



American
Heart
Association®

SCIENTIFIC 2014
SESSIONS
Chicago, Illinois

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

Dean J. Kereiakes

*The Christ Hospital Heart and Vascular Center/ The Lindner Research Center
Cincinnati, OH*

Ian T. Meredith, Stephan Windecker, R. Lee Jobe, Shamir R. Mehta, Ian J. Sarembock, Robert L. Feldman, Bernardo Stein, Christophe Dubois, Timothy Grady, Shigeru Saito, Takeshi Kimura, Thomas Christen, Dominic J. Allocco, and Keith D. Dawkins on behalf of the EVOLVE II investigators



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

IC-284205-AA NOV2014

Disclosures



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

DES Polymer Considerations

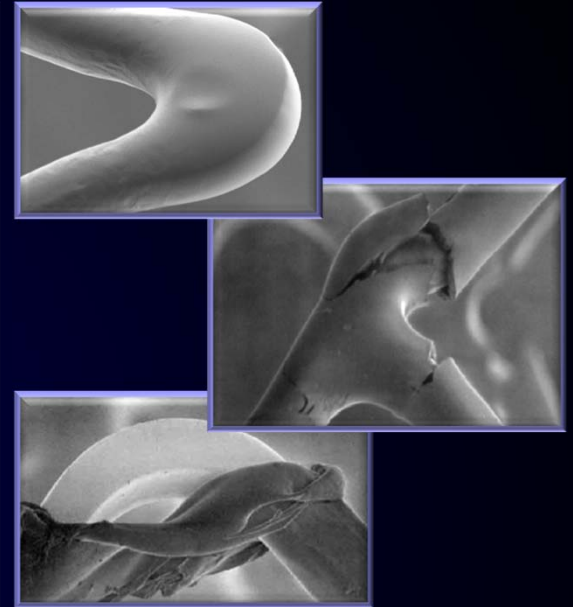


Purpose of polymer:

- 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

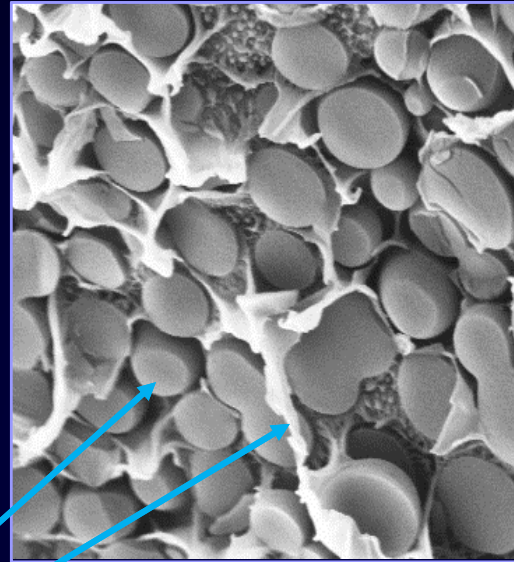
Efficacy

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

SYNERGY Stent

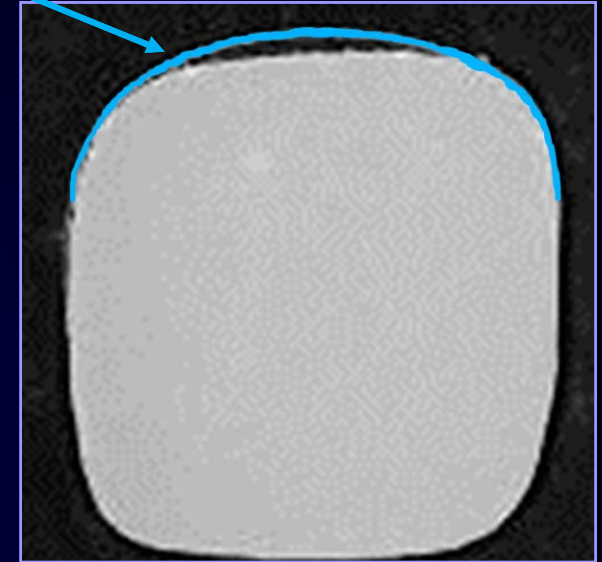


Everolimus Drug
PLGA Polymer



Drug & Polymer Coating

SEM of coating (x5000)



Abluminal (4 μ m)

Luminal

Platform

- Platinum chromium
- 74 μ m (0.0029in)

Polymer Coating

- PLGA
- Abluminal
 - 4 μ m thick
 - 85:15 ratio

Drug

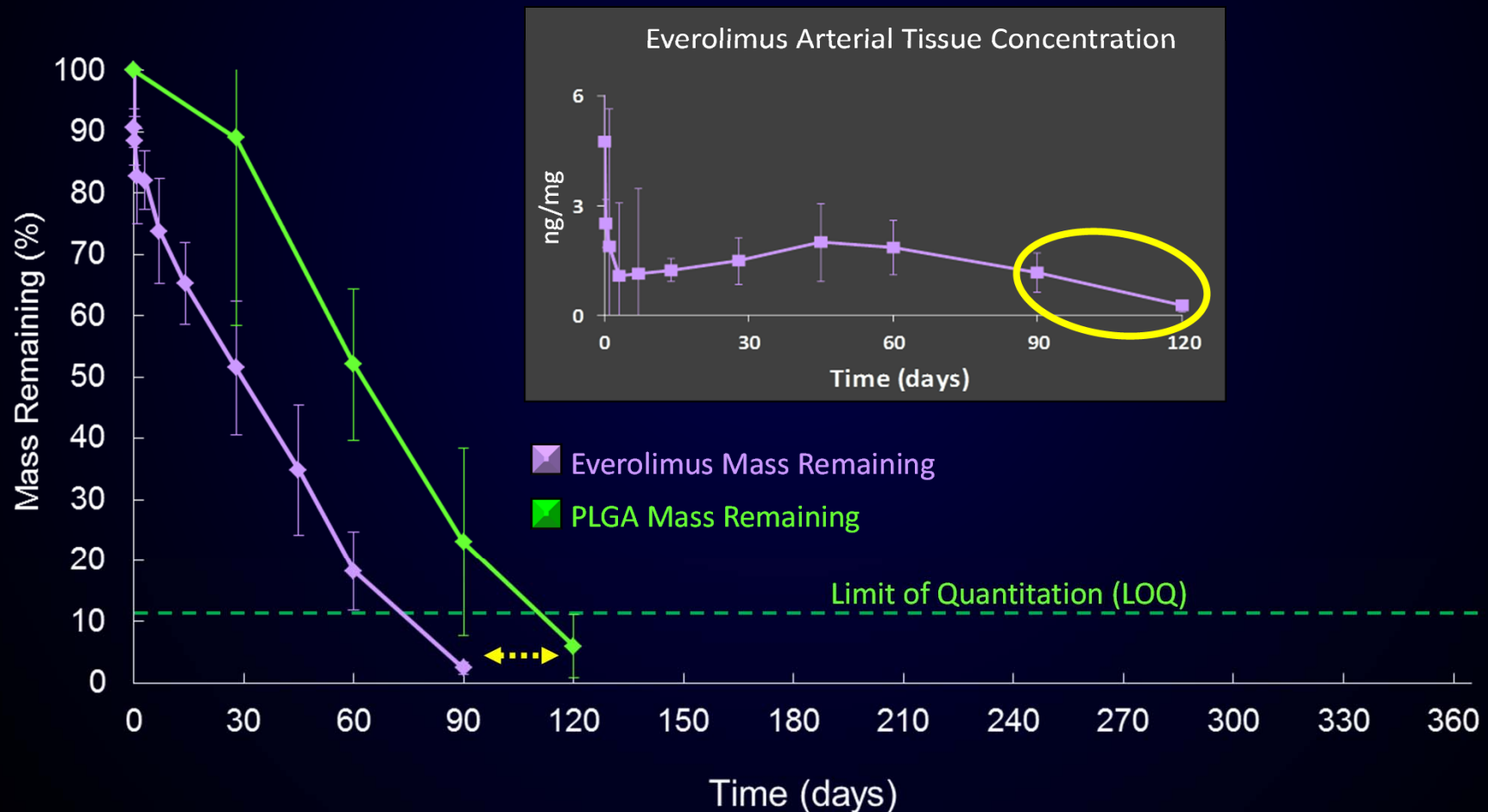
- Everolimus
- 100 μ g/cm²

SYNERGY Stent

Synchronous Drug Release & Polymer Absorption



Preclinical evaluation in porcine model

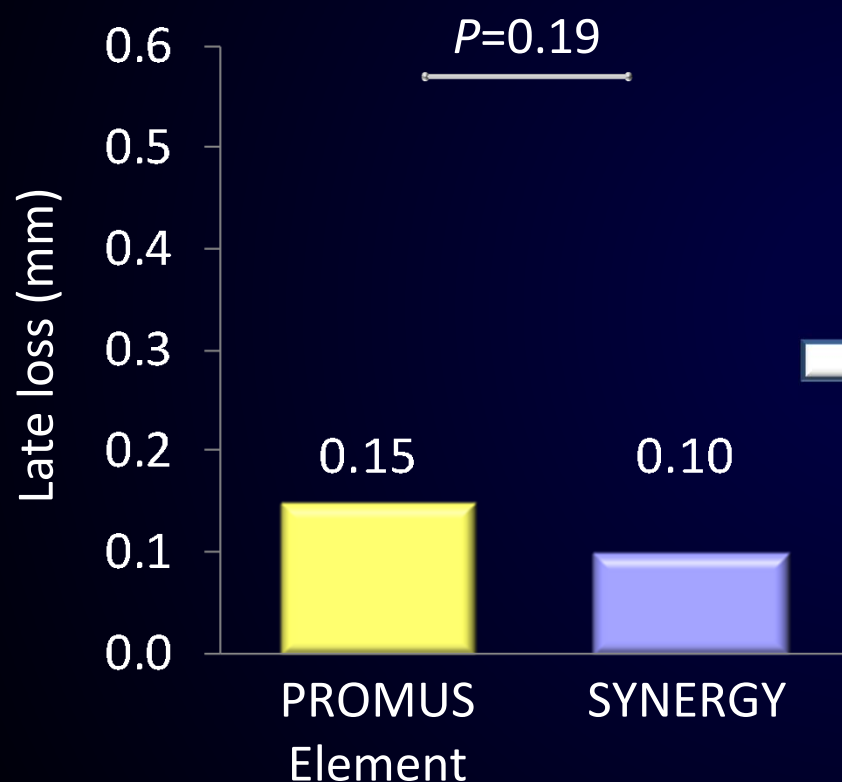


EVOLVE Trial: FHU

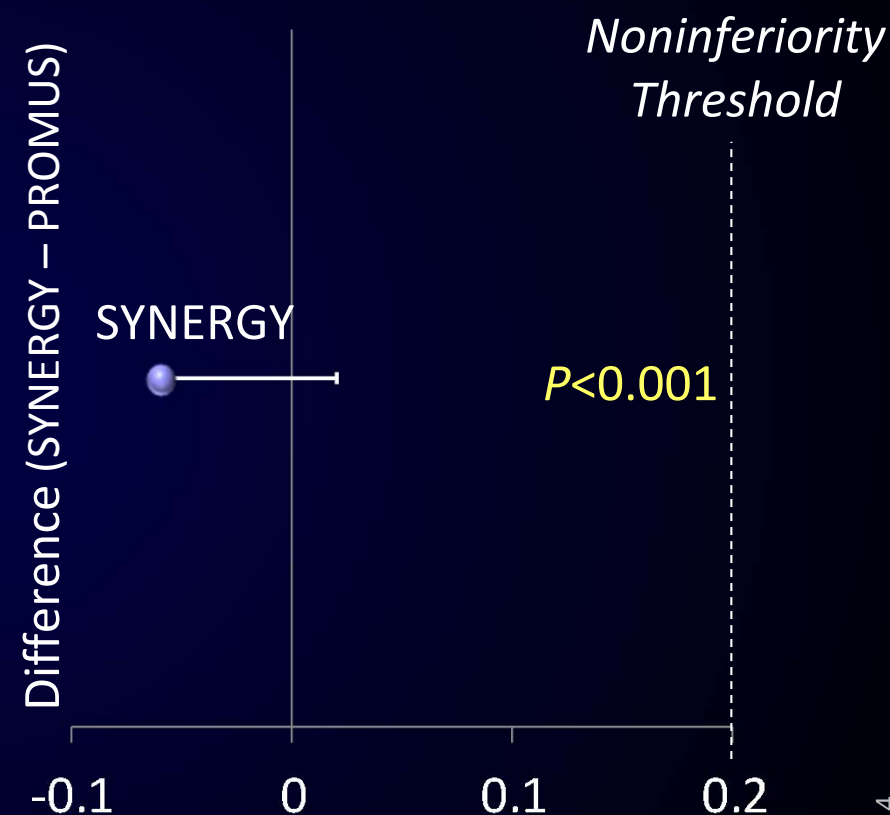


Primary Angiographic Endpoint: Late Loss at 6 Mo

Late Loss at 6 Months



Difference and 95.2% UCB

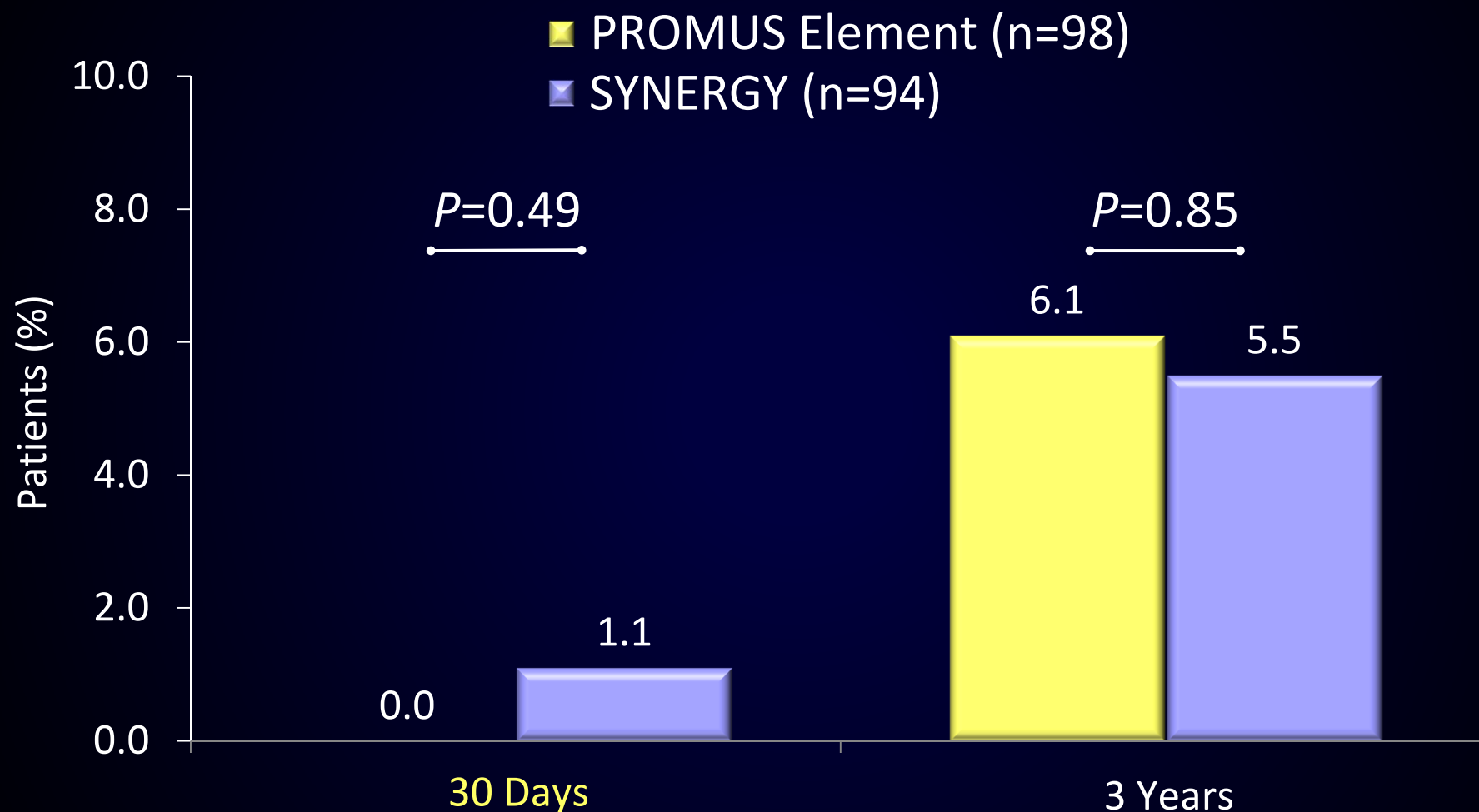


Noninferiority was proven because the upper 95.2% confidence bound of the difference in 6-month late loss is <0.20

EVOLVE Trial: FHU



Primary Clinical Endpoint: 30d Target Lesion Failure



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

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 $\geq 50 < 100$ (excluded LM disease, CTO, SVG, ISR or recent STEMI)

Randomized Cohort (RCT)

Up to 160 global sites

PROMUS Element Plus
N=842

SYNERGY
N=842

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

PK Substudy

SYNERGY
N=21

Diabetes Substudy

SYNERGY
N=203

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

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

Aug 29, 2013

Dec 5, 2013

**EVOLVE II
Enrollment
Commenced**

**RCT Enrollment
Complete**

**PK & DM
Enrollment
Complete**

16 Countries / 125 Centers



EVOLVE II Centers



Top 30 Enrolling Centers

 R. Lee Jobe (71) <i>Wake Medical Center</i>	 Annapoorna Kini (27) <i>Mount Sinai Medical Center</i>	 Mark Dorogy (23) <i>Medical Center of Central Georgia</i>
 Shamir Mehta (64) <i>Hamilton General Hospital</i>	 Luc Janssens (27) <i>Imelda Ziekenhuis</i>	 Barry Bertolet (22) <i>North Mississippi Medical Center</i>
 Ian Sarembock (63) <i>Lindner Center for Research and Education at Christ Hospital</i>	 Michael Foster (25) <i>Sisters of Charity Providence Hospital</i>	 Louis Cannon (21) <i>Northern Michigan Hospital</i>
 Robert Feldman (47) <i>Mediquest Research at Munroe Regional Medical Center</i>	 Robert Stoler (24) <i>Baylor Heart & Vascular Hospital</i>	 Juhani Airaksinen (21) <i>Turku University Hospital</i>
 Bernardo Stein (44) <i>Morton Plant Mease Healthcare System</i>	 Thomas Stuckey (24) <i>Moses H. Cone Memorial Hospital</i>	 Craig Siegel (21) <i>St. David's Round Rock Medical Center</i>
 Christophe Dubois (39) <i>UZ Gasthuisberg</i>	 Wayne Batchelor (24) <i>Tallahassee Memorial Hospital</i>	 Akil Loli (20) <i>Banner Good Samaritan Regional Medical Center</i>
 Timothy Grady (37) <i>Aspirus Heart and Vascular Institute</i>	 Josep Rodes-Cabau (24) <i>University of Laval</i>	 David Mego (20) <i>Arkansas Heart Hospital</i>
 Shigeru Saito (30) <i>Shonan Kamakura General Hospital</i>	 Tommy Lee (24) <i>Bakersfield Memorial Hospital</i>	 Kenji Ando (20) <i>Kokura Memorial Hospital</i>
 Ameer Kabour (29) <i>Mercy St. Vincent Medical Center</i>	 Arthur Reitman (24) <i>Wellstar Kennestone Hospital</i>	 Toshiya Muramatsu (20) <i>Saiseikai Yokohama-City Eastern Hospital</i>
 Alain Bouchard (27) <i>Baptist Medical Center Princeton</i>	 Andrejs Erglis (23) <i>P. Stradins University Hospital</i>	 Francis Stammen (20) <i>H.-Hartziekenhuis Roeselare-Menen</i>

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 > 99 th percentile of the URL + evidence of myocardial ischemia. **Peri-PCI MI**: ≥ 1 of the following: i) **CK-MB > 3 X 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 ($1-\beta$) = approximately **0.89**

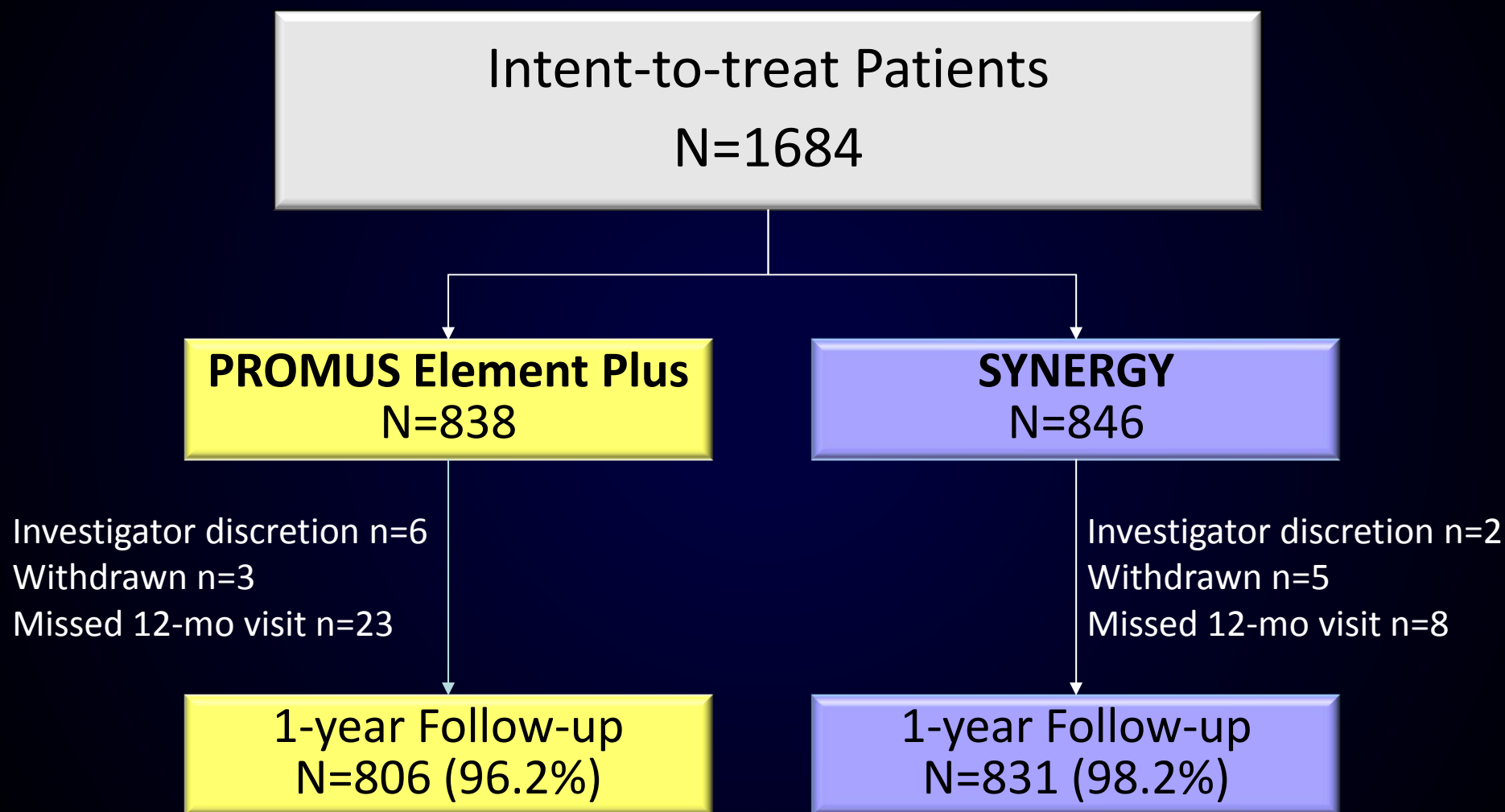
Expected rate of attrition = **5%**

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**

EVOLVE II Patient Disposition



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

Baseline Lesion Characteristics (QCA)



Per Patient* Per Lesion [†]		PROMUS Element Plus <i>n=1043 lesions</i> <i>n=838 patients</i>	SYNERGY <i>n=1059 lesions</i> <i>n=846 patients</i>	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

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

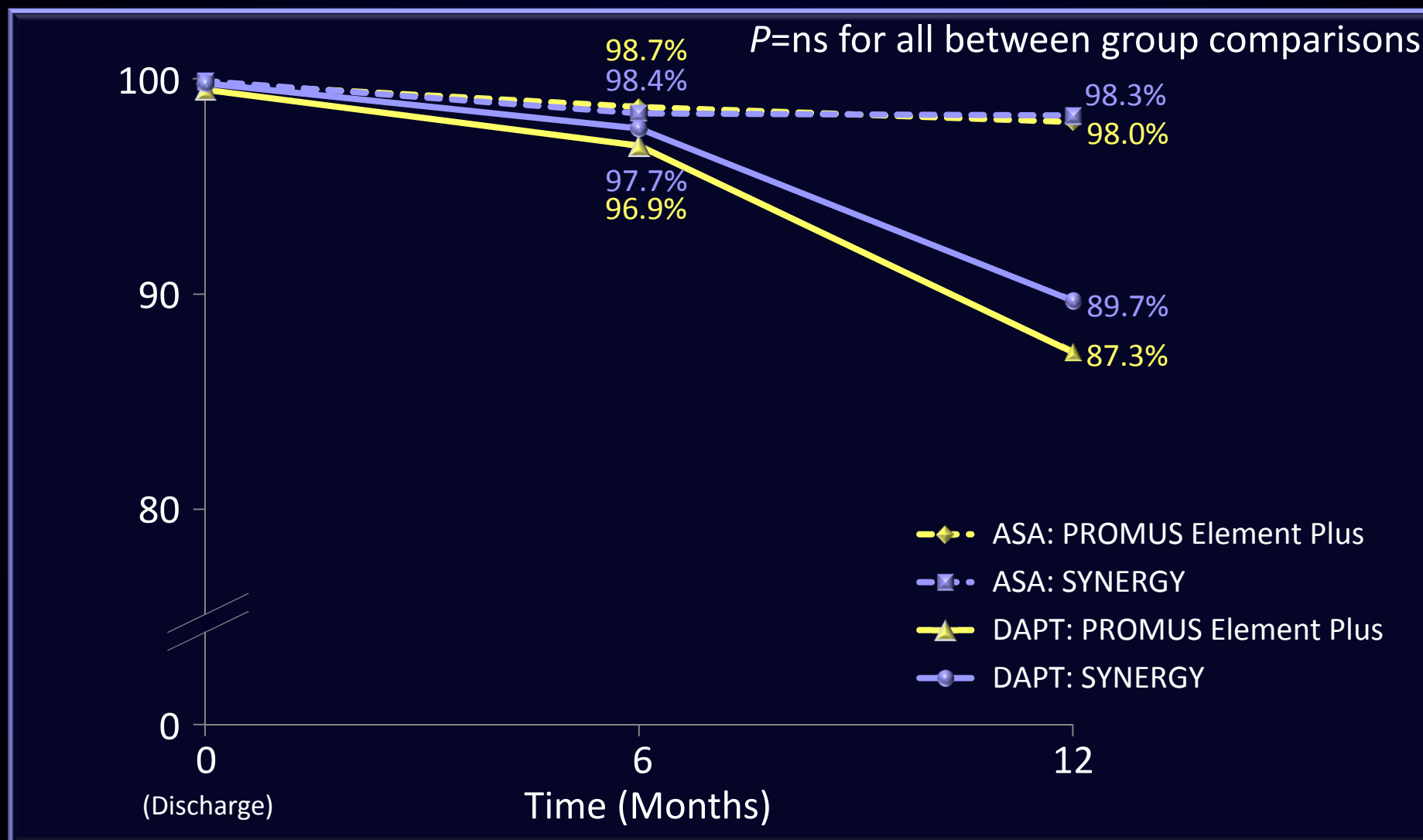
[§]LSD occurred in a PROMUS Element Plus stent used in a SYNERGY patient

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

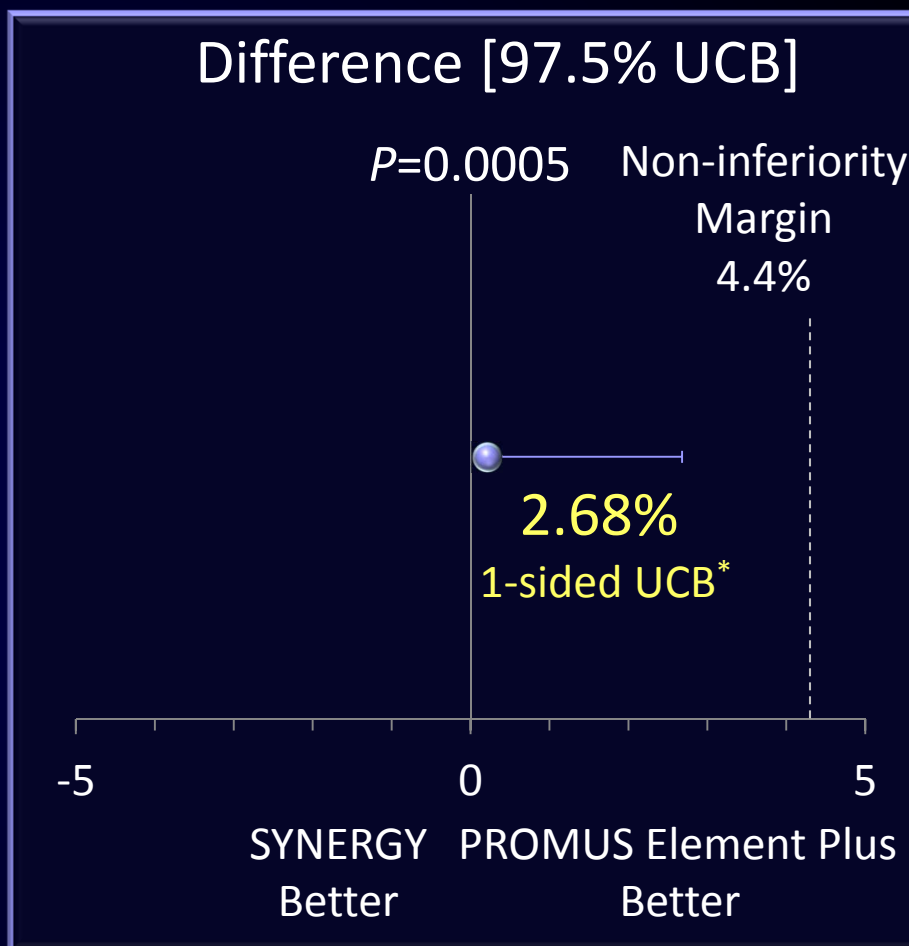
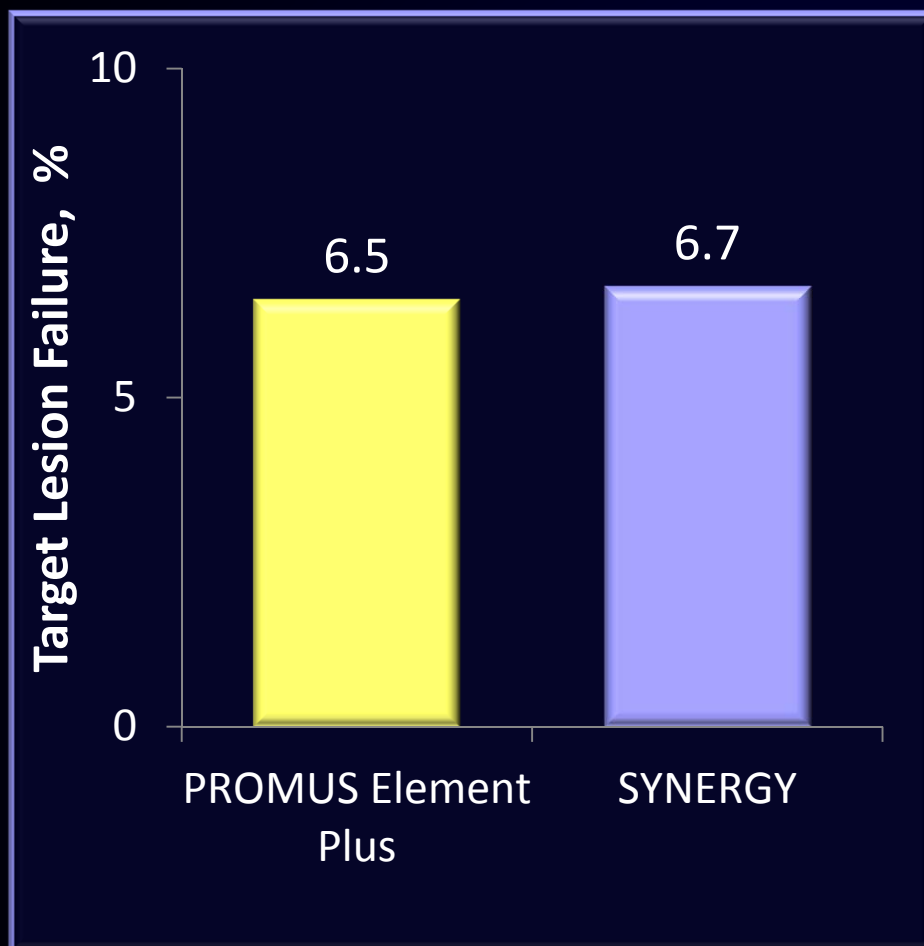
Antiplatelet Medication Usage*



*Per protocol, patients were treated with one of the following P2Y₁₂ 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

EVOLVE II Primary Endpoint:

12-month TLF : ITT Population

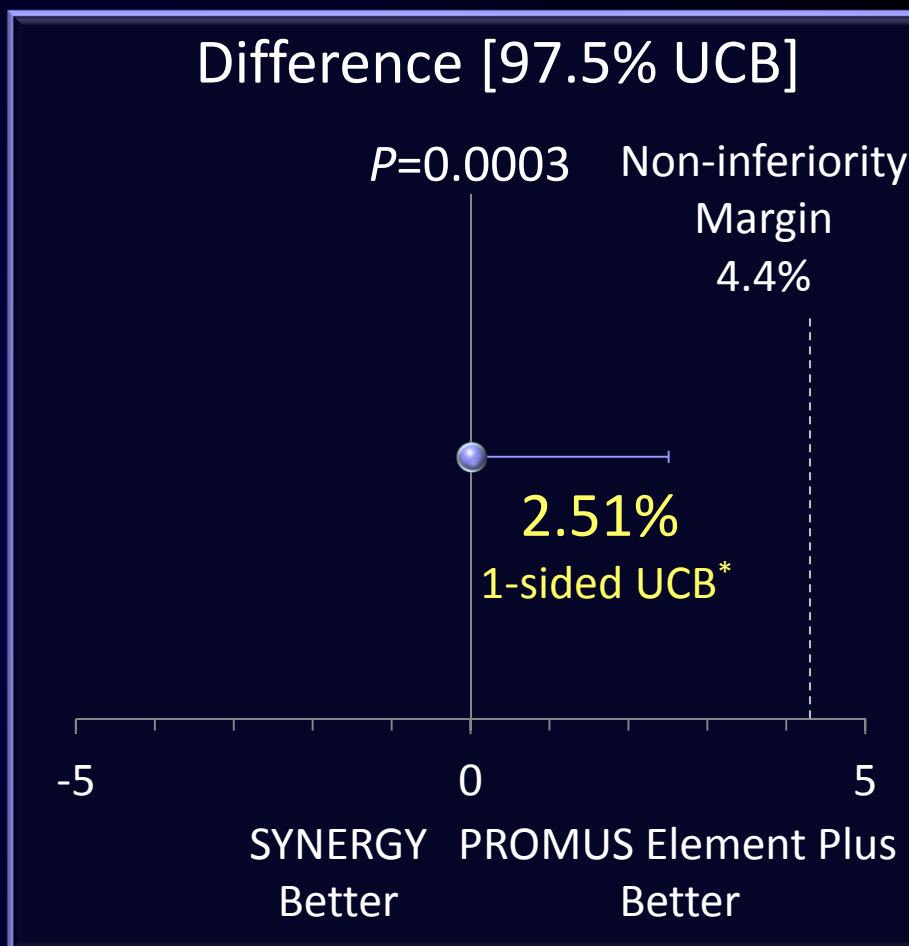
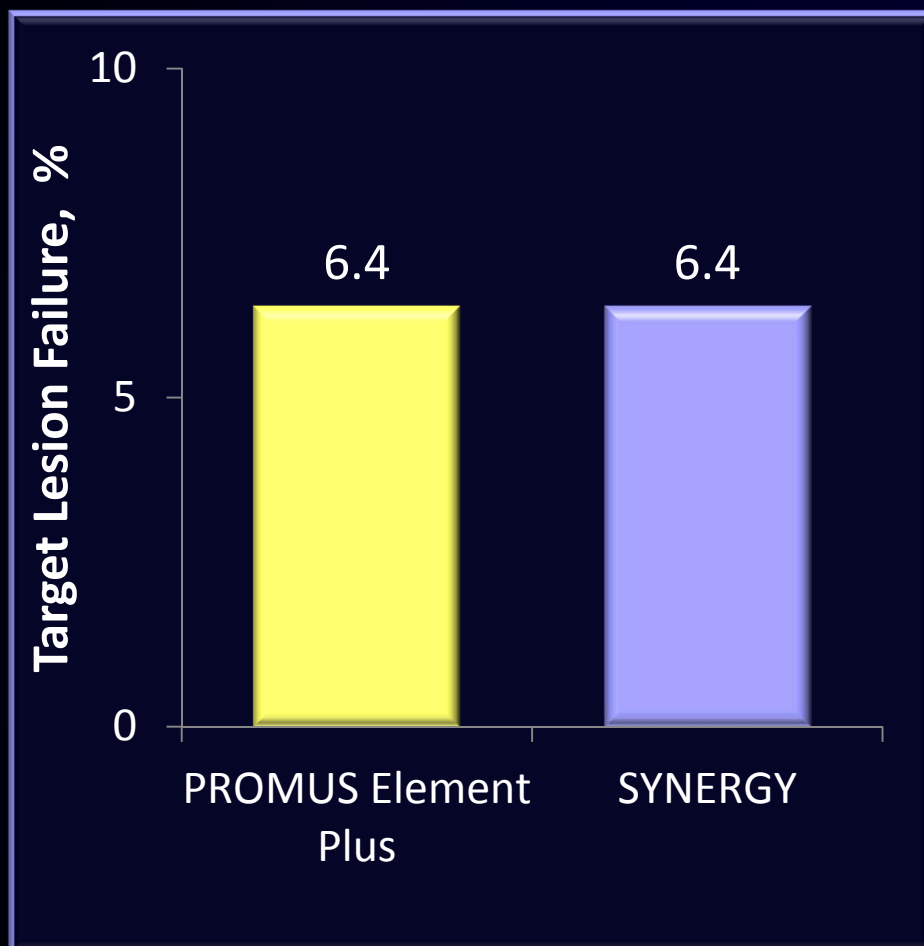


Noninferiority is proven because the one-sided upper 97.5% confidence bound for the difference in 12-month TLF is <4.4%

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

EVOLVE II Primary Endpoint:

12-month TLF : Per Protocol

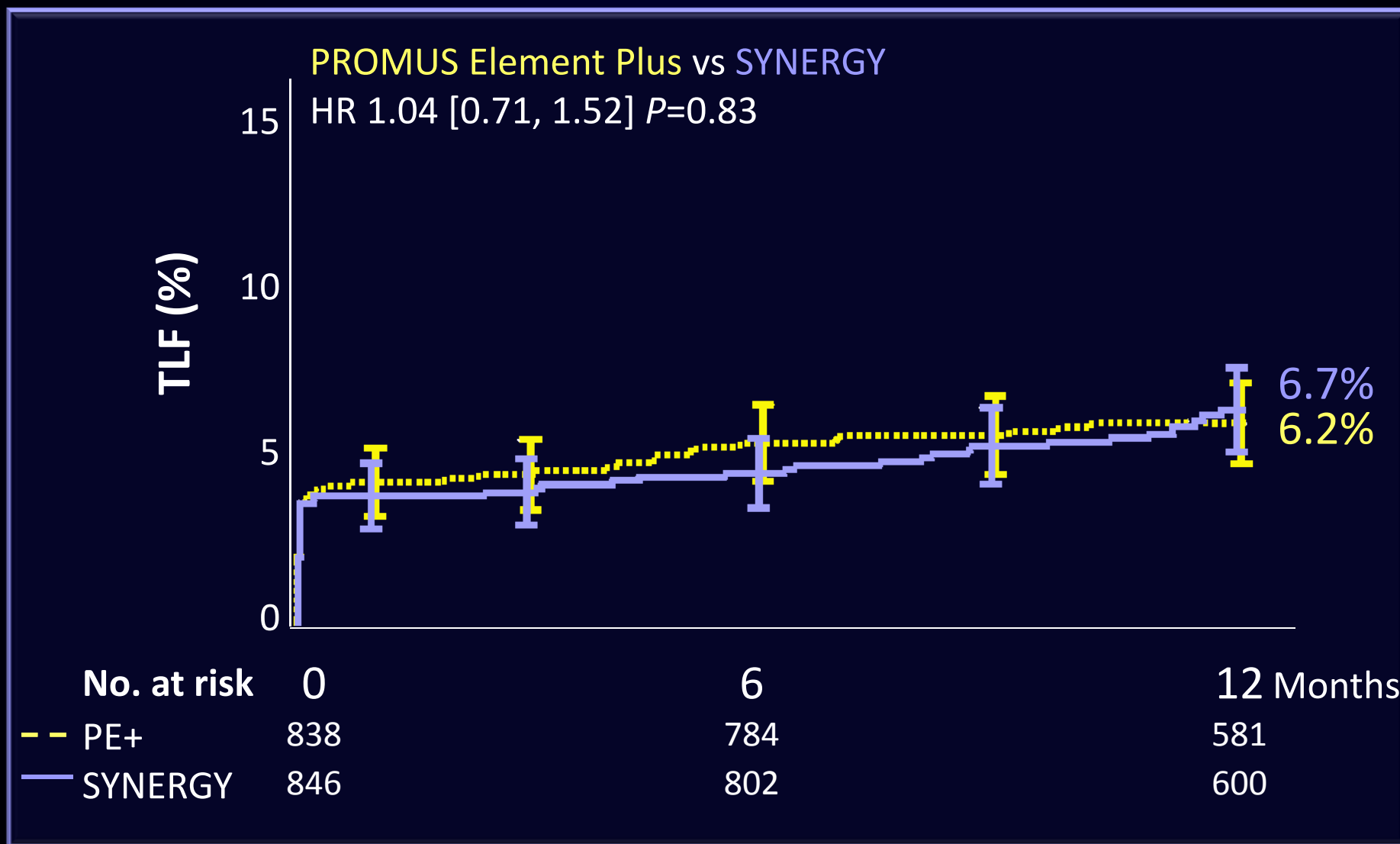


Noninferiority is proven because the one-sided upper 97.5% confidence bound for the difference in 12-month TLF is <4.4%

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

EVOLVE II Primary Endpoint:

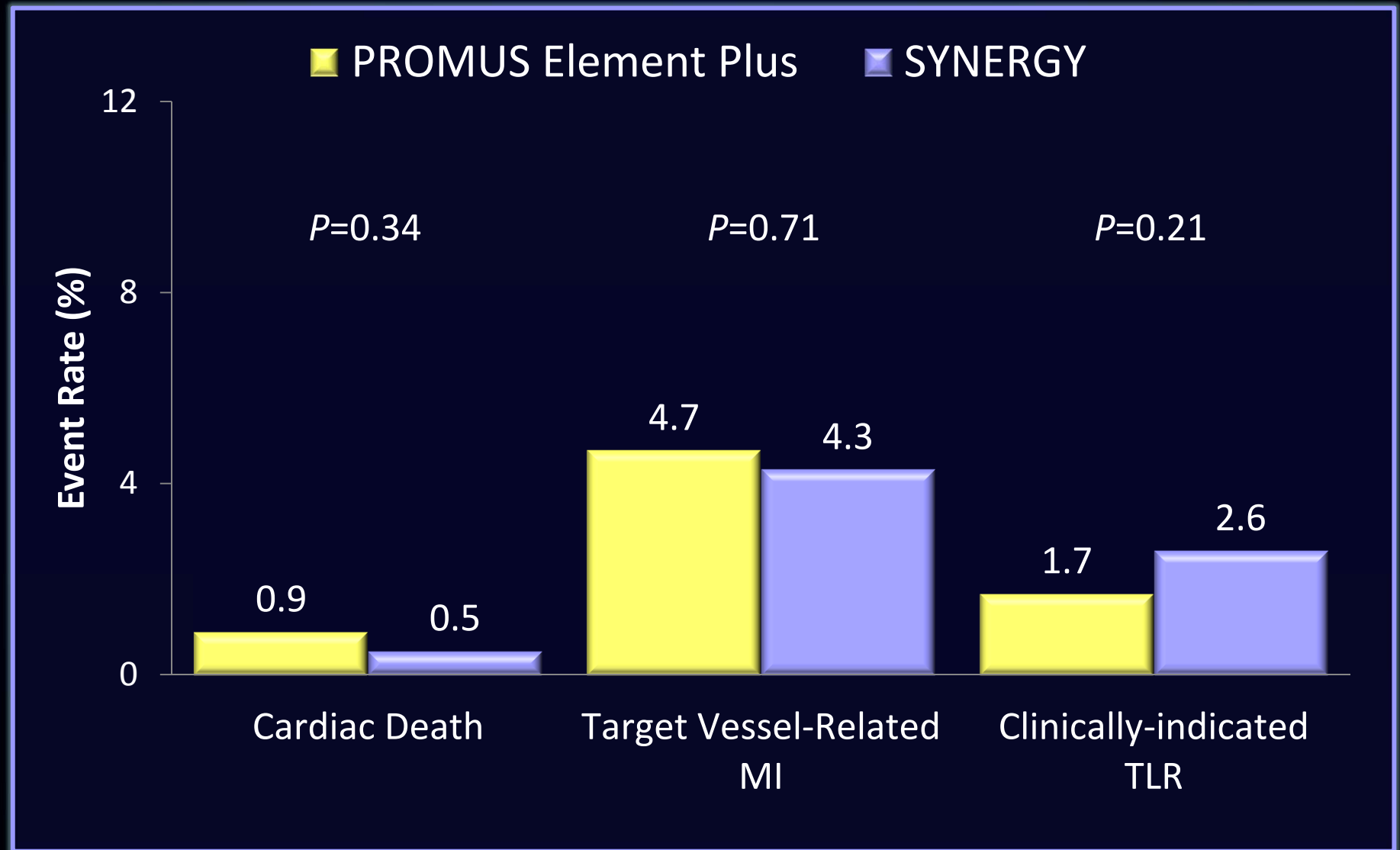
12-month TLF : ITT



ITT; KM Event Rate; log-rank P values

Components of TLF

ITT Population



*Per protocol spontaneous MI is defined as rise and/or fall of cardiac biomarkers with ≥ 1 value >99 th 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

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

Stent Thrombosis through 12-months

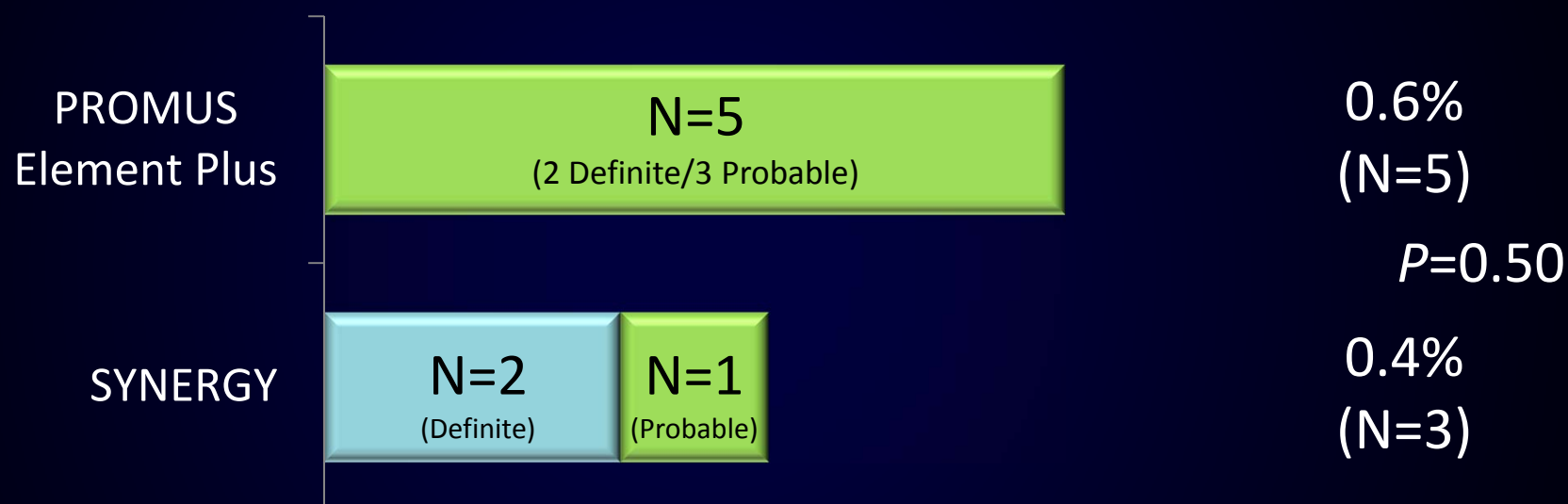
Definite/Probable : ITT Population



■ Acute (≤ 1 day)

■ Subacute (2-30 days)

■ Late (30 days – 1 year)



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

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, $\geq 75\%$ 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.