American Heart Association. | SCIENTIFIC SESSIONS 2014 Chicago, Illinois

Primary Outcomes of the EVOLVE II Trial: A Prospective Randomized Investigation of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent

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EVOLVE II SYNERGY

Session - Ischemic Heart Disease: Drugs, Devices, and Systems of Care
Wed. Nov. 19th, 2014
10:55-11:05am
North Hall B

Disclosures

- Honoraria for speaking/consultancy from Boston Scientific
- Consultant for Abbott Vascular, Reva Medical

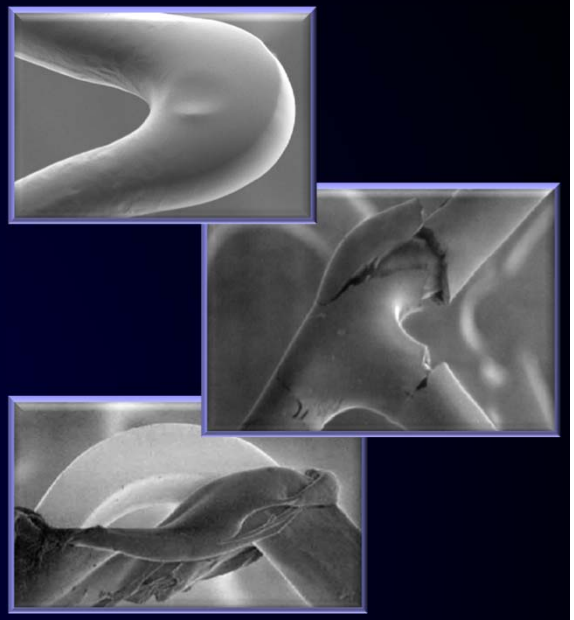
DES Polymer Considerations

Purpose of polymer:

- Provide mechanically stable reservoir for drug
- Modulate drug release - programmed drug delivery

Polymer has no function after drug release is complete

- All polymer coatings have potential to be damaged
- Damaged durable polymers are permanent



Safety

- Late / very late stent thrombosis
- Higher risk in certain patient populations
- Potentially require long-term DAPT

Efficacy

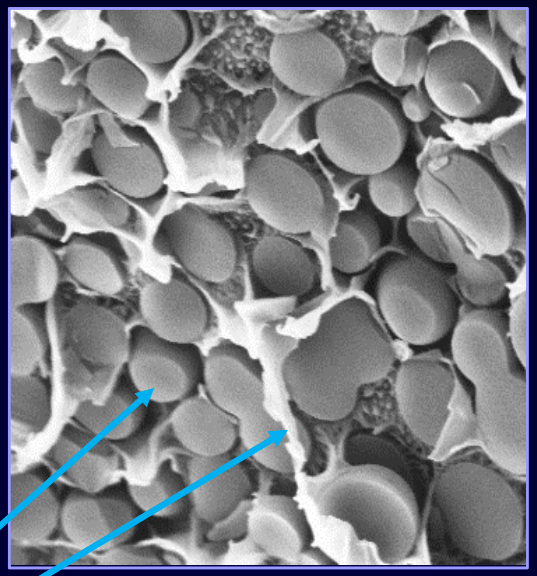
- Chronic inflammation with neoatherosclerosis
- Constant irritant may lead to late restenosis
- Hypersensitivity

SYNERGY Stent

EVOLVE II SYNERGY

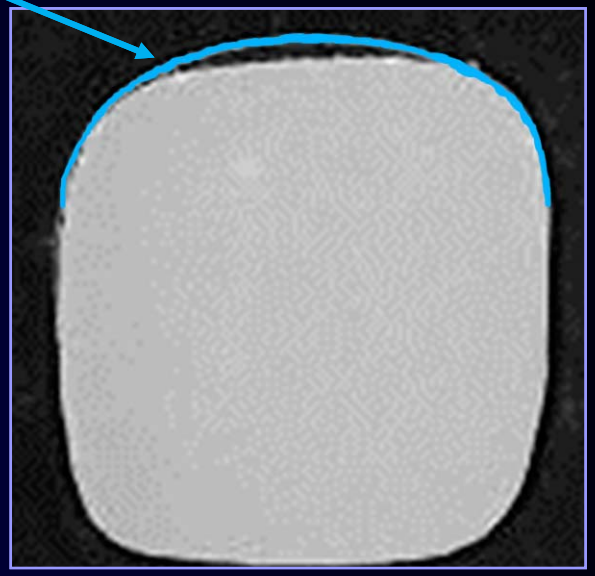
Everolimus Drug
PLGA Polymer

Drug & Polymer Coating



SEM of coating (x5000)

Abluminal (4µm)



Luminal

Platform

Platinum chromium

- 74 µm (0.0029in)

Polymer Coating

PLGA

- Abluminal
- 4 µm thick
- 85:15 ratio

Drug

Everolimus

- 100 µg/cm^2

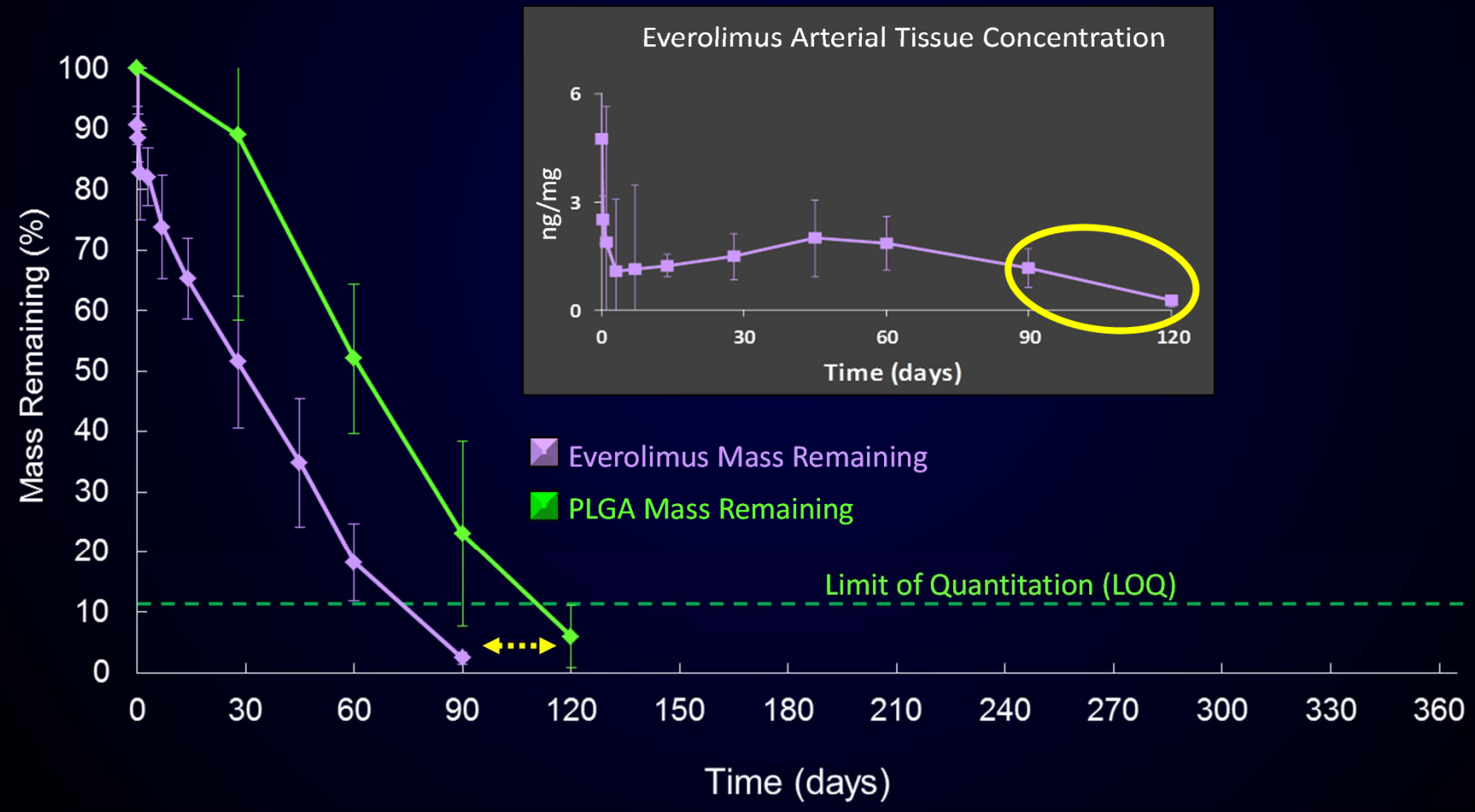
The SYNERGY™ stent is an investigational device and not for sale in the US.

SYNERGY Stent

Synchronous Drug Release & Polymer Absorption

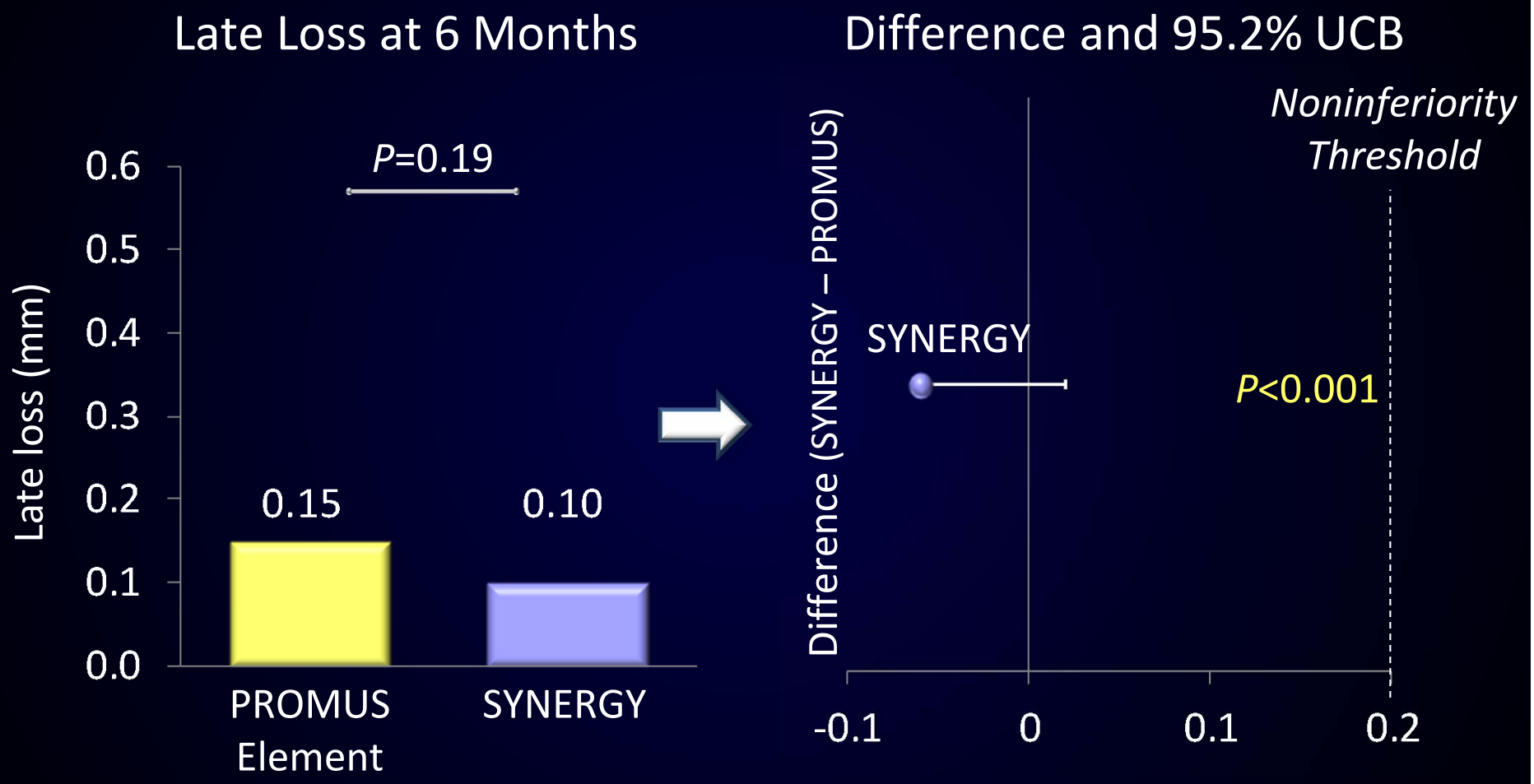
EVOLVE II SYNERGY

Preclinical evaluation in porcine model



EVOLVE Trial: FHU

Primary Angiographic Endpoint: Late Loss at 6 Mo



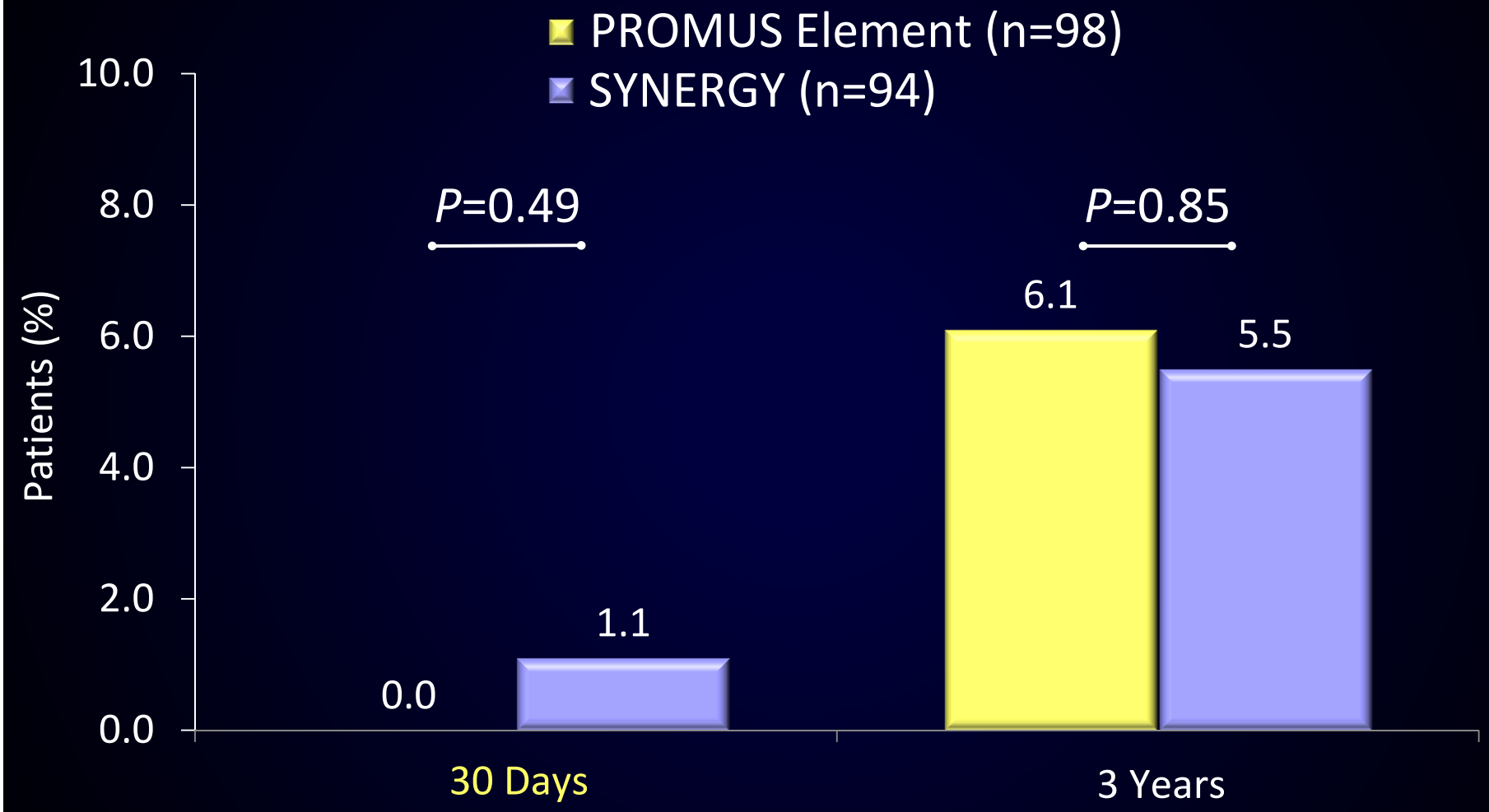
Noninferiority was proven because the upper 95.2% confidence bound of the difference in 6-month late loss is <0.20

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

The SYNERGY™ stent is an investigational device and not for sale in the US.

EVOLVE Trial: FHU

Primary Clinical Endpoint: 30d Target Lesion Failure

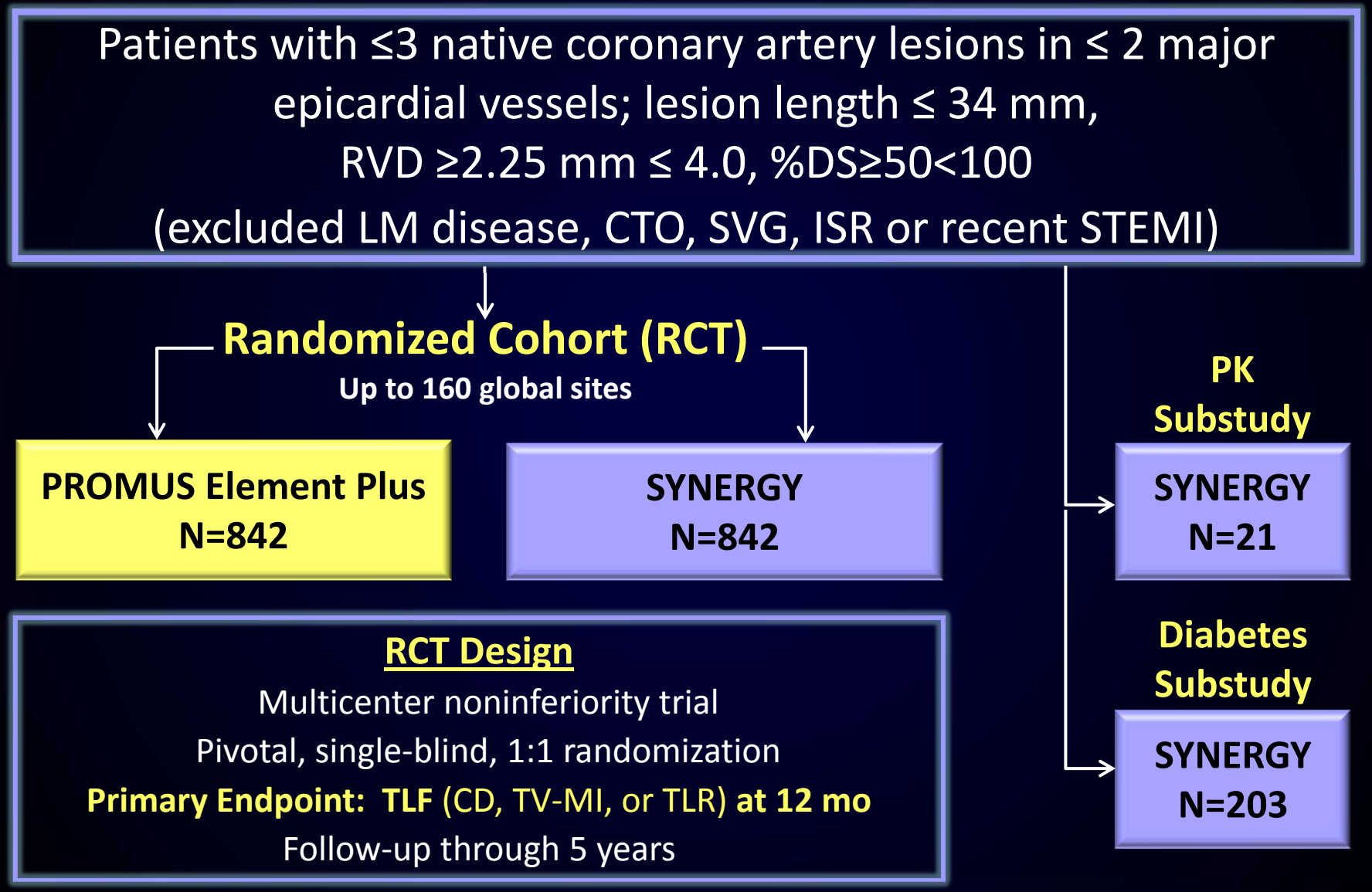


No instances of stent thrombosis in either group through 3-year follow up

30 day data: Meredith et al. *J Am Coll Cardiol.* 2012; 59 (15):1362; 3-year data: Presented by Ian Meredith AM MBBS PhD at EuroPCR 2014

The SYNERGY™ stent is an investigational device and not for sale in the US.

EVOLVE II Pivotal Trial Design



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

The SYNERGY™ stent is an investigational device and not for sale in the US.

EVOLVE II Trial Support

Coordinating Principal Investigator	Dean Kereiakes The Christ Hospital Heart and Vascular Center/ The Lindner Research Center Cincinnati, OH, USA	
Coordinating Co-Principal Investigators	Ian Meredith Monash Medical Centre Clayton, Australia	Stephan Windecker Bern University Hospital Bern, Switzerland
Angiographic Core Lab	Jeffrey J. Popma (Director) Beth Israel Deaconess Medical Center Boston, MA	
Clinical Events Committee	Joseph Kannam (chair) Germano DiSciascio	Claude Hanet Goran Stankovic
Data Monitoring Committee	W. Douglas Weaver (chair) David Faxon Steven Bailey	Jan Tijssen David Rizik

EVOLVE II SYNERGY Stent Pivotal Trial

Enrollment Highlights

Nov 26, 2012 — **EVOLVE II Enrollment Commenced**

Aug 29, 2013 — **RCT Enrollment Complete**

Dec 5, 2013 — **PK & DM Enrollment Complete**

16 Countries / 125 Centers

The SYNERGY™ stent is an investigational device and not for sale in the US.

EVOLVE II Centers

Top 30 Enrolling Centers

R. Lee Jobe (71)
Wake Medical Center

Shamir Mehta (64)
Hamilton General Hospital

Ian Sarembock (63)
Lindner Center for Research and Education at Christ Hospital

Robert Feldman (47)
Mediquest Research at Munroe Regional Medical Center

Bernardo Stein (44)
Morton Plant Mease Healthcare System

Christophe Dubois (39)
UZ Gasthuisberg

Timothy Grady (37)
Aspirus Heart and Vascular Institute

Shigeru Saito (30)
Shonan Kamakura General Hospital

Ameer Kabour (29)
Mercy St. Vincent Medical Center

Alain Bouchard (27)
Baptist Medical Center Princeton

Annapoorna Kini (27)
Mount Sinai Medical Center

Luc Janssens (27)
Imelda Ziekenhuis

Michael Foster (25)
Sisters of Charity Providence Hospital

Robert Stoler (24)
Baylor Heart & Vascular Hospital

Thomas Stuckey (24)
Moses H. Cone Memorial Hospital

Wayne Batchelor (24)
Tallahassee Memorial Hospital

Josep Rodes-Cabau (24)
University of Laval

Tommy Lee (24)
Bakersfield Memorial Hospital

Arthur Reitman (24)
Wellstar Kennestone Hospital

Andrejs Erglis (23)
P. Stradins University Hospital

Mark Dorogy (23)
Medical Center of Central Georgia

Barry Bertolet (22)
North Mississippi Medical Center

Louis Cannon (21)
Northern Michigan Hospital

Juhani Airaksinen (21)
Turku University Hospital

Craig Siegel (21)
St. David's Round Rock Medical Center

Akil Loli (20)
Banner Good Samaritan Regional Medical Center

David Mego (20)
Arkansas Heart Hospital

Kenji Ando (20)
Kokura Memorial Hospital

Toshiya Muramatsu (20)
Saiseikai Yokohama-City Eastern Hospital

Francis Stammen (20)
H.-Hartziekenhuis Roeselare-Menen

EVOLVE II Major Endpoints

Primary endpoint

- Target lesion failure (TLF) at 12 months
  - Cardiac death, or
  - MI* related to the target vessel, or
  - Ischemia-driven target lesion revascularization
- ITT and Per Protocol patient populations

Additional endpoints

- Components of TLF
- Stent thrombosis (ARC definite/probable)
- Technical success
- Clinical procedural success
- Longitudinal stent deformation

***Spontaneous MI : rise and/or fall of cardiac biomarkers with ≥1 value >99th percentile of the URL + evidence of myocardial ischemia. Peri-PCI MI: ≥1 of the following: i) CK-MB >3X URL within 48 hrs, ii) new pathological Q waves, iii) autopsy evidence.**

EVOLVE II Sample Size & Power Calculation

Primary Endpoint: 12-month Target Lesion Failure

Expected SYNERGY (test) rate = **8.0%***

Expected PROMUS Element Plus (control) rate = **8.0%***

Non-inferiority margin (Δ) = **4.4%**

Test significance level (α) = 0.025 (1-sided)

Power (1–β) = approximately **0.89**

Expected rate of attrition = **5%**

N = **1684 patients** (842 per group at 1:1 ratio)

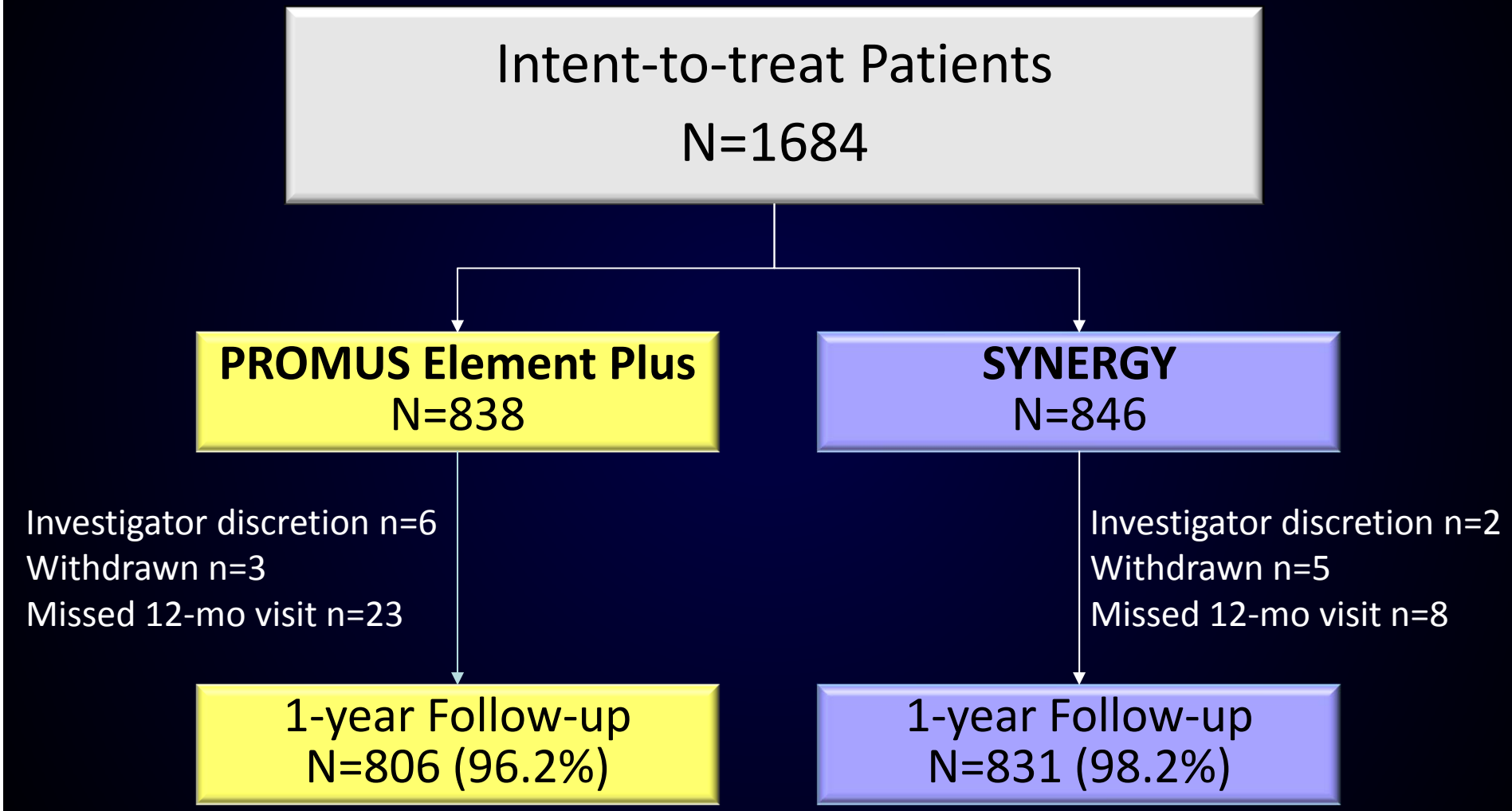
If the *P* value from the one-sided Farrington-Manning test is <0.025**, SYNERGY will be concluded to be noninferior to PROMUS Element Plus

*The expected rate of 8.0% for 12-month TLF for both SYNERGY and PROMUS Element Plus was based on results from the PLATINUM, SPIRIT, COMPARE, and Resolute All-comers trials adjusted for use of a more sensitive MI definition.

**ITT and per protocol

The SYNERGY™ stent is an investigational device and not for sale in the US.

EVOLVE II Patient Disposition



The SYNERGY™ stent is an investigational device and not for sale in the US.

Baseline Clinical Characteristics

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

The SYNERGY™ stent is an investigational device and not for sale in the US.

Baseline Lesion Characteristics (QCA)

EVOLVE II SYNERGY

Per Patient* Per Lesion†		PROMUS Element Plus *n=1043 lesions* n=838 patients	SYNERGY *n=1059 lesions* n=846 patients	*P* value
Target lesions*		1.24 ± 0.49	1.25 ± 0.50	0.77
- 2 lesions treated		**19.3%**	**18.6%**	0.69
- 3 lesions treated		**2.4%**	**3.3%**	0.26
- >3 lesions treated		**0.1%**	**0.0%**	0.50
Target lesion location†:	LAD	41.5%	41.3%	0.91
	LCx	26.4%	25.0%	0.48
	RCA	32.0%	33.7%	0.41
	LM	0.1%	0.0%	0.50‡
RVD†, mm		**2.63 ± 0.50**	**2.62 ± 0.49**	0.63
- RVD <2.25 mm		**23.3%**	**23.9%**	0.76
MLD†, mm		0.89 ± 0.36	0.89 ± 0.35	0.99
Diameter Stenosis†, %		66.26 ± 11.75	66.02 ± 12.03	0.65
Lesion length†, mm		**13.67 ± 7.00**	**14.09 ± 7.50**	0.18
- Length >20 mm		16.7%	19.2%	0.14
Modified AHA/ACC B2/C†		**74.3%**	**76.8%**	0.19

Intent-to-treat; *P* values from Student's t test or Chi-square (Fisher's Exact test denoted by ‡); MLD=minimum lumen diameter; RVD=reference vessel diameter

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Procedural Characteristics

Per Patient* Per Lesion† Per Stent‡	PROMUS Element Plus n=1043 lesions n=838 patients n=1079 stents	SYNERGY n=1059 lesions n=846 patients N=1011	*P* value
Technical success†	96.9%	98.3%	**0.04**
Clinical procedural success*	94.3%	94.9%	0.56
Stents per patient*	1.29 ± 0.56	1.31 ± 0.60	0.46
Stents per target lesion†	1.04 ± 0.25	1.05 ± 0.25	0.32
Total Stent Length Implanted† (mm)	20.81 ± 9.16	21.45 ± 9.04	0.11
Pre-dilatation†, %	98.0%	97.1%	0.18
Post-dilatation†, %	61.0%	60.7%	0.90
Max pressure overall† (atm)	16.09 ± 3.13	15.98 ± 3.06	0.41
Longitudinal Stent Deformation‡	**0.1%**	**0.1%§**	>0.99

§LSD occurred in a PROMUS Element Plus stent used in a SYNERGY patient

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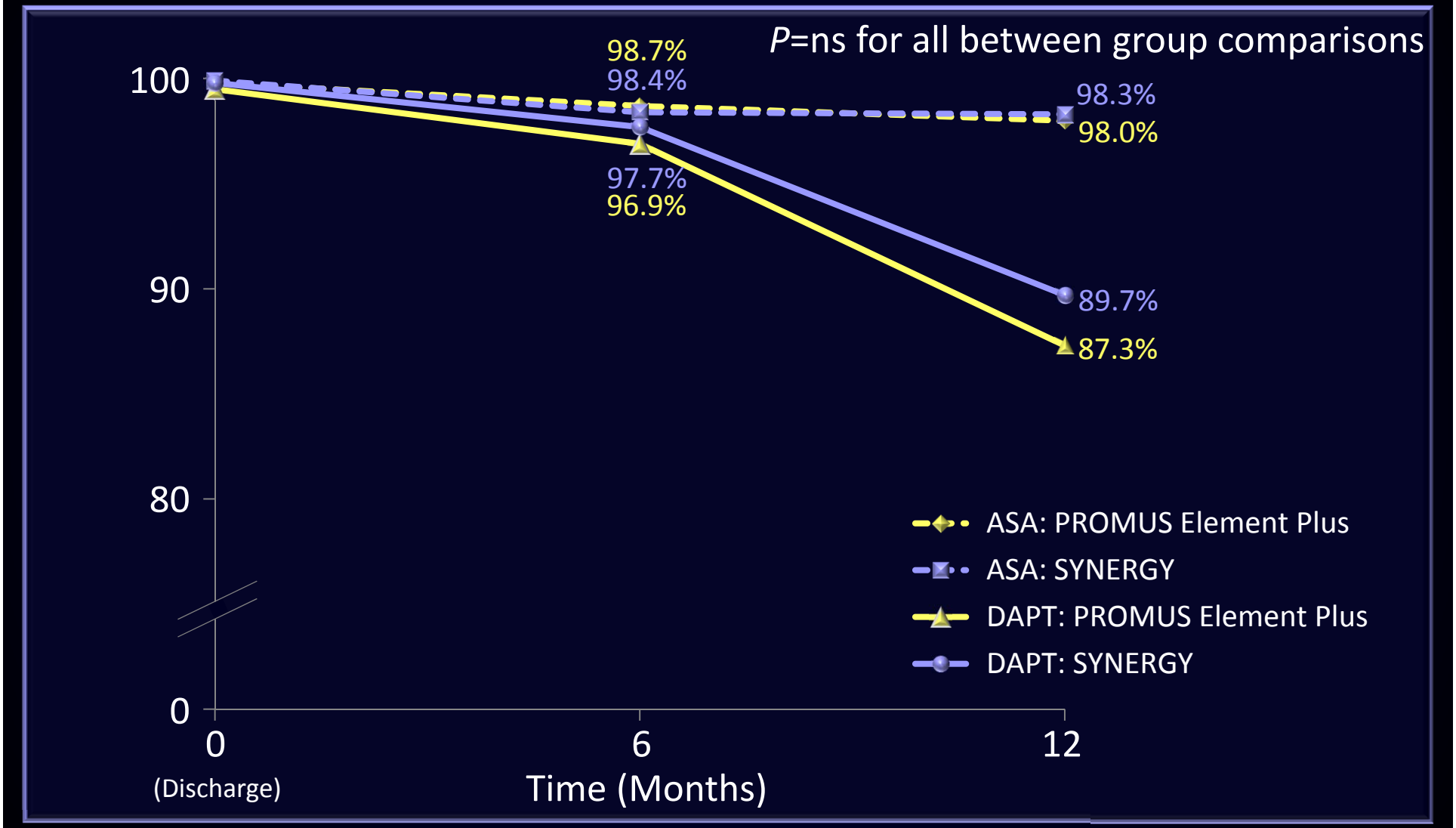
Post-procedural Angiographic Characteristics

Per Lesion	PROMUS Element Plus n=1043 lesions	SYNERGY n=1059 lesions	*P* value
MLD, in-stent, mm	2.46 ± 0.44	2.44 ± 0.44	0.23
MLD, in-segment, mm	2.10 ± 0.47	2.10 ± 0.47	0.78
%DS, in-stent, %	6.55 ± 9.71	7.19 ± 9.16	0.12
%DS, in-segment, %	20.93 ± 9.13	20.60 ± 8.41	0.39
Acute gain, in-stent, mm	1.57 ± 0.45	1.55 ± 0.45	0.33
Acute gain, in-segment, mm	1.21 ± 0.47	1.22 ± 0.48	0.72

Antiplatelet Medication Usage*



*Per protocol, patients were treated with one of the following $P2Y_{12}$ inhibitors (clopidogrel, ticlopidine, prasugrel, or ticagrelor) for at least 6 months following the index procedure. Intent-to-treat.

ASA=acetylsalicylic acid; DAPT=dual antiplatelet therapy

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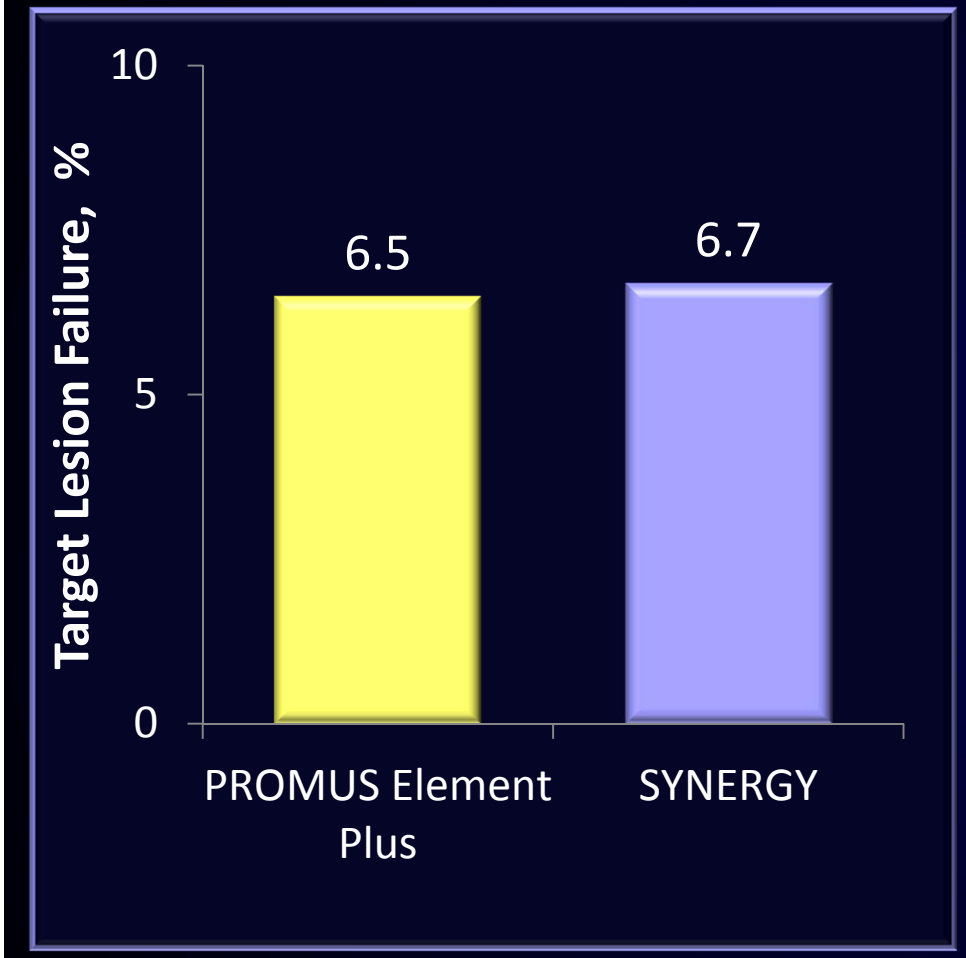
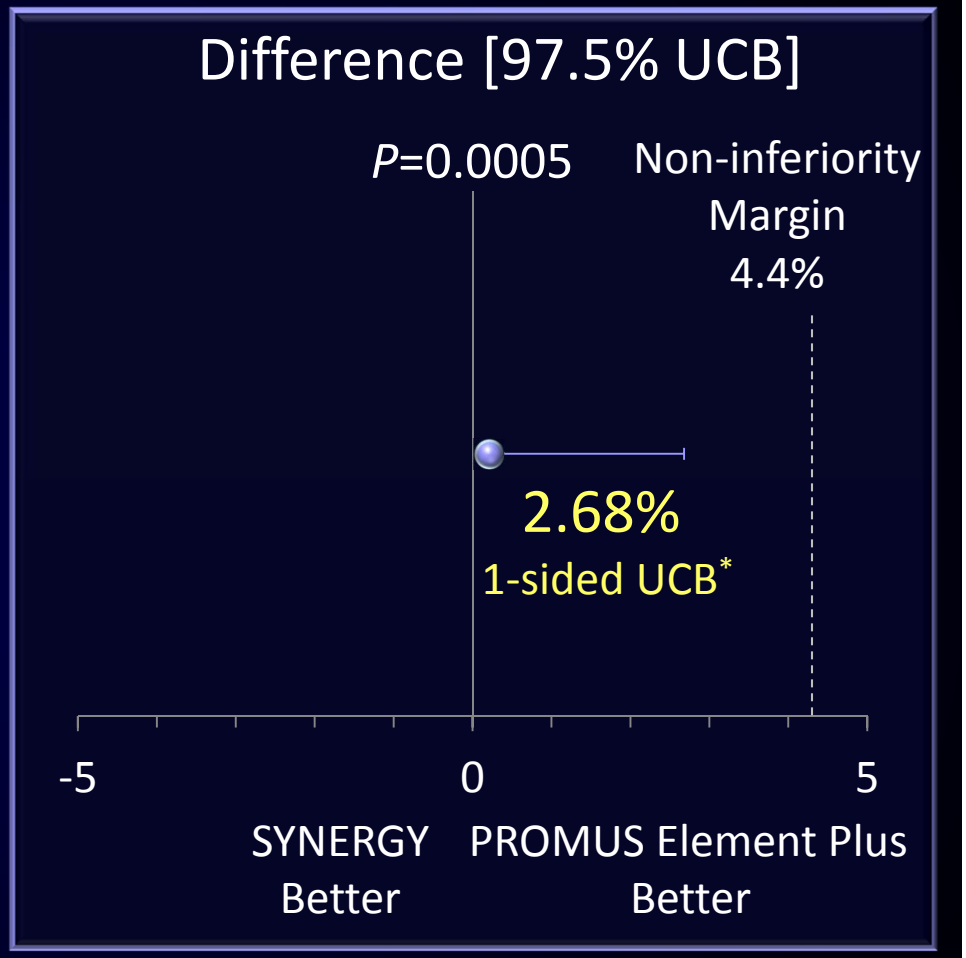
EVOLVE II Primary Endpoint:

12-month TLF : ITT Population



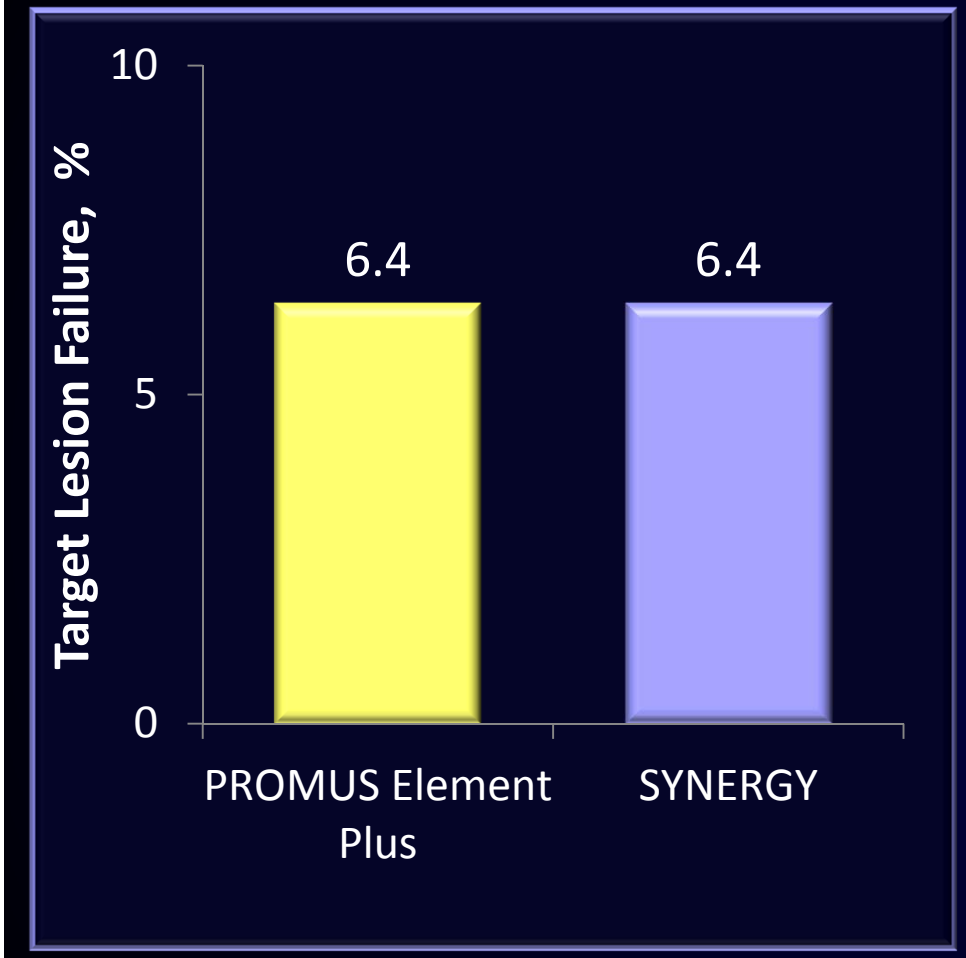


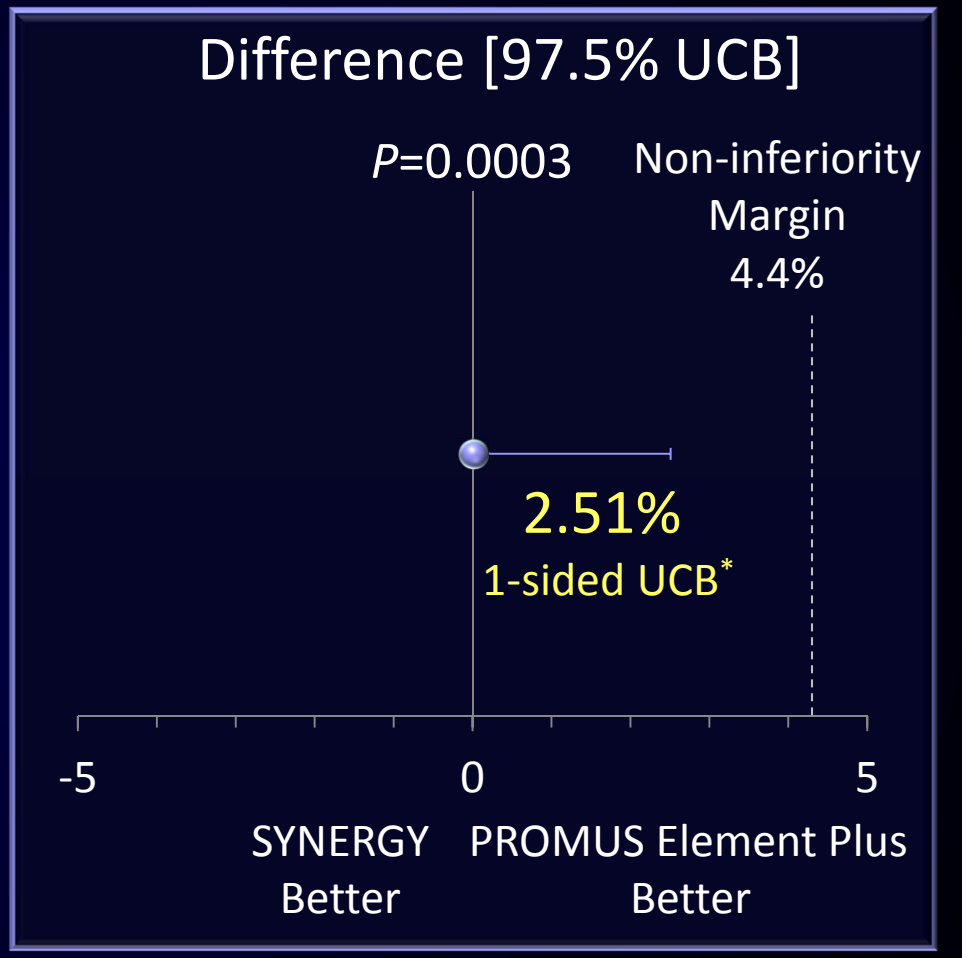
Noninferiority is proven because the one-sided upper 97.5% confidence bound for the difference in 12-month TLF is <4.4%

***One-sided 97.5% Farrington-Manning Upper Confidence Bound (UCB)**

EVOLVE II Primary Endpoint:

12-month TLF : Per Protocol



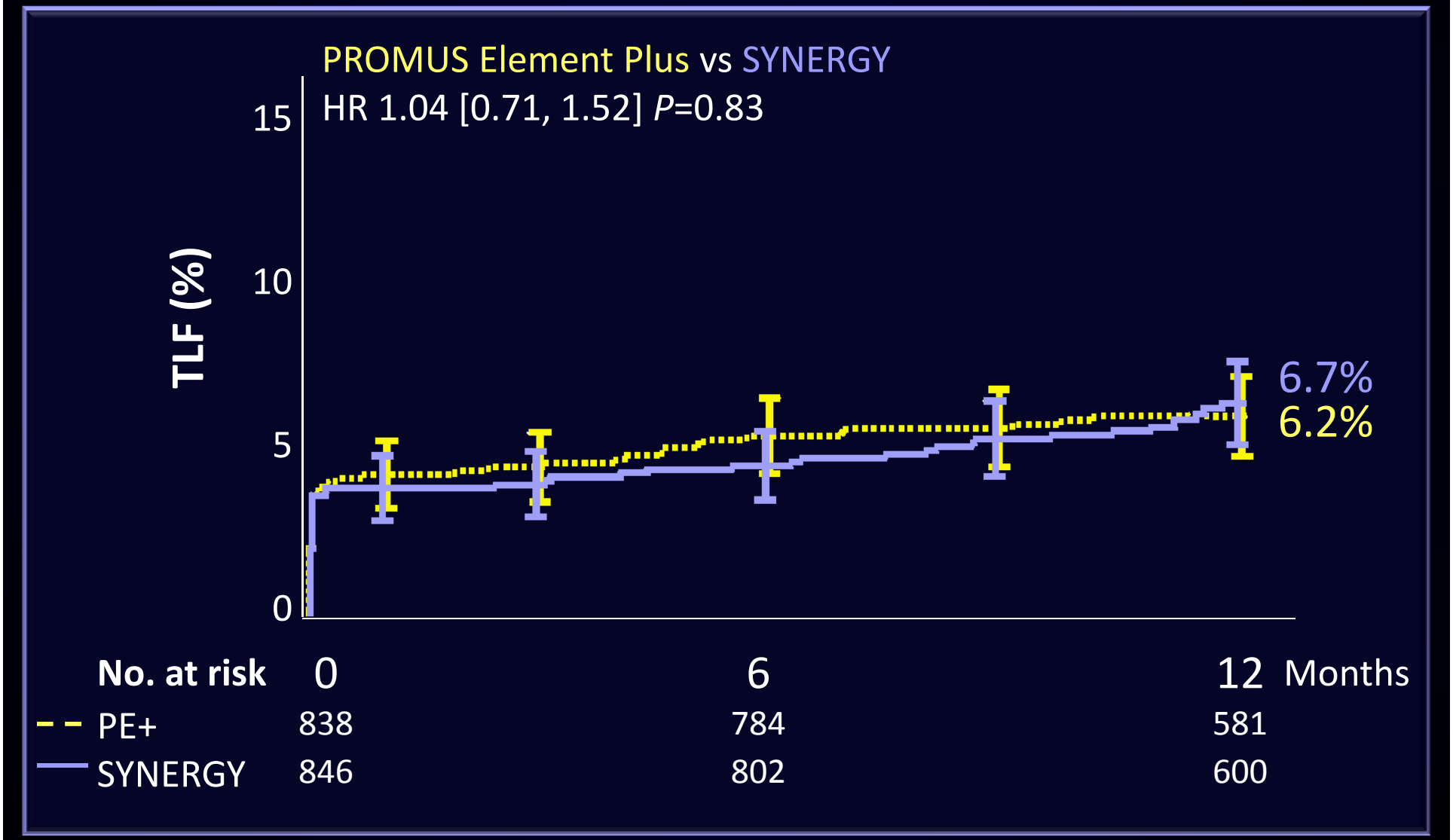


Noninferiority is proven because the one-sided upper 97.5% confidence bound for the difference in 12-month TLF is <4.4%

***One-sided 97.5% Farrington-Manning Upper Confidence Bound**

EVOLVE II Primary Endpoint:

12-month TLF : ITT



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

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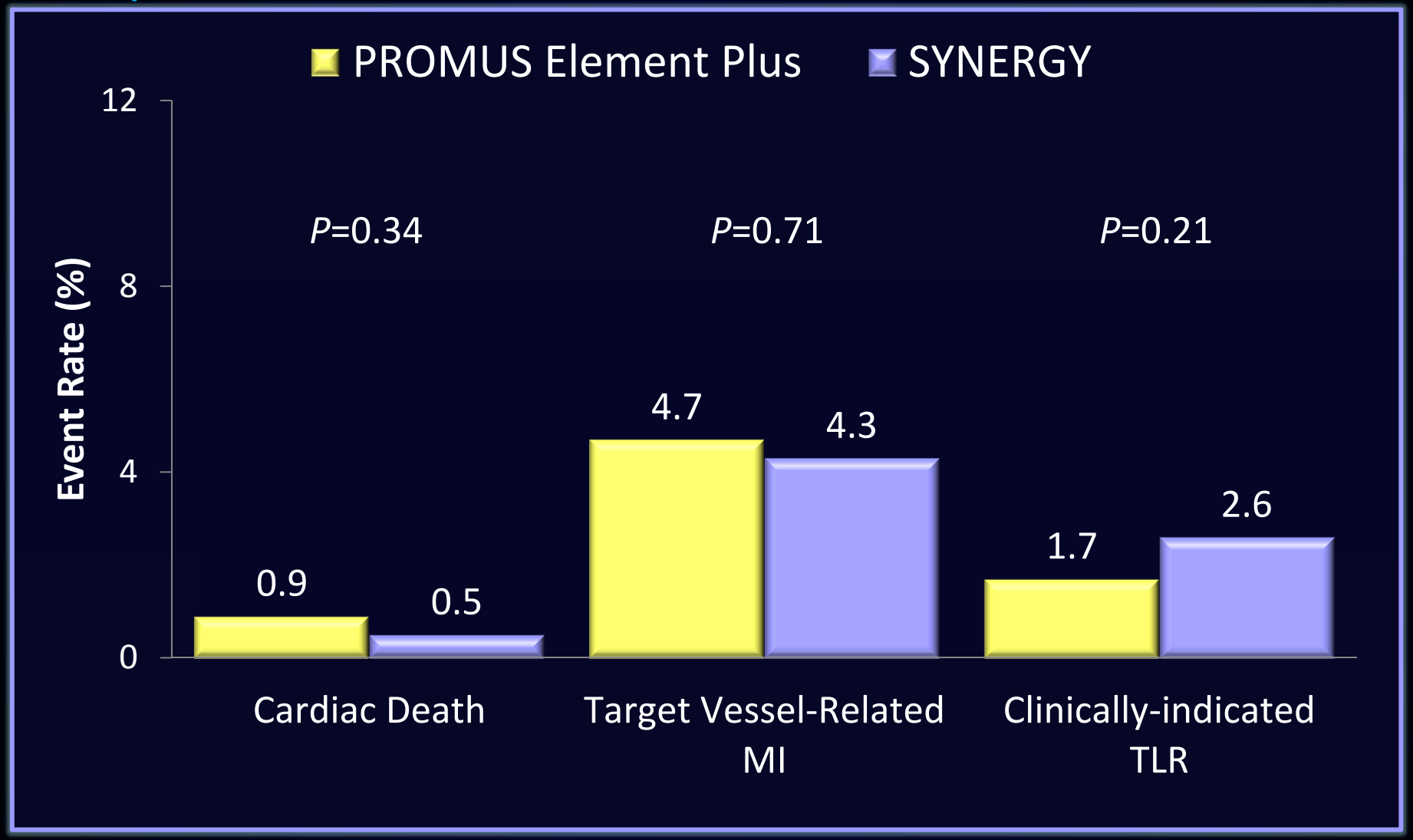
Components of TLF

ITT Population



*Per protocol spontaneous MI is defined as rise and/or fall of cardiac biomarkers with ≥1 value >99th percentile of the URL + evidence of myocardial ischemia. Peri-PCI MI is defined as ≥1 of the following: i) biomarker elevations within 48 hours of PCI (based on CK-MB >3X URL), ii) new pathological Q waves, or iii) autopsy evidence of acute MI

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Revascularization and Stent Thrombosis at 12 months

ITT Population

	PROMUS Element Plus n=838	SYNERGY n=846	*P* value
TVR	3.6%	3.8%	0.78
TLR	1.7%	2.6%	0.21
TLR, PCI	1.7%	2.0%	0.64
TLR, CABG	0.0%	0.6%	0.06
TVR non-TLR	2.2%	1.8%	0.54
ARC* Stent Thrombosis Definite/Probable	0.6%	0.4%	0.50
Definite	0.2%	0.2%	>0.99
Probable	0.4%	0.1%	0.37
Possible	0.1%	0.2%	>0.99

*Cutlip et al, *Circulation*. 2007; 115(17):2344

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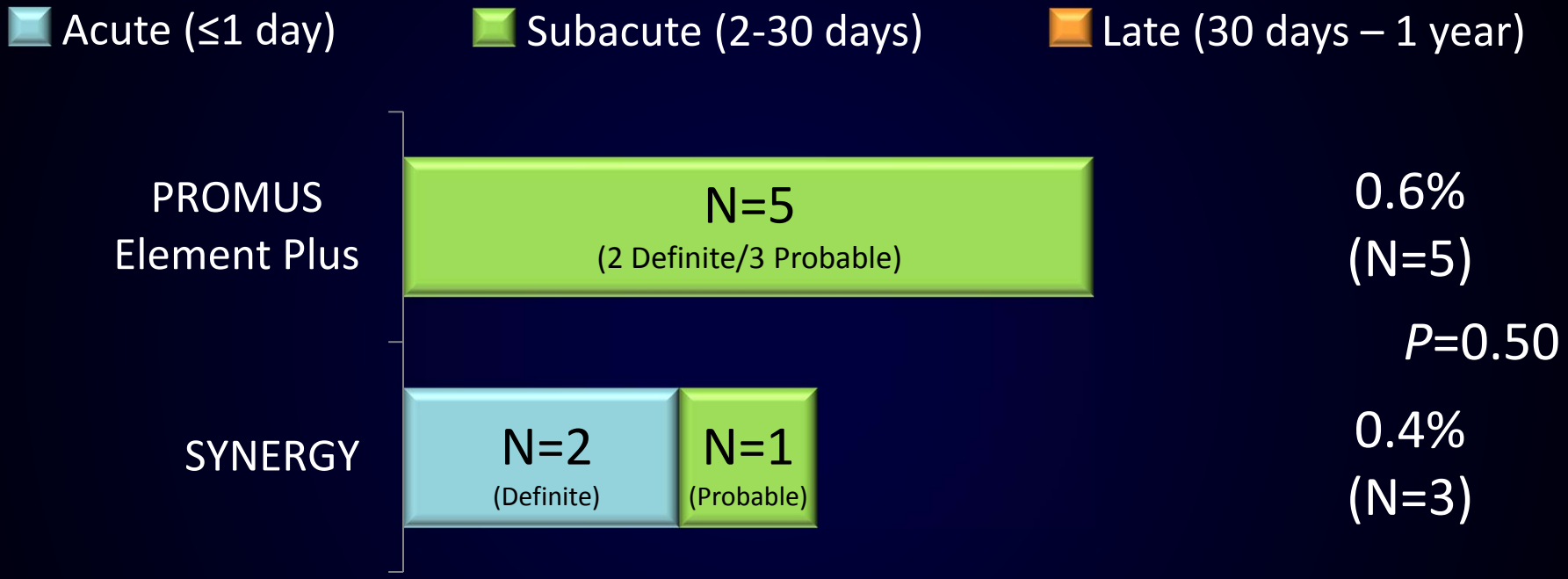
Stent Thrombosis through 12-months

Definite/Probable : ITT Population



No Definite/Probable stent thrombosis in the SYNERGY arm after Day 6

The SYNERGY™ stent is an investigational device and not for sale in the US.

Conclusions and Significance

- In this pivotal non-inferiority trial designed to support approval of the first bioresorbable polymer DES in the U.S., the SYNERGY stent proved non-inferior to the Promus Element Plus stent for TLF at 1 year.
- Procedural, angiographic and clinical outcomes were comparable between stents in a "more comers" population (>60% ACS, >25% MI, 31% diabetes, smaller vessels, longer lesions, ≥75% AHA/ACC B2/C lesion morphology).
- Despite the clinical and angiographic complexity of the study population, definite/probable stent thrombosis rates were low. Definite ST not observed beyond 24 hrs following SYNERGY.
- The longer term relative efficacy and safety of the SYNERGY stent is currently under evaluation.