**MHIF FEATURED STUDY:**

# OCS DCD Heart CAP

**OPEN and ENROLLING:**

**EPIC message to *Research MHIF Patient Referral***

| CONDITION: | PI: | RESEARCH CONTACT: | SPONSOR: |
|---|---|---|---|
| Heart Failure / Transplant | Karol Mudy, MD | Kari Thomas<br>Kari.M.Thomas@allina.com \| 612-863-7493 | TransMedics, Inc. |

**DESCRIPTION:** The Portable Organ Care System (OCS™) Heart for Resuscitation, Preservation and Assessment of Hearts from Donors After Circulatory Death Continued Access Protocol (OCS DCD Heart CAP)

To enable continued clinical access to DCD heart transplantation in the U.S. and to continue to collect additional data on the performance of the OCS Heart System to resuscitate, preserve and assess hearts donated after circulatory death for transplantation to increase the pool of donor hearts available for transplantation.

A prospective, single arm, continues access protocol.

## CRITERIA LIST/ QUALIFICATIONS:

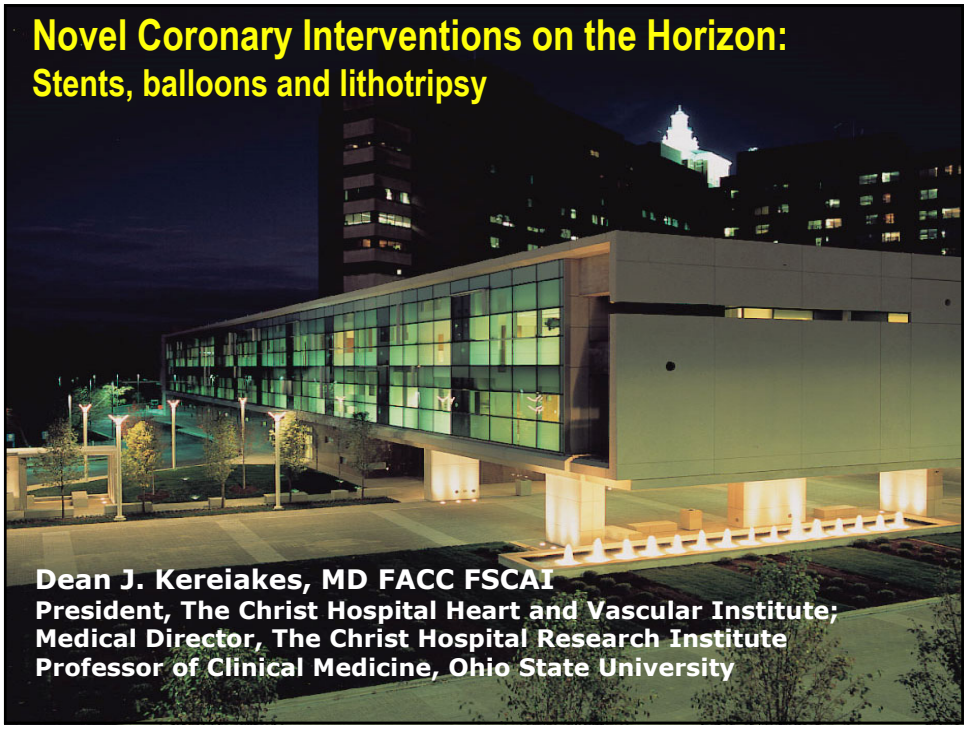
Donor Heart Inclusion

- Maastricht Category III DCD donor, defined as expected death after the withdrawal of life-supportive therapy (WLST)
- Donor age 18-49 years old inclusive
- Warm ischemic time (WIT) ≤ 30 mins, with warm ischemic time defined as: Time from when
- mean systolic blood pressure (SBP) is < 50 mmHg or peripheral saturation < 70% to aortic crossclamp
- and administration of cold cardioplegia in the donor.

**To date, MHIF has had eight successful uses of the TransMedics Organ Care System (OCS™), aka "Heart in the Box"**

HOPE DISCOVERED HERE™

Minneapolis Heart Institute Foundation®
Creating a world without heart and vascular disease

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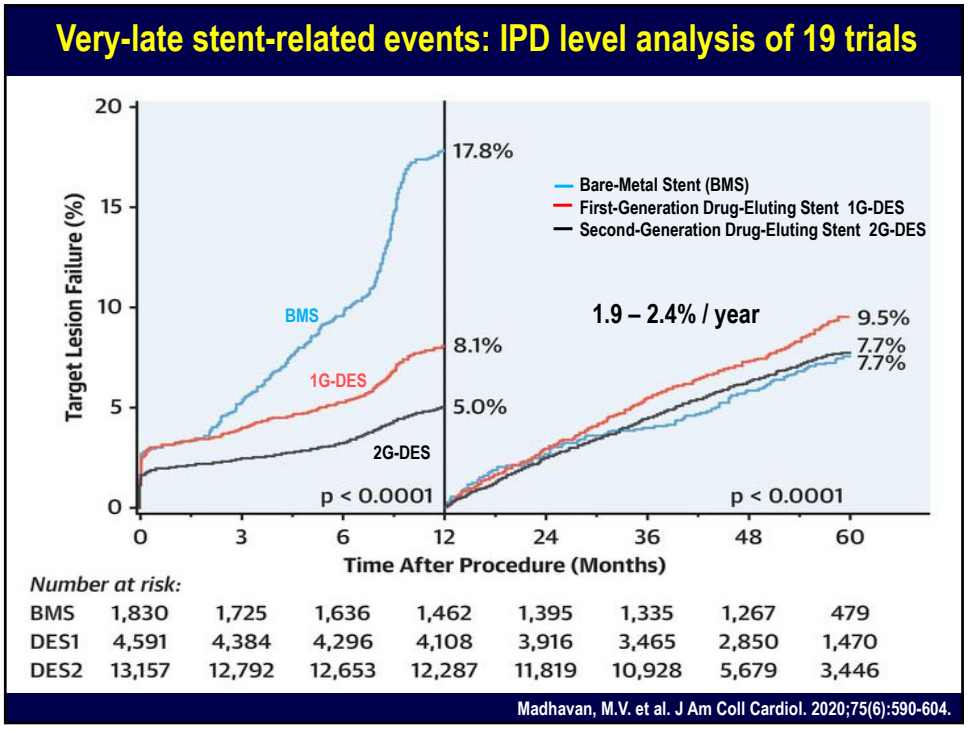
## Disclosure Statement of Financial Interest

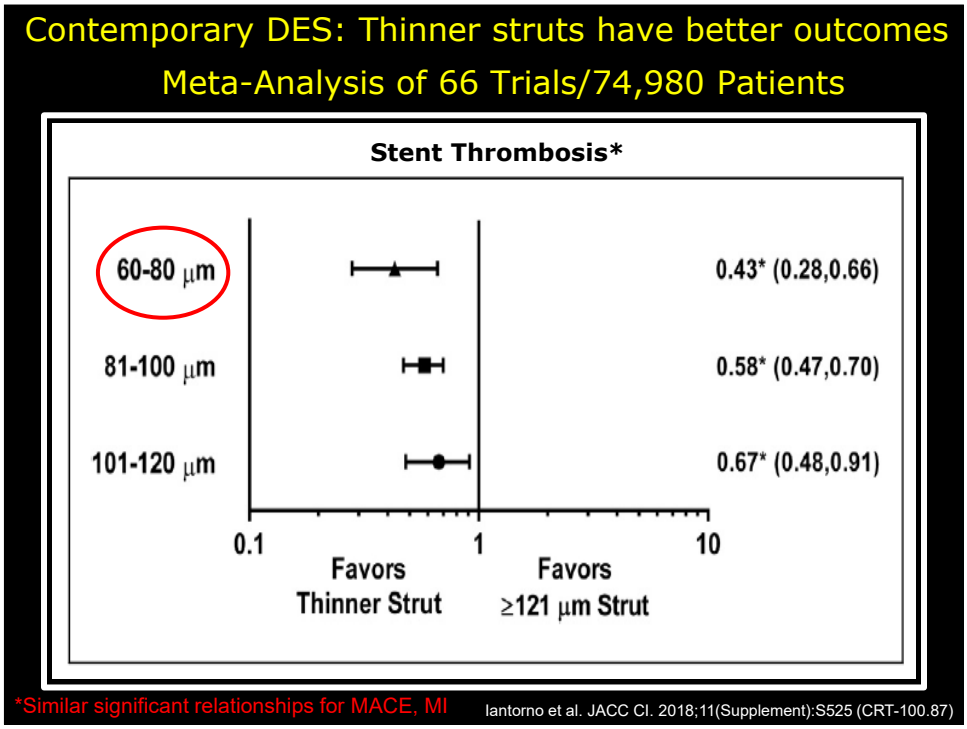
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

| 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 |
| Major Stock Shareholder/Equity | Ablative Solutions, Inc. |

2


Very-late stent-related events: IPD level analysis of 19 trials
Target Lesion Failure (%)
20
15
10
5
0
17.8%
8.1%
5.0%
BMS
1G-DES
2G-DES
p < 0.0001
1.9 – 2.4% / year
9.5%
7.7%
7.7%
p < 0.0001
Bare-Metal Stent (BMS)
First-Generation Drug-Eluting Stent 1G-DES
Second-Generation Drug-Eluting Stent 2G-DES
0 3 6 12 24 36 48 60
Time After Procedure (Months)
Number at risk:
BMS 1,830 1,725 1,636 1,462 1,395 1,335 1,267 479
DES1 4,591 4,384 4,296 4,108 3,916 3,465 2,850 1,470
DES2 13,157 12,792 12,653 12,287 11,819 10,928 5,679 3,446
Madhavan, M.V. et al. J Am Coll Cardiol. 2020;75(6):590-604.

3


Contemporary DES: Thinner struts have better outcomes
Meta-Analysis of 66 Trials/74,980 Patients
Stent Thrombosis*
60-80 μm
81-100 μm
101-120 μm
0.43* (0.28,0.66)
0.58* (0.47,0.70)
0.67* (0.48,0.91)
0.1
1
10
Favors Thinner Strut
Favors ≥121 μm Strut
*Similar significant relationships for MACE, MI
Iantorno et al. JACC CI. 2018;11(Supplement):S525 (CRT-100.87)

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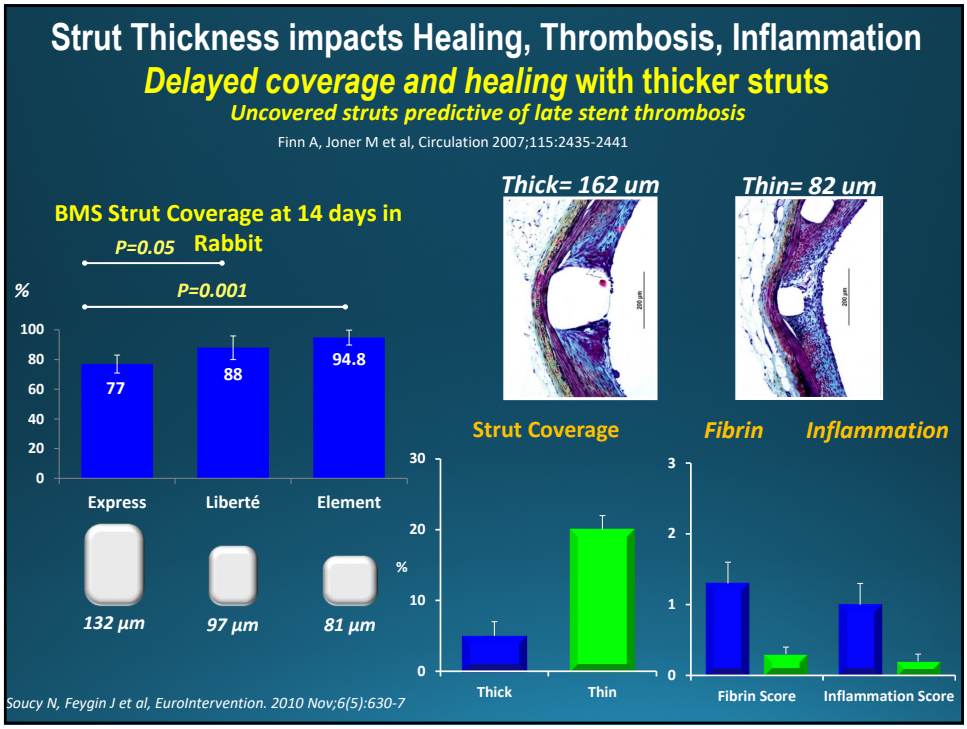
Strut Thickness impacts Healing, Thrombosis, Inflammation
Delayed coverage and healing with thicker struts
Uncovered struts predictive of late stent thrombosis
Finn A, Joner M et al, Circulation 2007;115:2435-2441
BMS Strut Coverage at 14 days in Rabbit
P=0.05
P=0.001
%
100
80
60
40
20
0
77
88
94.8
Express
Liberté
Element
132 µm
97 µm
81 µm
Thick= 162 um
Thin= 82 um
Strut Coverage
Fibrin
Inflammation
30
20
10
0
%
Thick
Thin
3
2
1
0
Fibrin Score
Inflammation Score
Soucy N, Feygin J et al, EuroIntervention. 2010 Nov;6(5):630-7

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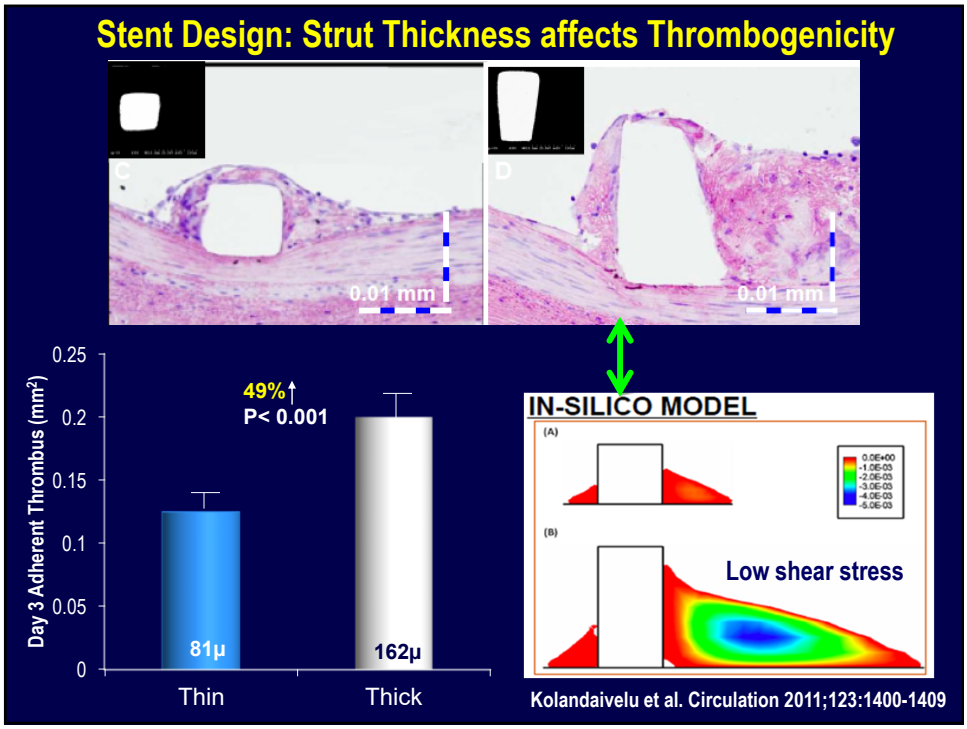
Stent Design: Strut Thickness affects Thrombogenicity
C
D
0.01 mm
0.01 mm
Day 3 Adherent Thrombus (mm²)
0.25
0.2
0.15
0.1
0.05
0
49%↑
P< 0.001
81µ
162µ
Thin
Thick
IN-SILICO MODEL
(A)
(B)
Low shear stress
Kolandaivelu et al. Circulation 2011;123:1400-1409

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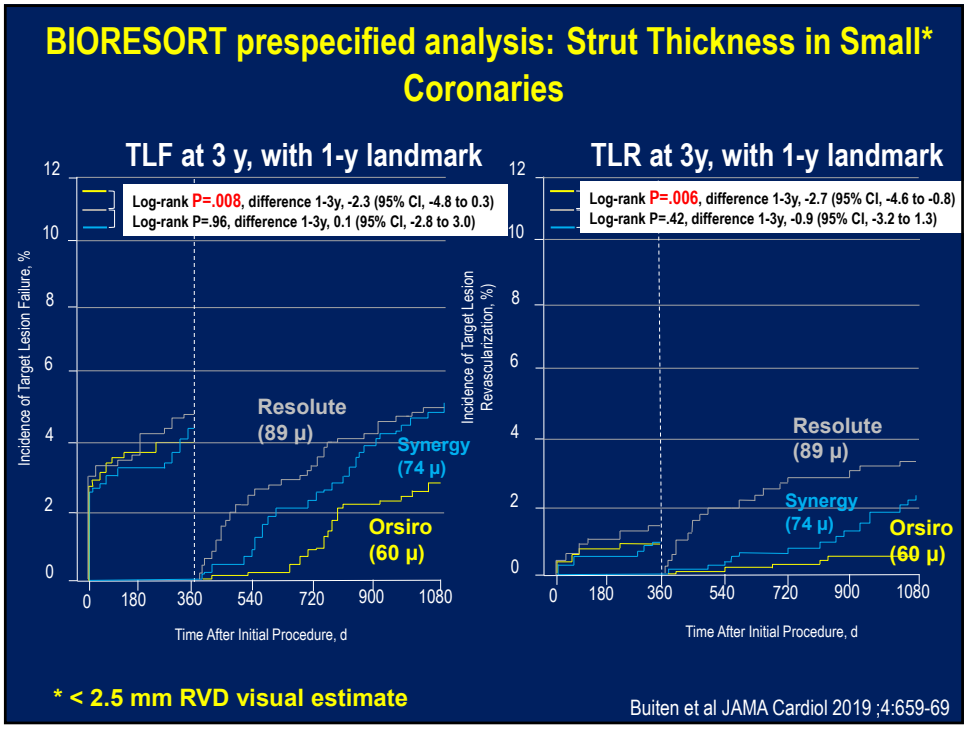
BIORESORT prespecified analysis: Strut Thickness in Small* Coronaries
TLF at 3 y, with 1-y landmark
Log-rank P=.008, difference 1-3y, -2.3 (95% CI, -4.8 to 0.3)
Log-rank P=.96, difference 1-3y, 0.1 (95% CI, -2.8 to 3.0)
Incidence of Target Lesion Failure, %
Resolute (89 µ)
Synergy (74 µ)
Orsiro (60 µ)
Time After Initial Procedure, d
TLR at 3y, with 1-y landmark
Log-rank P=.006, difference 1-3y, -2.7 (95% CI, -4.6 to -0.8)
Log-rank P=.42, difference 1-3y, -0.9 (95% CI, -3.2 to 1.3)
Incidence of Target Lesion Revascularization, %)
Resolute (89 µ)
Synergy (74 µ)
Orsiro (60 µ)
Time After Initial Procedure, d
* < 2.5 mm RVD visual estimate
Buiten et al JAMA Cardiol 2019 ;4:659-69

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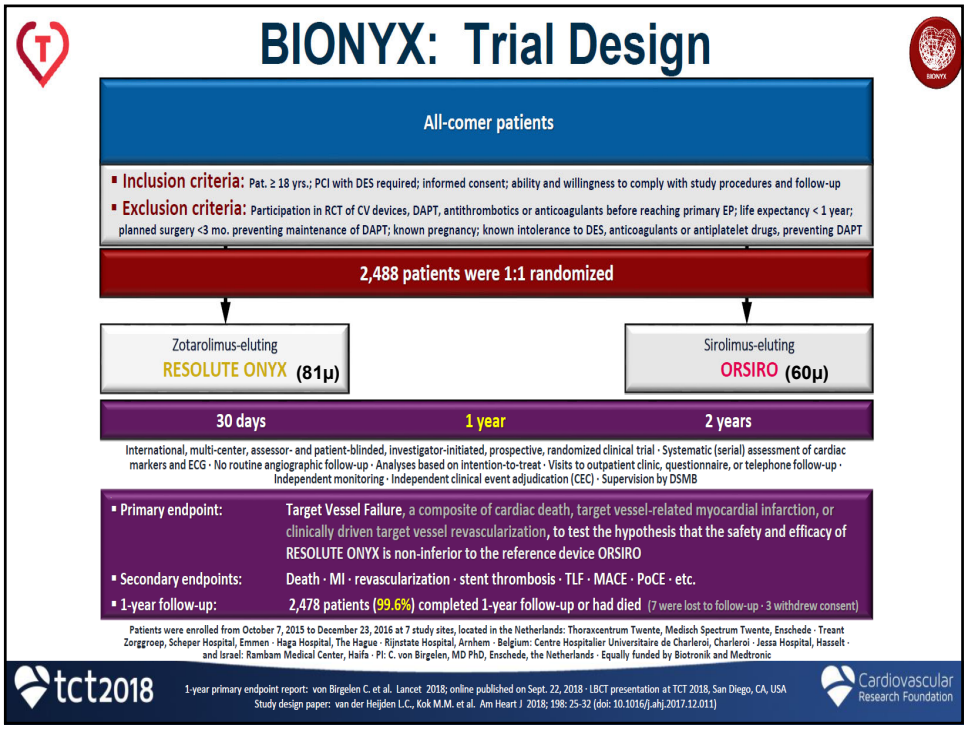
BIONYX: Trial Design
All-comer patients
Inclusion criteria: Pat. ≥ 18 yrs.; PCI with DES required; informed consent; ability and willingness to comply with study procedures and follow-up
Exclusion criteria: Participation in RCT of CV devices, DAPT, antithrombotics or anticoagulants before reaching primary EP; life expectancy < 1 year; planned surgery <3 mo. preventing maintenance of DAPT; known pregnancy; known intolerance to DES, anticoagulants or antiplatelet drugs, preventing DAPT
2,488 patients were 1:1 randomized
Zotarolimus-eluting RESOLUTE ONYX (81µ)
Sirolimus-eluting ORSIRO (60µ)
30 days
1 year
2 years
International, multi-center, assessor- and patient-blinded, investigator-initiated, prospective, randomized clinical trial · Systematic (serial) assessment of cardiac markers and ECG · No routine angiographic follow-up · Analyses based on intention-to-treat · Visits to outpatient clinic, questionnaire, or telephone follow-up · Independent monitoring · Independent clinical event adjudication (CEC) · Supervision by DSMB
Primary endpoint: Target Vessel Failure, a composite of cardiac death, target vessel-related myocardial infarction, or clinically driven target vessel revascularization, to test the hypothesis that the safety and efficacy of RESOLUTE ONYX is non-inferior to the reference device ORSIRO
Secondary endpoints: Death · MI · revascularization · stent thrombosis · TLF · MACE · PoCE · etc.
1-year follow-up: 2,478 patients (99.6%) completed 1-year follow-up or had died (7 were lost to follow-up · 3 withdrew consent)
Patients were enrolled from October 7, 2015 to December 23, 2016 at 7 study sites, located in the Netherlands: Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede · Treant Zorggroep, Scheper Hospital, Emmen · Haga Hospital, The Hague · Rijnstate Hospital, Arnhem · Belgium: Centre Hospitalier Universitaire de Charleroi, Charleroi · Jessa Hospital, Hasselt · and Israel: Rambam Medical Center, Haifa · PI: C. von Birgelen, MD PhD, Enschede, the Netherlands · Equally funded by Biotronik and Medtronic
tct2018
1-year primary endpoint report: von Birgelen C. et al. Lancet 2018; online published on Sept. 22, 2018 · LBCT presentation at TCT 2018, San Diego, CA, USA
Study design paper: van der Heijden L.C., Kok M.M. et al. Am Heart J 2018; 198: 25-32 (doi: 10.1016/j.ahj.2017.12.011)
Cardiovascular Research Foundation

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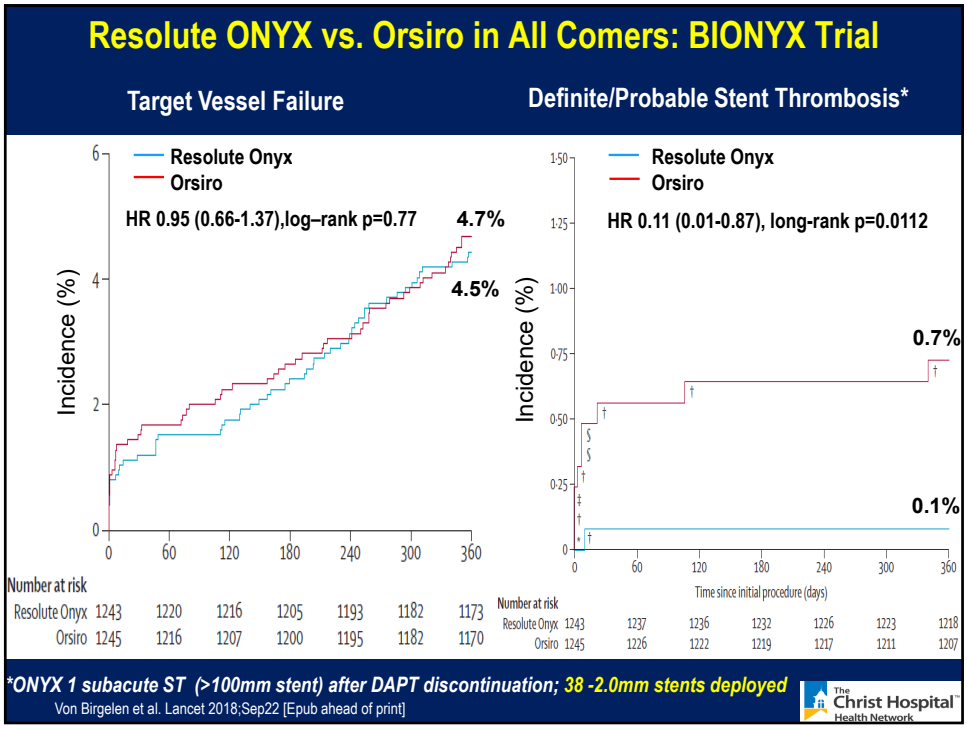
Resolute ONYX vs. Orsiro in All Comers: BIONYX Trial
Target Vessel Failure
Definite/Probable Stent Thrombosis*
Resolute Onyx
Orsiro
HR 0.95 (0.66-1.37),log–rank p=0.77
4.7%
4.5%
Incidence (%)
Number at risk
Resolute Onyx 1243 1220 1216 1205 1193 1182 1173
Orsiro 1245 1216 1207 1200 1195 1182 1170
HR 0.11 (0.01-0.87), long-rank p=0.0112
0.7%
0.1%
Time since initial procedure (days)
Resolute Onyx 1243 1237 1236 1232 1226 1223 1218
Orsiro 1245 1226 1222 1219 1217 1211 1207
*ONYX 1 subacute ST (>100mm stent) after DAPT discontinuation; 38 -2.0mm stents deployed
Von Birgelen et al. Lancet 2018;Sep22 [Epub ahead of print]
The Christ Hospital Health Network

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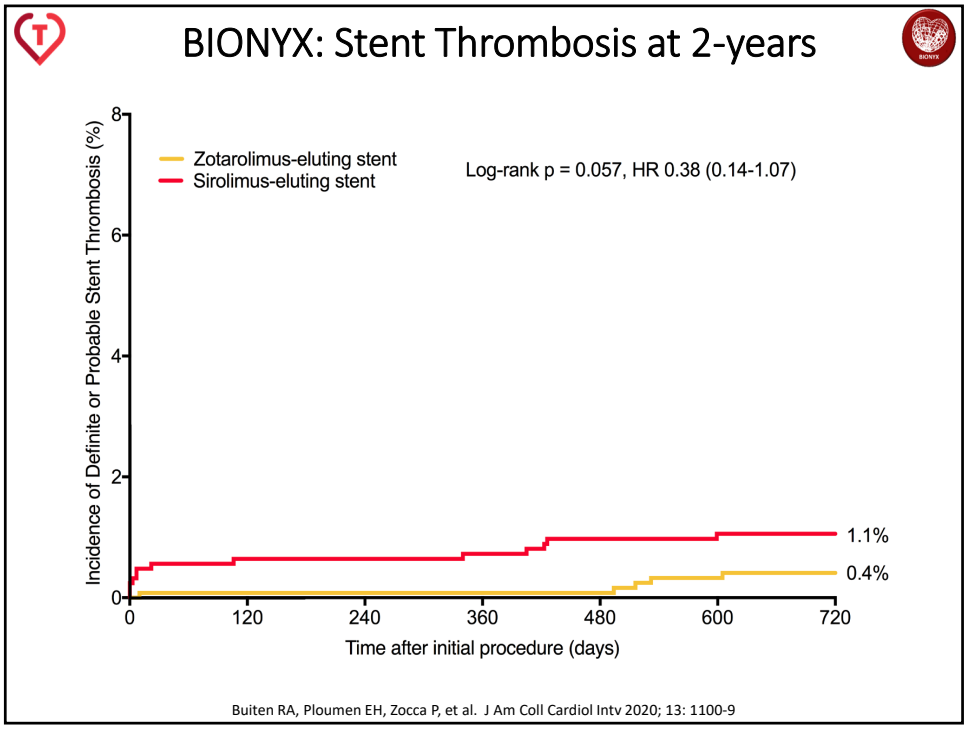
BIONYX: Stent Thrombosis at 2-years
Zotarolimus-eluting stent
Sirolimus-eluting stent
Log-rank p = 0.057, HR 0.38 (0.14-1.07)
Incidence of Definite or Probable Stent Thrombosis (%)
1.1%
0.4%
Time after initial procedure (days)
Buiten RA, Ploumen EH, Zocca P, et al. J Am Coll Cardiol Intv 2020; 13: 1100-9

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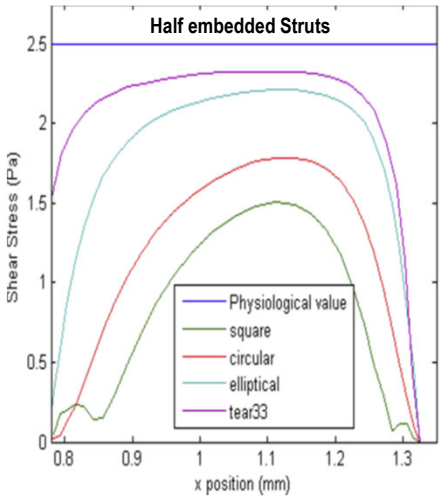
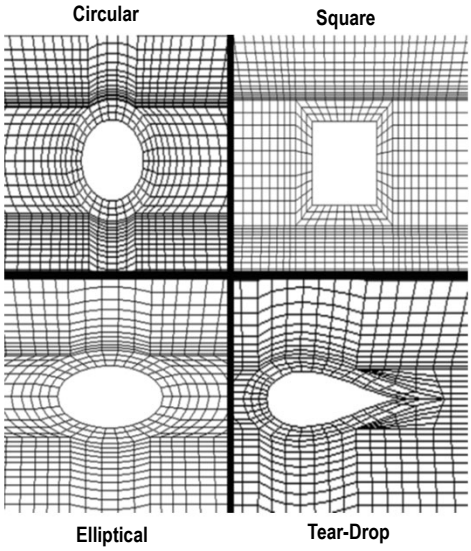
## Stent strut geometry affects *strut level shear stress distribution**

**Shear Stress Between First/Second Struts**




**Stent Strut Profiles**




*degree embedment, EC coverage/healing, shear

Mejia, Bertrandt et al Biomedical Engineering Online 2009

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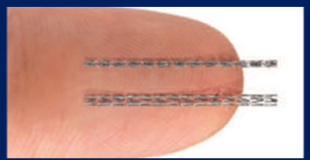
## SLENDER Integrated Stent Delivery System (IDS) Designed to Facilitate TRI, Direct Stenting

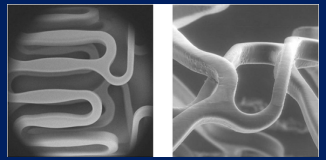
**Drug-Eluting Coronary Stent-on-a-Wire Integrated Delivery System (IDS)**

- Lowest profile DES system available, downsizes sheaths and catheters (0.047" ID* compatible)

0.031" crossing profile


| Ultra-low Profile, Conformable Stent | Technology Designed for Direct Stenting | Asahi Wire Tip Technology |
|---|---|---|
| | bioresorbable amino acid drug coating (PEA; DISCREET) | Asahi ACT ONE™ wire tip technology<br>World's leading guidewire brand |





ASAHI TECHNOLOGY
Incorporates Asahi Wire Tip Technology

*5F diagnostic catheter

Enzymatic resorption 12 months

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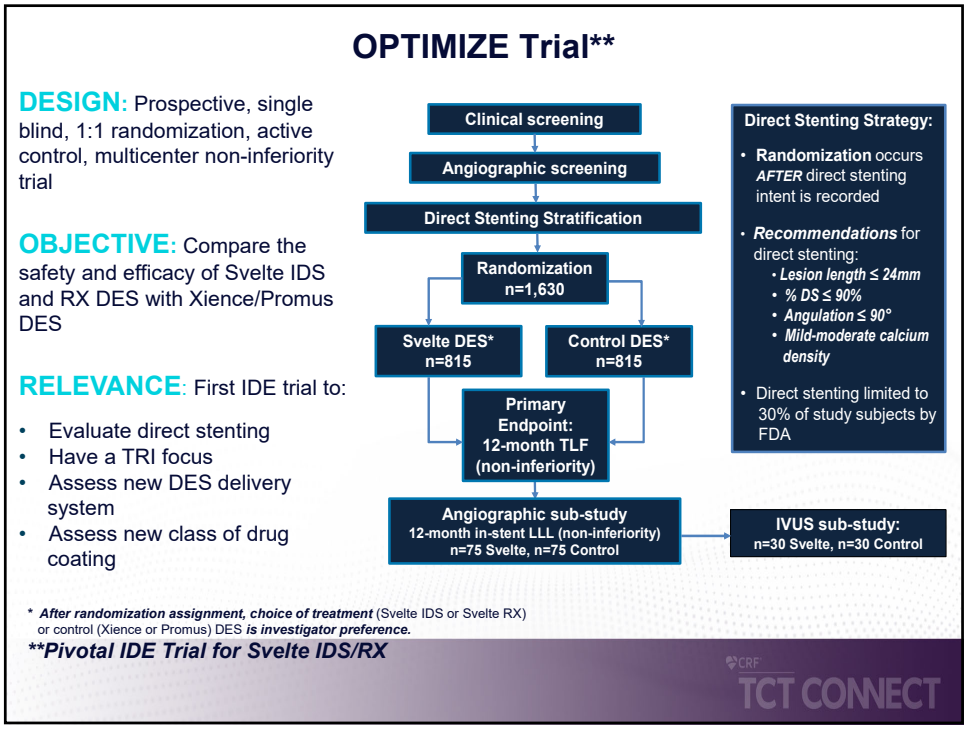
OPTIMIZE Trial**
DESIGN: Prospective, single blind, 1:1 randomization, active control, multicenter non-inferiority trial
OBJECTIVE: Compare the safety and efficacy of Svelte IDS and RX DES with Xience/Promus DES
RELEVANCE: First IDE trial to:
• Evaluate direct stenting
• Have a TRI focus
• Assess new DES delivery system
• Assess new class of drug coating
Clinical screening
Angiographic screening
Direct Stenting Stratification
Randomization n=1,630
Svelte DES* n=815
Control DES* n=815
Primary Endpoint: 12-month TLF (non-inferiority)
Angiographic sub-study
12-month in-stent LLL (non-inferiority)
n=75 Svelte, n=75 Control
IVUS sub-study:
n=30 Svelte, n=30 Control
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.
**Pivotal IDE Trial for Svelte IDS/RX
TCT CONNECT

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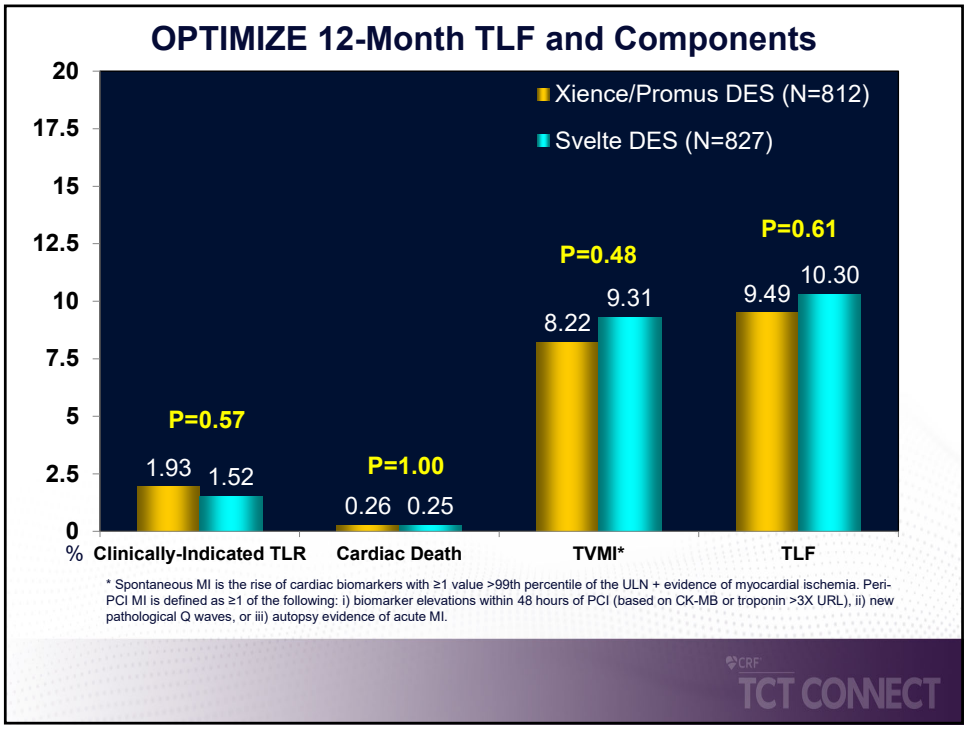
OPTIMIZE 12-Month TLF and Components
Xience/Promus DES (N=812)
Svelte DES (N=827)
20
17.5
15
12.5
10
7.5
5
2.5
0
%
P=0.57
1.93
1.52
P=1.00
0.26
0.25
P=0.48
8.22
9.31
P=0.61
9.49
10.30
Clinically-Indicated TLR
Cardiac Death
TVMI*
TLF
* Spontaneous MI is the rise of cardiac biomarkers with ≥1 value >99th 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.
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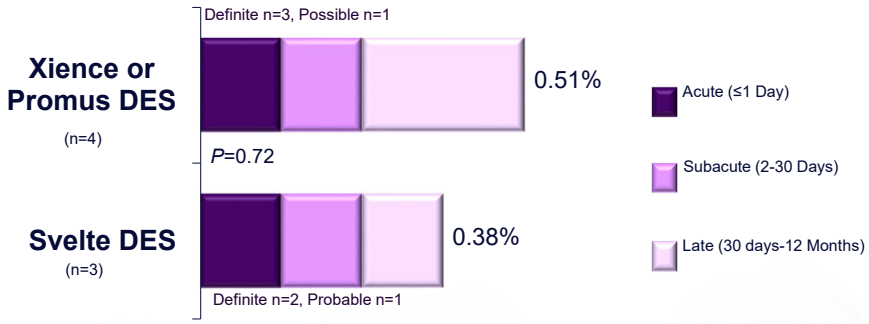
## OPTIMIZE All Stent Thrombosis Through 12 Months




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)

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## OPTIMIZE Angiographic Sub-Study Procedural and 12-Month IVUS Observations

| Per Lesion | Xience/Promus DES n=28 Subjects *n=30 Lesions* | Svelte DES n=29 Subjects *n=35 Lesions* | *P* value |
|---|---|---|---|
| Mean Stent Diameter Procedure, mm | 2.81 ± 0.34 | 2.90 ± 0.50 | 0.44 |
| Mean Stent Diameter 12-Month, mm | 2.93 ± 0.36 | 2.88 ± 0.43 | 0.65 |
| Mean Plaque Burden Procedure (% Area) | 49.35 ± 5.83 | 49.37 ± 7.71 | 1.00 |
| Mean Plaque Burden 12-Month (% Area) | 56.97 ± 5.88 | 57.07 ± 6.98 | 0.95 |
| In-Stent Obstruction Volume Procedure, % | 20.15 ± 16.79 | 15.28 ± 11.66 | 0.22 |
| In-Stent Obstruction Volume 12-Month, % | 22.15 ± 14.77 | 18.93 ± 20.21 | 0.53 |
| NIH Volume 12-Month, % | 11.90 ± 8.13 | 14.11 ± 6.29 | 0.26 |
| **ISA Procedure, %** | **40.7%** | **14.3%** | **0.04** |
| **ISA 12-Month, %** | **15.4%** | **0.00%** | **0.04** |
| **ISA Late Acquired, %** | 8.7% | 0.00% | 0.49 |

**ISA = Incomplete Stent Apposition**
Saito et al, TCT 2020

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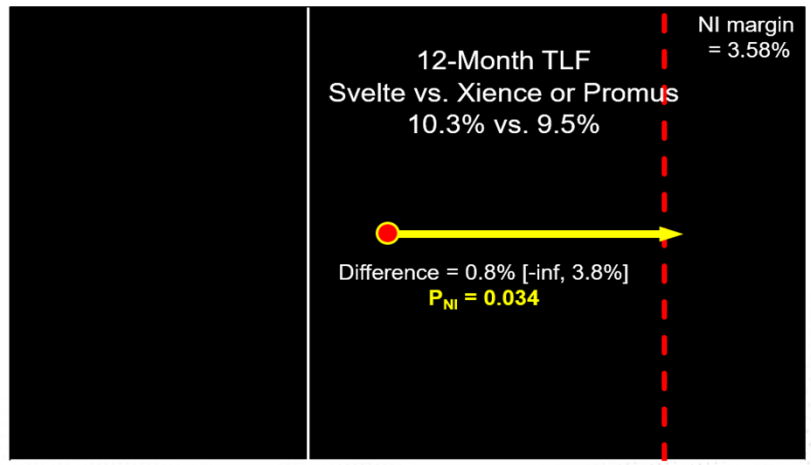
## OPTIMIZE Primary Endpoint: 12-Month TLF (ITT)

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## OPTIMIZE Statistical Design

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

**Expected TLF** based on EVOLVE II trial control **observed TLF** = **6.5%***

**Fixed Non-inferiority margin** (Δ) = **3.58%****

Test significance level ($\alpha$) = 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).

- ***TVMI diagnosis established- CKMB 91%; CK 8%; TPN 1%**
- ****55% of TLF (1.55 Relative Risk) per FDA guidance**

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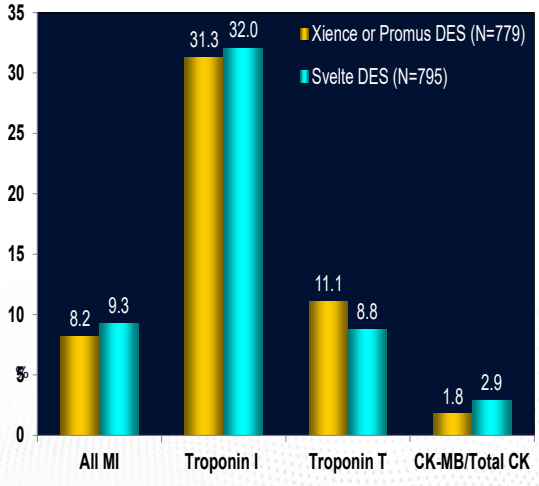
## OPTIMIZE 12-Month TVMI* by Biomarker and Device

- **TLF (10.3%) driven by TVMI (9.3%) 90% of TVMI is peri-procedural**
- **25% of all subjects in trial had only troponin assays- account for 80% of TVMIs**
- **TPN+ subjects:**
  - **3.8% had ECG changes**
  - **87.5% discharged without delay**




*** Definition TVMI: >3X ULN without clinical, angiographic or imaging correlates (>TVMI= >TLF= < Power)**

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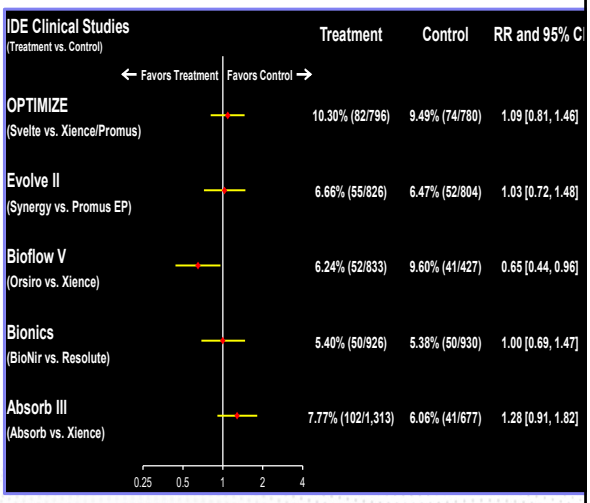
## Post-hoc analyses of 12-month TLF: Relative Risk vs. Other IDE Studies

- **Relative Risk (RR) reflects difference of TLF rates across treatment groups**
- **Independent analysis conducted to determine if OPTIMIZE RR 1.09 is < pre-specified protocol 1.55 NIM**
  - **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)**

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## 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 TVM | 9.49% (74/780) | 10.30% (82/796) | Absolute Margin 3.58% | 0.81% [-2.15%, 3.78%] | 0.034 |
| TLF: Protocol Defined TVM | 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 |

**Svelte is non-inferior to Xience/Promus by 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).

CRF TCT CONNECT

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American Heart Association. Scientific Sessions

## BuMA Supreme HT-DES Technology Overview

**Topcoat**

**Biodegradable PLGA polymer** coating **containing sirolimus (~1.2 µg/mm² )**

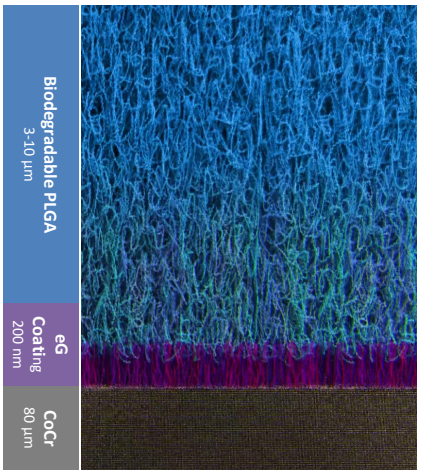
**Base Layer**

Ultra-thin permanent poly n-butyl methacrylate **electro-grafted PBMA** (*e*G Coating™) **coating**

- **interdigitates with PLGA: prevents flaking, cracking**
- **Surface modification: accelerates EC migration/ coverage (vs BMS)**

**Metal Stent**

**Thin-strut CoCr** designed for deliverability and durability




#AHA20

Lansky, Kereiakes,Leon, et al. **PIONEER III** AHA 2020

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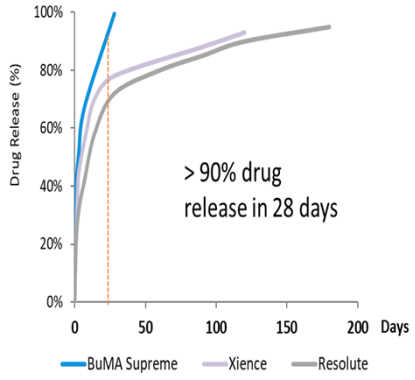
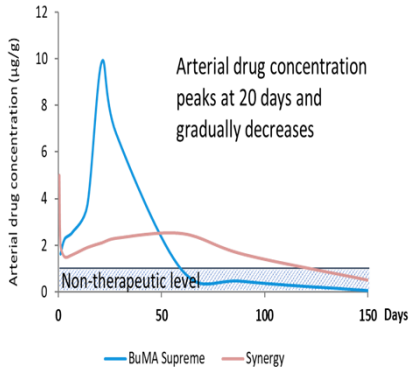
## BuMA Supreme pharmacokinetic profile

**Drug Release Comparison,**
measured in vitro



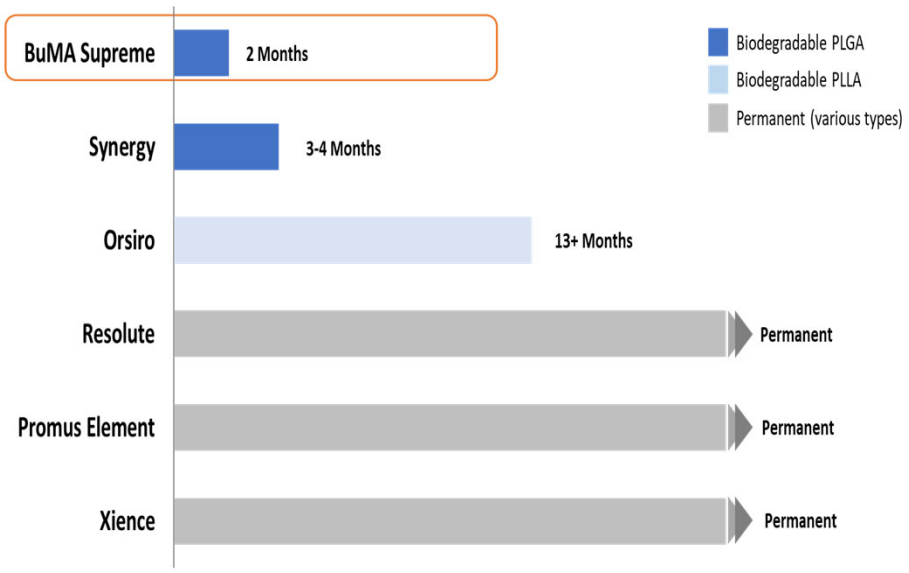

**Arterial Sirolimus Concentration**
measured in vivo




Source: Data on file.

23

## BuMA's PLGA polymer degrades in 45-60 days, leaving eG Coated stent

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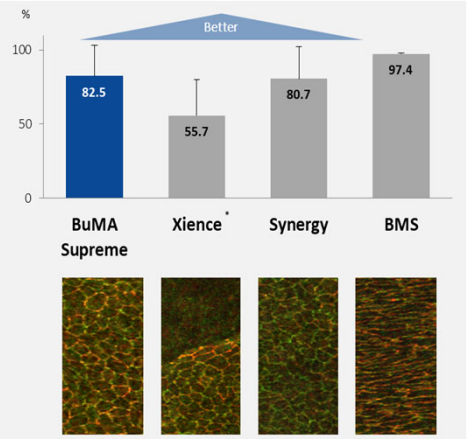
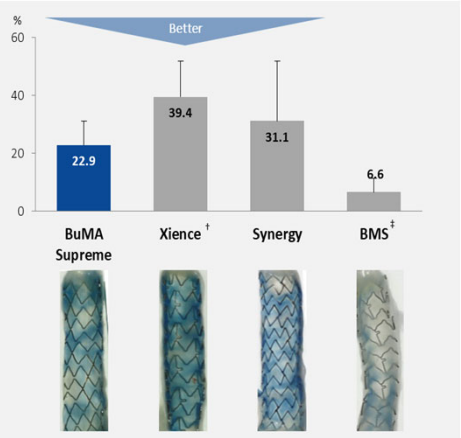
## Supreme HT-DES Promotes functional healing

**Endothelial Cell Barrier Proteins[1],**
measured at 90 days post implantation




**Evans Blue Uptake,**
measured at 90 days post implantation




[1] **VE-cadherin (EC junction maturation/ function)**

* Value is significantly lower than BMS

† Value is significantly higher than BuMA Supreme

‡ Value is significantly lower than DES

Source: Finn A., TCT 2017.

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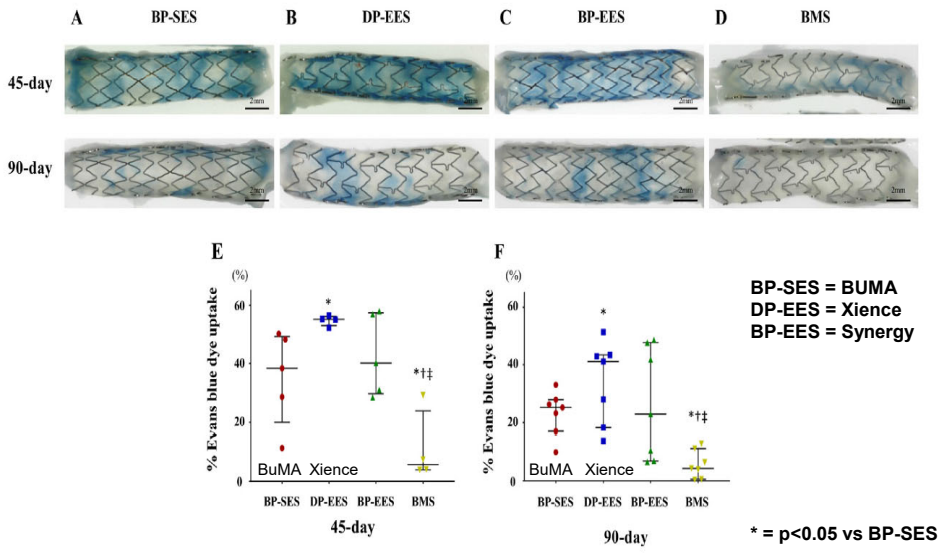
## Evans Blue Staining: Endothelial Permeability in Rabbit Iliac




Sakamoto A, Finn A, et al. *Cardiovasc Revasc Med*. 2021 Mar;24:1-10.

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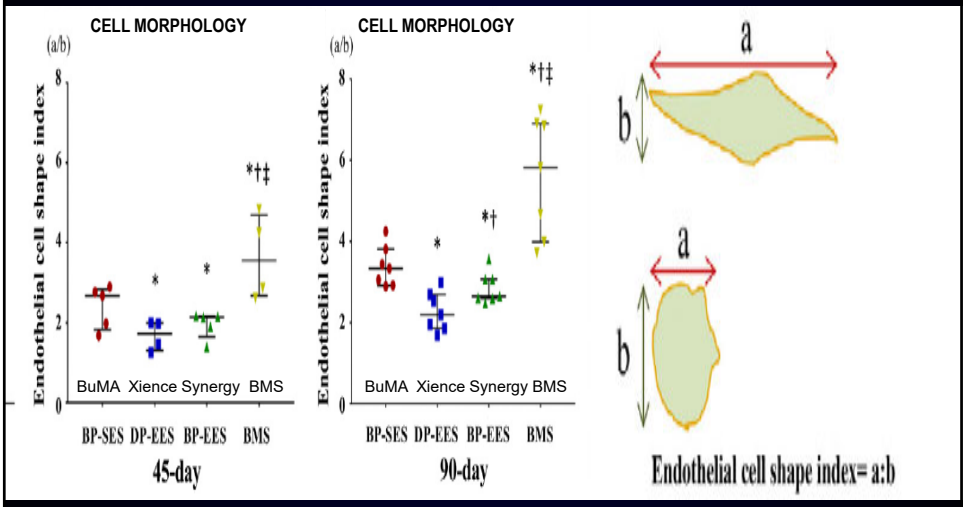
## Cell Morphology and Cell Shape Index in Rabbit Iliac




Sakamoto A, Finn A, et al. *Cardiovasc Revasc Med.* 2021 Mar;24:1-10.

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American Heart Association. Scientific Sessions

## PIONEER III Trial Design

Subjects with CCS and ACS (no STEMI)
Up to 3 *de novo* native lesions in up to 2 major vessels
RVD ≥ 2.25 to ≤ 4.0 mm, Length ≤ 31 mm
**N = 1632**

**Supreme (HT-DES)** n=1088

2:1 Randomization
74 sites (US, CAN, JP, EU)

**Xience/Promus (DP DES)** n=544

Primary Endpoint

Clinical F/U: 30d | 6mo | 12mo | 2yr | 3yr | 4yr | 5yr

Angio Baseline

**Primary Endpoint: TLF (DoCE) = Cardiac Death, Target Vessel MI, ID-TLR at 12mo**
**Powered Secondary Endpoints: TLF from 1-5 years by landmark analysis**
**Secondary Endpoints: Lesion, device success, TLF, TVF, TLR, MACE (all death, all MI*, any revascularization), Stent thrombosis (ARC defined) at each F/U time point**

*Third universal MI definition

#AHA20

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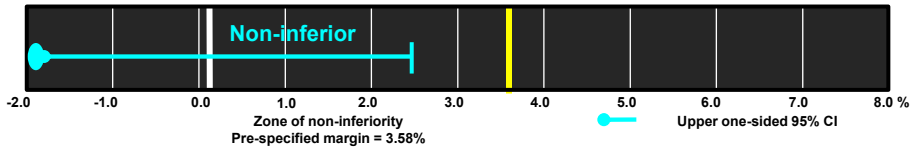
American Heart Association. Scientific Sessions

## TLF at 12 months (ITT)

| Primary Endpoint | HT-DES (N = 1088 Patients) | DP-DES (N = 543 Patients) | Difference (95% CI) | One Sided 95% Upper Confidence Boundary | Non-inferiority Margin | P-value[2] For non-inferiority |
|---|---|---|---|---|---|---|
| TLF at 365 days | 5.4% (57/1057) | 5.1% (27/532) | 0.32% (-1.87%,2.5%) | 2.5% | 3.58% | 0.002 |




**Primary non-inferiority endpoint met***

#AHA20

* No differences in TLF components or ST

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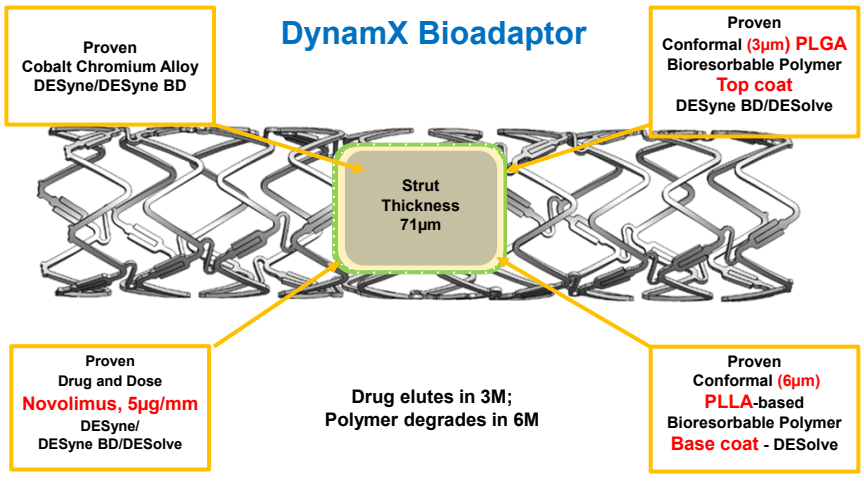
## DynamX Bioadaptor is the First Fundamental Innovation in Metallic Implant Design




CRT20

CRTonline.org

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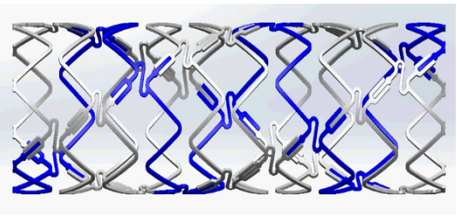
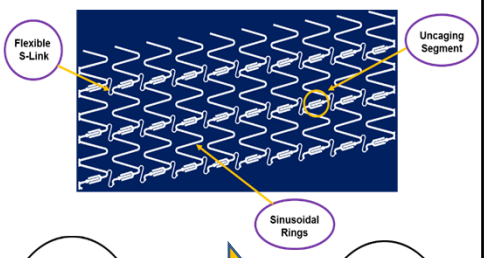
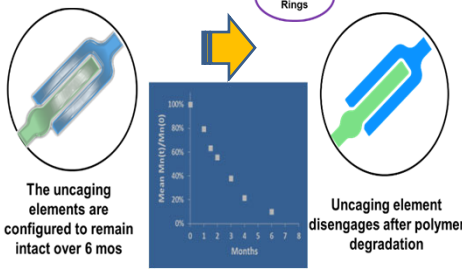
## DynamX Bioadaptor Unique Design Features Engineered to Adapt to Physiology






- **Uncaging elements** at low-stress regions of each sinusoidal ring in a helical pattern while maintaining longitudinal continuity of the bioadaptor




The uncaging elements are configured to remain intact over 6 mos

Uncaging element disengages after polymer degradation

CRT20 CRTonline.org

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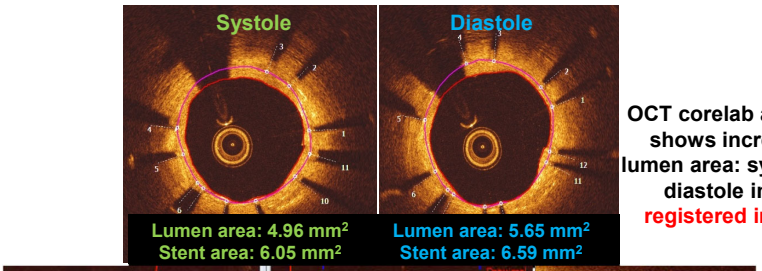
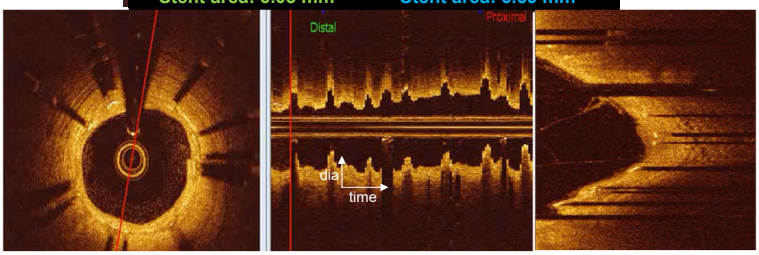
## Uncaged Pulsatility Analysis: Stationary OCT Acquisition




**OCT corelab analysis shows increased lumen area: systole vs diastole in co-registered images**

CRT20 Verheye, Colombo et al. *EuroIntervention.* 2020 Sep 8. CRTonline.org

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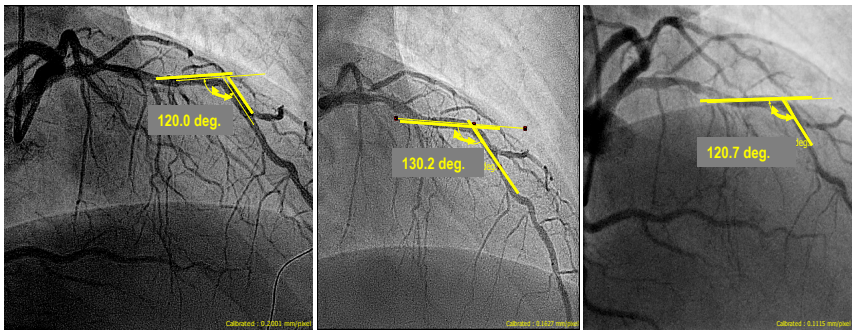
## DynamX Bioadaptor Uncaged Restores Vessel Angulation

### Reduces Geometric Distortion*

Pre-Bioadaptor | Post-Bioadaptor | 12-Month Follow-up




Patient: 28-501
3.5 x 18 mm DynamX Bioadaptor

* 60% increase in conformability

CRT 20

* Abnormal CFV, shear stress (MACE, restenosis)

CRTonline.org

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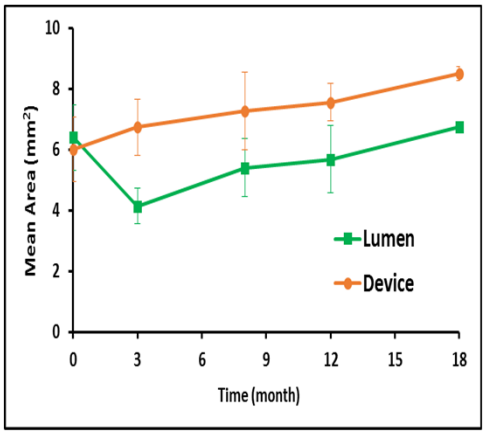
## DynamX Bioadaptor Preserves Positive Adaptive Remodeling

### Serial In-vivo OCT evaluation in adult porcine coronary model




Increase in mean device and lumen area

- No early or chronic recoil prior to uncaging
- Maintains uniform, thin NIH
- Uncaging results in increased Mean Device and Lumen Area

DynamX Bioadaptor allows the vessel to accommodate NIH and restores Lumen Area

CRT 20

Data on file at Elixir Medical

Preclinical Studies conducted at AccelLAB, Montreal, Canada

CRTonline.org

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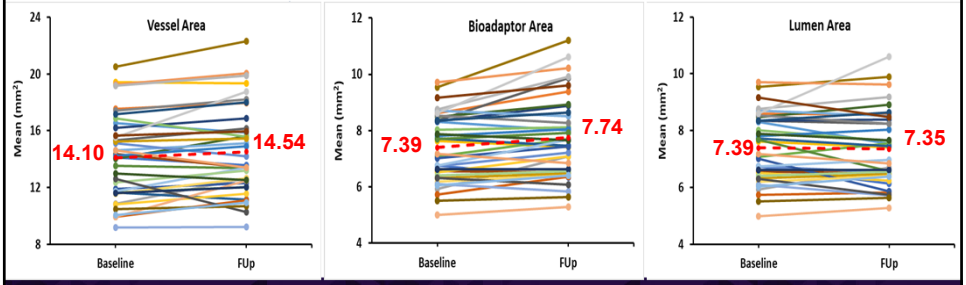
## DynamX Bioadaptor Paired IVUS studies: Adaptive remodeling accommodates NIH/Disease Progression to Maintain Lumen Area:

| IVUS Parameter | 9 + 12 Months (n=38) | | | |
|---|---|---|---|---|
| | Post-Procedure | 9 + 12 Month Follow-up | Change from Post-Procedure | p |
| Mean Vessel Area (mm²) | 14.10 ± 2.99 | 14.54 ± 3.12 | 3% | 0.0170 |
| Mean Bioadaptor Area (mm²) | 7.39 ± 1.20 | 7.74 ± 1.46 | 5% | 0.0005 |
| Mean Lumen Area (mm²) | 7.39 ± 1.20 | 7.35 ± 1.31 | 0% | 0.5940 |




CRT 20 Verheye, Colombo et al. *EuroIntervention.* 2020 Sep 8. CRTonline.org

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## QCA at Post-Procedure, 9 and 12 Month Follow-up

| | 9 + 12 Month Follow-up (n=45) | |
|---|---|---|
| Variable | Post-Procedure | 9 + 12 Month Follow-up |
| **In-Segment** | | |
| RVD Interp (mm) | 2.93 ± 0.38 | 2.90 ± 0.36 |
| MLD (mm) | 2.56 ± 0.31 | 2.45 ± 0.34 |
| %DS | 12.14 ± 8.7 | 15.0 ± 10.1 |
| Acute gain (mm) | 1.44 ± 0.36 | -- |
| Balloon-Artery Ratio | 1.14 ± 0.09 | -- |
| Late Lumen Loss (mm) | -- | 0.11 ± 0.14 |
| **In-Bioadaptor** | | |
| RVD Interp (mm) | 2.95 ± 0.36 | 2.92 ± 0.36 |
| MLD (mm) | 2.74 ± 0.30 | 2.64 ± 0.36 |
| %DS | 6.69 ± 6.8 | 9.3 ± 10.2 |
| **Acute gain (mm) (Mean ± SD)** | **1.62 ± 0.34** | -- |
| **Late Lumen Loss (mm) (Mean ± SD)** | -- | **0.11 ± 0.17** |
| **Late Lumen Loss (mm) (Median, IQR)** | -- | **0.03 (0.01, 0.17)** |

CRT 20 Verheye, Colombo et al. *EuroIntervention.* 2020 Sep 8. CRTonline.org

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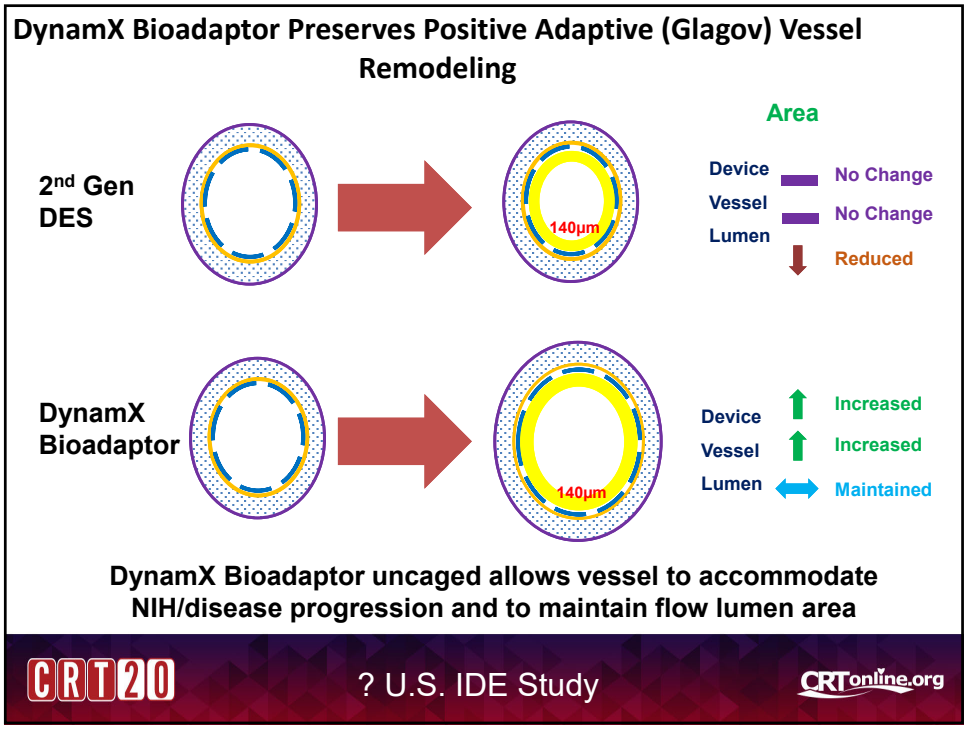


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## Evolution of DEBs: Drugs, Coatings and Beyond

| | 1st-Generation Paclitaxel-Coated Balloon | 2nd-Generation Sirolimus-Coated Balloon | 3rd-Generation Sirolimus-Eluting Balloon |
|---|---|---|---|
| | Crystalline / Non-Crystaline Amorphous Coating | Spray-Coated Nanocarrier[1] / Microparticle Coating[2] / Spray-Coated Crystalline[3] | Nanosphere-Encapsulated (Particle Delivery via Microporous Balloon, w/out Coating) |
| *Efficacy* | | | |
| Drug | PTX | SIR | SIR |
| Elution Control | - | - / + ~10 Days / 30 Days + | ++ Mimics DES |
| Dose Uniformity | - | ? | + |
| *Safety* | | | |
| Coating | YES | YES | NO |
| Particulate Debris/ Microembolization | + | + | - - No Particulates |
| Drug Loss in Transit | + | + | - - No Drug Loss in Transit |
| Drug Deposition | +/- | + / - Endo-luminal | + + Trans-mural |

[1]Concept Medical MagicTouch; [2]Med Alliance Selution; [3]B. Braun Sequent Please Sirolimus

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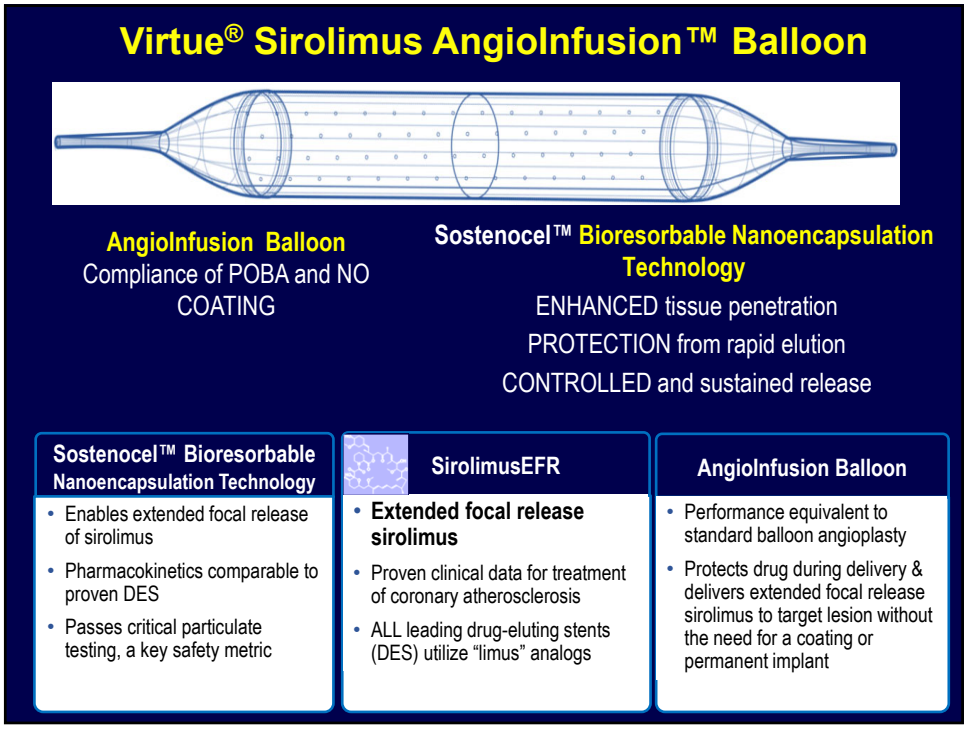
Virtue® Sirolimus AngioInfusion™ Balloon
AngioInfusion Balloon
Compliance of POBA and NO COATING
Sostenocel™ Bioresorbable Nanoencapsulation Technology
ENHANCED tissue penetration
PROTECTION from rapid elution
CONTROLLED and sustained release
Sostenocel™ Bioresorbable Nanoencapsulation Technology
• Enables extended focal release of sirolimus
• Pharmacokinetics comparable to proven DES
• Passes critical particulate testing, a key safety metric
SirolimusEFR
• Extended focal release sirolimus
• Proven clinical data for treatment of coronary atherosclerosis
• ALL leading drug-eluting stents (DES) utilize "limus" analogs
AngioInfusion Balloon
• Performance equivalent to standard balloon angioplasty
• Protects drug during delivery & delivers extended focal release sirolimus to target lesion without the need for a coating or permanent implant

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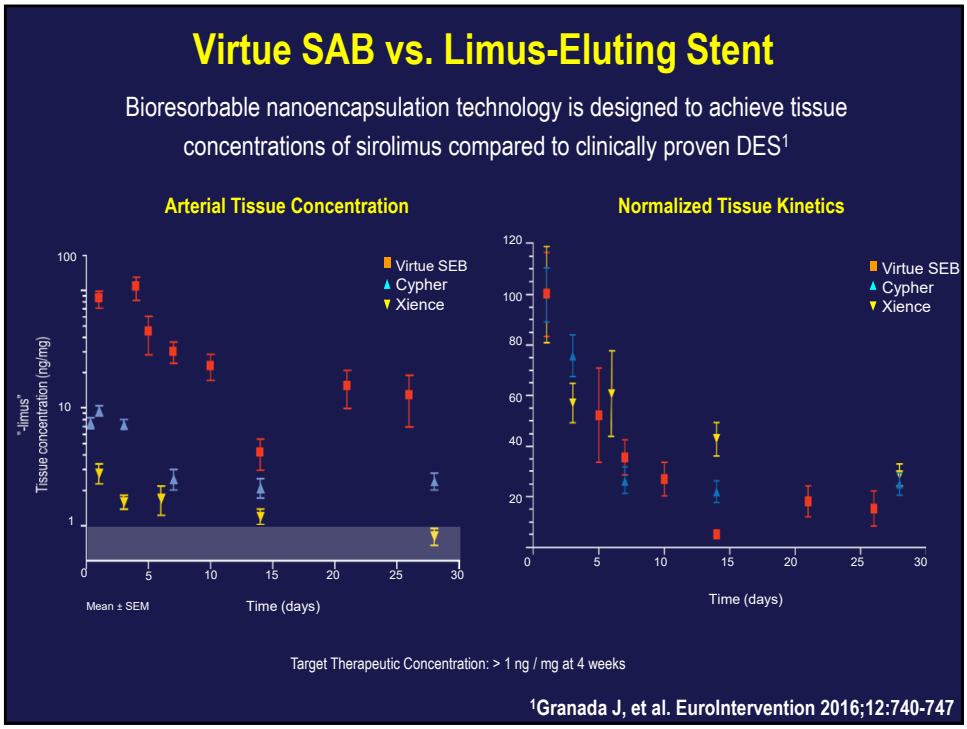
Virtue SAB vs. Limus-Eluting Stent
Bioresorbable nanoencapsulation technology is designed to achieve tissue concentrations of sirolimus compared to clinically proven DES[1]
Arterial Tissue Concentration
Normalized Tissue Kinetics
Virtue SEB
Cypher
Xience
Tissue concentration (ng/mg) "-limus"
Mean ± SEM
Time (days)
Target Therapeutic Concentration: > 1 ng / mg at 4 weeks
[1]Granada J, et al. EuroIntervention 2016;12:740-747

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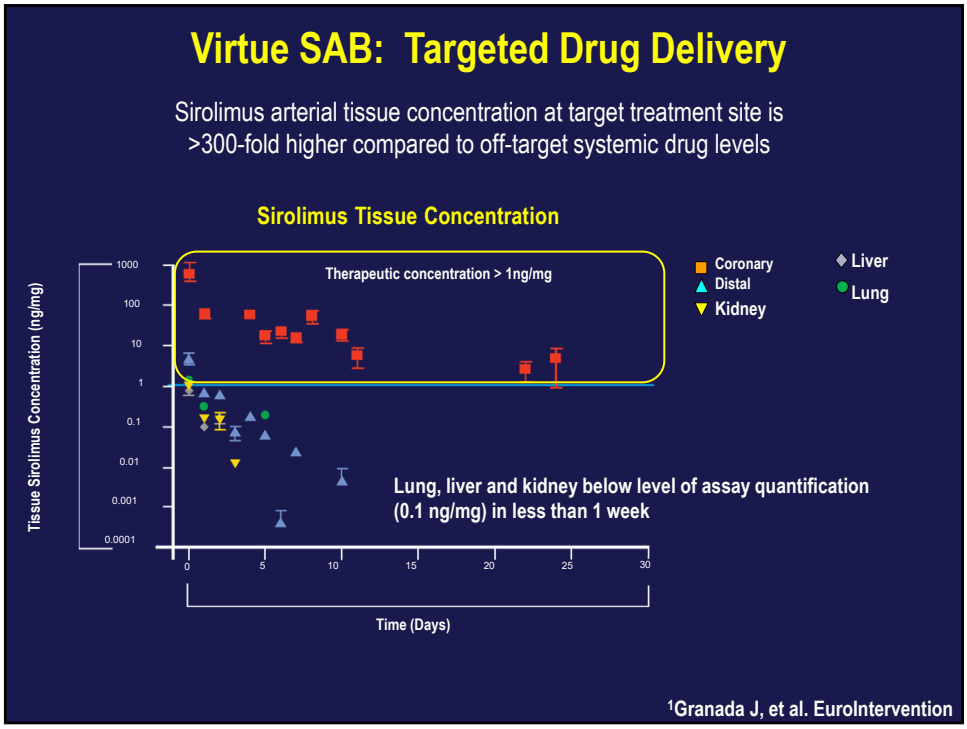
Virtue SAB: Targeted Drug Delivery
Sirolimus arterial tissue concentration at target treatment site is >300-fold higher compared to off-target systemic drug levels
Sirolimus Tissue Concentration
Therapeutic concentration > 1ng/mg
Coronary
Distal
Kidney
Liver
Lung
Tissue Sirolimus Concentration (ng/mg)
1000
100
10
1
0.1
0.01
0.001
0.0001
0
5
10
15
20
25
30
Time (Days)
Lung, liver and kidney below level of assay quantification (0.1 ng/mg) in less than 1 week
[1]Granada J, et al. EuroIntervention

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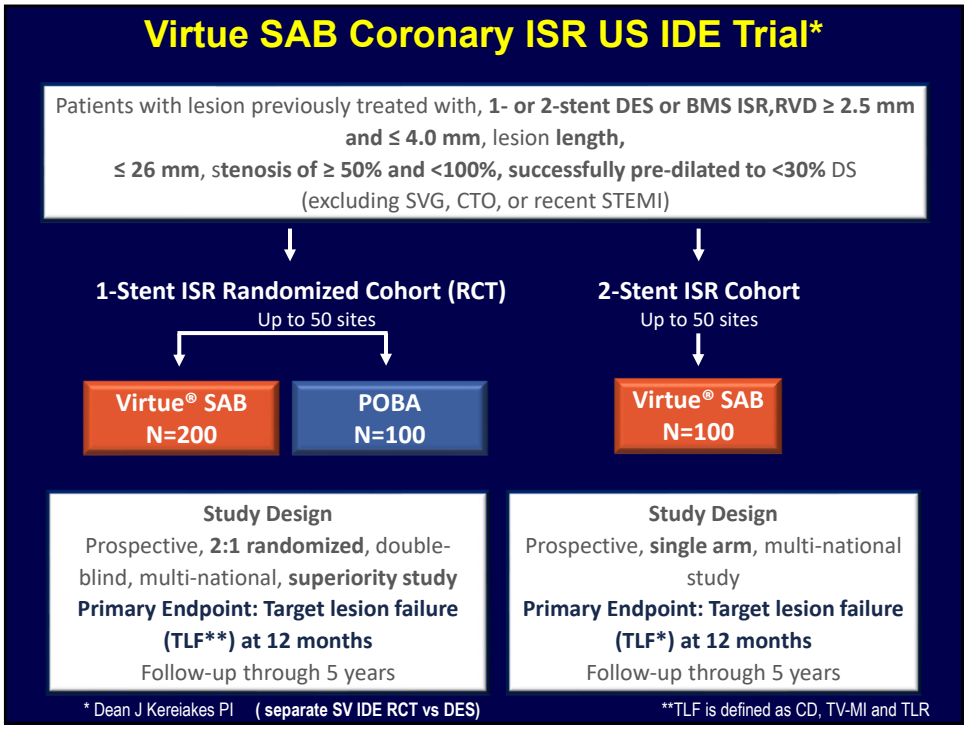
Virtue SAB Coronary ISR US IDE Trial*
Patients with lesion previously treated with, 1- or 2-stent DES or BMS ISR,RVD ≥ 2.5 mm and ≤ 4.0 mm, lesion length, ≤ 26 mm, stenosis of ≥ 50% and <100%, successfully pre-dilated to <30% DS (excluding SVG, CTO, or recent STEMI)
1-Stent ISR Randomized Cohort (RCT)
Up to 50 sites
2-Stent ISR Cohort
Up to 50 sites
Virtue® SAB N=200
POBA N=100
Virtue® SAB N=100
Study Design
Prospective, 2:1 randomized, double-blind, multi-national, superiority study
Primary Endpoint: Target lesion failure (TLF**) at 12 months
Follow-up through 5 years
Study Design
Prospective, single arm, multi-national study
Primary Endpoint: Target lesion failure (TLF*) at 12 months
Follow-up through 5 years
* Dean J Kereiakes PI ( separate SV IDE RCT vs DES)
**TLF is defined as CD, TV-MI and TLR

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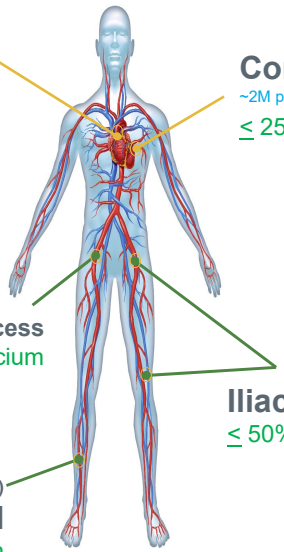
## Vascular calcium*: Increasing Problem



**Aortic Valve**
Aortic Leaflet Restoration
ALR or TAVL
Calcium significant problem

**Coronary Arteries**
~2M procedures
≤ 25% Mod/Severe Calcium

**EVAR ,TEVAR, TAVR, MCS Access**
Limited TF Access due to Calcium

**Iliac, Femoral**
≤ 50% Mod/Severe Calcium

Below the Knee (BTK)
**PVD-CLI**
≤ 75% Mod/Severe Calcium

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*** Increasing age, diabetes, CKD**

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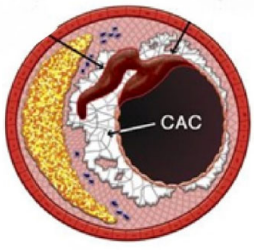
## Challenges With Coronary Calcification

**CAC is an independent predictor of worse prognosis**

- **Meta analysis of 7 contemporary PCI trials: impact of severely calcified* lesions on patient outcomes to 3 years**

| | With Severe Calcification (N=1291) | Without Severe Calcification (N = 5005) | P Value |
|---|---|---|---|
| **Mortality** | **10.8%** | **4.4%** | **P <0.001** |
| **Combined Endpoint:** | | | |
| **MI & Death** | **22.9%** | **10.9%** | **P <0.001** |
| **MI, Death & Revascularization** | **31.8%** | **22.4%** | **P <0.001** |




***Severe Calcium:** **radiopacities** noted **without cardiac motion** before contrast, **generally on both sides of arterial lumen***

Bourantas, et al. Heart 2014; 100: 1158-1164.

The Christ Hospital Health Network

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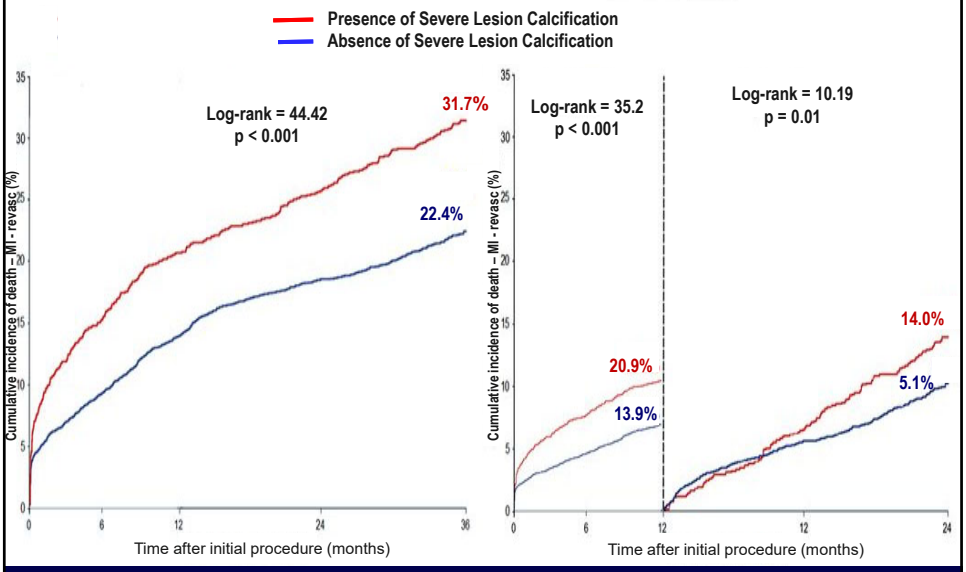
## Coronary Calcification Impacts Outcomes after Stenting*

### Death, MI, Repeat Revasc




*7 PCI Trials / 6296 Patients

Bourantas et al. Heart 2014;100:1158-1164

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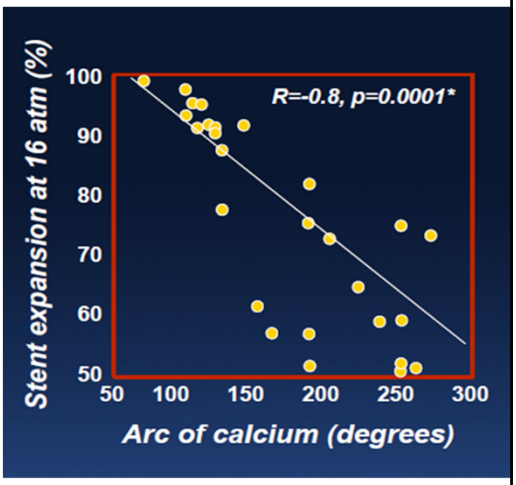
## Challenges With Coronary Calcification

**The greater the arc, length, or thickness of calcium, the greater the likelihood of stent underexpansion[1]**

- **Asymmetrical stent expansion:** up to **50% of stents** deployed in calcified lesions[2]
- **Stent underexpansion* and poor apposition:**
- associated with **increased ischemic events** at 1 year[3]

***Independent predictor of ST and Restenosis**




**Increase Arc of Ca++ leads to decrease in stent expansion[2]**

1. Mintz, G; I. J Am Coll Cardiol Imaging 2015;8(4): 461-71.
2. Chambers JW, et al. J Am Coll Cardiol Intv 2014; 7:510–8.
3. Généreux P, et al. JACC 2014; 63(18);1845-54
4. *Vavarunakis et al. Catheter Cardiovasc Interv 2001;52:164-172*

The Christ Hospital Health Network

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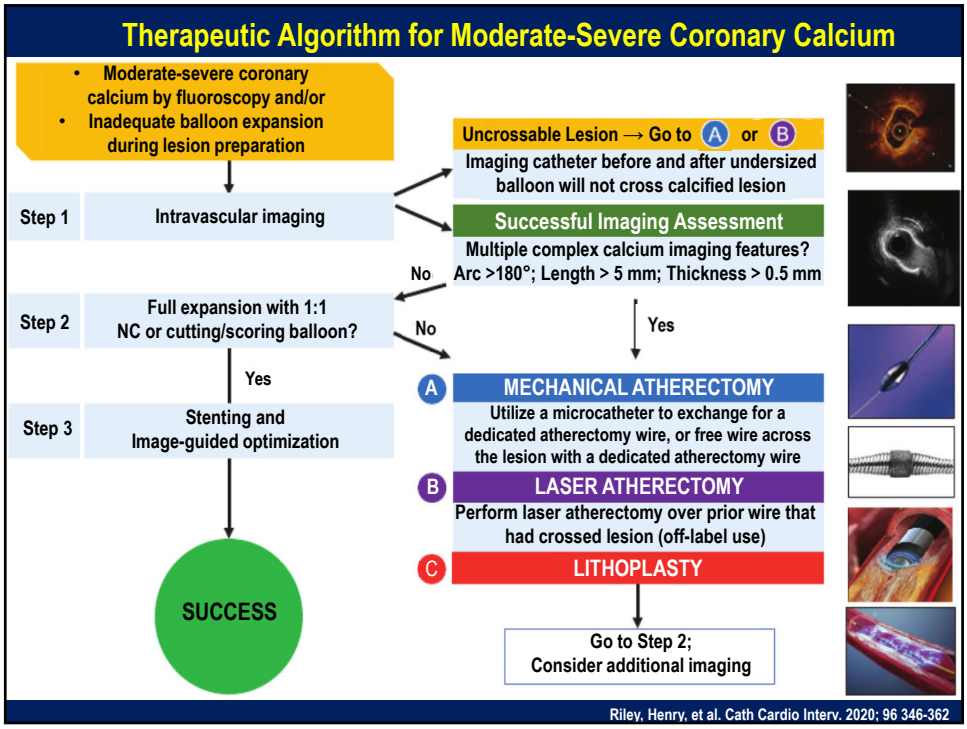
Therapeutic Algorithm for Moderate-Severe Coronary Calcium
• Moderate-severe coronary calcium by fluoroscopy and/or
• Inadequate balloon expansion during lesion preparation
Step 1
Intravascular imaging
Uncrossable Lesion → Go to A or B
Imaging catheter before and after undersized balloon will not cross calcified lesion
Successful Imaging Assessment
Multiple complex calcium imaging features?
Arc >180°; Length > 5 mm; Thickness > 0.5 mm
No
Yes
Step 2
Full expansion with 1:1 NC or cutting/scoring balloon?
No
Yes
Step 3
Stenting and Image-guided optimization
SUCCESS
A
MECHANICAL ATHERECTOMY
Utilize a microcatheter to exchange for a dedicated atherectomy wire, or free wire across the lesion with a dedicated atherectomy wire
B
LASER ATHERECTOMY
Perform laser atherectomy over prior wire that had crossed lesion (off-label use)
C
LITHOPLASTY
Go to Step 2;
Consider additional imaging
Riley, Henry, et al. Cath Cardio Interv. 2020; 96 346-362

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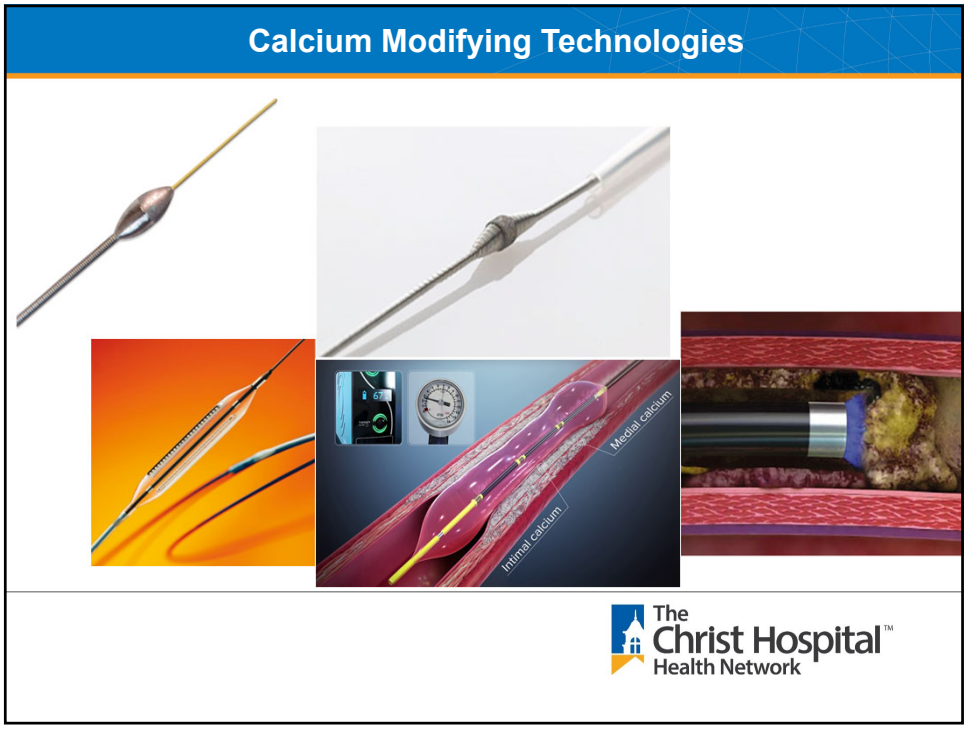
Calcium Modifying Technologies
Medial calcium
Intimal calcium
The Christ Hospital Health Network

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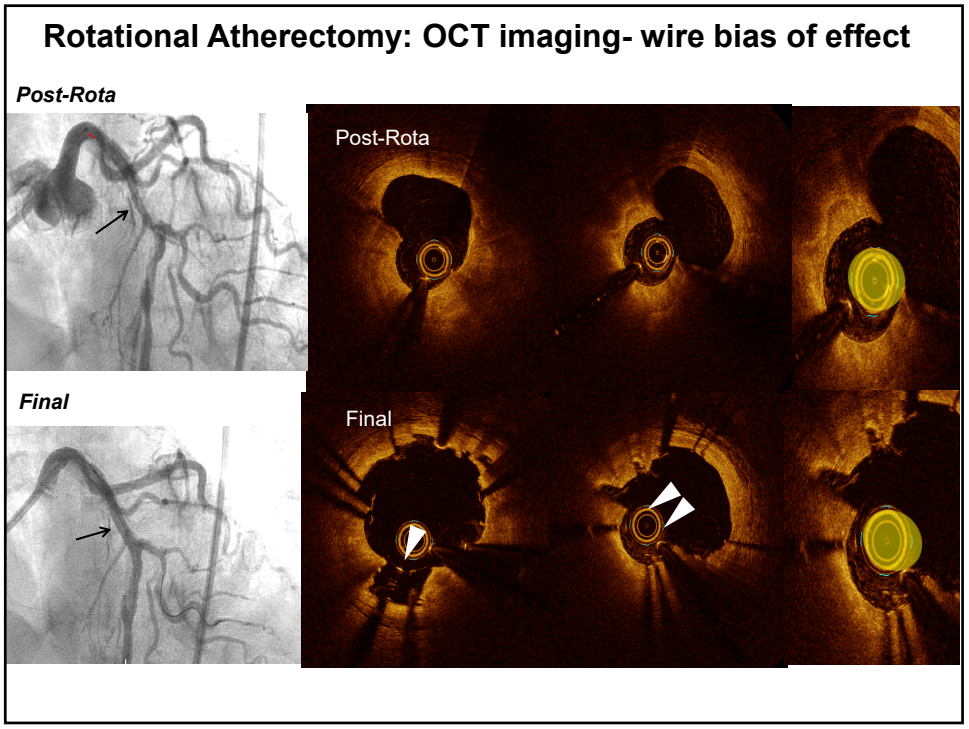
Rotational Atherectomy: OCT imaging- wire bias of effect
Post-Rota
Post-Rota
Final
Final

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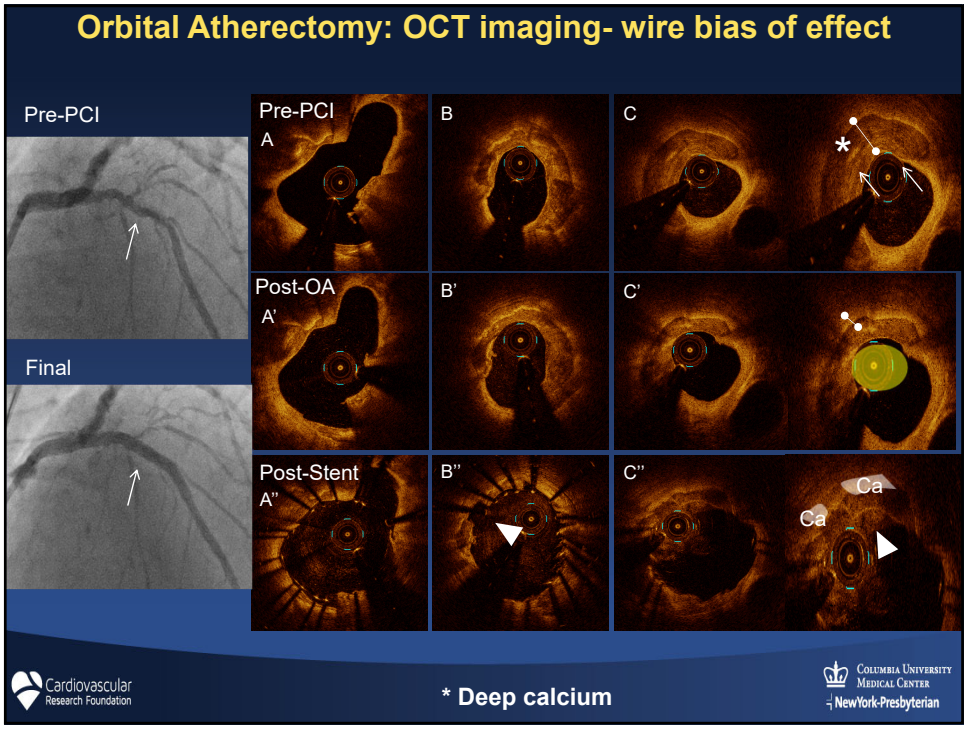
Orbital Atherectomy: OCT imaging- wire bias of effect
Pre-PCI
Final
Pre-PCI
A
B
C
Post-OA
A'
B'
C'
Post-Stent
A''
B''
C''
Ca
Ca
Cardiovascular Research Foundation
* Deep calcium
Columbia University Medical Center
NewYork-Presbyterian

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Acoustic Pressure Waves Fracture Calcium
DISRUPT CAD III
SHOCKWAVE
77
Acoustic pressure waves (1 pulse/sec) travel through tissue with an effective pressure of ~50 atm and fractures both superficial and deep calcium
CRF
TCT CONNECT

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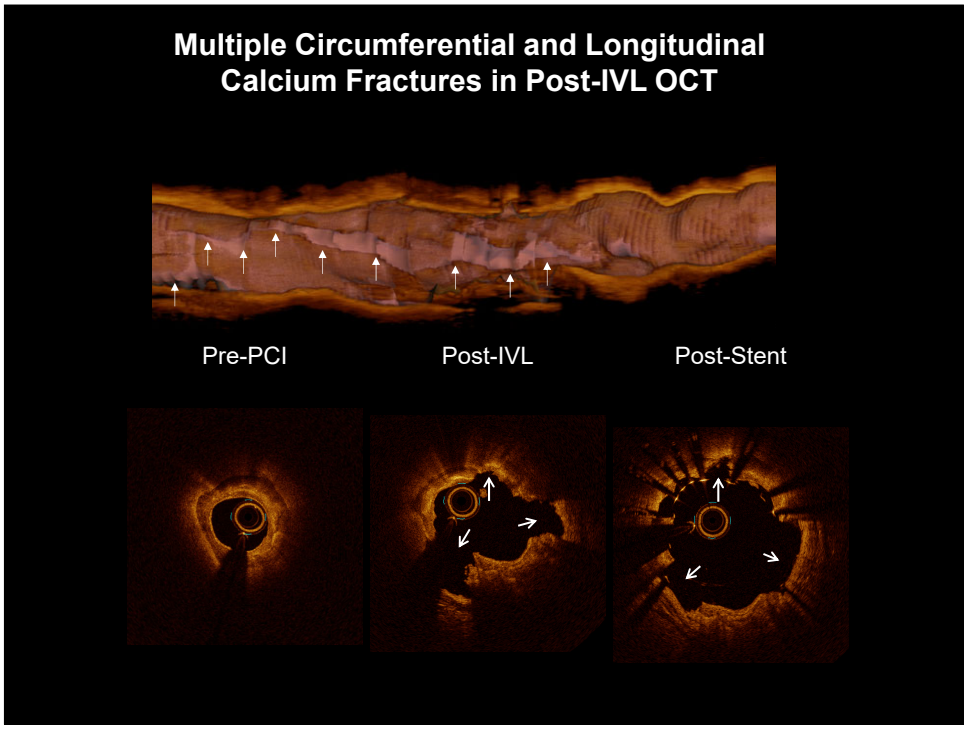
Multiple Circumferential and Longitudinal Calcium Fractures in Post-IVL OCT
Pre-PCI
Post-IVL
Post-Stent

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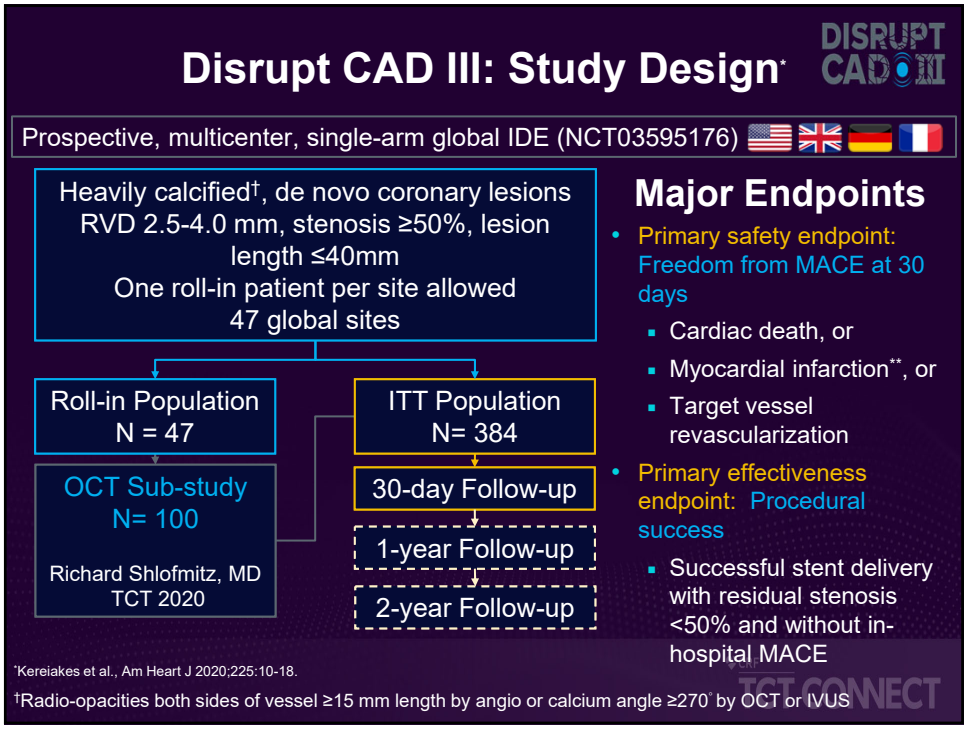
Disrupt CAD III: Study Design*
DISRUPT CAD III
Prospective, multicenter, single-arm global IDE (NCT03595176)
Heavily calcified†, de novo coronary lesions
RVD 2.5-4.0 mm, stenosis ≥50%, lesion length ≤40mm
One roll-in patient per site allowed
47 global sites
Roll-in Population
N = 47
OCT Sub-study
N= 100
Richard Shlofmitz, MD
TCT 2020
ITT Population
N= 384
30-day Follow-up
1-year Follow-up
2-year Follow-up
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
*Kereiakes et al., Am Heart J 2020;225:10-18.
†Radio-opacities both sides of vessel ≥15 mm length by angio or calcium angle ≥270° by OCT or IVUS
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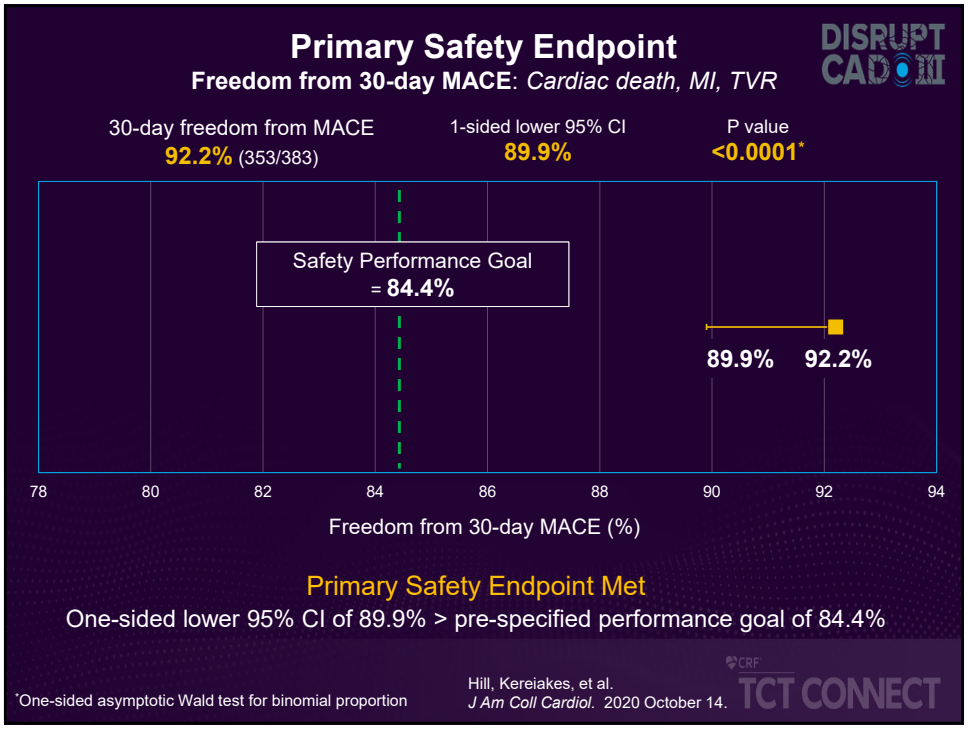
Primary Safety Endpoint
Freedom from 30-day MACE: Cardiac death, MI, TVR
DISRUPT CAD III
30-day freedom from MACE
92.2% (353/383)
1-sided lower 95% CI
89.9%
P value
<0.0001*
Safety Performance Goal
= 84.4%
89.9%
92.2%
78
80
82
84
86
88
90
92
94
Freedom from 30-day MACE (%)
Primary Safety Endpoint Met
One-sided lower 95% CI of 89.9% > pre-specified performance goal of 84.4%
*One-sided asymptotic Wald test for binomial proportion
Hill, Kereiakes, et al.
J Am Coll Cardiol. 2020 October 14.
CRF
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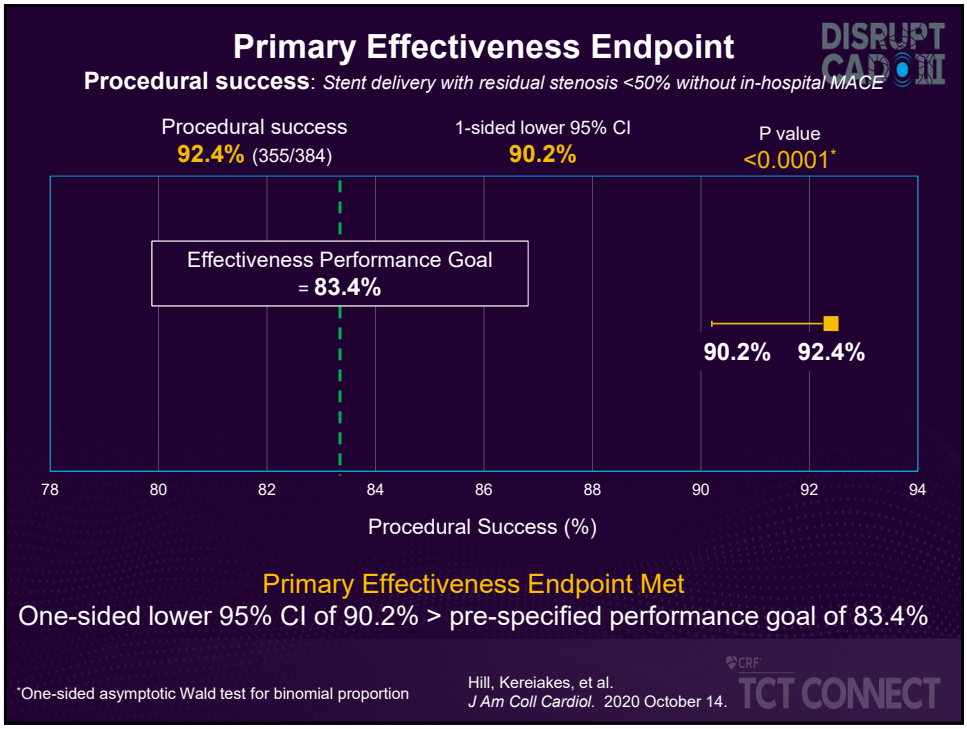
Primary Effectiveness Endpoint
DISRUPT CAD II
Procedural success: Stent delivery with residual stenosis <50% without in-hospital MACE
Procedural success
92.4% (355/384)
1-sided lower 95% CI
90.2%
P value
<0.0001*
Effectiveness Performance Goal
= 83.4%
90.2%
92.4%
78
80
82
84
86
88
90
92
94
Procedural Success (%)
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
Hill, Kereiakes, et al.
J Am Coll Cardiol. 2020 October 14.
CRF TCT CONNECT

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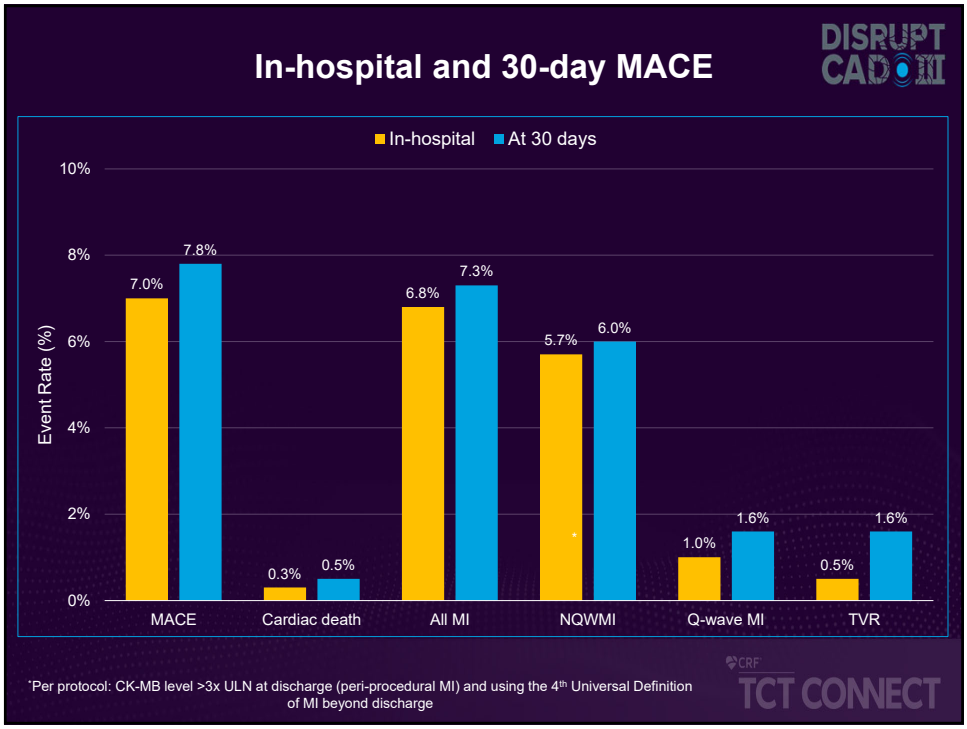
In-hospital and 30-day MACE
DISRUPT CAD II
In-hospital
At 30 days
10%
8%
6%
4%
2%
0%
Event Rate (%)
7.0%
7.8%
0.3%
0.5%
6.8%
7.3%
5.7%
6.0%
1.0%
1.6%
0.5%
1.6%
MACE
Cardiac death
All MI
NQWMI
Q-wave MI
TVR
*Per protocol: CK-MB level >3x ULN at discharge (peri-procedural MI) and using the 4th Universal Definition of MI beyond discharge
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## Angiographic Complications

DISRUPT CAD II

| 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% |

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## IVL-induced Ventricular Capture*

DISRUPT CAD II

| | 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

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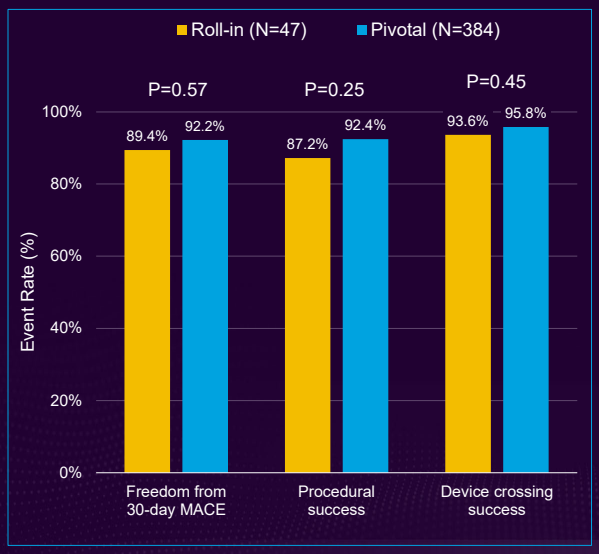
## IVL Learning Curve




- Roll-in patients represent the first case for each site in the study
- Baseline clinical and angiographic characteristics were similar between the two groups
- Key study outcomes were similar between roll-in and pivotal patients

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## Serial OCT Measurements

| | Pre-IVL N=97 | Post-IVL N=92 | Post-stent N=98 |
|---|---|---|---|
| At MLA site | | | |
| Minimum Lumen area, $mm^2$ | 2.2 ± 0.8* | 3.6 ± 1.4* | 6.5 ± 2.0* |
| Maximum Area stenosis | 72 ± 12%* | 56 ± 16%* | 22 ± 19%* |
| **At Maximum $Ca^{++}$ site** | | | |
| **Maximum calcium angle, °** | **293 ± 77** | | |
| **Maximum calcium thickness**, mm | **0.96 ± 0.25** | | |
| **Stent expansion** | | | **102 ± 29%** |
| At MSA site | | | |
| **Minimum stent area, $mm^2$** | | | **6.5 ± 2.1** |
| Any malapposed strut | | | 4.1% |

St. Francis Hospital, The Heart Center® Catholic Health Services

*P<0.01 for all comparisons between pre-IVL, post-IVL, post-stent

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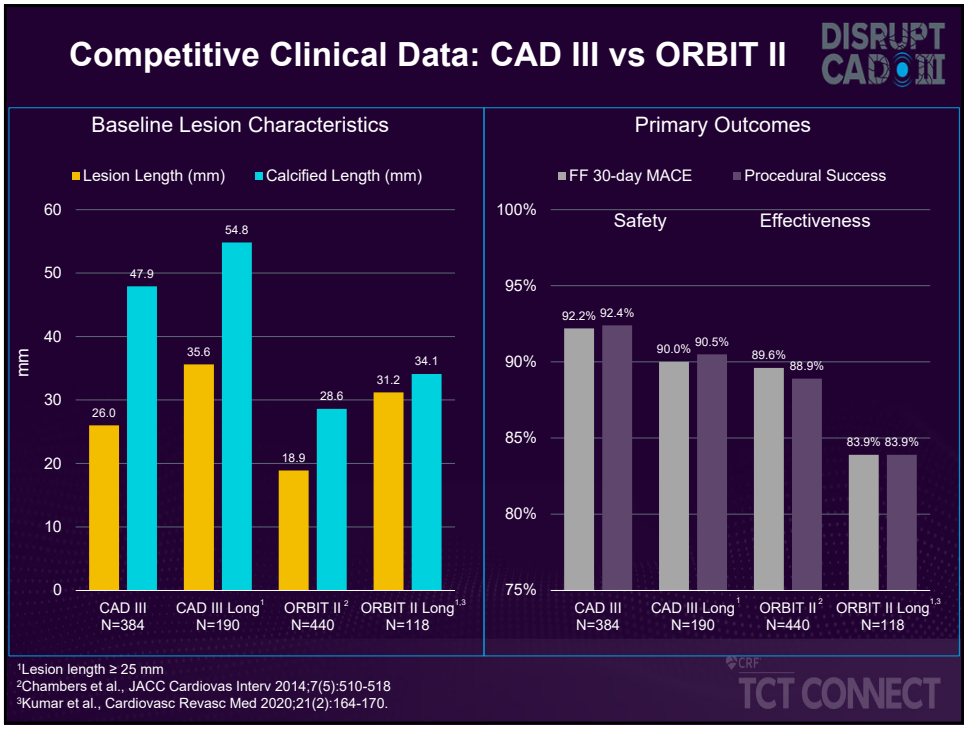


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## Innovation in Coronary Intervention: Conclusions

DISRUPT CAD III

- **Stent related adverse events (TLF;ST) are influenced by stent strut thickness. The role of strut geometry remains to be determined.**
- **The 2-4% annualized rate of adverse events beyond 1-year after stent implant regardless of device appears related to the common presence of a metallic prosthesis that constrains and distorts the vessel. The impact of DynamX Bioadaptor on this annualized event rate remains to be determined.**
- **Drug delivery without a scaffold (DCB,DEB) will enter IDE evaluation for treatment of ISR and small vessels (where stent strut thickness/volume is exaggerated)**
- **Vascular calcium increases early and late complications after stenting due to stent malapposition and under-expansion.**
- **IVL safely improves transmural vessel compliance, reduces fibro-elastic recoil and mitigates high pressure balloon inflation (barotrauma) by creating multi-plane, circumferential and longitudinal calcium fractures.**

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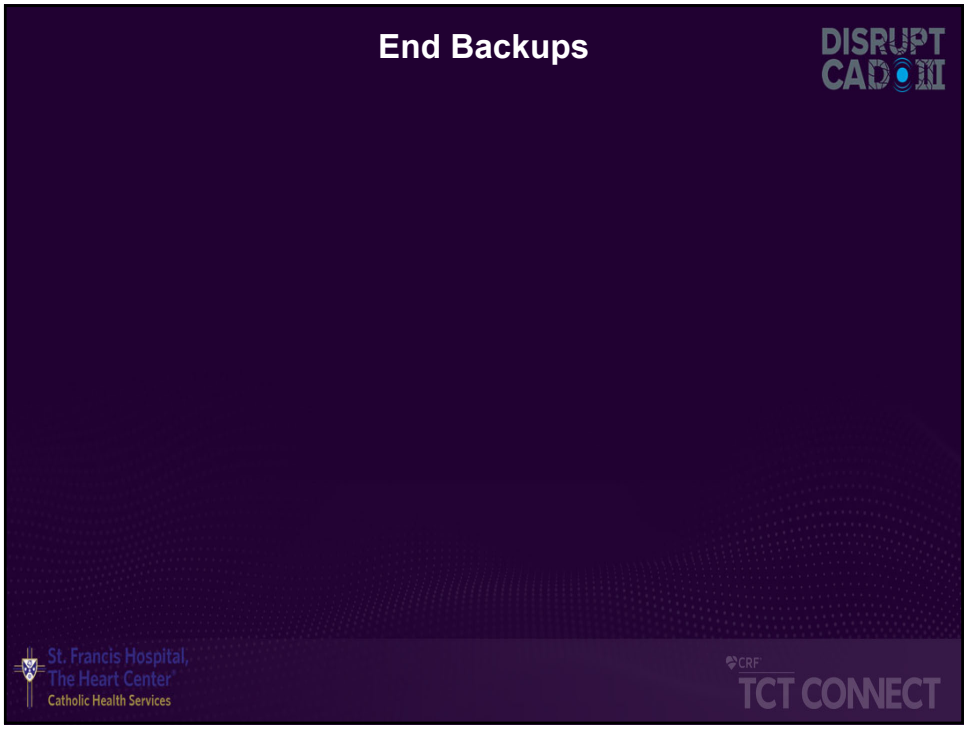
End Backups
DISRUPT CAD II
St. Francis Hospital, The Heart Center
Catholic Health Services
CRF
TCT CONNECT

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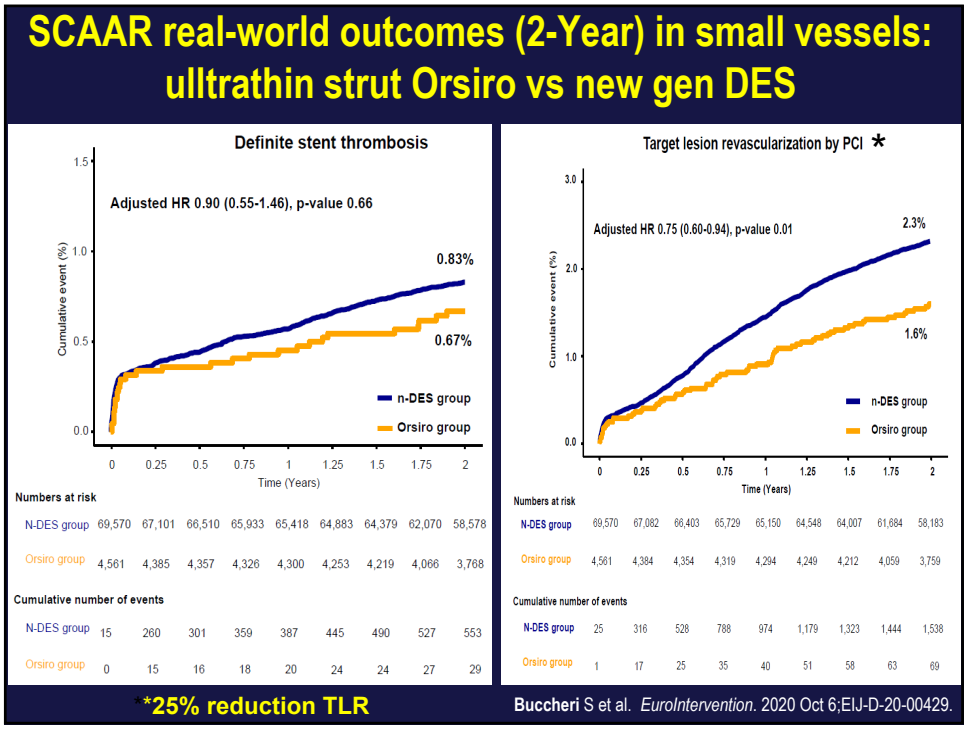
SCAAR real-world outcomes (2-Year) in small vessels: ulltrathin strut Orsiro vs new gen DES
Definite stent thrombosis
Adjusted HR 0.90 (0.55-1.46), p-value 0.66
Cumulative event (%)
0.83%
0.67%
n-DES group
Orsiro group
Time (Years)
Numbers at risk
N-DES group 69,570 67,101 66,510 65,933 65,418 64,883 64,379 62,070 58,578
Orsiro group 4,561 4,385 4,357 4,326 4,300 4,253 4,219 4,066 3,768
Cumulative number of events
N-DES group 15 260 301 359 387 445 490 527 553
Orsiro group 0 15 16 18 20 24 24 27 29
Target lesion revascularization by PCI *
Adjusted HR 0.75 (0.60-0.94), p-value 0.01
2.3%
1.6%
N-DES group 69,570 67,082 66,403 65,729 65,150 64,548 64,007 61,684 58,183
Orsiro group 4,561 4,384 4,354 4,319 4,294 4,249 4,212 4,059 3,759
N-DES group 25 316 528 788 974 1,179 1,323 1,444 1,538
Orsiro group 1 17 25 35 40 51 58 63 69
**25% reduction TLR
Buccheri S et al. EuroIntervention. 2020 Oct 6;EIJ-D-20-00429.

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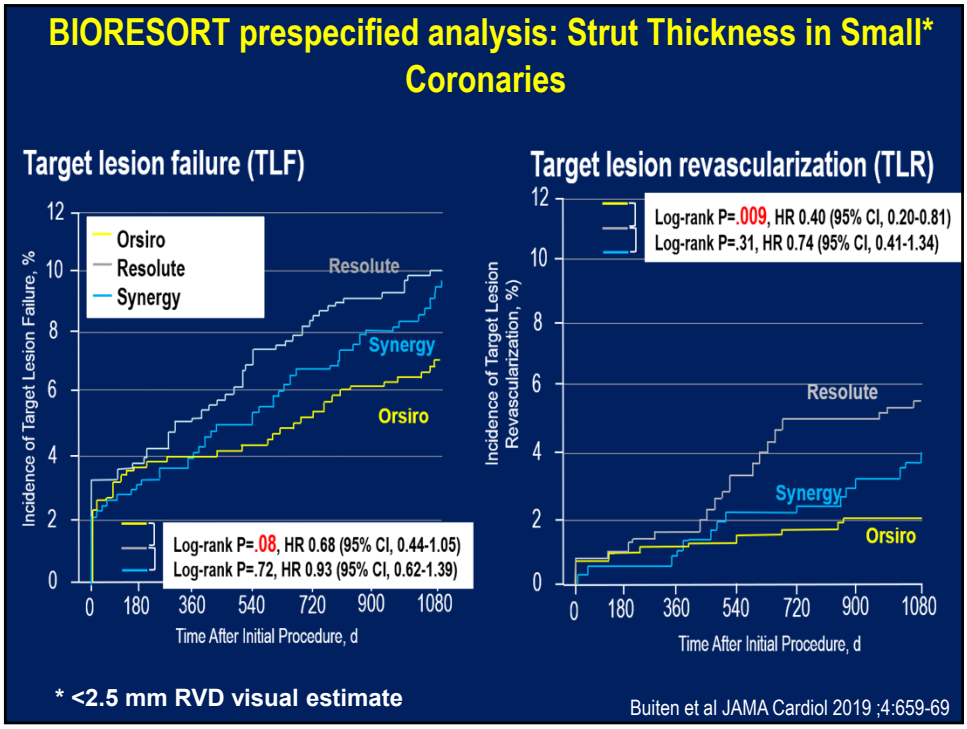
BIORESORT prespecified analysis: Strut Thickness in Small* Coronaries
Target lesion failure (TLF)
Incidence of Target Lesion Failure, %
Orsiro
Resolute
Synergy
Log-rank P=.08, HR 0.68 (95% CI, 0.44-1.05)
Log-rank P=.72, HR 0.93 (95% CI, 0.62-1.39)
Time After Initial Procedure, d
Target lesion revascularization (TLR)
Incidence of Target Lesion Revascularization, %
Log-rank P=.009, HR 0.40 (95% CI, 0.20-0.81)
Log-rank P=.31, HR 0.74 (95% CI, 0.41-1.34)
Time After Initial Procedure, d
* <2.5 mm RVD visual estimate
Buiten et al JAMA Cardiol 2019 ;4:659-69

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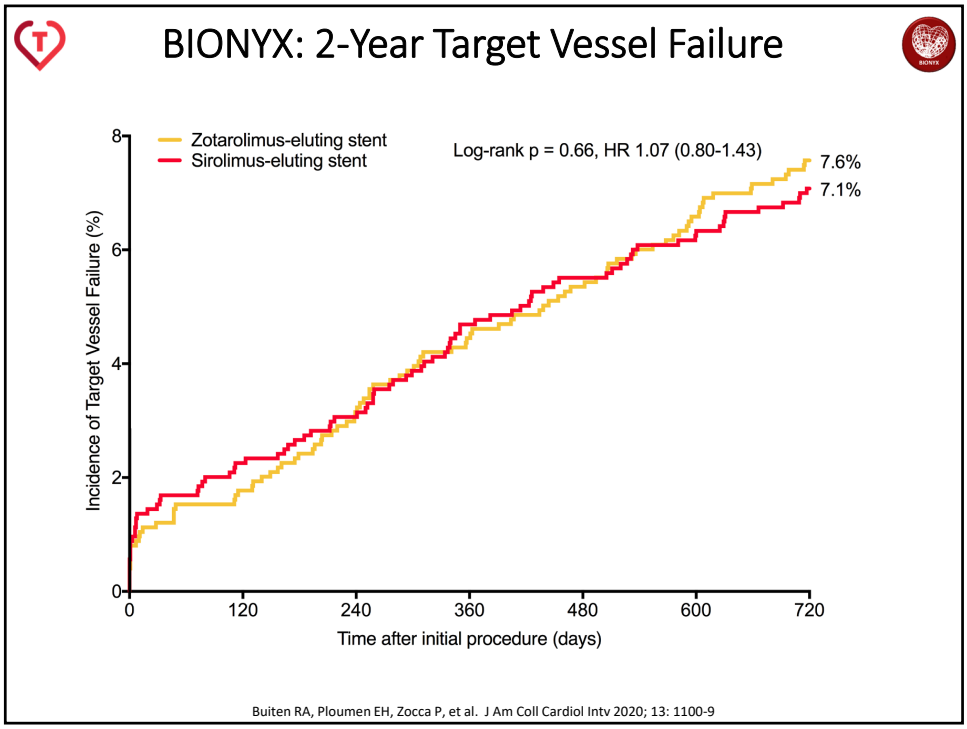
BIONYX: 2-Year Target Vessel Failure
Zotarolimus-eluting stent
Sirolimus-eluting stent
Log-rank p = 0.66, HR 1.07 (0.80-1.43)
7.6%
7.1%
Incidence of Target Vessel Failure (%)
Time after initial procedure (days)
Buiten RA, Ploumen EH, Zocca P, et al. J Am Coll Cardiol Intv 2020; 13: 1100-9

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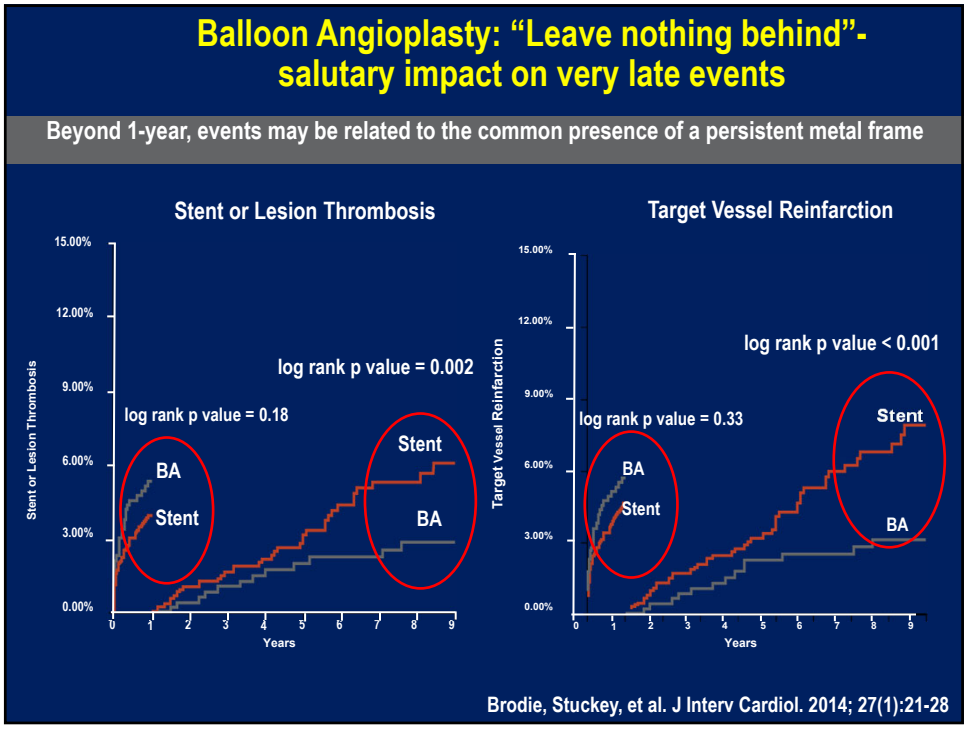
Balloon Angioplasty: "Leave nothing behind"- salutary impact on very late events
Beyond 1-year, events may be related to the common presence of a persistent metal frame
Stent or Lesion Thrombosis
Target Vessel Reinfarction
Stent or Lesion Thrombosis
Target Vessel Reinfarction
15.00%
12.00%
9.00%
6.00%
3.00%
0.00%
log rank p value = 0.18
log rank p value = 0.002
log rank p value = 0.33
log rank p value < 0.001
BA
Stent
Stent
BA
Years
Brodie, Stuckey, et al. J Interv Cardiol. 2014; 27(1):21-28

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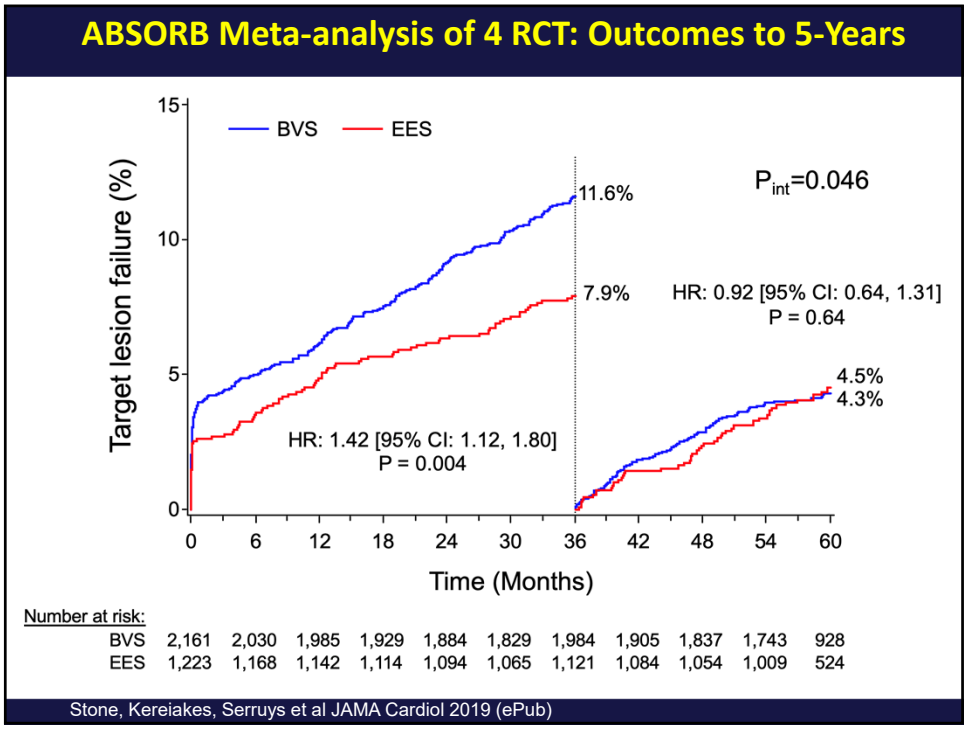
ABSORB Meta-analysis of 4 RCT: Outcomes to 5-Years
BVS
EES
Target lesion failure (%)
15
10
5
0
11.6%
7.9%
4.5%
4.3%
P_int=0.046
HR: 1.42 [95% CI: 1.12, 1.80]
P = 0.004
HR: 0.92 [95% CI: 0.64, 1.31]
P = 0.64
0 6 12 18 24 30 36 42 48 54 60
Time (Months)
Number at risk:
BVS 2,161 2,030 1,985 1,929 1,884 1,829 1,984 1,905 1,837 1,743 928
EES 1,223 1,168 1,142 1,114 1,094 1,065 1,121 1,084 1,054 1,009 524
Stone, Kereiakes, Serruys et al JAMA Cardiol 2019 (ePub)

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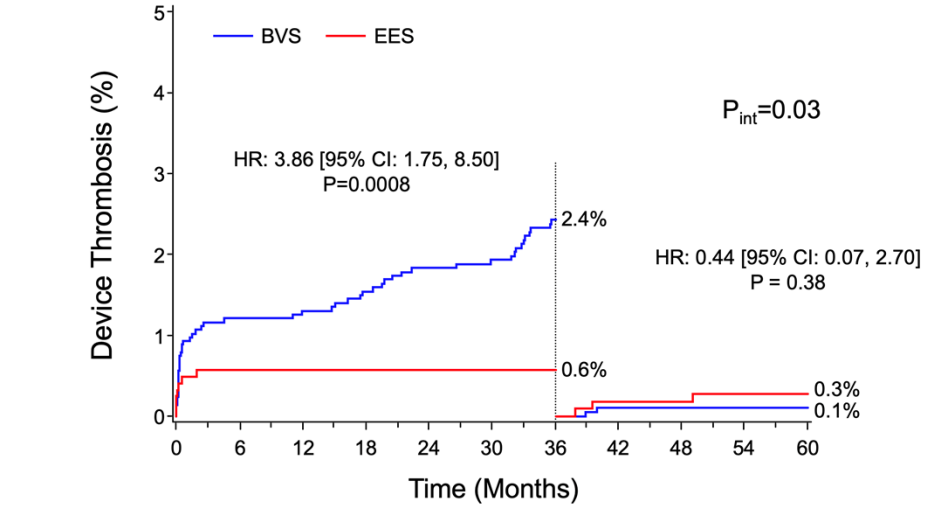
## ABSORB Meta-analysis of 4 RCT: Outcomes to 5-Years




Number at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BVS | 2,161 | 2,107 | 2,079 | 2,043 | 2,021 | 1,984 | 1,984 | 1,931 | 1,877 | 1,792 | 960 |
| EES | 1,223 | 1,202 | 1,188 | 1,167 | 1,154 | 1,131 | 1,121 | 1,094 | 1,070 | 1,029 | 536 |

Stone, Kereiakes, Serruys, et al JAMA Card 2019 (ePub)

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