Novelties in the Interventional Cardiology Laboratory

Bioabsorbable Polymer Stents: Is The Future?

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Humanitas University
Rozzano, Milan - Italy

Torino, 27.10.2017
Potential Conflicts of Interest

Speaker's name: Giulio Stefanini

I have the following potential conflicts of interest to report:

Receipt of grants/research support:
  Boston Scientific

Receipt of honoraria or consultation fees:
  B.Braun, Biosensors, Boston Scientific, Edwards Lifesciences
# Progress with Metallic Drug-Eluting Stents


## Antiproliferative Drug

<table>
<thead>
<tr>
<th>Paclitaxel</th>
<th>Sirolimus-analogue</th>
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</thead>
<tbody>
<tr>
<td>SES</td>
<td>BES</td>
</tr>
<tr>
<td>ZES</td>
<td>SES</td>
</tr>
<tr>
<td>SES</td>
<td>EES</td>
</tr>
<tr>
<td>ZES</td>
<td>EES</td>
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<tr>
<td>SES</td>
<td>NES</td>
</tr>
<tr>
<td>SES</td>
<td>SES</td>
</tr>
<tr>
<td>SES</td>
<td>SES</td>
</tr>
</tbody>
</table>

## Polymer Material

- Taxus 132
- Cypher 140
- BioMatrix; Nobori 120
- Endeavor 91
- Yukon PC 87
- Xience; Promus 81
- Resolute 91
- Synergy 74
- Orsiro 60
- DESyne 81
- Combo 100
- Mistent 64
- Ultimaster 80

## Platform Material and Strut Thickness

- Early generation
- New generation

- Durable polymer
- Biodegradable polymer
- Stainless steel
- Cobalt-chromium or platinum-chromium
Inflammatory response to durable polymer coatings plays a central role in delayed arterial healing.
BIOABSORBABLE POLYMER DES VERSUS DURABLE POLYMER SES THROUGH 4 YEARS


Definite ST

0 to 1 year:
HR 0.80
(95% CI 0.47-1.38)
p=0.43

1 to 4 years:
HR 0.22
(95% CI 0.08-0.61)
p=0.004

Cardiac Death or MI

0 to 1 year:
HR 1.02
(95% CI 0.78-1.31)
p=0.91

1 to 4 years:
HR 0.73
(95% CI 0.53-1.00)
p=0.05
BERN-ROTTERDAM COHORT STUDY II

Very Late Definite ST (1-4 yrs)

Räber L et al. Circulation 2012; 125:1110-21

EES vs. SES HR* = 0.33, 95% CI 0.15 – 0.72,
P=0.006

EES vs. PES HR* = 0.24, 95% CI 0.13-0.47,
P <0.0001

Sirolimus Stent 1.6%
Paclitaxel Stent 2.4%
Everolimus Stent 0.6%

*from Cox proportional hazards model

Very Late Definite ST (1-4 yrs)

Sirolimus Stent 1.6%
Paclitaxel Stent 2.4%
Everolimus Stent 0.6%
LONG-TERM SAFETY OF CoCr-EES: A NETWORK META-ANALYSIS

## Novel Bioabsorbable Polymer DES

<table>
<thead>
<tr>
<th>BioMatrix</th>
<th>Orsiro</th>
<th>Ultimaster</th>
<th>Synergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platform material</td>
<td>SS</td>
<td>CoCr</td>
<td>CoCr</td>
</tr>
<tr>
<td>Strut thickness (µm)</td>
<td>120</td>
<td>60</td>
<td>80</td>
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<tr>
<td>Polymer material</td>
<td>PDLLA</td>
<td>PLLA</td>
<td>PDLLA-PCL</td>
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<tr>
<td>Coating distribution</td>
<td>Abluminal</td>
<td>Conformable</td>
<td>Abluminal</td>
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<tr>
<td>Polymer thickness (µm)</td>
<td>10</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Additional coating</td>
<td>-</td>
<td>Silicon carbide</td>
<td>-</td>
</tr>
<tr>
<td>Drug released</td>
<td>Biolimus</td>
<td>Sirolimus</td>
<td>Sirolimus</td>
</tr>
</tbody>
</table>
THIN-STRUT DES WITH BIOABSORBABLE POLYMER COATINGS

**Orsiro**

**Ultimaster**

**Synergy**

**BIOSCIENCE Trial**
(N=2119)

**CENTURY-2 Trial**
(N=1123)

**EVOLVE-2 Trial**
(N=1684)

P-noninferiority <0.001

CoCr
80
Biodegradable
PDLLA-PCL
Abluminal
15
Sirolimus
4,4

PtCr
74
Biodegradable
PLGA
Abluminal
4
Everolimus
6,4
THIN-STRUT DES WITH BIOABSORBABLE POLYMER COATINGS

**Orsirio**

![Graph showing TLF comparison between DP-EES and Ultimaster]

- **TLF**
  - **P-noninferiority** <0.001

- **CoCr**
- **60**
- **Biodegradable**
- **PLLA**
- **Circumferential**
- **Sirolimus**

**BIOSCIENCE Trial**
(N=2119)

- **DP-EES**: 6.6
- **Ultimaster**: 6.5

**CENTURY-2 Trial**
(N=1123)

- **DP-EES**: 4.9
- **Ultimaster**: 4.4

**EVOLVE-2 Trial**
(N=1684)

- **DP-EES**: 6.4
- **Synergy**: 6.4

P-noninferiority <0.001
RR (95%CI)=1.00 (0.77-1.31), P=0.98

10.5% - BP SES
10.4% - DP EES

RR (95%CI)=1.01 (0.62-1.63), P=0.98

3.2% - DP EES
3.2% - BP SES

RR (95%CI)=0.91 (0.60-1.39), P=0.67

4.5% - DP EES
4.1% - BP SES

RR (95%CI)=1.17 (0.81-1.71), P=0.40

6.0% - BP SES
5.1% - DP EES

Zbinden et al. JAHA 2016; in press
DEFINITE STENT THROMBOSIS AT 12 AND 24 MONTHS

1 Year

<table>
<thead>
<tr>
<th>%</th>
<th>RR 2.25 (95% CI 0.69-7.31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
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</table>

2 Years

<table>
<thead>
<tr>
<th>%</th>
<th>RR 1.38 (95% CI 0.56-3.44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

P for interaction = 0.144

Zbinden et al. JAHA 2016
**BioFlow V: BP-SES vs. DP-EES**


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**Primary Endpoint: TLF at 12 Months**

HR 0.64 (95% CI 0.42–0.96); p=0.0322

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>BP SES</th>
<th>DP EES</th>
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<tbody>
<tr>
<td>Time after initial procedure (days)</td>
<td>884</td>
<td>450</td>
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<tr>
<td></td>
<td>848</td>
<td>421</td>
</tr>
<tr>
<td></td>
<td>828</td>
<td>411</td>
</tr>
<tr>
<td></td>
<td>814</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>792</td>
<td>392</td>
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</tbody>
</table>

1,334 Patients with stable CAD and NSTEMI with max 2 native vessels treated
CENTURY-II TRIAL: ULTIMASTER SES VS XIENCE

12-Months Clinical Outcomes


Ultimaster (N=551)  Xience (N=550)

<table>
<thead>
<tr>
<th>Event</th>
<th>Ultimaster</th>
<th>Xience</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>0.91</td>
<td>1.09</td>
<td>0.76</td>
</tr>
<tr>
<td>TV-MI</td>
<td>1.27</td>
<td>2.18</td>
<td>0.25</td>
</tr>
<tr>
<td>ci-TLR</td>
<td>2.18</td>
<td>1.64</td>
<td>0.51</td>
</tr>
<tr>
<td>Def/Prob ST</td>
<td>0.91</td>
<td>0.91</td>
<td>0.99</td>
</tr>
</tbody>
</table>
THIN-STRUT DES WITH BIOABSORBABLE POLYMER COATINGS

Orsiro

Ultimaster

Synergy

TLF

P-noninferiority <0.001

CoCr

60

Biodegradable

PLLA

Circumferential

7

Silicon carbide

Sirolimus

DP-EES

Ultimaster

DP-EES

Ultimaster

CoCr

60

Biodegradable

PLLA-Pt1

Abuminal

Sirolimus

 PtCr

74

Biodegradable

PLGA

Abluminal

-4

Everolimus

TLF

P-noninferiority <0.001

6,6

6,5

6,4

6,4

EVOLVE-2 Trial (N=1684)

BIOSCIENCE Trial (N=2119)

CENTURY-2 Trial (N=1123)
EVOLVE II TLR at 3 years

PROMUS Element Plus vs. SYNERGY

3 years
HR 1.29 [0.81, 2.06]
P = 0.28

ITT; Patients who did not receive a study stent were censored at 1 year; KM Event Rate; log-rank P values

Presented by Kereiakes ACC 2017
TLF and Components at 3 years

Components of TLF

- TLF: 10.0, 11.0
- Cardiac Death: 2.3, 1.7
- TV-MI: 5.7, 6.5
- TLR: 4.0, 5.0

P-values:
- TLF: P=0.53
- Cardiac Death: P=0.65
- TV-MI: P=0.55
- TLR: P=0.28

Presented by Kereiakes ACC 2017
Stent Thrombosis at 3 years
Definite/Probable: ITT Population

PROMUS Element Plus

- Acute (≤1 d): N=5 (2 Definite/3 Probable)
- Subacute (2-30 d): N=1 (Def)
- Late (30 d – 1 y): 0.8% (N=6)
- Very Late (1 – 3 y): P=0.54

SYNERGY

- Acute (≤1 d): N=2 (Definite)
- Subacute (2-30 d): N=1 (Prob)
- Late (30 d – 1 y): N=1 (Def)
- Very Late (1 – 3 y): 0.5% (N=4)

CEC confirmed MI/TLR/ST Day 901 in the SYNERGY arm

Presented by Kereiakes ACC 2017
ST Landmark Analysis
Definite/Probable ST after 24 hours

PROMUS Element Plus vs SYNERGY
>24 h Landmark HR 0.33 [0.07, 1.61]
$P=0.15$
SCAAR Registry
SYNERGY vs New Generation DES (n-DES) in All-Comers

Definite Stent Thrombosis

<table>
<thead>
<tr>
<th>Time after PCI (months)</th>
<th>n-DES</th>
<th>SYNERGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>1 month</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>6 months</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>12 months</td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

0.4% vs. 0.5%, adjusted HR: 0.97; 95% CI: 0.63-1.50; P=0.17

Restenosis

<table>
<thead>
<tr>
<th>Time after PCI (months)</th>
<th>n-DES</th>
<th>SYNERGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>1.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>1 month</td>
<td>1.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>6 months</td>
<td>1.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>12 months</td>
<td>1.0%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

1.1% vs. 1.0%, adjusted HR: 1.24; 95% CI: 0.88-1.75; P=0.21

*S-DES includes: BioMatrix, Orsiro, Promus Element Plus, Promus PREMIER, Xience Xpedition, Resolute/Resolute Integrity, Ultimaster, & Resolute Onyx.

IMPACT OF STENT STRUT THICKNESS ON ARTERIAL HEALING AND ACUTE THROMBOGENICITY

Endothelialization above struts rabbit, 28 days

Platelet Deposition
Immuno-fluoroscent staining (CD61/CD42b) in porcine ex-vivo arterio-venous shunt model

Strut thickness

Synergy 74µm
BioMatrix 120µm
Absorb 150µm

PtCr PLGA 74 µm
PtCr bare 74 µm
316L PLA 120 µm
PLLA PDLA 150 µm

Courtesy: M Joner
Patients With CAD At High Bleeding Risk (N=1023)

PCI with Synergy EES

- Age ≥75 years
- Need for OAC
- Hb <11 g/l
- Recent transfusion
- Platelets <100’000
- Bleeding event <12 months
- Stroke <12 months
- History of ICH
- Severe chronic liver disease
- GFR <40 ml/min
- Cancer <3 years
- Planned major surgery
- Need for glucocorticoids/NSAIDS
- Non-adherence to >30 days DAPT

Multicenter trial

1-month clinical follow-up

12-month clinical follow-up

1EP: cardiac death, MI, or def/prob ST @12 months

Antithrombotic Strategy

Need for OAC:

- NO
  - Clop
  - ASA
- YES
  - Clop
  - OAC

NCT03112707
## Ongoing Studies on Short DAPT

<table>
<thead>
<tr>
<th>Study</th>
<th>Device</th>
<th>DAPT Duration</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>COBRA REDUCE</td>
<td>Cobra PzF</td>
<td>2 weeks</td>
<td>recruiting</td>
</tr>
<tr>
<td>MASTER-DAPT</td>
<td>Ultimaster</td>
<td>1 month</td>
<td>recruiting</td>
</tr>
<tr>
<td>POEM</td>
<td>Synergy</td>
<td>1 month</td>
<td>recruiting</td>
</tr>
<tr>
<td>RESOLUTE ONYX</td>
<td>Resolute</td>
<td>1 month</td>
<td>announced</td>
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<tr>
<td>ONE-MONTH DAPT</td>
<td></td>
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<tr>
<td>SENIOR</td>
<td>Synergy</td>
<td>1 month (SCAD)</td>
<td>recruit complete</td>
</tr>
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<td></td>
<td></td>
<td>6 months (ACS)</td>
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<tr>
<td>LBT Presentation</td>
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<tr>
<td>TCT 2017</td>
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<td>Nov 1st at 11:00 AM</td>
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<tr>
<td>ISAR-DAPT</td>
<td>Coroflex-ISAR</td>
<td>3 months</td>
<td>recruiting</td>
</tr>
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</table>
Are Bioabsorbable Polymer DES the Future?

Technology Advances

Future Outlook

Available Evidence on BP-DES
**NOT ALL BIORESORBABLE TECHNOLOGIES ARE EQUAL**

**Time Course For Polymer Bioabsorption**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Drug Release</th>
<th>Bioabsorbable Polymer</th>
<th>Bioresorbable Scaffold (BRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioMime (PLLA+PLGA)</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>SYNERGY (PLGA)</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ultimaster (PLLA - CL)</td>
<td>3-4</td>
<td>3-4</td>
<td></td>
</tr>
<tr>
<td>MiStent (PLGA)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABLUMINUS (PLA)</td>
<td>3</td>
<td>6</td>
<td>6-8</td>
</tr>
<tr>
<td>ELIXIR DESyne BD (PLA)</td>
<td>3</td>
<td>9</td>
<td>6-9</td>
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<tr>
<td>FIREHAWK (PLA)</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>BIOMATRIX (PLA)</td>
<td>3</td>
<td>9</td>
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<tr>
<td>NOBORI (PLA)</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>SVELTE (Amino Acid)</td>
<td>2</td>
<td>12</td>
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</tr>
<tr>
<td>ORSIRO (PLLA)</td>
<td>3</td>
<td>15</td>
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<tr>
<td>DREAMS 2 (Mg w/PLA coat)</td>
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<tr>
<td>ART (PDLLA)</td>
<td></td>
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<td>ELIXIR DESolve (PLLA)</td>
<td>3</td>
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<td>12-18</td>
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<tr>
<td>BVS (PLLA)</td>
<td>3</td>
<td></td>
<td>24</td>
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<tr>
<td>REVA ReZolve (Polycarb)</td>
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<td></td>
<td>36</td>
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<tr>
<td>Ultimaster (PLLA - CL)</td>
<td>3-4</td>
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<td>MiStent (PLGA)</td>
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<td>ELIXIR DESyne BD (PLA)</td>
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<td>6-9</td>
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<td>1</td>
<td>9</td>
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<tr>
<td>REVA ReZolve (Polycarb)</td>
<td>3</td>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>

*Time (Months)*
BIO-RESORT Trial
Primary Non-inferiority Endpoint

SYNERGY Not Inferior to Permanent Polymer DES Resolute Integrity

Randomized 1:1:1
Stratified for Diabetes Mellitus

SYNERGY (n=1172)
Biodegradable Polymer-EES (Abluminal)

1° Non-inferiority Endpoint:
1-year TVF

Absolute difference= -0.7%
Upper 1-sided 95% CI=0.8%

\[ P_{\text{non-inferiority}} < 0.0001 \]

RESOLUTE INTEGRITY (n=1173)
Permanent Polymer-ZES (Circumferential)

1° Non-inferiority Endpoint:
1-year TVF

Absolute difference= -0.7%
Upper 1-sided 95% CI=0.8%

\[ P_{\text{non-inferiority}} < 0.0001 \]

ORSIRO (n=1169)
Biodegradable Polymer-SES (Circumferential)
BIO-RESORT Trial

Components of Primary Non-inferiority Endpoint: 1-Year TVF

Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary

Robert A. Byrne¹, Patrick W. Serruys², Andreas Baumbach³, Javier Escaned⁴, Jean Fajadet⁵, Stefan James⁶, Michael Joner⁷, Semih Oktay⁸, Peter Jüni⁹, Adnan Kastrati¹, George Sianos¹⁰, Giulio G. Stefanini¹¹, William Wijns¹², and Stephan Windecker¹¹*
CONCLUSIONS

• Thin-strut DES with bioabsorbable polymer coatings have similar safety and efficacy profiles as the current benchmark of fluoropolymer coated EES.

• Theoretical advantages of bioasorbable polymer coatings may translate in marginal long-term benefits that need to be confirmed in large scale trials.

• Contemporary metallic DES with durable or bioabsorbable polymer coatings represent a mature technology providing optimal safety and efficacy outcomes.
# Bioabsorbable Polymer Stents: Is The Future?

Stefanini, Taniwaki, Windecker. *Heart.* 2014; 100(13):1051-61

**Novel DES Are Based on Bioabsorbable Polymer Coatings!**

<table>
<thead>
<tr>
<th>BioMatrix</th>
<th>Nobori</th>
<th>Endeavor</th>
<th>Yukon PC</th>
<th>Xience Promus</th>
<th>Resolute</th>
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<th>DESyne</th>
<th>Combo</th>
<th>Mistent</th>
<th>Ultimaster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biodegradable</td>
<td>Biodegradable</td>
<td>Durable</td>
<td>Biodegradable</td>
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<td>Durable</td>
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</tr>
<tr>
<td>PDLLA</td>
<td>MPA/HPMA/3-MPMA</td>
<td>PDLLA</td>
<td>PBMA/PVDF-HFP</td>
<td>PBMA/PHMA/PVP/PVA</td>
<td>PLGA</td>
<td>PLLA</td>
<td>PLLA</td>
<td>PDLLA/PLGA</td>
<td>PLGA</td>
<td>PDLLA-PCL</td>
<td></td>
</tr>
<tr>
<td>Abluminal</td>
<td>Circumferential</td>
<td>Circumferential</td>
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THANKS FOR YOUR KIND ATTENTION!

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