Drug-eluting stent technology: progress beyond the polymer

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The polymer matrix represents an integral part of drug-eluting stents (DES) and controls the release of the antiproliferative drug over the course of several weeks to months in order to maximize the anti-restenotic effectiveness. Polymers are applied to the surface circumferentially or only at the abluminal side and can be categorized according to their persistence as permanent or biodegradable. Evidence from histopathological studies of early-generation DES have revealed a chronic inflammatory response to components of the permanent polymer matrix resulting in delayed arterial healing, which has been associated with increased risks of both very late stent thrombosis and late restenosis. Biodegradable polymers have been embraced as a promising development to overcome this limitation.

However, refinements of new-generation DES were not limited to the composition, distribution, and thickness of the polymer, but also extended to the material of the stent platform, its geometry and strut thickness, as well as the selection and dosage of antiproliferative agents. Stent platforms consisting of cobalt–chromium or cobalt–platinum instead of stainless-steel allowed the thickness of stent struts to be reduced by more than half compared with early-generation platforms, while maintaining radial force and stent visibility. Thin-strutted bare-metal stents have been associated with a reduced risk of restenosis. Moreover, experimental data indicate a lower thrombogenicity, which may be related to more rapid endothelialization compared with thick-strutted stent types. Antiproliferative substances of the rapamycin family prevailed over paclitaxel in new-generation DES and brought forth several-limus analogues with comparable efficacy. The combined effects of technological progress on different levels translated into improved clinical outcomes, with elimination of previous concerns over very late stent thrombosis, while the anti-restenotic efficacy of early-generation DES have been preserved, and this constitutes the current standard of care.

Several studies have investigated biodegradable polymer DES with permanent polymer early- and new-generation DES (Table 1). Final 5 year outcomes of the LEADERS trial corroborated non-inferiority with respect to the primary endpoint (major adverse cardiac events) and demonstrated a reduction of the patient-oriented composite endpoint of all-cause death, myocardial infarction, and revascularization in favour of biodegradable polymer biolimus-eluting Biomatrix stents compared with permanent polymer sirolimus-eluting Cypher stents (0.7 vs. 2.5%, RR 0.26, 95% CI 0.10–0.68, P = 0.003). In an individual patient data pooled analysis, biodegradable polymer DES based on early-generation stainless-steel platforms have been shown to reduce the risk of stent thrombosis [hazard ratio (HR) 0.56, 95% CI 0.35–0.90] and repeat revascularizations (HR 0.62, 95% CI 0.68–0.98) compared with early-generation, permanent polymer sirolimus-eluting Cypher stents (0.7 vs. 2.5%, RR 0.26, 95% CI 0.10–0.68, P = 0.003). Of note, stainless-steel, biodegradable polymer biolimus-eluting Biomatrix stents significantly reduced the rate of very late stent thrombosis between 1 and 5 years in comparison to early-generation, permanent polymer sirolimus-eluting Cypher stents (0.7 vs. 2.5%, RR 0.26, 95% CI 0.10–0.68, P = 0.003). Of note, stainless-steel, biodegradable polymer biolimus-eluting Biomatrix stents significantly reduced the rate of very late stent thrombosis between 1 and 5 years in comparison to early-generation, permanent polymer sirolimus-eluting Cypher stents (0.7 vs. 2.5%, RR 0.26, 95% CI 0.10–0.68, P = 0.003). Of note, stainless-steel, biodegradable polymer biolimus-eluting Biomatrix stents significantly reduced the rate of very late stent thrombosis between 1 and 5 years in comparison to early-generation, permanent polymer sirolimus-eluting Cypher stents (0.7 vs. 2.5%, RR 0.26, 95% CI 0.10–0.68, P = 0.003).

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>Candidate</th>
<th>Comparator</th>
<th>Result</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADERS</td>
<td>All-cause death, MI, and revascularization</td>
<td>Biomatrix</td>
<td>Cypher</td>
<td>Non-inferiority</td>
<td>0.003</td>
</tr>
<tr>
<td>IPD analysis</td>
<td>Stent thrombosis, repeat revascularization</td>
<td>Early-generation stainless-steel</td>
<td>Permanent polymer</td>
<td>Reduction</td>
<td>0.56, 95% CI 0.35–0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduction</td>
<td>0.62, 95% CI 0.68–0.98</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Trial</th>
<th>Study stent</th>
<th>Comparator</th>
<th>Study design (number of patients)</th>
<th>Primary endpoint*</th>
<th>Event rates</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADERS²⁻⁶</td>
<td>Biomatrix</td>
<td>Cypher</td>
<td>Non-inferiority (n = 1707)</td>
<td>*Cardiac death, MI, clinically-indicated TVR at 9 months</td>
<td>9.2% 10.5%</td>
<td>RR 0.88 (95% CI 0.64 – 1.19)</td>
</tr>
<tr>
<td></td>
<td>Stainless-steel platform 120 μm strut thickness Abluminal PDLLA polymer (10 μm)</td>
<td>Stainless-steel platform 140 μm strut thickness Circumferential PEVA/PBMA polymer (13 μm) Biolimus A9</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Detroit Laboratories Inc.</td>
<td>Cardiac death, MI, clinically-indicated TVR at 5 years</td>
<td>22.3% 26.1%</td>
<td>RR 0.83 (95% CI 0.68 – 1.02)</td>
</tr>
<tr>
<td>COMPARE II³</td>
<td>Nobori</td>
<td>Xience/Promus</td>
<td>Non-inferiority (n = 2707)</td>
<td>*Cardiac death, non-fatal MI, clinically-indicated TVR at 12 months</td>
<td>5.2% 4.8%</td>
<td>RR 1.07 (95% CI 0.75 – 1.52)</td>
</tr>
<tr>
<td></td>
<td>Stainless-steel platform 120 μm strut thickness Abluminal PDLLA polymer (10 μm) Biolimus A9</td>
<td>Cobalt–chromium platform 81 μm strut thickness Circumferential PBMA/PVDF-HFP polymer (8 μm) Everolimus</td>
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<td></td>
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</tbody>
</table>
Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; PBMA/PVDF-HFP, poly n-butyl methacrylate/co-polymer of vinylidene fluoride and hexafluoropropylene; PDLLA, poly-DL-lactic acid; PEVA/PBMA, poly-ethylene-co-vinyl-acetate/poly n-butyl methacrylate; RR, relative risk; TLR, target lesion revascularization; TVR, target vessel revascularization; TV MI, target-vessel related myocardial infarction.
Several competing technologies follow a similar strategy of combining biodegradable polymer technology with thin-strut stent platforms. The Synergy stent (Boston Scientific, MA, USA) releases everolimus from an abluminal biodegradable poly-lactic co-glycolic acid (PLGA) polymer applied to a 74-μm-thick platinum–chromium stent platform, which is resorbed during a period of 3–4 months. This stent was found to be non-inferior at 6 months to the permanent polymer everolimus-eluting Promus Element stent in the EVOLVE I study (a randomized comparison with a primary angiographic endpoint) investigating two different doses of everolimus (full-dose 113 μg/20 mm and half-dose 56 μg/20 mm stent surface; results for late lumen loss, full-dose 0.10 ± 0.25 mm vs. half-dose 0.13 ± 0.26 mm vs. Promus 0.15 ± 0.34 mm, P non-inferiority < 0.001 for both comparisons). The full-dose platform is currently assessed in the larger scale EVOLVE II trial, powered for clinical endpoints, compared with permanent polymer everolimus-eluting Promus Element stents. The Orsiro stent (Biotronik, Germany) releases sirolimus from biodegradable poly-L-lactic acid (PLLA) applied to a 60-μm-thick cobalt–chromium platform. This stent was found to be non-inferior to the permanent polymer everolimus-eluting Xience stent at 9 months in the randomized Bioflow II study (late lumen loss, 0.10 ± 0.32 vs. 0.11 ± 0.29 mm, P non-inferiority < 0.0001). Several ongoing trials powered for clinical endpoints are comparing the Orsiro stent with other new-generation DES. Additional new-generation biodegradable polymer DES using thin-strut platforms include the DESyne BD stent (Elixir, CA, USA), the Combo stent (OrbusNeich, FL, USA), and the MiStent (Micell Technologies, NC, USA).

It remains to be shown whether the late benefit of biodegradable polymers observed with early-generation, thick-strut, stainless-steel stent platforms will translate into a similar benefit with new-generation, thin-strut, cobalt–chromium platforms. Of note, the permanent polymers used in early-generation SES (poly-ethylene-co-vinyl acetate/poly n-butyl methacrylate) were modified with new-generation permanent polymer EES (poly n-butyl methacrylate/co-polymer of vinylidene fluoride and hexafluoropropylene). Very low event rates observed with new-generation permanent polymer EES beyond 1 year after implantation set the bar high for any competitor, and any difference may be detectable only during very long-term follow-up or in larger patient populations. Alternatively, intracoronary high-resolution imaging modalities, such as optical coherence tomography, may be able to provide more insights into the long-term healing pattern of various stent platforms.

In summary, the Century II trial is one of the first studies to report outcomes of a newer-generation biodegradable polymer-based DES with thin-strut cobalt–chromium technology, which appears similarly effective during 9 months of follow-up compared with the current gold-standard durable polymer EES. Ongoing studies and longer-term follow-up will determine whether biodegradable polymers in combination with further refinement of stent technology, including ultrathin strut and polymer thickness as well as drug modifications, will further enhance outcomes beyond the excellent results achieved with the present-generation DES.

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References


