Bioresorbable polymer stents for high-risk coronary artery disease patients

Evaluating new evidence on small vessel disease from the BIO-RESORT trial

Introduction

Over the last decade, the technology of intravascular stents has evolved into three main classes following disappointing results with the fully bioresorbable stent scaffold. These are bare metal stents, durable polymer drug-eluting stents (DP-DESs) and hybrid biodegradable polymer drug-eluting stents (BP-DESs). In the BP-DES class, results are influenced by factors such as differences in thickness of stent struts, attributes of the biodegradable polymer (duration of degradation, situation on stent), and the selected antiproliferative agent and its release kinetics.1

Increasingly, patients with diabetes and small-vessel disease and those at high bleeding risk are set to benefit further as data emerge on the advantages of the newer-generation BP-DESs in these high-risk patients requiring percutaneous coronary intervention (PCI). Results from clinical trials of differing stent types are presented in this review and illustrate the benefits of these new technologies.
KEY MESSAGES

- Newer-generation BP-DESs have been shown to be non-inferior to contemporary thicker-strut second-generation DP-DESs in treating all-comer patients

- Newer-generation BP-DESs improve long-term, five-year clinical outcomes for coronary artery disease (CAD) in comparison with second-generation DP-DESs

- In small-vessel lesions, biodegradable ultra-thin-strut sirolimus-eluting stents (Orsiro-SES) showed fewer repeated target lesion revascularisations and stent thrombosis than durable thin-strut zotarolimus-eluting stents.

The BIO-RESORT and BIOFLOW-V trials of BP-DESs vs DP-DESs in CAD

More than 3000 patients with obstructive CAD were randomly assigned (1:1:1) in the BIO-RESORT trial to the ultra-thin-strut bioresorbable sirolimus-eluting stent, Orsiro-SES; a very thin-strut biodegradable everolimus-eluting stent, Synergy-EES; or a previous-generation zotarolimus-eluting durable stent, Resolute Integrity-ZES (Table 1). The primary endpoint was a composite of safety (cardiac death or target vessel-related myocardial infarction (MI)) and efficacy (target lesion revascularisation (TLR)) at 12 months of follow-up.

Table 1. Attributes of stents used in the BIO-RESORT trial

<table>
<thead>
<tr>
<th>Type of stent</th>
<th>Uncoated strut</th>
<th>Coated strut</th>
<th>Coating type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orsiro-SES*</td>
<td>60µm (≤3.00mm) (ultra-thin)</td>
<td>71µm</td>
<td>Asymmetrical</td>
</tr>
<tr>
<td>Synergy-EES</td>
<td>74µm (≤3.00mm) (very thin)</td>
<td>78µm</td>
<td>Abluminal</td>
</tr>
<tr>
<td>Resolute Integrity-ZES</td>
<td>91µm (thin)</td>
<td>102µm</td>
<td>Conformal</td>
</tr>
</tbody>
</table>

All DESs were available in 2.25-4.00mm + lengths of 8-40mm
* click here to view attributes of Orsiro-SES

In this assessor- and patient-blinded evaluation of outcomes at one year, both the ultra-thin and very thin-strut DESs (with dissimilar biodegradable polymer coatings eluting either everolimus or sirolimus) were shown to be non-inferior to the durable polymer stent in treating all-comer patients, with a high proportion (70%) of these patients presenting with acute coronary syndromes (ACSs).2

In another large clinical outcome trial, the BIOFLOW-V trial3 of the ultra-thin Orsiro bioresorbable stent versus contemporary second-generation durable stents, the Orsiro stent was shown to be superior at reducing target lesion failure (TLF) over a five-year period, driven by less target-vessel MI (Figure 1).
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While five-year results from the BIO-RESORT trial are not yet available, three-year results in prespecified subgroups have just been released and are yielding important new insights.

**BIO-RESORT outcomes in small coronary vessels at three years**

Treatment of lesions in small vessels is associated with worse clinical outcomes. In the DUTCH-PEERS randomised trial, an evaluation of the size of treated vessels that resulted in increased TLF showed that the threshold of <2.5mm is a suitable point to identify small target-vessel size that will contribute to higher TLF rates.4

The Small Vessel Subgroup analysis of the BIO-RESORT trial used this reference size in its assessor- and patient-blinded evaluation (Figure 2).5 Patients with small-vessel disease included in the sub-study were aged 34-70 years with a mean age of 64 years. Two-thirds presented with ACS, 30% of the population were women and 20% had diabetes. Most patients presented with complex target lesions (Table 2).
**Table 2. Baseline lesion characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Orsiro (n=636)</th>
<th>Synergy (n=581)</th>
<th>Resolute Integrity (n=602)</th>
<th>p-value Orsiro vs. Resolute Integrity</th>
<th>p-value Synergy vs. Resolute Integrity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACC-AHA lesion class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, No. (%)</td>
<td>42/633 (6.6)</td>
<td>34/581 (5.9)</td>
<td>40/600 (6.7)</td>
<td>0.01</td>
<td>0.20</td>
</tr>
<tr>
<td>B1, No. (%)</td>
<td>139/633 (22.0)</td>
<td>148/581 (25.5)</td>
<td>180/600 (30.0)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>B2/C (complex lesion), No. (%)</td>
<td>452 (71.4)</td>
<td>399 (68.7)</td>
<td>380 *63.3)</td>
<td>0.002</td>
<td>0.05</td>
</tr>
<tr>
<td>Chronic total occlusion, No. (%)</td>
<td>24 (3.8)</td>
<td>21 (3.6)</td>
<td>26 (4.3)</td>
<td>0.63</td>
<td>0.54</td>
</tr>
<tr>
<td>In-stent restenosis, No. (%)</td>
<td>3 (0.5)</td>
<td>12 (2.1)</td>
<td>13 (2.2)</td>
<td>0.009</td>
<td>0.91</td>
</tr>
<tr>
<td>Severe calcification, No. (%)</td>
<td>113 (17.8)</td>
<td>111 (19.1)</td>
<td>126 (20.9)</td>
<td>0.16</td>
<td>0.43</td>
</tr>
<tr>
<td>Bifurcated lesion, No. (%)</td>
<td>222 (34.9)</td>
<td>206 (35.5)</td>
<td>205 (34.1)</td>
<td>0.75</td>
<td>0.61</td>
</tr>
<tr>
<td>Left main stem lesion, No. (%)</td>
<td>5 (0.8)</td>
<td>10 (1.7)</td>
<td>7 (1.2)</td>
<td>0.50</td>
<td>0.42</td>
</tr>
<tr>
<td>Lesion length, mean (SD) mm</td>
<td>16.61±10.07</td>
<td>16.50±11.26</td>
<td>16.16±11.11</td>
<td>0.46</td>
<td>0.61</td>
</tr>
<tr>
<td>Reference vessel diameter, mean (SD), mm</td>
<td>2.11±0.28</td>
<td>2.12±0.28</td>
<td>2.11±0.28</td>
<td>0.83</td>
<td>0.61</td>
</tr>
<tr>
<td>Total stent length, mean (SD), mm</td>
<td>28.2±17.7</td>
<td>27.4±18.0</td>
<td>28.3±19.5</td>
<td>0.89</td>
<td>0.40</td>
</tr>
<tr>
<td>Number of stents per lesion, mean (SD)</td>
<td>1.4±0.7</td>
<td>1.3±0.7</td>
<td>1.4±0.7</td>
<td>0.42</td>
<td>0.10</td>
</tr>
<tr>
<td>Predilation performed, No. (%)</td>
<td>516 (81.1)</td>
<td>479 (82.4)</td>
<td>491 (81.6)</td>
<td>0.85</td>
<td>0.69</td>
</tr>
<tr>
<td>Postdilation performed, No. (%)</td>
<td>428 (67.3)</td>
<td>433 (74.5)</td>
<td>418 (69.4)</td>
<td>0.42</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Figure 2. Small vessel subgroup analysis – study overview**

**Design**
Small Vessel, defined as vessels with a reference diameter <2.5mm subgroup analysis of a large scale, all-corners, multi-centre, assessor and patient-blinded, randomised, non-inferiority trial.

**Principal Investigators**
Prof. Clemens von Birgelen, Thoraxcentrum Twente, Netherlands

**Clinical Endpoint**
- Target Lesion Failure (TLF), defined as the composite of: Cardiac Death, Target Vessel Myocardial Infarction (TV-MI) and clinically-driven Target Lesion Revascularisation (CD-TLR)
- Stent Thrombosis (ST)

1506 of 3514 patients 4 centers in Netherlands

1 : 1 : 1 randomization

Orsiro n=525 Synergy n=496 Resolute Integrity n=485

24-month clinical follow-up

24-month clinical follow-up

36-month clinical follow-up
During three years of follow-up, there was a significantly lower incidence of TLF in patients treated with the ultra-thin-strut DES (Orsiro) compared to those treated with the thin-strut DES (Resolute Integrity-ZES); this difference emerged during the second year of follow-up (Figure 3). Stent thrombosis rates were also lower when ultra-thin stents were used in these smaller vessels (Figure 4); as was TLR, with 60% lower rates at three years (Figure 5).

Figure 3. Small-vessel subgroup Target Lesion Failure (TLF) and components at three years

Figure 4. Small-vessel subgroup stent thrombosis (ST) rates at three years

Dual antiplatelet therapy was discontinued at 12 months per protocol. Stent thrombosis was classified according to the Academic Research Consortium definitions.

Figure 4. Small-vessel subgroup stent thrombosis (ST) rates at three years
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The BIO-RESORT trial and patients at high bleeding risk

A substantial portion of PCI patients are at high bleeding risk and also have an increased risk of ischaemic events. Theoretically, BP-DESs should offer these patients better outcomes with reduced inflammation and better healing rates, but to date no unequivocal benefit of BP-DESs over contemporary DP-DESs has been shown. For this reason, there is special interest in the recent evaluation of patients at high bleeding risk as a subgroup within the BIO-RESORT trial.

In this evaluation, patients were classified as being at high bleeding risk if they:
1. Were older than 75 years
2. Were users of anticoagulation therapy
3. Had a haemoglobin level of <6.8 mmol/l
4. Had a platelet count of <100 000/mm³
5. Had previous gastrointestinal bleeding or stroke, or intracranial bleeding
6. Had renal insufficiency requiring dialysis or were current users of non-steroidal anti-inflammatory drugs.

In the first year of follow-up, the primary endpoint of target-vessel failure occurred in 6.5% of patients treated with BP-DESs compared to 7.3% treated with DP-DESs. This overall reduction was not statistically significant. The event rates in the BIO-RESORT high-bleeding-risk group was shown to be lower than in other trials such as the ZEUS trial, which used early-generation DP-DESs. Also, differing dual antiplatelet therapy duration in these trials may have played a role in the reduced event rate.

At the forthcoming 2019 ESC Congress, further long-term results from the BIO-RESORT series will be announced.

References

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