Biodegradable Polymer Drug-Eluting Stents Versus Durable Polymer Sirolimus-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention

A Pooled Analysis of Individual Patient Data from ISAR-TEST 3, ISAR-TEST 4, and LEADERS Randomized Trials at 4 Years

Robert A. Byrne, Giulio Stefanini, Patrick W. Serruys, Antoinette de Waha, Bernhard Meier, Steffen Massberg, Patrick W. Serruys, Peter Jüni, Stephan Windecker, Adnan Kastrati
Disclosures

Speaker’s name: Dr. Robert A. Byrne

I do not have any potential conflict of interest
The efficacy of durable polymer drug-eluting stents (DES) is delivered at the expense of delayed healing of the stented segment and an excess of late stent thrombosis.

Biodegradable polymer DES aim to avoid this shortcoming and may potentially improve long-term clinical outcomes, with benefit expected to accrue over time.
Introduction

• Detection of differences in the rates of rarely-occurring late adverse events require the analysis of large patient numbers

• First results from large-scale clinical trials with biodegradable polymer DES showed a reduction in stent thrombosis at long-term follow-up that was not statistically significant

Byrne et al. ISAR-TEST 4 JACC 2011, Stefanini et al. LEADERS Lancet 2011
Objective

• We sought to compare long-term clinical outcomes in large numbers of patients treated with:

biodegradable polymer drug-eluting stents

vs.

durable polymer sirolimus-eluting stents
Methods

- We pooled the 4-year outcome data from the **3 largest randomized clinical trials** comparing biodegradable polymer with durable polymer sirolimus-eluting DES

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-TEST 3</td>
<td>Mehilli et al. EHJ 2008</td>
</tr>
<tr>
<td>ISAR-TEST 4</td>
<td>Byrne et al. EHJ 2009</td>
</tr>
<tr>
<td>LEADERS</td>
<td>Windecker et al. Lancet 2008</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov: identifiers NCT0059867, NCT00389220, NCT00350454
## Methods

<table>
<thead>
<tr>
<th>Primary Safety Endpoint</th>
<th>definite stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Efficacy Endpoint</td>
<td>clinically-indicated target lesion revascularization</td>
</tr>
<tr>
<td>Statistical methodology</td>
<td>random effects individual patient data meta-analysis</td>
</tr>
</tbody>
</table>

- Investigator-initiated, industry-independent
Randomized patients treated with biodegradable polymer DES or durable polymer sirolimus-eluting stent in ISAR-TEST 3, ISAR-TEST 4, LEADERS (n= 4062)

Study Flow

Biodegradable polymer stent (n= 2358)
- Sirolimus-eluting stent (Yukon Choice) (n= 1501)
  - 4-year clinical follow-up

Durable polymer stent (n= 1704)
- Sirolimus-eluting stent (Cypher) (n= 1704)
  - 4-year clinical follow-up
- Biolimus-eluting stent (Biomatrix Flex) (n= 857)
  - 4-year clinical follow-up
### Trial Characteristics

<table>
<thead>
<tr>
<th>Trials</th>
<th>ISAR-TEST 3</th>
<th>ISAR-TEST 4</th>
<th>LEADERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>605</td>
<td>2603</td>
<td>1707</td>
</tr>
<tr>
<td>Mean age</td>
<td>66.1 yrs</td>
<td>66.8 yrs</td>
<td>64.6 yrs</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27%</td>
<td>29%</td>
<td>24%</td>
</tr>
<tr>
<td>Exclusion</td>
<td>LMS/Bypass/Restenosis</td>
<td>LMS/Bypass/Restenosis</td>
<td>None</td>
</tr>
<tr>
<td>Lesion/patients</td>
<td>1.2</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>4 years</td>
<td>4 years</td>
<td>4 years</td>
</tr>
</tbody>
</table>
Definite Stent Thrombosis

Cumulative Incidence (%)

HR 0.56 (95% CI 0.35, 0.90)
p=0.015

Durable polymer 2.8%

Biodegradable polymer 1.3%

Years after randomization
Definite Stent Thrombosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>BP: No. of patients with event/total no.</th>
<th>DP: No. of patients with event/total no.</th>
<th>Hazard ratio (95% CI) Definite stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-TEST 3</td>
<td>1/202</td>
<td>2/202</td>
<td>0.47 (0.04, 5.04)</td>
</tr>
<tr>
<td>ISAR-TEST 4</td>
<td>9/1299</td>
<td>10/652</td>
<td>0.45 (0.18, 1.12)</td>
</tr>
<tr>
<td>LEADERS</td>
<td>20/857</td>
<td>32/850</td>
<td>0.62 (0.35, 1.08)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>30/2358</strong></td>
<td><strong>44/1704</strong></td>
<td><strong>0.56 (0.35, 0.90)</strong></td>
</tr>
</tbody>
</table>

Test for Heterogeneity: $P=0.84$
Test for Inconsistency: $I^2=0$
Test for Overall Effect: $z=-2.43$ ( $P=0.015$)
Definite Stent Thrombosis

Cumulative Incidence (%)

Years after randomization

HR 0.80
(95% CI 0.47, 1.38)
p=0.43

HR 0.22 (95% CI 0.08, 0.61)
p=0.004

Durable polymer 1.3%

Biodegradable polymer 0.2%
Target lesion revascularization

Cumulative Incidence (%)

HR 0.82 (95% CI 0.68, 0.98)
p=0.029

Durable polymer 13.7%
Biodegradable polymer 12.0%

Years after randomization
## Target lesion revascularization

<table>
<thead>
<tr>
<th>Trial</th>
<th>BP</th>
<th>DP</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-TEST 3</td>
<td>21/202</td>
<td>28/202</td>
<td>0.69 (0.39, 1.21)</td>
</tr>
<tr>
<td>ISAR-TEST 4</td>
<td>169/1299</td>
<td>96/652</td>
<td>0.87 (0.68, 1.12)</td>
</tr>
<tr>
<td>LEADERS</td>
<td>74/857</td>
<td>93/850</td>
<td>0.78 (0.57, 1.05)</td>
</tr>
<tr>
<td>Overall</td>
<td>264/2358</td>
<td>217/1704</td>
<td>0.82 (0.68, 0.98)</td>
</tr>
</tbody>
</table>

- **Test for Heterogeneity** $P=0.71$
- **Test for Inconsistency** $I^2=0$
- **Test for Overall Effect** $z=-2.19$ ( $P=0.029$)

The Hazard ratio favors BP ($0.82$) compared to DP.
Target lesion revascularization

Cumulative Incidence (%)

- Durable polymer 6.3%
- Biodegradable polymer 5.2%

HR 0.82 (95% CI 0.65, 1.03)
p = 0.09

HR 0.81 (95% CI 0.60, 1.09)
p = 0.16
Cardiac Death/Myocardial Infarction/TLR

HR 0.85 (95% CI 0.74, 0.98)

p=0.027

Durable polymer 21.6%

Biodegradable polymer 19.0%

Years after randomization
Conclusions

• Biodegradable polymer DES as compared to durable polymer SES demonstrate a **lower risk of definite stent thrombosis at 4 years**

• This differences driven by a statistically significant and likely clinically important **78% risk reduction in late stent thrombosis between 1 and 4 years**

• In addition **target lesion revascularization was significantly lower** at 4 years with biodegradable polymer DES
Conclusions

- These findings may represent an important step in the proof-of-concept chain of investigation for biodegradable polymer DES.

- The enhanced late safety profile with biodegradable polymer DES may have implications regarding requirement for an extended duration of dual antiplatelet therapy following coronary stenting.
Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials

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Aims
The efficacy of durable polymer drug-eluting stents (DES) is delivered at the expense of delayed healing of the stented vessel. Biodegradable polymer DES aim to avoid this shortcoming and may potentially improve long-term clinical outcomes, with benefit expected to accrue over time. We sought to compare long-term outcomes in patients treated with biodegradable polymer DES vs. durable polymer sirolimus-eluting stents (SES).

Methods and results
We pooled individual patient data from three large-scale multicentre randomized clinical trials (ISAR-TEST 3, ISAR-TEST 4, and LEADERS) comparing biodegradable polymer DES with durable polymer SES and assessed clinical outcomes during follow-up through 4 years. The efficacy endpoint of interest was target lesion revascularization and the safety endpoint of interest was definite stent thrombosis. Out of 4062 patients included in the present analysis, 2358 were randomly assigned to treatment with biodegradable polymer DES (sirolimus-eluting, n = 1501; biolimus-eluting,