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

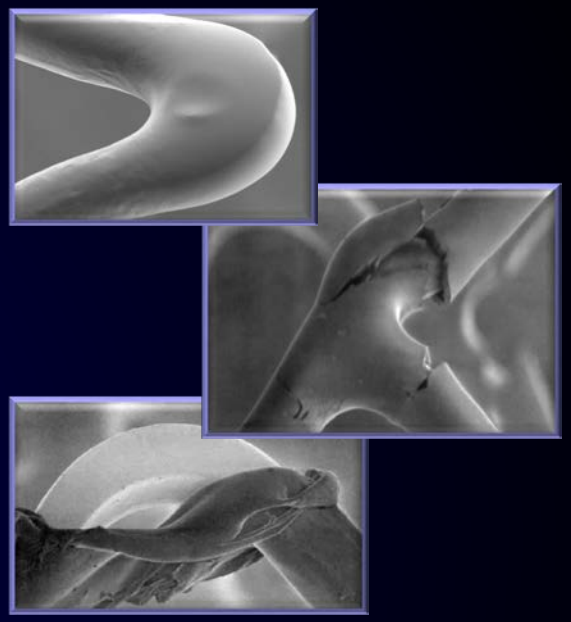
EVOLVE II SYNERGY

***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**

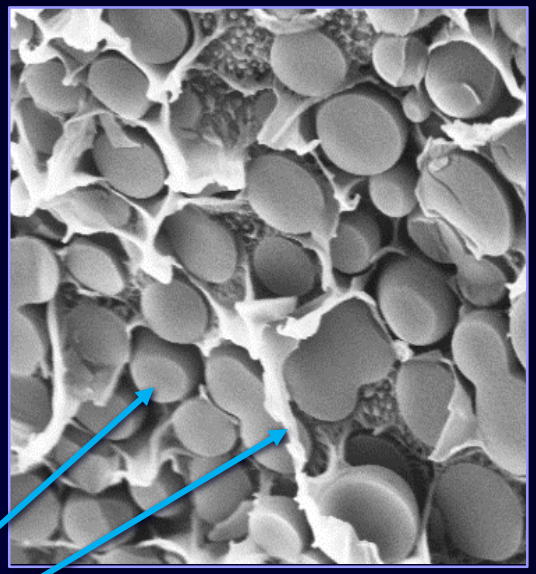
- Chronic inflammation with neoatherosclerosis
- Constant irritant may lead to late restenosis
- Hypersensitivity

# SYNERGY Stent

EVOLVE II SYNERGY

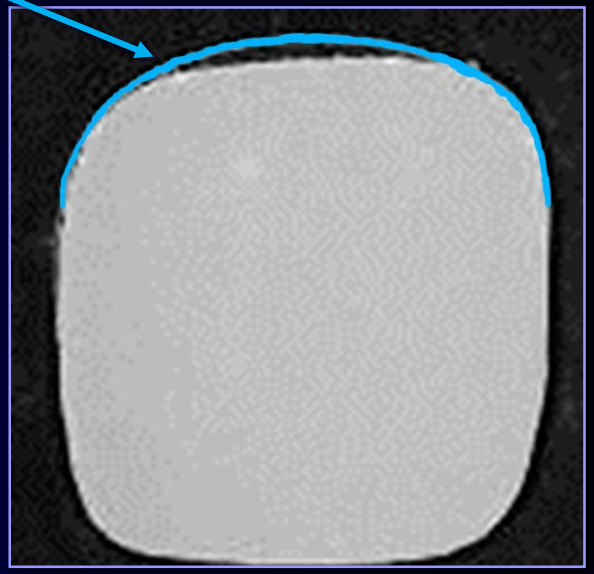
Everolimus Drug
PLGA Polymer

Drug & Polymer Coating



SEM of coating (x5000)

Abluminal (4µm)



Luminal

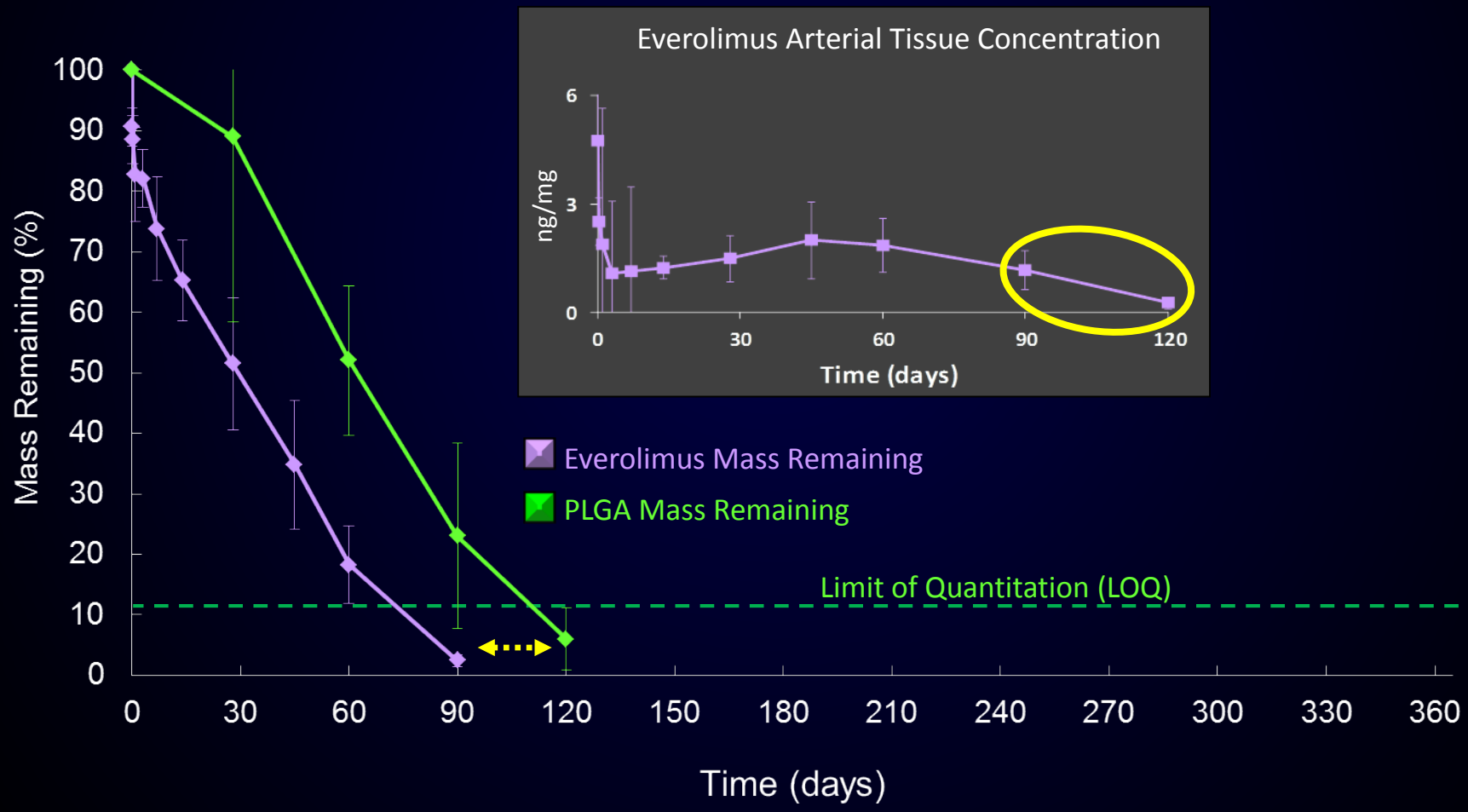
| Platform | Polymer Coating | Drug |
|---|---|---|
| Platinum chromium<br>• 74 µm (0.0029in) | PLGA<br>• Abluminal<br>• 4 µm thick<br>• 85:15 ratio | Everolimus<br>• 100 µg/cm$^2$ |

# SYNERGY Stent

## Synchronous Drug Release & Polymer Absorption

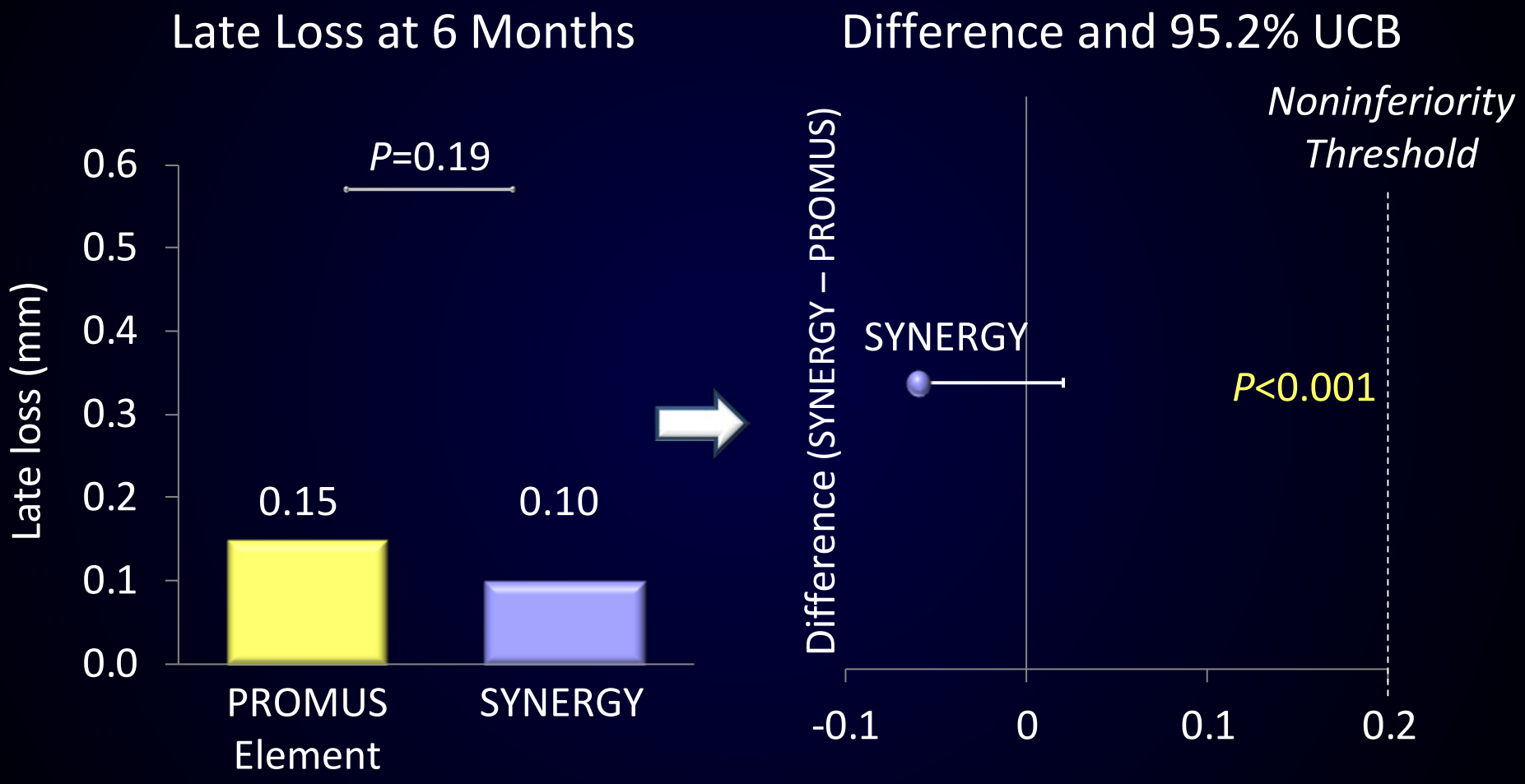
EVOLVE II SYNERGY

### Preclinical evaluation in porcine model



# EVOLVE Trial: FHU

## Primary Angiographic Endpoint: Late Loss at 6 Mo

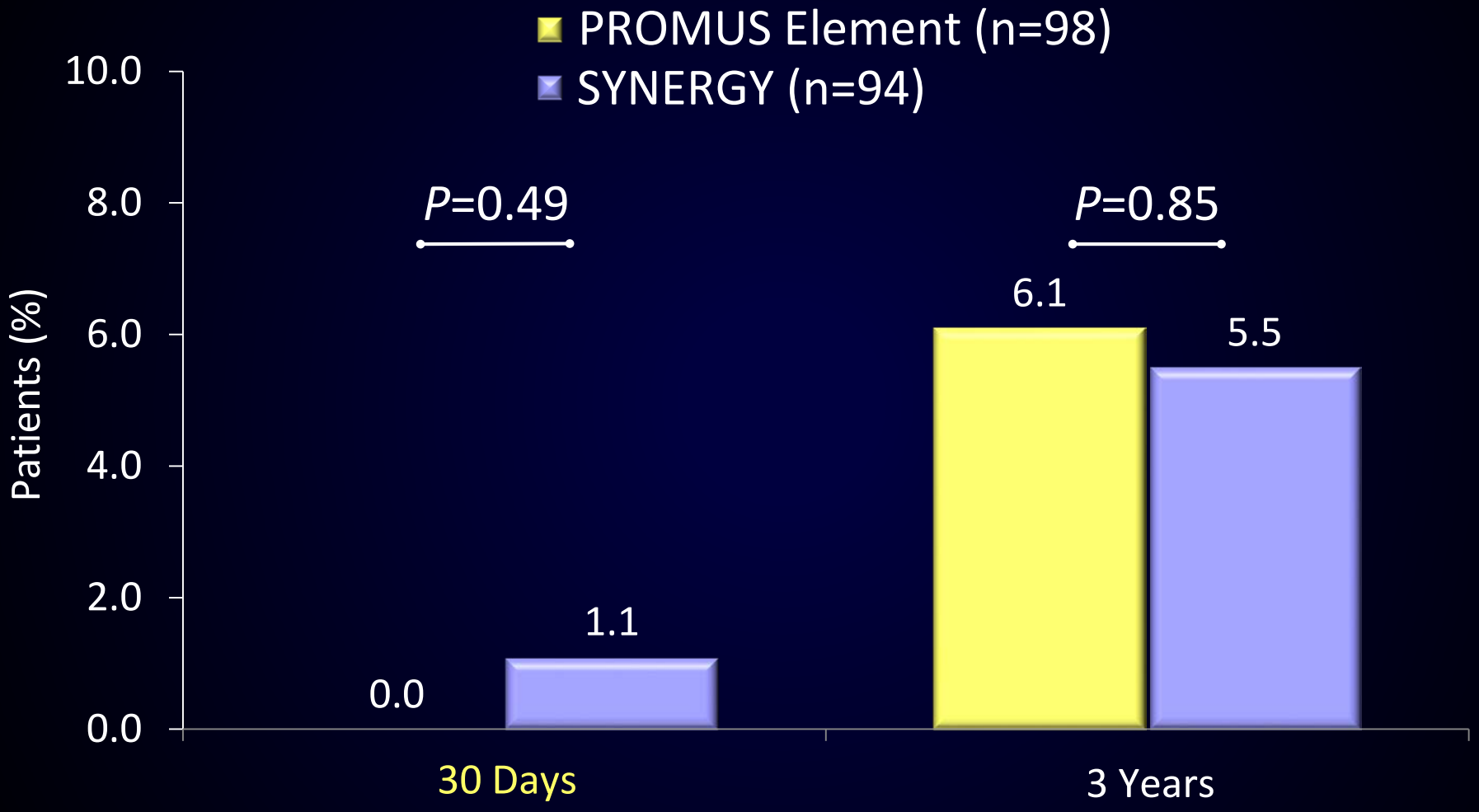



Noninferiority was proven because the upper 95.2% confidence bound of the difference in 6-month late loss is <0.20

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

# 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

# EVOLVE II Pivotal Trial Design

EVOLVE II SYNERGY

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)**

**Up to 160 global sites**

**PROMUS Element Plus N=842**

**SYNERGY N=842**

**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**

# EVOLVE II Trial Support

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

EVOLVE II SYNERGY

- 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

EVOLVE II SYNERGY

## 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

EVOLVE II SYNERGY

*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 ($\alpha$) = 0.025 (1-sided)

Power (1–$\beta$) = approximately **0.89**

Expected rate of attrition = **5%**

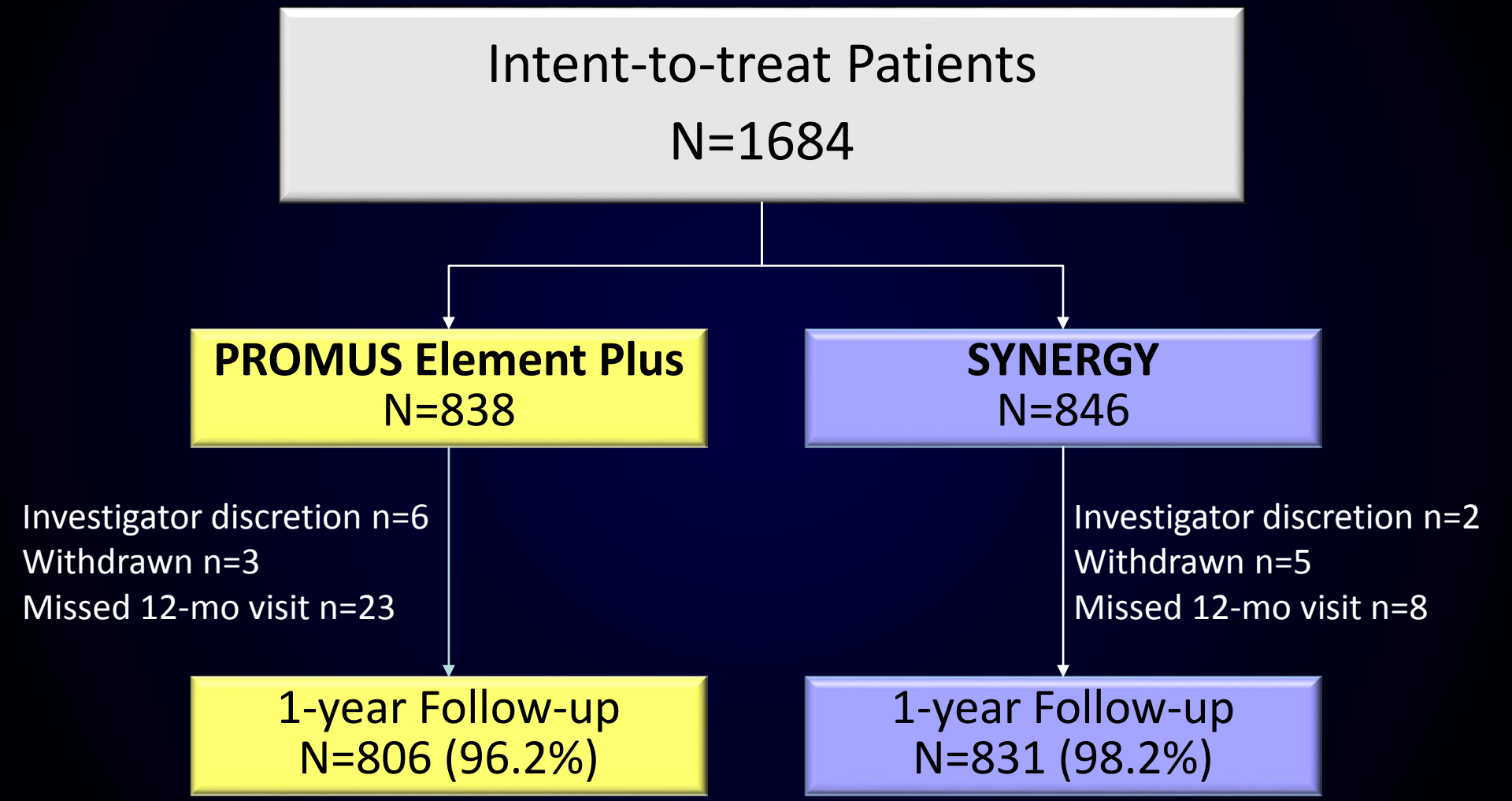
N = **1684 patients** (842 per group at 1:1 ratio)

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

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

# 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

# Procedural Characteristics

EVOLVE II SYNERGY

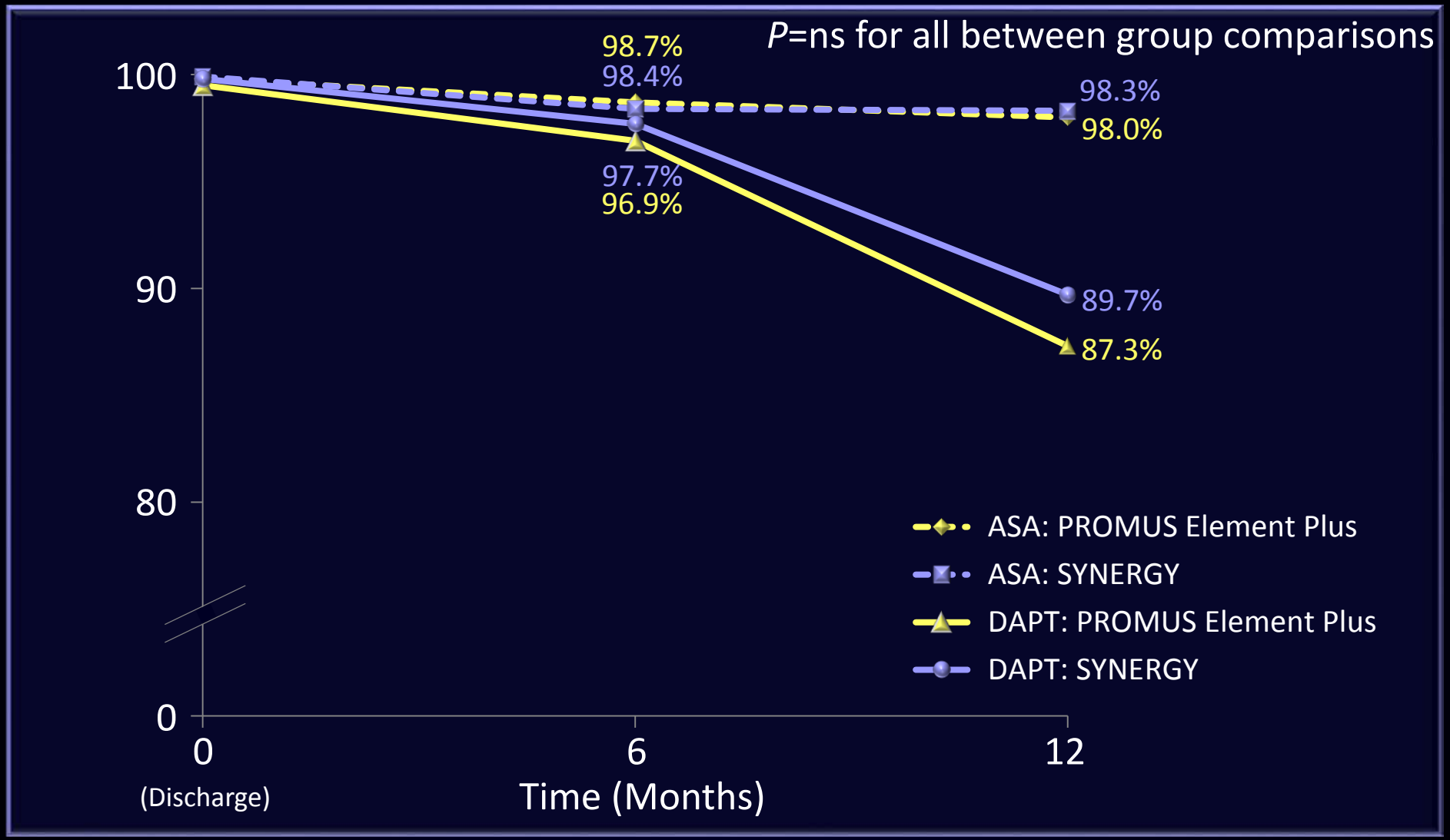
| Per Patient* Per Lesion† Per Stent‡ | PROMUS Element Plus n=1043 lesions n=838 patients n=1079 stents | SYNERGY n=1059 lesions n=846 patients N=1011 | *P* value |
|---|---|---|---|
| Technical success† | 96.9% | 98.3% | **0.04** |
| Clinical procedural success* | 94.3% | 94.9% | 0.56 |
| Stents per 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 |

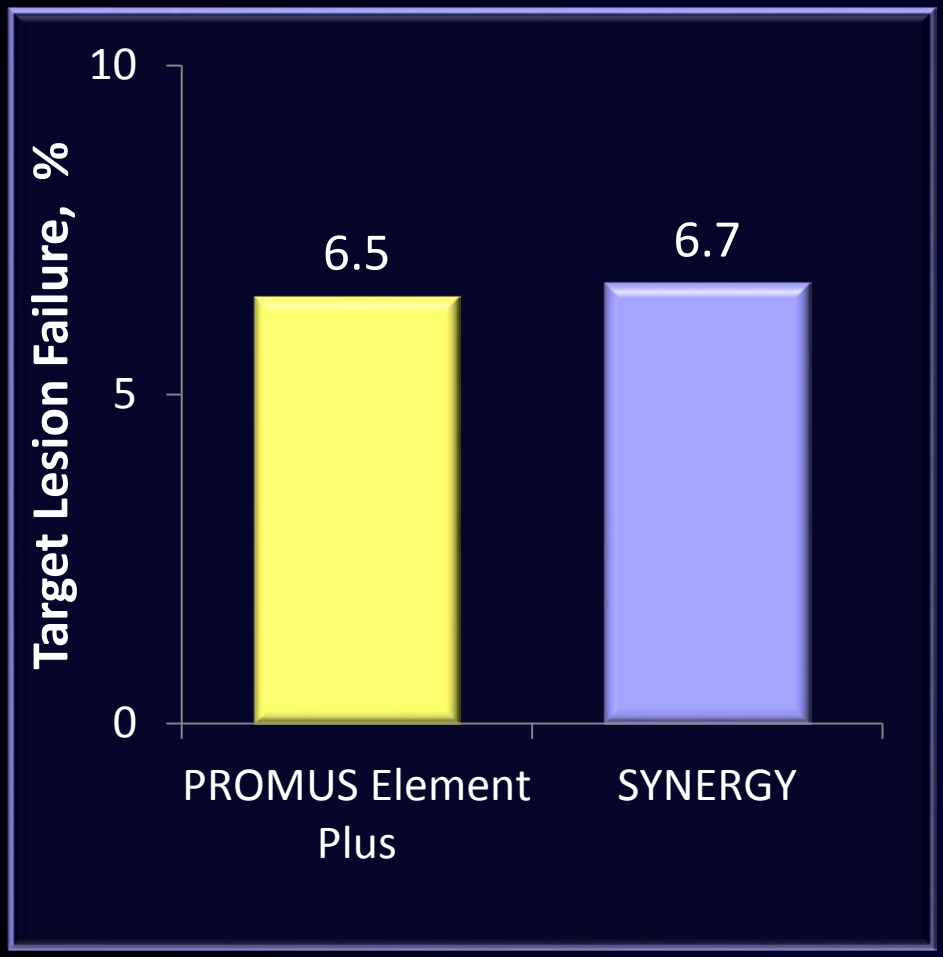
# Antiplatelet Medication Usage*

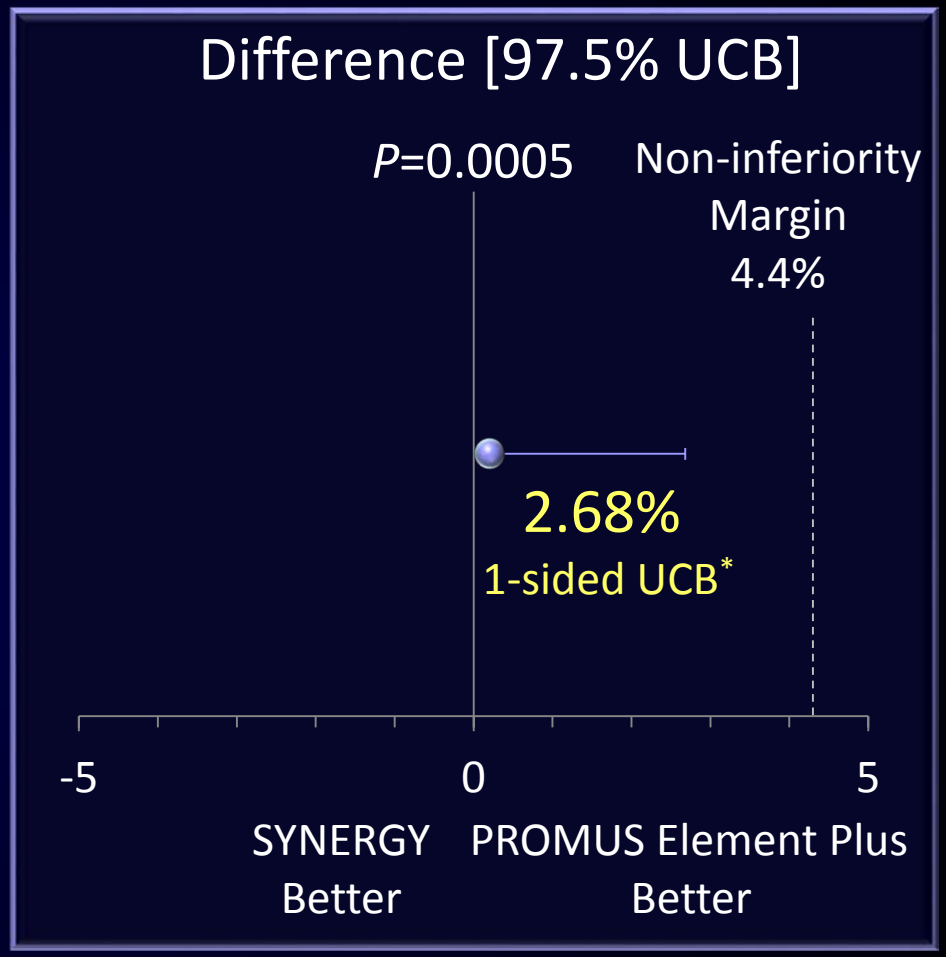



*Per protocol, patients were treated with one of the following $P2Y_{12}$ inhibitors (clopidogrel, ticlopidine, prasugrel, or ticagrelor) for at least 6 months following the index procedure. Intent-to-treat. ASA=acetylsalicylic acid; DAPT=dual antiplatelet therapy

# EVOLVE II Primary Endpoint:

## 12-month TLF : ITT Population



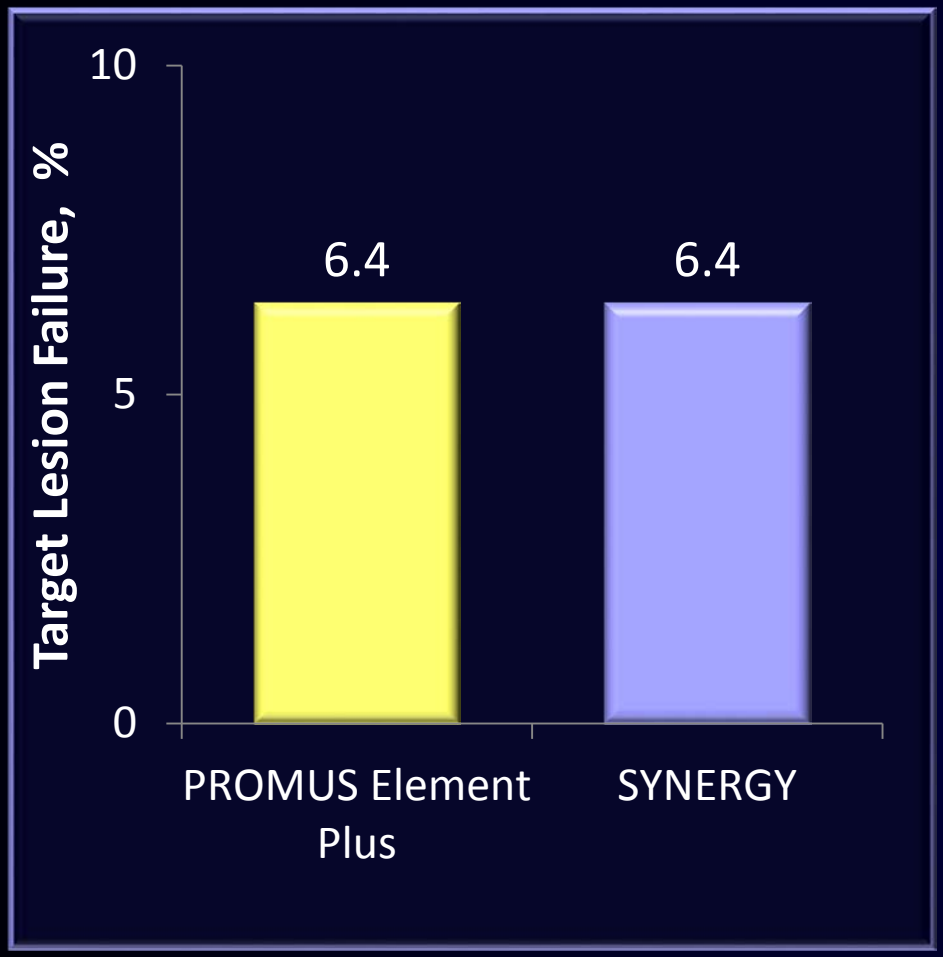



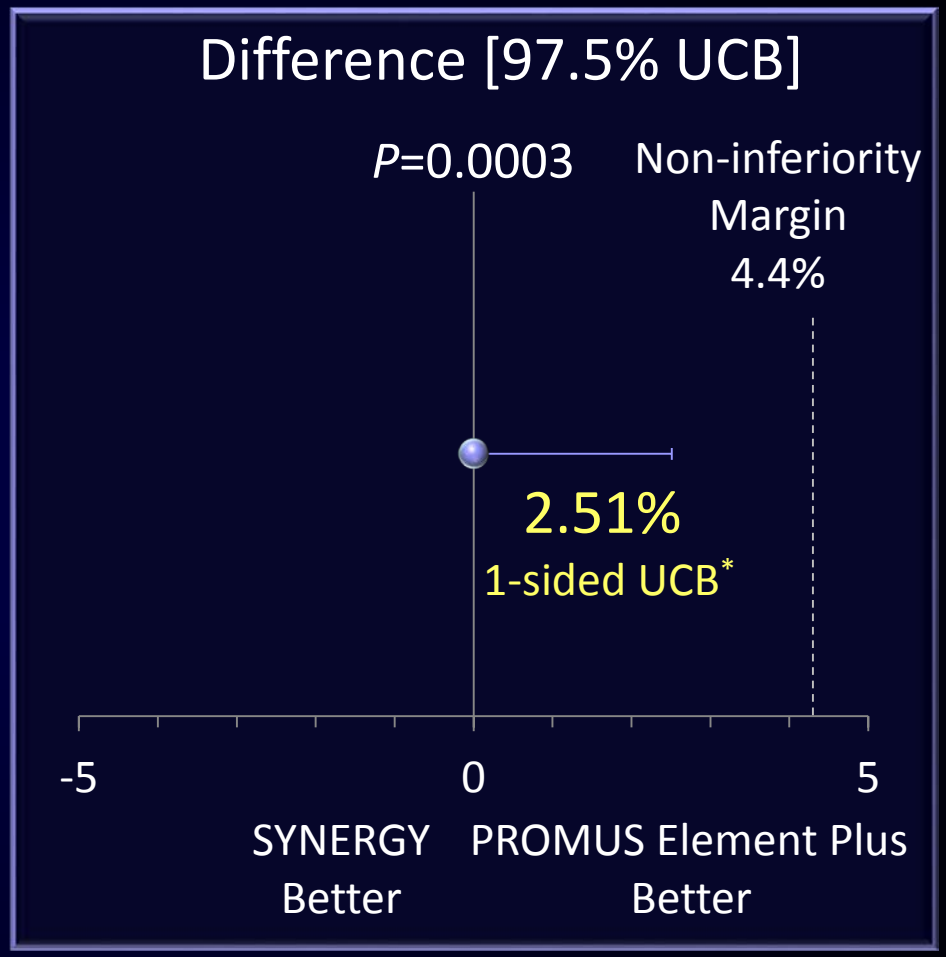

***Noninferiority is proven because the one-sided upper 97.5% confidence bound for the difference in 12-month TLF is <4.4%***

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

# EVOLVE II Primary Endpoint:

## 12-month TLF : Per Protocol



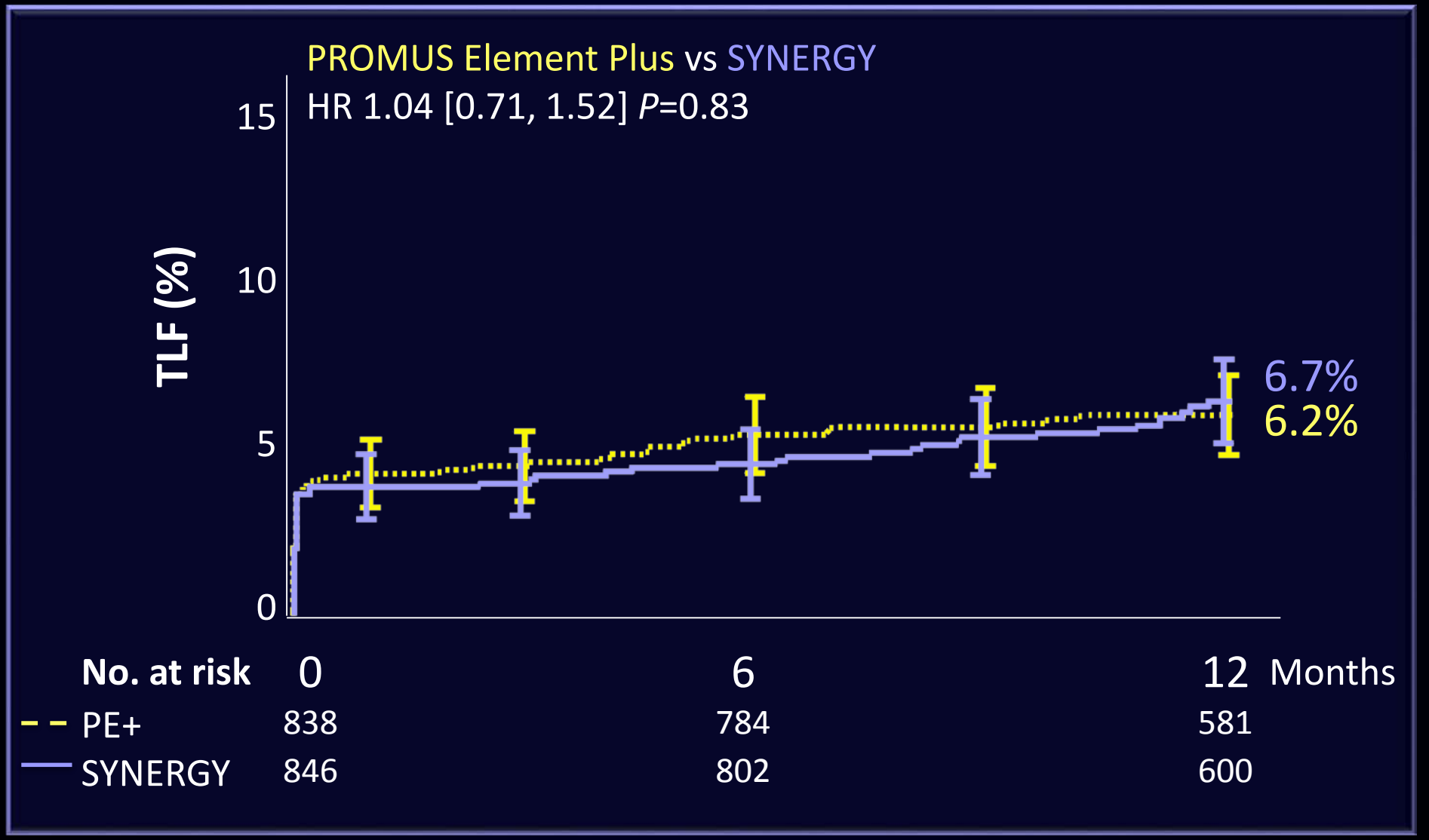




***Noninferiority is proven because the one-sided upper 97.5% confidence bound for the difference in 12-month TLF is <4.4%***

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

# EVOLVE II Primary Endpoint:

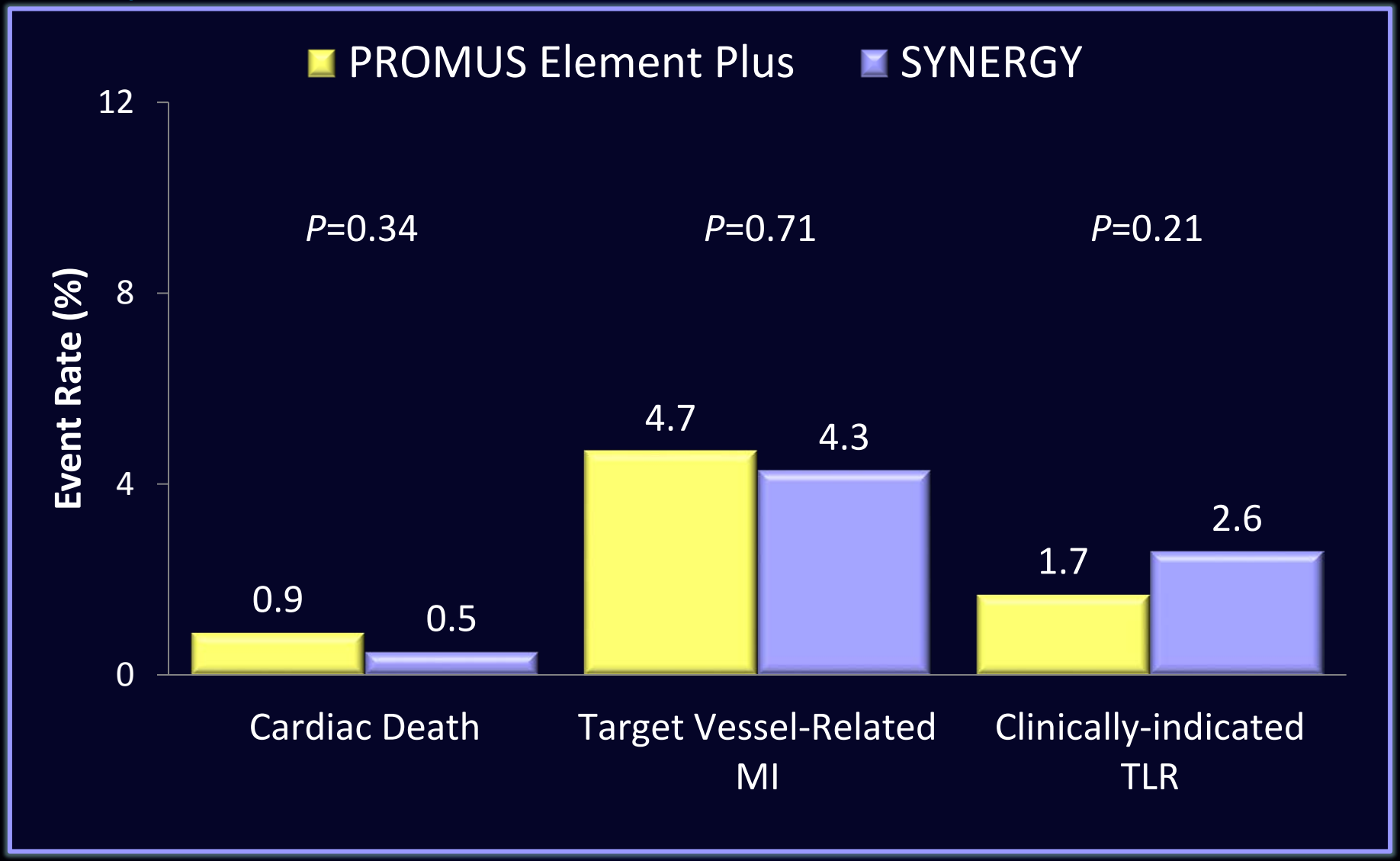
## 12-month TLF : ITT




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 >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

# Revascularization and Stent Thrombosis at 12 months

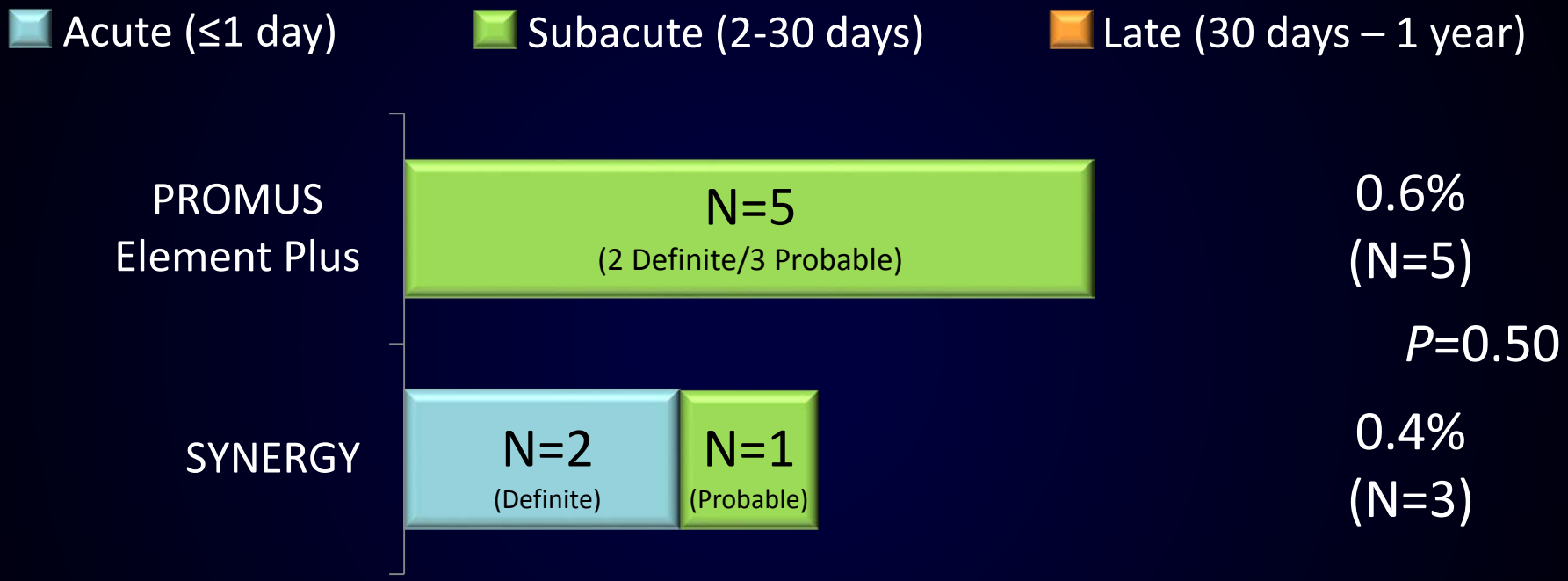
## ITT Population

| | 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




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

# Conclusions and Significance

EVOLVE II SYNERGY

- 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.