Leading Innovation and Technology

SYNERGY™ Stent Platform

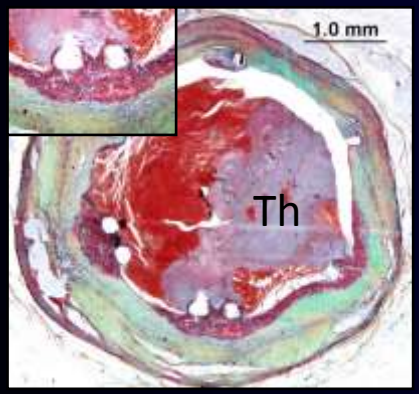
Everolimus-Eluting Platinum Chromium Stent System with Abluminal Bioabsorbable Polymer

Professor Darren Walters
Executive Director Heart Lung Stream
The Prince Charles Hospital
University of Queensland

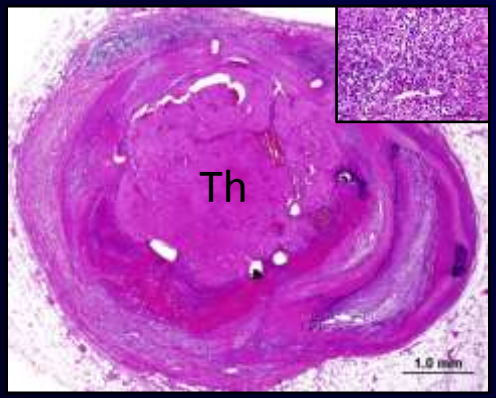
1st-Generation DES was not ideal for healing

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

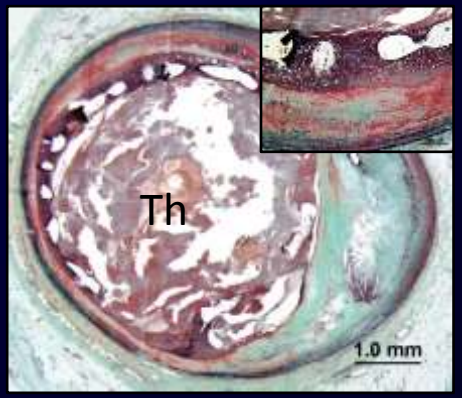
✓Uncovered struts
✓Hypersensitivity
✓Malapposition
✓Late stent thrombosis
✓Neoatherosclerosis



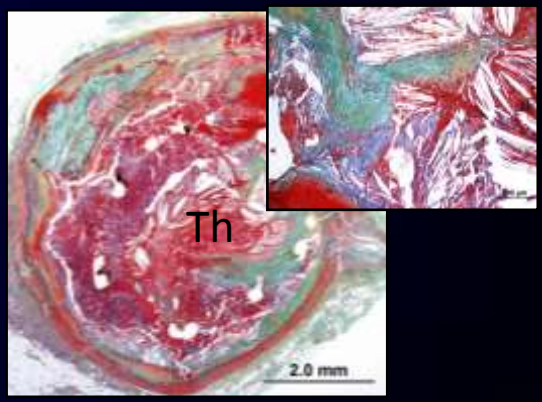
Uncovered struts



Hypersensitivity reaction



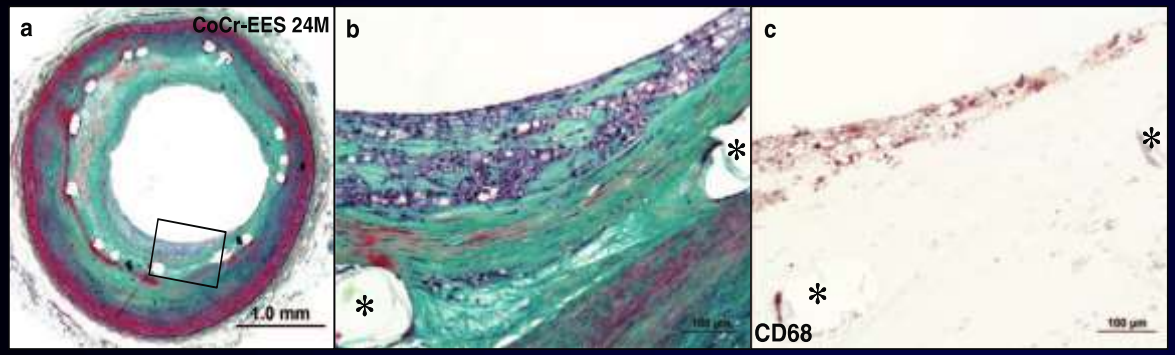
Malapposition from excessive fibrin deposition



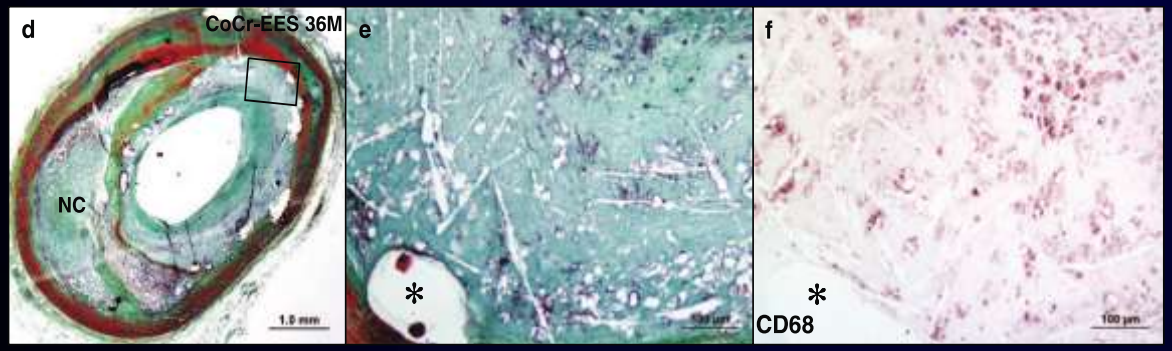
Neoatherosclerosis

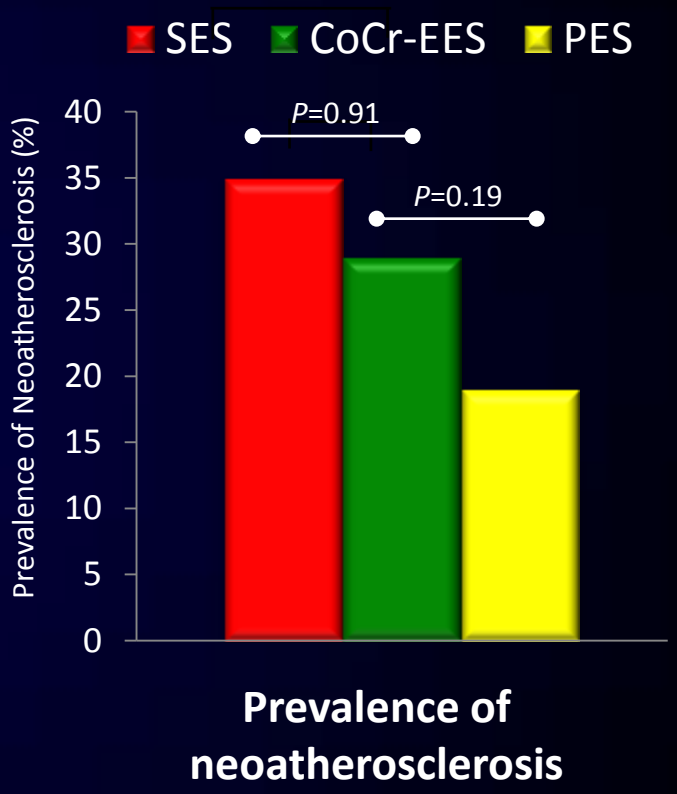
Neoatherosclerosis remains a concern for 1st and Current Generation PERMANENT Polymer DES

CoCr EES 24-month



CoCr EES 36-month



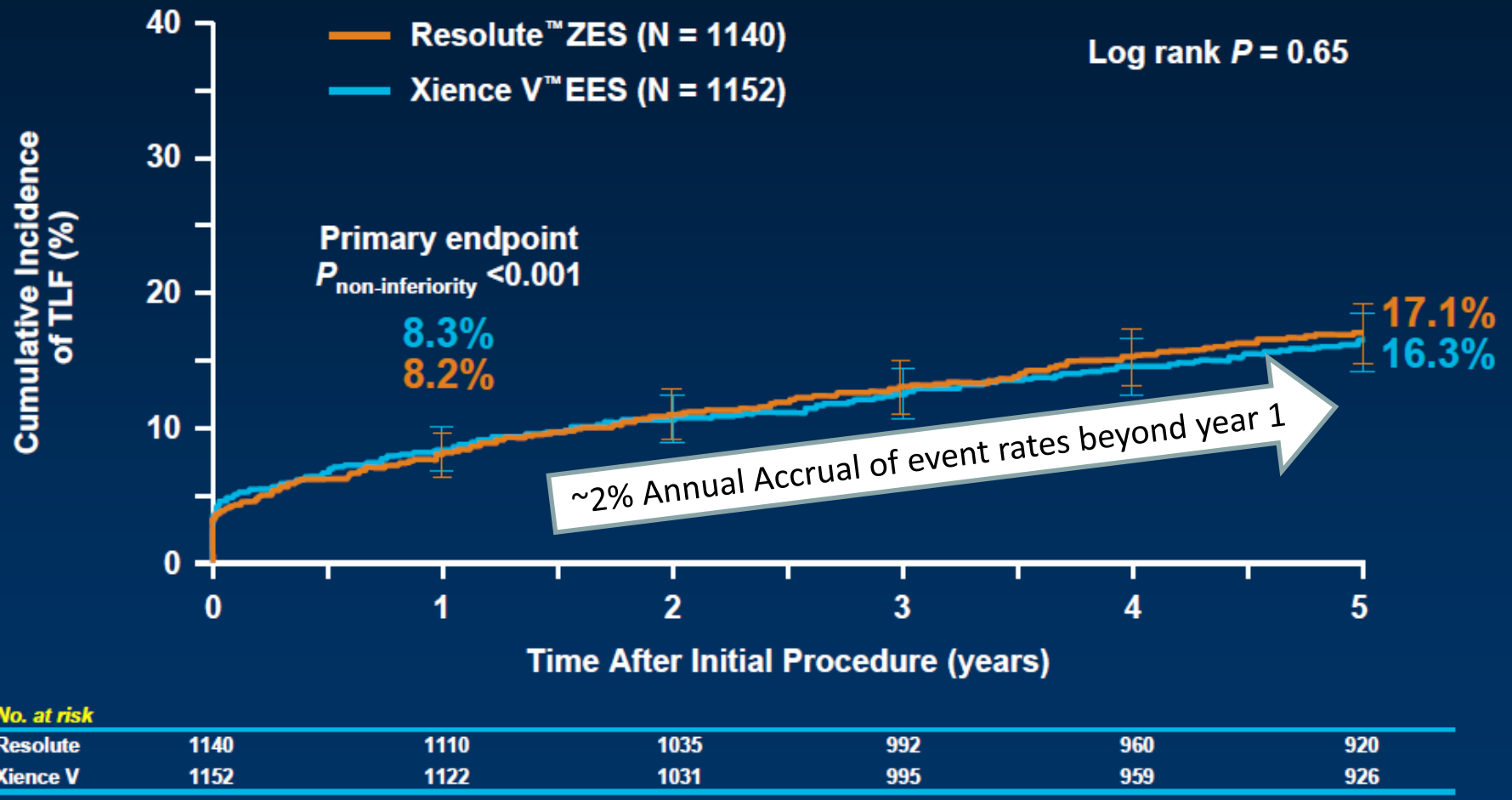


Neoatherosclerosis occurs sooner in DES than in BMS
May be Important factor in late stent thrombosis
Predisposed by dysfunction endothelialisation

Otsuka. et al. Circulation, 2014

Event rates persist beyond 1 year with current PERMANENT Polymer DES

Resolute All Comers 5-year TLF



No. at risk						
Resolute	1140	1110	1035	992	960	920
Xience V	1152	1122	1031	995	959	926

TLF (target Lesion Failure) is defined as cardiac death, TVMI, of clinically driven TLR.

Next phase for the future of PCI: Optimal Healing

PCI EVOLUTION
Continuous improvement in platform design and acute performance

1977
- POBA: Getting Artery Open

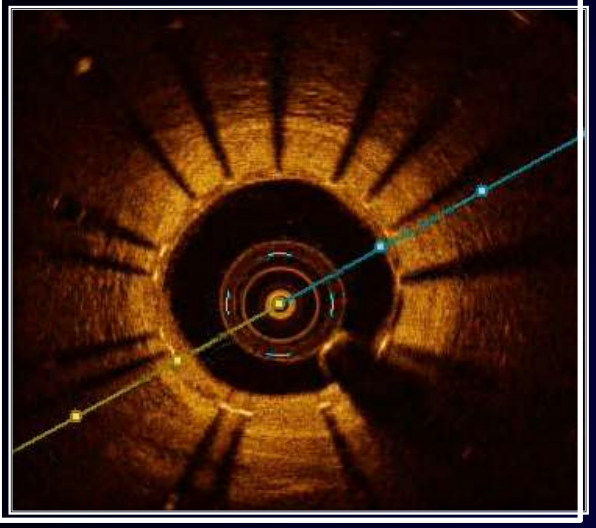
1986
- BMS: Keeping Artery Open

2003
- DES Decrease Restenosis

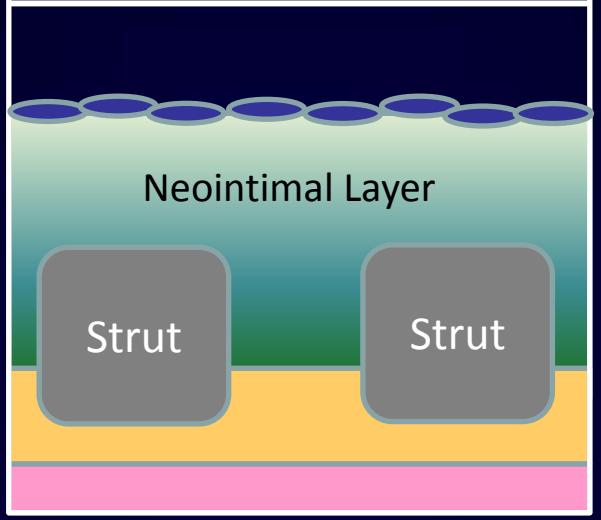
2015+
- Future DES: Optimize Healing
  - Lower late events rates – ST, TLR
  - Reduced need for prolonged DAPT
  - Reduced risk of neoatherosclerosis

What is optimal healing post-implant?

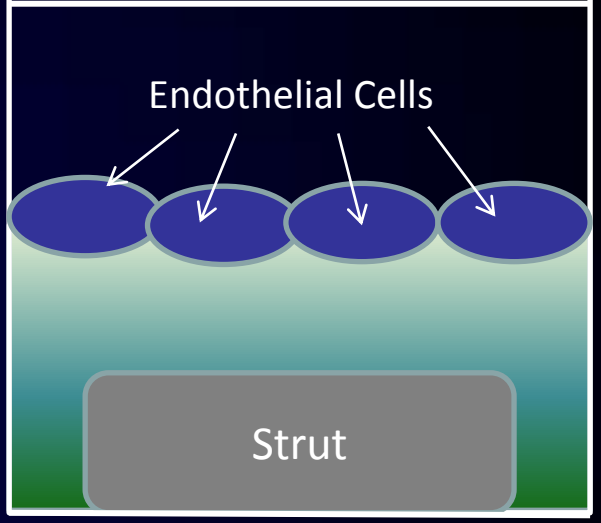
Uniform
Strut Coverage



Mature
Neointimal Layer



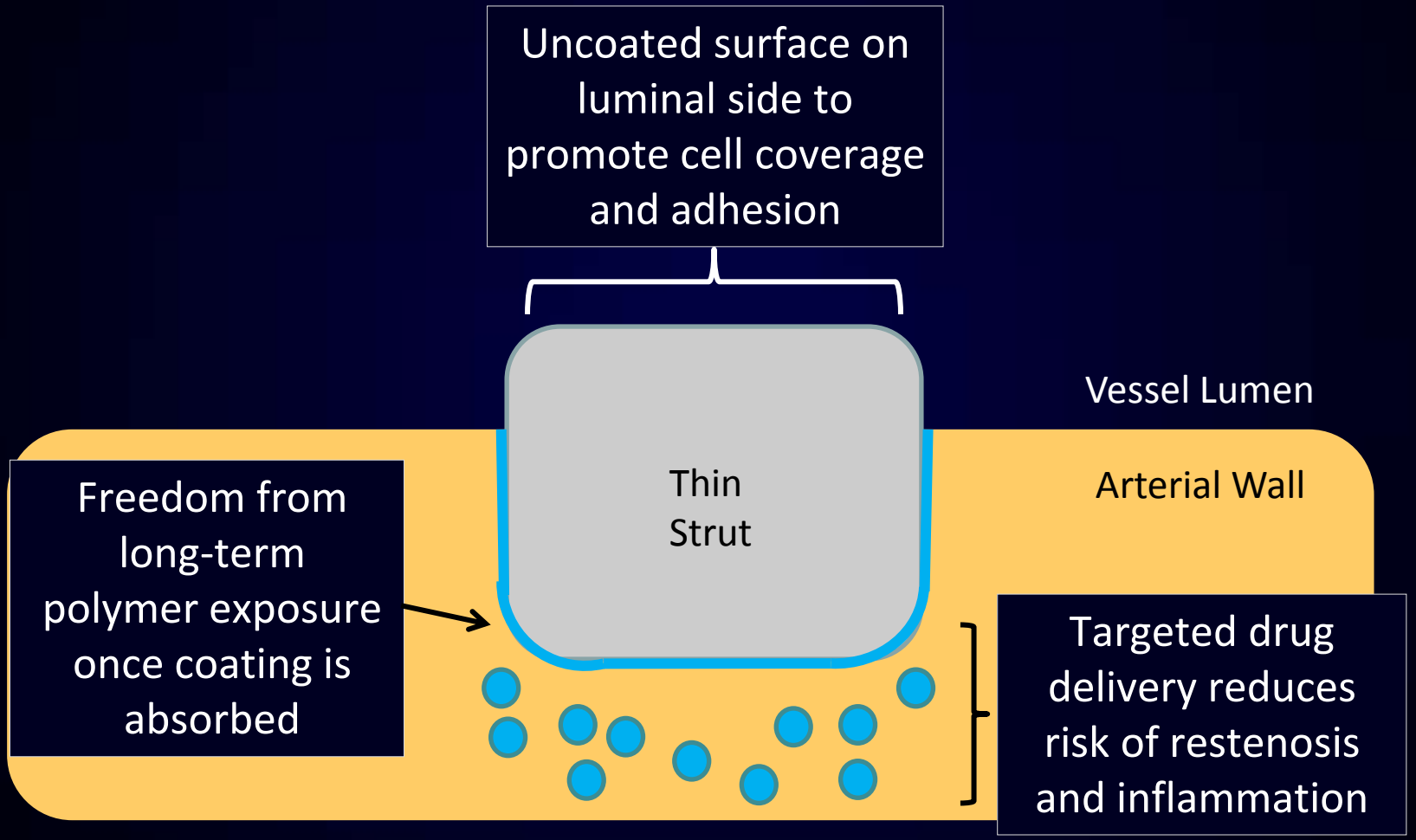
CONTINUOUS, FUNCTIONAL
Endothelial Layer



Role of Endothelial Cell:

- Communicate
- Stabilize
- Prevent further neointimal formation
- Provide a barrier for thrombosis

How may an abluminally coated bioabsorbable polymer DES be optimal for healing?



SYNERGY Stent Technology Design

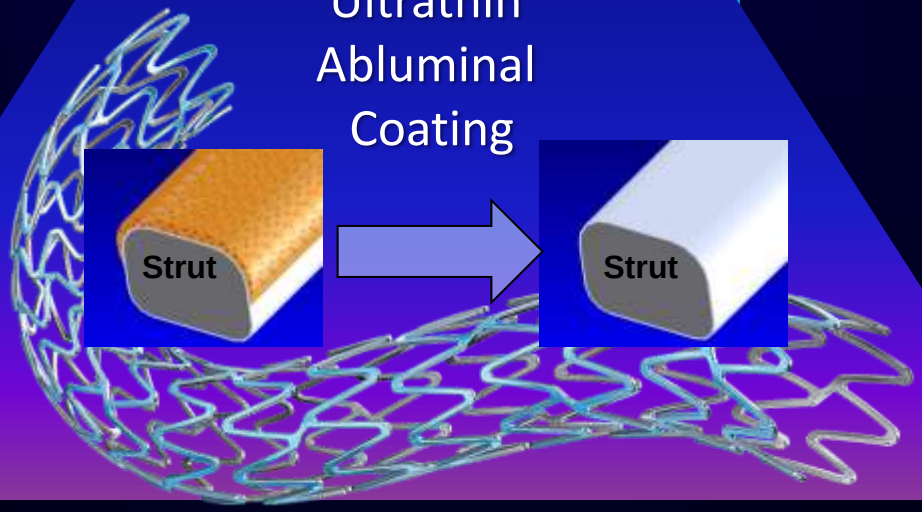
Platinum Chromium Platform

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

Everolimus-Eluting

- 100µg/cm^2
- 3 month release time

Ultrathin Abluminal Coating



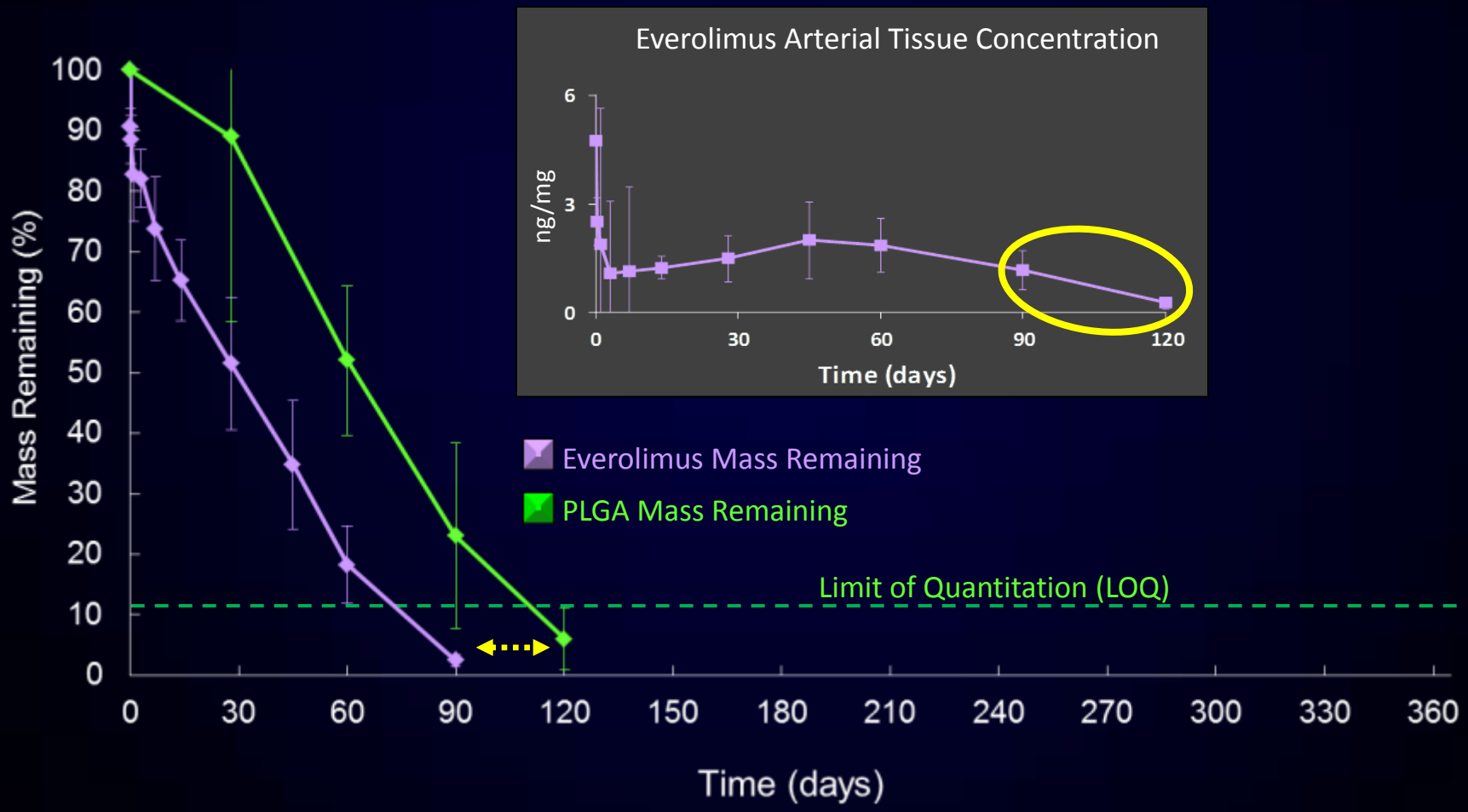
Bioabsorbable Polymer Coating (PLGA)

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

SYNERGY Stent

Synchronous Drug Release & Polymer Absorption

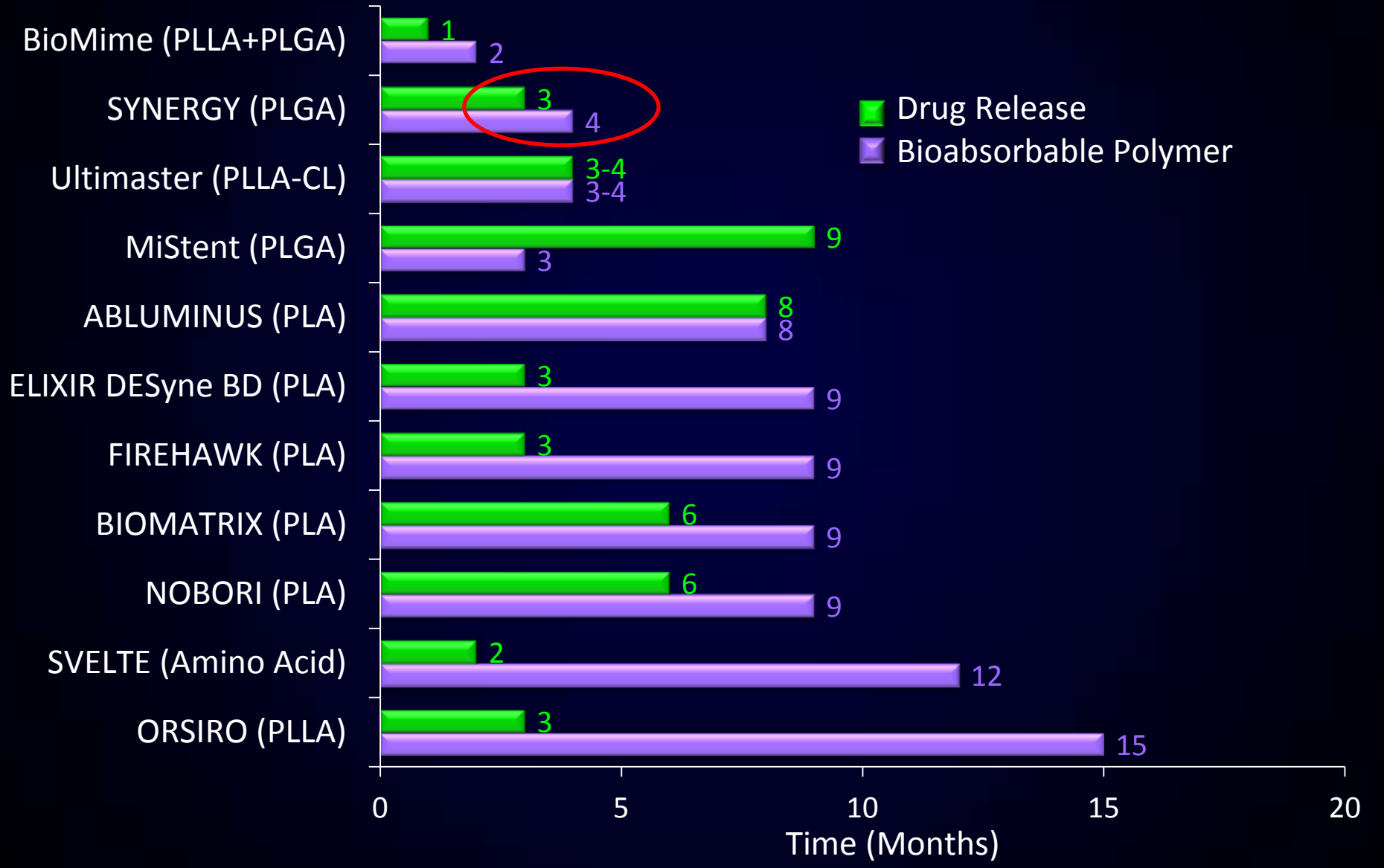
Preclinical evaluation in porcine model



Wilson, G. J., et al. *Cathet. Cardiovasc. Intervent*. doi: 10.1002/ccd.25993

Time Course For Polymer Bioabsorption

Not all bioabsorbable technologies are the same



Non-head to head trials not for comparative purposes. Provided for educational information only.

Contemporary DES Platforms

Strut and Coating Thickness In Perspective

	Durable Polymer Coated		Bioabsorbable Polymer Coated					
	Xience CoCr-EES	Resolute	Biomatrix	Nobori	Ultimaster	SYNERGY	MiStent	Orsiro
	Promus PtCr-EES	CoNi-ZES	316L-BES	316L-BES	CoCr-SES	PtCr-EES	CoCr-SES	CoCr-SES
								
Strut thickness	**81 µm 0.0032”**	**89 µm 0.0035”**	**120 µm 0.0046”**	**125 µm 0.0047”**	**80 µm 0.0031”**	**74 µm 0.0029”**	**64 µm 0.0025”**	**61 µm 0.0024”**
Polymer	**PVDF**	**BioLINX**	**PLA**	**PLA**	**PDLLA + PCL**	**PLGA**	**PLGA**	**PLLA Probio***
Distribution / thickness	Conformal 7-8µm / side	Conformal 6µm / side	**Abluminal 10 µm**	**Abluminal 20 µm**	**Abluminal 15 µm**	**Abluminal 4 µm**	**Conformal 5 µm / 15 µm**	**Conformal 3.5 µm / 7.5 µm**

*silicon carbide

EVOLVE Trial

Design and Methods

Patients with *de novo* native coronary lesions
≤ 28 mm in length, RVD ≥2.25 mm ≤ 3.5, %DS>50%
(excluded LM disease, CTO, AMI or recent MI)

Randomized 1:1:1 at 29 sites
(Europe, Australia, New Zealand)

- PROMUS Element N=98
- SYNERGY N=94
- SYNERGY ½ Dose N=99

Single-blind, noninferiority design

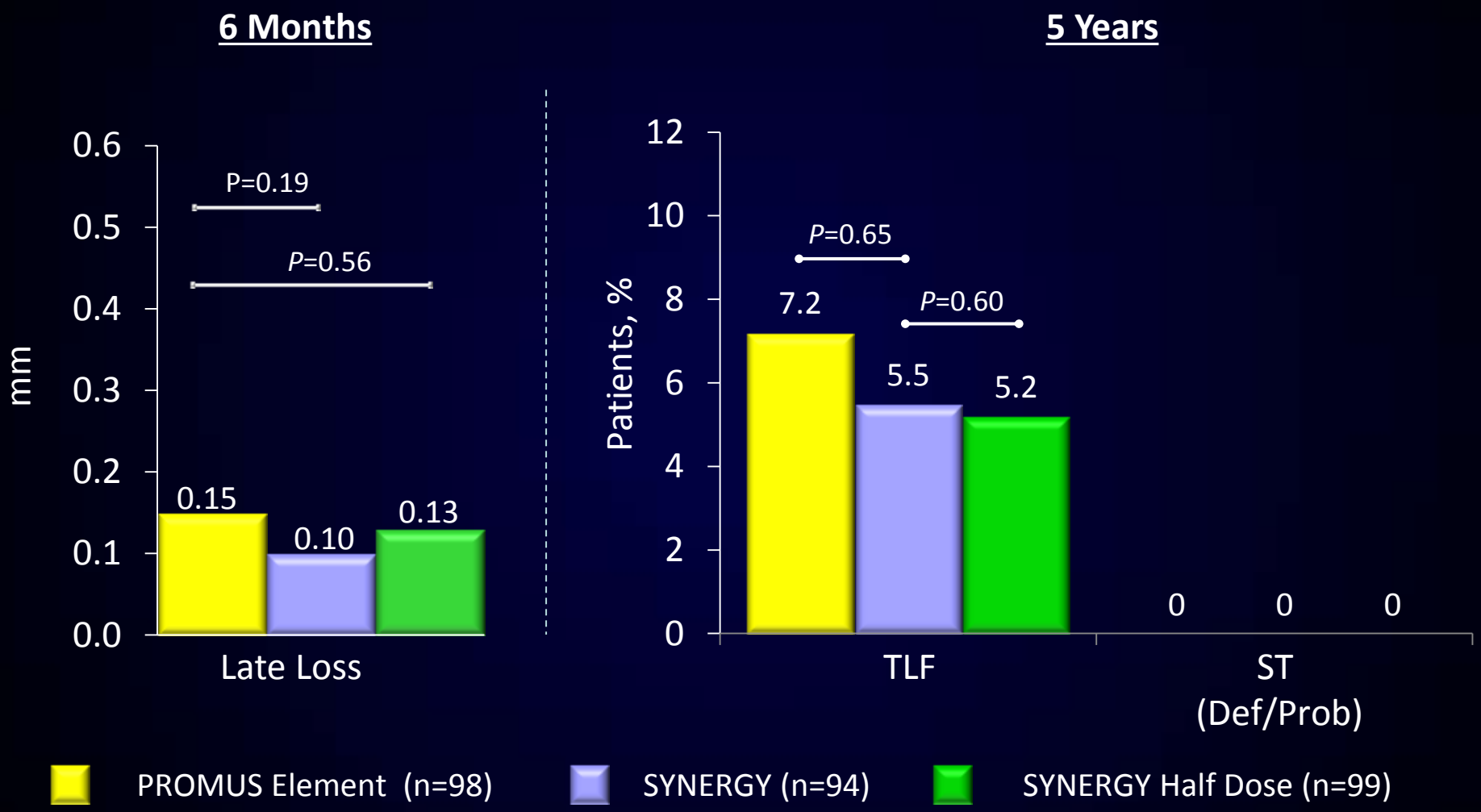
Primary Clinical Endpoint: TLF (TV-CD, TV-MI, or TLR) at 30 days

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

Per protocol patients were treated with clopidogrel, ticlopidine or prasugrel for at least 6 months following the index procedure

Meredith et al. *J Am Coll Cardiol.* 2012; 59 (15):1362

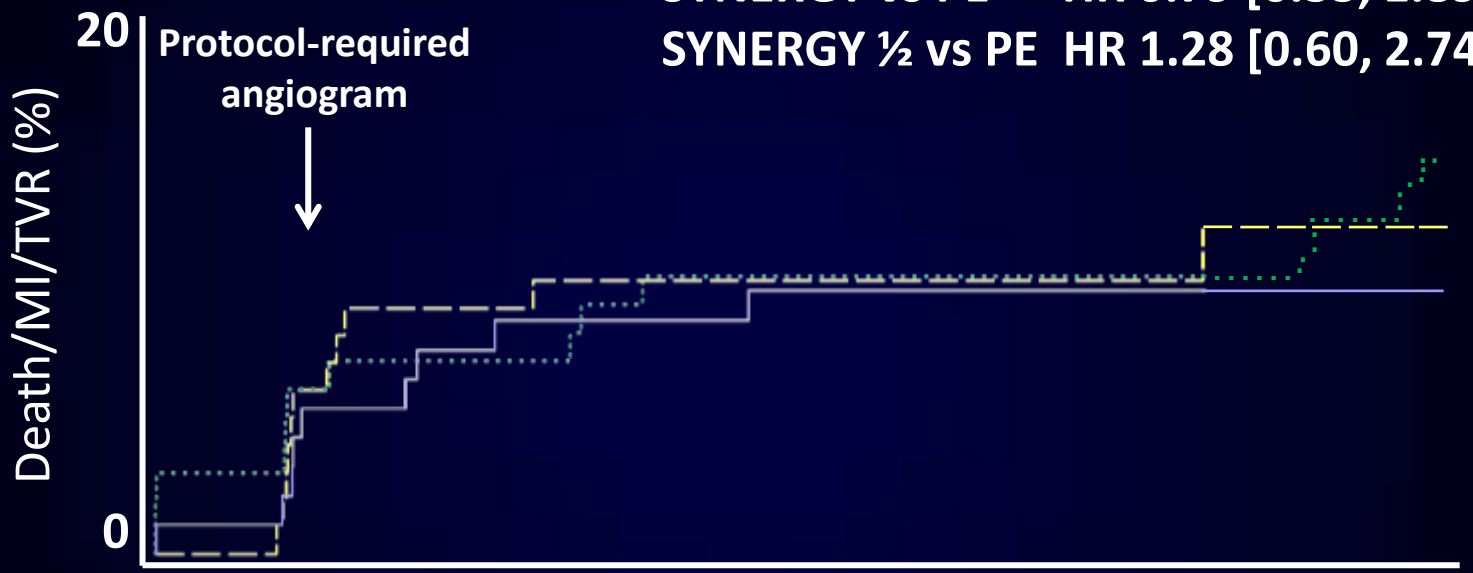
EVOLVE Trial
Key Results



Meredith et al. *J Am Coll Cardiol*. 2012; 59 (15):1362.; Presented by Meredith at EuroPCR 2016.
Intent-to-treat; *P* values are versus PROMUS Element (Fisher exact test)

Late Events with Permanent vs. Bioabsorbable Polymer DES

5-year Death/MI/TVR in EVOLVE Trial

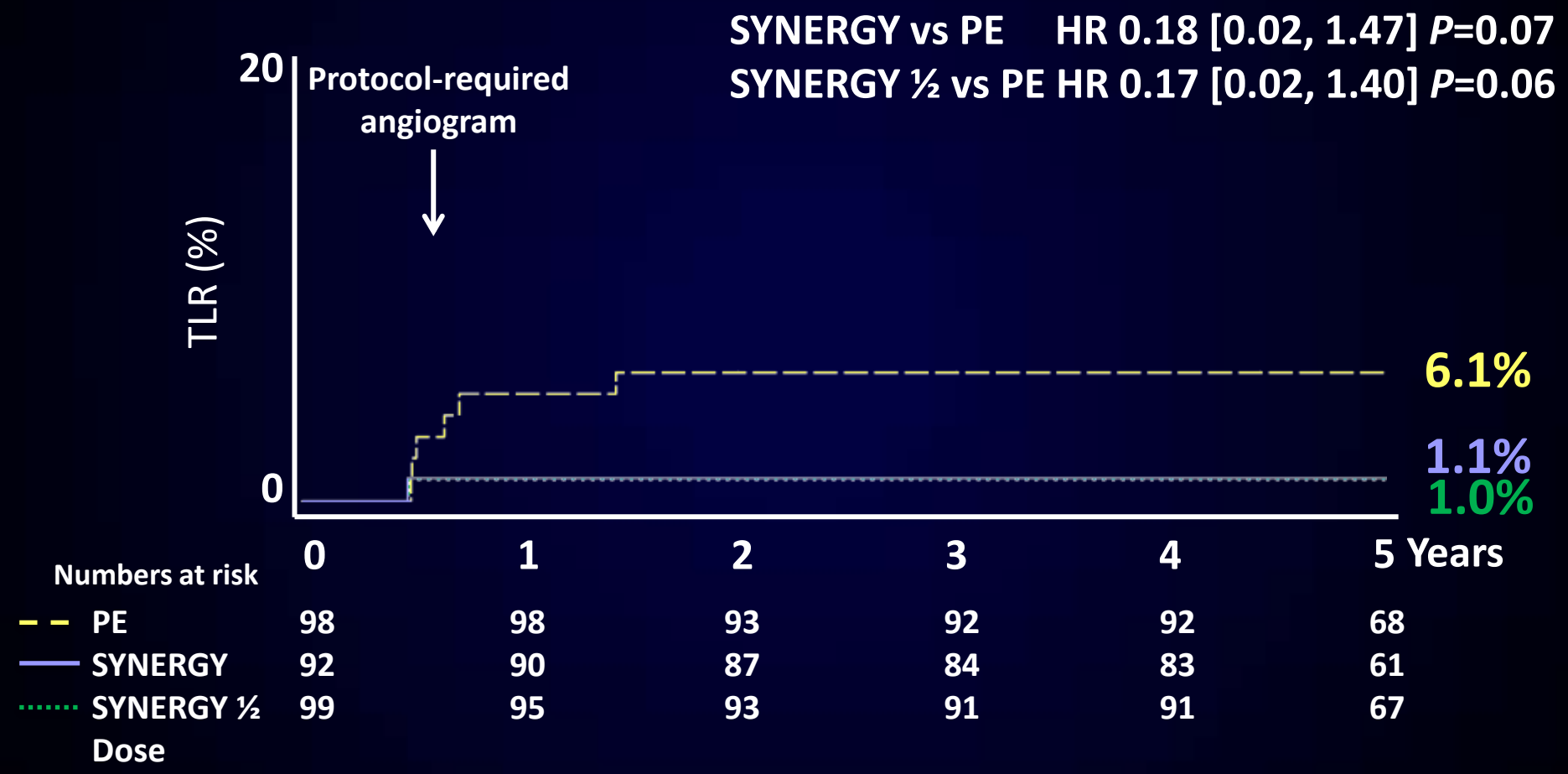


Numbers at risk	0	1	2	3	4	5 Years
PE	98	96	89	88	88	65
SYNERGY	92	90	84	81	80	59
SYNERGY ½ Dose	99	92	88	85	85	65

Safety Population; KM Event Rate; log-rank *P* values. Presented by Meredith at EuroPCR 2016.

Late Events with Permanent vs. Bioabsorbable Polymer DES

5-year TLR in EVOLVE Trial



Safety Population; KM Event Rate; log-rank *P* values. Presented by Meredith at EuroPCR 2016.

IVUS Characteristics at 6 Months

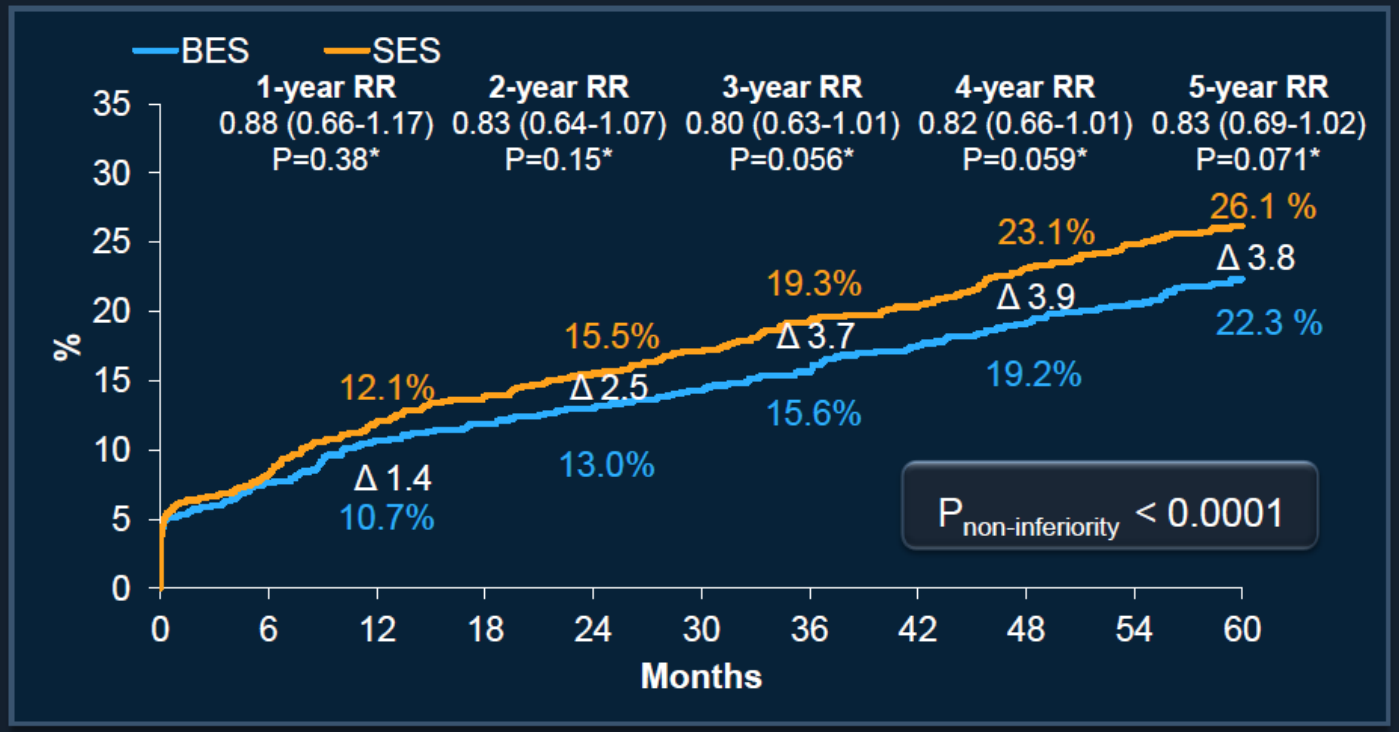
EVOLVE

	PROMUS Element n=98	SYNERGY n=94	*P* value	SYNERGY ½ Dose n=99	*P* value
Net volume obstruction, %	3.40 ± 5.06	2.68 ± 4.60	0.34	3.09 ± 4.29	0.68
Neointimal area, mm^2	0.22 ± 0.32	0.18 ± 0.33	0.34	0.22 ± 0.29	0.90
Lumen area, mm^2	6.81 ± 1.95	6.86 ± 2.11	0.89	7.29 ± 1.95	0.14
Stent area, mm^2	7.04 ± 1.93	7.03 ± 2.10	0.99	7.50 ± 1.92	0.14
Minimum lumen diameter, mm	2.42 ± 4.29	2.46 ± 0.45	0.50	2.52 ± 0.38	0.13
Lumen volume, mm^3	157.99 ± 66.66	164.22 ± 75.86	0.58	168.03 ± 65.32	0.36

Values are mean ± standard deviation
Intent-to-treat; *P* values are versus PROMUS Element

The LEADERS trial demonstrates that benefits of bioabsorbable polymer may become evident long-term

MACE (Cardiac Death, MI and ci-TVR)



Number at risk

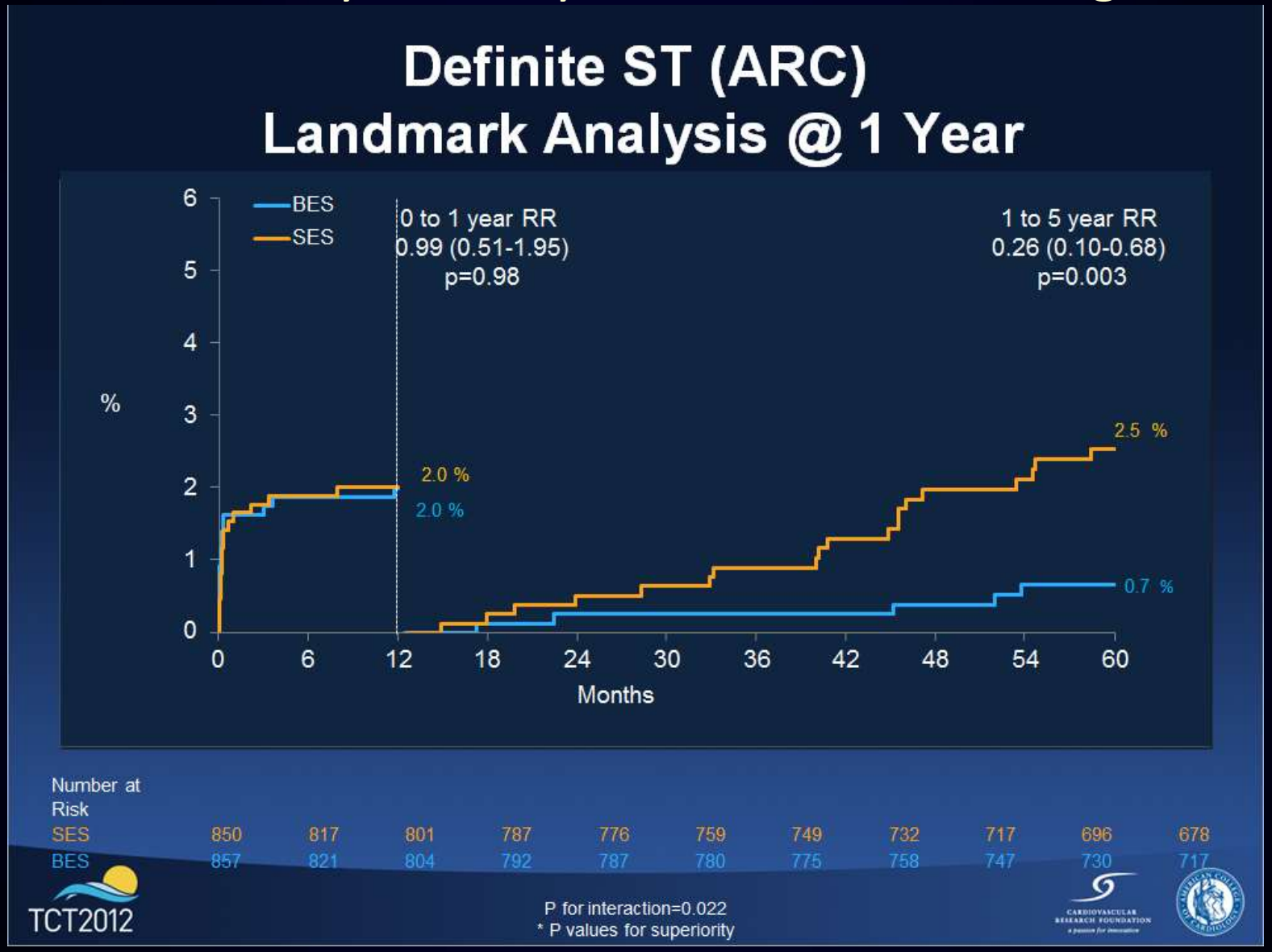
SES	850	774	738	718	701	676	655	640	616	589	572
BES	857	780	749	733	723	710	697	675	657	635	618

BIOSENSORS INTERNATIONAL™

MACE = cardiac death, MI, or clinically-indicated TVR
* p-value for superiority
Serruys et al., oral abstract presentation, TCT 2012

LEADERS

The LEADERS trial Demonstrates that Benefits of Bioabsorbable Polymer may become Evident Long-Term



Serruys, et al. *JACC* Vol. 6, No. 8, 2013.

EVOLVE II Pivotal Trial Design

Patients with ≤3 native coronary artery lesions in ≤ 2 major epicardial vessels; lesion length ≤ 34 mm, RVD ≥2.25 mm ≤ 4.0, %DS≥50<100 (excluded LM disease, CTO, SVG, ISR or recent STEMI)

Randomized Cohort (RCT)
125 global sites

PROMUS Element Plus N=838

SYNERGY N=846

PK Substudy

SYNERGY N=21

Diabetes Substudy

SYNERGY N=203

RCT Design

Multicenter noninferiority trial

Pivotal, single-blind, 1:1 randomization

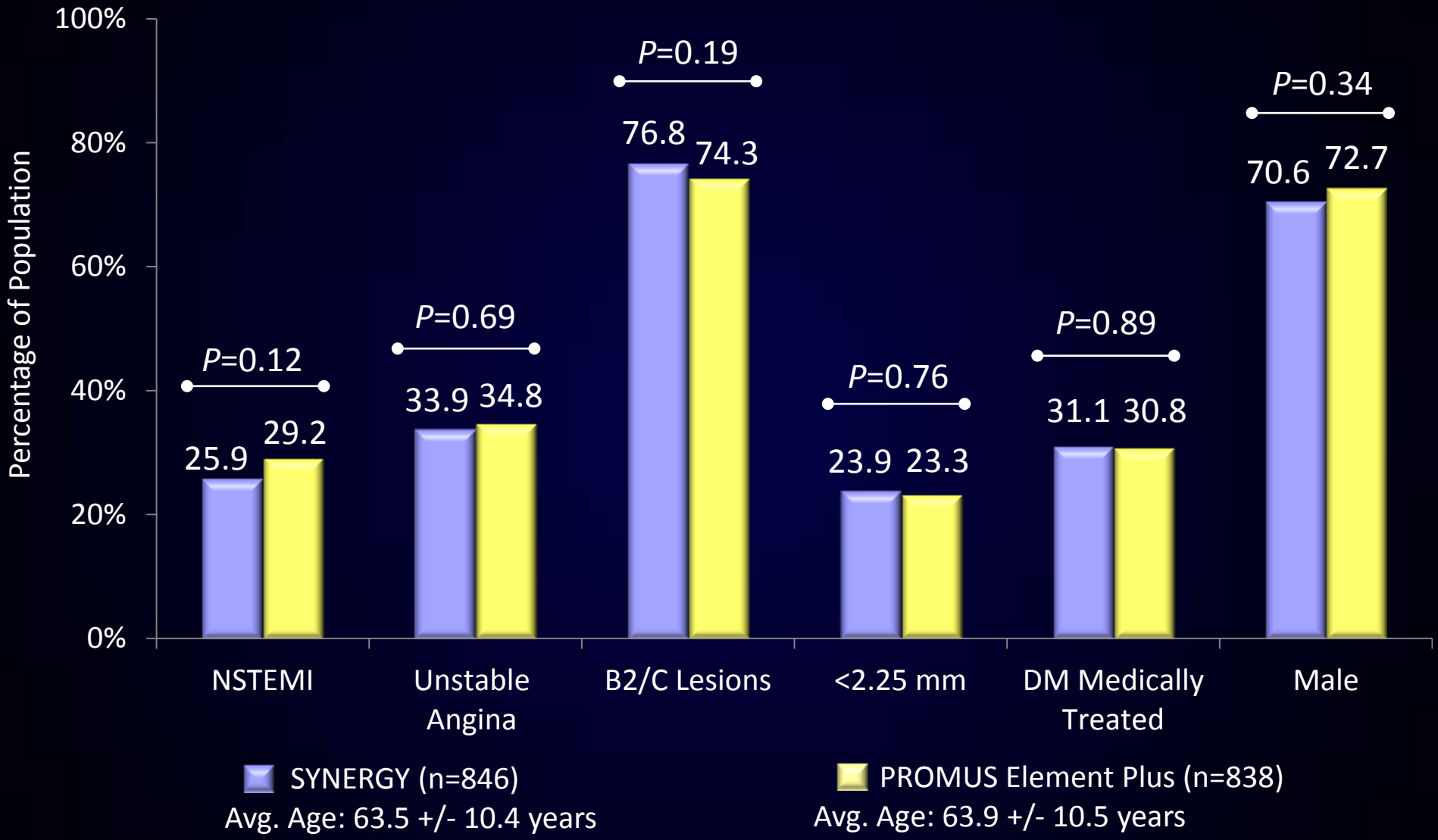
Primary Endpoint: TLF (CD, TV-MI, or TLR) **at 12 mo**

Follow-up through 5 years

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

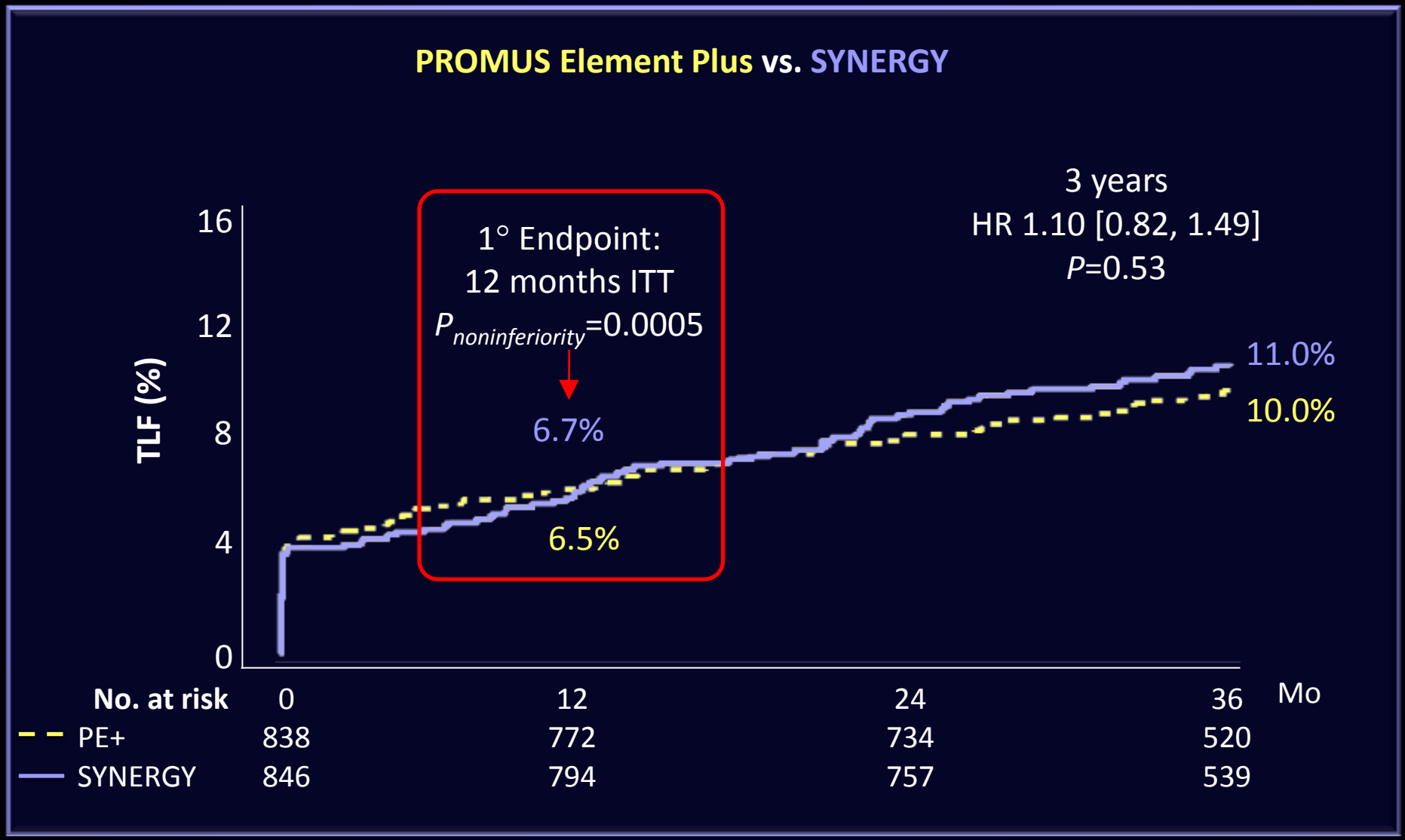
Kereiakes, et al. *Circ Cardiovasc Interv*. 2015;8:e002372. DOI: 10.1161/CIRCINTERVENTIONS.114.002372.

EVOLVE II Clinical Trial Baseline Demographics



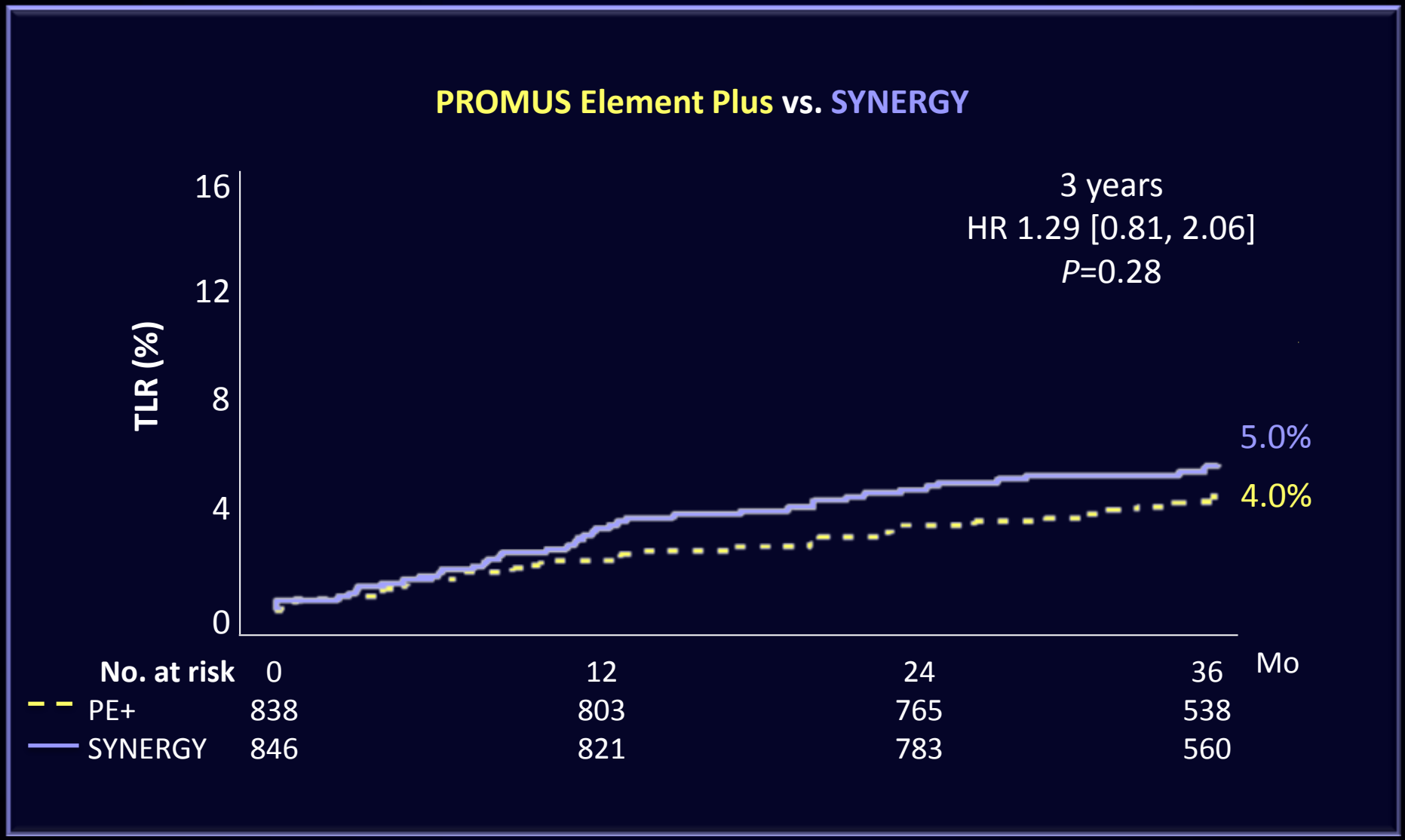
Kereiakes, et al. *Circ Cardiovasc Interv*. 2015;8:e002372. DOI: 10.1161/CIRCINTERVENTIONS.114.002372.

EVOLVE II TLF at 3 years



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

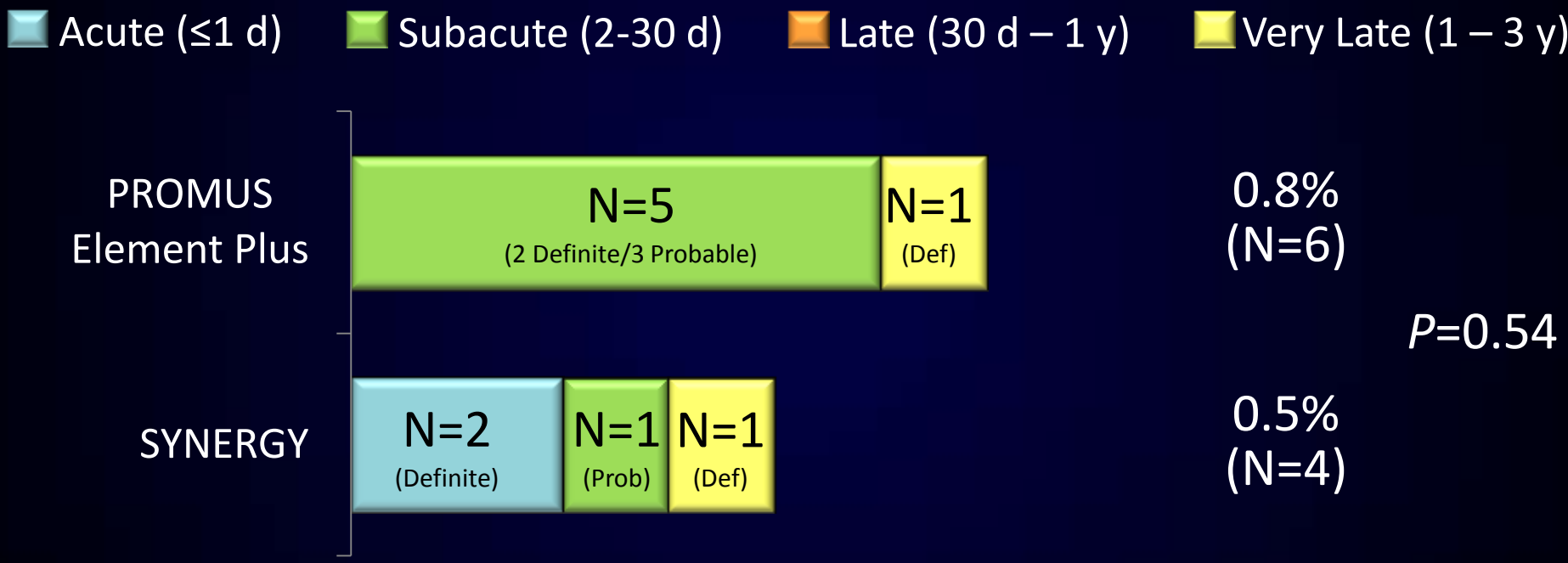
EVOLVE II TLR at 3 years



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

Stent Thrombosis at 3 years

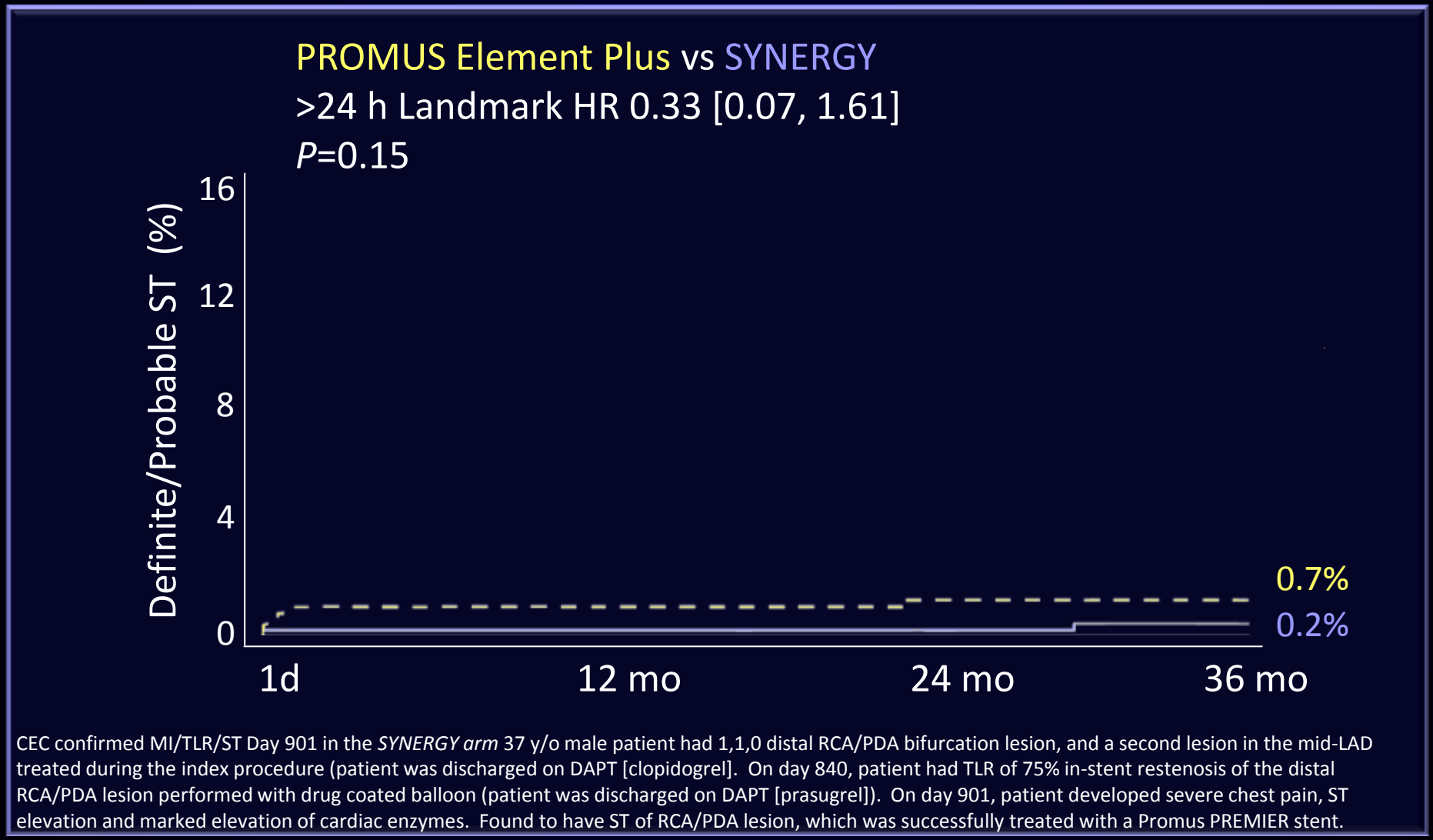
Definite/Probable: ITT Population



CEC confirmed MI/TLR/ST Day 901 in the *SYNERGY arm*

ST Landmark Analysis

Definite/Probable ST after 24 hours



CEC confirmed MI/TLR/ST Day 901 in the *SYNERGY arm* 37 y/o male patient had 1,1,0 distal RCA/PDA bifurcation lesion, and a second lesion in the mid-LAD treated during the index procedure (patient was discharged on DAPT [clopidogrel]. On day 840, patient had TLR of 75% in-stent restenosis of the distal RCA/PDA lesion performed with drug coated balloon (patient was discharged on DAPT [prasugrel]). On day 901, patient developed severe chest pain, ST elevation and marked elevation of cardiac enzymes. Found to have ST of RCA/PDA lesion, which was successfully treated with a Promus PREMIER stent.

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

Belfast Experience with SYNERGY

- Single-center, retrospective assessment of 185 patients who underwent PCI with SYNERGY between Aug 2013-Feb 2016
- Assessment of 1-year clinical outcomes with early cessation of DAPT
- Primary Endpoint: 1-year TLF (composite of TLR, TV-MI, and CD)

Patient/Lesion/Procedural Characteristics

Characteristics	N=185
Mean Age (years)	72.0±11.0
AHA/ACC class C lesion	97.3%
Multi-vessel disease	33.0%
CTO	33.0%
Discontinued DAPT at 3 months	78.4%

Clinical Outcomes at 1 Year

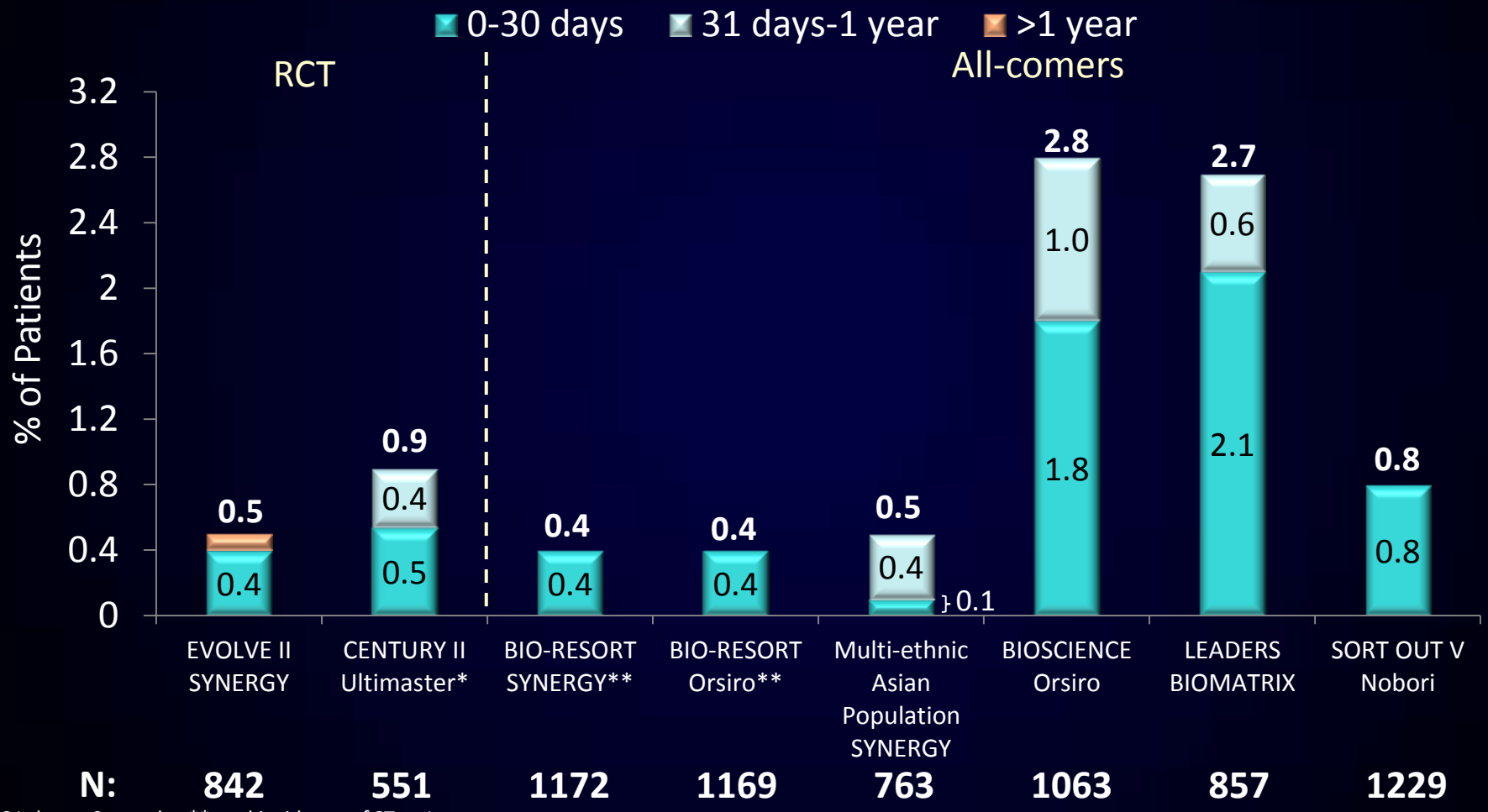
Outcomes	N=185
TVF	1.2%*
TVR	1.16%
Myocardial Infarction	0.0%
ARC ST	0.0%

*Percentage of lesions, all others percentage of patients

Noad, R. et al. *J Invasive Cardiol.* 2017;29(2):36-41

Bioabsorbable Polymer DES Platforms

Definite/Probable ST In Perspective



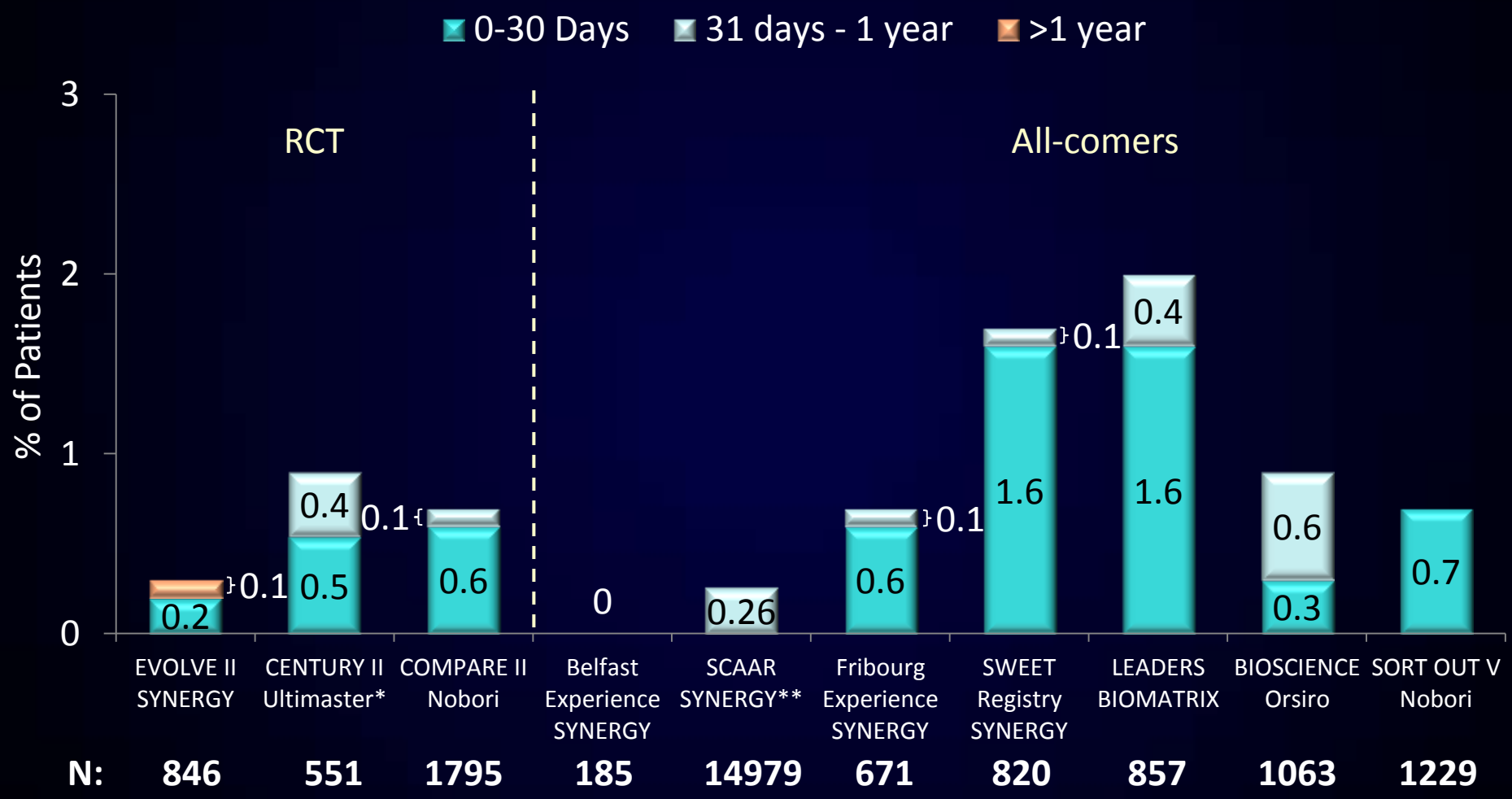
*31 days – 9 months, **total incidence of ST at 1 year

Results from different studies are not directly comparable. Information provided for educational purposes only.

EVOLVE II: Kereiakes, ACC 2017; CENTURY II: Saito S. et al. *EHJ* 2014; BIO-RESORT: Von Birgelen TCT2016; BIOSCIENCE: Pilgrim, et al. *Lancet* 2014; 384: 2111-12; LEADERS: Serruys, et al. JACC 2013; SORT OUT V: Christiansen, et al. *Lancet* 2013; 381:661-69. Multi-ethnic Asian Population: Loh ACC 2017

Bioabsorbable Polymer DES Platforms

Definite ST in Perspective



*31 days – 9 months, **aggregate unadjusted ST not separated by 1 month or up to 1 year

Results from different studies are not directly comparable. Information provided for educational purposes only.

EVOLVE II: Kereiakes, ACC 2017; CENTURY II: Saito S. et al. *EHJ* 2014; COMPARE II: Smits, et al. Lancet 2013; Belfast Experience: Noad TCT 2015; SCAAR: James TCT 2016; Fribourg Experience: Arroyo CRT 2016; SWEET Registry: Puricel TCT 2015; LEADERS: Serruys, et al. JACC 2013; BIOSCIENCE: Pilgrim, et al. *Lancet* 2014; 384: 2111-12; SORT OUT V: Christiansen, et al. *Lancet* 2013; 381:661-69.

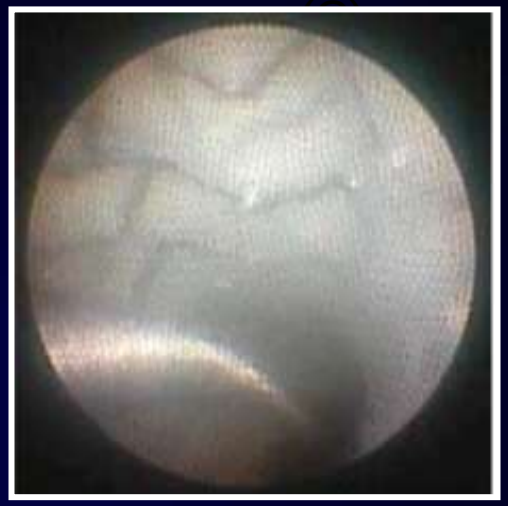
Neointimal Coverage of Current Gen DES

Angioscopic images of stented human vessel at 12 & 13 months

CoCr EES*

(e.g. XIENCE)

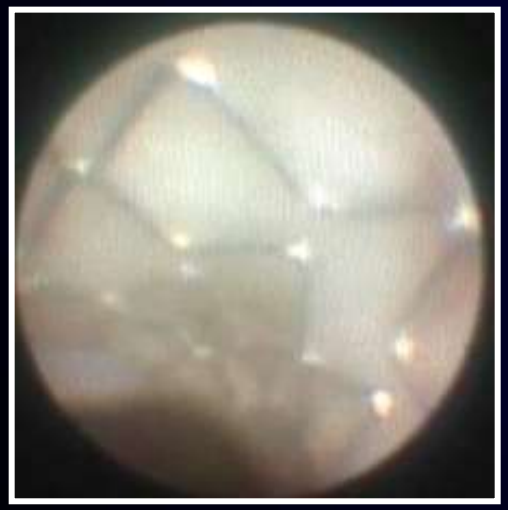
Mild coverage
Some thrombus
and yellow plaque



PtCr EES*

(e.g. PREMIER)

Mild coverage
Some thrombus
and yellow plaque



ZES*

(e.g. Resolute Integrity/Onyx)

Mild coverage
Some thrombus
and yellow plaque

PtCr BP EES**

(e.g. SYNERGY)

Moderate coverage
No thrombus
No yellow plaque

*Image captured at 12 month follow-up, **Image captured at 13 months, Case study not necessarily representative of all cases. Results in other cases may vary.

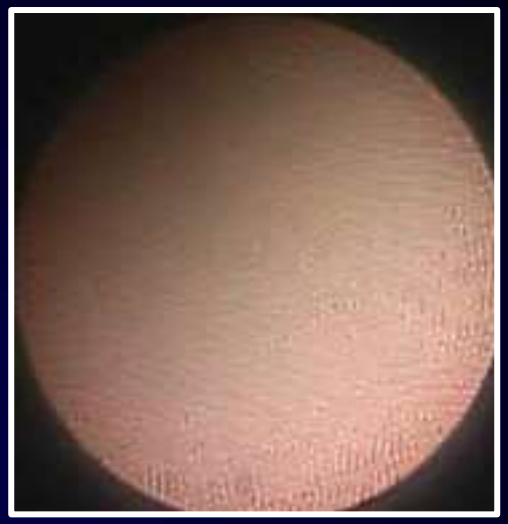
Neointimal Coverage with Current Gen DES

Angioscopic videos of stented human vessels at 12 & 13 months

(B)

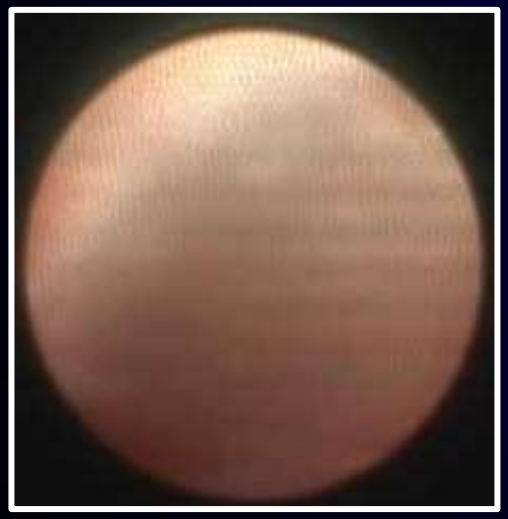
CoCr EES*
(e.g. XIENCE)

Mild coverage
Some thrombus
and yellow plaque



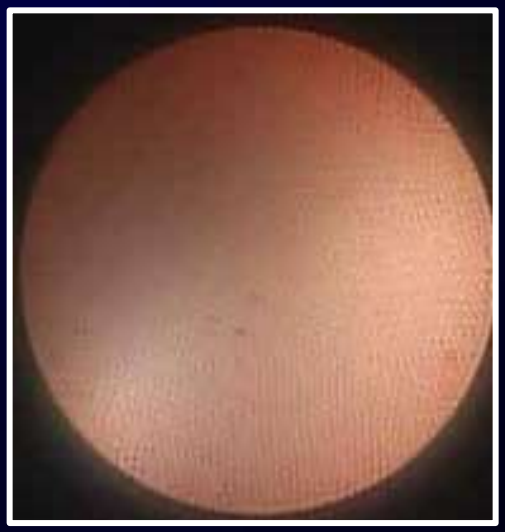
PtCr EES*
(e.g. PREMIER)

Mild coverage
Some thrombus
and yellow plaque



ZES*
(e.g. Resolute
Integrity/Onyx)

Mild coverage
Some thrombus
and yellow plaque

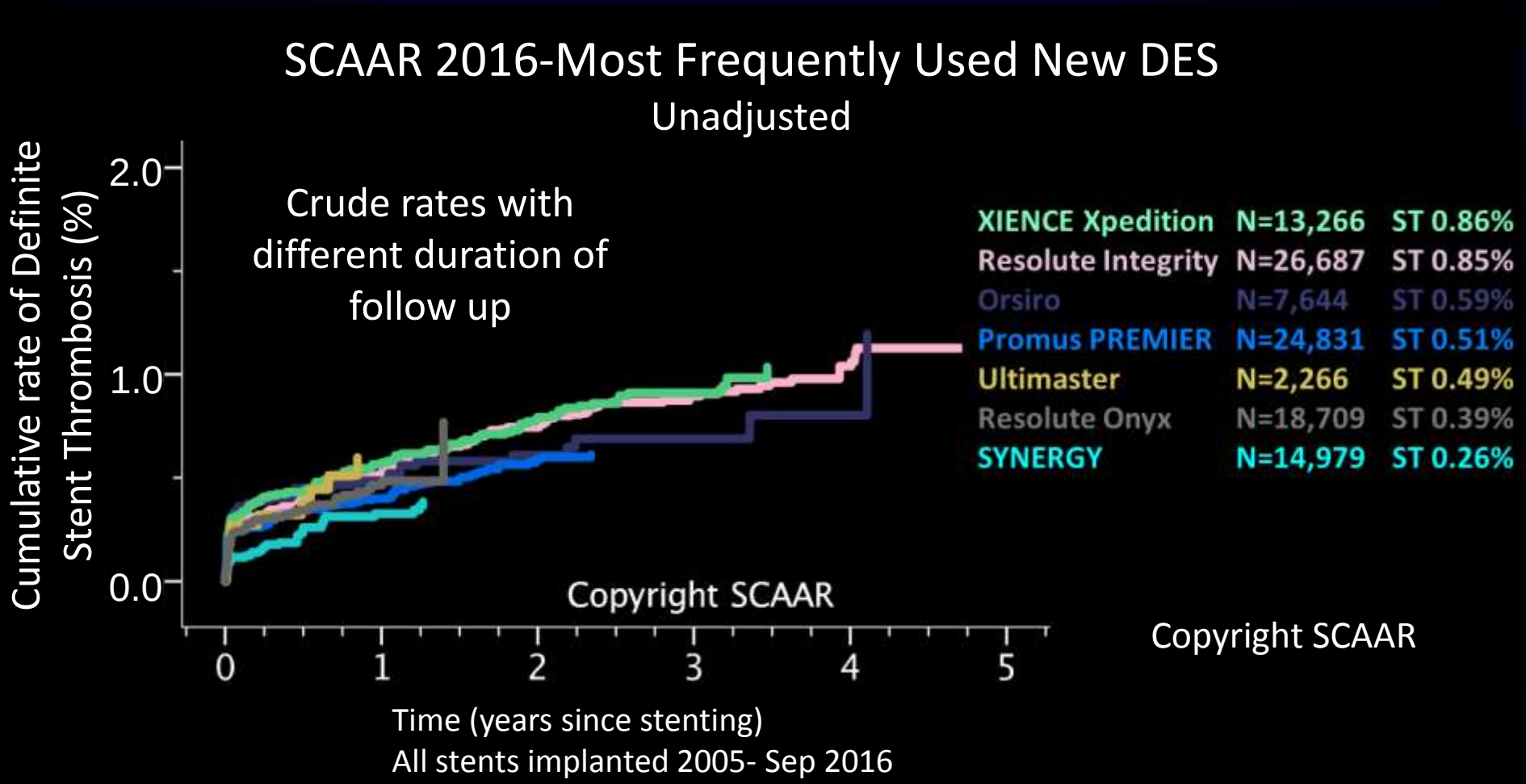


PtCr BP EES**
(e.g. SYNERGY)

Moderate coverage
No thrombus
No yellow plaque

*Video captured at 12 month follow-up, **Video captured at 13 months, Case study not necessarily representative of all cases. Results in other cases may vary.

SYNERGY Stent reported lowest rates of ST in real-world SCAAR Registry



EVOLVE Short DAPT Study Design

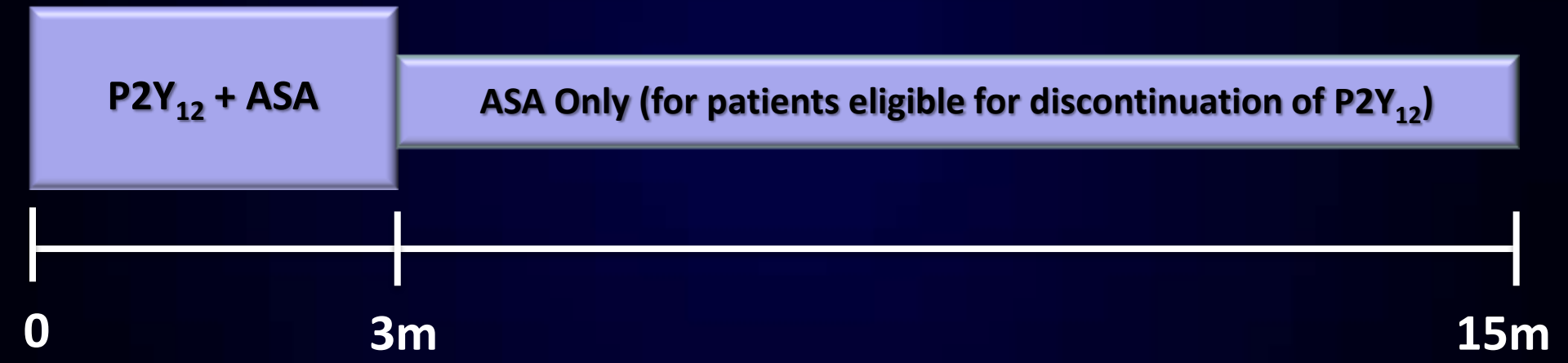
Prospective, N=2000, ~100 global sites

Key Inclusion Criteria

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

i) ≥75 years of age and high bleeding risk
ii) long term anticoagulation therapy
iii) history of major bleeding
iv) stroke, or renal insufficiency/failure

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



Co-primary Endpoints: Death or MI, ARC def/prob ST

Secondary Endpoint: Rate of major bleeding (BARC bleeding classification 2,3,5)

Primary and secondary endpoints evaluated between 3 and 15 months

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

Presented by Mauri at TCT 2015.

SENIOR Trial Design

Randomized, prospective, multicenter, single-blind trial

Patients ≥75 years old with ≥1 stenosis in epicardial coronary and with 1 of the following: silent ischemia, stable angina, or ACS, N=1201

Randomized

SYNERGY | **REBEL BMS**

DAPT: ASA + Clopidogrel, Prasugrel, or Ticagrelor
- ➔ 1 month for stable angina or silent ischemia
- ➔ 6 months for ACS patients

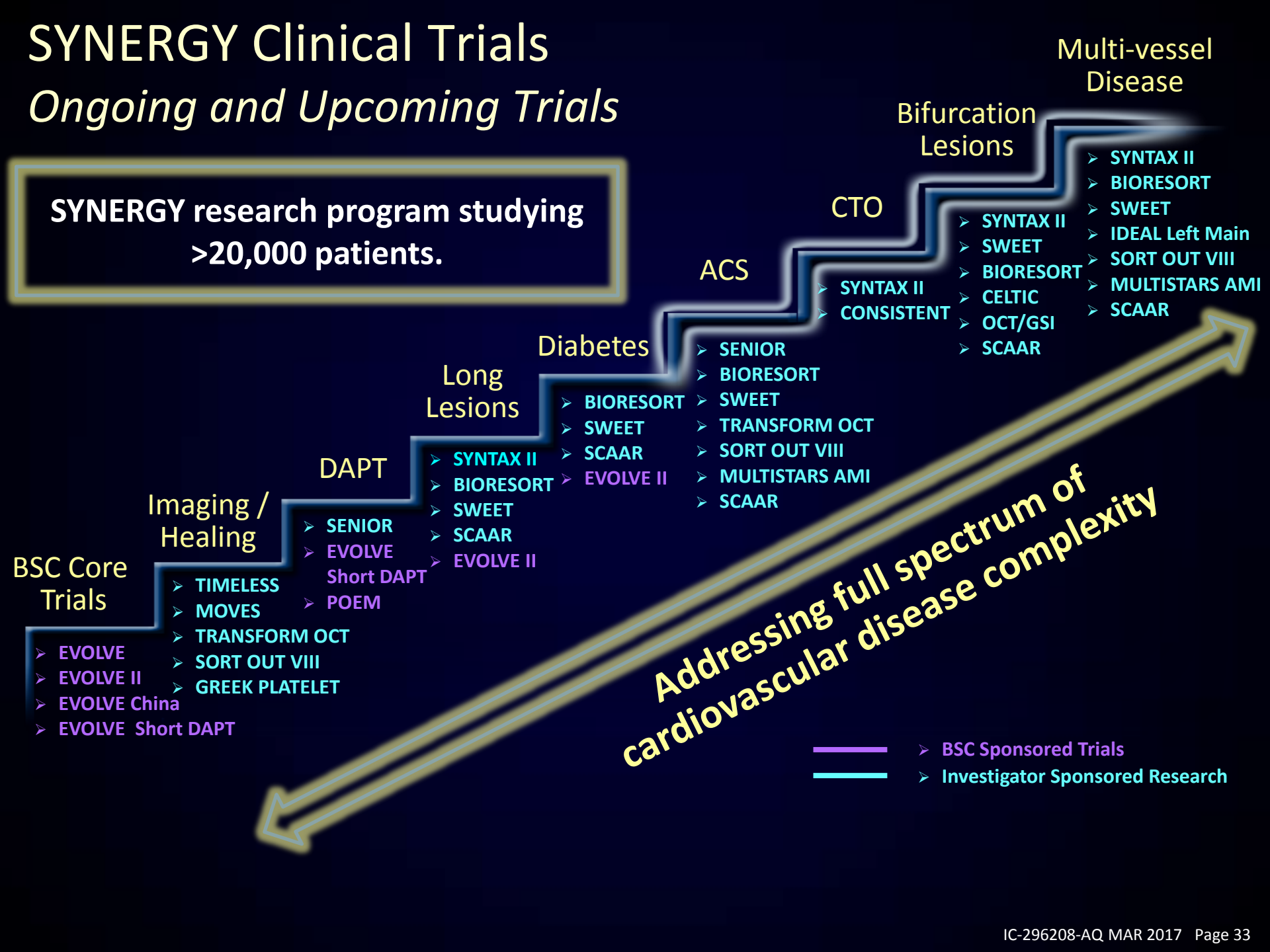
- **Primary Endpoint:** Composite measure of MACCE* at 12 months
- **Secondary Endpoints:**
  - Individual components of MACCE, TLR, TVR, non-TVR, bleeding**, ARC Def/Prob ST follow up at 30 days, 6 months, 1 and 2 years
  - Quality of life and depression at 12 and 24 months
  - Cost effectiveness at 12 months

*All-cause mortality, MI, stroke, ischemia-driven TLR; **BARC Type 2, 3 and 5; Varenne, O., et al. EuroIntervention 2015; Presented by Varenne, O. EuroPCR 2016

SYNERGY Clinical Trials

Ongoing and Upcoming Trials

SYNERGY research program studying >20,000 patients.



Summary

- The SYNERGY Stent design goals are to address needs surrounding complex PCI
  - Best in class deliverability & acute performance
  - Optimal healing / rapid endothelialization
    - Thin struts
    - Abluminal coating
    - Low polymer load
    - Synchronous drug release and polymer absorption
    - Short-term polymer exposure
    - Drug present in artery while polymer degrades

- Positive clinical performance of SYNERGY supported by:
  - 5-year EVOLVE FHU Trial data with 0% def/prob ST in all arms to 5 years
  - 3-year EVOLVE II Trial data proving non-inferiority to the Promus Element Plus Stent for TLF in more comers population (>60% ACS, >25% MI, 31% diabetes, smaller vessels, longer lesions, ≥75% AHA/ACC B2/C lesion morphology)
  - 3-year EVOLVE II Trial data with no definite ST after 24 hours
  - 0% def/prob ST + similar clinical outcomes to EVOLVE II at 12 months in EVOLVE China

- Bioabsorbable polymer-coated DES may enhance healing and improve late outcomes (ST, TLR).