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Tel-Aviv, 14 December 2015

BIOABSORBABLE POLYMER DES IN HIGH-RISK PATIENTS

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Lausanne University Hospital
Switzerland
Speaker's name: **Juan F. IGLESIAS, MD**

☐ I have no potential conflicts of interest
☑ I have the following potential conflicts of interest to report:

- Consultant:

- Employment in industry:

- Honoraria/speaker’s fee: BIOTRONIK, ASTRA ZENECA

- Institutional grant/research support: BIOTRONIK, ASTRA ZENECA

- Owner of a healthcare company:

- Stockholder of a healthcare company:
• The **optimal management** of patients at **higher risk** of adverse clinical events remains a **clinical challenge**.

• **Newer-generation DES with durable polymer** (DP-DES):
  – significantly improved **safety** and **efficacy** outcomes (**death**, **myocardial infarction**, **repeat revascularization**, **stent thrombosis**), compared with both **BMS** and early-generation durable polymer DES;
  – represent the current **standard-of-care** for PCI in **all patient and lesion subsets**.

• **Newer-generation DP-DES in high-risk patients** remains associated with **higher rates** of **DES failure**, including **increased risk** of **ISR**, **TVR** and **late/very late ST**.
• **Permanent polymer coatings** on newer generation DP-DES have been recently associated with **chronic inflammation, hypersensitivity reactions**, and **neoatherosclerosis**, resulting in **late thrombotic events** and raising concerns about **long-term durable polymer biocompatibility**.

• **Biodegradable polymer DES** (BP-DES) were recently introduced to overcome current limitations of newer-generation DP-DES:
  - enhance **biocompatibility**, promote **vascular healing**, reduce **inflammation** and **hypersensitivity reactions**, and reduce **long-term adverse outcomes**.
  - represent a **safe** and **effective alternative** to newer-generation DP-DES in large all-comers patient populations.

• **Long-term potential benefit** of BP-DES for the management of **high-risk subgroups** remains **unclear**.
INCIDENCE OF ANGIOGRAPHICALLY DOCUMENTED IN-STENT RESTENOSIS (1998-2009, N=12’904)

NEWER-GENERATION DP-DES
HIGH-RISK SUBGROUPS: IN-STENT RESTENOSIS

PREDICTORS OF ISR

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Lower Risk</th>
<th>Higher Risk</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st generation DES vs BMS</td>
<td></td>
<td></td>
<td>0.35 [0.31-0.39]</td>
</tr>
<tr>
<td>2nd generation DES vs 1st generation DES</td>
<td></td>
<td></td>
<td>0.67 [0.58-0.77]</td>
</tr>
<tr>
<td>Female gender</td>
<td></td>
<td></td>
<td>0.93 [0.83-1.03]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td>1.32 [1.19-1.46]</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td></td>
<td></td>
<td>1.04 [0.93-1.16]</td>
</tr>
<tr>
<td>History of by-pass surgery</td>
<td></td>
<td></td>
<td>1.38 [1.20-1.58]</td>
</tr>
<tr>
<td>STEMI</td>
<td></td>
<td></td>
<td>1.01 [0.88-1.15]</td>
</tr>
<tr>
<td>NSTEMI</td>
<td></td>
<td></td>
<td>0.97 [0.87-1.08]</td>
</tr>
<tr>
<td>Left main stenting</td>
<td></td>
<td></td>
<td>1.35 [1.02-1.81]</td>
</tr>
<tr>
<td>Left circumflex stenting</td>
<td></td>
<td></td>
<td>1.05 [0.95-1.16]</td>
</tr>
<tr>
<td>Complex lesion</td>
<td></td>
<td></td>
<td>1.35 [1.21-1.51]</td>
</tr>
<tr>
<td>Chronic occlusion</td>
<td></td>
<td></td>
<td>1.21 [1.00-1.48]</td>
</tr>
<tr>
<td>Lesion length (for 10 mm increase)</td>
<td></td>
<td></td>
<td>1.02 [0.96-1.08]</td>
</tr>
<tr>
<td>Vessel size (for 0.5 mm reduction)</td>
<td></td>
<td></td>
<td>1.59 [1.52-1.68]</td>
</tr>
<tr>
<td>Stenosis severity (for 5% DS increase)</td>
<td></td>
<td></td>
<td>1.03 [1.02-1.05]</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio (for 0.1 unit increase)</td>
<td></td>
<td></td>
<td>0.89 [0.85-0.93]</td>
</tr>
<tr>
<td>Maximal balloon pressure (for 1 atm increase)</td>
<td></td>
<td></td>
<td>1.01 [1.00-1.03]</td>
</tr>
<tr>
<td>Stented length (for 10 mm increase)</td>
<td></td>
<td></td>
<td>1.27 [1.21-1.33]</td>
</tr>
</tbody>
</table>

LONG-TERM MORTALITY

Cassese S, Heart 2014
Cassese S, Eur Heart J 2015
NEWER-GENERATION DP-DES
HIGH-RISK SUBGROUPS: STENT THROMBOSIS

RATES OF DEFINITE/PROBABLE STENT THROMBOSIS @ 1 YEAR (N= 12’198)

STEMI: INDEPENDENT PREDICTOR OF DEFINITE STENT THROMBOSIS

HR 3.07

Loh JP, Am J Cardiol. 2014
RECENT INNOVATIONS IN DES TECHNOLOGY
NEWER-GENERATION BIODEGRADABLE POLYMER DES

**NEW METALLIC PLATFORM MATERIALS**
- 316L-BES
- CoCr-SES
- PtCr-EES
- CoCr-SES
- PLLA-EES

**THINNER STRUTS**

**THINNER, MORE BIocompatible, BIODEGRADABLE POLYMERS**

**NEW LIMUS-ANALOGUES ANTIPROLIFERATIVE DRUGS**

**REDUCED DRUG LOAD**

**IMPROVED CONTROLLED DRUG RELEASE**

**IMPROVE BIocompatibility, REDUCE CHRONIC INFLAMMATION AND HYPERSENSITIVITY REACTIONS.**

Iglesias JF, Minerva Cardioangiologica 2015 (adapted from Stefanini GG, Heart 2014)
NEWER-GENERATION BIODEGRADABLE POLYMERIC DES 
ORSIRO® DRUG-ELUTING STENT (BIOTRONIK AG, SWITZERLAND)

**UNIQUE HYBRID TECHNOLOGY**

**Stent platform:** PRO-Kinetic Energy
- Cobalt Chromium, L-605
- 60 µm struts, double helix design

**Passive coating:** proBIO
- Silicon carbide** layer that permanently encapsulates the stent surface, reducing ion release

**Active coating:** BIOlute
- PLLA* bioabsorbable polymer matrix
- Limus drug (drug load is 1.4 µg/mm²)

**ULTRATHIN STRUTS**

**REDUCED THROMBOGENICITY (PLATELET ADHESION)**

**BIOCOMPATIBLE POLYMER BIOABSORBABLE POLYMER THIN POLYMER COATING**

**REDUCED LIMUS DRUG LOAD**

**REDUCE INFLAMMATORY RESPONSE, IMPROVE ENDOTHELIALIZATION, PROMOTE VASCULAR HEALING**
ORSIRO® HYBRID DRUG-ELUTING STENT
DIFFERENCES BETWEEN BIODEGRADABLE POLYMERS

PRE-CLINICAL HISTOLOGY DATA (MEAN VALUES @ 28 DAYS)

ORSIRO FORMULATION: LOW-INFLAMMATION RESPONSE

Intimal area (mm)  Injury score  Fibrin score

ORSIRO FORMULATION:
LOW-INFLAMMATION RESPONSE

0.0  1.0  2.0  3.0

BMS  PEVA/PBMA SES  PUR SES  PLLA SES  PLGA SES

1st GENERATION DP-DES  2nd GENERATION DP-DES  3rd GENERATION BP-DES

PEVA/PBMA – permanent cypher-like; PUR – pellethane, permanent

Koppara T, Thromb Haemost. 2012
ULTRATHIN-STRUT BP-SES vs. THIN-STRUT DP-EES @ 9 MONTHS (N=452)

PRIMARY ENDPOINT: IN-STENT LATE LUMEN LOSS

0.10 ± 0.32 mm

P non-inferiority = <0.0001
Difference = 0.00063
95% CI = -0.06 to 0.07

0.11 ± 0.29 mm

Windecker S, Circ Cardiovasc Interv. 2015
LONG-TERM CLINICAL RESULTS: TARGET LESION FAILURE @ 36 MONTHS

**Endpoints (%)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Orsiro N=298</th>
<th>Xience N=154</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Death</td>
<td>0.7</td>
<td>1.3</td>
<td>0.5069</td>
</tr>
<tr>
<td>Target vessel MI</td>
<td>3.4</td>
<td>2.6</td>
<td>0.6590</td>
</tr>
<tr>
<td>TLR (Clinically driven)</td>
<td>5.6</td>
<td>6.7</td>
<td>0.6361</td>
</tr>
<tr>
<td>CABG (Emergent)</td>
<td>0.0</td>
<td>0.0</td>
<td>&gt;0.9999</td>
</tr>
</tbody>
</table>

P=0.5800

Slagboom et al. Poster EuroPCR 2015, Paris, France
LOW TLF AND ST RATES IN AN UNSELECTED, ALL-COMERS POPULATION WITH COMPLEX CORONARY ARTERY DISEASE

Waltenberger J, Eurointervention 2015
ORSIRO® HYBRID DRUG-ELUTING STENT
BIOSCIENCE

ULTRATHIN-STRUT BP-SES vs. THIN-STRUT DP-EES @ 2 YEARS (N=2’119)

TARGET LESION FAILURE

DEFINITE STENT THROMBOSIS

SIMILAR LONG-TERM EFFICACY AND SAFETY COMPARED TO BEST-IN-CLASS NEWER-GENERATION DP-DES IN ALL-COMERS POPULATION WITH COMPLEX PATIENT AND LESION CHARACTERISTICS

Courtesy: Thomas Pilgrim
ORSIRO® HYBRID DRUG-ELUTING STENT
SORT OUT VII

ULTRATHIN-STRUT BP-SES vs. THICK-STRUT BP-BES @ 12 MONTHS (N=2’525)

TARGET LESION FAILURE

DEFINITE STENT THROMBOSIS

RR 0.83; 95% CI 0.56-1.21; p for non inferiority <0.0001

RR 0.33; 95% CI 0.12-0.92 p=0.03

TARGET LESION FAILURE

DEFINITE STENT THROMBOSIS

IMPROVED SHORT-TERM EFFICACY AND SAFETY COMPARED TO FIRST-GENERATION BP-DES IN ALL-COMERS PATIENTS WITH COMPLEX PATIENT AND LESION CHARACTERISTICS

Jensen LO. EuroPCR 2015, Paris, France
NEWER-GENERATION BIODEGRADABLE POLYMER DES

CLINICAL PERFORMANCE: EFFICACY

RATES OF TARGET LESION FAILURE (%) @ 9-12 MONTHS

THIN-STRUT BP-DES

THICK-STRUT BP-DES

ORSIRO SES

SES

EES

BES

<table>
<thead>
<tr>
<th>Device</th>
<th>Rates of Target Lesion Failure (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIOFLOW-II</td>
<td>6.5</td>
<td>452</td>
</tr>
<tr>
<td>BIOFLOW-III</td>
<td>5.1</td>
<td>1'356</td>
</tr>
<tr>
<td>BIOSCIENCE</td>
<td>6.5</td>
<td>2'119</td>
</tr>
<tr>
<td>SORT-OUT VII</td>
<td>3.8</td>
<td>2'525</td>
</tr>
<tr>
<td>CENTURY II</td>
<td>4.4</td>
<td>1'101</td>
</tr>
<tr>
<td>EVOLVE II</td>
<td>6.7</td>
<td>1'684</td>
</tr>
<tr>
<td>NEXT</td>
<td>4.2</td>
<td>3'235</td>
</tr>
<tr>
<td>COMPARE II</td>
<td>5.2</td>
<td>2'707</td>
</tr>
<tr>
<td>SORT-OUT VII</td>
<td>4.6</td>
<td>2'525</td>
</tr>
</tbody>
</table>
NEWER-GENERATION BIODEGRADABLE POLYMER DES
CLINICAL PERFORMANCE: SAFETY

RATES OF DEFINITE STENT THROMBOSIS (%) @ 9-12 MONTHS

THIN-STRUT BP-DES

THICK-STRUT BP-DES

ORSIRO SES

SES

EES

BES

BIOFLOW-II  N = 452
BIOFLOW-III  1’356
BIOSCIENCE  2’119
SORT-OUT VII  2’525
CENTURY II  1’101
EVOLVE II  1’684
NEXT  3’235
COMPARE II  2’707
SORT-OUT VII  2’525

0 0.2 0.9 0.4 0.9 0.2 0.25 0.7 1.2

1 1.5 2 2.5 3
ORSIRO® HYBRID DRUG-ELUTING STENT
HIGH-RISK SUBGROUPS

RATES OF TARGET Lesion FAILURE (%) @ 9-12 MONTHS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall population</th>
<th>Diabetics</th>
<th>Small vessels</th>
<th>Long lesions</th>
<th>Complex coronary lesions</th>
<th>Multivessel disease</th>
<th>Chronic total occlusion</th>
<th>ST-segment elevation myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIOFLOW II</td>
<td>6.5</td>
<td>6.0</td>
<td>7.7</td>
<td>7.4</td>
<td>6.1</td>
<td>6.6</td>
<td>1.8</td>
<td>7.2</td>
</tr>
<tr>
<td>BIOFLOW III</td>
<td>6.5</td>
<td>6.0</td>
<td>7.7</td>
<td>7.4</td>
<td>6.1</td>
<td>6.6</td>
<td>1.8</td>
<td>7.2</td>
</tr>
<tr>
<td>BIOSCIENCE</td>
<td>5.1</td>
<td>3.8</td>
<td>4.7</td>
<td>5.8</td>
<td>2.9</td>
<td>5.1</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>SORT-OUT VII</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>6.4</td>
</tr>
</tbody>
</table>

LOW TLF RATES IN HIGH-RISK SUBGROUPS, SIMILAR TO RATES IN LOW-RISK PATIENTS

Iglesias JF, Minerva Cardioangiologica 2015
NEWER-GENERATION DP-DES vs. BP-DES IN STEMI
BIOSCIENCE: STEMI SUBGROUP ANALYSIS

ULTRATHIN-STRUT BP-SES vs. THIN-STRUT DP-EES @ 1 YEAR (N=407)

TARGET LESION FAILURE
Rate ratio = 0.38 (95% CI 0.16-0.91)
P=0.024
8.8% - DP EES
3.4% - BP SES

CARDIAC DEATH
Rate ratio = 0.31 (95% CI 0.08-1.14)
P=0.062
4.7% - DP EES
1.5% - BP SES

STRONG SIGNAL TOWARDS A SIGNIFICANT REDUCTION IN TLF IN THE PRESPECIFIED SUBGROUP OF PATIENTS WITH STEMI

P=0.082
2.6% - DP EES
0.5% - BP SES

P= 0.41
2.7% - DP EES
1.5% - BP SES

62% RRR 5.4% ARR

Pilgrim T, Lancet 2014
EARLY- vs. NEWER-GENERATION DP-DES IN STEMI
CONFIRMATION FROM META-ANALYSIS

META-ANALYSIS, 28 RCTs, 34’068 PATIENT-YEARS OF FOLLOW-UP
BMS, SES, PES, EES, ZES, OR ZES-R FOR STEMI

TARGET LESION REVASCULARIZATION

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratio</th>
<th>95% Crl</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES vs. BMS</td>
<td></td>
<td>0.46</td>
<td>0.36</td>
</tr>
<tr>
<td>PES vs. BMS</td>
<td></td>
<td>0.69</td>
<td>0.53</td>
</tr>
<tr>
<td>EES vs. BMS</td>
<td></td>
<td>0.42</td>
<td>0.26</td>
</tr>
<tr>
<td>ZES vs. BMS</td>
<td></td>
<td>0.96</td>
<td>0.43</td>
</tr>
<tr>
<td>ZES-R vs. BMS</td>
<td></td>
<td>0.26</td>
<td>0.04</td>
</tr>
<tr>
<td>PES vs. SES</td>
<td></td>
<td>1.49</td>
<td>1.14</td>
</tr>
<tr>
<td>EES vs. SES</td>
<td></td>
<td>0.90</td>
<td>0.56</td>
</tr>
<tr>
<td>ZES vs. SES</td>
<td></td>
<td>2.11</td>
<td>0.94</td>
</tr>
<tr>
<td>ZES-R vs. SES</td>
<td></td>
<td>0.57</td>
<td>0.08</td>
</tr>
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</table>

PROBABLE/DEFINITE STENT THROMBOSIS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratio</th>
<th>95% Crl</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES vs. BMS</td>
<td></td>
<td>0.94</td>
<td>0.69</td>
</tr>
<tr>
<td>PES vs. BMS</td>
<td></td>
<td>1.11</td>
<td>0.75</td>
</tr>
<tr>
<td>EES vs. BMS</td>
<td></td>
<td>0.39</td>
<td>0.18</td>
</tr>
<tr>
<td>ZES vs. BMS</td>
<td></td>
<td>0.09</td>
<td>0.23</td>
</tr>
<tr>
<td>PES vs. SES</td>
<td></td>
<td>1.18</td>
<td>0.74</td>
</tr>
<tr>
<td>EES vs. SES</td>
<td></td>
<td>0.42</td>
<td>0.19</td>
</tr>
<tr>
<td>ZES vs. SES</td>
<td></td>
<td>0.73</td>
<td>0.25</td>
</tr>
</tbody>
</table>

NO SIGNIFICANT DIFFERENCE BETWEEN EARLY- AND NEWER-GENERATION DES WITH DURABLE POLYMER (EES/ZES/ZES-R) IN TERMS OF CLINICAL OUTCOME IN PATIENTS WITH STEMI
NEWER-GENERATION BP-DES vs. EARLY-GENERATION DP-DES IN STEMI
LEADERS: STEMI SUBGROUP ANALYSIS

BIODEGRADABLE-POLYMER BES vs. DURABLE-POLYMER SES @ 5 YEARS (N=275)

CARDIAC DEATH, MI, CLINICALLY-INDICATED TVR

PROBABLE/DEFINITE STENT THROMBOSIS

IMPROVED LONG-TERM EFFICACY

TREND TOWARDS IMPROVED LONG-TERM SAFETY

STRONG SIGNAL TOWARDS A SIGNIFICANT REDUCTION OF MACE IN PATIENTS WITH STEMI

Zhang YJ, Heart 2015
NEWER-GENERATION BP-DES vs. EARLY-GENERATION DP-DES IN STEMI
CONFIRMATION FROM META-ANALYSIS

POOLED ANALYSIS FROM ISAR-TEST 3, ISAR-TEST 4 AND LEADERS TRIALS (N= 497)
FIRST-GENERATION DP-SES vs. THIRD-GENERATION BP-BES @ 4 years

TARGET LESION REVASCULARIZATION

46% RRR
5.7% ARR

HR 0.54 (95% CI: 0.30-0.98)
p = 0.04

Permanent polymer 13.1%
Biodegradable polymer 7.4%

PROBABLE/DEFINITE STENT THROMBOSIS

51% RRR
3.5% ARR

HR 0.49 (95% CI: 0.22-1.11)
p = 0.09

Permanent polymer 7.1%
Biodegradable polymer 3.6%

IMPROVED LONG-TERM EFFICACY

IMPROVED LONG-TERM SAFETY

De Waha A, Eurointervention 2014
A Comparison of an Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent for Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: the BIOSTEMI trial.

**DESIGN:**
Investigator-initiated, prospective, multicenter, international, single-blind, superiority, randomized controlled trial.

**OBJECTIVE:**
To compare the ultrathin strut Orsiro® sirolimus-eluting stent to the thin strut Xience® everolimus-eluting stent (1:1 randomization) in patients with acute STEMI undergoing primary PCI within 12 hours of the symptom’s onset.

**PRIMARY ENDPOINT:**
TLF (composite of cardiac death, target vessel myocardial infarction, or clinically-driven target lesion revascularization) at 12 months.

**PRINCIPAL INVESTIGATORS:**
Dr JF. Iglesias, Dr O. Muller, Pr E. Eeckhout (Lausanne, CH)
Dr T. Pilgrim, Pr S. Windecker (Bern, CH)
CONCLUSIONS

- The ultrathin-strut biodegradable polymer Orsiro sirolimus-eluting stent:
  - designed to enhance biocompatibility, promote vascular healing, and reduce hypersensitivity and chronic inflammatory reactions associated with persisting long-term adverse clinical events.
  - comparable clinical performance to the current state-of-the-art newer-generation thin-strut durable polymer Xience everolimus-eluting stent in broadly inclusive patient populations.
  - despite the lack of randomized data, low rates of TLF and ST in high-risk subgroups of patients with increased risk of cardiovascular events (diabetes mellitus, small vessels, long lesions, complex coronary lesions, multivessel disease, chronic total occlusion, or STEMI) similar to rates in lower-risk patients.
  - potential clinical superiority of the Orsiro SES over the best-in-class newer-generation durable polymer Xience everolimus-eluting stent in the subgroup of patients with STEMI warrants confirmation in the future BIOSTEMI randomized controlled trial.
THANK YOU FOR YOUR ATTENTION
BIOABSORBABLE POLYMER DES IN HIGH-RISK PATIENTS

Juan F. Iglesias
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Lausanne University Hospital
Switzerland