

Prospective, Randomized Evaluation of Sirolimus-Eluting Coronary Stents with Fixed-Wire and Rapid-Exchange Delivery Systems and a Novel Bioresorbable Drug Carrier: the OPTIMIZE IDE Trial

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

Consulting Fees/Honoraria

Consulting Fees/Honoraria

Consulting Fees/Honoraria

Consulting Fees/Honoraria

Consulting Fees/Honoraria

Consulting Fees/Honoraria

Major Stock Shareholder/Equity

Company

Boston Scientific Corporation

Caliber Therapeutics/ Orchestra Biomed

Elixir Medical, Inc.

Shockwave

SINO Medical Sciences Technologies, Inc.

Svelte Medical Systems, Inc.

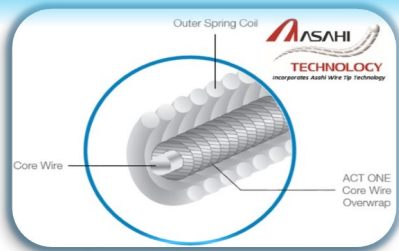
Ablative Solutions, Inc.

Faculty disclosure information can be found on the app

SLENDER Integrated Delivery System (IDS) Designed to Facilitate Direct Stenting, TRI



Asahi Wire Tip Technology

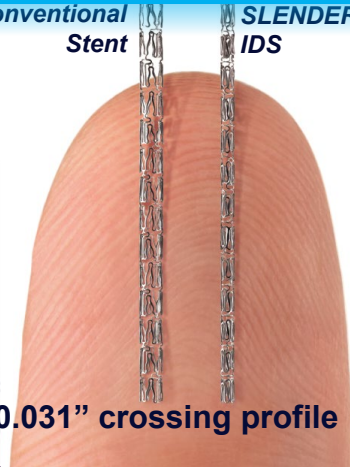


- Middleweight wire (1.2g tip load)
- Braiding similar to Sion line of wires

World's Lowest Profile DES

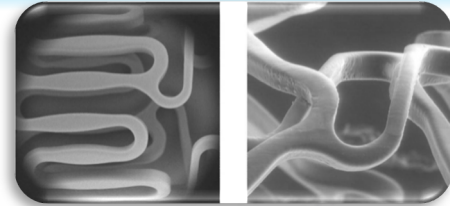
Conventional Stent

SLENDER IDS



- 0.031" crossing profile

Designed for Direct Stenting



- Low compliant, higher pressure SDS balloon ($\frac{1}{4}$ size > RBP)
- New class of drug coating (PEA), enzymatic-mediated bioresorption

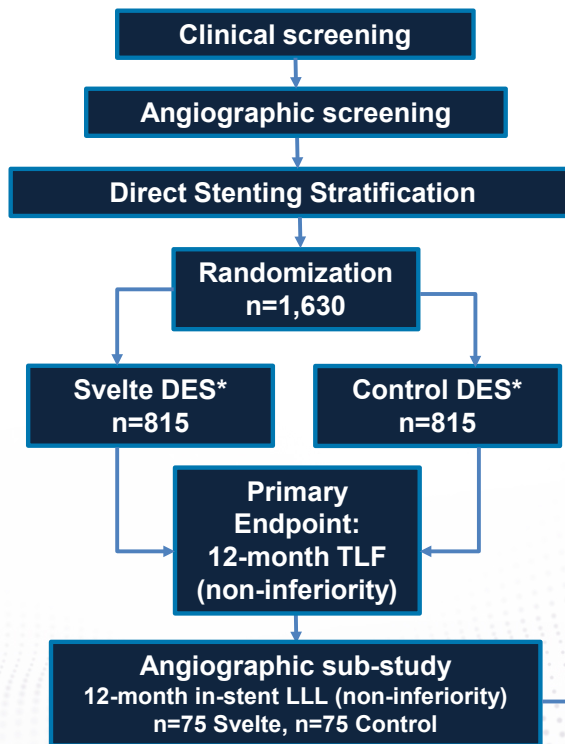
OPTIMIZE Pivotal Trial

DESIGN: Prospective, single blind, 1:1 randomization, active control, multicenter non-inferiority trial

OBJECTIVE: Compare the safety and efficacy of Svelte IDS and RX DES with Xience/Promus DES

RELEVANCE: First IDE trial to:

- Evaluate direct stenting
- Have a TRI focus
- Assess new DES delivery system
- Assess new class of drug coating



Direct Stenting Strategy:

- **Randomization** occurs *AFTER* direct stenting intent is recorded
- **Recommendations** for direct stenting:
 - Lesion length $\leq 24\text{mm}$
 - % DS $\leq 90\%$
 - Angulation $\leq 90^\circ$
 - Mild-moderate calcium density
- Direct stenting limited to 30% of study subjects by FDA

* After randomization assignment, choice of treatment (Svelte IDS or Svelte RX) or control (Xience or Promus) DES is investigator preference.

OPTIMIZE Leadership and Support

Co-Principal Investigators

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The Lindner Research Center
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Sunil Rao, MD

Duke University Medical Center
Veterans Administration Medical Center
Durham, NC, USA

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John Lasala, MD, Washington University-St. Louis, MO
Pieter Stella, MD, UMC Utrecht, NL

S. Chiu Wong, MD, Weill Cornell Medical Center, NY, NY
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James Zidar, MD, NC Heart & Vascular, Raleigh, NC

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Japan and Angio Sub-Study PI: Shigeru Saito, MD
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QCA:
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IVUS:
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Event Adjudication Safety Monitoring

Clinical Events Committee:
Mun Hong, MD (Chair)
IK Jang, MD
Steven Marx, MD

Data and Safety Monitoring Board:
Zoltan Turi, MD (Chair)
Sanjit Jolly, MD
Issam Moussa, MD
Gerry Gray, PhD (statistician)

OPTIMIZE Top 25 Enrolling Sites



55 Sites



9 Sites



10 Sites

Top Enroller: Robert Feldman, MD, MediQuest Research at AdventHealth Ocala, Ocala FL – 110 Subjects

Subjects

107	A.J.J. Ijsselmuiden, MD <i>Amphia Hospital, Breda, NL</i>
100	Floris Kauer, MD <i>A. Schweitzer Hospital, Dordrecht, NL</i>
95	Giovanni Amoroso, MD <i>OLVG Hospital, Amsterdam, NL</i>
89	Dean Kereiakes, MD <i>The Christ Hospital, Cincinnati, OH</i>
75	James Zidar, MD <i>NC Heart & Vascular, Raleigh, NC</i>
72	Pim Tonino, MD <i>Catharina Hospital, Eindhoven, NL</i>
71	Samer Somi, MD <i>HAGA Hospital, Den Haag, NL</i>
64	Ron Caputo, MD <i>St. Joseph's Hospital, Syracuse, NY</i>

Subjects

59	Craig Siegel, MD <i>St. David's MC, Round Rock, TX</i>
47	Barry Bertolet, MD <i>North Mississippi MC, Tupelo, MS</i>
43	Frank Eefting, MD <i>St. Antonius, Nieuwegein, NL</i>
36	Shigeru Saito, MD <i>Shonan Kamakura GH, Kamakura, JP</i>
35	Edgar Carrell, MD <i>AMITA Health, Hinsdale, IL</i>
35	Bart de Smet, MD <i>Meander Hospital, Amersfoort, NL</i>
31	Giora Weisz, MD <i>Montefiore MC, Bronx, NY</i>
27	Natalia Berry, MD <i>Brigham & Women's Hospital, Boston, MA</i>

Subjects

27	Jeremiah Depta, MD <i>Rochester General Hospital, Rochester, NY</i>
35	Kenji Ando, MD <i>Kokura Memorial Hospital, Kitakyushu, JP</i>
20	Muhammad Arida, MD <i>LeBauer Heart Care, Greensboro, NC</i>
20	David Trice, MD <i>Thomas Hospital, Fairhope, AL</i>
18	Sammy Elmariah, MD <i>Massachusetts General Hospital, Boston, MA</i>
17	Donald Westerhausen, MD <i>Elkhart General Hospital, Elkhart, IN</i>
17	Atsushi Hirohata, MD <i>Sakikibara Heart Institute, Okayama, JP</i>
17	Akihiko Takahashi, MD <i>Sakuraki Takahashi Hospital, Kobe, JP</i>

OPTIMIZE Major Endpoints

Primary Endpoint: 12-Month Target Lesion Failure (TLF)

- Cardiac Death
- Target Vessel Myocardial Infarction (TVMI, including Q wave and non-Q wave)
 - *Peri-procedural MI: CK-MB or troponin >3x ULN within 48 hours*
- Clinically-driven Target Lesion Revascularization (TLR)

Secondary Endpoints

- Components of TLF
- TVF, MACE
- Stent Thrombosis (ARC definition)
- Lesion, device, procedure and direct stent strategy success

OPTIMIZE Statistical Design

Primary Endpoint: 12-Month Target Lesion Failure (TLF)

Expected TLF based on EVOLVE II trial = 6.5%*

Non-inferiority margin (Δ) = 3.58%

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

Power ($1-\beta$) = 0.80

Expected rate of attrition = 5%

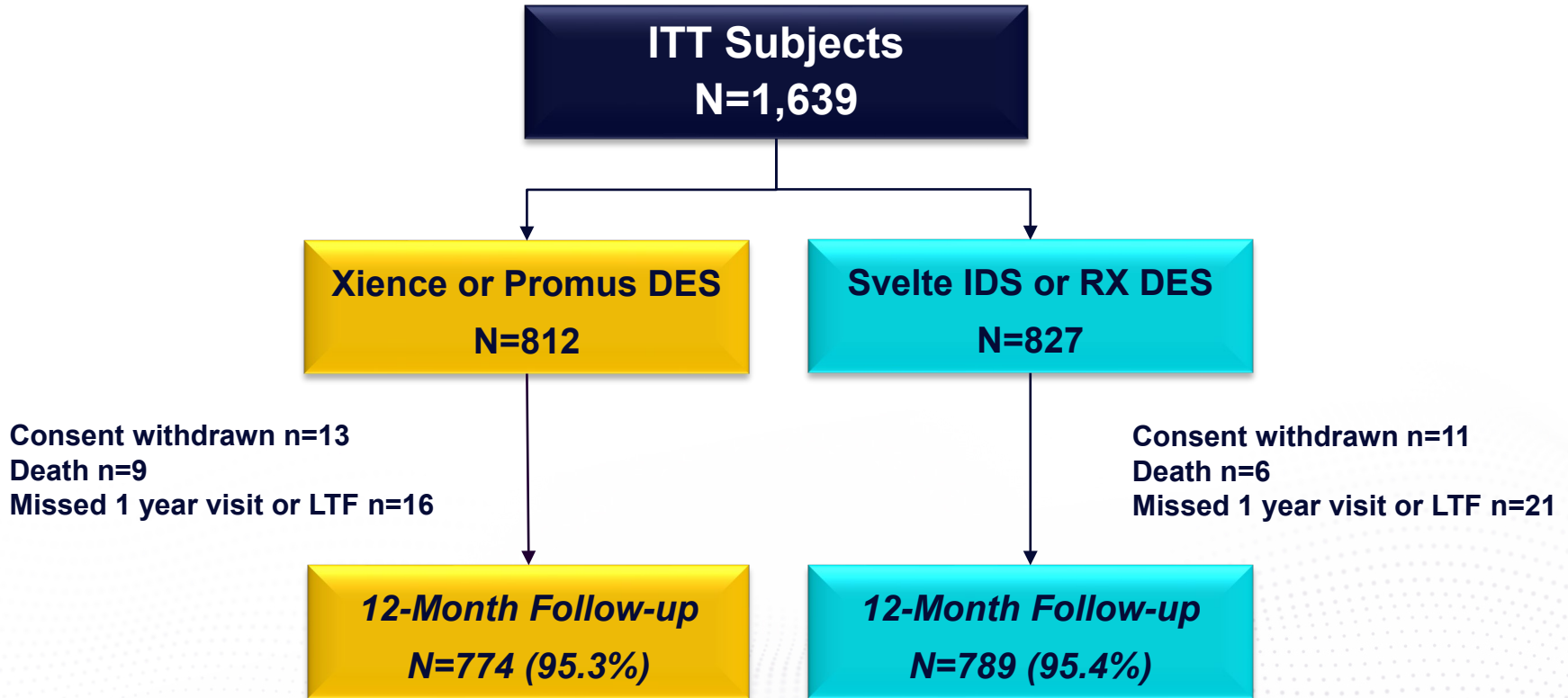
N = 1,630 subjects (815 per group at 1:1 ratio)

* If the P value from the one-sided Farrington-Manning test is <0.025 (ITT analysis), the Svelte DES is considered non-inferior to the Xience and Promus DES (pooled control).

OPTIMIZE Key Eligibility Criteria

- ≤ 3 native coronary artery lesions in ≤ 2 major epicardial vessels
- Evidence of ischemia
- RVD ≥ 2.25 mm ≤ 4.0
- Lesion length ≤ 34 mm, %DS $\geq 50 < 100$, TIMI flow > 1 (site determined)
- LM disease, CTO, SVG, ISR or acute STEMI excluded
 - Subjects treated with PCI for STEMI were included if cardiac enzymes were decreasing ≥ 72 hours prior to the study procedure (≥ 24 hours for NSTEMI)
- Pre-procedure CK-MB elevation, troponin elevation $> 20\%$ excluded
- Scheduled or expected cardiac intervention (PCI, TAVR, etc.) excluded
- Subjects receiving chronic anticoagulation therapy (other than for ACS) excluded

OPTIMIZE Study Flow



OPTIMIZE Baseline Clinical Characteristics

Per Subject	Xience/Promus DES n=812 Subjects	Svelte DES n=827 Subjects	P value
Age (mean, years)	65.8 ± 10.3	65.1 ± 10.0	0.16
Male	70.8%	72.7%	0.41
Race (Caucasian)	82.4%	81.4%	0.61
Race (Asian)	11.0%	10.9%	1.00
Smoking History	61.3%	63.7%	0.33
Current Smoker	17.2%	16.2%	0.60
Diabetes	30.7%	28.5%	0.36
Insulin-Dependent	8.4%	8.7%	0.86
Hypertension	74.6%	74.5%	0.96
Hyperlipidemia	54.1%	54.9%	0.77
Prior Revascularization	34.5%	36.9%	0.33
CHF	5.9%	6.9%	0.42
Unstable Angina	25.0%	25.5%	0.82
MI	32.8%	31.4%	0.60

OPTIMIZE Baseline Lesion Characteristics (QCA)

Per Subject* Per Lesion†		Xience/Promus DES n=812 Subjects n=970 Lesions	Svelte DES n=827 Subjects n=1,018 Lesions	P value
Target Lesions*		1.22 ± 0.45	1.27 ± 0.52	0.55
2 Lesions Treated		19.2%	20.0%	0.71
3 Lesions Treated		1.6%	3.5%	0.02
Target Lesion Location†:	LAD	45.8%	42.9%	0.21
	LCx	26.5%	27.3%	0.72
	RCA	27.7%	29.6%	0.37
	LM	0.00%	0.20%	0.50
RVD†, mm		2.77 ± 0.50	2.78 ± 0.51	0.74
RVD ≤2.25 mm		10.6%	10.3%	0.87
MLD†, mm		1.00 ± 0.40	1.00 ± 0.41	0.92
% Diameter Stenosis†		63.79 ± 12.90	63.84 ± 13.09	0.94
Lesion Length†, mm		14.25 ± 7.52	14.88 ± 7.04	0.05
Length >20 mm		16.1%	19.0%	0.10
Bend ≥ 45°†		20.1%	20.3%	0.91
Moderate-Severe Tortuosity†		22.3%	24.1%	0.37
Moderate-Severe Calcification†		36.7%	34.9%	0.40
Modified AHA/ACC B2/C†		72.0%	75.3%	0.10

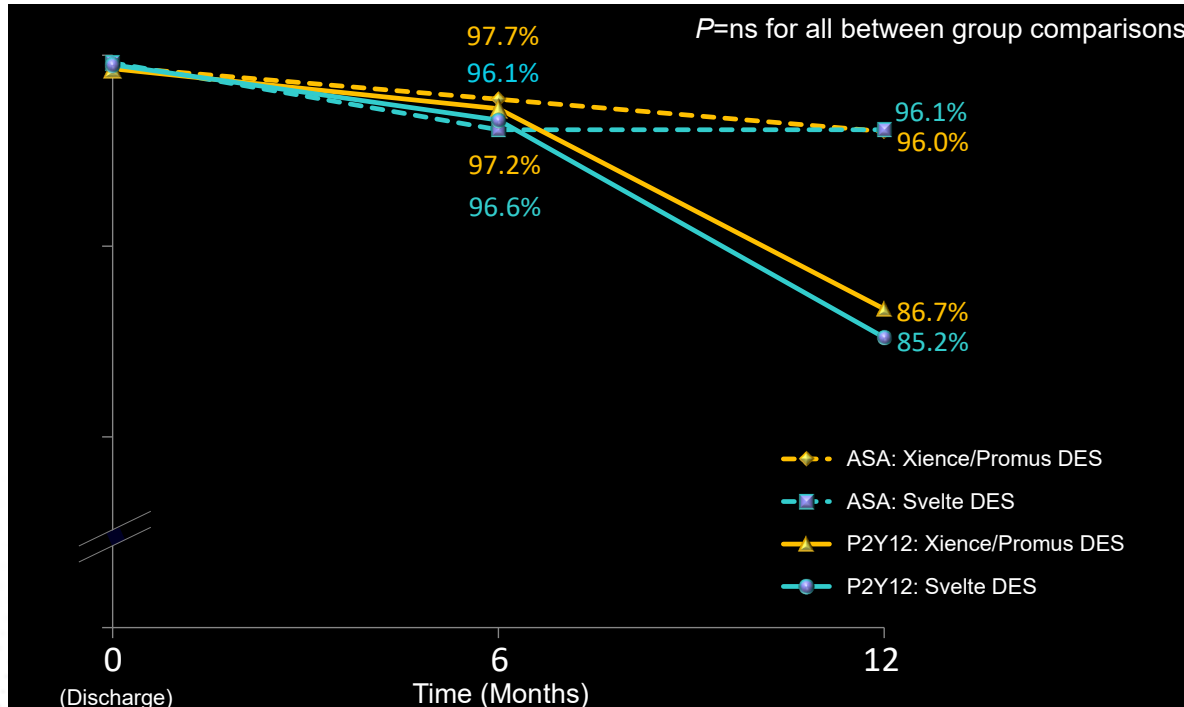
OPTIMIZE Procedural Characteristics

Per Subject* Per Lesion†	Xience/Promus DES n=812 Subjects n=970 Lesions	Svelte DES n=827 Subjects n=1,018 Lesions	P value
Lesion Success†	99.1%	99.3%	0.62
Device Success†	95.2%	95.4%	0.92
Direct Stent Strategy Success†	95.2%	92.9%	0.29
Procedure Success*	91.6%	91.4%	0.93
Transradial Approach*	78.1%	79.1%	0.63
Stents Implanted*, n	1.34 ± 0.69	1.39 ± 0.73	0.20
Non-Study Stents Implanted*	3.4%	1.6%	0.03
Overlapping Stents†	5.3%	5.0%	0.84
Total Stented Length†, mm	19.49 ± 8.51	20.00 ± 8.17	0.18
Maximum Pressure: SDS Balloon†, atm	13.74 ± 4.62	14.87 ± 4.22	< 0.01
Maximum Pressure: Post-Dil Balloon†, atm	17.32 ± 3.82	17.53 ± 3.88	0.38
Maximum Stent/Vessel Diameter Ratio†	1.10 ± 0.13	1.10 ± 0.14	0.66
Pre-dilatation†	72.2%	68.2%	0.05
Post-dilatation†	51.6%	46.0%	0.01

OPTIMIZE Post-Procedural Characteristics (QCA)

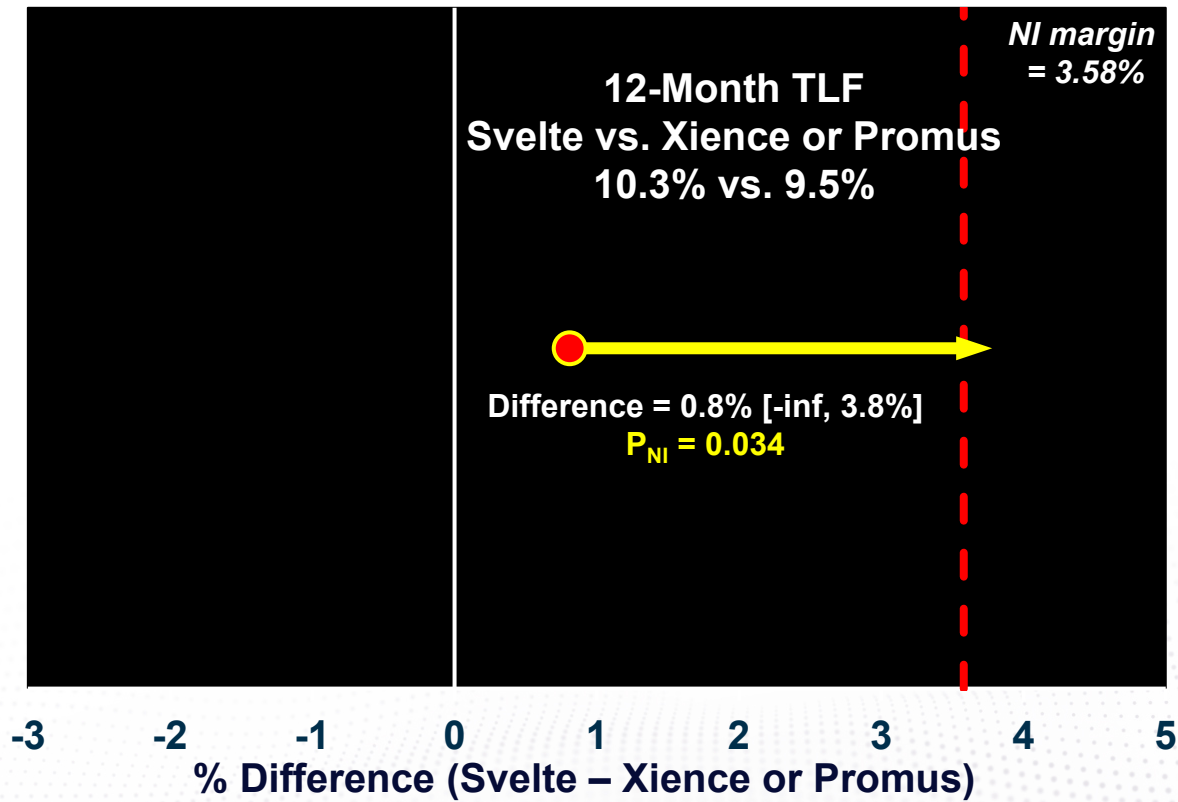
Per Lesion	Xience/Promus DES n=812 Subjects n=970 Lesions	Svelte DES n=827 Subjects n=1,018 Lesions	P value
RVD	2.89 ± 0.49	2.91 ± 0.48	0.33
MLD, In-Stent, mm	2.71 ± 0.44	2.71 ± 0.46	0.95
MLD, In-Segment, mm	2.60 ± 0.49	2.61 ± 0.48	0.46
%DS, In-Stent, %	6.07 ± 8.38	6.78 ± 8.49	0.06
%DS, In-Segment, %	10.13 ± 7.68	10.32 ± 6.12	0.54
Acute Gain, In-Stent, mm	1.70 ± 0.48	1.71 ± 0.50	0.98
Acute Gain, In-Segment, mm	1.60 ± 0.52	1.61 ± 0.51	0.52

OPTIMIZE Antiplatelet Medication Use*

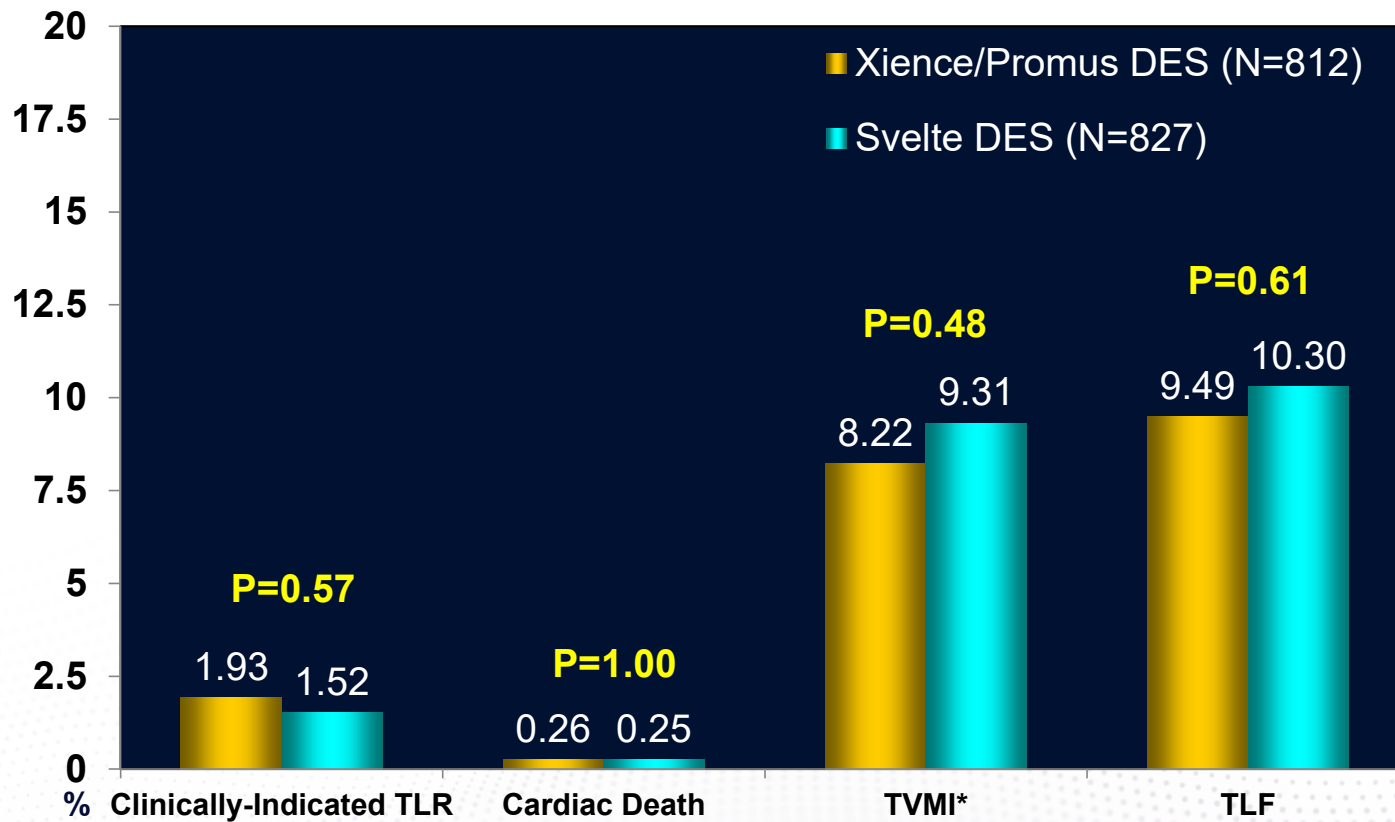


* The study protocol provided investigators with recommendations for the administration of DAPT (P2Y₁₂ inhibitors clopidogrel, ticlopidine, prasugrel, or ticagrelor + aspirin) but loading dose, duration of ongoing administration and use of antiplatelet agents not aforementioned was left to the discretion of investigators.

OPTIMIZE Primary Endpoint: 12-Month TLF (ITT)



OPTIMIZE 12-Month TLF Components



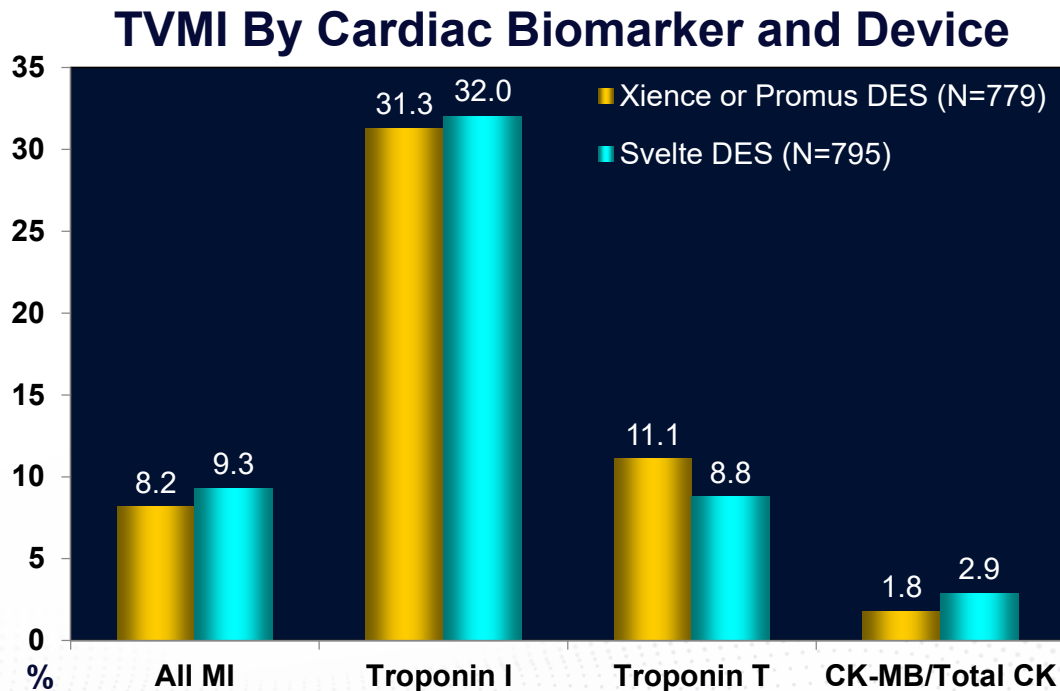
* Spontaneous MI is the rise of cardiac biomarkers with ≥ 1 value >99 th percentile of the ULN + evidence of myocardial ischemia. Peri-PCI MI is defined as ≥ 1 of the following: i) biomarker elevations within 48 hours of PCI (based on CK-MB or troponin $>3X$ URL), ii) new pathological Q waves, or iii)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

CRF

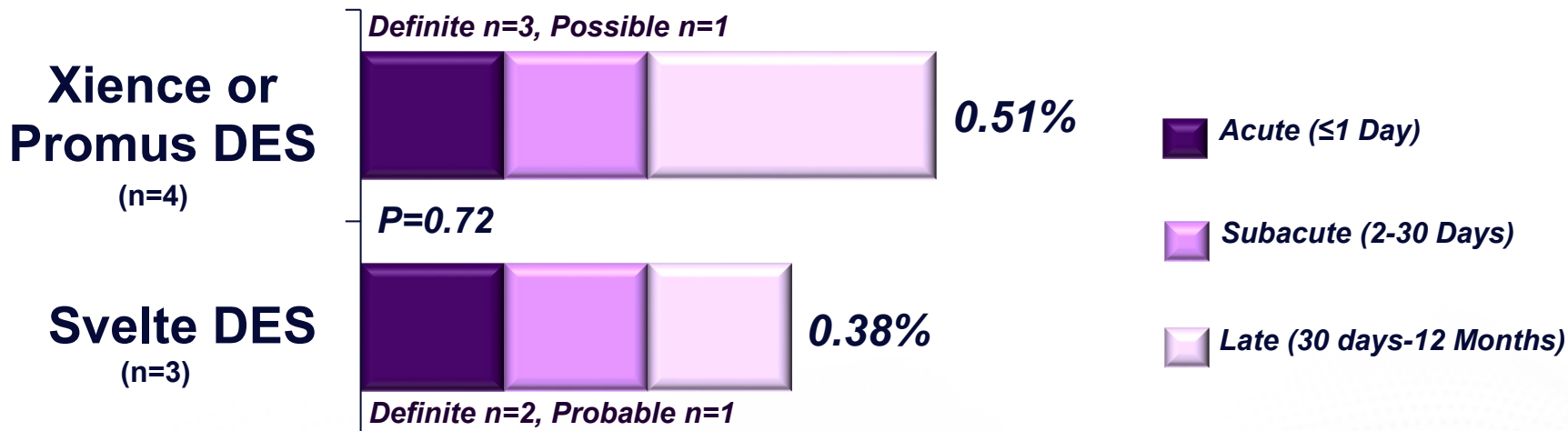
TCT CONNECT

OPTIMIZE 12-Month TVMI

- TLF (9.9%) driven by TVMI (8.8%); 90% of TVMI is peri-procedural
- 25% of subjects with troponin assays account for 80% of TVMIs
- TPN+ subjects:
 - 3.8% had ECG changes
 - 87.5% discharged without delay



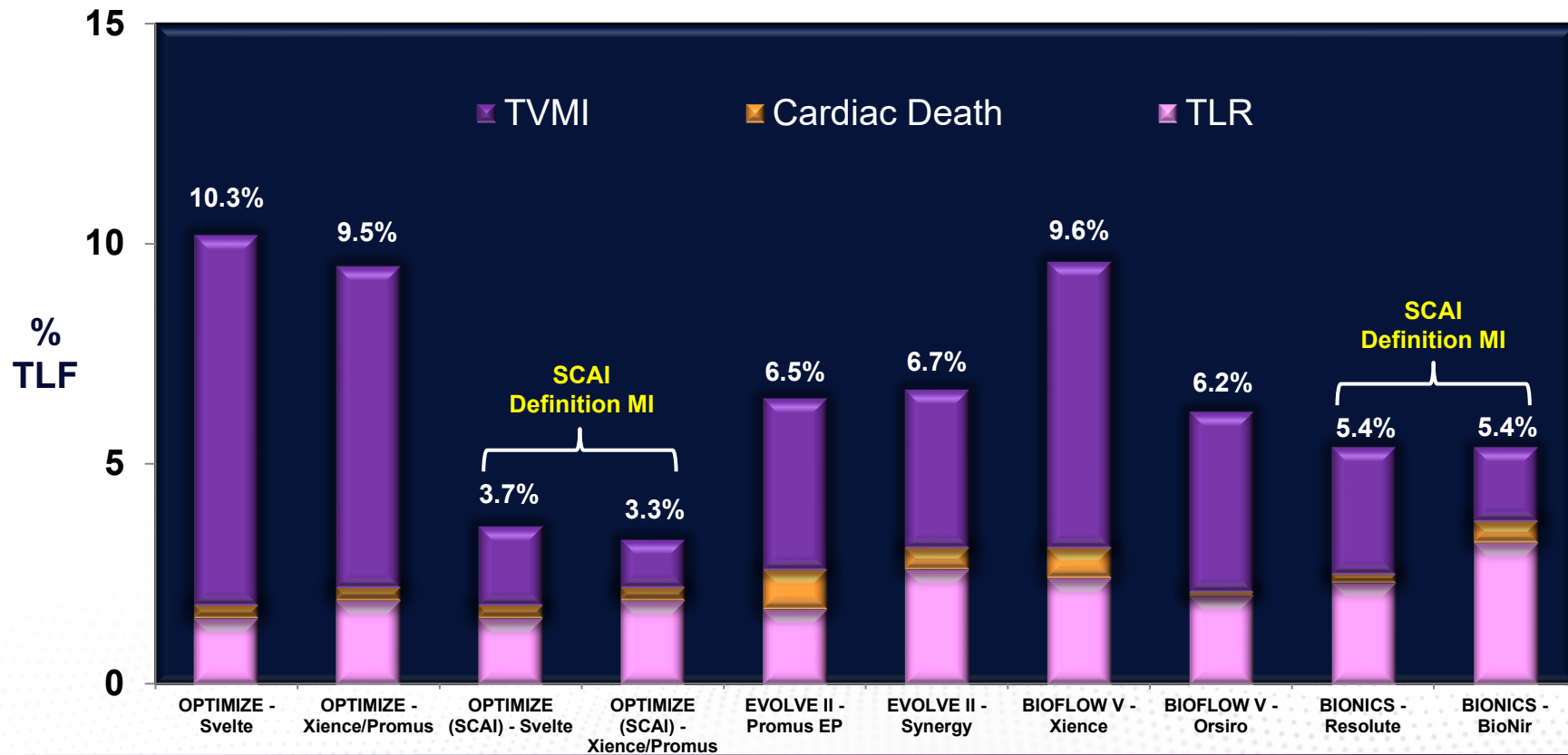
OPTIMIZE All Stent Thrombosis Through 12 Months



Definite / Probable ST

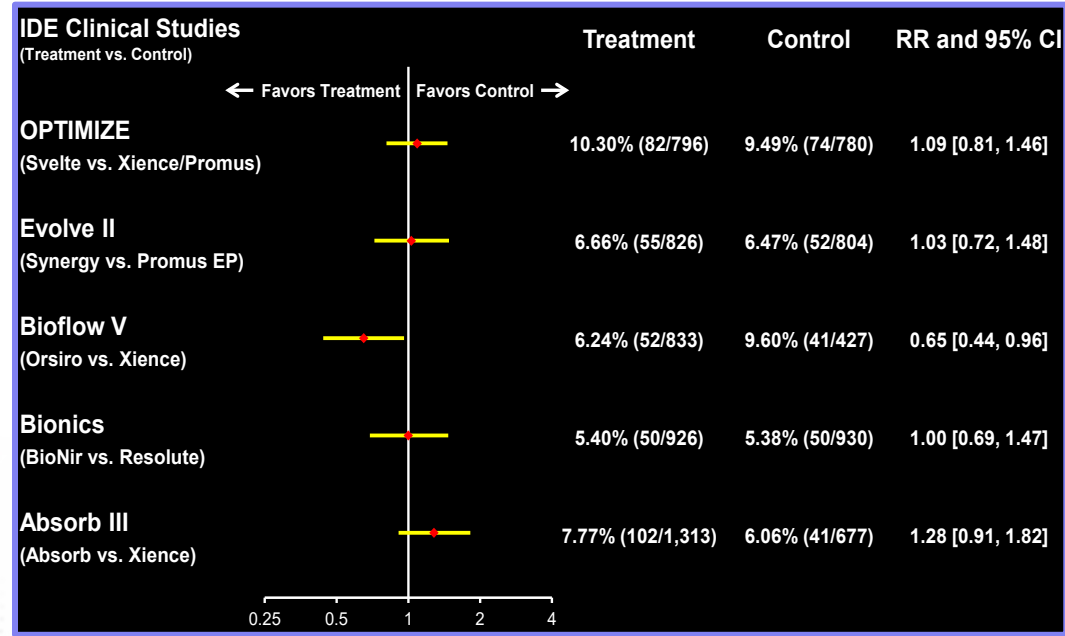
- Xience or Promus (n=3): Day 0, 7, 73; 3/3 subjects DAPT compliant
- Svelte (n=3): Day 0, 4, 302; 1/3 subjects DAPT compliant (1 clopidogrel allergy, 1 non-compliant)

MI Definitions Impact TLF Rates in IDE Studies



Relative Risk and Assessment vs. Other IDE Studies

- Relative Risk (RR) indicates if TLF rates differ across treatment groups
- Independent analysis conducted to determine if OPTIMIZE RR is < pre-specified protocol 1.55 NI margin
 - Test significance level=0.025 (1-sided)
 - 55% RR margin assigned based on ratio of NI margin compared with estimated TLF (3.58% / 6.5% = 55%)
- RR = 1.09 (95% CI 0.81 – 1.46)**



- Conclusion: Svelte DES is non-inferior to Xience/Promus DES (p=0.009)**

OPTIMIZE Non-Inferiority Assessment

OPTIMIZE Study Endpoint Analysis	Xience/Promus DES n=812 Subjects	Svelte DES n=827 Subjects	Non-Inferiority	Confidence Interval	P Value
TLF: Protocol Defined TVMI	9.49% (74/780)	10.30% (82/796)	Absolute Margin 3.58%	0.81% [-2.15%, 3.78%]	0.034
TLF: Protocol Defined TVMI	9.49% (74/780)	10.30% (82/796)	Relative Margin 1.55	1.09 [0.81, 1.46]	0.009
TLF: SCAI Defined TVMI	3.33% (26/780)	3.66% (29/793)	Absolute Margin 2.97%	0.32% [-1.60%, 2.24%]	0.003

OPTIMIZE study non-inferiority is met applying the SCAI definition of MI OR a relative NI margin using the protocol definition of MI

TLF: Protocol Defined TVMI analysis is based on independent CEC-adjudicated OPTIMIZE outcomes using the protocol definition for MI, with a relative non-inferiority margin of 1.55 (absolute margin of 3.58% / estimated TLF of 6.5%).

TLF: SCAI Defined TVMI analysis is based on independent CEC-adjudicated OPTIMIZE outcomes using the SCAI definition for MI, with a non-inferiority margin based on 5.4% TLF rate observed in the BIONICS study (which used SCAI definition for MI).



Conclusions (1)

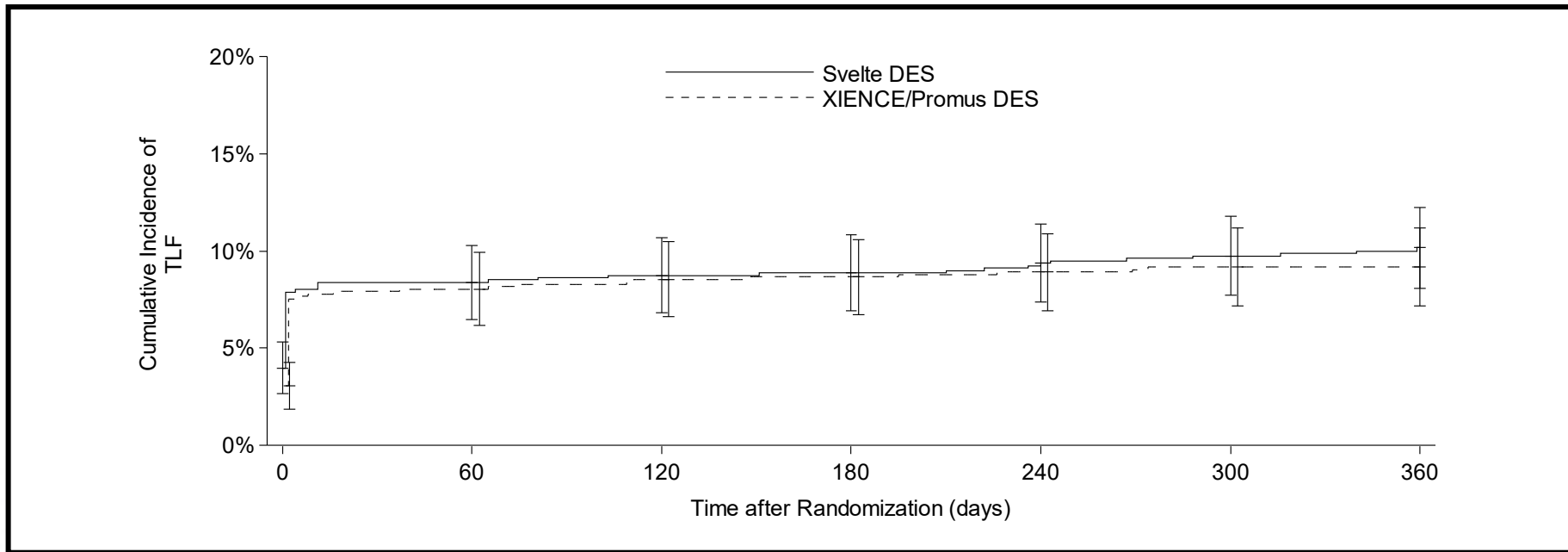
- **Based on the prespecified study statistical analysis plan, Svelte DES did not meet the threshold for non-inferiority using the prespecified absolute non-inferiority margin**
- **An unprecedented rate of TVMI (~8.8% in both groups), reflecting the frequency of troponin use as biomarker, contributed to a high rate of TLF (9.9% vs. 6.5% expected), effectively underpowering the OPTIMIZE study**
 - **Powering based on TLF rates observed in OPTIMIZE would have required a 3x increase in the IDE study population (n~4,698)**
 - **OPTIMIZE was powered based on EVOLVE II TLF (6.5%) derived from control population using 99% CK/CK-MB**

Conclusions (2)

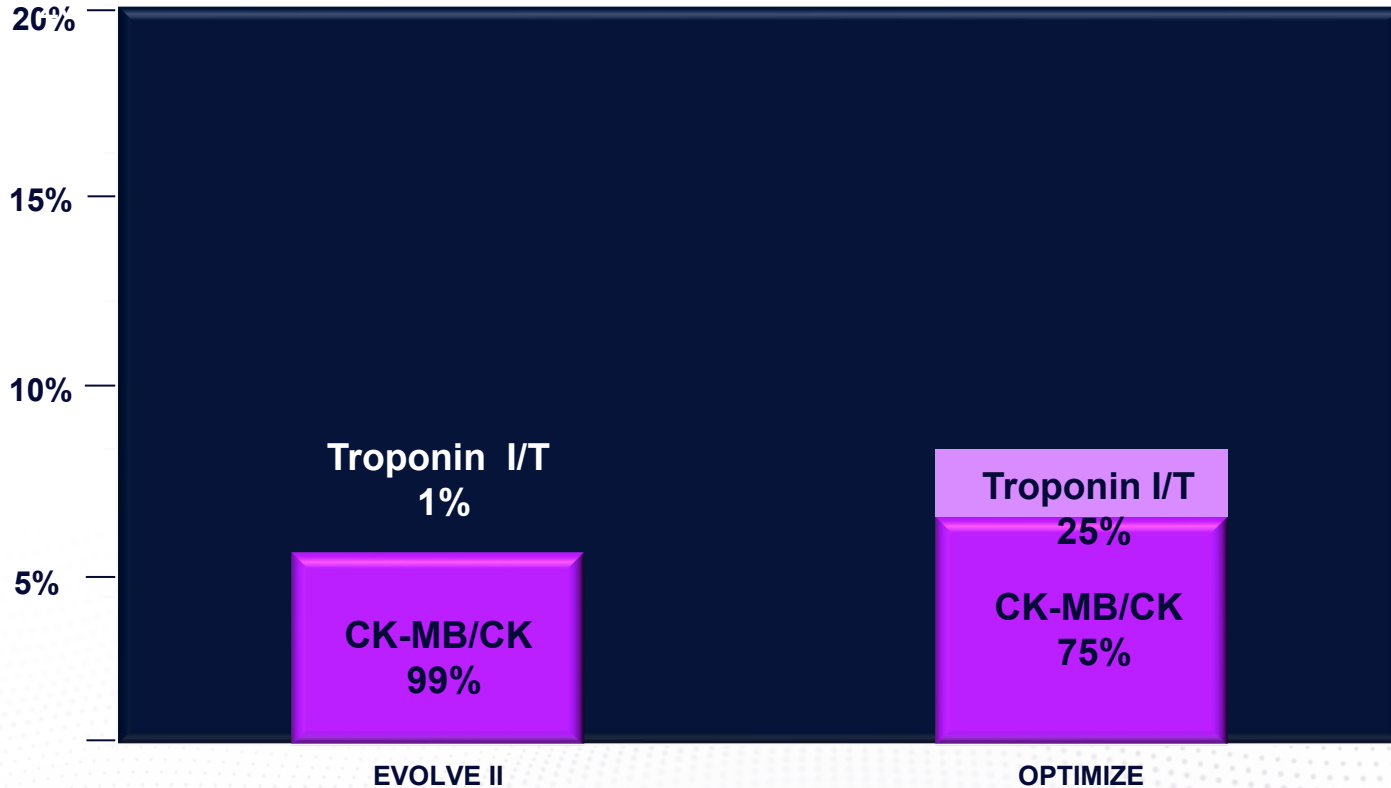
- Exploratory analyses of OPTIMIZE results using either a comparable relative non-inferiority margin with the protocol definition of MI or the SCAI definition of MI demonstrated non-inferiority of Svelte DES vs Xience/Promus
- No differences between Xience/Promus and Svelte DES were observed for any primary or secondary endpoints (including the very low rate of TLR and stent thrombosis) in this ‘more comers’ study population
- Standardization of IDE study definitions and biomarkers used in assessment of TVMI is urgently needed as evolving changes in biomarker selection will impact the size and integrity of future pivotal DES trials

Backups

OPTIMIZE Primary Endpoint: 12-Month TLF (ITT)



Cardiac Biomarkers, TVMI Definition Impact TLF

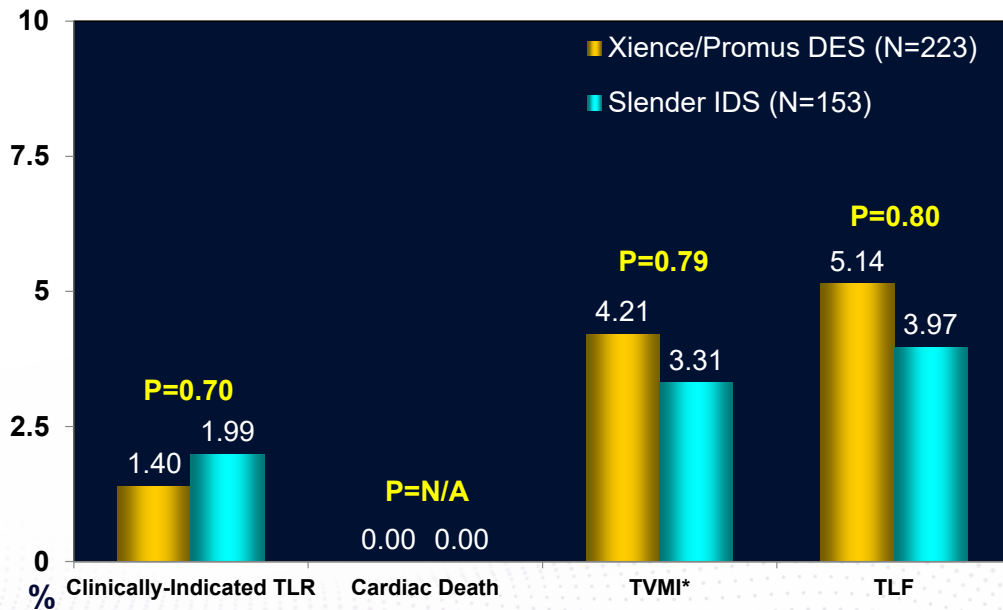


Direct Stenting Subset: Slender IDS vs. Control

Baseline Characteristics

Per Subject* Per Lesion†	Xience/Promus DS Cohort n=223 Subjects N=251 Lesions	Slender IDS DS Cohort n=153 Subjects N=178 Lesions	P value
Diabetes*	27.8%	24.8%	0.55
Insulin-Dependent	9.0%	6.5%	0.44
RVD†, mm	2.82 ± 0.48	2.83 ± 0.45	0.80
MLD†, mm	1.08 ± 0.37	1.05 ± 0.39	0.34
% DS†	61.3 ± 11.98	62.7 ± 12.79	0.25
Lesion Length†, mm	13.1 ± 6.51	13.9 ± 5.85	0.22
Length >20 mm	12.7%	13.6%	0.80
Bend ≥ 45*†	18.8%	21.8%	0.40
Moderate-Severe Tortuosity†	18.0%	23.0%	0.17
Moderate-Severe Calcification†	28.2%	30.0%	0.71
Modified AHA/ACC B2/C†	64.9%	71.6%	0.10
Lesion Success†	99.6%	98.9%	0.57
Device Success†	96.4%	98.9%	0.13
Direct Stent Strategy Success†	95.2%	95.5%	1.00
Procedure Success*	96.4%	96.7%	1.00
Post-dilatation†	37.9%	27.0%	0.02

12-Month TLF



* Spontaneous MI is the rise of cardiac biomarkers with ≥1 value >99th percentile of the ULN + 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 or troponin >3X URL), ii) new pathological Q waves, or iii) autopsy evidence of acute MI.