD,[b] Do-Yoon Kang, MD,[c] Seung-Sik Hwang, MD, PhD,[d] Tae-Jin Youn, MD, PhD,[a] Hyo-Soo Kim, MD, PhD[b]

ABSTRACT

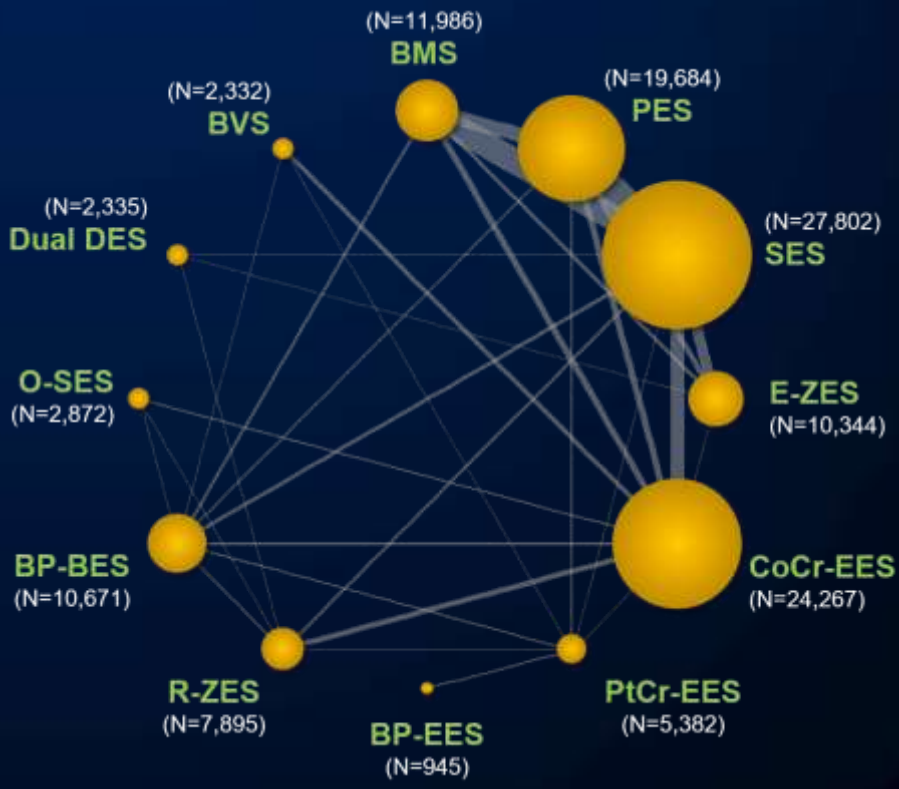
OBJECTIVES This study sought to perform a systematic review and network meta-analysis to compare the relative safety and efficacy of contemporary DES and BVS.

BACKGROUND To improve outcomes of patients undergoing percutaneous coronary revascularization, there have been advances in the design of drug-eluting stents (DES), including the development of drug-eluting bioresorbable vascular scaffolds (BVS).

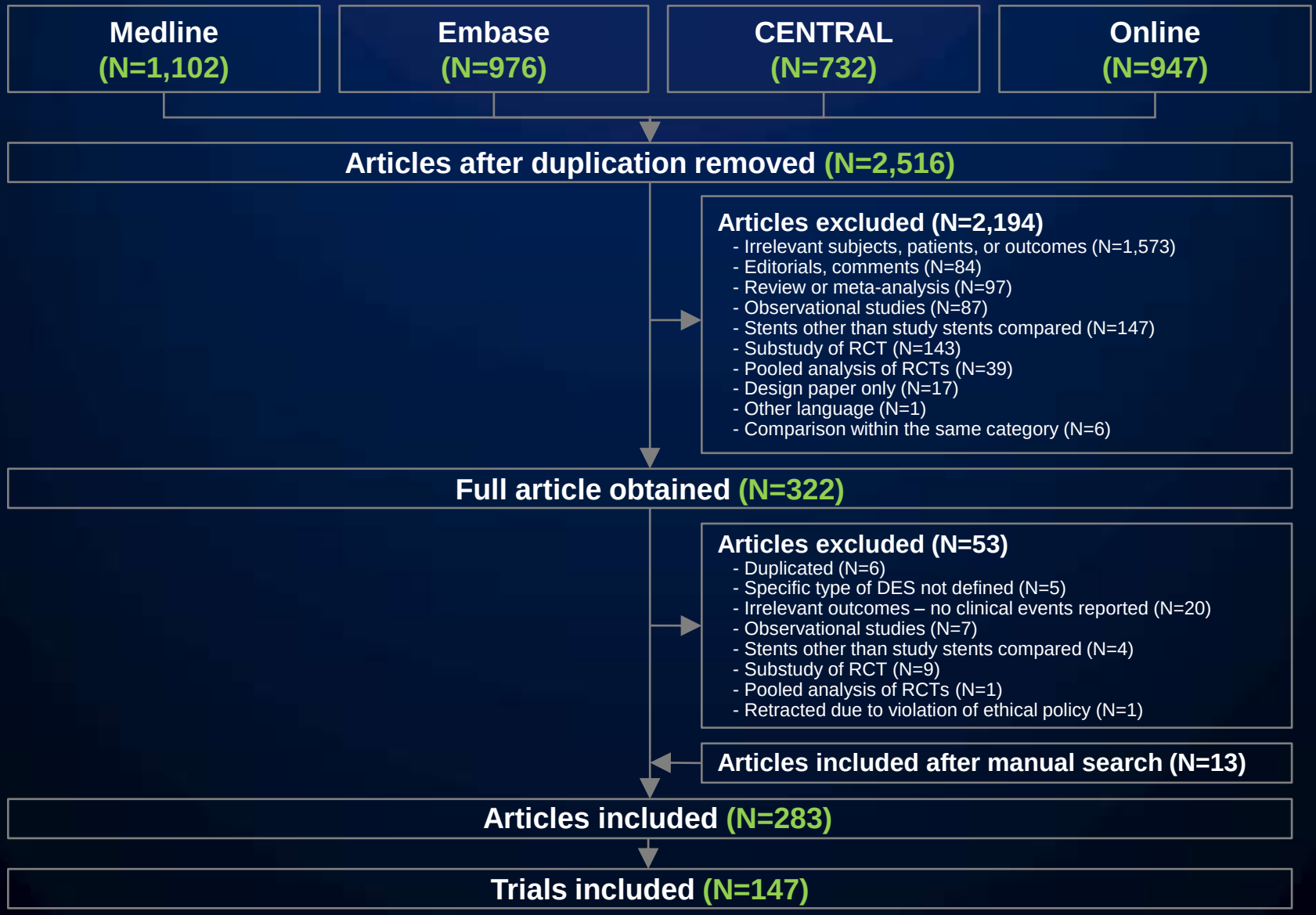
METHODS Prospective, randomized, controlled trials comparing bare-metal stents (BMS), paclitaxel-eluting stents (PES), sirolimus-eluting stents (SES), Endeavor zotarolimus-eluting stents (E-ZES), cobalt-chromium (CoCr) everolimus-eluting stents (EES), platinum-chromium (PtCr)-EES, biodegradable polymer (BP)-EES, Resolute zotarolimus-eluting stents (R-ZES), BP biolimus-eluting stents (BP-BES), hybrid sirolimus-eluting stents (H [Orsiro]-SES), polymer-free sirolimus- and probucol-eluting stents, or BVS were searched in online databases. The primary endpoint was definite or probable stent thrombosis at 1 year.

Study Aim

- To compare the safety of contemporary DES including BVS in terms of th e risk of stent thrombosis (ST) or device thrombosis.
- We performed a systematic literature review of randomized controlled trials and updated a multiple-treatment network meta-analysis using a Bayesian framework.

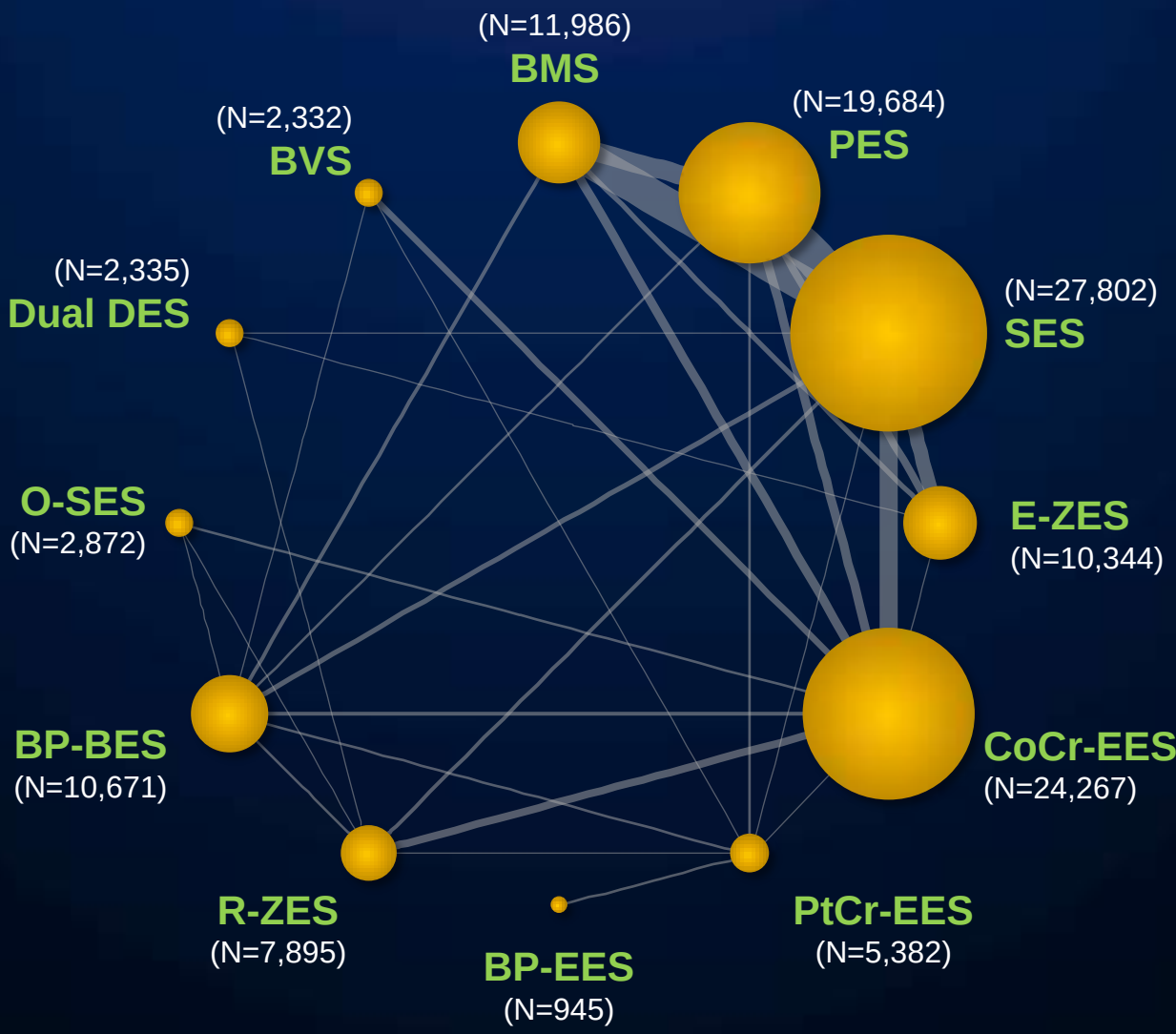


Flow Diagram of Systematic Review



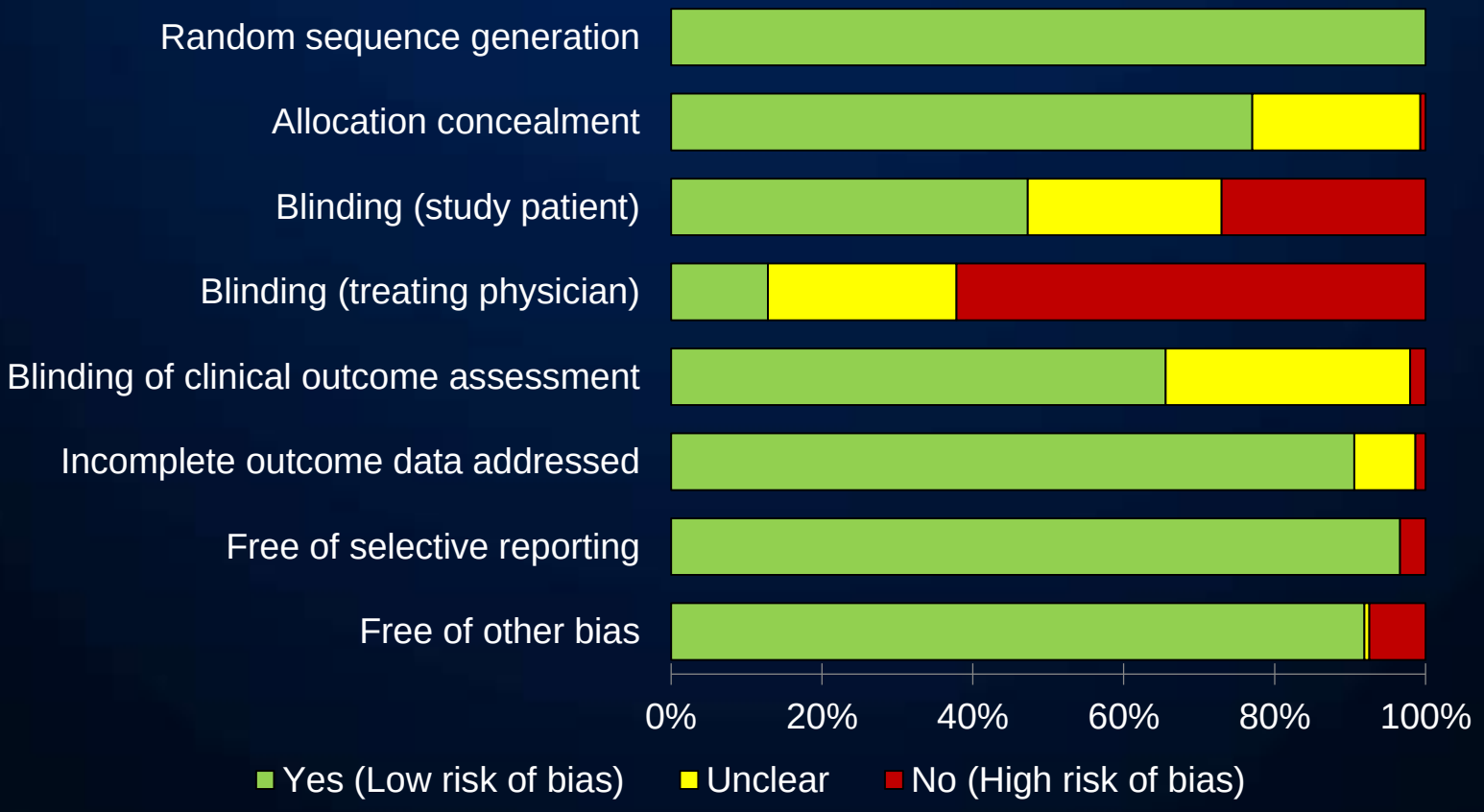
Network Plot of Included Trials

147 trials with 126,526 patients



Risk of Bias Assessment

- Open-label / single-blind designs > a double-blind design
- Clinical outcome assessment blinding in 66% of the trials



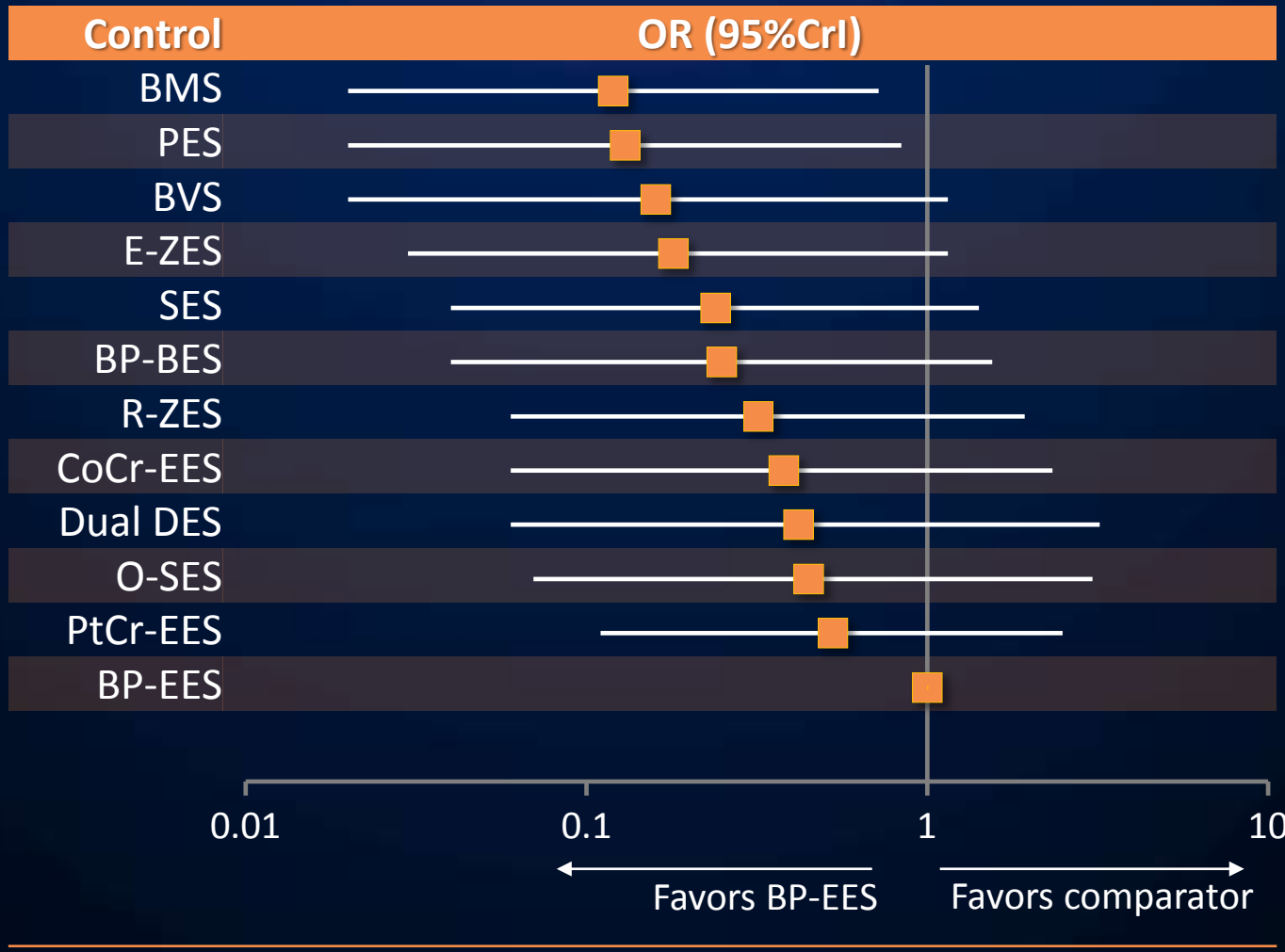
Risk of definite or probable ST at 1 Year

	BMS	PES	BVS	E-ZES	SES	BP-BES	R-ZES	CoCr-EES	Dual DES	O-SES	PtCr-EES	BP-EES
vs. BMS	-	0.87 (0.64-1.18)	**0.73 (0.31-2.06)**	**0.64 (0.43-0.90)**	**0.51 (0.38-0.69)**	**0.48 (0.31-0.72)**	**0.37 (0.21-0.63)**	**0.31 (0.22-0.44)**	**0.28 (0.10-0.69)**	**0.25 (0.13-0.48)**	**0.22 (0.09-0.55)**	**0.12 (0.02-0.72)**
vs. PES	1.15 (0.85-1.56)	-	0.85 (0.36-2.34)	**0.73 (0.50-1.05)**	**0.59 (0.45-0.80)**	**0.55 (0.33-0.85)**	**0.43 (0.24-0.71)**	**0.36 (0.26-0.49)**	**0.32 (0.12-0.78)**	**0.29 (0.15-0.55)**	**0.26 (0.10-0.62)**	**0.13 (0.02-0.84)**
vs. BVS	1.38 (0.49-3.21)	1.18 (0.43-2.77)	-	0.88 (0.29-2.09)	0.71 (0.25-1.65)	0.65 (0.22-1.59)	0.51 (0.17-1.22)	**0.44 (0.16-0.93)**	0.39 (0.10-1.22)	**0.35 (0.11-0.91)**	**0.31 (0.08-0.96)**	0.16 (0.02-1.15)
vs. E-ZES	**1.57 (1.11-2.31)**	1.36 (0.95-2.00)	1.13 (0.48-3.39)	-	0.81 (0.57-1.17)	0.75 (0.44-1.25)	0.58 (0.32-1.03)	**0.49 (0.33-0.75)**	0.44 (0.16-1.08)	**0.40 (0.21-0.80)**	**0.35 (0.14-0.89)**	0.18 (0.03-1.15)
vs. SES	**1.95 (1.45-2.61)**	**1.70 (1.25-2.23)**	1.41 (0.61-3.93)	1.24 (0.85-1.77)	-	0.93 (0.61-1.37)	0.72 (0.42-1.17)	**0.61 (0.44-0.81)**	0.54 (0.21-1.30)	**0.50 (0.27-0.92)**	0.43 (0.17-1.03)	0.24 (0.04-1.42)
vs. BP-BES	**2.10 (1.39-3.25)**	**1.81 (1.18-3.06)**	1.54 (0.63-4.52)	1.33 (0.80-2.28)	1.07 (0.73-1.63)	-	0.77 (0.45-1.29)	**0.66 (0.43-0.99)**	0.58 (0.22-1.44)	**0.53 (0.30-0.96)**	0.47 (0.19-1.12)	0.25 (0.04-1.55)
vs. R-ZES	**2.69 (1.59-4.79)**	**2.33 (1.41-4.12)**	1.96 (0.82-5.87)	1.71 (0.97-3.12)	1.39 (0.85-2.41)	1.30 (0.78-2.23)	-	0.84 (0.55-1.38)	0.74 (0.34-1.62)	0.69 (0.35-1.42)	0.60 (0.27-1.38)	0.32 (0.06-1.93)
vs. CoCr-EES	**3.20 (2.27-4.54)**	**2.79 (2.03-3.88)**	**2.28 (1.07-6.29)**	**2.02 (1.33-3.07)**	**1.63 (1.23-2.26)**	**1.53 (1.01-2.31)**	1.18 (0.73-1.83)	-	0.89 (0.35-2.10)	0.80 (0.47-1.44)	0.71 (0.30-1.65)	0.38 (0.06-2.33)
vs. Dual DES	**3.63 (1.44-9.57)**	**3.13 (1.27-8.27)**	2.59 (0.82-10.3)	2.29 (0.92-6.10)	1.86 (0.77-4.82)	1.71 (0.70-4.48)	1.35 (0.62-2.94)	1.12 (0.48-2.82)	-	0.94 (0.33-2.64)	0.82 (0.26-2.53)	0.42 (0.06-3.21)
vs. O-SES	**3.94 (2.10-7.52)**	**3.40 (1.80-6.48)**	**2.83 (1.10-8.90)**	**2.50 (1.26-4.85)**	**2.02 (1.09-3.74)**	**1.88 (1.04-3.37)**	1.45 (0.71-2.89)	1.24 (0.69-2.14)	1.06 (0.38-2.99)	-	0.87 (0.32-2.36)	0.45 (0.07-3.06)
vs. PtCr-EES	**4.56 (1.82-11.3)**	**3.87 (1.60-9.81)**	**3.28 (1.04-12.1)**	**2.88 (1.12-7.28)**	2.31 (0.97-5.76)	2.12 (0.89-5.27)	1.67 (0.73-3.76)	1.42 (0.60-3.34)	1.22 (0.39-3.80)	1.15 (0.42-3.14)	-	0.53 (0.11-2.50)
vs. BP-EES	**8.51 (1.39-54.7)**	**7.44 (1.19-46.9)**	6.13 (0.87-49.5)	5.50 (0.87-33.8)	4.24 (0.70-27.6)	4.05 (0.65-26.1)	3.09 (0.52-18.2)	2.64 (0.43-16.5)	2.36 (0.31-16.2)	2.20 (0.33-14.8)	1.90 (0.40-8.84)	-

- All DES except for PES and BVS > BMS
- All the others except BVS > PES
- CoCr-EES, O-SES, and PtCr-EES > BVS and E-ZES
- CoCr-EES and O-SES > SES and BP-BES.

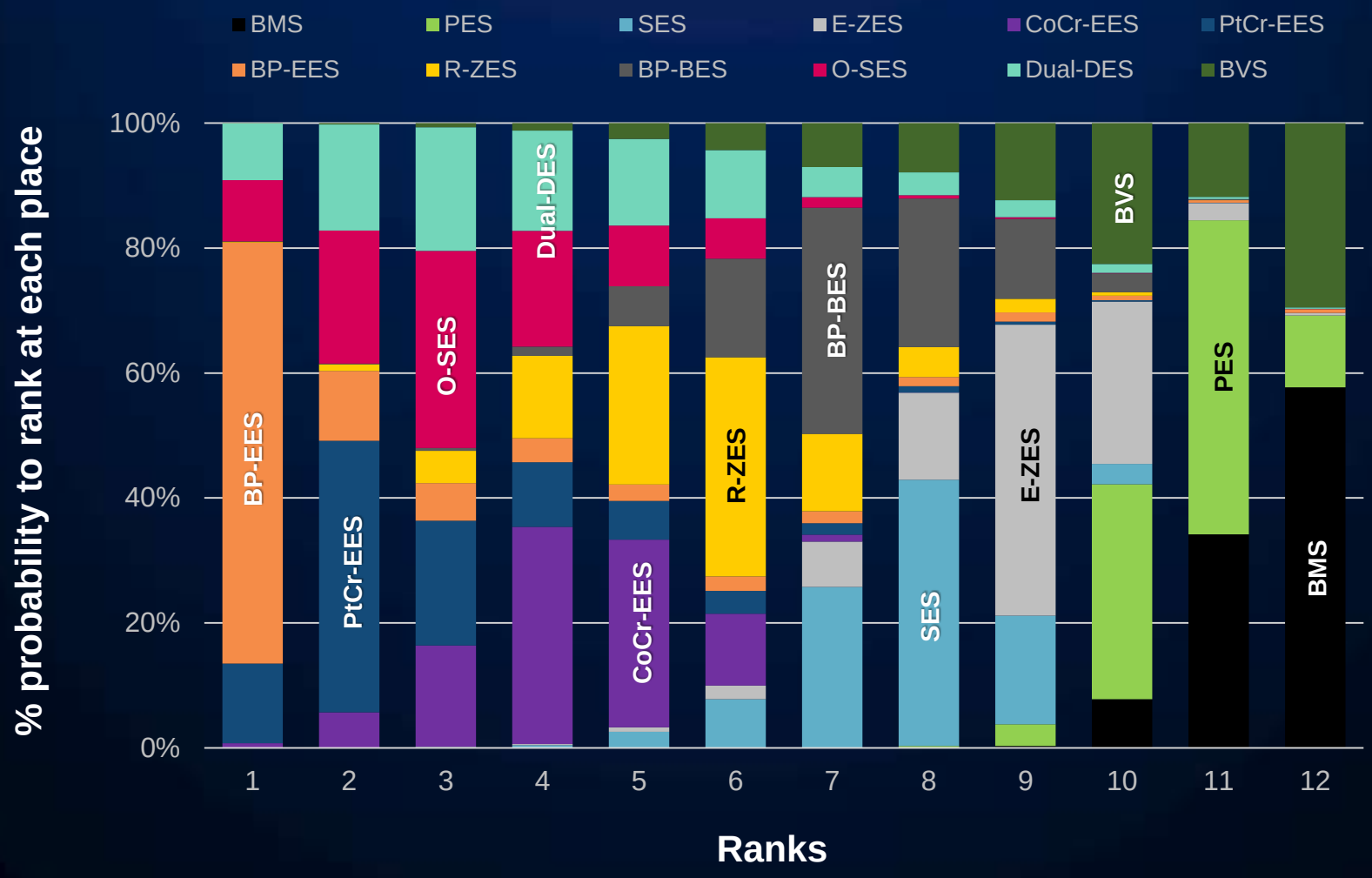
Stent Thrombosis

definite or probable ST at 1 year



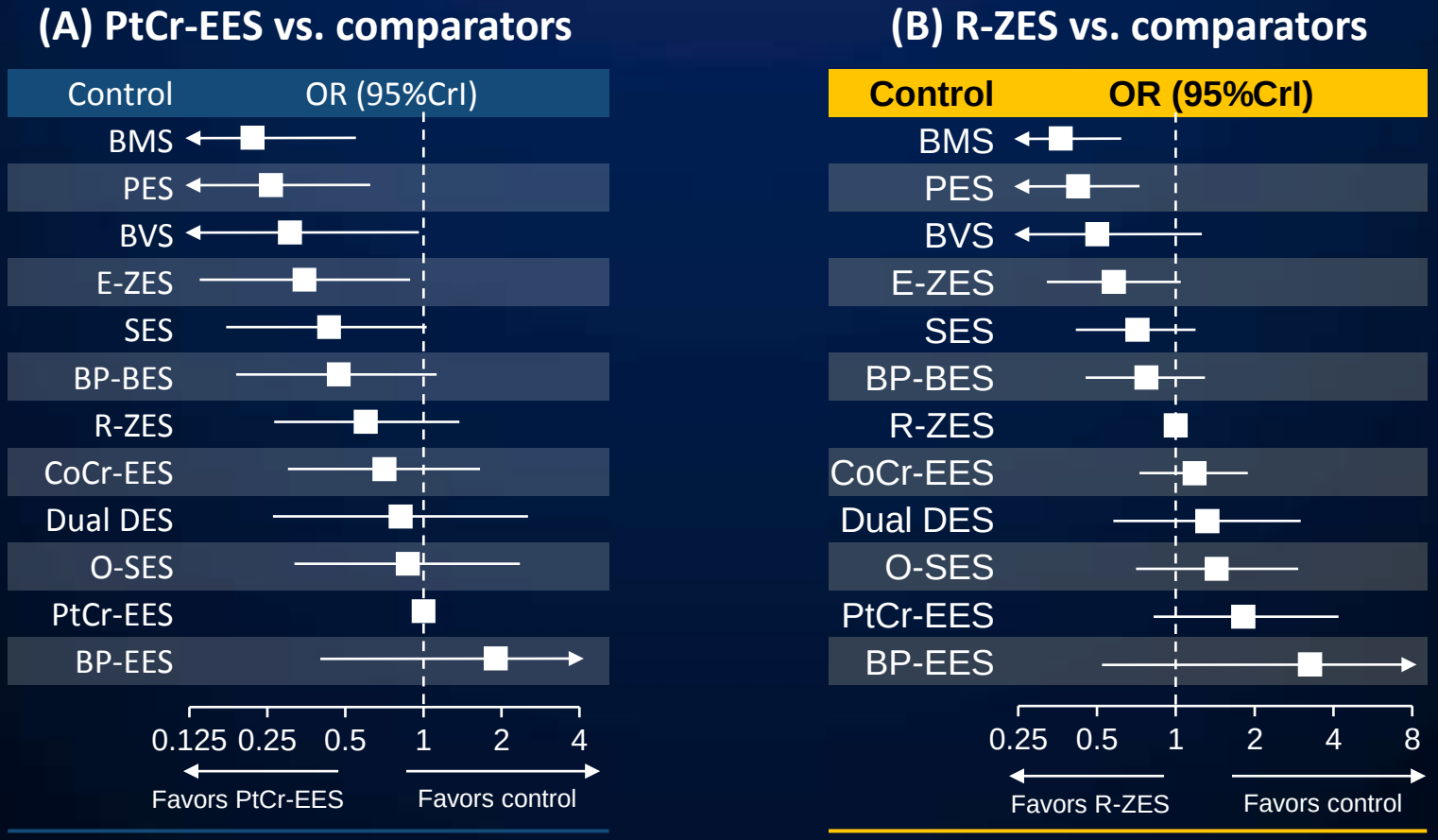
Rankogram

definite or probable ST at 1 year



Stent Thrombosis

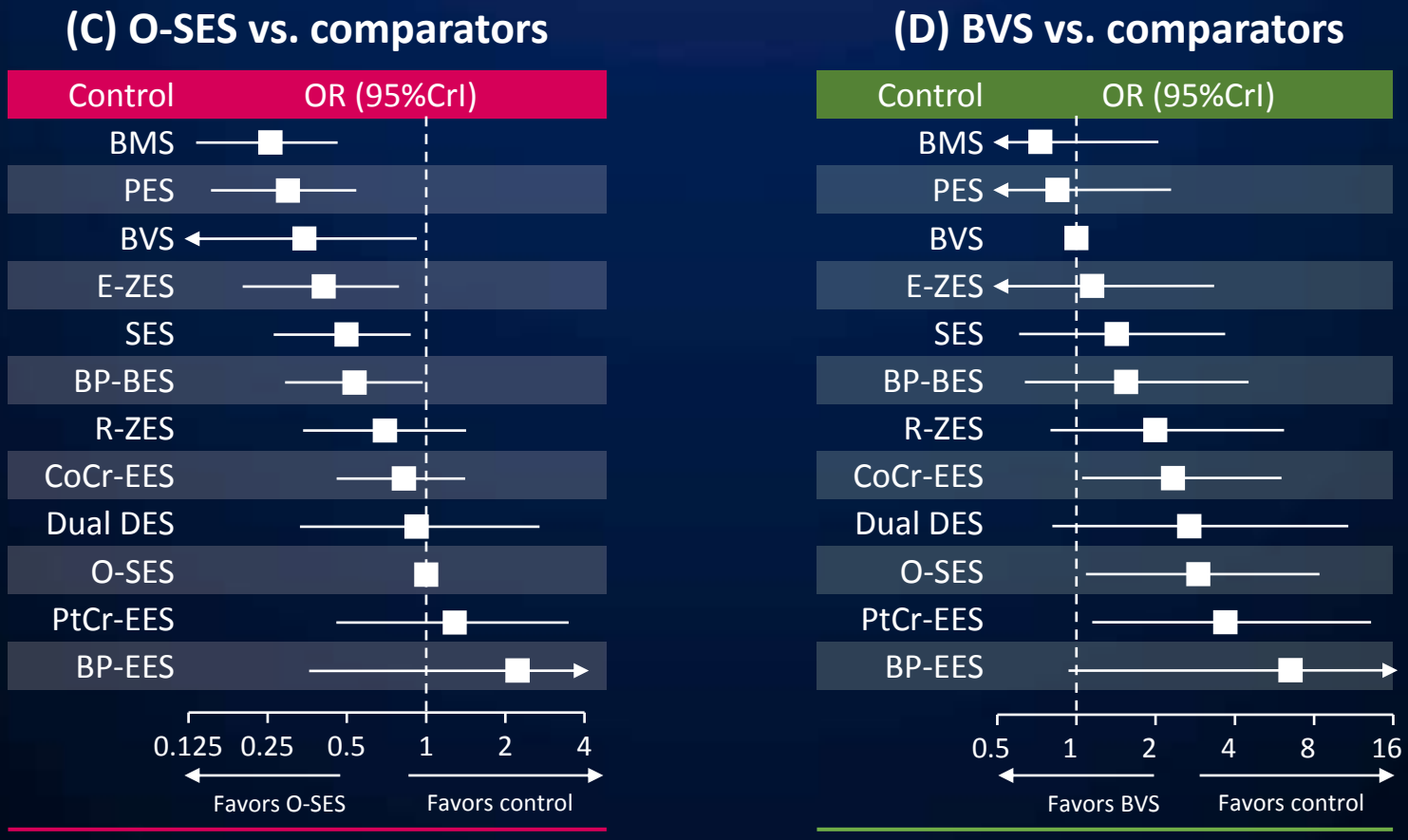
definite or probable ST at 1 year



(BP-EES ≒ PtCr-EES ≒ O-SES ≒ Dual DES ≒ CoCr-EES)
> (ZES-R ≥ BP-BES ≥ SES) > (E-ZES) > (BVS ≥ PES ≥ BMS)

Stent Thrombosis

definite or probable ST at 1 year



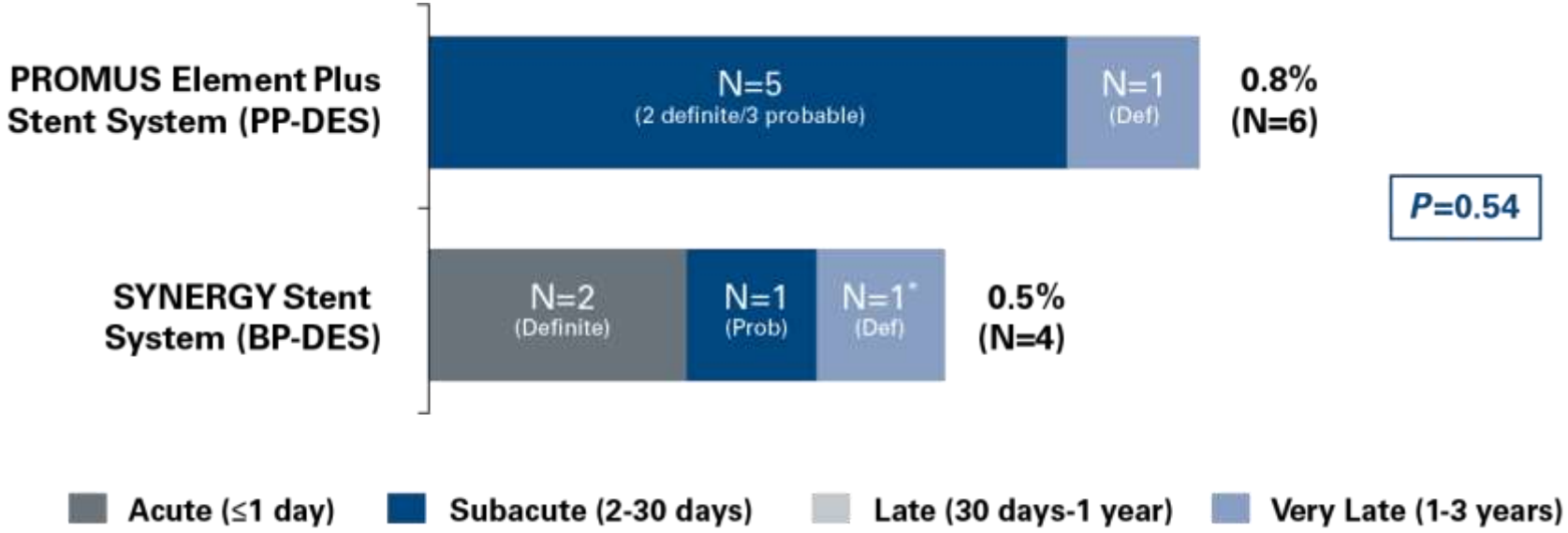
(BP-EES ≒ PtCr-EES ≒ O-SES ≒ Dual DES ≒ CoCr-EES)
> (ZES-R ≥ BP-BES ≥ SES) > (E-ZES) > (BVS ≥ PES ≥ BMS)

Summary

- **All currently available DES** including biocompatible DP-DES, BP-DES, and polymer-free dual DES were associated with **low risk of ST** when compared to BMS or first-generation devices.
- In particular, **BP-EES, PtCr-EES, O-SES, and CoCr-EES** exhibited excellent safety.
- The risk of **device thrombosis** after treatment with **BVS** was significantly higher than that of CoCr-EES, PtCr-EES, or O-SES.

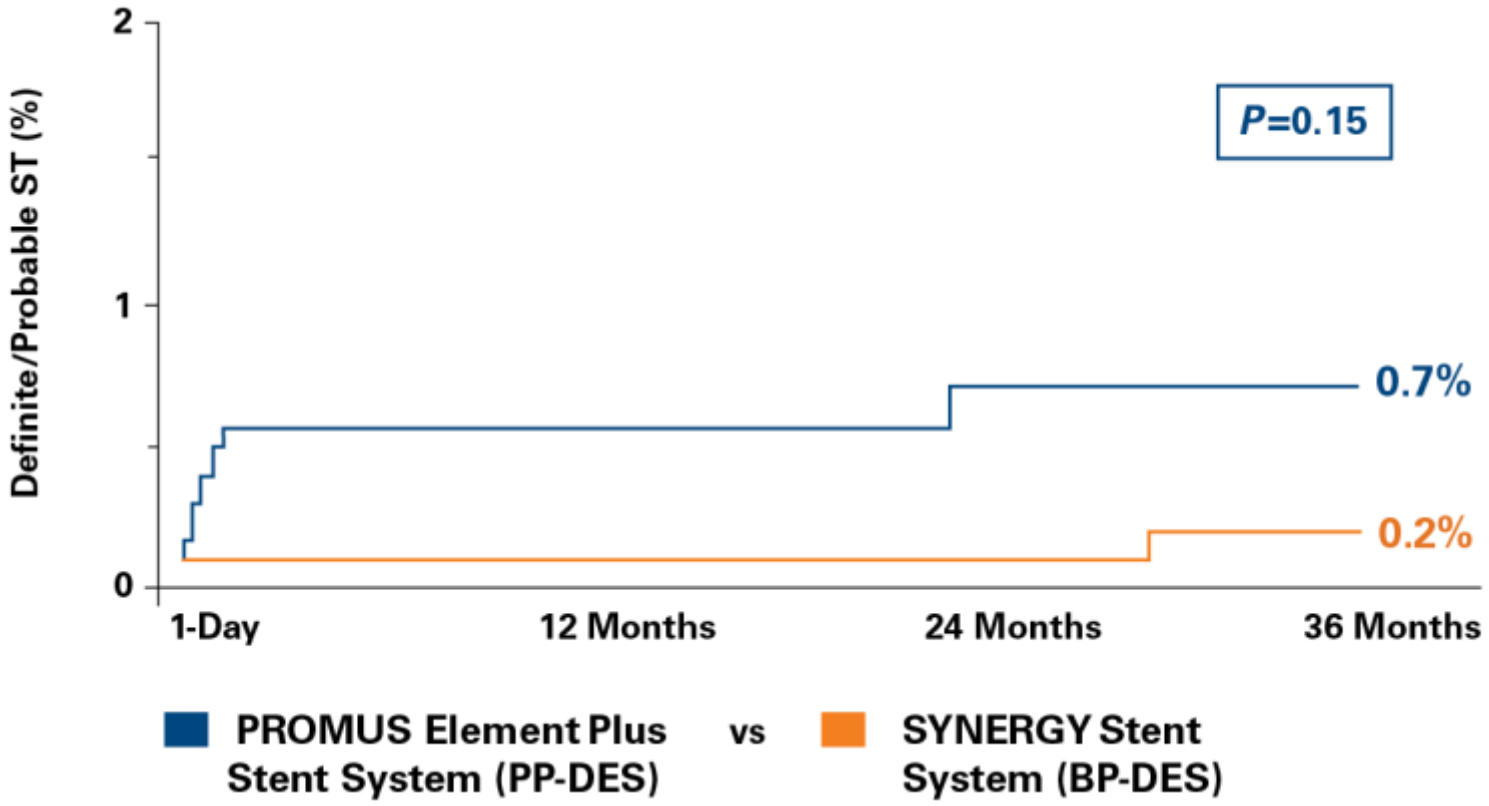
EVOLVE II trial

Risk of Stent Thrombosis

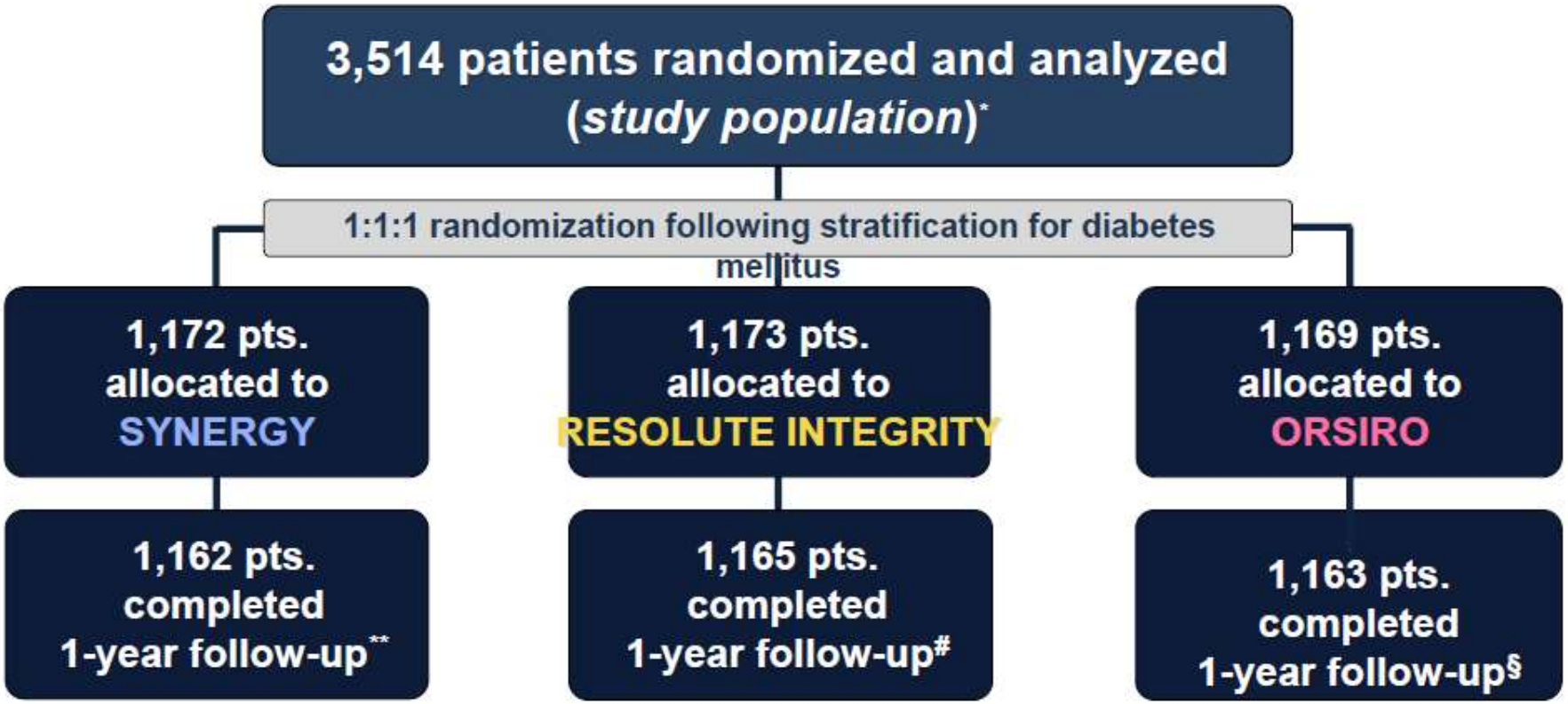


EVOLVE II trial

Definite/Probable ST after 24 hours to 3-Years



Study Flow Diagram

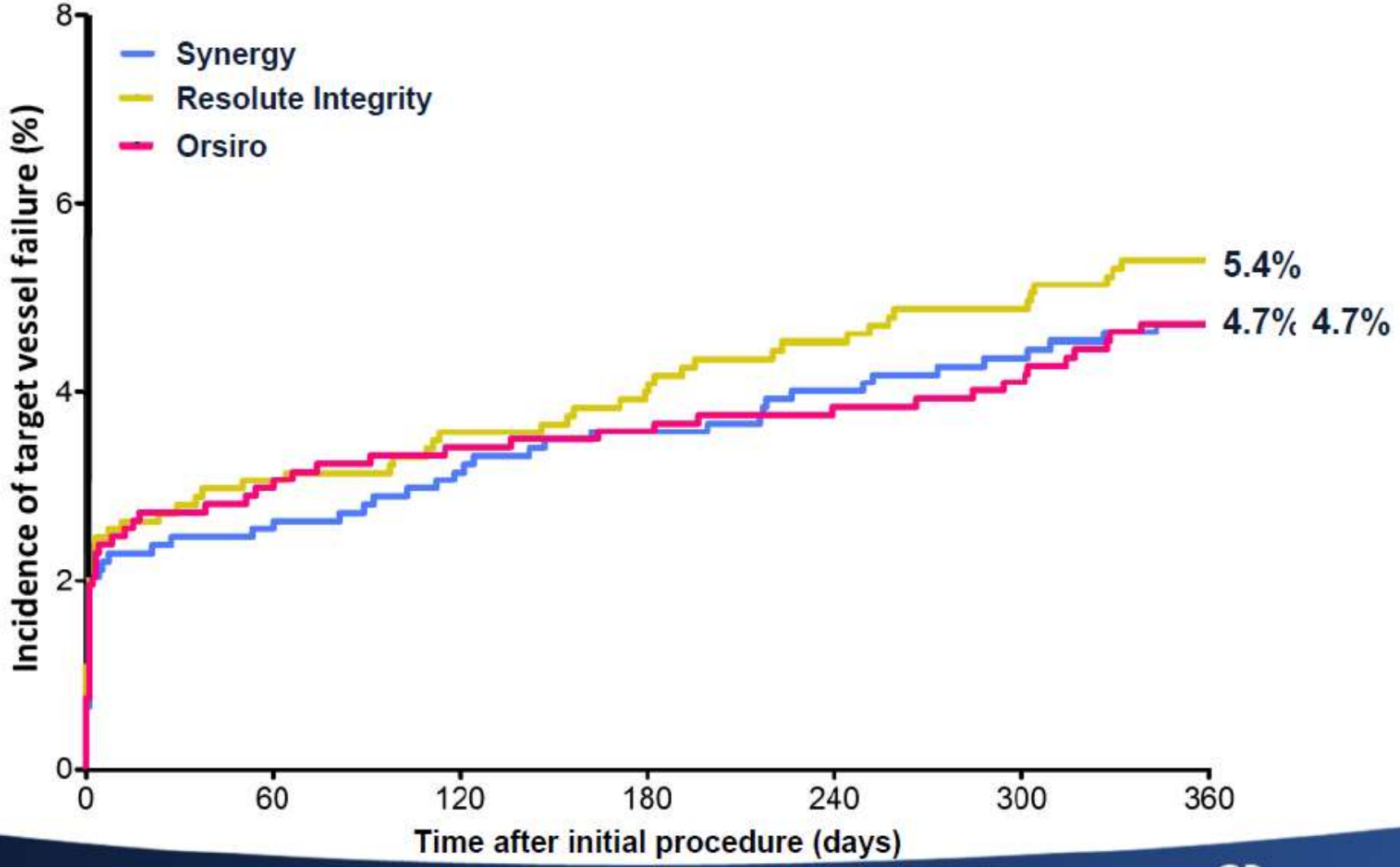


- 1-year follow-up data were obtained from 99.3% of the study population, which represents 99.9% of the patients who still participated in the trial or had died.
- During the first year of follow-up, 21 patients (0.6%) withdrew consent, while only
  3[illegible] patients (< 1 %) were actually "lost" (i.e. could not be contacted)

* During active study enrollment, 7,928 patients were treated with DES (no data on the number of eligible patients are available); 3,545 pts. were initially randomized; 31 pts. were excluded; 3,514 pts. were analyzed and represent the study population.
** 2 patients lost to follow-up, 8 patients withdrew consent; # 1 patient lost to follow-up, 7 patients withdrew consent;
§ 6 patients withdrew consent. Monitoring and an independent clinical event adjudication (CEC) by CRO Diagram, Zwolle. Analyses were based on

Primary Endpoint

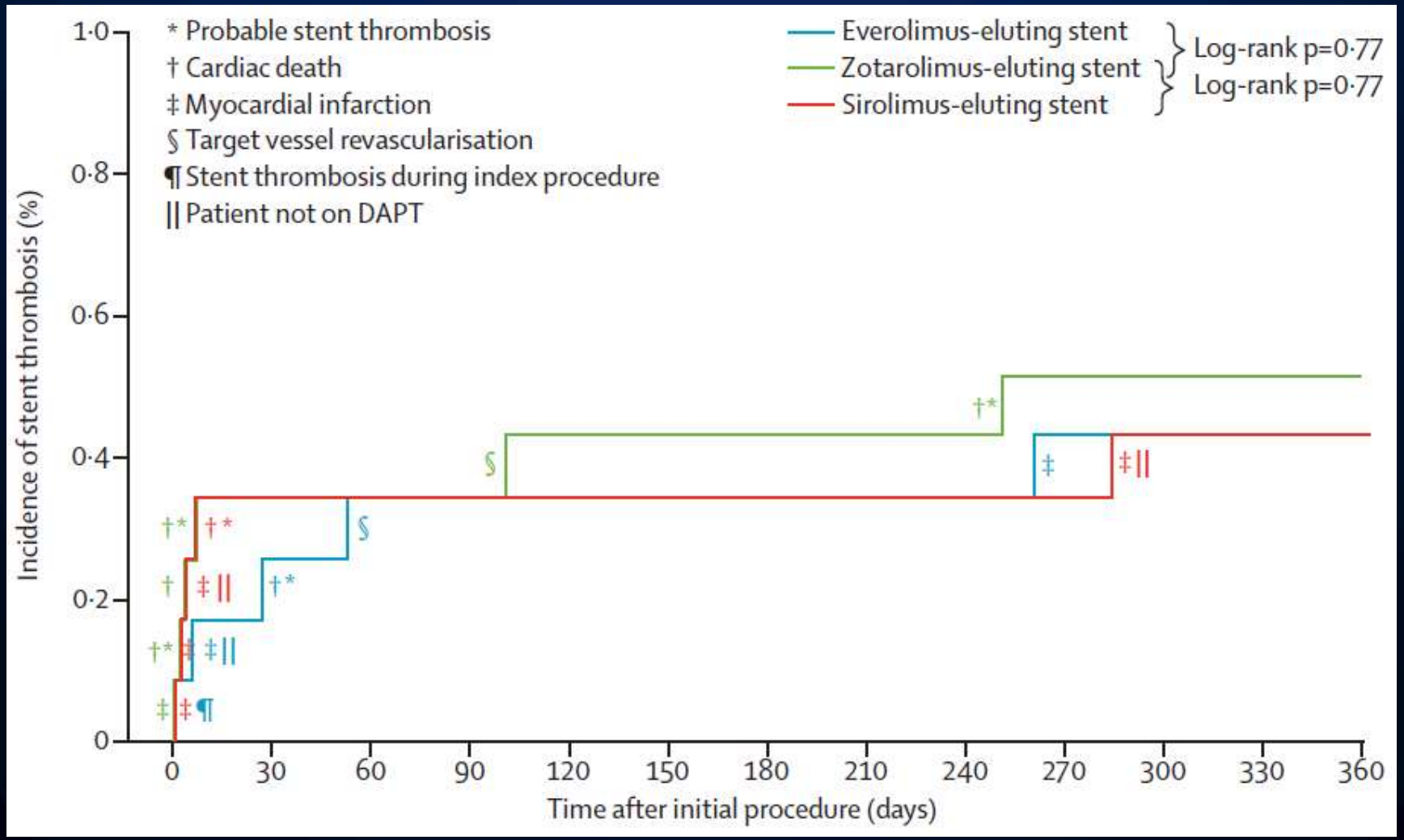
Target Vessel Failure at 1-Year Follow-Up



Target Vessel Failure is a composite of cardiac death, target vessel-related MI, or clinically driven target vessel revascularization.

BIO-RESORT (TWENTE III)

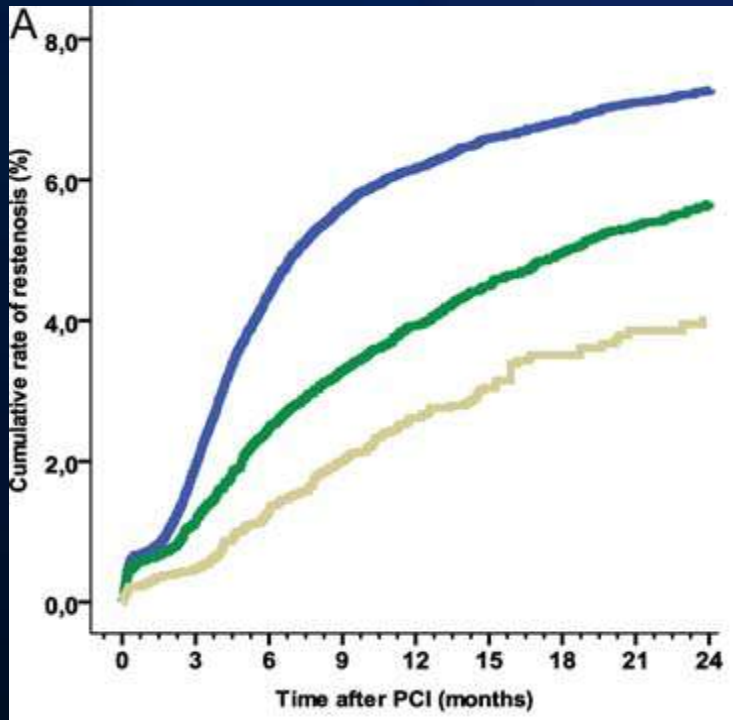
definite or probable ST at 1 year



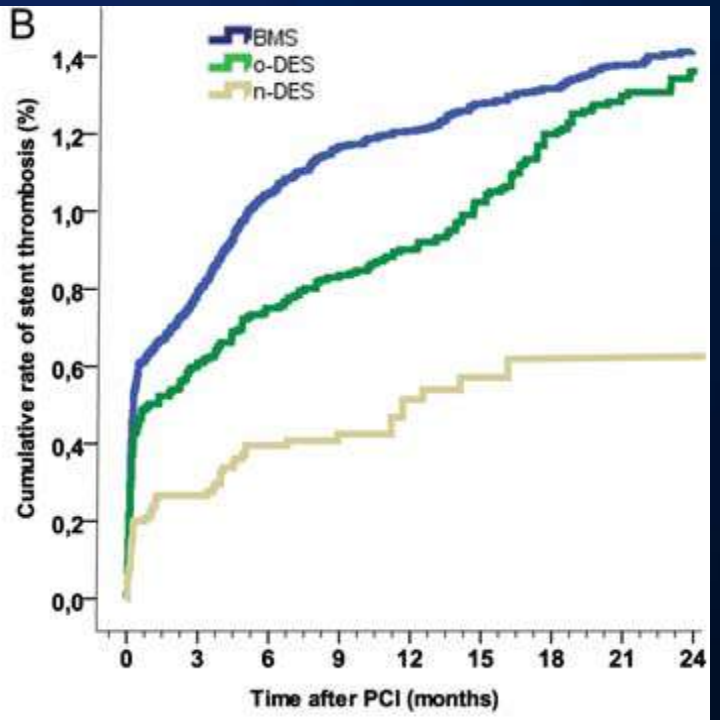
von Birgelen et al. Lancet 2016

SCAAR Registry

(A) Restenosis

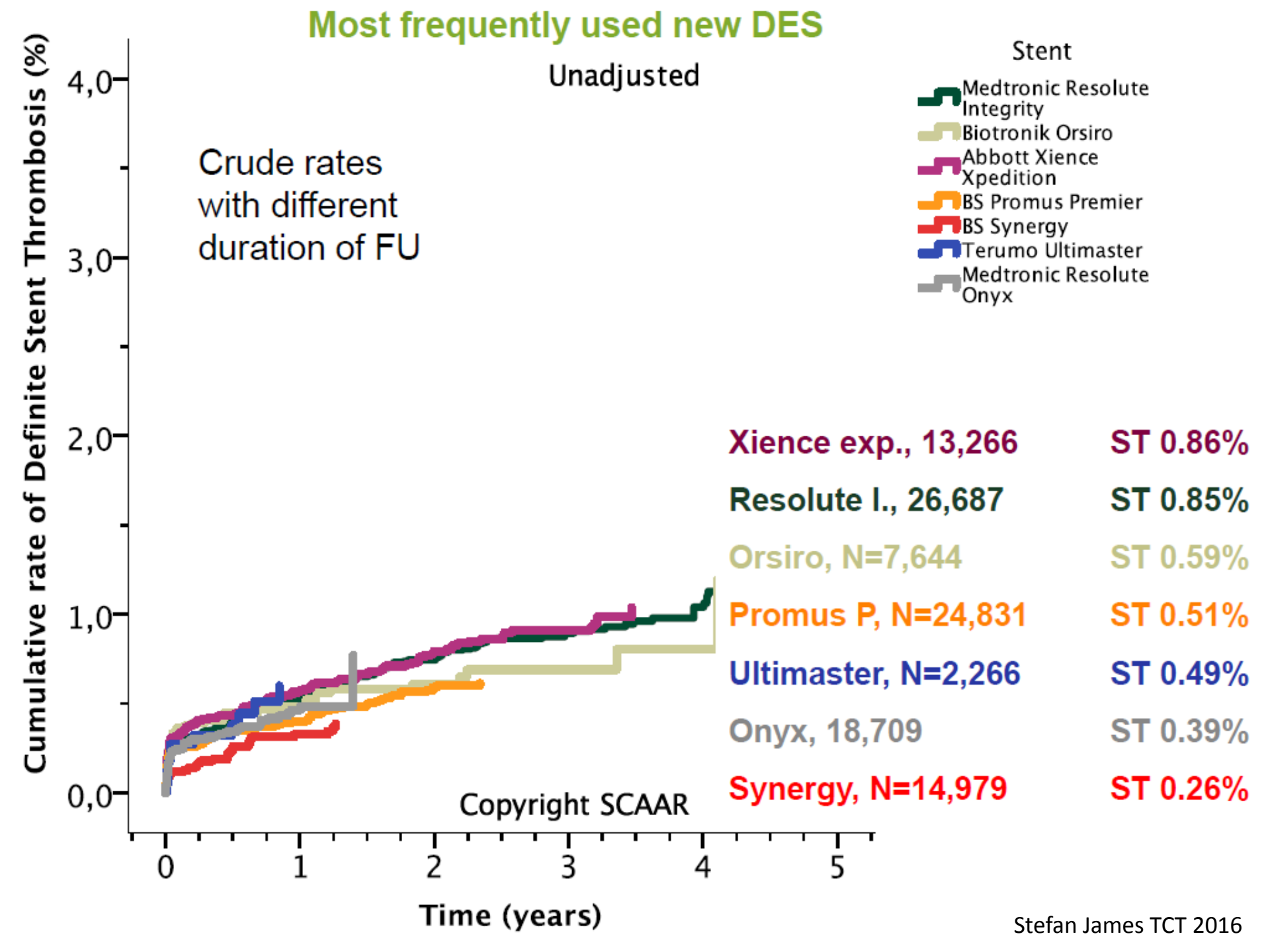


(B) Definite stent thrombosis



N at risk	0 months	6 months	12 months	18 months	24 months
BMS	64631	56070	47968	40539	32698
o-DES	19202	17862	16014	13517	10533
n-DES	10551	8092	4188	2005	847

Sarno et al. EHJ 2012

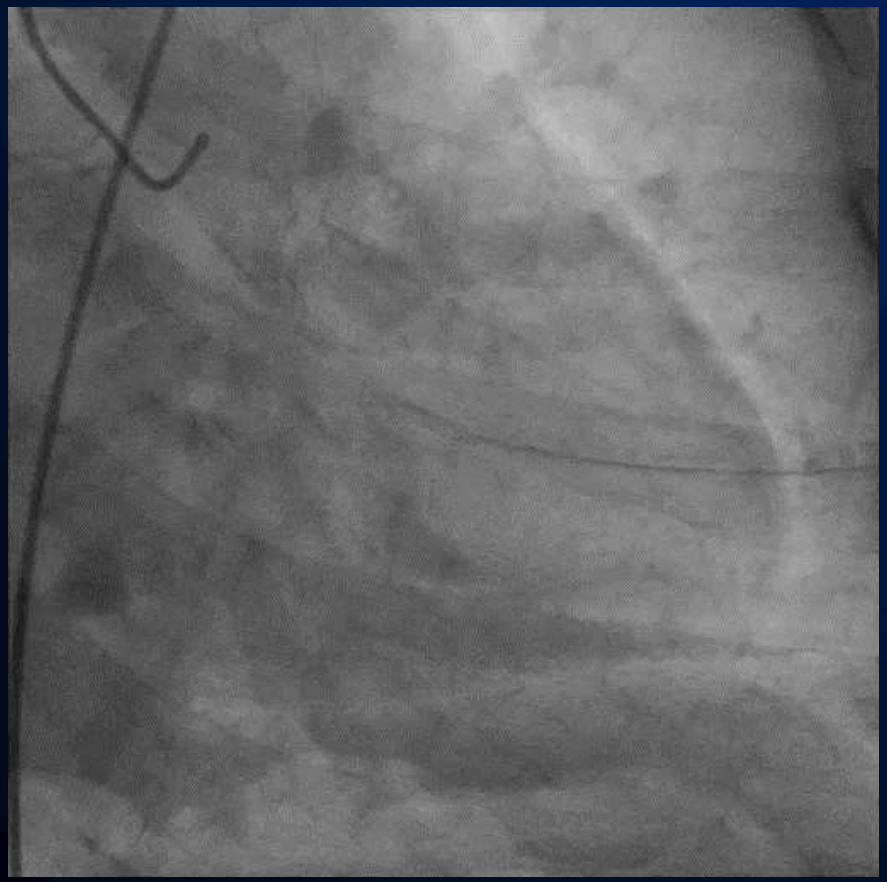


Stefan James TCT 2016

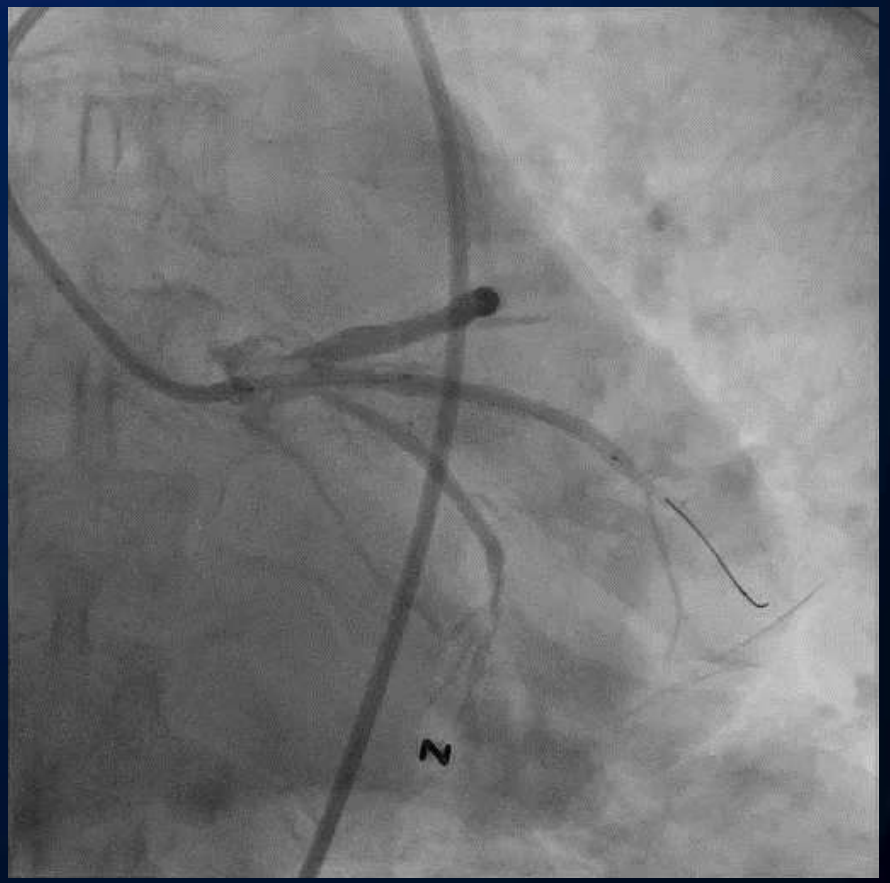
Dual antiplatelet therapy

M/56

STEMI, lateral wall

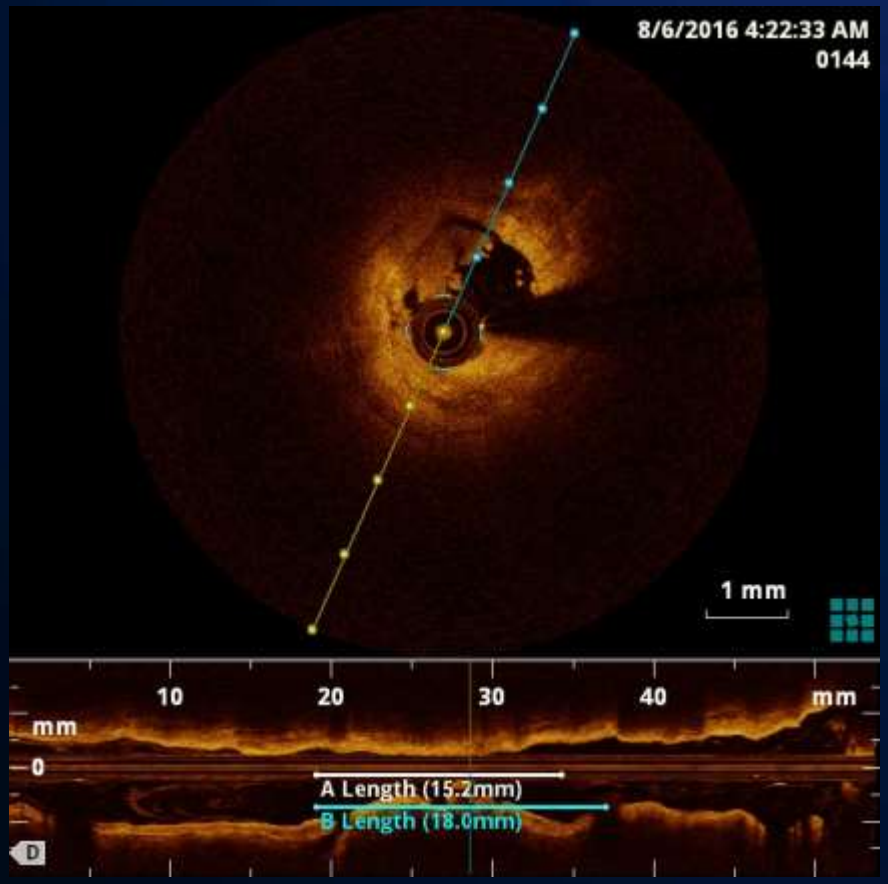


PCI with Absorb (3.0 x 18 mm)

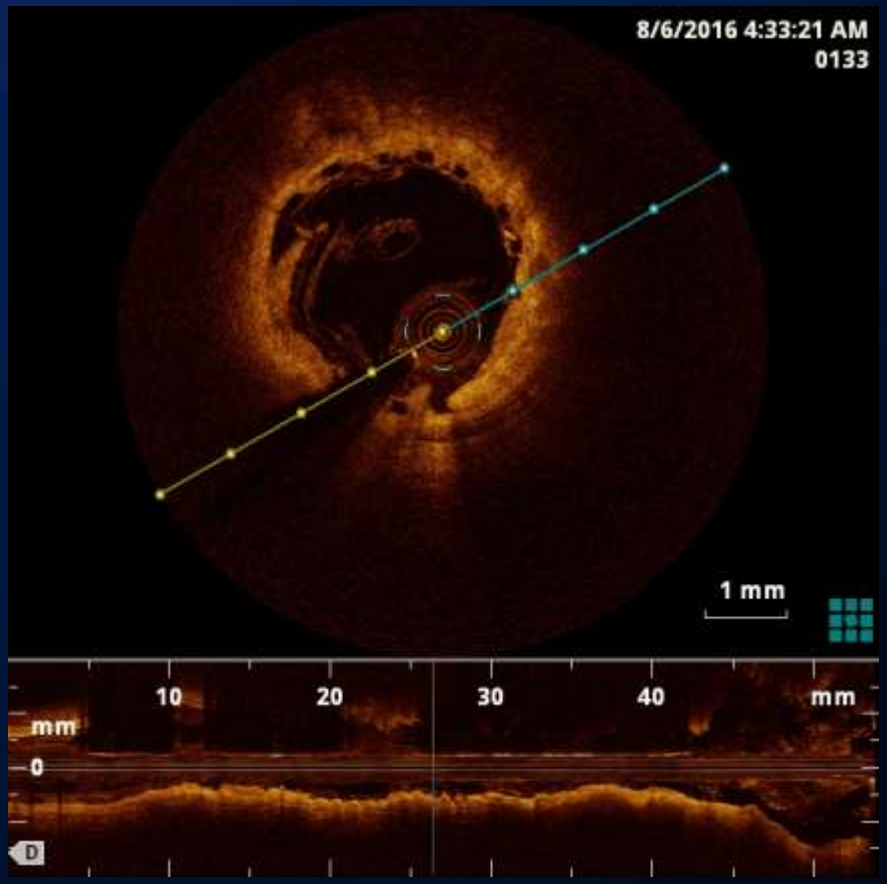


Dual antiplatelet therapy

Pre-PCI



Post-PCI



Discharge with aspirin + ticagrelor

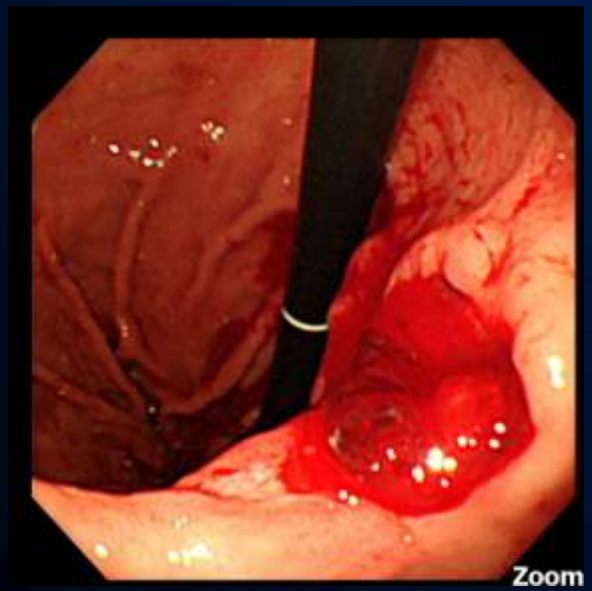
With considering extended period of DAPT..

Patient Course

Post-PCI 2M

ER admission for melena

EGD: R/O benign ulcer



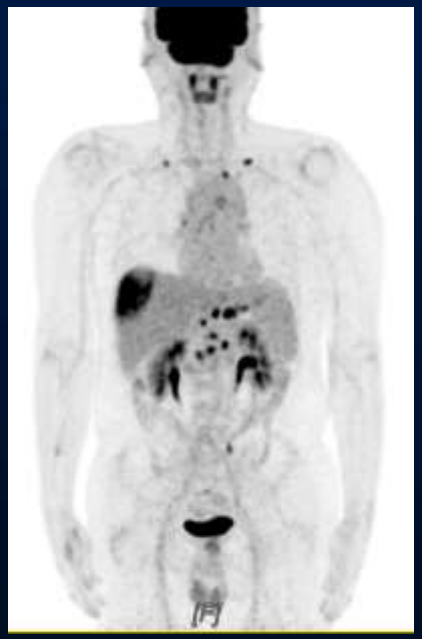
Post-PCI 4M

Epigastric pain & melena

Biopsy: adenocarcinoma

Dx: AGC, stage IV

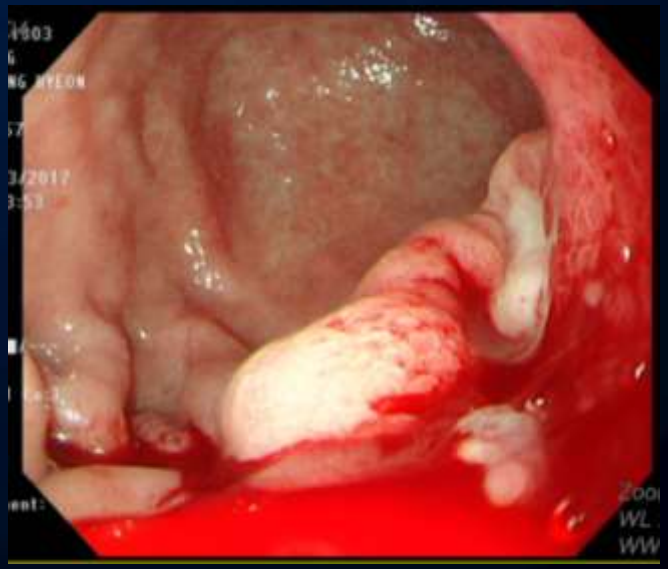
Palliative chemotherapy



Post-PCI 7M

Hematemesis & melena

Switch to single antiplatelet therapy



EVOLVE Short DAPT Study

Laura Mauri, PI

"The EVOLVE Short DAPT study was designed to evaluate the safety of a planned DAPT duration of 3 months with the SYNERGY Stent in patients at high risk for bleeding."

EVOLVE Short DAPT Study Design

Prospective, N~2000,
Up to 110 global sites

Patients considered by the treating physician to be at high risk for bleeding

i) ≥75 years of age with bleeding risk

ii) History of major bleeding

iii) Long term anticoagulation therapy

iv) Stroke or renal insufficiency/failure

(excluded LM disease, ostial lesions, >2 lesions, CTO, SVG, ISR, NSTEMI, or STEMI)

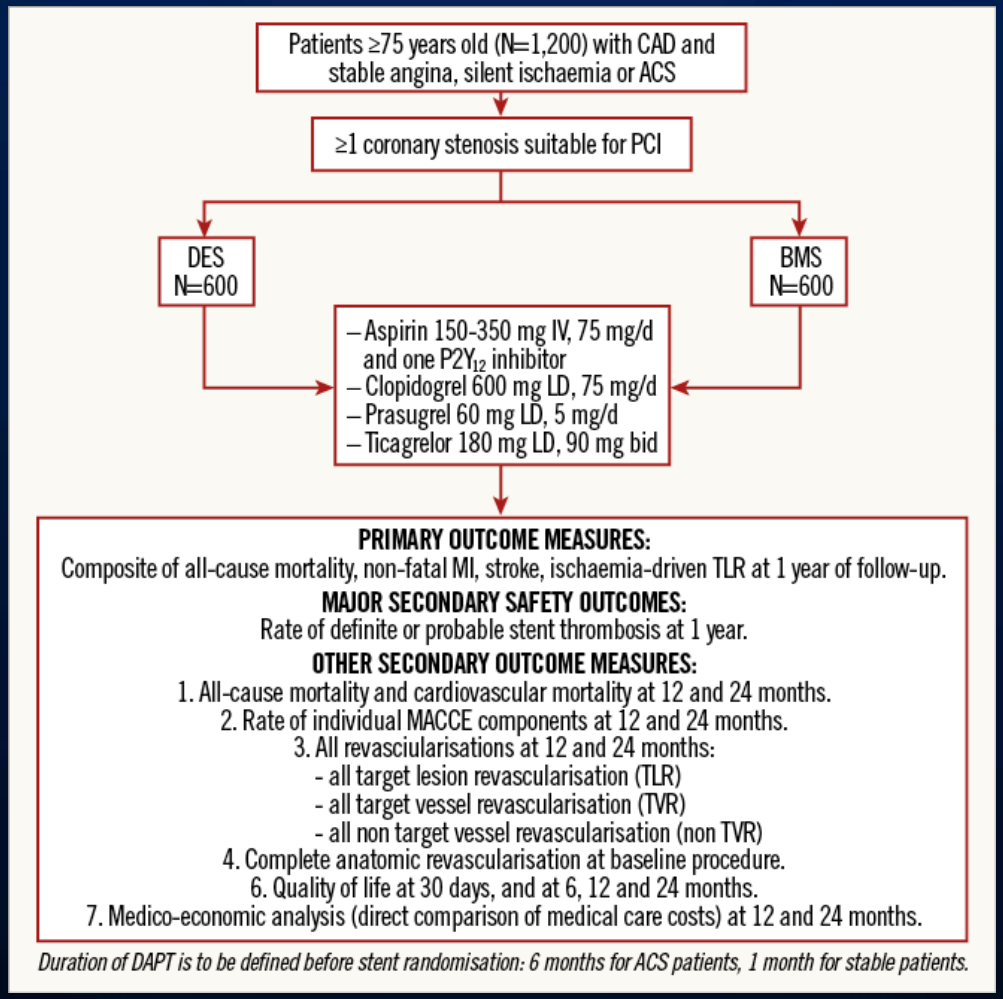
- Primary Endpoint: Death and MI, ARC definite/probable ST
- Secondary Endpoint: Rate of major bleeding (GUSTO severe/life-threatening + moderate)

Propensity adjusted comparison to historical control patients treated with standard DAPT will be performed

clinicaltrials.gov ID: NCT02605447

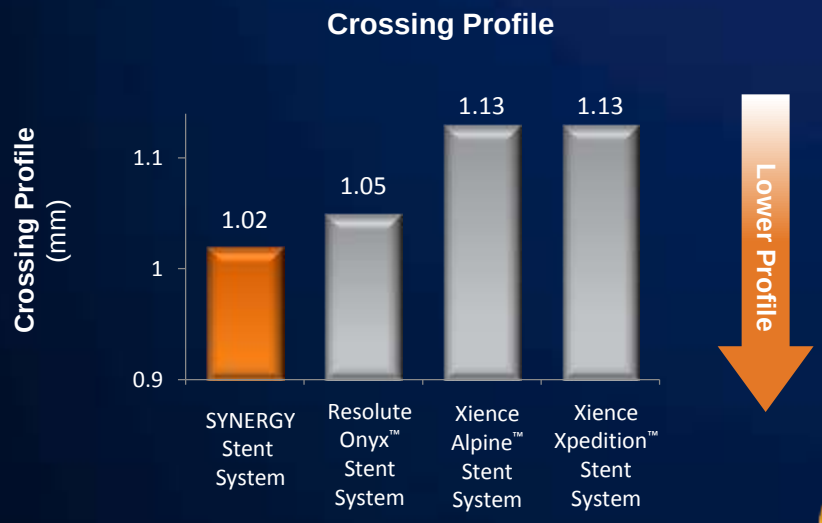
SENIOR trial

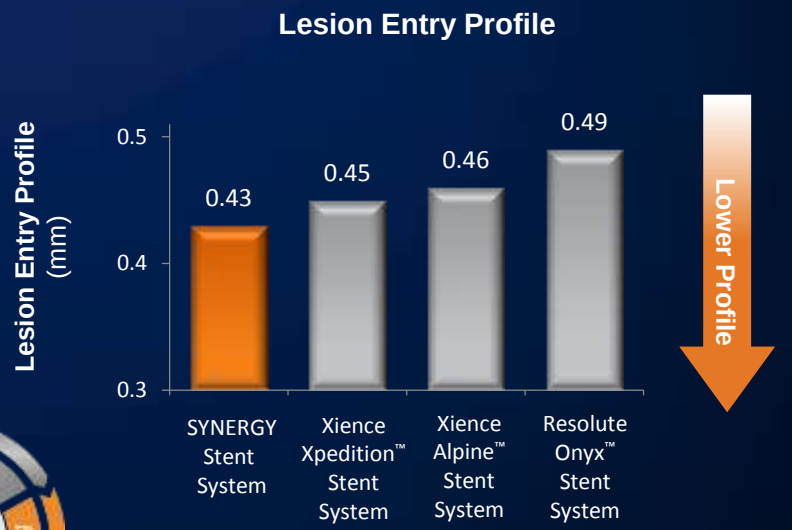
(SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularisation associated with a short dual antiplatelet therapy)

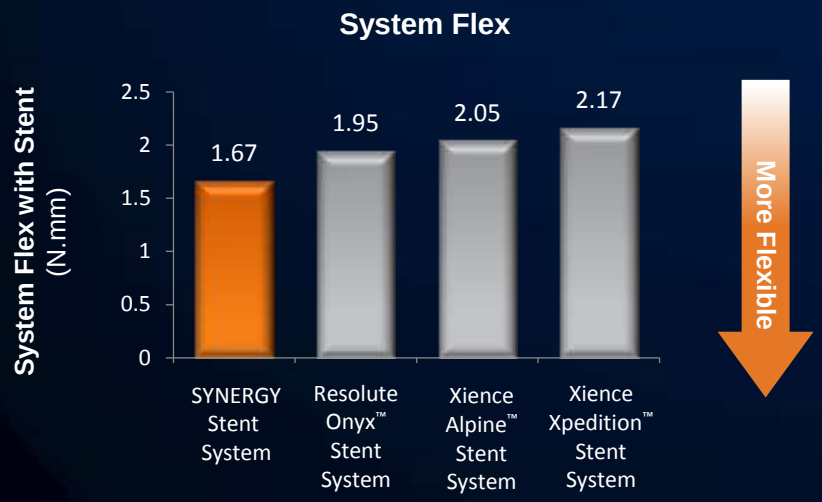


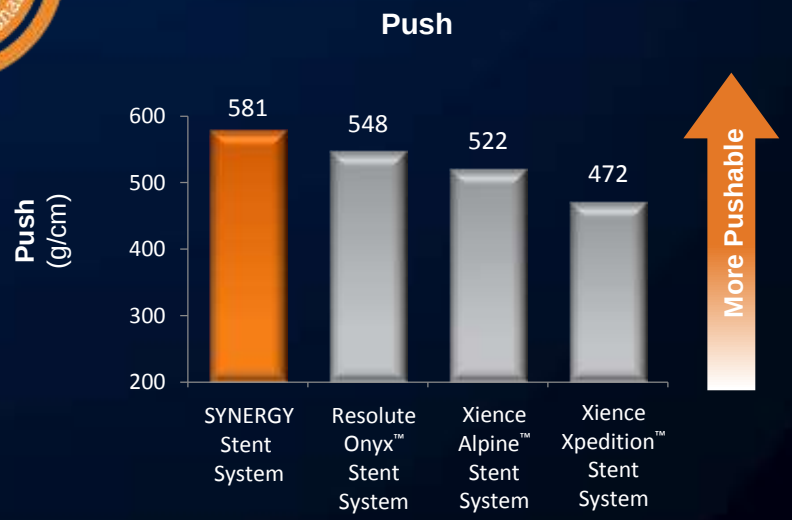
Varrene et al. Eurointervention 2015

Superior Deliverability





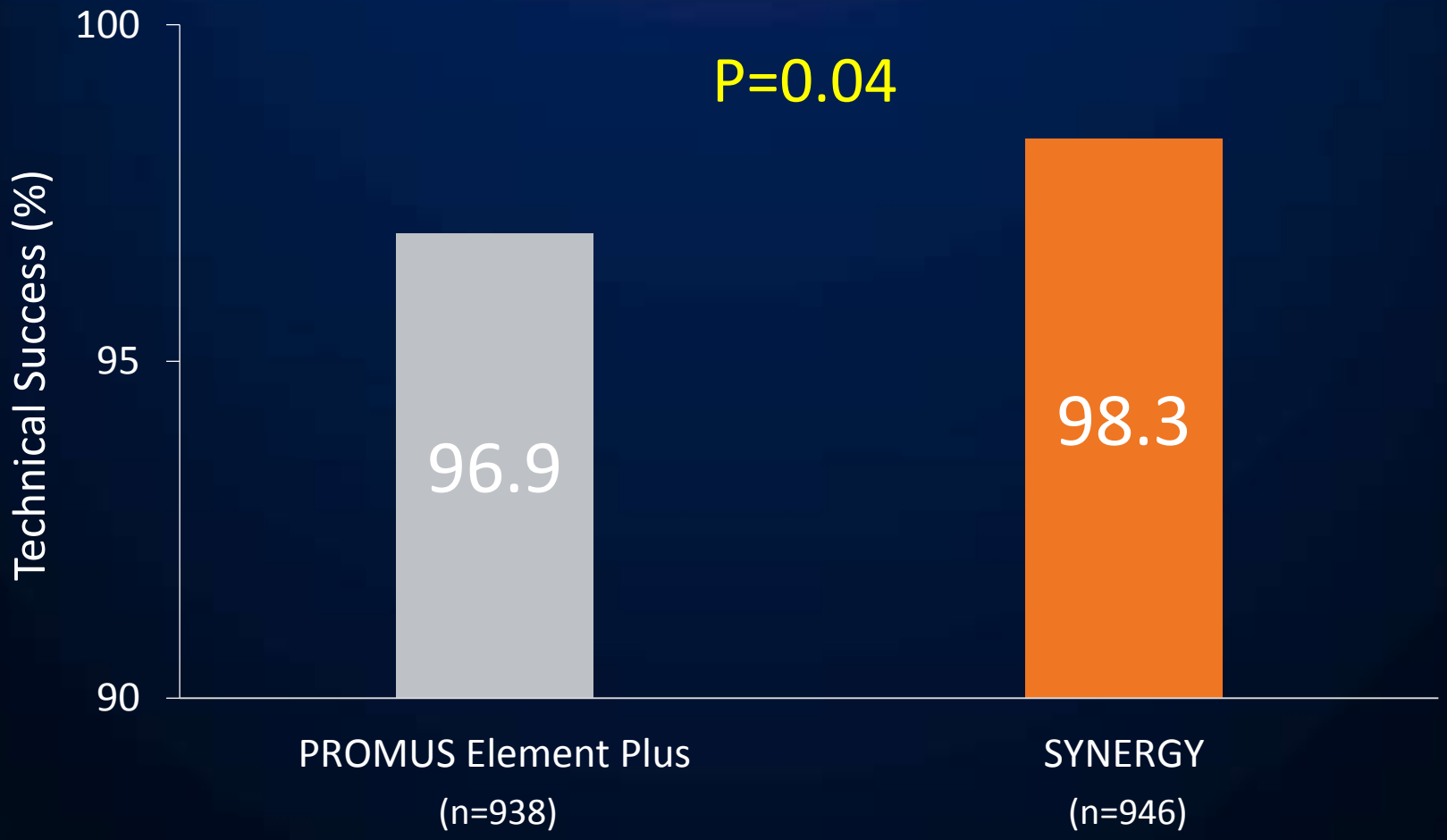




Adopted from Boston Scientific

EVOLVE II Trial

Technical Success

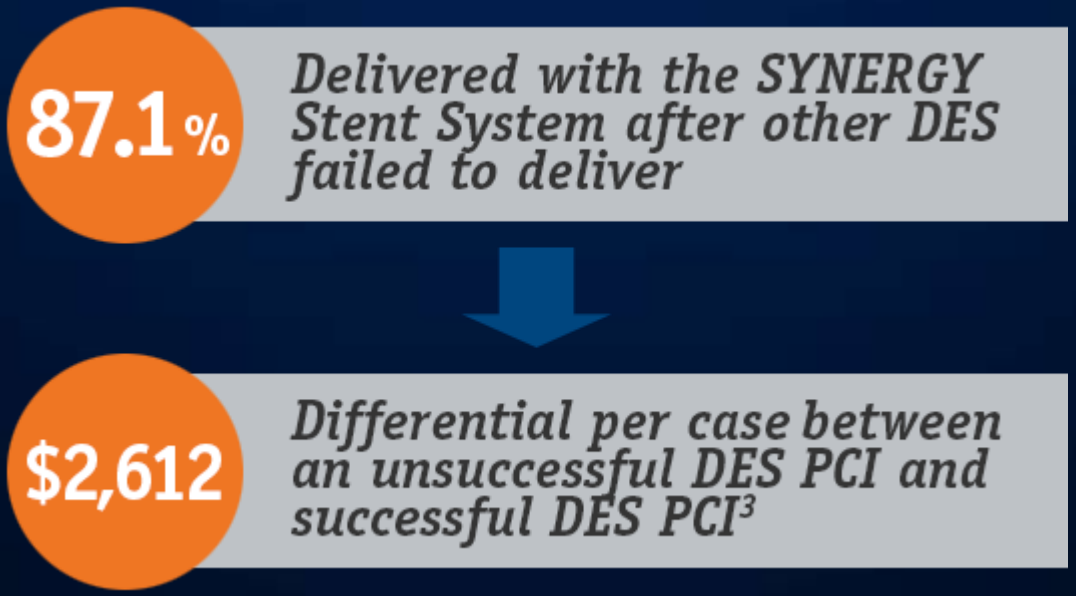


Kereiakes et al. The EVOLVE II Trial. Circ Cardiovasc Interv. 2015

SYNERGY as a bail-out strategy

116 complex PCI cases

bail-out strategy after failed implantation of a second generation DES (Promus Element, Xience Prime, Resolute Integrity)



Sharar et al. CRT 2016

Conclusion

- Stent thrombosis is a multifactorial problem, which is associated with high risk of mortality and morbidity.
- Contemporary thin-strutted DES showed low risk of stent thrombosis.
- SYNERGY biodegradable polymer everolimus-eluting stent showed long-term safety and efficacy.
- Definite/probable stent thrombosis risk was especially low with SYNERGY.