EDITORIAL COMMENT

“Capturing” the Benefits of Dual-Therapy Stent Technology
Is This a Promise or Reality?*

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Since its first appearance in clinical practice, drug-eluting stent (DES) technology has been in continuous evolution (1). Through the abluminal elution of a cytotoxic or a cytostatic antiproliferative drug from a polymer, a DES successfully prevents the development of exuberant neointimal hyperplastic response and subsequent in-stent restenosis (1). However, although first-generation permanent polymer DES substantially improved the efficacy of percutaneous coronary intervention (PCI) compared with bare-metal stents, safety issues arose early because of increased risk for in-stent thrombosis (ST) (2). Intravascular imaging and histopathologic studies identified incomplete DES strut endothelialization as an important pathological substrate of ST (2). De-endothelialized DES struts act as triggers for local platelet activation and blood flow turbulence, with subsequent unleashing of intra-arterial thrombogenic pathways. The local release of the antiproliferative drug and the local vascular inflammation induced by the permanent polymer were identified as key contributors to the patterns of incomplete endothelial coverage and delayed vascular healing observed with first-generation DES (2). For that reason, second-generation DES evolved. Through improved biocompatibility and drug-release kinetics, second-generation DES significantly improved the safety of intracoronary DES implantation while preserving proper antirestenotic effectiveness (1). Unfortunately, even with second-generation DES, some limitations remain, including very late ST, in-stent restenosis, and in-stent neoatherosclerosis (2).

The hypothesis behind dual-therapy stent (DTS) technology is that through the addition of a circulating bone marrow-derived CD34+ endothelial progenitor cell capture system on the luminal stent surface, endothelial coverage will be maintained while the antiproliferative effect of the eluted drug on the abluminal side is maintained (3). The endothelial progenitor cell capture system promotes luminal DES strut endothelialization by capturing circulating CD34+ cells through anti-CD34 antibodies located on the luminal aspect of the DES platform (3). In the COMBO DTS (Orbus-Neich Medical, Fort Lauderdale, Florida), the combination of this luminal mechanism of action with the abluminal release of a potently active antiproliferative drug from a biodegradable polymer promise to challenge the 2 main mechanisms of DES failure: ST (on the luminal side) and in-stent restenosis (on the abluminal side). Additionally, a DES associated with more predictable and uniform pattern of endothelialization, alongside a polymer that disappears after release of the antiproliferative drug, potentially allows more flexible and confident use of shorter periods of mandatory dual antiplatelet therapy (DAPT) (4,5).

With this compelling scientific background in mind, in this issue of JACC: Cardiovascular Interventions, Woudstra et al. (6) report the 1-year results of the REMEDEE (Randomized Study to Evaluate the Safety and Effectiveness of an Abluminal Sirolimus Coated Bio-Engineered Stent) study, an investigator-initiated, multicenter, prospective,

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post-market registry designed to assess the efficacy and safety of the dual-therapy COMBO DES in a real-world all-comer population. A total of 1,000 patients with planned COMBO stent implantation between June 2013 and March 2014 were included in the registry. Exclusion criteria were few. Follow-up was performed by means of telephone calls or scheduled outpatient visits at 30 days, 6 months, and 1 year. DAPT was recommended for 6 months after elective stenting and 12 months after PCI for acute coronary syndromes. The primary outcome of interest of the registry was target lesion failure, defined as the composite of cardiac death, target vessel-related nonfatal myocardial infarction, or target lesion revascularization (TLR). All clinical events were adjudicated by an independent clinical event committee, improving the reliability of the measured outcomes in the registry. Patients enrolled in the registry reflected a real-world PCI population in terms of baseline clinical and angiographic characteristics. Device success was achieved in 98.7% of patients. At 1 year, the primary outcome of target lesion failure occurred in 5.7% of patients, mostly represented by TLR with PCI (3.4%). Importantly, most of the events occurred within 6 months after the procedure. Definite ST occurred in 5 patients (0.5%), of which all occurred in the early post-PCI period (particularly within 9 days). These results are overall comparable with other last-generation DES.

Although certainly this study does not provide definitive evidence regarding the efficacy and safety of the COMBO stent compared with currently used DES platforms (because of its nonrandomized design and lack of a matched control cohort), real-world registry-based data are important to consolidate the performance of any new developed device. In this study, the COMBO stent appeared to be associated with excellent device-oriented outcomes at 1 year, with no cases of ST occurring after 9 days, possibly as a result

**FIGURE 1** Completed and Ongoing Studies Investigating the Efficacy and Safety of the COMBO Dual-Therapy Stent

<table>
<thead>
<tr>
<th>Study</th>
<th>Status</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>EGO-COMBO Evaluation of Endothelial ProGenitor Cell Capture Sirolimus-Eluting Stent by Optical Coherence Tomography</td>
<td>Completed</td>
<td>Non-inferiority randomized trial. COMBO stent non-inferior to paclitaxel-eluting stent on int- llate lumen loss at 6 months.</td>
</tr>
<tr>
<td>HARMONEE Harmonized Assessment by Randomized, Multi-Center Study of OrbusNEich’s Combo STent</td>
<td>Completed</td>
<td>Non-randomized optical coherence tomography imaging study. COMBO stent associated with 100% endothelial coverage at 150-day optical coherence tomography serial follow-up. Possible neointimal regression between 9 and 24 months.</td>
</tr>
<tr>
<td>REMEDEEE Registry Multinational Abluminal Sirolimus Coated B</td>
<td>Completed</td>
<td>Non-randomized, observational study. COMBO stent associated with 1-year 5.7% rate of target lesion failure, 1-year 0.5% rate of definite stent thrombosis, and no cases of late stent thrombosis.</td>
</tr>
<tr>
<td>HARMONEE Japan-US Trial</td>
<td>Ongoing</td>
<td>Non-inferiority randomized trial comparing COMBO stent versus everolimus-eluting stent. Primary endpoint: target vessel failure (cardiac death, target-vessel myocardial infarction or ischemia-driven target vessel revascularization) at 1 year.</td>
</tr>
<tr>
<td>REDUCE Trial Randomized Evaluation of Short-term DUal Anti Platelet Therapy in Patients With Acute Coronary Syndrome Treated With the COMBO Dual-therapy stEnt</td>
<td>Ongoing</td>
<td>Non-inferiority randomized trial comparing 3 versus 12 months dual antiplatelet therapy after COMBO stent implantation in patients with acute coronary syndrome. Primary endpoint: all-cause mortality, myocardial infarction, stent thrombosis, stroke or bleeding at 12 months.</td>
</tr>
<tr>
<td>MASCOT Registry Multinational Abluminal Sirolimus Coated B</td>
<td>Ongoing</td>
<td>Non-randomized, observational post-market registry. Primary endpoint target lesion failure (cardiac death, non-fatal myocardial infarction or target lesion revascularization) at 12 months.</td>
</tr>
<tr>
<td>RECOVERY China Safety and Effectiveness Study of Combo Bio-engineered Sirolimus Eluting Stent</td>
<td>Ongoing</td>
<td>Non-inferiority randomized trial comparing COMBO stent versus Nano Polymer-free sirolimus-eluting stent system. Primary endpoint: in-stent late lumen loss at 9 months.</td>
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EGO-COMBO = Evaluation of Endothelial ProGenitor Cell Capture Sirolimus-Eluting Stent by Optical Coherence Tomography; HARMONEE = Harmonized Assessment by Randomized, Multi-Center Study of OrbusNEich’s Combo STent; MASCOT = Multinational Abluminal Sirolimus Coated B| Engineered STent; RECOVERY = Safety and Efficacy of the Combo Bio-engineered Sirolimus-eluting Stent Versus the Nano Polymer-free Sirolimus-eluting Stent in the Treatment of Patients With de Novo Stenotic Lesions; REDUCE = Randomized Evaluation of Short-term DUal Anti Platelet Therapy in Patients With Acute Coronary Syndrome Treated With the COMBO Dual-therapy STent; REMEDEE = Safety and Effectiveness Study of Combo Bio-engineered Sirolimus Eluting Stent.
of the faster and more homogeneous pattern of endothelial coverage of this device. Rates of TLR were in line with those of other new-generation DES platforms, compatible with preserved antirestenotic effectiveness of the DTS. Most of the TLRs occurred within 6 months of the procedure, however whether a better endothelialization profile affects long-term angiographic efficacy and lower late catch-up phenomenon (possibly due to in-stent neoatherosclerosis) warrants further investigation. Furthermore, whether the DTS technology allows more flexible and shorter duration of DAPT, even in high-risk clinical and anatomic subsets, is a compelling hypothesis that needs to be demonstrated.

Previously, in the REMEDEE trial, the COMBO stent already demonstrated the angiographic non-inferiority compared with the first-generation paclitaxel-eluting stent (7). However, a superior effectiveness of the DTS and other upcoming DES technologies over currently used metallic DES may be hard to demonstrate in a randomized controlled trial, given the impressive efficacy and safety profile of second-generation metallic DES (8), even in high-risk patient and lesions subsets (9). Although the second-generation metallic DES may be hard to beat, the benefits of newer DES technologies could shift from the usual device-oriented endpoints (such as ST and TLR) to other biometrics of clinical benefit, especially within specific subgroups of patients. For example, in the LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom Stent) trial, in which 2,466 patients at high risk for bleeding were randomized to either a polymer-free DES or a bare-metal stent on a background of only 1 month of DAPT, patients receiving a polymer-free DES had lower rates of both the efficacy (TLR) and safety (cardiac death, myocardial infarction, or ST) endpoints (10).

The DTS technology needs to be viewed in perspective with the other emerging last-generation DES technologies. It is plausible that the interventional cardiology practice will reach a status in which each type of emerging DES technology will be used according to the individual clinical and anatomic background in order to maximize their peculiar benefits. Polymer-free DES may represent a valuable therapeutic option for patients at high risk for bleeding who cannot tolerate or comply with standard mandatory (3 or 6 months) periods of DAPT and need coronary revascularization. Biodegradable scaffolds may become the preferred stent in younger patients with more simple lesions in whom PCI is indicated and who may benefit of surgical revascularization in future. Instead, DTS may represent a very attractive solution for patients with complex lesions and high atherosclerotic burden in which a metallic stent with fast and predictable endothelialization may provide an optimal balance between efficacy and safety, especially in patients at high risk for bleeding who cannot benefit of longer periods of DAPT. On the background, most likely we will not stop using the current second-generation permanent polymer metallic DES, which are familiar and known to be associated with excellent outcomes.

Ongoing studies will consolidate the role of DTS in clinical practice (Figure 1). At this time, however, although the results of this “real-world” registry are promising, the true value of such technology lies on the ongoing randomized controlled trials, which should clarify if the COMBO DTS will progress from a “promise” to an “advance” for the percutaneous treatment of patients with coronary artery disease.

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REFERENCES