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

Dean J. Kereiakes, MD

The Christ Hospital Heart and Vascular Center / The Lindner Research Center

Cincinnati, OH

Sunil Rao, MD, A.J.J. Ijsselmuiden, MD, Robert Feldman, MD, James Zidar, MD, Steven Yakubov, MD, S. Chiu Wong, MD, John Lasala, MD, Pieter Stella, MD, David Cohen, MD and Shigeru Saito, MD on behalf of the OPTIMIZE Investigators

TCT Late Breaking Trials
Main Arena
Saturday, October 17, 2020 11:40 AM EST

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Disclosure Statement of Financial Interest

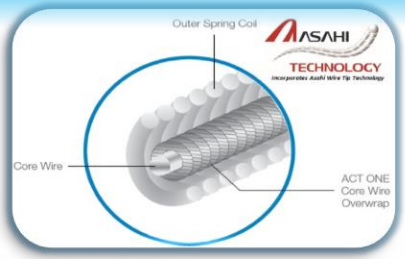
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Consulting Fees/Honoraria	Boston Scientific Corporation
Consulting Fees/Honoraria	Caliber Therapeutics/ Orchestra Biomed
Consulting Fees/Honoraria	Elixir Medical, Inc.
Consulting Fees/Honoraria	Shockwave
Consulting Fees/Honoraria	SINO Medical Sciences Technologies, Inc.
Consulting Fees/Honoraria	**Svelte Medical Systems, Inc.**
Major Stock Shareholder/Equity	Ablative Solutions, Inc.

Faculty disclosure information can be found on the app

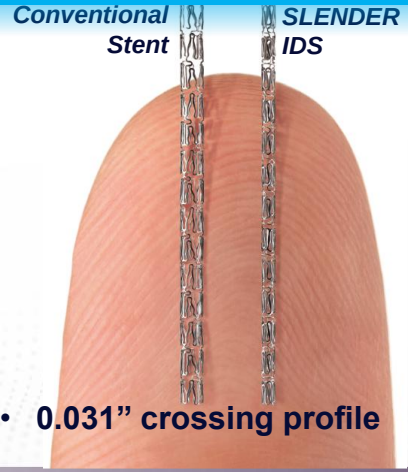
SLENDER Integrated Delivery System (IDS) Designed to Facilitate Direct Stenting, TRI

Asahi Wire Tip Technology



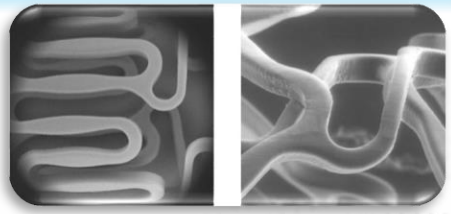
- Middleweight wire (1.2g tip load)
- Braiding similar to Sion line of wires

World's Lowest Profile DES



- 0.031" crossing profile

Designed for Direct Stenting



- Low compliant, higher pressure SDS balloon (¼ size > RBP)
- New class of drug coating (PEA), enzymatic-mediated bioresorption

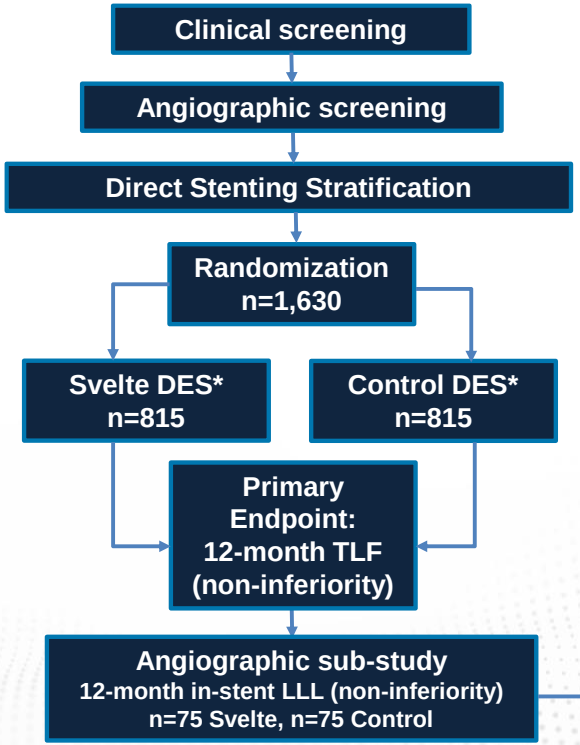
OPTIMIZE Pivotal Trial

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 ≤ 24mm***
  - ***% DS ≤ 90%***
  - ***Angulation ≤ 90°***
  - ***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	**Dean Kereiakes, MD** The Christ Hospital Heart and Vascular Center / The Lindner Research Center Cincinnati, OH, USA	**Sunil Rao, MD** Duke University Medical Center Veterans Administration Medical Center Durham, NC, USA
Steering Committee	David Cohen, MD, University of Missouri-Kansas City, MO John Lasala, MD, Washington University-St. Louis, MO Pieter Stella, MD, UMC Utrecht, NL	S. Chiu Wong, MD, Weill Cornell Medical Center, NY, NY Steven Yakubov, MD, Ohio Health, Columbus, OH James Zidar, MD, NC Heart & Vascular, Raleigh, NC
OUS Principal Investigators	Europe PI: A.J.J. Ijsselmuiden, MD Amphia Hospital, Breda, NL	Japan and Angio Sub-Study PI: Shigeru Saito, MD Shonan Kamakura General Hospital, Kamakura, JP
Angiographic Core Laboratory	QCA: Alexandra Lansky, MD (Director) Yale Cardiovascular Research Group New Haven, CT, USA	IVUS: Robert Wyza, MS (Manager) University Hospitals Cleveland Medical Ctr Cleveland, OH, USA
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		Subjects		Subjects	
107	**A.J.J. Ijsselmuiden, MD** *Amphia Hospital, Breda, NL*	59	**Craig Siegel, MD** *St. David's MC, Round Rock, TX*	27	**Jeremiah Depta, MD** *Rochester General Hospital, Rochester, NY*
100	**Floris Kauer, MD** *A. Schweitzer Hospital, Dordrecht, NL*	47	**Barry Bertolet, MD** *North Mississippi MC, Tupelo, MS*	35	**Kenji Ando, MD** *Kokura Memorial Hospital, Kitakyushu, JP*
95	**Giovanni Amoroso, MD** *OLVG Hospital, Amsterdam, NL*	43	**Frank Eefting, MD** *St. Antonius, Nieuwegein, NL*	20	**Muhammad Arida, MD** *LeBauer Heart Care, Greensboro, NC*
89	**Dean Kereiakes, MD** *The Christ Hospital, Cincinnati, OH*	36	**Shigeru Saito, MD** *Shonan Kamakura GH, Kamakura, JP*	20	**David Trice, MD** *Thomas Hospital, Fairhope, AL*
75	**James Zidar, MD** *NC Heart & Vascular, Raleigh, NC*	35	**Edgar Carrell, MD** *AMITA Health, Hinsdale, IL*	18	**Sammy Elmariah, MD** *Massachusetts General Hospital, Boston, MA*
72	**Pim Tonino, MD** *Catharina Hospital, Eindhoven, NL*	35	**Bart de Smet, MD** *Meander Hospital, Amersfoort, NL*	17	**Donald Westerhausen, MD** *Elkhart General Hospital, Elkhart, IN*
71	**Samer Somi, MD** *HAGA Hospital, Den Haag, NL*	31	**Giora Weisz, MD** *Montefiore MC, Bronx, NY*	17	**Atsushi Hirohata, MD** *Sakikibara Heart Institute, Okayama, JP*
64	**Ron Caputo, MD** *St. Joseph's Hospital, Syracuse, NY*	27	**Natalia Berry, MD** *Brigham & Women's Hospital, Boston, MA*	17	**Akihiko Takahashi, MD** *Sakuraki Takahashi Hospital, Kobe, JP*

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%

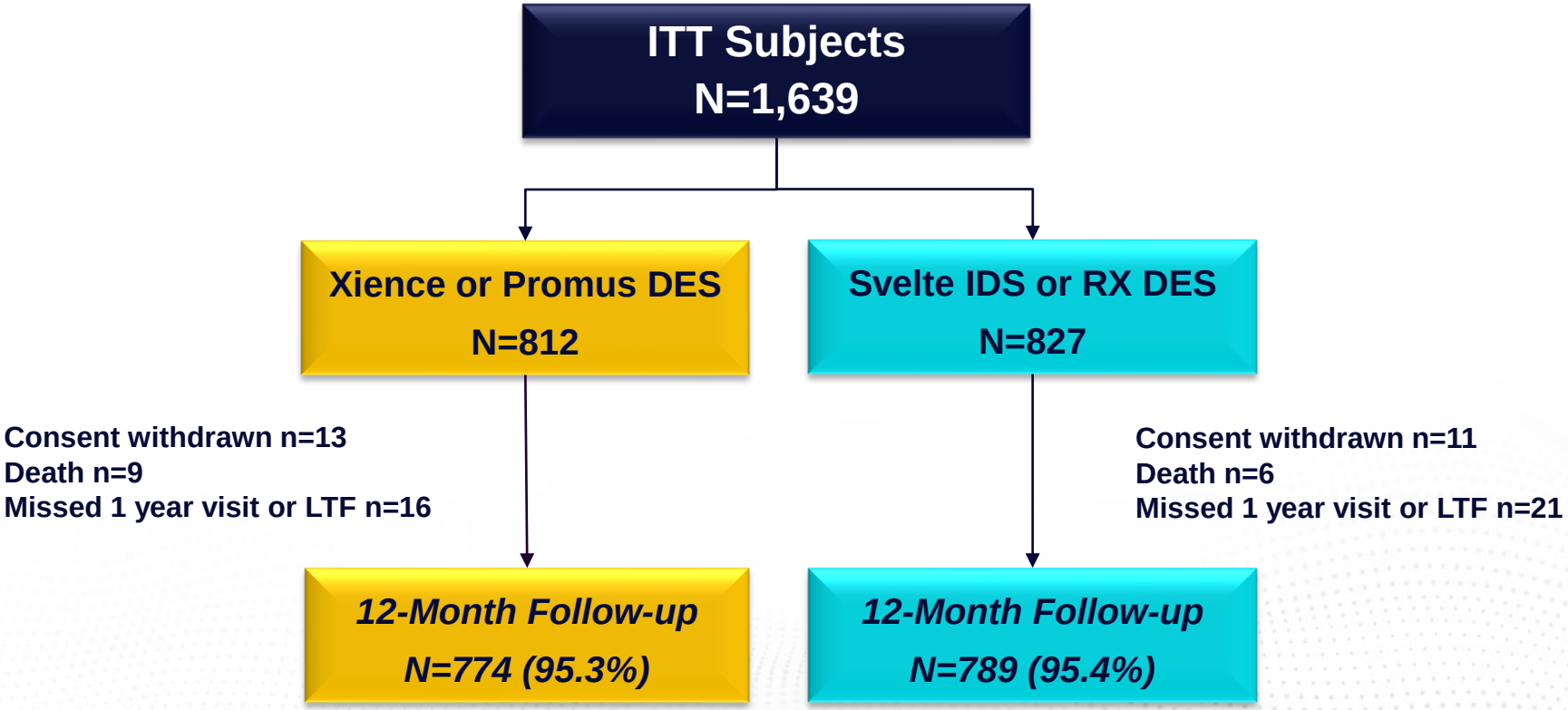
N = 1,630 subjects (815 per group at 1:1 ratio)

* 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 ≥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

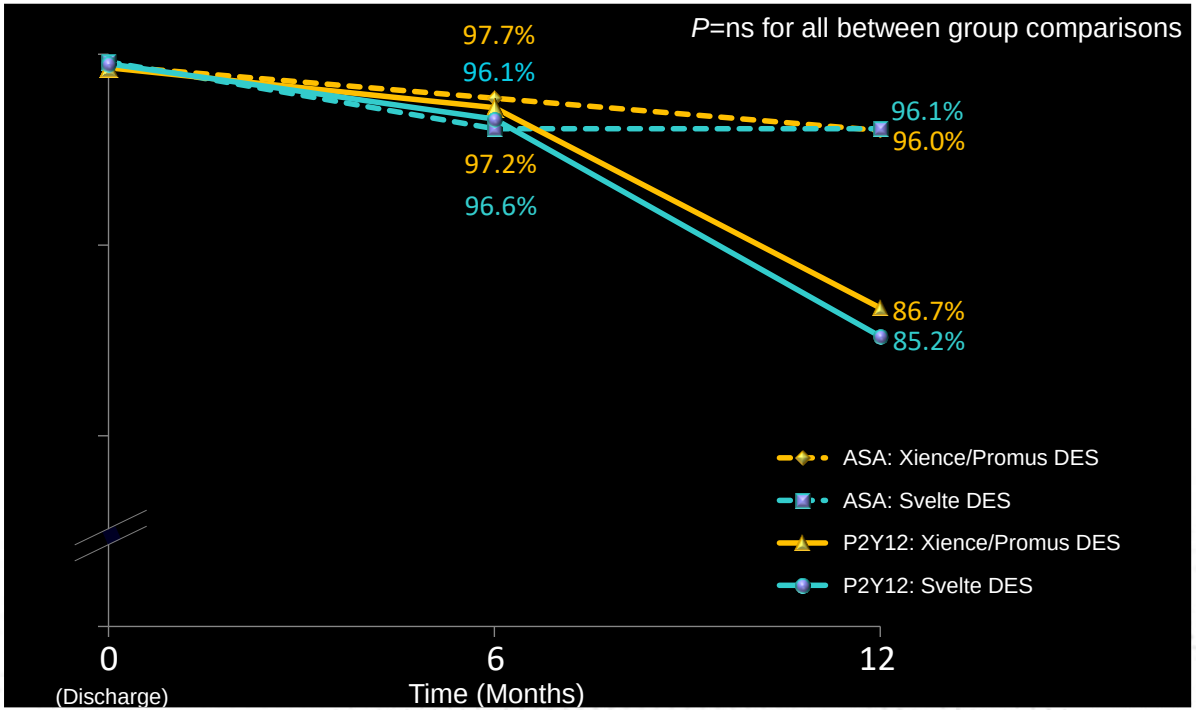
OPTIMIZE Procedural Characteristics

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)

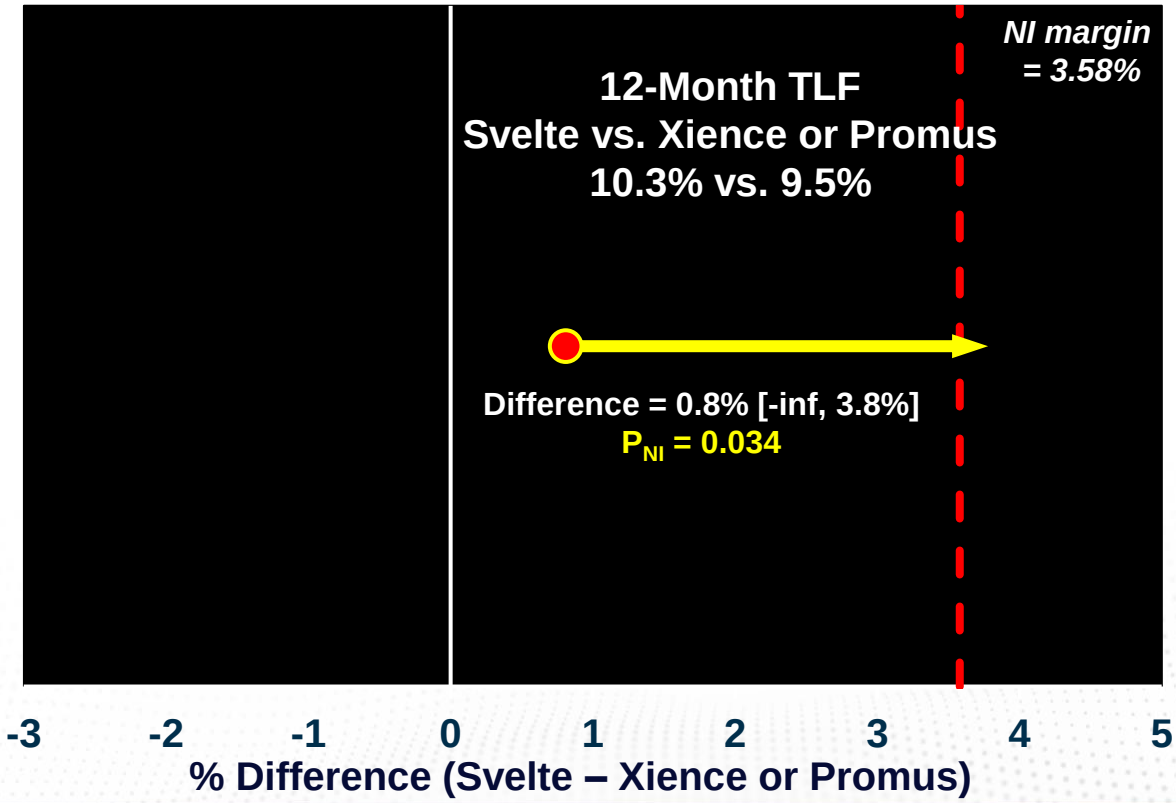
Per Lesion	Xience/Promus DES n=812 Subjects *n=970 Lesions*	Svelte DES n=827 Subjects *n=1,018 Lesions*	*P* value
RVD	2.89 ± 0.49	2.91 ± 0.48	0.33
MLD, In-Stent, mm	2.71 ± 0.44	2.71 ± 0.46	0.95
MLD, In-Segment, mm	2.60 ± 0.49	2.61 ± 0.48	0.46
%DS, In-Stent, %	6.07 ± 8.38	6.78 ± 8.49	0.06
%DS, In-Segment, %	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*

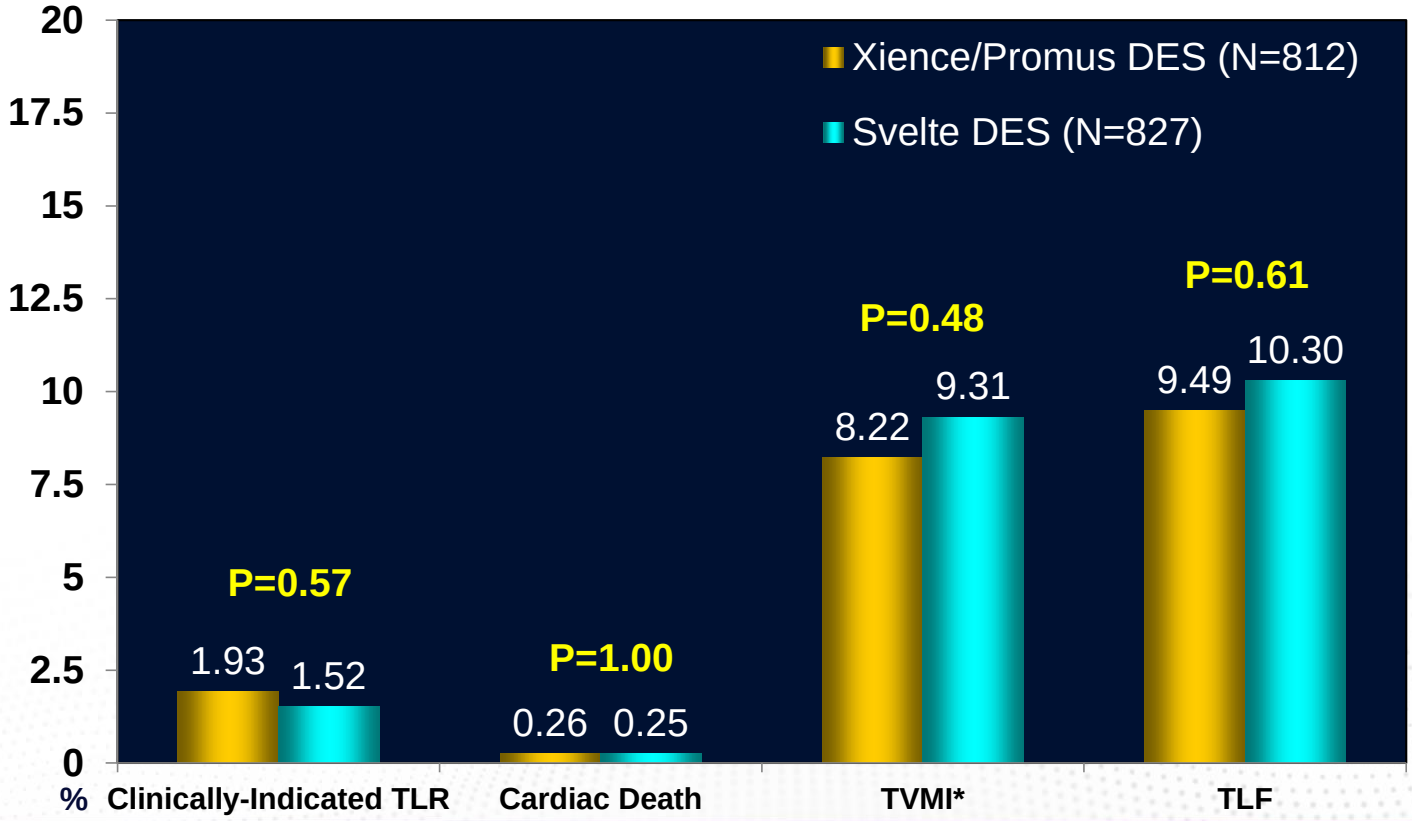


* The study protocol provided investigators with recommendations for the administration of DAPT ($P2Y_{12}$ inhibitors clopidogrel, ticlopidine, prasugrel, or ticagrelor + aspirin) but loading dose, duration of ongoing administration and use of antiplatelet agents not aforementioned was left to the discretion of investigators.

OPTIMIZE Primary Endpoint: 12-Month TLF (ITT)



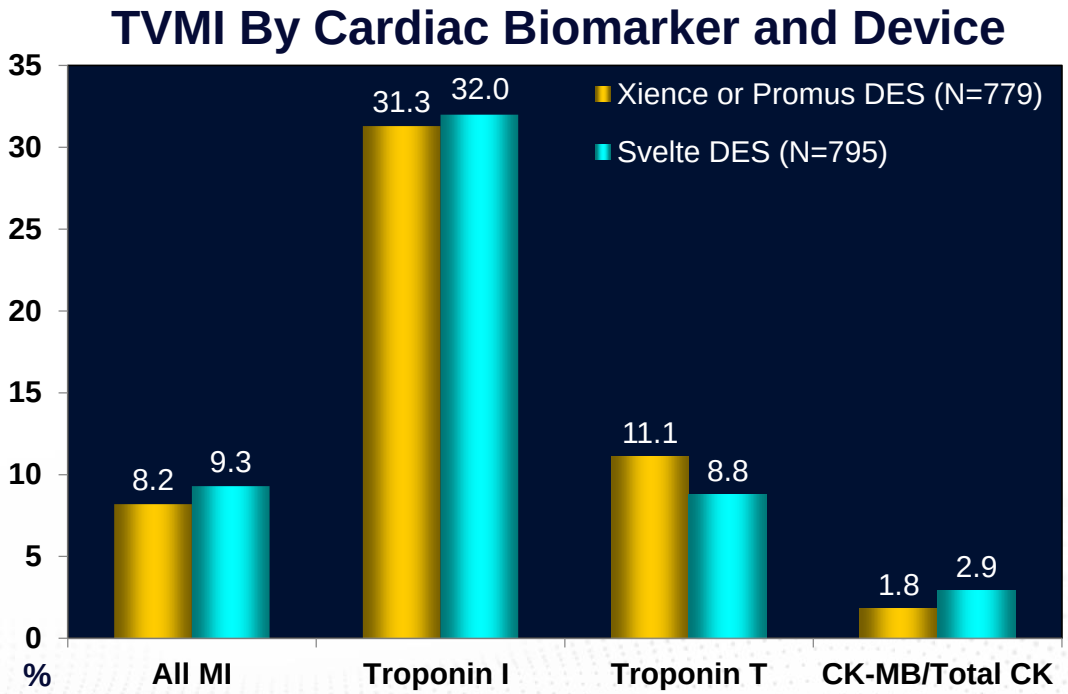
OPTIMIZE 12-Month TLF Components



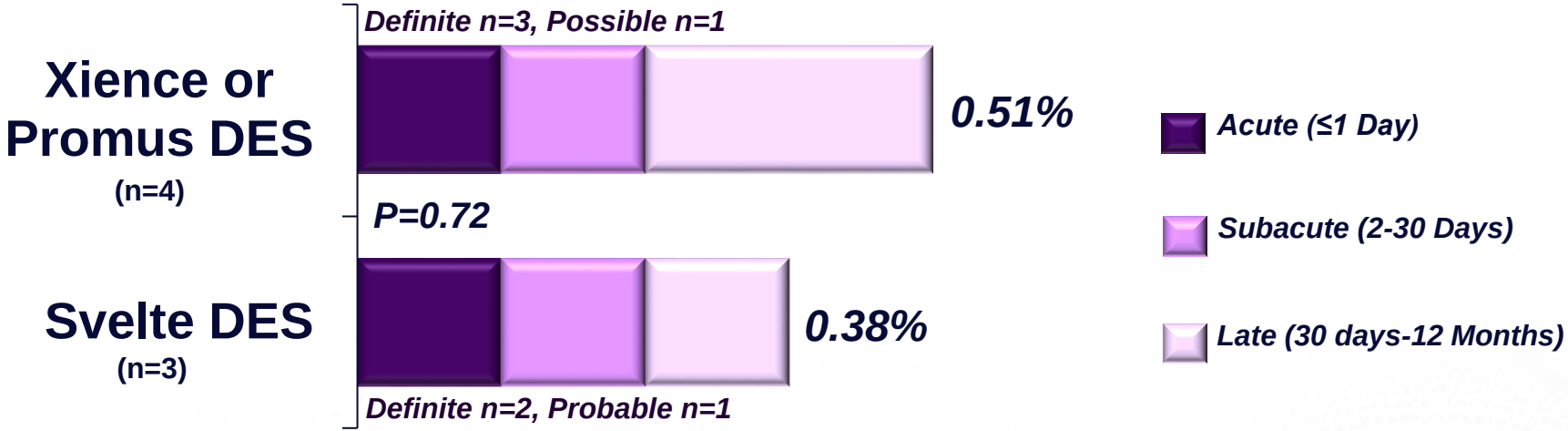
* Spontaneous MI is the rise of cardiac biomarkers with ≥1 value >99th percentile of the ULN + evidence of myocardial ischemia. Peri-PCI MI is defined as ≥1 of the following: i) biomarker elevations within 48 hours of PCI (based on CK-MB *or* troponin >3X URL), ii) new pathological Q waves, or iii) autopsy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

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**



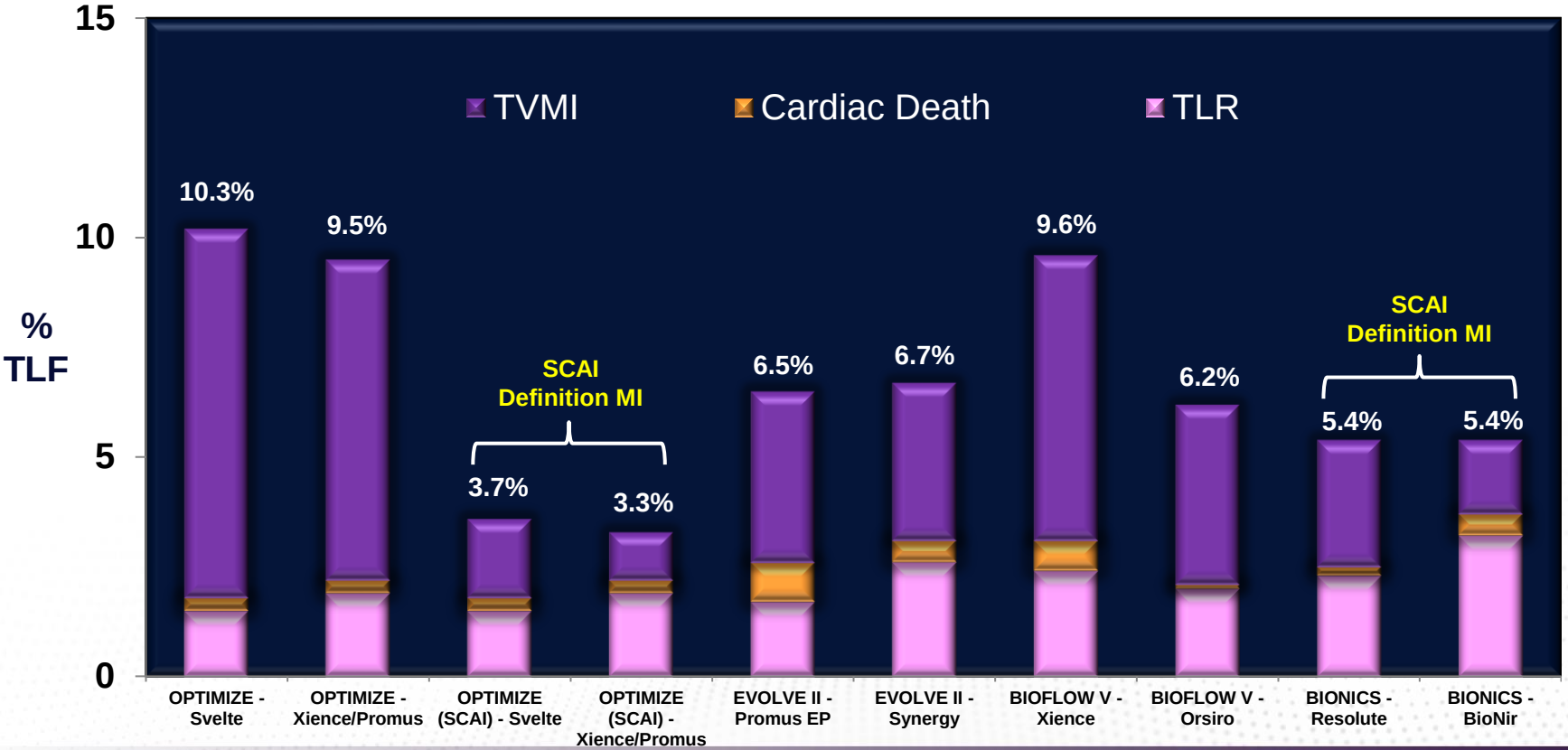
OPTIMIZE All Stent Thrombosis Through 12 Months



Definite / Probable ST

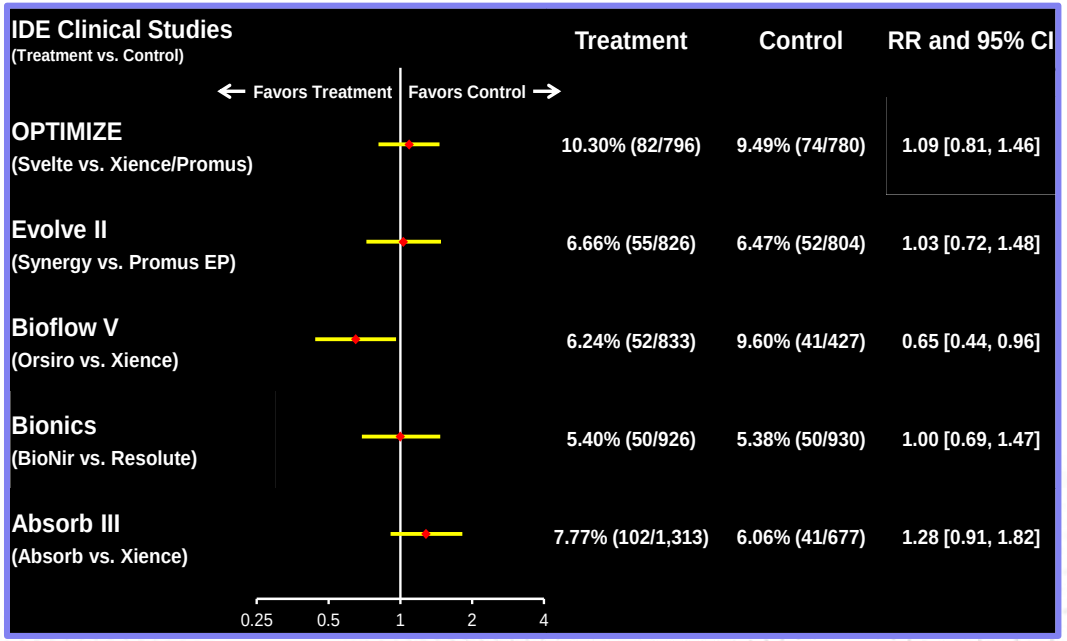
- Xience or Promus (n=3): Day 0, 7, 73; 3/3 subjects DAPT compliant
- Svelte (n=3): Day 0, 4, 302; 1/3 subjects DAPT compliant (1 clopidogrel allergy, 1 non-compliant)

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 Intverval	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)

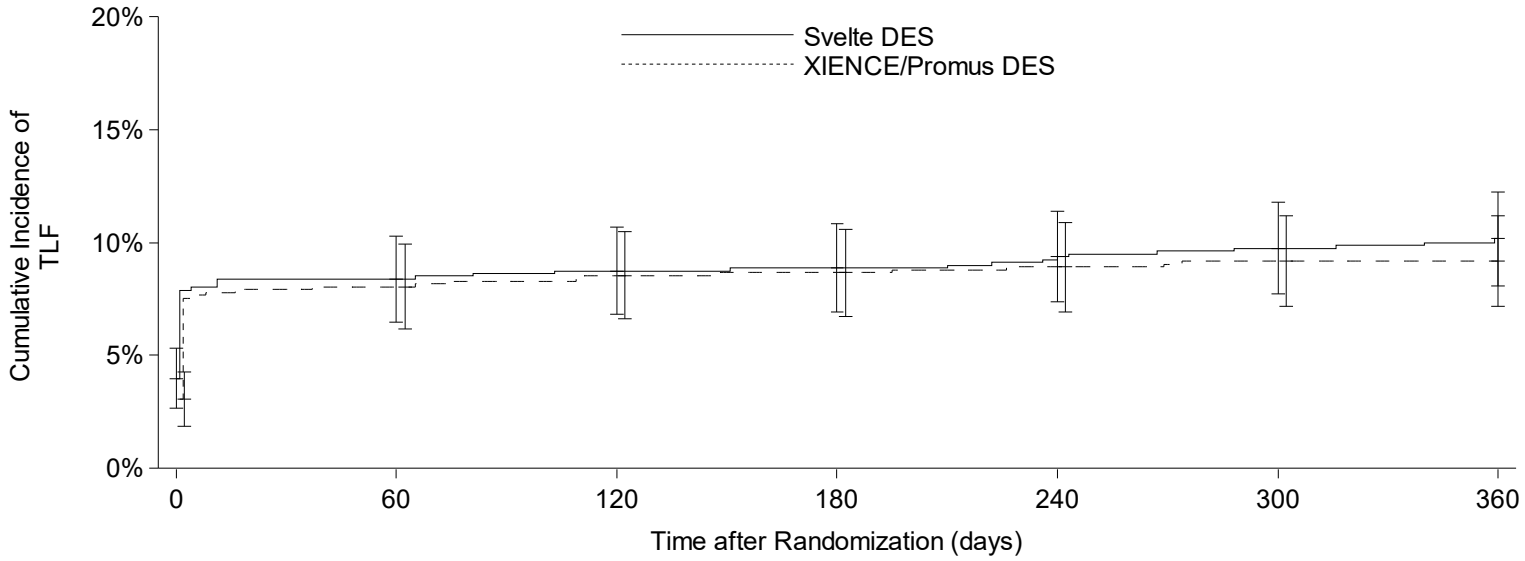
- **Based on the prespecified study statistical analysis plan, Svelte DES did not meet the threshold for non-inferiority using the prespecified absolute non-inferiority margin**
- **An unprecedented rate of TVMI (~8.8% in both groups), reflecting the frequency of troponin use as biomarker, contributed 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)

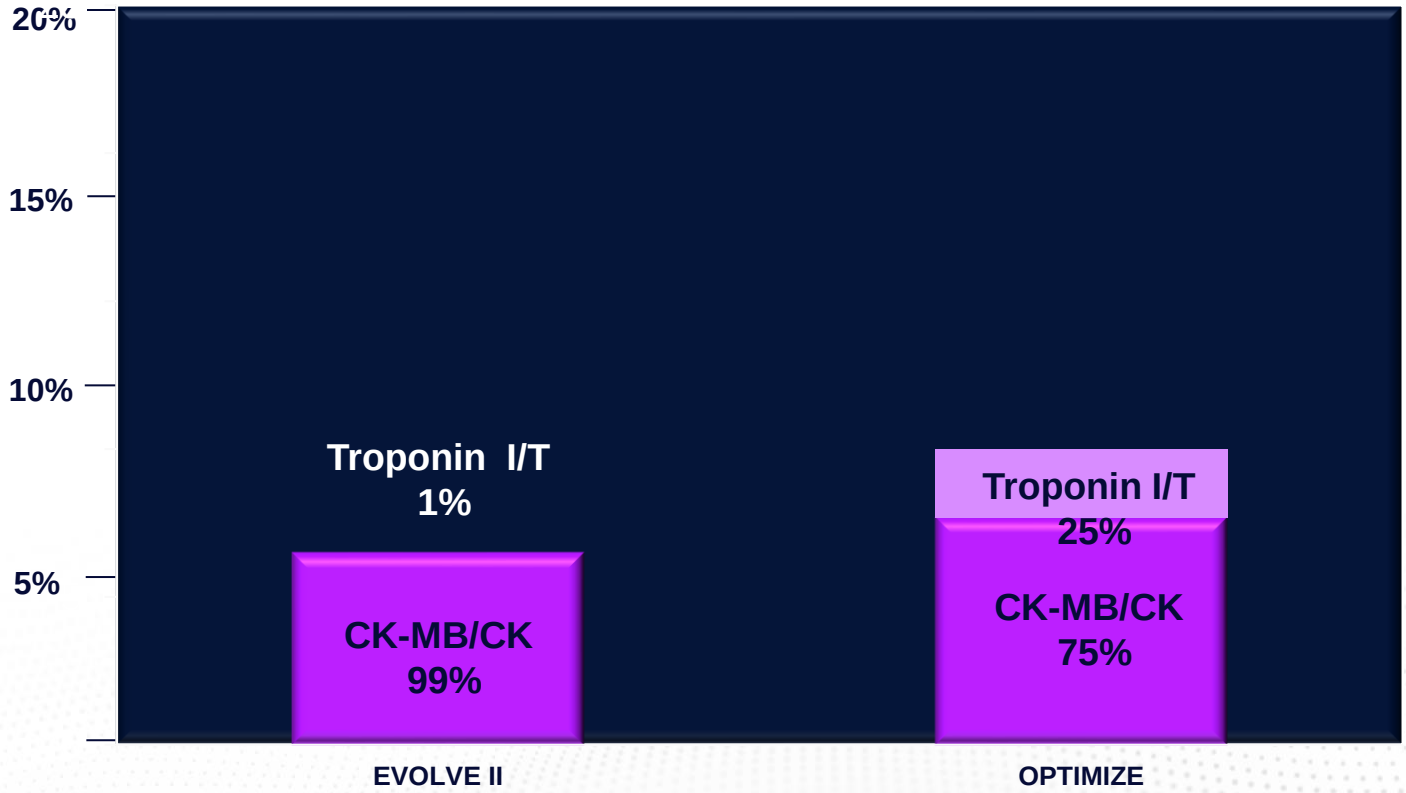
- **Exploratory analyses of OPTIMIZE results using either a comparable *relative* non-inferiority margin with the protocol definition of MI or the SCAI definition of MI demonstrated non-inferiority of Svelte DES vs Xience/Promus**
- **No differences between Xience/Promus and Svelte DES were observed 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

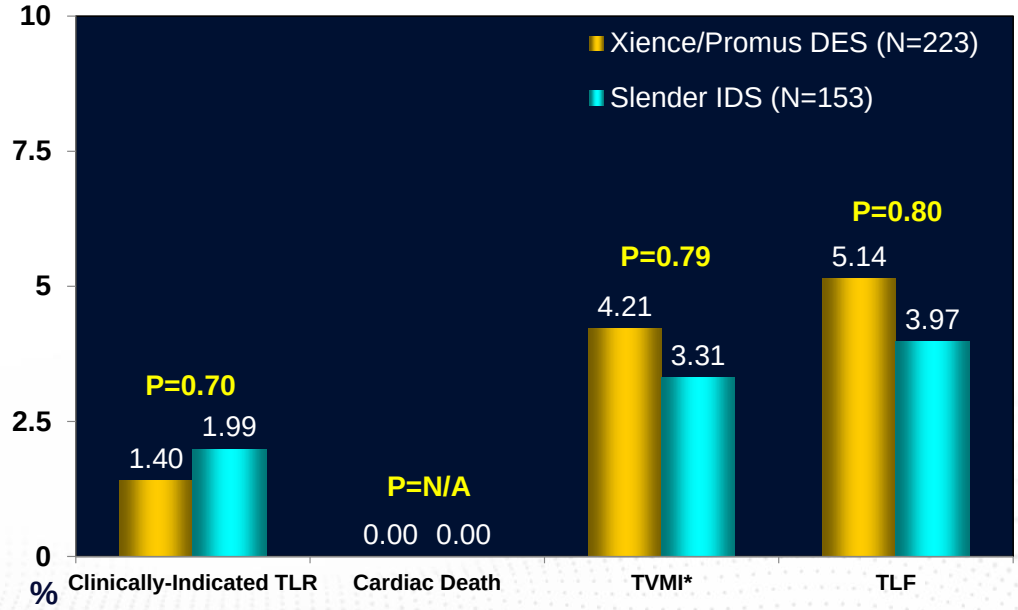


Direct Stenting Subset: Slender IDS vs. Control

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.**