Primary Clinical Outcomes of the EVOLVE II Diabetes Substudy Evaluating a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent in Diabetic Patients

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Session: PCI with DES: how to further improve outcomes?
Date: Tuesday, 19th May, 2015
Session Time: 12:00-13:30
Location: Room 343
Presentation Time: 13:05-13:12

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Potential conflicts of interest

Speaker's name: Stephan Windecker

Honorarium:

Astra Zeneca, Bayer, Eli Lilly, Abbott, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic

Institutional grant/research support:

Abbott, Biosensors, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, St Jude

Introduction: Bioabsorbable polymer

- Durable polymer coatings on drug-eluting stents have been associated with chronic inflammation and impaired healing.

Potential advantages of bioabsorbable polymer stents:

- Reduced polymer load
- Short-term polymer exposure

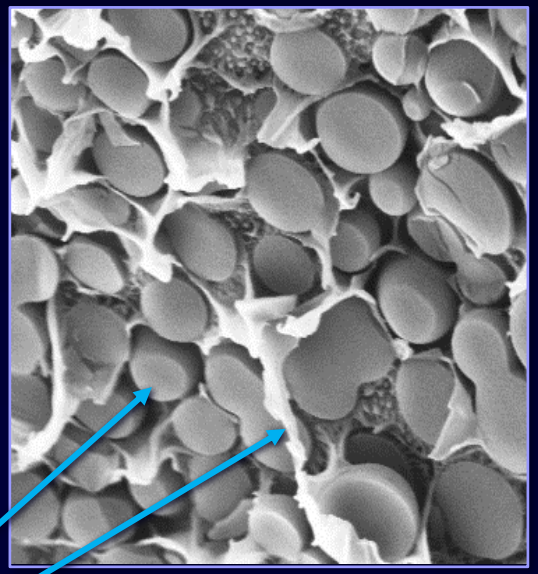
may

- Decrease risk of late events including ST and TLR
- Reduce required duration of DAPT and risk if interrupted

SYNERGY Stent

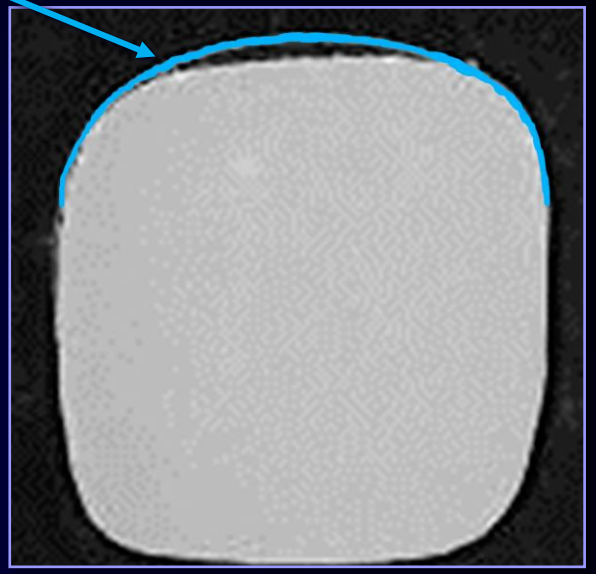
Everolimus Drug
PLGA Polymer

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

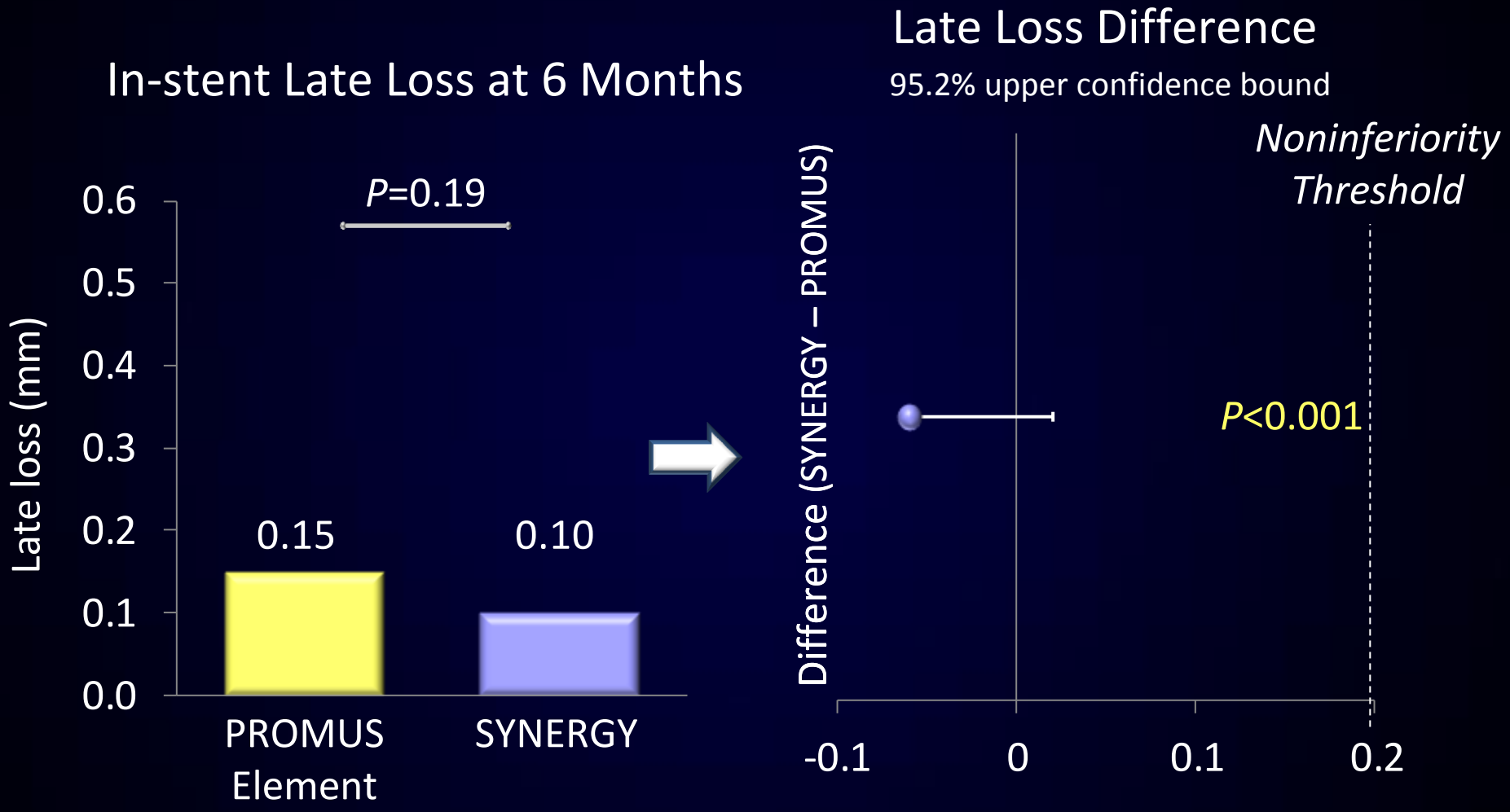
Drug

Everolimus

- 100 µg/cm^2

EVOLVE Trial: First Human Use

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 II Clinical Program

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)

EVOLVE II Randomized Cohort

PROMUS Element Plus N=838

SYNERGY N=846

RCT Design

Multicentre, single-blind, 1:1 randomisation

1° Endpoint: TLF at 12 mo

Presented at AHA 2014

1° endpoint met

EVOLVE II Diabetes Substudy

Diabetic Patients from:

SYNERGY cohort EVOLVE II RCT N=263 + **Single-arm Diabetes Study N=203**

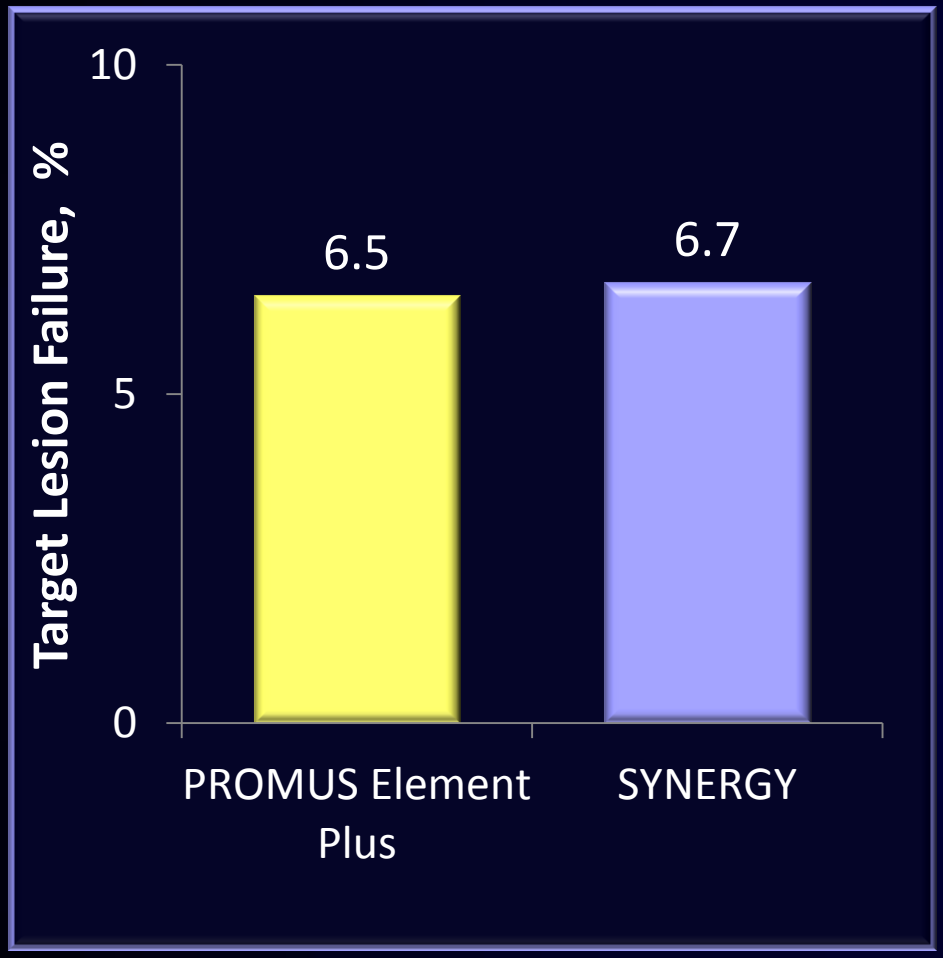
EVOLVE II Diabetes Substudy Design

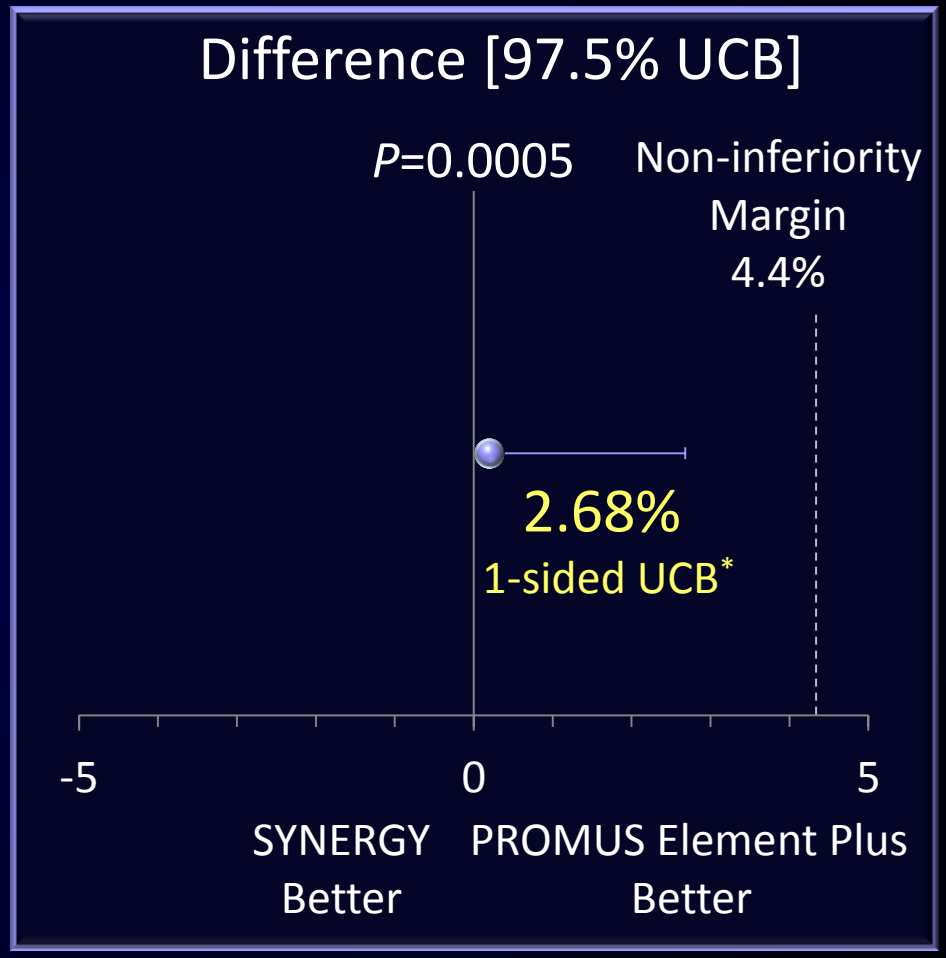
Consecutive, multicentre, single-arm, non-randomised

1° Endpoint: TLF at 12 mo

EVOLVE II RCT 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 Diabetes Substudy Design

Design

- Prospective, single-arm, multicentre, observational study
- Diabetic subjects randomized to the SYNERGY cohort of the EVOLVE II RCT pooled with subjects enrolled in the consecutive Diabetes single-arm study following completion of EVOLVE II RCT enrollment

Primary endpoint

- Target lesion failure (TLF) at 12 months
  - Cardiac death, or
  - MI related to the target vessel (based on CK-MB >3x URL), or
  - Ischemia-driven target lesion revascularisation
- Compared to a performance goal based on historical results in diabetic patients[1-4]

1. Stone GW et al. J Am Coll Cardiol. 2011;57(16):1700-8; 2. Stone GW et al. N Engl J Med. 2010;362(18):1663-74.; 3. Kedhi E et al. Lancet. 2010;375(9710):201-9.; 4. Meredith IT et al. J Am Coll Cardiol. 2012;59:1362-1370.

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EVOLVE II Diabetes Sample Size & Power Calculation

Primary Endpoint: 12-month TLF

Expected SYNERGY (test) rate = 10.0%

Margin (Δ) = 4.5%

Performance Goal = 14.5%

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

Expected rate of attrition = 5%

Power = 80%

If the *P*-value from the one-sided Clopper-Pearson test is <0.025, the 12-month TLF rate from SYNERGY will be concluded to be less than the performance goal

EVOLVE II Centres

Top Enrolling Centres for Diabetic Patients

R. Lee Jobe (25)
Wake Medical Center

Ian Sarembock (18)
Lindner Center for Research and Education at Christ Hospital

Shamir Mehta (16)
Hamilton General Hospital

Bernardo Stein (15)
Morton Plant Mease Healthcare System

Andrejs Erglis (13)
P. Stradins University Hospital

Raul Moreno (13)
Hospital La Paz

Monica Masotti (12)
Hospital Clinic de Barcelona

Didier Carrié (11)
Centre Hopital Universitaire Rangueil

Robert Feldman (11)
Mediquest Research at Munroe Regional Medical Center

Juhani Airaksinen (11)
Turku University Hospital

Francis Stammen (11)
H.-Hartziekenhuis Roeselare-Menen

Michael Foster (10)
Sisters of Charity Providence Hospital

Michael Ball (9)
St. Vincent's Hospital

Aaron Wong (9)
National Heart Centre

Jacques Berland (9)
Clinique Saint-Hilaire Rouen

Mark Dorogy (9)
Medical Center of Central Georgia

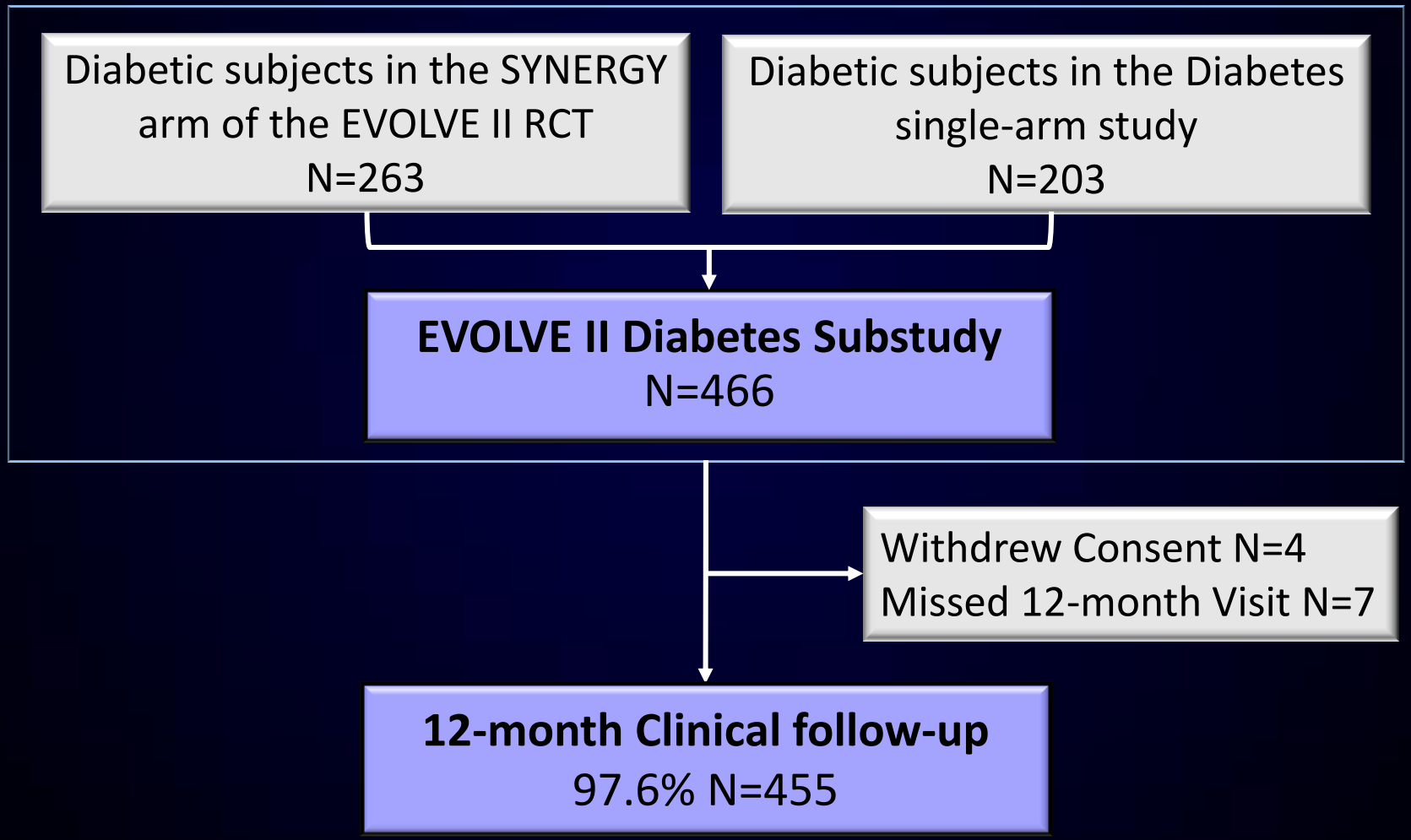
Arthur Reitman (9)
Wellstar Kennestone Hospital

Simon Elhadad (8)
CH Lagny-Marne-la-Vallee

Luc Janssens (8)
Imelda Ziekenhuis

Craig Siegel (8)
St. David's Round Rock Medical Center

EVOLVE II Diabetes Patient Disposition



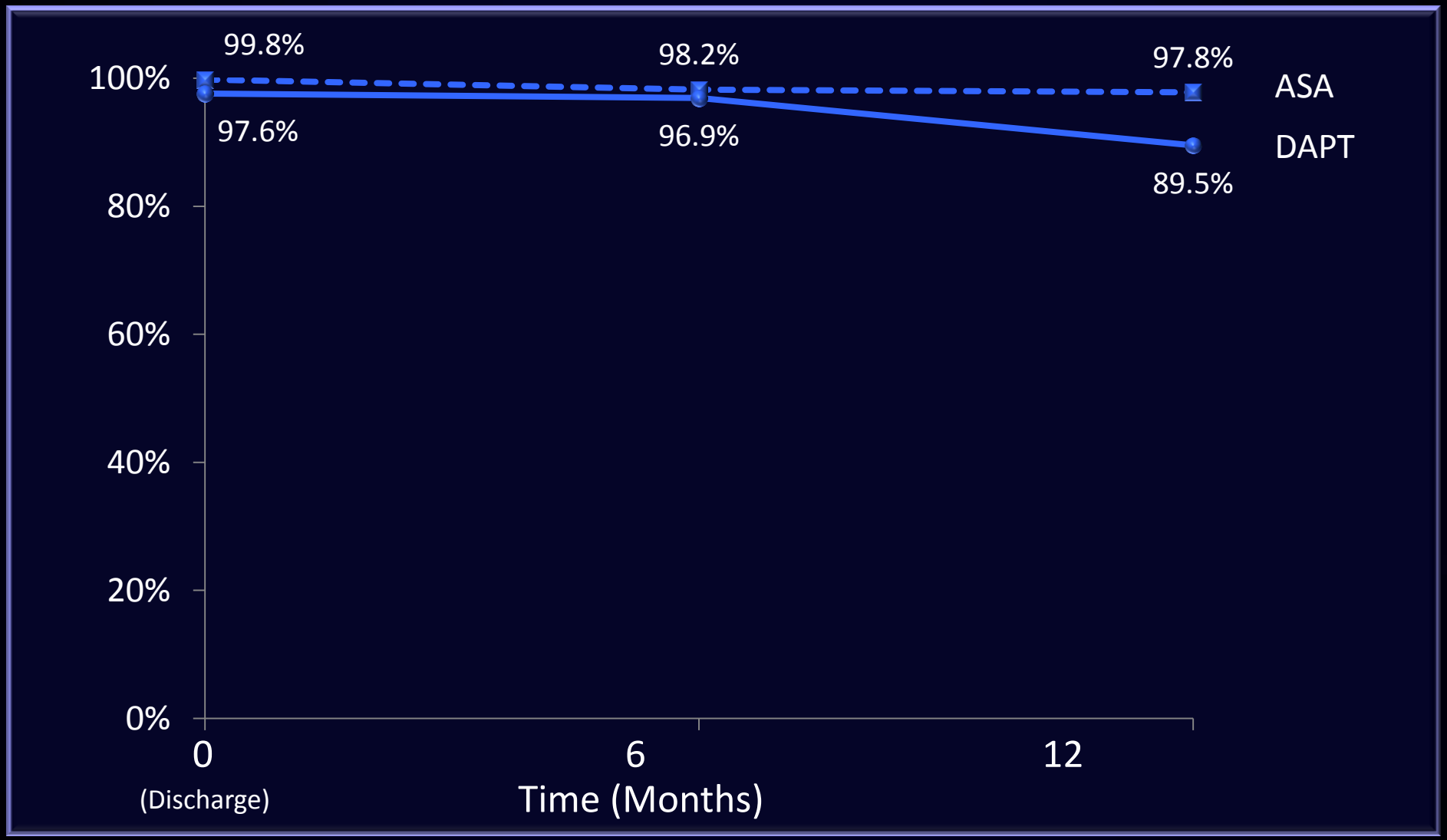
Baseline Clinical and Lesion Characteristics

Clinical Characteristics	SYNERGY n=466 patients
Male	70.2%
Age (yr) ± SD	64.8 ± 9.7
Caucasian	75.3%
Smoking, Ever	59.6%
Current Smoker	16.6%
Diabetes	100%
Treated with Insulin	37.3%
Hyperlipidemia	84.5%
Hypertension	88.8%
Previous PCI	41.8%
Previous CABG	7.5%
History of CHF	10.3%
Unstable Angina	35.6%
NSTEMI	26.2%

Lesion Characteristics (Core laboratory)		SYNERGY n=466 patients
Target Lesions		1.26 ± 0.51
- 2 Lesions Treated		20.0%
- 3 Lesions Treated		3.2%
Target Lesion Location†:	LAD	39.7%
	LCx	26.0%
	RCA	34.3%
	LM	0.0%
RVD†, mm		2.56 ± 0.50
- RVD <2.25 mm		27.2%
MLD†, mm		0.89 ± 0.36
Diameter Stenosis†, %		65.47 ± 11.70
Lesion Length†, mm		14.10 ± 7.49
- Length >20 mm		19.7%
Modified AHA/ACC B2/C†		74.9%

Intent-to-treat; Per patient unless per lesion indicated by '†' (N=589 lesions); SD=standard deviation

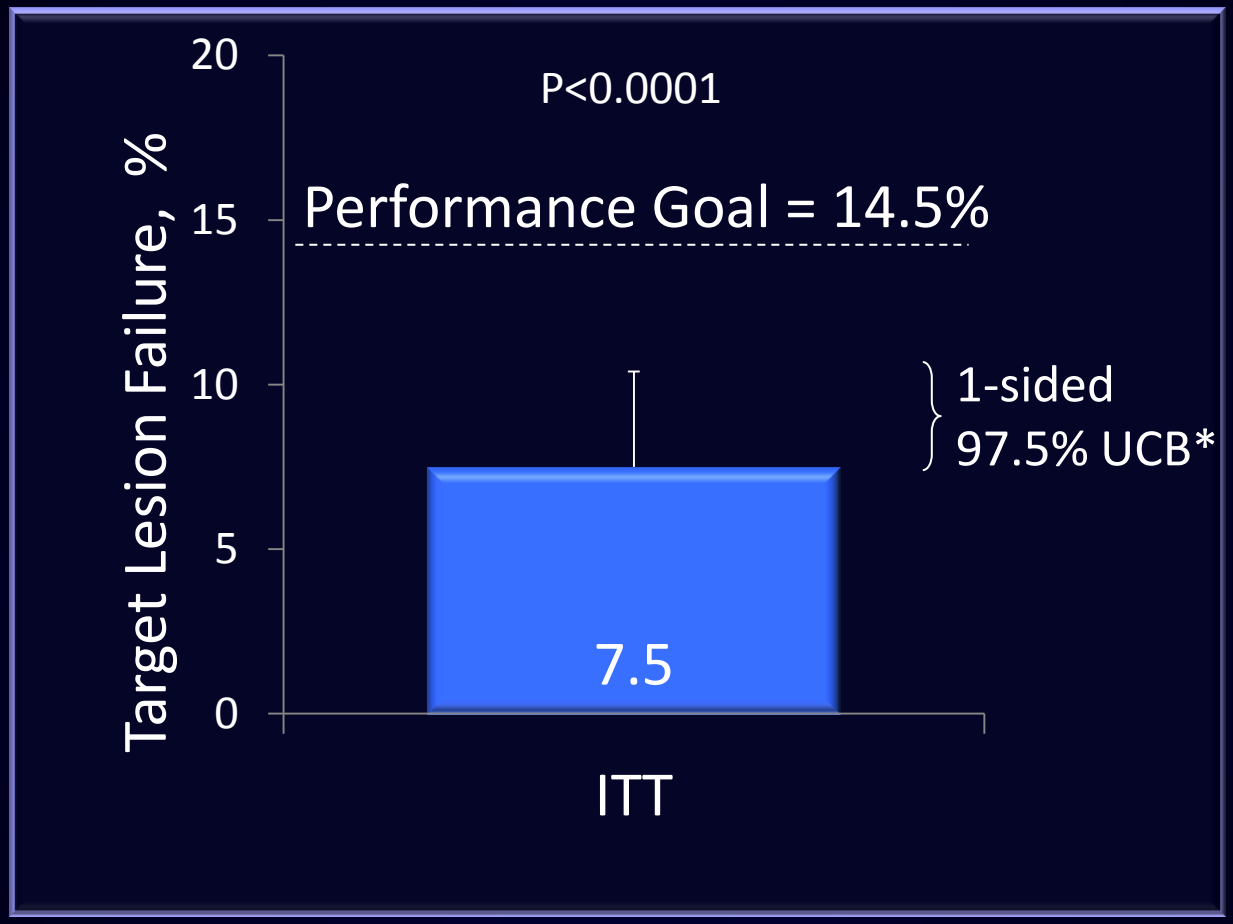
Antiplatelet Medication Usage*



*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 Diabetes 1° Endpoint:

12-month TLF

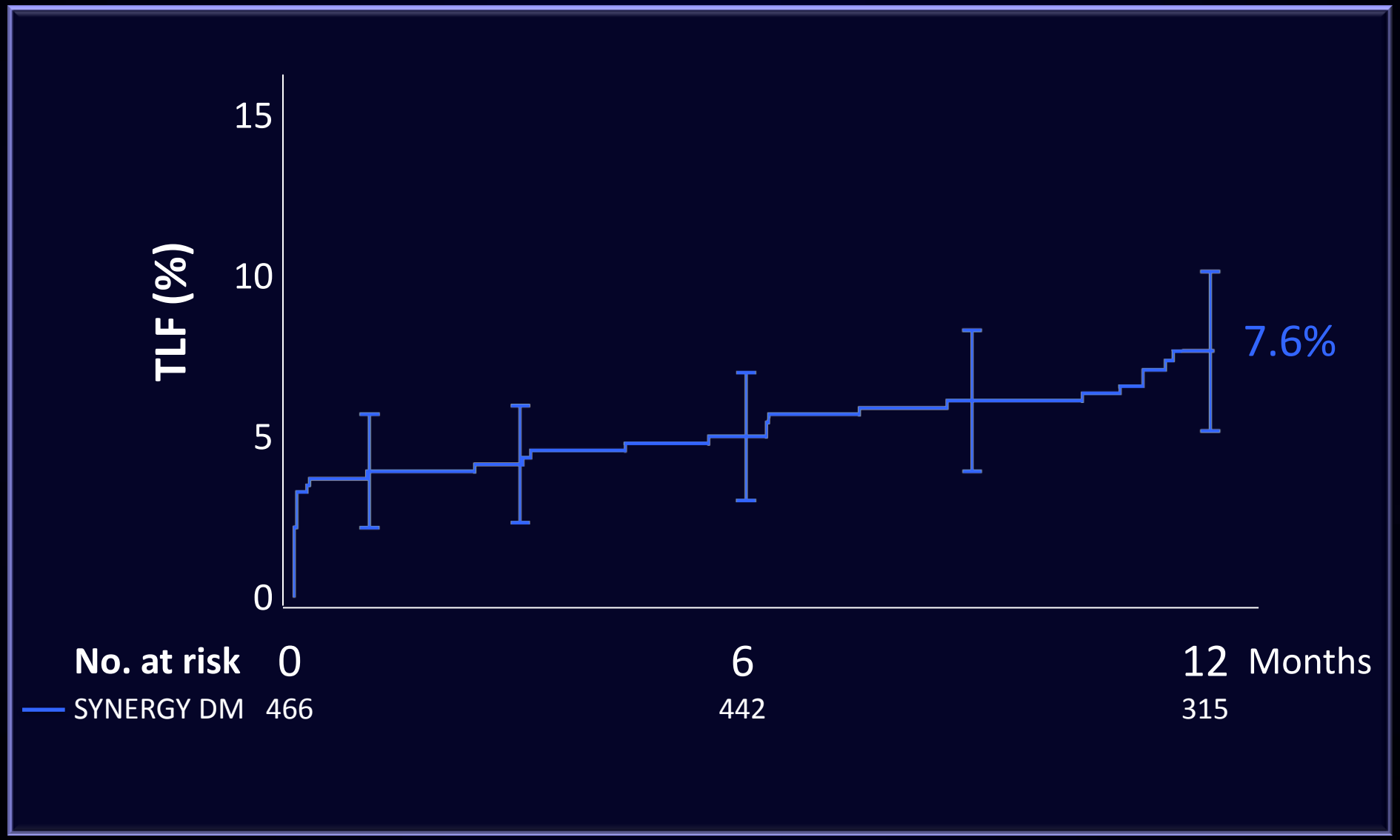


P-value from the one-sided Clopper-Pearson test is <0.025, the 12-month TLF rate from SYNERGY is concluded to be less than the performance goal (14.5%)

*One-sided 97.5% Clopper Pearon Upper Confidence Bound (UCB)

EVOLVE II Diabetes 1° Endpoint:

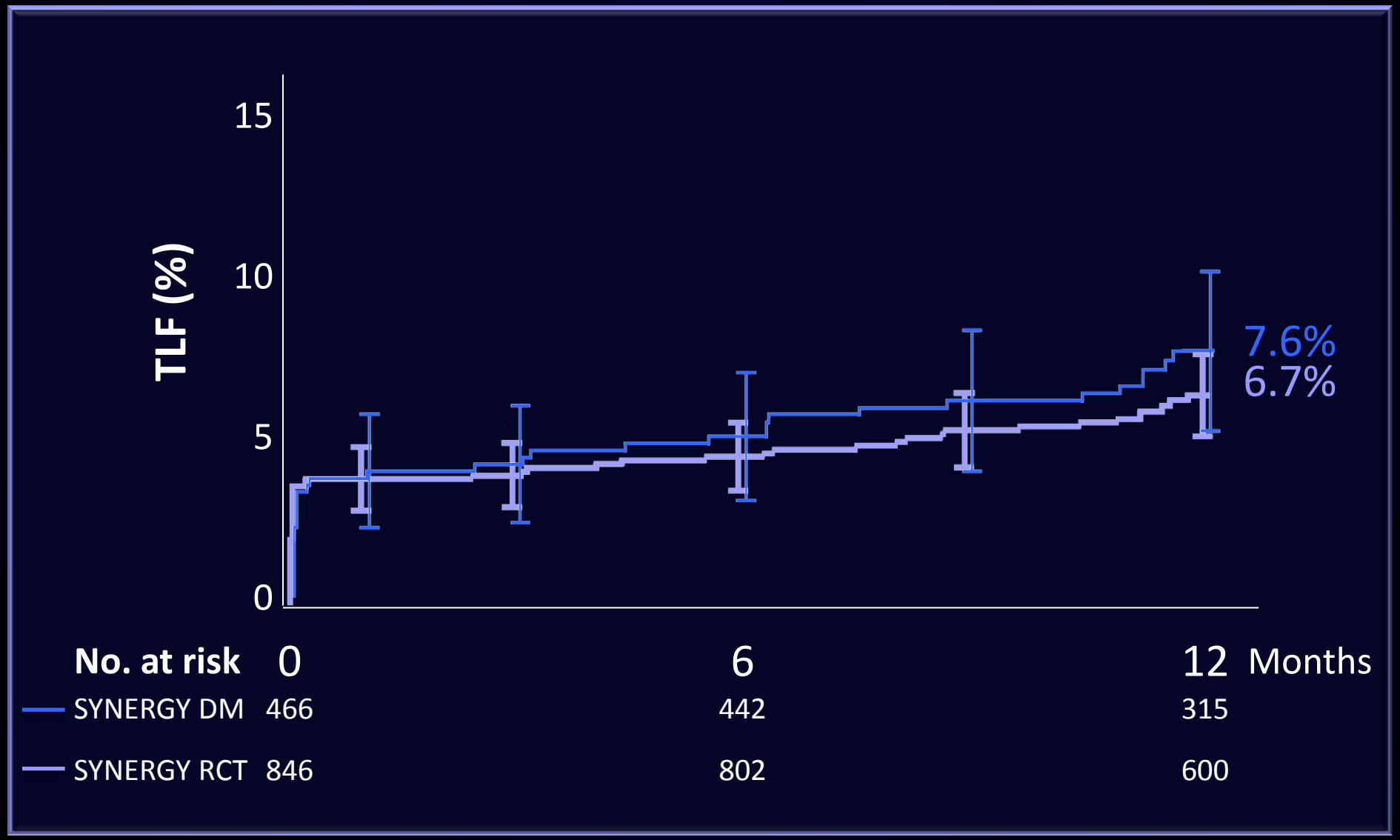
12-month TLF : ITT



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

EVOLVE II Diabetes 1° Endpoint:

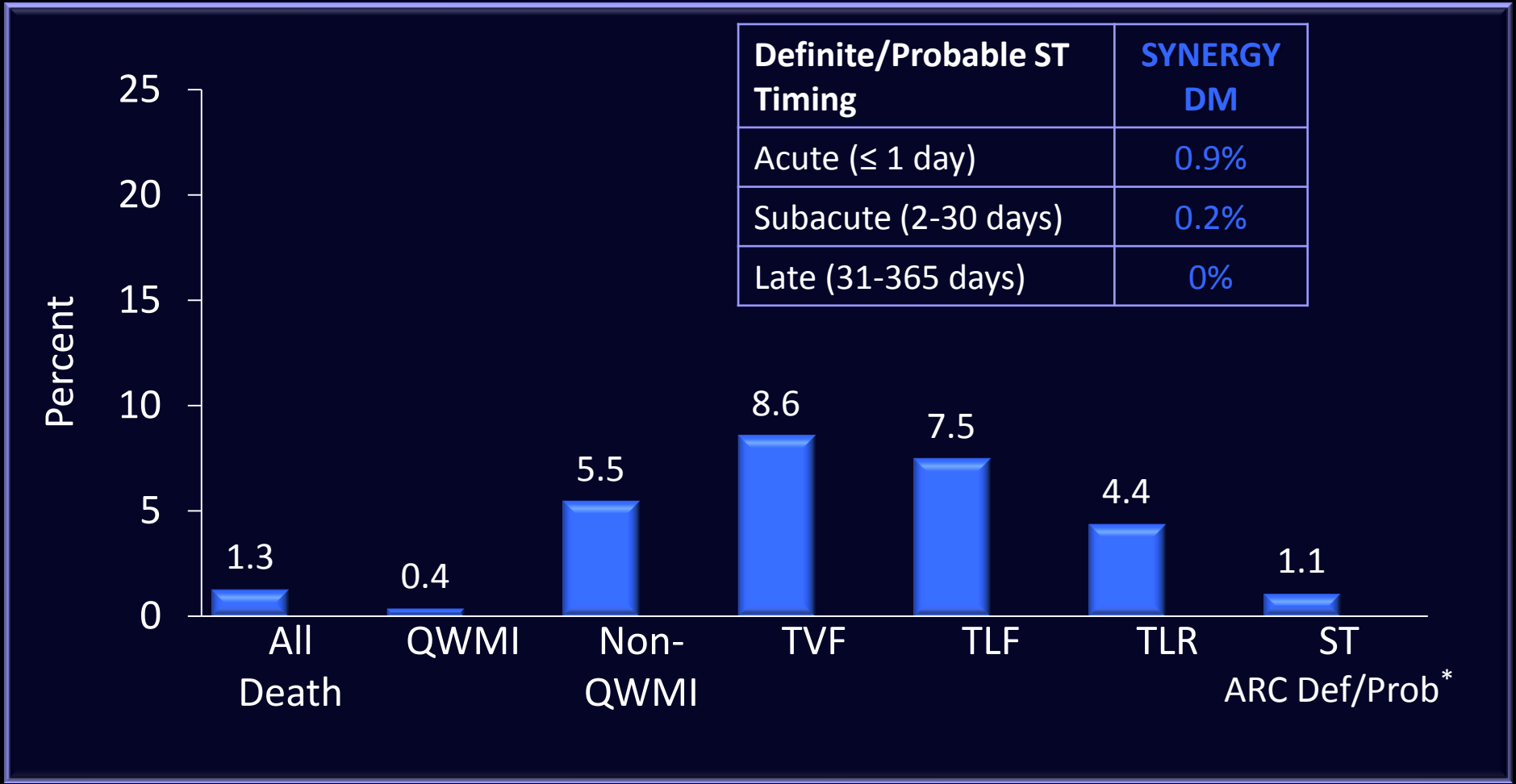
12-month TLF : ITT



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

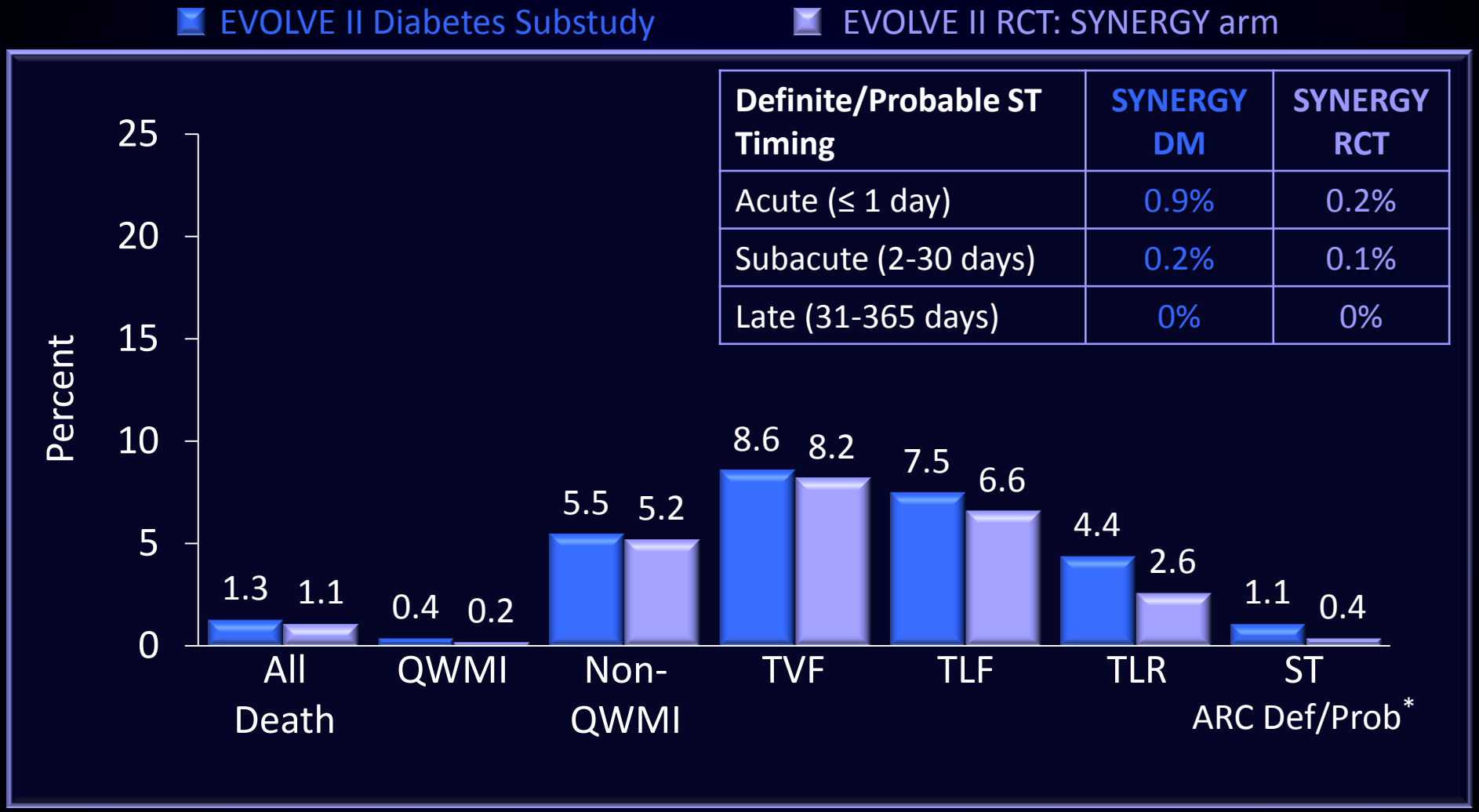
Clinical Outcomes at 12 months

EVOLVE II Diabetes Substudy



*Cutlip et al, *Circulation*. 2007; 115(17):2344; Spontaneous MI was defined as the rise and/or fall of cardiac biomarkers with ≥1 value >99th percentile of the upper reference limit (URL) with ≥1 of the following: symptoms of ischemia, ECG changes, and or evidence of loss of myocardium. Peri-PCI MI was defined by any of the following: i) CK-MB >3X URL within 48 hours, ii) new pathological Q waves, iii) autopsy evidence. All ST were definite.

Clinical Outcomes at 12 months



Definite/Probable ST Timing	SYNERGY DM	SYNERGY RCT
Acute (≤ 1 day)	0.9%	0.2%
Subacute (2-30 days)	0.2%	0.1%
Late (31-365 days)	0%	0%

*Cutlip et al, *Circulation*. 2007; 115(17):2344; Spontaneous MI was defined as the rise and/or fall of cardiac biomarkers with ≥1 value >99th percentile of the upper reference limit (URL) with ≥1 of the following: symptoms of ischemia, ECG changes, and or evidence of loss of myocardium. Peri-PCI MI was defined by any of the following: i) CK-MB >3X URL within 48 hours, ii) new pathological Q waves, iii) autopsy evidence.

Conclusions and Significance

In this single-arm trial designed to evaluate clinical outcomes in medically-treated diabetic patients treated with SYNERGY stent(s):

- The rate of TLF was 7.5% at 12-months, significantly less than the performance goal based on historical results in diabetic patients
- Overall, clinical events were low at 12-months including 1.2% all-cause death
- These data support the safety and efficacy of the SYNERGY stent in diabetic patients