Intravascular Lithotripsy for Treatment of Severely Calcified Coronary Artery Disease
The Disrupt CAD III Study

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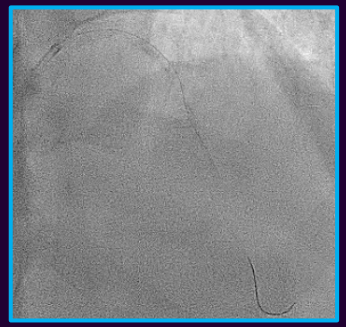
Disclosure Statement of Financial Interest

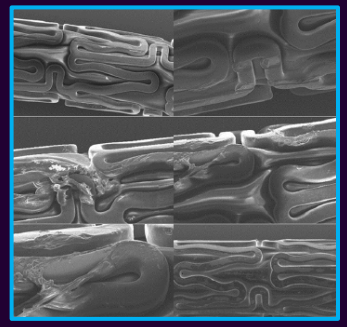
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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

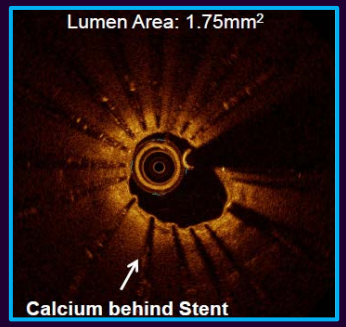
Coronary Calcification Impacts PCI



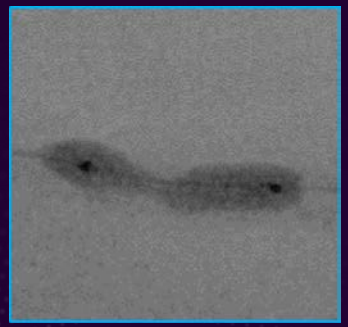
Impairs device crossing



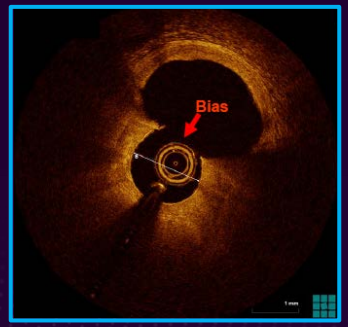
Delamination

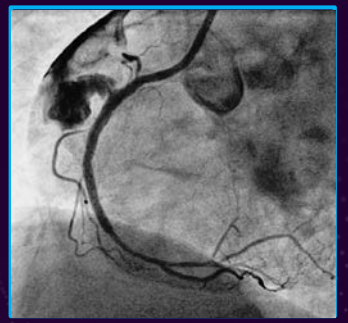


Under expansion



Balloon:
Insufficient force





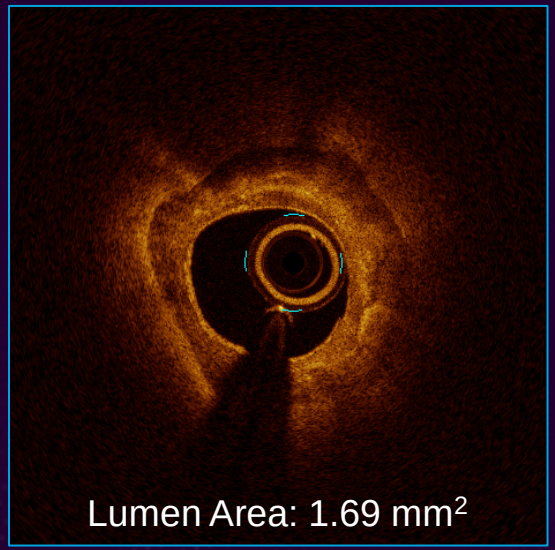
Atheroablative technologies
Atherectomy: Wire bias
Laser: Unpredictable

Acoustic Pressure Waves Fracture Calcium

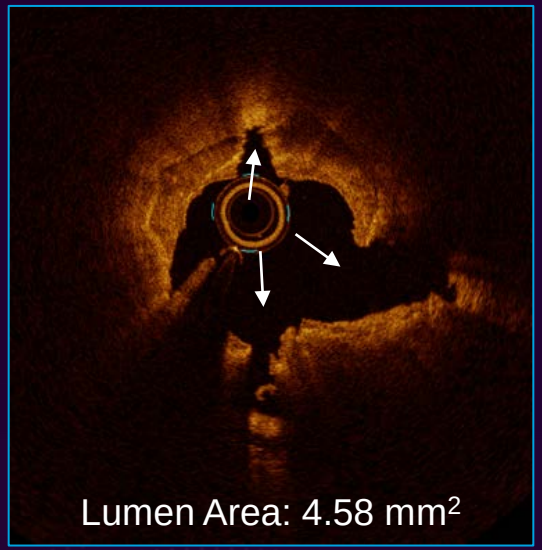
Acoustic pressure waves (1 pulse/sec) travel through tissue with an effective pressure of **~50 atm and fractures both superficial and deep calcium**

Multi-plane and Longitudinal Calcium Fracture

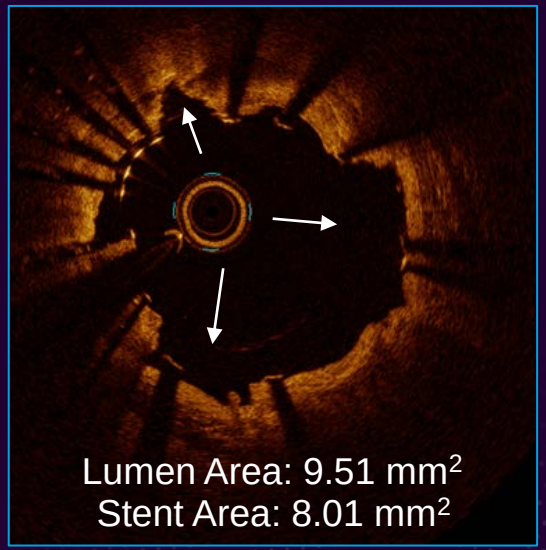
Pre-procedure



Post-IVL



Post-stent



Disrupt CAD III: Study Design*

Prospective, multicenter, single-arm global IDE
NCT03595176

Heavily calcified†, *de novo* coronary lesions
RVD 2.5-4.0 mm, stenosis ≥50%, lesion length ≤40mm
One roll-in patient per site allowed
47 global sites

Roll-in Population
N = 47

ITT Population
N= 384

30-day Follow-up

1-year Follow-up

2-year Follow-up

OCT Sub-study
N= 100

Richard Shlofmitz, MD
TCT 2020

*Kereiakes et al., *Am Heart J* 2020;225:10-18.
†Radio-opacities both sides of vessel ≥15 mm length by angiography or calcium angle ≥270 ° by OCT or IVUS

Major Endpoints

- Primary safety endpoint: Freedom from MACE at 30 days
  - Cardiac death, or
  - Myocardial infarction*, or
  - Target vessel revascularization
- Primary effectiveness endpoint: Procedural success
  - Successful stent delivery with residual stenosis <50% and without in-hospital MACE
- Secondary endpoints:
  - Device crossing success†
  - Angiographic success‡
  - Procedural success with residual stenosis ≤30% and without in-hospital MACE
  - Sensitivity analysis for peri-procedural MI using the SCAI and 4th Universal Definitions§

*CK-MB level >3x ULN through discharge (peri-procedural MI) and using the 4th Universal Definition of MI beyond discharge
†Delivery of IVL across the target lesion and delivery of lithotripsy without serious angiographic complications immediately after IVL
‡Stent delivery with < 50% or ≤ 30% residual stenosis and without serious angiographic complications at any time during the procedure
§ Moussa et al., *J Am Coll Cardiol* 2013;62:1563-70; Thygesen et al., *J Am Coll Cardiol* 2018;72:2231-64.

Key Clinical and Angiographic Eligibility Criteria

DISRUPT CAD III

Inclusion

- Biomarkers (troponin or CK-MB) normal within 12 hours prior to procedure
- LVEF >25% within 6 months of procedure
- Single *de novo* target lesion with stenosis ≥70% and <100% or ≥50% and <70% with evidence of ischemia, or FFR ≤0.80, or lumen area ≤4.0 mm^2 by IVUS or OCT
- Target vessel RVD ≥2.5 mm and ≤4.0 mm
- Lesion length ≤40 mm
- Lesion site severe calcification:
  - Angiographic radio-opacities prior to contrast involving both sides of arterial wall with total calcium length ≥15 mm, or presence of ≥270° of calcium on at least one cross section by IVUS or OCT

Exclusion

- Renal failure (serum creatinine >2.5 or chronic dialysis)
- Acute MI within 30 days prior to index procedure

Statistical Methods

- Pre-specified performance goals (PG) were based on the rates from the predicate single-arm, non-randomized ORBIT II IDE study*:
  - Enrolled similar patient population with similar endpoints and definitions
  - Relative risk of 1.5 was utilized
- Primary safety performance goal: 84.4%
  - Calculation: 100% - (1.5 * observed 30-day MACE rate in ORBIT II of 10.4%)
- Primary effectiveness performance goal: 83.4%
  - Calculation: 100% - (1.5 * observed procedural failure rate in ORBIT II of 11.1%)
- Power ≈ 81% for both co-primary PGs at a 1-sided type 1 error rate of 5%
  - Expected freedom from MACE at 30-days = 89.6% power
  - Expected procedural success rate = 88.9% power
  - N = 392 evaluable patients with expected rate of attrition = 5%

*Chambers et al., *JACC Cardiovasc Interv*. 2014;7(5): 510-518
Kereiakes et al., *Am Heart J* 2020;225:10-18

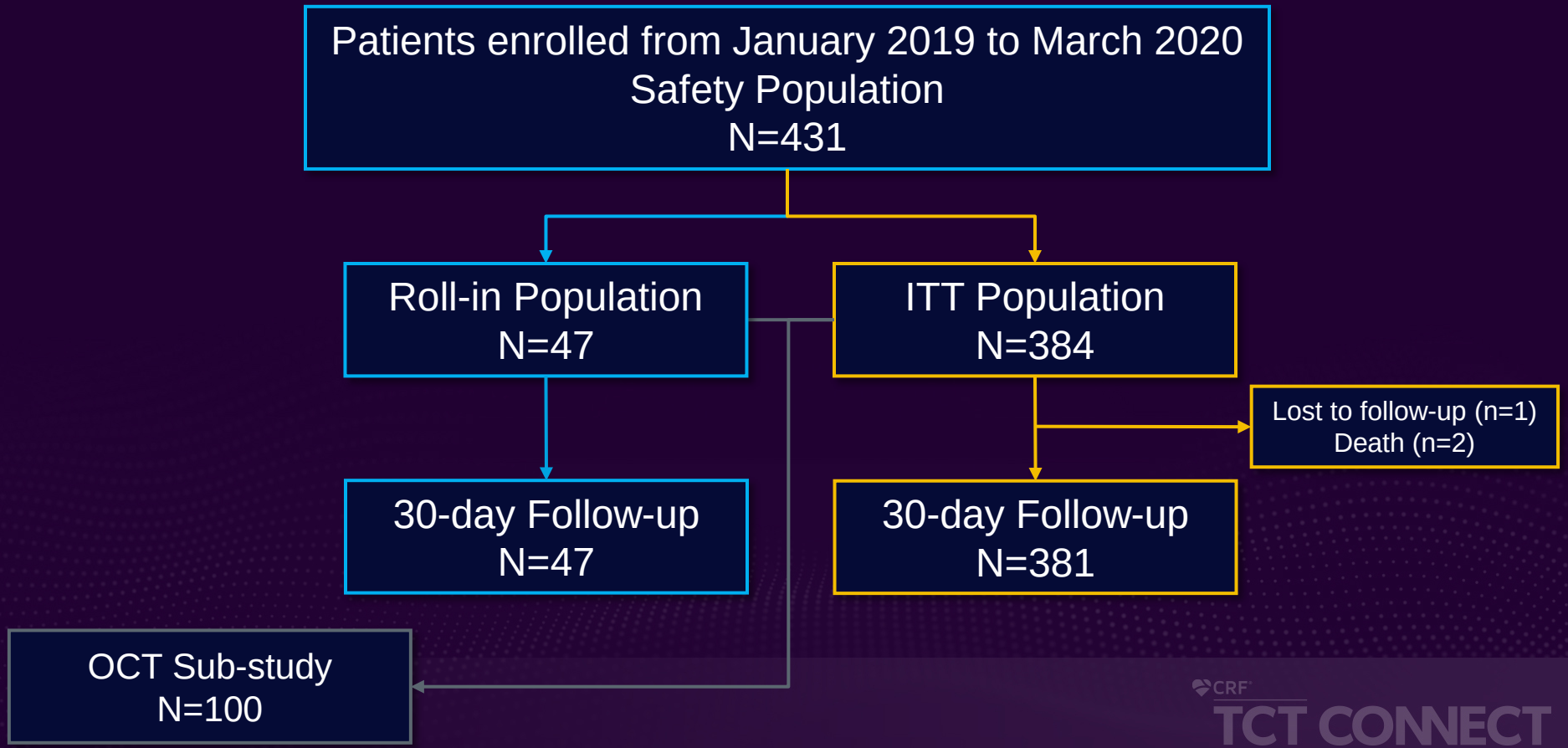
Disrupt CAD III Study Support

Principal Investigators	Dean Kereiakes The Christ Hospital, Cincinnati, OH Jonathan Hill Royal Brompton Hospital, London, UK
Study Chairman	Gregg W. Stone Mount Sinai Heart Health System, New York, NY
Clinical Events Committee	Steven Marx (Chair) Cardiovascular Research Foundation, New York, NY
Data Safety Monitoring Board	Ehtisham Mahmud (Chair) Cardiovascular Research Foundation, New York, NY
Angiographic Core Laboratory	Maria Alfonso (Director) Cardiovascular Research Foundation, New York, NY
OCT Core Laboratory	Akiko Maehara (Director) Cardiovascular Research Foundation, New York, NY

Disrupt CAD III: Top Enrolling Centers

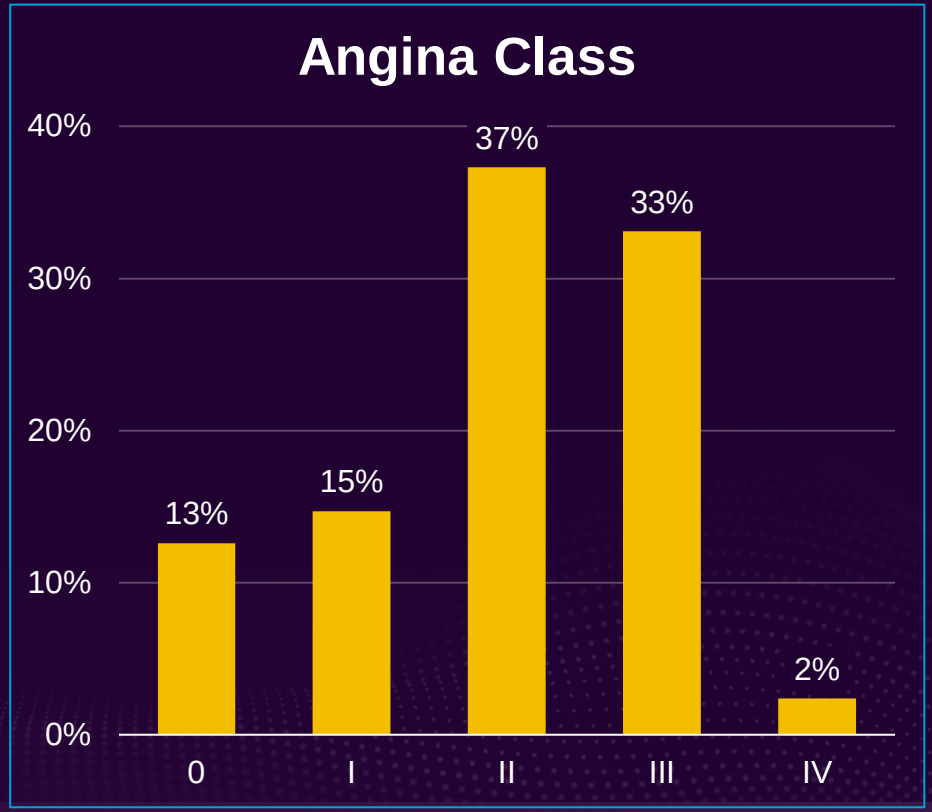
1. Richard Shlofmitz St. Francis Hospital	8. Barry Bertolet North Mississippi Medical Center
2. Andrew Klein Piedmont Heart Institute	9. John Wang MedStar Union Memorial Hospital
3. Robert Riley The Christ Hospital	10. Jean Fajadet Clinique Pasteur
4. Matthew Price Scripps Clinic	10. Alpesh Shah Houston Methodist Hospital
5. Howard Herrmann University of Pennsylvania	12. Sarang Mangalmurti Bryn Mawr Hospital
6. William Bachinsky UPMC Pinnacle Health	13. Robert Stoler Baylor Heart and Vascular Hospital
6. Ron Waksman MedStar Washington Hospital Center	13. Janusz Lipiecki Clinique des Domes

Study Flow and Follow-up



Baseline Clinical Characteristics

Characteristic	N=384
Age	71.2 ± 8.6
Male	76%
Hypertension	89%
Hyperlipidemia	89%
Diabetes mellitus	40%
Current smoker	12%
Prior MI	18%
Prior CABG	9%
Prior Stroke	8%
Renal insufficiency*	26%



*Defined as eGFR <60ml/min/1.73m^2; eGFR=estimated glomerular filtration rate using the MDRD formula

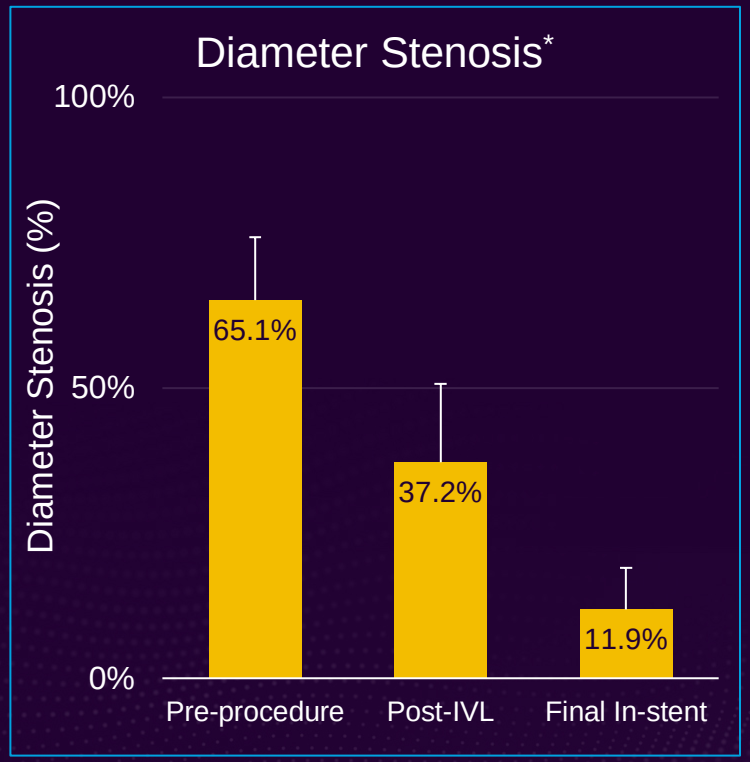
Angiographic Characteristics

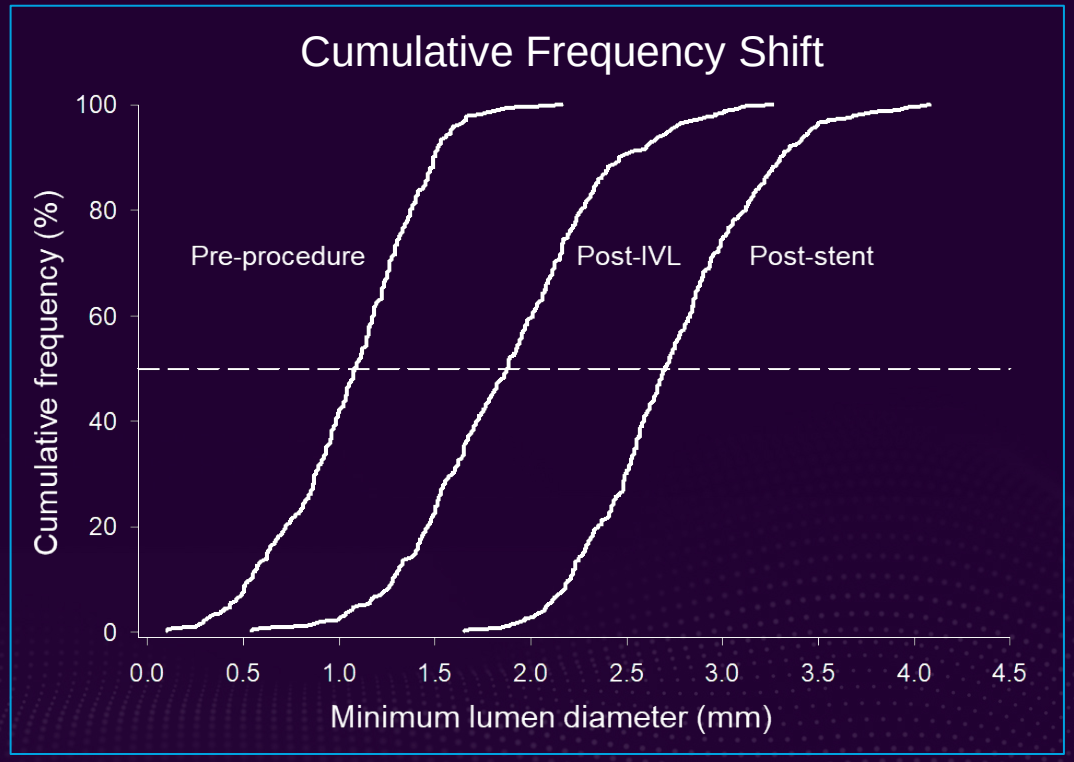
Core Lab Analysis		N=384
Target vessel	LAD	56.5%
	LCx	12.8%
	RCA	29.2%
	LM	1.6%
Reference vessel diameter, mm		3.0 ± 0.5
Minimum lumen diameter, mm		1.1 ± 0.4
Diameter stenosis		65.1 ± 10.8%
Lesion length, mm		26.0 ± 11.7
Calcified length, mm		47.9 ± 18.8
Severe calcification		100%

Procedural Characteristics

Characteristic	N=384
Total procedure time, min	59.0 ± 29.6
Pre-dilatation	55.2%
IVL catheters	1.2 ± 0.5
IVL pulses	68.8 ± 31.9
Max IVL inflation pressure, atm	6.0 ± 0.3
Post-IVL dilatation	20.7%
Number of stents	1.3 ± 0.5
Stent delivery	99.2%
Post-stent dilatation	99.0%

Angiographic Outcomes





*Final in-stent diameter stenosis ≤30% achieved in 99.5% of patients

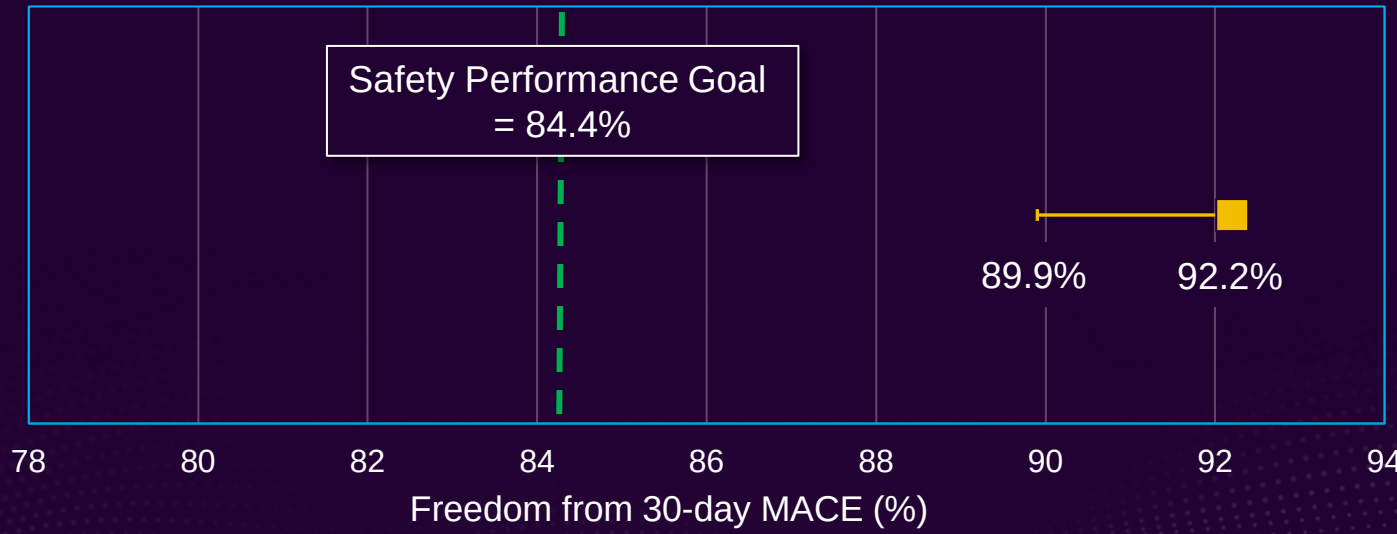
Angiographic Complications

Core Lab Analysis	Immediately Post-IVL	Final Post-stent
Any serious angiographic complication	2.6%	0.5%
Severe dissection (Type D-F)	2.1%	0.3%
Perforation	0.0%	0.3%
Abrupt closure	0.0%	0.3%
Slow flow	0.6%	0.0%
No-reflow	0.0%	0.0%

Primary Safety Endpoint

Freedom from 30-day MACE: *Cardiac death, MI, TVR*

30-day freedom from MACE	1-sided lower 95% CI	*P* value
92.2% (353/383)	**89.9%**	**<0.0001***



Primary Safety Endpoint Met

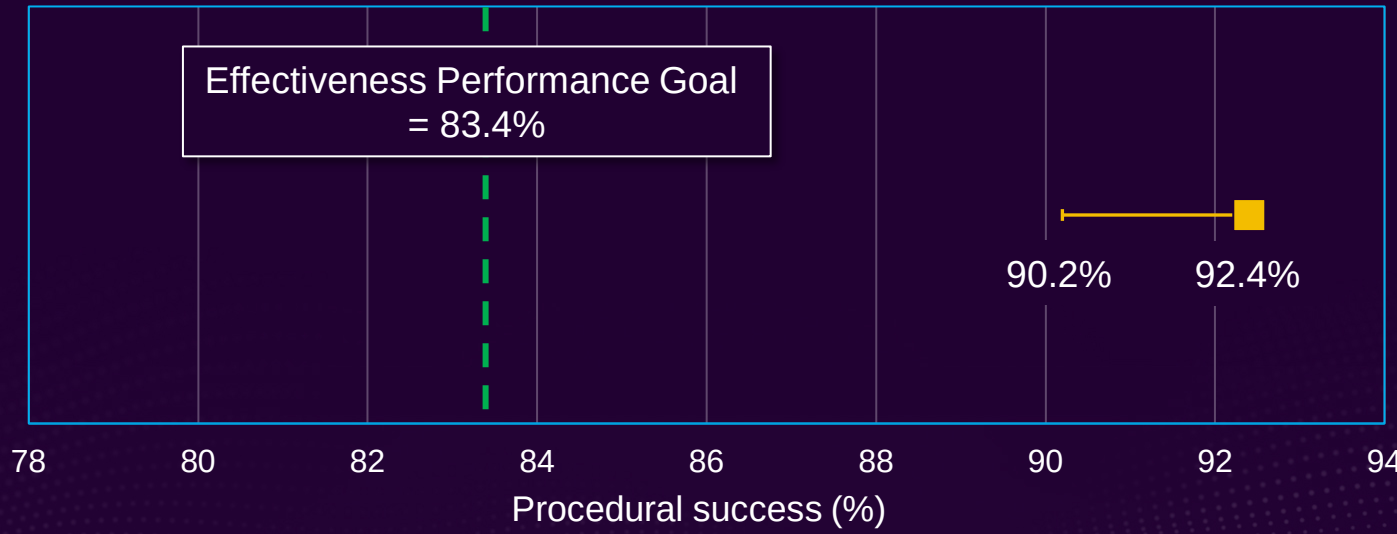
One-sided lower 95% CI of 89.9% > pre-specified performance goal of 84.4%

*One-sided asymptotic Wald test for binomial proportion

Primary Effectiveness Endpoint

Procedural success: *Stent delivery with residual stenosis <50% without in-hospital MACE*

Procedural success	1-sided lower 95% CI	*P* value
92.4% (355/384)	**90.2%**	**<0.0001***

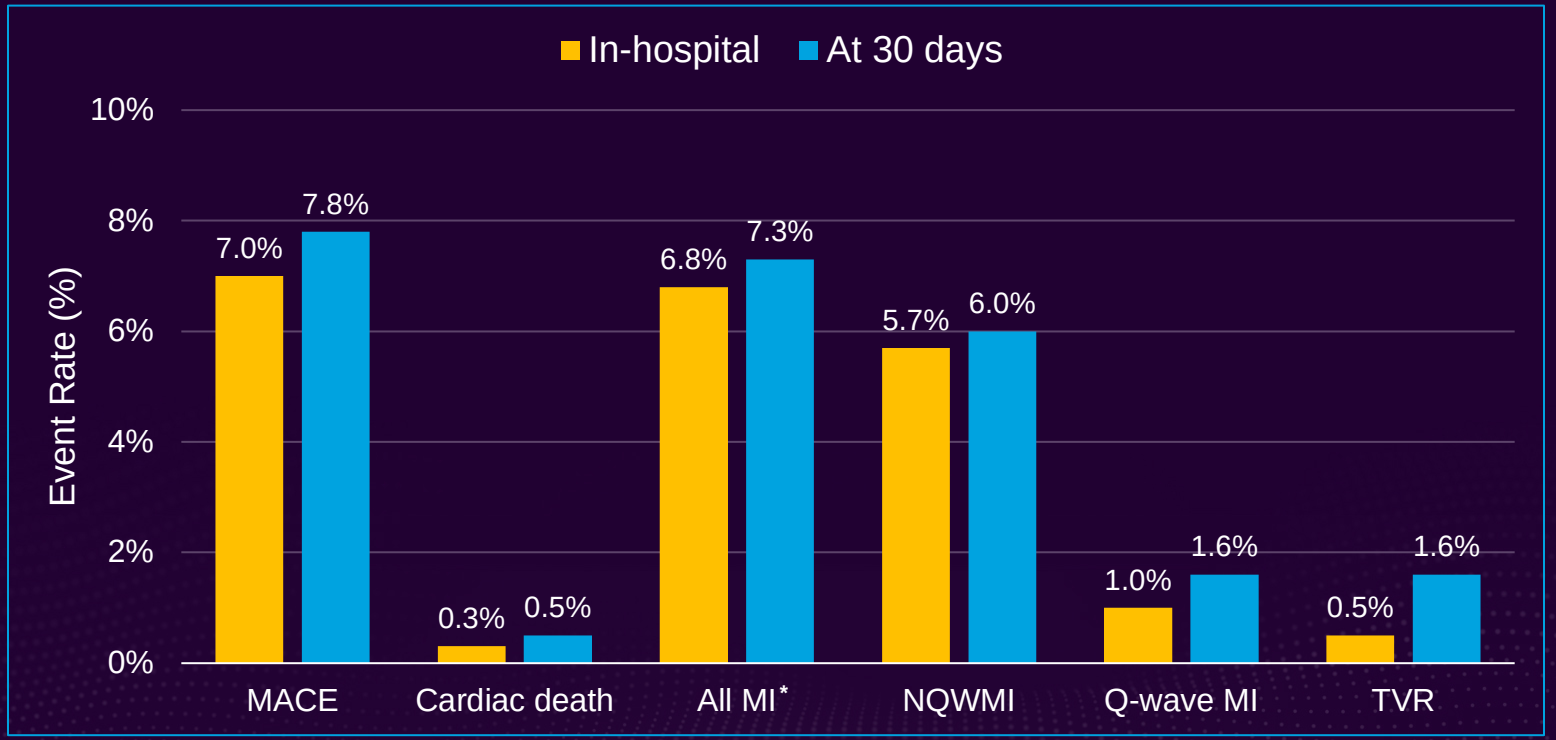


Primary Effectiveness Endpoint Met

One-sided lower 95% CI of 90.2% > pre-specified performance goal of 83.4%

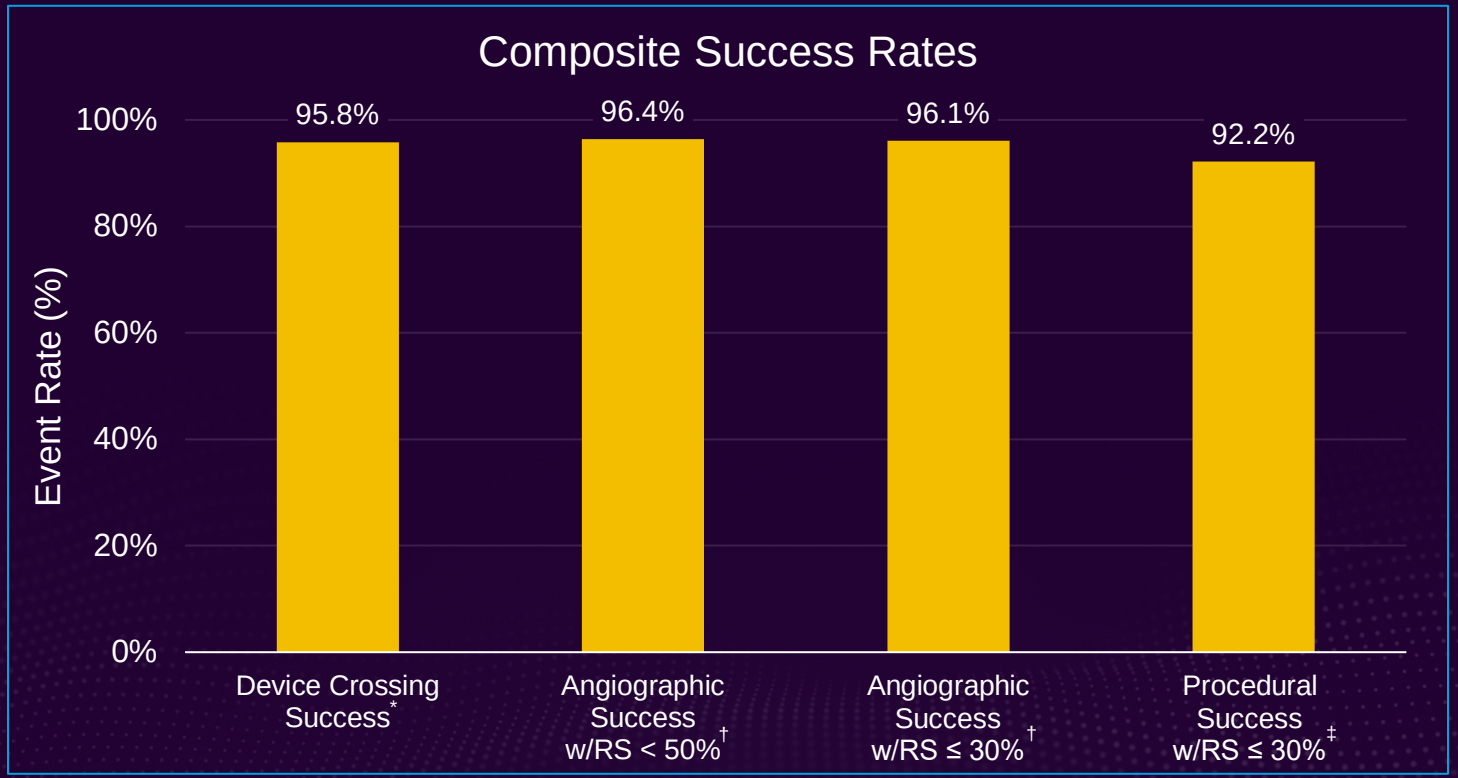
*One-sided asymptotic Wald test for binomial proportion

In-hospital and 30-day MACE



*Per protocol: CK-MB level >3x ULN at discharge (peri-procedural MI) and using the 4th Universal Definition of MI beyond discharge

Secondary Endpoints



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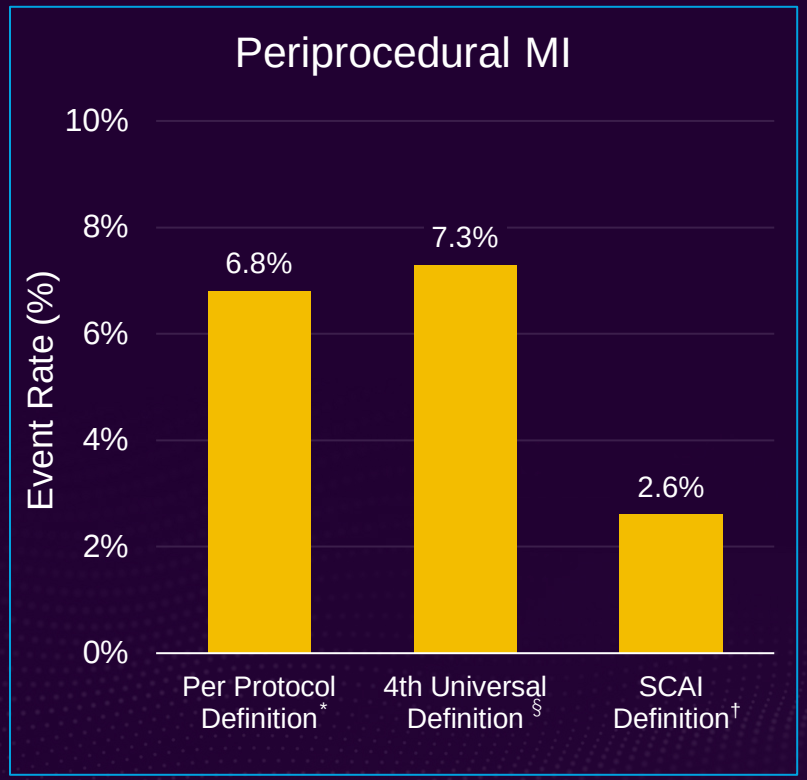
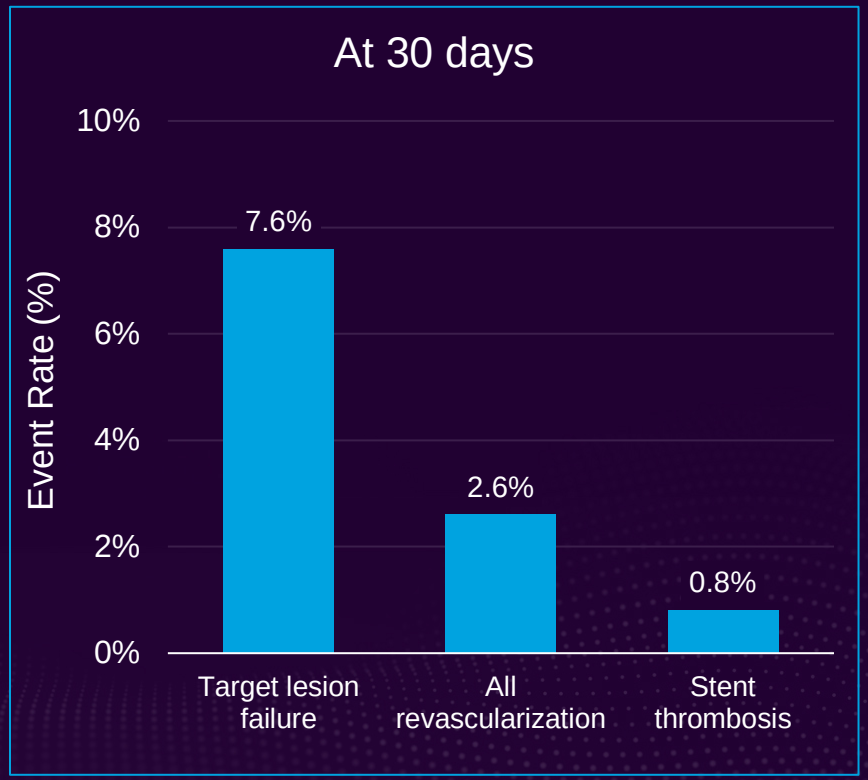
Secondary Endpoints





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†Moussa et al., *J Am Coll Cardiol* 2013. 62:1563-70;

§ Thygesen et al., *J Am Coll Cardiol* 2018. 72:2231-64.

IVL-induced Ventricular Capture*

	No IVL-induced capture (N=245)	IVL-induced capture (N=171)	*P* value
Pre-procedure heart rate, bpm	69.0 ± 11.9	65.9 ± 11.4	0.009
Drop in systolic BP during procedure	24.5%	40.5%	0.0007
Magnitude of systolic BP decrease, mmHg	23.5 ± 15.0	18.9 ± 14.2	0.07
Sustained ventricular arrhythmia during or immediately after IVL procedure	0.4%	0.0%	1.0

*41% of patients with no sustained ventricular arrhythmias or clinical sequalae

Conclusions

- Disrupt CAD III trial success was achieved as both primary safety and effectiveness endpoints were met following treatment with coronary IVL in severely calcified lesions
- Coronary IVL prior to DES implantation was well tolerated with a low rate of major peri-procedural clinical and angiographic complications
- Transient IVL-induced ventricular capture was common, but was benign with no clinical sequelae in any patient
- Although this study represents the initial coronary IVL experience for U.S. operators, high procedural success and low angiographic complications were achieved, reflecting the relative ease of use of IVL technology