Are All New-Generation Drug-Eluting Stents Equal?
— Long-Term Follow-up Is Necessary —

Kengo Tanabe, MD, PhD

The sirolimus-eluting stent (SES: Cypher, Cordis Corp.) and paclitaxel-eluting stent (PES: TAXUS, Boston Scientific), the so-called 1st-generation drug-eluting stents (DES), dramatically reduced the incidence of in-stent restenosis. As their use became widespread worldwide, new enemies emerged at long-term follow-up such as late restenosis, very late thrombosis, delayed arterial healing, and neoatherosclerosis. Thus, follow-up of patients with newer generation DES is imperative for long-term evaluation of the incidence of such adverse phenomena. In this issue of the Journal, Park et al report the 3-year clinical outcomes of the everolimus-eluting stent (EES: Xience, Abbott Vascular; Promus, Boston Scientific) in comparison with those for the SES in the prospective EXCELLENT randomized trial. From 1 to 3 years, death, myocardial infarction (MI), and major adverse cardiac events were significantly less prevalent in the EES group than in the SES group. Furthermore, the prevalence of definite or probable stent thrombosis (ST) in the SES arm (1.37%) was 3-fold higher that in the EES arm (0.46%), although the difference did not reach statistical significance (P=0.08). In fact, this is not the first study to investigate the long-term outcome of EES in comparison with SES. Although the incidence of ST is rare, ranging from 0.5% to 3% at around 3 years, it is of paramount importance to survey its incidence because it induces catastrophic events once it occurs. In this regard, accumulation of long-term follow-up data from many prospective trials is necessary to objectively judge this rare event associated with each new-generation DES. The safety data reported by Park et al are basically in accordance with the findings of previous trials, thus reinforcing the data from a meta-analysis that demonstrated that the incidence of EES thrombosis is lower than that of bare-metal stent (BMS) and 1st-generation DES thrombosis. The biocompatible and thromboresistant profile of fluorinated polymer on EES is considered to play a key role in reducing thrombosis. Morino et al have also recently demonstrated early vascular healing in EES by using serial optical coherence tomography assessment in primary percutaneous coronary intervention (PCI) for acute MI. The new-generation DES available in Japan at

### Table. Comparison of Drug-Eluting Stents Currently Available in Japan

<table>
<thead>
<tr>
<th>Product name</th>
<th>XIENCE Alpine</th>
<th>Resolute Onyx</th>
<th>Synergy</th>
<th>BMX-J</th>
<th>Ultimaster</th>
<th>Orsiro</th>
<th>BioFreedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Everolimus</td>
<td>Zotarolimus</td>
<td>Everolimus</td>
<td>BiolimusA9</td>
<td>Sirolimus</td>
<td>Sirolimus</td>
<td>BiolimusA9</td>
</tr>
<tr>
<td>Polymer</td>
<td>Fluorinated polymer</td>
<td>BioLinx</td>
<td>PLA</td>
<td>PLGA</td>
<td>PLA</td>
<td>PDLA-PCL</td>
<td>Passive coating: amorphous silicon carbide</td>
</tr>
<tr>
<td>Type of polymer</td>
<td>Durable</td>
<td>Durable</td>
<td>Biodegradable</td>
<td>Biodegradable</td>
<td>Biodegradable</td>
<td>Biodegradable</td>
<td>No</td>
</tr>
<tr>
<td>Coating</td>
<td>Entire</td>
<td>Entire</td>
<td>Abluminal</td>
<td>Abluminal</td>
<td>Abluminal</td>
<td>Abluminal</td>
<td>Entire</td>
</tr>
<tr>
<td>Stent</td>
<td>Multilink 8</td>
<td>Onyx (S10)</td>
<td>PromusPREMIRE</td>
<td>S-stent</td>
<td>Kaname</td>
<td>PRO-Kinetik Energy</td>
<td>Juno™ stent</td>
</tr>
<tr>
<td>Material</td>
<td>CoCr</td>
<td>CoCr/Pt-Ir</td>
<td>PtCr</td>
<td>SiSt</td>
<td>CoCr</td>
<td>CoCr</td>
<td>SiSt</td>
</tr>
<tr>
<td>Strut thickness (μm)</td>
<td>81</td>
<td>81</td>
<td>74 (2.25–2.75 mm)</td>
<td>125</td>
<td>80</td>
<td>60μm (2.25–3.00 mm)</td>
<td>120 (2.5–3.0 mm)</td>
</tr>
</tbody>
</table>

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.
Received March 15, 2018; accepted March 19, 2018; released online April 13, 2018
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Circulation Journal Vol.82, June 2018
present (March, 2018) are listed in the Table. The so-called 3rd-generation DES, which became available in the market after the EES and zotarolimus-eluting stent (ZES; Resolute, Medtronic), apply biodegradable polymer\(^1\)\(^9\) or have no polymer\(^10\) on the surface of the stent. When the 3rd-generation DES were developed, the drawbacks of the 1st-generation DES were considered to be attributable to the durable polymer on the SES and PES. Therefore, the aim was to develop a DES that becomes bare metal as early as possible by using biodegradable polymer or applying no polymer coating. It is interesting that at the introduction of the BMS, the bare metal surface itself was thought to be thrombogenic. Therefore, a heparin-coated stent was developed but failed to show efficacy and safety over the BMS.\(^11\) To date, among biocompatible durable polymer such as fluorinated polymer, biodegradable polymer, and no polymer, the best surface material for DES remains unknown.

Another essential aspect of the DES components is strut thickness. Up to 2016, stents with thin struts has shown better results in terms of ex vivo thrombogenicity\(^6\) and restenosis rate\(^14\) than those with thick struts. For the first time, in the PRISON IV trial,\(^13\) which compared the angiographic outcomes following recanalization with the SES (Orsiro, Biotronik) with an ultrathin strut (60 \(\mu\)m) for chronic total occlusion with those with EES (81 \(\mu\)m), the DES with the thinner strut was inferior regarding restenosis rate at 9 months in 2017. On the other hand, the EES had never been shown to be inferior in prospective head-to-head randomized clinical trials up to 2016. However, the EES was inferior to the SES with an ultrathin strut randomized trial.\(^7\) in 2017. The incidence of target-vessel revascularization (TVR) at 2 years was found to occur at around 4-fold higher rate than with the EES;\(^14\) thus, the BVS is no longer on the market.

A completely bioresorbable vascular scaffold (BVS; Abbott Vascular) was expected to make a revolutionary change in the field of interventional cardiology by providing antiproliferative drug-eluting capability without the chronic limitations of permanent metallic implants. Although BVS showed non-inferior clinical outcomes to the EES in a relatively short-term period, scaffold thrombosis at 2 years was found to occur at around 4-fold higher rate than with the EES;\(^14\) thus, the EES is no longer on the market.

A small, but sizable number of patients develop late adverse events such as late restenosis, late thrombosis, and neoatherosclerosis even after EES implantation.\(^15\) In addition, enhancing the acute performance of stents (deliverability etc.) is valuable in daily clinical practice. Considering the fact that the 1st-generation BVS showed disappointing results in 2017, it is important to further develop new-generation DES. Most of the 3rd-generation DES have shown clinical outcomes that are non-inferior to those of the EES at around 1 year. Long-term follow-up is necessary to demonstrate at least equal outcomes to those of the EES.

**Conflicts of Interest**

The author received remuneration from Abbott Vascular, Kaneka, Daiichisankyo, and Terumo.

**References**