EDITORIAL COMMENT

Angiographic Restenosis and Clinical Recurrence After Sirolimus- and Paclitaxel-Eluting Stent Implantation*

Pieter J. Vlaar, MSc, Felix Zijlstra, MD, PhD

Groningen, the Netherlands

The coronary artery stent has succeeded in reducing procedural complications, restenosis, clinical recurrence, and revascularization after percutaneous coronary interventions (PCI). In around 90% of PCIs, a stent is implanted, of which the majority are drug-eluting stents (DES) (1). At the moment, 4 DES are approved by the U.S. Food and Drug Administration for sale in the U.S.: the Cordis Cypher (Johnson & Johnson, Miami, Florida) sirolimus-eluting stent (SES), Boston Scientific Taxus Express2 (Natick, Massachusetts) paclitaxel-eluting stent (PES), Medtronic Endeavor (Minneapolis, Minnesota) zotarolimus-eluting, and the Abbott/Boston Scientific Xience V/Promus everolimus-eluting stent. Besides the type of antiproliferative agent, these stents differ on major points, including the architecture of the stent itself and the manner in which the drug is embedded and released. Each of these characteristics can theoretically cause differences in efficacy and safety. For that reason, it is important to investigate the performance of these stents in the setting of both randomized trials and registries.

As SES and PES were for almost 5 years the only approved DES in the U.S., they are the most widely tested stents in a variety of patient subsets. At the moment, around 20 randomized controlled trials (which included a total of ∼10,000 patients) and several meta-analyses have been published comparing the SES and PES in a head-to-head fashion (2–8). The majority of these trials performed protocol-mandated follow-up angiography to assess angiographic restenosis and late luminal loss after stent implantation using automated edge detection systems (quantitative coronary analysis). In these trials (Table 1), which included a total of 5,765 patients, SES were associated with substantially less angiographic in-stent restenosis and late luminal loss than were PES (Figs. 1 and 2). However, the lingering question remains whether this better ability to reduce neointima proliferation also translates into a lower rate of recurrence of ischemic symptoms mandating reintervention (clinical recurrence).

Two recent meta-analyses comparing SES and PES found a significant reduction of the risk of target lesion revascularizations (TLR) associated with SES as compared with PES (2,3). However, the majority of the included trials in these meta-analyses performed protocol-mandated follow-up angiography, which may have resulted in more revascularizations in the PES group through the “oculostenotic reflex” (9). Data supporting this hypothesis come from the SORT OUT II (Danish Organization on Randomized Trials with Clinical Outcome) trial (8). This trial was adequately powered for clinical events and did not include routine angiography during follow-up. As part of this trial, 2,098 unselected patients were randomized to SES or PES. During follow-up, repeat angiography was driven by clinical recurrence. At 9-month follow-up, there was no difference between the SES and PES group regarding major adverse cardiac events (10.0% vs. 11.6%, p = NS) or TLR (4.5% vs. 5.9%, p = NS). The results of this trial suggest that, in contradistinction to what the angiographic data would suggest, the difference between the 2 types of stents in an unselected population is of limited clinical relevance. Future stent trials should aim to provide more data on the clinical impact of restenosis: for example, by integrating the routine use of fractional flow reserve measurements during follow-up angiographies to function as gatekeepers of reinterventions (10).

Beside randomized controlled trials, registries can offer important information on the possible clinical differences between SES and PES in routine practice. The 2 largest published registries comparing PES with SES are the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) (11) and WDHR (Western Denmark Heart Registry) (12) databases. The SCAAR registry included 19,004 patients undergoing PCI in Sweden between 2004 and 2008. The primary end point was clinically driven restenosis rate, defined as angiographically significant restenosis detected at any repeat angiography performed for ischemic symptoms. After 1 and 2 years, there were no significant differences in restenosis rates between SES (3.3% and 4.9%, respectively) and PES (3.7% and 5.1%, respectively). No difference in survival between the 2 types of stents was found. In contrast, the WDHR registry included 12,395 consecutive patients undergoing PCI and found large differences in terms of stent thrombosis, mortality, reinfarction, and revascularization rates between the 2 stent types. The results of the WHDR registry are in contrast

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From Department of Cardiology, University Medical Center Groningen, Thorax Center, Groningen, the Netherlands.
with available randomized data on SES versus PES that showed no difference in mortality and reinfarction between the 2 types of stents (2,3). In addition, previous analyses of the SCAAR registry on bare-metal stents versus DES caused confusion as they suggested a late-occurring increase in mortality after DES implantation (13). The sometimes conflicting and confusing results of these registries demonstrate that nonrandomized data, even from carefully controlled registries, should be interpreted with caution.

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**Table 1. Randomized Controlled Trials With Protocol-Mandated Follow-Up Angiography**

<table>
<thead>
<tr>
<th>Trial/Author (Ref. #)</th>
<th>n</th>
<th>Population</th>
<th>PES</th>
<th>SES</th>
<th>PES Available (%)</th>
<th>SES Available (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES-DIABETES (4)</td>
<td>400</td>
<td>DM</td>
<td>188 days</td>
<td>187 days</td>
<td>77</td>
<td>88</td>
</tr>
<tr>
<td>DiabeDES (5)</td>
<td>153</td>
<td>DM</td>
<td>8 months</td>
<td>8 months</td>
<td>82</td>
<td>88</td>
</tr>
<tr>
<td>Kim et al. (6)</td>
<td>169</td>
<td>DM</td>
<td>6 months</td>
<td>6 months</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ISAR-DIABETES (3)</td>
<td>250</td>
<td>DM</td>
<td>196 days</td>
<td>196 days</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>ISAR-DESIRE (3)</td>
<td>200</td>
<td>ISR</td>
<td>197 days</td>
<td>197 days</td>
<td>92</td>
<td>91</td>
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<tr>
<td>ISAR-SMART III (3)</td>
<td>360</td>
<td>Small, non-DM</td>
<td>196 days</td>
<td>196 days</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>LONG DES II (3)</td>
<td>500</td>
<td>Long lesions</td>
<td>186 days</td>
<td>188 days</td>
<td>82</td>
<td>84</td>
</tr>
<tr>
<td>Pan et al. (7)</td>
<td>205</td>
<td>Bifurcation lesions</td>
<td>8 months</td>
<td>8 months</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>Petronio et al. (3)</td>
<td>100</td>
<td>Complex lesions</td>
<td>9 months</td>
<td>9 months</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>Cervinka et al. (3)</td>
<td>70</td>
<td>Complex lesions</td>
<td>6 months</td>
<td>6 months</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>CORPAL (3)</td>
<td>652</td>
<td>Complex lesions</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PROSIT (3)</td>
<td>308</td>
<td>AMI</td>
<td>197 days</td>
<td>210 days</td>
<td>75</td>
<td>78</td>
</tr>
<tr>
<td>REALITY (3)</td>
<td>1,386</td>
<td>Unselected</td>
<td>8 months</td>
<td>8 months</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>SIRTAX (3)</td>
<td>1,012</td>
<td>Unselected</td>
<td>8 months</td>
<td>8 months</td>
<td>54</td>
<td>53</td>
</tr>
</tbody>
</table>

— = not available; AMI = acute myocardial infarction; CORPAL = Drug-Eluting Stents for Complex Lesions: Randomized Rapamycin Versus Paclitaxel trial; DES-DIABETES = A Randomized Comparison of Sirolimus- Versus Paclitaxel-Eluting Stent Implantation in Patients With Diabetes Mellitus trial; DiabeDES = Diabetes and Drug-Eluting Stent trial; DM = diabetes mellitus; ISAR-DESIRE = Drug-Eluting Stents for In-Stent Restenosis trial; ISAR-DIABETES = Paclitaxel-Eluting Stent Versus Sirolimus-Eluting Stent for the Prevention of Restenosis in Diabetic Patients With Coronary Artery Disease trial; ISAR-SMART 3 = Drug Eluting Stenting to Abrogate Restenosis in Small Arteries trial; ISR = in-stent restenosis; LONG DES II = Randomized Comparison of the Efficacy of Sirolimus Eluting Stent Versus Paclitaxel Eluting Stent in the Treatment of Long Native Coronary Lesions trial; PES = paclitaxel-eluting stent(s); PROSIT = Prospective Randomized Trial of Sirolimus- Versus Paclitaxel-Eluting Stents for the Treatment of Acute ST-Elevation Myocardial Infarction trial; REALITY = Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent (Cypher) and the Paclitaxel Eluting Stent (Taxus) trial; SES = sirolimus-eluting stent(s); SIRTAX = Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization trial.

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**Figure 1. Late Luminal Loss After SES and PES Implantation**

Late luminal loss after SES and PES implantation in trials with protocol mandated follow-up angiography. *In-segment instead of in-stent late luminal loss. Abbreviations as in Table 1.

**Figure 2. In-Stent Restenosis Rates of SES and PES**

In-stent restenosis rates of SES and PES in trials with protocol-mandated follow-up angiography. *In-segment instead of in-stent restenosis. Abbreviations as in Table 1.
In this issue of *JACC: Cardiovascular Interventions*, Novack et al. (14) present data of another large registry. The EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry included 6,035 unselected patients who underwent PCI with either SES (n = 3,443) or PES (n = 2,592) at 47 centers in the U.S. At 1-year follow-up, there was a significantly higher TLR rate for SES than for PES (4.4% vs. 3.3%, p = 0.020), which remained significant after adjustment for clinical, angiographic, and procedural characteristics. No significant differences between the 2 types of stents were found in terms of cardiac death, reinfarction, or stent thrombosis. Novack et al. (14) also investigated the impact of stent preference at the site level on clinical outcomes. This was done by dividing the 47 participating centers into 3 equal groups based on the proportion of DES implanted during the study period that were SES. Interestingly, after adjusting for site-level stent preference, the observed adjusted difference in TLR between SES and PES was no longer present. Operator and center preference for a specific treatment or device is an important confounder in retrospective analyses and registries. The finding of Novack et al. (14) emphasizes this and further underscores some of the fundamental limitations of registries.

In conclusion, there is no evidence that SES is associated with a relevant reduction in clinical recurrence as compared with PES. Further randomized controlled trials will be necessary to investigate the impact of new generation DES on clinical events.

Reprint requests and correspondence: Pieter J. Vlaar, Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, Thorax Center, 9713 AV Groningen, Groningen, the Netherlands. E-mail: p.j.j.vlaar@thorax.umcg.nl.

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