Prognostic factors in primary and elective percutaneous coronary intervention
Claessen, B.E.P.M.

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Chapter 16

Current Status of the XIENCEV Everolimus-Eluting Coronary Stent System

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Claessen BE, Caixeta A, Henriques JPS, Piek JJ
The introduction of drug-eluting stents has led to a marked reduction of restenosis, which is a major limitation of percutaneous coronary intervention for coronary artery disease. The next-generation Xience V® everolimus-eluting stent was designed to address the limitations of first-generation drug-eluting stents. The cobalt-chromium stent platform with an open-cell design offers excellent deliverability. Moreover, the combination of a thin fluoropolymer eluting the antirestenotic drug everolimus provides both an effective suppression of neointimal tissue and rapid reendothelialization above and between stent struts in preclinical studies. Large randomized clinical trials comparing the everolimus-eluting stent with the Taxus Express® and Liberté® paclitaxel-eluting stents have shown reduced rates of repeat revascularization, myocardial infarction, and stent thrombosis at one year follow-up with the everolimus-eluting stent. However, we will have to await long-term (five-year) data from these randomized clinical trials with the everolimus-eluting stent to determine whether the observed benefit is robust. Furthermore, data are currently limited on the clinical performance of the everolimus-eluting stent relative to drug-eluting stents other than the Taxus Express and Liberté paclitaxel-eluting stents, although a large number of trials are now being conducted to address these questions. In this review, we provide a comprehensive overview of (pre-)clinical studies with the everolimus-eluting stent.
Bare-metal stents (BMS) succeeded balloon angioplasty as the default treatment strategy for coronary artery disease in interventional cardiology in the early 1990’s. Bare metal stents successfully reduced the incidence of acute coronary artery closure, a common complication after balloon angioplasty. Furthermore, BMS reduced restenosis rates from 30-40% in the balloon angioplasty era to 20-25% by providing a mechanical scaffold to maintain radial support, minimizing elastic recoil.\textsuperscript{1,2} Subsequently, first-generation drug-eluting stents (DES) were designed to target in-stent restenosis caused by neoointimal hyperplasia. To this end, coronary artery stents were coated with a polymer allowing controlled local delivery of a pharmaceutical agent with antineoplastic and anti-inflammatory properties.

In the beginning of the 21\textsuperscript{st} century, a number of randomized trials proved DES to be effective in reducing the need for repeat coronary intervention to below 10%, leading to the approval of the sirolimus-eluting stent (SES, Cypher, Cordis, a Johnson & Johnson company, Warren, NJ) and the paclitaxel-eluting stent (PES, TAXUS, Boston Scientific, Natick, MA).\textsuperscript{3-7} Subsequently, DES replaced BMS in the majority of percutaneous coronary intervention (PCI) procedures. However, as the use of DES expanded beyond the well-studied indications of the randomized controlled trials, concern arose regarding the safety profile of the first-generation DES.\textsuperscript{8,9} After an initial case report describing 4 cases of late and very late stent thrombosis in first-generation DES, a large two-institution all-comers registry reported that late stent thrombosis occurs steadily at an annual rate of 0.4% to 0.6% for up to 4 years after stent implantation.\textsuperscript{10-12} Although late stent thrombosis in DES is higher compared with BMS, the attention to this matter has also taught us that late stent thrombosis may also occur in BMS, whether or not by a different mechanism. In addition, the attention for late stent thrombosis has also re-emphasized the matter of stent underexpansion in DES and any stent in general. Lessons from intravascular ultrasound and optical coherence tomography reports have greatly supported the importance of proper stent expansion.\textsuperscript{13,14} Another issue is that restenosis after DES can still occur, especially in patients with complex coronary artery disease. The three main components of DES (1, the stent platform 2, a polymer eluting the drug and 3, the drug) became the focus of further research and development to reduce the incidence of late stent thrombosis and DES restenosis. Although all DES currently marketed consist of the aforementioned basic components, their clinical effectiveness and safety profiles differ significantly. This review focuses on the everolimus-eluting stent (EES, Xience V, Abbott Vascular, Santa Clara, CA/Promus, Boston Scientific, Natick, MA), and appraises recently published long-term results of clinical trials and post-marketing registries.

**First-Generation Drug Eluting Stents**

**Sirolimus-eluting stents**

The Cypher SES is composed of the Bx velocity 316L stainless steel stent platform with a closed cell geometry, coated with a two-layer polyethylene-co-vinyl acetate and poly-n-butyl methacrylate polymer containing the drug sirolimus. The naturally occurring macrolide sirolimus has potent antiproliferative, anti-inflammatory and immunosuppressive effects and is also known as rapamycin, as it was first discovered to be produced by a bacterium in a soil sample from Easter Island (also known as Rapa Nui).\textsuperscript{15} The antirestenotic properties of sirolimus are shown schematically in figure 1. In short, by binding to the FK506-binding protein 12 (FKBP12), the sirolimus/FKBP12 complex causes the cell cycle to stop in the G1 phase through inhibition of the mammalian target of rapamycin (mTOR), an important cell cycle regulatory protein.\textsuperscript{16-18} Table 1 shows an overview of initial randomized studies which reported marked reduction of in-stent late loss and repeat revascularization rates with the Cypher SES relative to BMS.\textsuperscript{4,5,19-21} A patient-level pooled meta-analysis of these trials demonstrated that use of the Cypher SES compared with BMS resulted in persistent reduction of repeat revascularization without an increase in death, myocardial infarction, or stent thrombosis.\textsuperscript{23} Moreover, several post-marketing registries ascertained the safety and
efficacy of the SES in ‘real world use’.\textsuperscript{22-25} However, a number of in vitro studies showed unfavourable effects of sirolimus; by upregulating tissue factor and plasminogen activator inhibitor-1 sirolimus could theoretically have prothrombotic properties.\textsuperscript{26,27} Furthermore, concern exists about the deliverability of the SES, which is relatively poor compared to other DES due to its high strut- and polymer thickness and the closed cell stent strut geometry.

**Paclitaxel-eluting Stents**

The Taxus PES is based on a stainless-steel platform (either Express or the thinner-strut Liberté) with a 17.8µm-thick 3-layer polymer coating (Styrene-Isobutylene-Styrene) which elutes Paclitaxel. The drug is eluted in a biphasic manner by the polymer, during the first 48 hours after implantation an early burst release is produced followed by a slow release for the subsequent 10 days.\textsuperscript{3} Figure 1 shows the antirestenotic properties of paclitaxel, a lipophilic molecule derived from the Pacific yew tree *Taxus brevifolia*; by stabilizing the microtubules in the mitotic phase of the cell cycle, the drug inhibits smooth muscle cell proliferation and migration. However, as with sirolimus, a number of prothrombotic effects (upregulation of tissue factor and plasminogen activator inhibitor-1) have been demonstrated in vitro.\textsuperscript{26,28}

The TAXUS trials assessed the safety and efficacy of the Taxus PES in the treatment of coronary artery disease.\textsuperscript{3,7,29-32} Table 1 shows short- and long-term outcomes from the large-scale TAXUS IV and V trials, comparing the Taxus Express PES with an uncoated but otherwise identical BMS.\textsuperscript{6,30,32,33} The TAXUS ATLAS trials reported noninferiority of the next-generation TAXUS Liberté PES to a historical cohort of the TAXUS Express PES from the TAXUS IV and V trials.\textsuperscript{34,35} The TAXUS Liberté PES was subsequently approved by the United States Food and Drug Administration (FDA) in 2008. The polymer and drug coating on the TAXUS Liberté is identical to that of the TAXUS Express. However, TAXUS Liberté is based upon the thinner-strut VeriFLEX stent platform (97µm vs. 132µm). The next evolution of the PES, the TAXUS Element stent which uses a thin-strut (81 µm) platinum chromium stent platform is currently undergoing clinical evaluation. Preliminary data suggested that the TAXUS element was non-inferior to the TAXUS Express in terms of clinical, safety, and angiographic endpoints.\textsuperscript{36}

**Next-Generation Drug-Eluting Stents**

**Zotarolimus-Eluting Stents**

The zotarolimus-eluting stent (ZES, Endeavor or Endeavor resolute, Medtronic, Santa Rosa, CA) is based on the cobalt-chromium Driver stent platform, coated with a biomimetic non-erodable polymer (Endeavor: phosphorylcholine, Endeavor Resolute: Biolinx) in order to minimize the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Short and Long-Term Event rates with Cypher sirolimus-eluting stents and Taxus paclitaxel-eluting stents from major randomized clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized trials with the Cypher SES</strong></td>
<td><strong>Randomized trials with the TAXUS PES</strong></td>
</tr>
<tr>
<td><strong>RAVEL</strong>\textsuperscript{4}</td>
<td><strong>TAXUS IV</strong>\textsuperscript{7}</td>
</tr>
<tr>
<td>Year</td>
<td>2002</td>
</tr>
<tr>
<td>DES</td>
<td>120</td>
</tr>
<tr>
<td>BMS</td>
<td>118</td>
</tr>
<tr>
<td>follow-up</td>
<td>1 year</td>
</tr>
<tr>
<td>In-stent late loss (mm)</td>
<td>0.01 vs. 0.33*</td>
</tr>
<tr>
<td>(DES vs. BMS)</td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>0.0% vs 22.9%</td>
</tr>
<tr>
<td>(DES vs. BMS)</td>
<td>4.1% vs. 16.6%</td>
</tr>
</tbody>
</table>

DES= Drug-eluting stent, BMS= Bare metal stent, TLR= Target lesion revascularization, MI= Myocardial infarction, SES= Sirolimus-eluting stent, PES= Paclitaxel-eluting stent n.a.= not available *angiographic follow-up in RAVEL was obtained at 6-month follow-up.
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<table>
<thead>
<tr>
<th>Year</th>
<th>Follow-up</th>
<th>In-stent late loss (mm) (DES vs. BMS)</th>
<th>TLR (DES vs. BMS)</th>
<th>MI (DES vs. BMS)</th>
<th>Death (DES vs. BMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVEL</td>
<td>2002</td>
<td>-0.01 vs. 0.33*</td>
<td>0.0% vs 22.9%</td>
<td>3.3% vs. 4.2%</td>
<td>1.7% vs. 1.7%</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>2003</td>
<td>0.17 vs. 1.00</td>
<td>4.1% vs. 16.6%</td>
<td>2.8% vs. 3.2%</td>
<td>1.1% vs. 0.6%</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>2003</td>
<td>0.20 vs. 1.05</td>
<td>4.0% vs. 20.9%</td>
<td>4.6% vs. 2.3%</td>
<td>1.1% vs. 0.6%</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>2004</td>
<td>0.12 vs. 0.79</td>
<td>4.0% vs. 18.0%</td>
<td>2.0% vs. 4.0%</td>
<td>0.0% vs. 0.0%</td>
</tr>
<tr>
<td>TAXUS IV</td>
<td>2003</td>
<td>0.39 vs. 0.92</td>
<td>3.0% vs. 11.3%</td>
<td>9.1% vs. 20.5%</td>
<td>1.4% vs. 1.1%</td>
</tr>
<tr>
<td>TAXUS V</td>
<td>2005</td>
<td>0.49 vs. 0.90</td>
<td>8.6% vs. 15.7%</td>
<td>5.4% vs. 4.6%</td>
<td>1.3% vs. 1.4%</td>
</tr>
</tbody>
</table>

DES = Drug-eluting stent, BMS = Bare metal stent, TLR = Target lesion revascularization, MI = Myocardial infarction, SES = Sirolimus-eluting stent, PES = Paclitaxel-eluting stent n.a. = not available *angiographic follow-up in RAVEL was obtained at 6-month follow-up.

In-stent late loss was significantly higher in patients treated with the Endeavor ZES in the ENDEAVOR III and IV trials, which compared the Endeavor ZES to the Cypher SES and the Taxus PES, respectively. In both trials, clinical event rates were similar between the ZES and its control groups. However, these trials were underpowered to detect differences in clinical endpoints. In the near future, the large-scale (n=8800) “Patient Related OuTcomes with Endeavor versus Cypher stenting Trial” (PROTECT) will provide definitive answers about the relative safety and efficacy of the Endeavor ZES and Cypher SES.

An updated version of the ZES, the Endeavor Resolute which is coated with a different polymer that facilitates longer and more effective drug elution received Conformité Européenne (CE) approval in 2007. The Endeavor Resolute ZES is currently being investigated in a number of clinical trials.

Figure 1. Antirestenotic properties of Sirolimus and Paclitaxel

- **Sirolimus/EVEROLimus**
- **FKBP12**
- **β-tubulin subunit of microtubules**
- **Paclitaxel**

<table>
<thead>
<tr>
<th>MI (DES vs. BMS)</th>
<th>Death (DES vs. BMS)</th>
<th>TLR (DES vs. BMS)</th>
<th>5-year follow-up MI (DES vs. BMS)</th>
<th>Death (DES vs. BMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3% vs. 4.2%</td>
<td>1.7% vs. 1.7%</td>
<td>(pooled meta-analysis)</td>
<td>9.6% vs. 24.7%</td>
<td>7.9% vs. 6.8%</td>
</tr>
<tr>
<td>2.8% vs. 3.2%</td>
<td>0.9% vs. 0.6%</td>
<td></td>
<td>7.9% vs. 6.8%</td>
<td>8.9% vs 8.2%</td>
</tr>
<tr>
<td>4.6% vs. 2.3%</td>
<td>1.1% vs. 0.6%</td>
<td></td>
<td>9.1% vs. 20.5%</td>
<td>7.2% vs. 7.4%</td>
</tr>
<tr>
<td>2.0% vs. 4.0%</td>
<td>0.0% vs. 0.0%</td>
<td></td>
<td>10.0% vs. 11.2%</td>
<td></td>
</tr>
<tr>
<td>3.5% vs. 3.7%</td>
<td>1.4% vs. 1.1%</td>
<td></td>
<td>9.3% vs. 5.6%</td>
<td>10.2% vs. 8.5%</td>
</tr>
<tr>
<td>5.4% vs. 4.6%</td>
<td>1.3% vs. 1.4%</td>
<td></td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 16

Biolimus A9-Eluting Stents

The biolimus A9-eluting stent (BES, Biomatrix flex, Biosensors International, Singapore or Nobori, Terumo, Japan) consists of a stainless-steel stent platform (Nobori: S-stent platform, Biomatrix flex: Bioflex stent platform), coated on the abluminal side only with a biodegradable polylactic acid/biolimus A9 polymer/drug matrix. The very lipophilic sirolimus-analogue biolimus A9 was designed specifically to be used on DES. The polylactic acid polymer is biodegradable and breaks down into carbon dioxide and water concurrent with drug release in 6-9 months after stent implantation. The feasibility of biolimus A9 as a stent-delivered drug to reduce neointimal hyperplasia was established in the first-in-man “Stent Eluting A9 bioLimus Trial in Humans” (STEALTH) trial. The STEALTH trial randomized 120 patients with a single de novo coronary artery lesion in a 2:1 manner to BES or BMS. In-stent late loss was 0.26mm in the BES group and 0.74mm in the BMS group (p<0.01). Subsequently the non-inferiority of the BES relative to the SES was established in the “Limus Eluted from A Durable versus ERodable Stent coating” (LEADERS) trial. This 1707-patient “all-comer” trial randomized 857 unselected patients to BES and 850 patients to SES. The 9-month MACE (a composite of cardiac death, MI and TVR) rate was 9% in the BES group and 11% in the SES group. At two years follow-up, the MACE rates were 13.0% in the BES group and 15.4% in the SES group, follow-up will continue up to five years.

XIENCE V® everolimus-eluting stent

Everolimus (Certican, Novartis Corporation), a sirolimus analogue, is an immunosuppressive macrolide acting as an mTOR inhibitor after binding to FKBP12 (figure 1). As a result, several cell types (e.g. vascular smooth muscle cells) are arrested in the G1 phase of the cell cycle. Oral administration of everolimus has been studied in renal, lung and heart transplant recipients, proving it effective in preventing graft rejection and cardiac allograft vasculopathy.

To determine the optimal concentration of everolimus on the EES, three formulations were compared against an identical bare-metal stent control in a porcine coronary artery model; 100 µg/cm² with 80% release at 28 days, 200 µg/cm² with 80% release at 28 days and 260 µg/cm² with 80% release at 60 days. The neointimal response was equally reduced by all three formulations, after which the lowest evaluated effective dose (100µg/cm²) was chosen for the Xience V EES.

Polymer

The co-polymer used in the EES consists of a primer layer and a drug-polymer reservoir layer with no topcoat. Poly-n-butyl methacrylate (PBMA) is used as a thin primer adhesion layer and the drug-polymer reservoir layer consist of polyvinylidene fluoride-co-hexafluoropropylene blended with everolimus in a 83/17 polymer/everolimus ratio by weight. The co-polymer is approximately 8µm thick and is coated at both the luminal and abluminal surface of the stent. It is lubricious and nonsticky, minimizing unwanted adhesion to the stent delivery balloon and between struts. The Figure 2 Scanning electron images of the Xience V stent crimped onto the delivery balloon (left) and of an expanded Xience V stent strut (right)
co-polymer on the EES releases approximately 25% of everolimus on the first day after implantation, 80% of the drug is released after 30 days and the drug is completely eluted after 4 months.\textsuperscript{49}

**Stent Platform**

The EES is based on the thin-strut (81 µm) cobalt chromium alloy Multi-LinkVision stent platform. Figures 2 and 3 show scanning electron microscopy pictures of the Xience V EES stent surface. The use of cobalt chromium alloy allows for thinner strut thickness with similar radiopacity and radial strength compared to 316L stainless steel stents. Thinner strut thickness is associated with reduced in-stent late loss and repeat revascularization.\textsuperscript{51-53} Furthermore, thinner struts allow for a lower device profile, which has a beneficial impact on device delivery characteristics. The Multi-Link Vision stent is fabricated from a single piece of L-605 cobalt chromium and has an open-cell design with nonlinear links to make it flexible and conformable to the vessel wall. The stent delivery balloon is short tapered to minimize vessel injury outside the stent during implantation. An evolution of the original Xience V EES called Xience Prime, which uses the same polymer and drug on the new Multi-Link 8 stent platform designed for superior deliverability has recently received Conformité Européenne (CE) approval.\textsuperscript{101}

**Preclinical Experience with the Everolimus-Eluting Stent**

Incomplete endothelialization of stent struts after first-generation DES implantation has been associated with the occurrence of late stent thrombosis.\textsuperscript{54,55} Joner et al. compared trends in endothelial coverage among SES, PES, ZES, EES and BMS in a rabbit iliac artery model.\textsuperscript{56} The stents were harvested at 14 or 28 days after implantation and endothelialization was assessed by en face scanning electron microscopy. In this study, varying rates of endothelial coverage were observed, most notably at 14 days when above struts coverage was ≤30% in SES, PES and ZES compared to 64% in EES, and 80% in BMS. At 28 days, no significant differences were observed, likely due to accelerated rates of arterial healing in rabbits compared to humans. This study suggested a superior safety profile for the EES compared to other DES types.

**Clinical Trials with the Everolimus-Eluting Stent**

**FUTURE I and II**

The “First Use To Underscore Restenosis reductions with Everolimus” (FUTURE) I and II trials were the first clinical experience with stent based delivery of everolimus. The EES used in these trials was a 316L stainless steel stent, coated only on the abluminal surface with a biodegradable polymer/drug matrix consisting of polylactic acid and everolimus. A similar version of this stent using the same stent platform and biodegradable polymer but with the sirolimus-analogue biolimus A9 instead of everolimus underwent further clinical testing (Biomatrix Flex, Biosensors International, Singapore/ Nobori, Terumo, Japan).

The FUTURE I trial enrolled 42 patients who were randomized in a 2:1 fashion to either EES or BMS. At 6-month angiographic follow-up, in-stent late loss (0.11mm vs. 0.85mm, p<0.01) was significantly reduced with the EES compared with the BMS.\textsuperscript{57} Tsuchiya et al. reported a pooled analysis of the FUTURE I and II trials which randomized 107 de novo coronary artery lesions to treatment with either EES (49 lesions) or BMS (58 lesions).\textsuperscript{58} They reported that the EES with bioabsorbable polymer was efficacious in reducing in-stent neointimal hyperplasia and binary angiographic restenosis regardless of vessel size.

**SPIRIT FIRST**

The SPIRIT first trial was the first-in-man trial of the Xience V EES. A total of 60 patients with a single de novo native coronary artery lesion were randomized to receive a 3.00x18mm EES (28 patients) or an identical uncoated BMS (32 patients).\textsuperscript{59} The primary endpoint was 6-month in-stent late loss as determined by quantitative angiography. The secondary clinical endpoint was a composite of cardiac death, MI, or ischemia-driven target vessel revascularization. The EES was
superior in reducing 6-month in-stent late loss compared to BMS (0.10mm vs 0.87mm, \( p<0.01 \)). Moreover, the incidence of the composite clinical endpoint was 7.7% in the EES arm compared to 21.4% in the BMS arm at 6 months.

Tsuchida et al. reported the one-year follow-up of the SPIRIT first trial. At one-year angiographic follow-up, in-stent late loss was 0.24 mm in the EES arm and 0.84mm in the BMS arm (\( p<0.01 \)). The incidence of the composite clinical endpoint was 15.4% in the EES arm and 21.4% in the BMS arm. The five-year follow-up of the SPIRIT first trial has recently been published. Between one and five years, no additional death, MI, TLR or TVR events were observed in the EES arm. However, as this is currently the only trial providing five-year follow-up data for the EES, no definitive statements can be made about the long-term safety and efficacy of the EES.

SPIRIT II

The SPIRIT II trial was a multicenter trial, randomizing 300 patients in a 3:1 manner to the Xience V EES or the Taxus (Express or Liberté) PES in 28 sites (located in Europe, India, and New Zealand). Patients in the SPIRIT II trial had somewhat more complex lesions compared to patients in the SPIRIT first trial; up to two de novo native coronary artery lesions which had to be located in different major epicardial vessels with a reference diameter between 2.5 and 4.25mm and a lesion length ≤28mm. The trial was powered to detect non-inferiority in terms of 6-month in-stent late loss. However, the EES was in fact superior to the PES regarding in-stent late loss (0.11mm vs. 0.36mm, \( P<0.01 \)). A late “catch up” in terms of in-stent late loss was observed in the EES arm in a subgroup of 152 patients who underwent repeat angiography at 2-years follow-up. At 2 years, in-stent late loss was similar in the EES arm and the PES arm (0.33mm vs. 0.34mm, \( P=0.84 \)). The late “catch up” in terms of late-loss was not accompanied by an increase in TLR. On the contrary, Garg et al. reported a trend towards lower major adverse cardiac events (cardiac death, MI or ischemia-driven TLR) in the EES arm (7.2% vs 15.9% \( p=0.05 \)) at three-year follow-up in the SPIRIT II trial. The clinical significance of this late “catch up” phenomenon remains to be determined until long-term follow-up in a large number of patients has been reported.

SPIRIT III

The Spirit III trial randomized 1002 patients with de novo native coronary artery disease to Xience V EES or Taxus Express PES in a 2:1 fashion in the United States (US). Inclusion criteria were similar to those for the out-of-US SPIRIT II trial, however the SPIRIT III included patients with a reference vessel between 2.5 and 3.75 mm. The primary endpoint was in-segment late-loss at 8-month angiographic follow-up. The major secondary endpoint was target vessel failure (TVF, a composite of cardiac death, MI attributable to the treated vessel, or clinically indicated TVR). The angiographic results confirmed the findings in the SPIRIT II trial, the EES was superior to the PES at 8 months in terms of in-segment (0.14mm vs 0.26mm, \( p<0.01 \)) and in-stent late loss (0.16mm vs. 0.30mm, \( p<0.01 \)). At one year, the TVF rate was 8.6% in the EES arm compared with 11.3% in the PES arm (\( p=0.20 \)), and ARC definite/probable stent thrombosis rates were 1.1% in the EES arm and 0.6% in the PES arm (\( p=0.73 \)). At three year follow-up, the TVF rates in both stent arms diverged further, and became statistically significant (EES 14.3% vs. PES 20.0%, \( p=0.03 \)). Moreover, rates of ARC defined very late definite/probable stent thrombosis were low (EES 0.3% vs. PES 1.0%, \( p=0.34 \)).

The SPIRIT III 4.0mm registry was a concurrent arm of the SPIRIT III trial consisting of 69 nonrandomized patients treated with a 4.0mm EES. The angiographic and clinical results from the SPIRIT III 4.0mm registry mirrored those from the randomized SPIRIT III trial. In-segment late loss at 8 months was 0.17mm in the 4.0mm EES arm compared to 0.26mm in the randomized PES arm and 0.14mm in the randomized EES arm (reference vessel diameter 2.25-3.75mm). The one-year TVF rate in the 4.0mm EES arm was 5.9% compared with 11.3% in the randomized PES arm and 8.6% in the randomized EES arm.
SPIRIT IV

The large-scale SPIRIT IV trial was powered to prove superiority of the Xience V EES over the Taxus Express PES in terms of the primary clinical endpoint of ischemia-driven target lesion failure (TLF, a composite endpoint of cardiac death, MI attributable to the target vessel, or clinically indicated TLR) at one-year follow-up.68 A total of 3690 patients were randomized in a 2:1 fashion to either the EES or the PES, randomization was stratified according to diabetes mellitus status and presence of complex lesions. Patients had up to three de novo native coronary artery lesions, with a lesion length ≤28mm and a reference vessel diameter between 2.5-3.75mm, with a maximum of 2 lesions per major epicardial vessel. Unlike the previous SPIRIT trials, no angiographic follow-up was mandated by the SPIRIT IV trial protocol.

The mean age of patients in SPIRIT IV was 63 years, and 32% had diabetes mellitus. The EES was superior over the PES in terms of the primary endpoint; one-year TLF was 4.2% in the EES group compared to 6.8% in the PES group (p<0.01). This difference was due to significantly lower rates of ischemia-driven TLR (2.5% vs. 4.6%, p<0.01) and MI (1.9% vs. 3.1%, p=0.02) in the EES group at one year. Moreover, the incidence of definite/probable stent thrombosis according to the Academic Research Consortium (ARC) definition was significantly lower in the EES group (0.3% vs. 1.1%, p<0.01). However, no significant differences in terms of TLF were observed in the 1140-patient subgroup with diabetes mellitus (EES 6.4% vs. PES 6.9%, p=0.80). The five-year results of this trial will have to be awaited in order to determine if the clinical superiority of the EES over the PES is robust.

SPIRIT V Diabetic Randomized Controlled Trial

The SPIRIT V diabetic randomized controlled trial randomized 324 patients with diabetes mellitus in a 2:1 ratio to either the Xience V EES (n=218) or the TAXUS Express PES (n=106). Patients had to be suitable to be optimally treated with a maximum of 4 planned stents and should have a maximum of one de novo target lesion per native major epicardial vessel. This study established superiority of the EES to the PES in patients with diabetes mellitus in terms of the primary endpoint of in-stent late loss at 9-months angiographic follow-up (0.19mm vs 0.39mm, p<0.01). At one year follow-up, there were no differences in the occurrence of TLF in both groups (EES 11.2% vs PES 12.5%, p=0.71). No stent definite/probable stent thromboses were observed in the EES group compared with 2 (1.9%) in the PES group.70

COMPARE

As opposed to the previous trials, the investigator-initiated COMPARE trial randomized 1800 consecutive, unselected “all-comer” patients to treatment with either EES or TAXUS Liberté PES.71 The primary endpoint was a composite of all-cause mortality, non-fatal MI and TVR at one year. As in the SPIRIT IV trial, there was no angiographic follow-up. The median age of patients in COMPARE was 63 years, 18% of patients had diabetes mellitus, and 60% of patients were treated for an acute coronary syndrome (12% unstable angina, 23% non-ST elevation MI, and 25% ST-elevation MI). The COMPARE trial confirmed the results from the SPIRIT IV trial; at one year the primary composite endpoint had occurred in 6% of the EES arm and in 9% of the PES arm (p=0.02). This difference was due to significant reductions in TVR (2% vs 6%) and MI (3% vs 5%, p<0.01) in the EES arm. As in SPIRIT IV, ARC definite/probable stent thrombosis was significantly less in the EES arm (0.7% vs 3%, p<0.01). Follow-up of the all-comer COMPARE trial will continue up to five years.

RESOLUTE All-Comers

This “all-comer” trial randomized 2300 consecutive, unselected patients to treatment with either the EES (n=1150) or the Resolute ZES (n=1150).72 This trial was powered to detect non-inferiority of the ZES to the EES in terms of TLF at one-year follow-up. A total of 23% of patients in RESOLUTE All-Comers had diabetes mellitus, 30% of patients were treated for an acute MI. Compared with the Resolute ZES group, patients in the Xience V EES group had a higher mean number of stents (2.0±1.3 vs. 1.9±1.2, p=0.02) and a longer mean stent length (37.0±25.6mm vs. 34.4±24.5mm, p=0.02). At one year follow-up, the EES group had lower rates of ischemia-driven target lesion failure (4.2% in EES vs 6.8% in ZES, p<0.01). This was driven by lower rates of ischemia-driven TLR (2.5% vs 4.7%, p<0.01) and MI (2.0% vs 4.4%, p<0.01) in the EES group. The incidence of definite/probable stent thrombosis was similar (0.3% vs 0.3%, p=0.80). Follow-up will continue up to five years.
year follow-up the EES and ZES had similar rates of the primary endpoint of TLF (8.2% vs 8.3%, p for non-inferiority <0.01). However, the incidence of definite stent thrombosis was significantly higher in the ZES group compared with the EES group (1.2% vs 0.3%, p=0.01).

**ISAR-TEST 4**

The ISAR-TEST-4 trial was performed to assess the non-inferiority of a biodegradable polymer SES (BP-SES) compared with the permanent polymer Cypher SES and Xience V EES. Interestingly, this is currently the only randomized comparison between the Cypher SES and Xience V EES. In total, 2603 patients with de novo native coronary artery disease were randomized to the BP-SES (n=1299), SES (n=652), or EES (n=652). This trial allowed the randomization of relatively complex patients and lesions; 29% had diabetes mellitus, 40% were treated for an acute coronary syndrome, 5.2% had a chronic total occlusion, and 17% had ostial lesions. The ISAR-TEST-4 investigators reported no differences in the primary endpoint (a composite of cardiac death, MI related to the target vessel or target lesion revascularization) which occurred in 13.8% in the BP-SES group, 15.2% in the SES group and 13.6% in the EES group at one year.

**Observational Studies with the Everolimus-Eluting Stent Rotterdam**

Onuma et al. recently reported the 6-month results from the “Xience V Stent Evaluated at Rotterdam Cardiac Hospital” (X-SEARCH) registry. A total of 649 consecutive unselected patients treated with EES were enrolled in this registry. The 6-month incidence of MACE (defined in this trial as a composite of all-cause mortality, MI or TVR) in the EES group was compared to historical cohorts of patients treated with BMS (n=450), SES (n=508), and PES (n=576). Patients in the EES cohort were older, presented more frequently with MI, and had more complicated lesions compared with the other cohorts. The unadjusted 6-month MACE rates were 9.2%, 7.3%, 9.9% and 10.4% in the EES, SES, PES and BMS groups, respectively. After multivariate analysis the adjusted 6-month MACE rate in the EES cohort (5.5%) was similar to that in the SES cohort (6.1%) and superior to those in the PES (8.6%) and BMS (11.0%) cohorts. The 6-month incidence of ARC definite stent thrombosis was similar among the groups, 0.6%, 0.6%, 1.4%, and 2.0%, in the EES, SES, PES, and BMS cohorts respectively.

**Table 2** Differences in stent design between various drug-eluting stents

<table>
<thead>
<tr>
<th>Stent Material</th>
<th>Strut thickness</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cypher SES</strong>4</td>
<td>316L stainless steel</td>
<td>140µm</td>
</tr>
<tr>
<td><strong>Taxus PES</strong>3</td>
<td>316L stainless steel</td>
<td>Express: 132µm, Liberté: 97µm, Element: 81µm</td>
</tr>
<tr>
<td><strong>Endeavor ZES</strong>37</td>
<td>L-605 cobalt chromium alloy</td>
<td>91µm</td>
</tr>
<tr>
<td><strong>Xience V/ Xience Prime / Promus EES</strong>39</td>
<td>L-605 cobalt chromium alloy (Xience V/Promus: Multi-Link Vision, Xience Prime: Multi-Link-8)</td>
<td>81µm</td>
</tr>
<tr>
<td><strong>Biomatrix Flex/ Nobori BES</strong>41</td>
<td>316L stainless steel (Nobori: S-stent, Biomatrix Flex: BioFlex stent)</td>
<td>112µm</td>
</tr>
</tbody>
</table>

SES= Sirolimus-eluting stent, PES= Paclitaxel-eluting stent, ZES= Zotarolimus-eluting stent, BES= Biolimus A9-eluting stent. PC= phosphorylcholine
### Milan

Between October 2006 and February 2008, 345 patients with 573 lesions were treated with an EES at the Centro Cuore Columbus in Milan, Italy. The mean age in this cohort was 65 years, 29% had diabetes mellitus, and 77% had multivessel disease. Mean lesion length was 13.6mm, and the mean reference vessel diameter was 2.74mm. At a median follow-up of 378 days, 2.3% of patients died, 2.1% had a MI, and 7.9% underwent TLR. Furthermore, a total of 3 patients (0.9%) had a definite/probable stent thrombosis. The results from this observational study mirror those from randomized trials, confirming the safety and efficacy of the EES.

### SPIRIT V registry

The SPIRIT V registry is a post-marketing registry that included 2,700 patients (3,645 lesions) with de novo coronary artery disease that was suitable to be optimally treated with a maximum of 4 EES. Therefore, this registry enrolled somewhat less complex patients relative to the Rotterdam and Milan cohorts, but more complex than the SPIRIT randomized trials. Mean age was 63 years, 30% had diabetes mellitus, and 82% of lesions were ACC type B2/C. Mean lesion length was 15.6mm and mean reference vessel diameter was 2.97mm. The one-year TLF rate was 5.1%, 1.7% of patients had died, 3.5% had an MI, and 1.8% had undergone TLR. The definite/probable stent thrombosis rate was 0.66% at one year. These results compare favorably to the results from the Milan and Rotterdam experience, which is likely due to the lower patient and lesion complexity in SPIRIT V.

### Expert Commentary

The SPIRIT and COMPARE trials have provided insight into the clinical safety and efficacy of the Xience V EES relative to the Taxus PES. However, every type of DES has its own unique design characteristics (table 2). For example, the ZES has a biomimetic durable polymer, designed to minimize thrombogenicity. The BES has a biodegradable polymer that is only applied to the abluminal surface, theoretically minimizing drug release to the blood stream. Randomized comparisons between the Xience V EES and DES other than the TAXUS PES are currently scarce, and it is therefore not possible to make any definite statements regarding the clinical performance of the Xience V EES relative to other DES. Currently several other randomized clinical trials are being conducted to

<table>
<thead>
<tr>
<th>Polymer thickness</th>
<th>Drug concentration</th>
<th>Drug release kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>14µm</td>
<td>1.4 µg/mm²</td>
<td>80% within 30 days, followed by gradual release in subsequent months</td>
</tr>
<tr>
<td>17.8µm</td>
<td>1µg/mm²</td>
<td>Burst release in the first 48 hours after implantation, slow release over the next 10 days</td>
</tr>
<tr>
<td>4µm (PC, Endeavor)</td>
<td>1.6µg/mm²</td>
<td>100% within 28 days (Endeavor) 85% within 60 days, 100% after 6 months (Endeavor Resolute)</td>
</tr>
<tr>
<td>8µm</td>
<td>1µg/mm²</td>
<td>80% within 30 days, 100% after 4 months</td>
</tr>
<tr>
<td>15µm (abluminal side only)</td>
<td>15.6µg/mm</td>
<td>Burst release post-implantation, gradual release up to 6-9 months</td>
</tr>
</tbody>
</table>
evaluate the relative efficacy of the Xience V and/or Xience Prime EES vs. various other DES. (Table 3) Moreover, at this time, long-term (5-year) data on the EES are only available for the very small SPIRIT FIRST trial. To evaluate the long-term safety and efficacy of the EES, long-term follow-up of larger trials is needed.

Five-Year View
In five years, we expect that the Xience Prime EES will have succeeded the Xience V EES. As mentioned before, a large number of clinical trials are currently investigating this version of the EES using the same polymer and drug combination on the new Multi-Link 8 stent platform. Of note is the “Evaluation of Xience prime versus Coronary artery bypass grafting for Effectiveness of Left main revascularization” (EXCEL) trial; instead of conventional head-to-head DES trials, EXCEL will compare the efficacy of the Xience Prime EES against coronary artery bypass graft surgery (CABG) in the treatment of left main disease. A recently published meta-analysis suggested that the “synergy between PCI with TAXUS and cardiac surgery (SYNTAX)” trial, which found that PCI with PES was inferior to CABG, entirely due to an increased rate of repeat revascularization in the PES arm, could have met its primary endpoint of the EES was used instead of the PES. 

Finally, a fully bioabsorbable EES is currently under investigation. The safety and feasibility of the fully bioabsorbable EES (also called bioabsorbable vascular scaffold) was established in the ABSORB trial. The ABSORB trial enrolled 30 patients with a single de novo native coronary artery lesion. All patients were treated with a bioabsorbable EES. At 6-month follow-up angiography, in-stent late loss was 0.44mm, mainly due to a mild reduction of stent area. At 1 year, only one adverse event had occurred, one patient (3.3%) had a MI. At 2 years after implantation, the stent was bioabsorbed and vasomotion was restored. Moreover, no additional adverse events had occurred and in-stent late loss remained stable (0.48mm). Although these first results in this selected low-risk patient population are promising, additional trials will be needed to confirm the clinical safety and efficacy of the fully bioabsorbable EES.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Number of patients</th>
<th>Comparator</th>
<th>Inclusion criteria (selected)</th>
<th>Powered for</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Xience V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPIRIT WOMEN registry</td>
<td>1550</td>
<td>SES</td>
<td>up to four de novo native coronary artery lesions</td>
<td>Clinical endpoints</td>
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<td>SPIRIT WOMEN</td>
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<td>randomized substudy</td>
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<td>RESET</td>
<td>3200</td>
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<td>all-comers</td>
<td>Clinical endpoints</td>
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<tr>
<td>SORT OUT IV</td>
<td>2678</td>
<td>SES</td>
<td>de novo native coronary artery lesions</td>
<td>Clinical endpoints</td>
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<tr>
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<td>all-comers</td>
<td>Angiographic endpoints</td>
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<tr>
<td>COMPARE 2</td>
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<td>Noboritm BES Resoluteitm ZES</td>
<td>all-comers</td>
<td>Clinical endpoints</td>
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<tr>
<td>TWENTE</td>
<td>1380</td>
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<td></td>
<td>Clinical endpoints</td>
</tr>
<tr>
<td>With Xience Prime</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>EXCEL</td>
<td>2500</td>
<td>CABG</td>
<td>Left main/ multivessel disease Up to two de novo</td>
<td>Clinical endpoints</td>
</tr>
<tr>
<td>SPIRIT PRIME</td>
<td>500</td>
<td>none</td>
<td>native coronary artery lesions</td>
<td>Clinical endpoints</td>
</tr>
</tbody>
</table>

SES= Sirolimus-eluting stent, BES= Biolimus-eluting stent, ZES= Zotarolimus-eluting stent, CABG= Coronary artery bypass grafting
CONCLUSION

The EES is a next-generation DES which has been shown to be superior in terms of efficacy and safety to the first-generation PES, at least up to one-year follow-up. Longer-term follow-up of large randomized controlled trials are needed to determine whether this benefit with the EES is sustained or increased. Currently, the EES is the most widely used DES worldwide and is considered the benchmark for newer-generation DES with ever-evolving stent designs to optimize safety and efficacy.

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Website reference