MHIF FEATURED STUDY:
OCS DCD Heart CAP

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”
Novel Coronary Interventions on the Horizon:
Stents, balloons and lithotripsy

Dean J. Kereiakes, MD FACC FSCAI
President, The Christ Hospital Heart and Vascular Institute;
Medical Director, The Christ Hospital Research Institute
Professor of Clinical Medicine, Ohio State University

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.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modest Consulting Fees</td>
<td>SINO Medical Sciences Technologies, Inc.</td>
</tr>
<tr>
<td>Significant Consulting Fees</td>
<td>Boston Scientific Corporation</td>
</tr>
<tr>
<td>Significant Consulting Fees</td>
<td>Elixir Medical, Inc.</td>
</tr>
<tr>
<td>Significant Consulting Fees</td>
<td>Svelte Medical Systems, Inc.</td>
</tr>
<tr>
<td>Significant Consulting Fees</td>
<td>Caliber Therapeutics/Orchestra Biomed</td>
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<tr>
<td>Significant Consulting Fees</td>
<td>Shockwave</td>
</tr>
<tr>
<td>Major Stock Shareholder/Equity</td>
<td>Ablative Solutions, Inc.</td>
</tr>
</tbody>
</table>
Very-late stent-related events: IPD level analysis of 19 trials

Contemporary DES: Thinner struts have better outcomes
Meta-Analysis of 66 Trials/74,980 Patients

Stent Thrombosis*
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**

<table>
<thead>
<tr>
<th>Strut Thickness</th>
<th>Express</th>
<th>Liberté</th>
<th>Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>132 (\mu m)</td>
<td>77</td>
<td>88</td>
<td>94.8</td>
</tr>
<tr>
<td>97 (\mu m)</td>
<td>97</td>
<td>100</td>
<td>94.8</td>
</tr>
<tr>
<td>81 (\mu m)</td>
<td>97</td>
<td>100</td>
<td>94.8</td>
</tr>
</tbody>
</table>

**Fibrin**

**Inflammation**

Stent Design: Strut Thickness affects Thrombogenicity

Low shear stress

Kolandaivelu et al. Circulation 2011;123:1400-1409

Day 3 Adherent Thrombus (mm²)

49% \(P< 0.001\)

IN-SILICO MODEL

Kolandaivelu et al. Circulation 2011;123:1400-1409
**BIORESORT prespecified analysis: Strut Thickness in Small* Coronaries**

**TLF at 3 y, with 1-y landmark**

<table>
<thead>
<tr>
<th>Time After Initial Procedure, d</th>
<th>Log-rank P = .008, difference 1-y, -2.3 (95% CI, -4.8 to -0.3)</th>
<th>Log-rank P = .36, difference 1-y, 0.1 (95% CI, -2.6 to 3.0)</th>
</tr>
</thead>
</table>

**TLR at 3y, with 1-y landmark**

<table>
<thead>
<tr>
<th>Time After Initial Procedure, d</th>
<th>Log-rank P = .008, difference 1-y, -2.7 (95% CI, -4.6 to -0.8)</th>
<th>Log-rank P = .42, difference 1-y, -0.9 (95% CI, -3.2 to 1.3)</th>
</tr>
</thead>
</table>

* < 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 device, DAPT, antithrombotics or anticoagulants before enrolling primary EP (life expectancy > 5 yrs); planned surgery (< 90 days) preventing maintenance of DAPT or known pregnancy; known intolerance to DES, anticoagulants or antithrombotics, preventing DAPT

- **Zotarolimus-eluting RESOLUTE ONYX (81 µ)**
- **Strontium-eluting ORSIRO (60 µ)**

- **30 days**
- **1 year**
- **2 years**

- **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, MACCE, etc.
- **1-year follow-up:** 2,488 patients (99.9%) completed 1-year follow-up or had died

Patients were enrolled from October 1, 2016 to December 31, 2018. All study sites are listed in the acknowledgment. This work was supported by Amgen, Inc. and the Amgen Foundation. The authors have no relevant conflicts of interest to disclose.
Resolute ONYX vs. Orsiro in All Comers: BIONYX Trial

Target Vessel Failure

<table>
<thead>
<tr>
<th></th>
<th>Resolute Onyx</th>
<th>Orsiro</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.95 (0.66-1.37)</td>
<td>0.11 (0.01-0.87)</td>
</tr>
<tr>
<td>log-rank p</td>
<td>0.77</td>
<td>0.0112</td>
</tr>
</tbody>
</table>

Definite/Probable Stent Thrombosis*

<table>
<thead>
<tr>
<th></th>
<th>Resolute Onyx</th>
<th>Orsiro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>4.7%</td>
<td>4.5%</td>
</tr>
<tr>
<td></td>
<td>0.7%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

*ONYX 1 subacute ST (>100mm stent) after DAPT discontinuation; 38-2.0mm stents deployed

BIONYX: Stent Thrombosis at 2-years

Log-rank p = 0.057, HR 0.38 (0.14-1.07)

Incidence of Definite or Probable Stent Thrombosis (%)
Stent strut geometry affects strut level shear stress distribution

Shear Stress Between First/Second Struts

Stent Strut Profiles

Circular
Square

Circular Square
Elliptical Tear-Drop

*degree embedment, EC coverage/healing, shear

Mejia, Bertrandt et al Biomedical Engineering Online 2009

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

World's leading guidewire brand

*5F diagnostic catheter

Enzymatic resorption 12 months
**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

*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**

OPTIMIZE 12-Month TLF and Components

- Xience/Promus DES (N=812)
- Svelte DES (N=827)

<table>
<thead>
<tr>
<th>Component</th>
<th>Xience/Promus</th>
<th>Svelte</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically-Indicated TLR</td>
<td>1.93</td>
<td>1.52</td>
<td>0.57</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0.26</td>
<td>0.25</td>
<td>1.00</td>
</tr>
<tr>
<td>TVMI*</td>
<td>8.22</td>
<td>9.31</td>
<td>0.48</td>
</tr>
<tr>
<td>TLF</td>
<td>9.49</td>
<td>10.30</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*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 All Stent Thrombosis Through 12 Months**

- **Xience or Promus DES**
  - **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)

**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)

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

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

ISA = Incomplete Stent Apposition
Saito et al, TCT 2020
OPTIMIZE Primary Endpoint: 12-Month TLF (ITT)

12-Month TLF
Svelte vs. Xience or Promus
10.3% vs. 9.5%

% Difference (Svelte – Xience or Promus)

-3 -2 -1 0 1 2 3 4 5

12-Month TLF
Svelte vs. Xience or Promus
10.3% vs. 9.5%

Difference = 0.8% [-inf, 3.8%]
P-nil = 0.034

NI margin = 3.58%

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 (α) = 0.025 (1-sided)
Power (1−β) = 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
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)

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)
### OPTIMIZE Non-Inferiority Assessment

<table>
<thead>
<tr>
<th>OPTIMIZE Study Endpoint Analysis</th>
<th>Xienc/Promus DES n=812 Subjects</th>
<th>Svelte DES n=827 Subjects</th>
<th>Non-Inferiority</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLF: Protocol Defined TVMI</td>
<td>9.46% (74/780)</td>
<td>10.33% (82/796)</td>
<td>Absolute Margin</td>
<td>3.58%</td>
<td>0.81% [2.15%, 3.78%]</td>
</tr>
<tr>
<td>TLF: Protocol Defined TVMI</td>
<td>9.46% (74/780)</td>
<td>10.33% (82/796)</td>
<td>Relative Margin</td>
<td>1.55</td>
<td>1.09 [0.81, 1.46]</td>
</tr>
<tr>
<td>TLF: SCAI Defined TVMI</td>
<td>3.33% (26/780)</td>
<td>3.66% (29/796)</td>
<td>Absolute Margin</td>
<td>2.97%</td>
<td>0.32% [-1.60%, 2.24%]</td>
</tr>
</tbody>
</table>

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 (with used SCAI definition for MI).

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### 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 (eG 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

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#AHA20

Lansky, Kereiakes, Leon, et al. PIONEER III AHA 2020
BuMA Supreme pharmacokinetic profile

Drug Release Comparison, measured in vitro

> 90% drug release in 28 days

Arterial Sirolimus Concentration, measured in vivo

Arterial drug concentration peaks at 20 days and gradually decreases

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

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Degradation Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>BuMA Supreme</td>
<td>2 Months</td>
</tr>
<tr>
<td>Synergy</td>
<td>3-4 Months</td>
</tr>
<tr>
<td>Orsiro</td>
<td>13+ Months</td>
</tr>
<tr>
<td>Resolute</td>
<td>Permanent</td>
</tr>
<tr>
<td>Promus Element</td>
<td>Permanent</td>
</tr>
<tr>
<td>Xience</td>
<td>Permanent</td>
</tr>
</tbody>
</table>

Source: Data on file.
Supreme HT-DES Promotes functional healing

Endothelial Cell Barrier Proteins\(^1\), measured at 90 days post implantation

<table>
<thead>
<tr>
<th>Protein</th>
<th>BuMA Supreme</th>
<th>Xience (^1)</th>
<th>Synergy</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>82.5%</td>
<td>55.7%</td>
<td>80.7%</td>
<td>97.4%</td>
</tr>
</tbody>
</table>

Evans Blue Uptake, measured at 90 days post implantation

<table>
<thead>
<tr>
<th>Protein</th>
<th>BuMA Supreme</th>
<th>Xience (^1)</th>
<th>Synergy</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>22.9%</td>
<td>36.4%</td>
<td>31.1%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

\(^1\) 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

Evans Blue Staining: Endothelial Permeability in Rabbit Iliac

BP-SES = BUMA
DP-EES = Xience
BP-EES = Synergy

\( * = p<0.05 \) vs BP-SES

**Cell Morphology and Cell Shape Index in Rabbit Iliac**

![Graph showing cell morphology and cell shape index](image)

**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**

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

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

**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*
### TLF at 12 months (ITT)

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>HT-DES (N = 1088 Patients)</th>
<th>DP-DES (N = 543 Patients)</th>
<th>Difference (95% CI)</th>
<th>One Sided 95% Upper Confidence Boundary</th>
<th>Non-Inferiority Margin</th>
<th>P-value$^2$ For non-inferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLF at 365 days</td>
<td>5.4% (57/1057)</td>
<td>5.1% (27/532)</td>
<td>0.32% (-1.87%, 2.5%)</td>
<td>2.5%</td>
<td>3.58%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Primary non-inferiority endpoint met**

* No differences in TLF components or ST

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

- **Proven Cobalt Chromium Alloy**
  - DESyne/DESyne BD

- **Proven Conformal (3µm) PLGA Biodegradable Polymer**
  - Top coat
  - DESyne BD/DESolve

- **Proven Drug and Dose**
  - Novolimus, 5µg/mm
  - DESyne/DESyne BD/DESolve

- **Proven Conformal (6µm)**
  - PLLA-based
  - Biodegradable Polymer
  - Base coat - DESolve

**Strut Thickness**

71µm

**Drug elutes in 3M; Polymer degrades in 6M**
• **Uncaging elements** at low-stress regions of each sinusoidal ring in a helical pattern while maintaining longitudinal continuity of the bioadaptor.

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

**Uncaged Pulsatility Analysis: Stationary OCT Acquisition**

OCT corelab analysis shows increased lumen area: systole vs diastole in co-registered images.
DynamX Bioadaptor Uncaged Restores Vessel Angulation

Reduces Geometric Distortion*

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

* 60% increase in conformability

Patient: 28-501
3.5 x 18 mm DynamX Bioadaptor

* Abnormal CFV, shear stress (MACE, restenosis)

OCT based measurements

- 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

Serial In-vivo OCT evaluation in adult porcine coronary model

Data on file at Elixir Medical
Preclinical Studies conducted at AccelLAB, Montreal, Canada

33

34
### DynamX Bioadaptor Paired IVUS studies: Adaptive remodeling accommodates NIH/Disease Progression to Maintain Lumen Area:

<table>
<thead>
<tr>
<th>IVUS Parameter</th>
<th>9 + 12 Months (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-Procedure</td>
</tr>
<tr>
<td>Mean Vessel Area (mm²)</td>
<td>14.10 ± 2.99</td>
</tr>
<tr>
<td>Mean Bioadaptor Area (mm²)</td>
<td>7.39 ± 1.20</td>
</tr>
<tr>
<td>Mean Lumen Area (mm²)</td>
<td>7.39 ± 1.20</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>9 + 12 Month Follow-up (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-Procedure</td>
</tr>
<tr>
<td>In-Segment</td>
<td></td>
</tr>
<tr>
<td>RVD Interp (mm)</td>
<td>2.93 ± 0.38</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.56 ± 0.31</td>
</tr>
<tr>
<td>%DS</td>
<td>12.14 ± 8.7</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>1.44 ± 0.36</td>
</tr>
<tr>
<td>Balloon-Artery Ratio</td>
<td>1.14 ± 0.09</td>
</tr>
<tr>
<td>Late Lumen Loss (mm)</td>
<td>--</td>
</tr>
<tr>
<td>In-Bioadaptor</td>
<td></td>
</tr>
<tr>
<td>RVD Interp (mm)</td>
<td>2.95 ± 0.36</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.74 ± 0.30</td>
</tr>
<tr>
<td>%DS</td>
<td>6.69 ± 6.8</td>
</tr>
<tr>
<td>Acute gain (mm) (Mean ± SD)</td>
<td>1.62 ± 0.34</td>
</tr>
<tr>
<td>Late Lumen Loss (mm) (Mean ± SD)</td>
<td>--</td>
</tr>
<tr>
<td>Late Lumen Loss (mm) (Median, IQR)</td>
<td>--</td>
</tr>
</tbody>
</table>

DynamX Bioadaptor Preserves Positive Adaptive (Glagov) Vessel Remodeling

2nd Gen DES

DynamX Bioadaptor

DynamX Bioadaptor uncaged allows vessel to accommodate NIH/disease progression and to maintain flow lumen area

Evolution of DEBs: Drugs, Coatings and Beyond

1st-Generation Paclitaxel-Coated Balloon 2nd-Generation Sirolimus-Coated Balloon 3rd-Generation Sirolimus-Eluting Balloon

<table>
<thead>
<tr>
<th></th>
<th>Crystalline / Non-Crystalline Amorphous Coating</th>
<th>Spray-Coated Nanocarrier1 / Microparticle Coating2 / Spray-Coated Crystalline3</th>
<th>Nanosphere-Encapsulated (Particle Delivery via Microporous Balloon, w/out Coating)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>PTX</td>
<td>SIR / +</td>
<td>SIR ++ / +</td>
</tr>
<tr>
<td>Elution Control</td>
<td>-</td>
<td>~10 Days / 30 Days +</td>
<td>Mimics DES</td>
</tr>
<tr>
<td>Dose Uniformity</td>
<td>-</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coating</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Particulate Debris/ Microemobilization</td>
<td>+</td>
<td>+</td>
<td>- - No Particulates</td>
</tr>
<tr>
<td>Drug Loss in Transit</td>
<td>+</td>
<td>+</td>
<td>No Drug Loss in Transit</td>
</tr>
<tr>
<td>Drug Deposition</td>
<td>+/-</td>
<td>+ / - Endo-luminal</td>
<td>+ + Trans-mural</td>
</tr>
</tbody>
</table>

1Concept Medical MagicTouch; 2Med Alliance Solution; 3B. Braun Sequent Please Sirolimus
**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

---

**Virtue SAB vs. Limus-Eluting Stent**

Bioresorbable nanencapsulation technology is designed to achieve tissue concentrations of sirolimus compared to clinically proven DES

**Arterial Tissue Concentration**

**Normalized Tissue Kinetics**

Target Therapeutic Concentration: > 1 ng / mg at 4 weeks

Sirolimus arterial tissue concentration at target treatment site is >300-fold higher compared to off-target systemic drug levels.

Virtue SAB: Targeted Drug Delivery

Therapeutic concentration > 1ng/mg

Lung, liver and kidney below level of assay quantification (0.1 ng/mg) in less than 1 week

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

Virtue® SAB
N=200

POBA
N=100

2-Stent ISR Cohort
Up to 50 sites

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

* Dean J Kereiakes PI (separate SV IDE RCT vs DES)

**TLF is defined as CD, TV-MI and TLR
**Vascular calcium**: Increasing Problem

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

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

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

- **Iliac, Femoral**
  - < 50% Mod/Severe Calcium

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

* Increasing age, diabetes, CKD

---

**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

<table>
<thead>
<tr>
<th></th>
<th>With Severe Calcification (N=1291)</th>
<th>Without Severe Calcification (N = 5005)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>10.8%</td>
<td>4.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Combined Endpoint:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI &amp; Death</td>
<td>22.9%</td>
<td>10.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI, Death &amp; Revascularization</td>
<td>31.8%</td>
<td>22.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


*Severe Calcium: radiopacities noted without cardiac motion before contrast, generally on both sides of arterial lumen*
Coronary Calcification Impacts Outcomes after Stenting*

Presence of Severe Lesion Calcification
Absence of Severe Lesion Calcification

Death, MI, Repeat Revasc

Log-rank = 44.42
p < 0.001

Log-rank = 35.2
p < 0.001

Log-rank = 10.19
p = 0.01

Cumulative incidence of death – MI - revasc (%)

Time after initial procedure (months)

**7 PCI Trials / 6296 Patients
Bourantas et al. Heart 2014;100:1158-1164

Challenges With Coronary Calcification

The greater the arc, length, or thickness of calcium, the greater the likelihood of stent underexpansion

- Asymmetrical stent expansion: up to 50% of stents deployed in calcified lesions

- Stent underexpansion* and poor apposition:
  - associated with increased ischemic events at 1 year

*Independent predictor of ST and Restenosis


Increase Arc of Ca++ leads to decrease in stent expansion
**Therapeutic Algorithm for Moderate-Severe Coronary Calcium**

1. **Moderate-severe coronary calcium by fluoroscopy and/or Inadequate balloon expansion during lesion preparation**

   **Step 1:** Intravascular imaging

2. **Full expansion with 1:1 NC or cutting/scoring balloon?**

   **Yes:**
   - Intravascular imaging
   - Full expansion with 1:1 NC or cutting/scoring balloon?

   **No: Uncrossable Lesion**
   - 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:**
   - Step 2
   - Step 3
   - Stenting and Image-guided optimization

   **SUCCESS**

   **MECHANICAL AHERECTOMY**
   - Utilize a microcatheter to exchange for a dedicated atherectomy wire, or free wire across the lesion with a dedicated atherectomy wire

   **LASER AHERECTOMY**
   - Perform laser atherectomy over prior wire that had crossed lesion (off-label use)

   **LITHOPLASTY**
   - Go to Step 2: Consider additional imaging

---

**Calcium Modifying Technologies**

- Calcium Modifying Technologies
- Calcium Modifying Technologies
- Calcium Modifying Technologies
Rotational Atherectomy: OCT imaging- wire bias of effect

Post-Rota

Final

Orbital Atherectomy: OCT imaging- wire bias of effect

Pre-PCI

Pre-PCI

A

Post-OA

A'

Post-Stent

A''

Final

B

B'

B''

C

C'

C''

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

Acoustic Pressure Waves Fracture Calcium

Multiple Circumferential and Longitudinal Calcium Fractures in Post-IVL OCT
Disrupt CAD III: Study Design

Prospective, multicenter, single-arm global IDE (NCT03595176)

MajorEndpoints

- **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

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

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

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%

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

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

Effectiveness Performance Goal = 83.4%

Primary Effectiveness Endpoint Met
One-sided lower 95% CI of 90.2% > pre-specified performance goal of 83.4%

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
### Angiographic Complications

<table>
<thead>
<tr>
<th>Core Lab Analysis</th>
<th>Immediately Post-IVL</th>
<th>Final Post-stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious angiographic complication</td>
<td>2.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Severe dissection (Type D-F)</td>
<td>2.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Perforation</td>
<td>0.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Abrupt closure</td>
<td>0.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Slow flow</td>
<td>0.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>No-reflow</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

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

Serial OCT Measurements

<table>
<thead>
<tr>
<th>Site</th>
<th>Pre-IVL (N=97)</th>
<th>Post-IVL (N=92)</th>
<th>Post-stent (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At MLA site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum Lumen area, mm²</td>
<td>2.2 ± 0.8*</td>
<td>3.6 ± 1.4*</td>
<td>6.5 ± 2.0*</td>
</tr>
<tr>
<td>Maximum Area stenosis</td>
<td>72 ± 12%</td>
<td>56 ± 16%</td>
<td>22 ± 19%</td>
</tr>
<tr>
<td>At Maximum Ca²⁺ site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum calcium angle, °</td>
<td>293 ± 77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum calcium thickness, mm</td>
<td>0.96 ± 0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent expansion</td>
<td></td>
<td></td>
<td>102 ± 29%</td>
</tr>
<tr>
<td>At MSA site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum stent area, mm²</td>
<td>6.5 ± 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any malapposed strut</td>
<td></td>
<td></td>
<td>4.1%</td>
</tr>
</tbody>
</table>

*P<0.01 for all comparisons between pre-IVL, post-IVL, post-stent
Competitive Clinical Data: CAD III vs ORBIT II

Baseline Lesion Characteristics

<table>
<thead>
<tr>
<th>Lesion Length (mm)</th>
<th>CAD III N=384</th>
<th>CAD III Long a N=190</th>
<th>ORBIT II N=440</th>
<th>ORBIT II Long a,b N=118</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>110</td>
<td>120</td>
<td>130</td>
<td>140</td>
</tr>
<tr>
<td>Calcified Length (mm)</td>
<td>29.0</td>
<td>35.6</td>
<td>31.2</td>
<td>34.1</td>
</tr>
</tbody>
</table>

Primary Outcomes

<table>
<thead>
<tr>
<th>Safety</th>
<th>CAD III N=384</th>
<th>92.2%</th>
<th>90.0%</th>
<th>90.5%</th>
<th>88.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural Success</td>
<td>CAD III Long a N=190</td>
<td>92.4%</td>
<td>90.5%</td>
<td>88.9%</td>
<td>83.9%</td>
</tr>
</tbody>
</table>

a Lesion length ≥ 25 mm
b Chambers et al., JACC Cardiovasc Interv 2014;7(5):510-518

Innovation in Coronary Intervention: Conclusions

- 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.
SCAAR real-world outcomes (2-Year) in small vessels: ulltrathin strut Orsiro vs new gen DES

**25% reduction TLR**

BIORESORT prespecified analysis: Strut Thickness in Small* Coronaries

* <2.5 mm RVD visual estimate

BIONYX: 2-Year Target Vessel Failure
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: Log rank p value = 0.002
- Target Vessel Reinfarction: Log rank p value < 0.001

Stone, Kereiakes, Serruys et al. JAMA Cardiol. 2019 (ePub)
**ABSORB Meta-analysis of 4 RCT: Outcomes to 5-Years**

- **BVS**
  - HR: 3.86 [95% CI: 1.75, 8.50]
  - P = 0.0008

- **EES**
  - HR: 0.44 [95% CI: 0.07, 2.70]
  - P = 0.38

**Number at risk:**
- **BVS:** 2,161, 2,107, 2,079, 2,043, 2,021, 1,984, 1,964, 1,931, 1,877, 1,792, 960
- **EES:** 1,223, 1,202, 1,186, 1,167, 1,154, 1,131, 1,121, 1,094, 1,070, 1,029, 536

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