Ten-Year Clinical Outcomes from a Trial of Three Limus-Eluting Stents With Different Polymer Coatings in Patients with Coronary Artery Disease

Sebastian Kufner, MD

on behalf of

Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST 4) Investigators
New-generation drug-eluting stents (DES) offer the potential for enhanced late outcomes in comparison with early-generation DES.

However, assessment of extended long-term outcomes for these devices is lacking, especially regarding the comparison between new-generation DES with biodegradable or permanent polymers.

Extended long-term follow-up data, up to 10 years, of new-generation DES with different polymer coating strategies remains a notable scientific gap.
Background

new-generation vs. early-generation DES

ISAR TEST 4 at 3 years
(Xience versus Cypher)

SORT OUT 4 at 5 years
(Xience versus Cypher)

Primary composite end point (%)

HR 0.87 [95% CI, 0.68-1.11], P=0.26
Sirolimus-eluting stent 22.3 %
Everolimus-eluting stent 19.6%

Months after randomization

HR 0.80 (95% CI, 0.66-0.97), P=0.02

Major Adverse Cardiac Events (%)

Follow-Up (Months)

Byrne et al. JACC, 2011

Jensen et al. JACC, 2016
**Background** biodegradable vs. permanent polymer DES

**ISAR TEST 4 at 5 years**
(Yukon Choice PC versus Xience)

**COMPARE II at 5 years**
(Nobori versus Xience)

**Kufner et al. Eurointervention, 2014**

Biodegradable polymer SES 20.5%
Permanent polymer EES 19.5%

**Vlachojannis et al. JACC Int. 2017**

\[ P_{\text{H}} = 0.26 \]
Patients enrolled between 09/2007 and 08/2008 at two centers in Munich, Germany

**Inclusion Criteria:**
- ischemic symptoms or evidence of myocardial ischemia +
- presence of ≥50% stenosis in native coronary arteries

**Exclusion Criteria:**
Target lesion in left main stem
In-stent restenosis lesion

**Primary Endpoint:**
MACE = combined incidence of all-cause death, myocardial infraction and target lesion revascularisation at 10 years

**Secondary Endpoints:**
1. individual components of the primary endpoint at 10 years
2. Definite or probable stent thrombosis at 10 years

**Methods**

**ISAR-TEST 4 study design**

Randomized patients  
n= 2603 (2:1:1 allocation)  

- **Sirolimus-eluting stent with biodegradable polymer**  
  Yukon Choice PC  
  (Translumina Therapeutics, Dehradun, India, Translumina, Hechingen, Germany)  
  n= 1299

- **Everolimus-eluting stent with permanent polymer**  
  Xience  
  (Abbott Vascular, Abbott Park, IL, USA)  
  n= 652

- **Sirolimus-eluting stent with permanent polymer**  
  Cypher  
  (Cordis Corporation, Miami Lakes, FL, USA)  
  n= 652

**annual patient contact**

- lost to follow-up: 228 patients (17.6%)*
- lost to follow-up: 116 patients (17.8%)*
- lost to follow-up: 106 patients (16.3%)*

10-year clinical follow-up  
1071 patients

10-year clinical follow-up  
536 patients

10-year clinical follow-up  
546 patients

10-year clinical follow-up analysis  
n=2153 (83%) median follow-up interval 10.6 years

* = in patients without complete follow-up out to 10 years, median follow-up interval was 5.9 years
## Results

**Patient characteristics at baseline**

<table>
<thead>
<tr>
<th></th>
<th>BP-SES</th>
<th>PP-EES</th>
<th>PP-SES</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=1299</td>
<td>n=652</td>
<td>n=652</td>
<td></td>
</tr>
<tr>
<td>Age – yr</td>
<td>66.7±11.1</td>
<td>66.7±10.3</td>
<td>66.8±11.1</td>
<td>0.96</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>978 (75.3)</td>
<td>507 (77.8)</td>
<td>495 (75.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Diabetes mellitus – no. (%)</td>
<td>376 (28.9)</td>
<td>184 (28.2)</td>
<td>193 (29.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Insulin-dependent</td>
<td>108 (8.3)</td>
<td>60 (9.2)</td>
<td>62 (9.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>Prior myocardial infarction – no. (%)</td>
<td>372 (28.6)</td>
<td>191 (29.3)</td>
<td>182 (27.9)</td>
<td>0.86</td>
</tr>
<tr>
<td>Prior CABG (%)</td>
<td>129 (9.9)</td>
<td>69 (10.6)</td>
<td>60 (9.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Clinical presentation – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>STEMI</td>
<td>167 (12.9)</td>
<td>70 (10.7)</td>
<td>70 (10.7)</td>
<td></td>
</tr>
<tr>
<td>NSTE-acute coronary syndrome</td>
<td>374 (28.8)</td>
<td>199 (30.5)</td>
<td>180 (27.6)</td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>758 (58.4)</td>
<td>383 (58.7)</td>
<td>402 (61.7)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease – no. (%)</td>
<td>1124 (86.5)</td>
<td>557 (85.4)</td>
<td>557 (87.3)</td>
<td>0.62</td>
</tr>
</tbody>
</table>
## Results

**Lesion characteristics at baseline**

<table>
<thead>
<tr>
<th>Lesions</th>
<th>BP-SES</th>
<th>PP-EES</th>
<th>PP-SES</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions</td>
<td>n=1683</td>
<td>n=850</td>
<td>n=839</td>
<td></td>
</tr>
<tr>
<td><strong>Target-vessel location – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>753 (44.7)</td>
<td>372 (43.8)</td>
<td>376 (44.8)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>454 (27.0)</td>
<td>223 (26.2)</td>
<td>230 (27.4)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>476 (28.3)</td>
<td>255 (30.0)</td>
<td>233 (27.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic total occlusion – no (%)</strong></td>
<td>89 (5.3)</td>
<td>36 (4.2)</td>
<td>50 (6.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Bifurcation – no (%)</td>
<td>421 (25.0)</td>
<td>185 (21.8)</td>
<td>198 (23.6)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ostial – no (%)</td>
<td>267 (15.9)</td>
<td>158 (18.6)</td>
<td>146 (17.4)</td>
<td>0.21</td>
</tr>
<tr>
<td>Complex morphology (B2/C) – no (%)</td>
<td>1225 (72.8)</td>
<td>604 (71.1)</td>
<td>614 (73.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>Lesion length – mm</td>
<td>14.8±8.8</td>
<td>15.2±8.9</td>
<td>14.8±8.2</td>
<td>0.55</td>
</tr>
<tr>
<td>Vessel size – mm</td>
<td>2.79±0.52</td>
<td>2.80±0.45</td>
<td>2.80±0.48</td>
<td>0.89</td>
</tr>
</tbody>
</table>
Results

**primary endpoint: MACE at 10 years**

- New generation BP-SES
- New generation PP-EES
- Early generation PP-SES

P-value\textsubscript{overall} = 0.003

- \text{HR}_{\text{BP-SES versus PP-SES}} = 0.82 (98.3\% CI, 0.69-0.96)
- \text{HR}_{\text{PP-EES versus PP-SES}} = 0.79 (98.3\% CI, 0.65-0.96)
- \text{HR}_{\text{BP-SES versus PP-EES}} = 1.04 (98.3\% CI, 0.87-1.24)
Results

all-cause mortality at 10 years

- new generation BP-SES
- new generation PP-EES
- early generation PP-SES

P-value overall = 0.02

HR_{BP-SES versus PP-SES} = 0.82 (95% CI, 0.70-0.97)
HR_{PP-EES versus PP-SES} = 0.78 (95% CI, 0.64-0.95)
HR_{BP-SES versus PP-EES} = 1.05 (95% CI, 0.88-1.26)
**Results**

**Target lesion revascularisation at 10 years**

- **new generation BP-SES**
- **new generation PP-EES**
- **early generation PP-SES**

\[
\text{P-value}_{\text{overall}} = 0.15
\]

- **HR** BP-SES versus PP-SES = 0.85 (95% CI, 0.69-1.06)
- **HR** PP-EES versus PP-SES = 0.78 (95% CI, 0.60-1.00)
- **HR** BP-SSES versus PP-EES = 1.10 (95% CI, 0.87-1.38)
Results

def/prob stent thrombosis at 10 years

HR BP-SES versus PP-SES = 0.50 (95% CI, 0.27-0.93)
HR PP-EES versus PP-SES = 0.70 (95% CI, 0.35-1.39)
HR BP-SES versus PP-EES = 0.71 (95% CI, 0.36-1.41)

P-value_{overall} = 0.09
## Results

**Clinical outcomes at 10 years**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BP-SES n=1299</th>
<th>PP-EES n=652</th>
<th>PP-SES n=652</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiac event</td>
<td>575 (47.7)</td>
<td>279 (46.0)</td>
<td>336 (54.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>All-cause death</td>
<td>374 (31.8)</td>
<td>179 (30.3)</td>
<td>223 (37.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>88 (7.7)</td>
<td>45 (7.9)</td>
<td>49 (9.1)</td>
<td>0.85</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>225 (20.3)</td>
<td>103 (18.2)</td>
<td>129 (22.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Def./prob. stent thrombosis</td>
<td>20 (1.8)</td>
<td>14 (2.5)</td>
<td>20 (3.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>12 (1.1)</td>
<td>5 (0.8)</td>
<td>14 (2.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Probable stent thrombosis</td>
<td>8 (0.7)</td>
<td>9 (1.6)</td>
<td>6 (1.3)</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Results

subgroup analysis

<table>
<thead>
<tr>
<th></th>
<th>BP-SES versus PP-SES</th>
<th>PP-EES versus PP-SES</th>
<th>BP-SES versus PP-EES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;67.6 yrs</td>
<td>0.83 (0.70 – 0.99)</td>
<td>0.75 (0.62 – 0.92)</td>
<td>1.10 (0.92 – 1.32)</td>
</tr>
<tr>
<td>≤67.6 yrs</td>
<td>0.79 (0.64 – 0.99)</td>
<td>0.78 (0.60 – 1.02)</td>
<td>1.01 (0.79 – 1.26)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.75 (0.58 – 0.97)</td>
<td>0.80 (0.58 – 1.09)</td>
<td>0.94 (0.71 – 1.25)</td>
</tr>
<tr>
<td>Men</td>
<td>0.84 (0.72 – 0.99)</td>
<td>0.79 (0.66 – 0.95)</td>
<td>1.07 (0.91 – 1.26)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.85 (0.67 – 1.07)</td>
<td>0.86 (0.65 – 1.13)</td>
<td>0.99 (0.77 – 1.26)</td>
</tr>
<tr>
<td>No</td>
<td>0.81 (0.68 – 0.95)</td>
<td>0.76 (0.63 – 0.92)</td>
<td>1.06 (0.89 – 1.26)</td>
</tr>
</tbody>
</table>

P interaction overall

0.85

0.64

0.75
Conclusion

In this unique long-term analysis...

• New-generation DES are superior to early-generation DES in terms of clinical outcomes

• The favorable outcome after new-generation DES is driven by increasing event rates over time in patients treated with early-generation DES

• Both, biodegradable polymer-based sirolimus-eluting stents and permanent polymer-based everolimus-eluting stents showed comparable clinical outcomes out to 10 years
Thank You