Intravascular Ultrasound Results From the NEVO ResElution-I Trial

A Randomized, Blinded Comparison of Sirolimus-Eluting NEVO Stents With Paclitaxel-Eluting Taxus Liberté Stents in De Novo Native Coronary Artery Lesions

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Background—The NEVO sirolimus-eluting stent (NEVO SES) is a novel cobalt-chromium stent combining sirolimus release from reservoirs with bioabsorbable polymer to reduce spatial and temporal polymer exposure. The aim of this study was to assess the arterial response to the NEVO SES in a randomized, blinded comparison versus the surface-coated TAXUS Liberté paclitaxel-eluting stent (TAXUS Liberté PES) in human native coronary lesions using intravascular ultrasound (IVUS).

Methods and Results—The NEVO ResElution-I IVUS substudy enrolled 100 patients (1:1 randomization). In addition to standard IVUS variables, uniformity of neointimal distribution within stents was evaluated in 3 dimensions by computing mean neointimal thickness within 12 equally spaced radial sectors on every 1-mm cross section along the stented segment. The NEVO SES showed significantly less neointimal proliferation (neointimal obstruction: 5.5±11.0% versus 11.5±9.7%, P=0.02), resulting in less late lumen area loss and smaller maximum cross-sectional narrowing at 6 months. The absolute variability of neointima distribution, assessed by the standard deviation of neointimal thickness within each stent, was significantly reduced with the NEVO SES compared with the TAXUS Liberté PES (0.04±0.04 mm versus 0.10±0.07 mm, P<0.0001). TAXUS Liberté PES showed significantly greater positive vessel remodeling than the NEVO SES (Δvessel volume index: 1.30±1.36 mm³/mm versus 0.36±0.63 mm³/mm, respectively, P=0.003).

Conclusions—The NEVO SES with focal release of sirolimus from reservoirs achieved significantly greater and more consistent suppression of neointimal hyperplasia than the surface-coated TAXUS Liberté PES. This was associated with less positive remodeling and no increased morphological or morphometric abnormalities surrounding the stent or at the stent margins.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00714883.

(Circ Cardiovasc Interv. 2011;4:146-154.)

Key Words: NEVO stent ■ paclitaxel-eluting stent ■ sirolimus-eluting stent ■ biodegradable polymer ■ volumetric IVUS analysis

Drug-eluting stents (DES) with controlled drug release from durable polymer surface coatings have achieved a significant reduction of angiographic restenosis compared with bare metal stents. Previous reports, however, have raised concerns regarding a higher incidence of late stent thrombosis, prolonged endothelial dysfunction, and a possibility of delayed neointimal proliferation after DES implantation compared with conventional bare metal stents. Although the causes of these phenomena may be multiple, previous investigators have implicated the durable polymer, which covers the entire surface of most DES. The NEVO sirolimus-eluting coronary stent (NEVO SES) (Cordis Cor-
Corporation, Bridgewater, NJ) is a new cobalt-chromium alloy stent platform that incorporates unique reservoir technology and a bioabsorbable polylactic-coglycolic acid (PLGA) polymer. These design elements, accomplished by creating multiple laser-cut reservoirs and then filling them with a blend of sirolimus and a bioabsorbable polymer, reduce the amount of tissue exposed to the polymer. Absorption within approximately 3 months limits the duration of vessel wall exposure to the polymer. Thereafter, only a biologically inert bare metal platform remains.

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This study is the first report investigating the midterm arterial response to this new drug-delivery technology using an intravascular ultrasound (IVUS) substudy of the NEVO ResElution-I trial, a randomized, blinded comparison of the NEVO SES versus the TAXUS Liberté paclitaxel-eluting stent (TAXUS Liberté PES) (Boston Scientific Corporation, Natick, MA) in human de novo native coronary lesions.

Methods

Study Design, Population, and Antiplatelet Therapy

The NEVO ResElution-I study was a multicenter, prospective, single-blind, 1:1 randomized study designed to demonstrate noninferiority of the NEVO SES for the primary end point of 6-month in-stent late loss compared with the TAXUS Liberté PES for the treatment of native coronary lesions. The first 50 patients in each treatment arm at selected study sites were predefined for inclusion in this IVUS substudy (Figure 1). A prespecified secondary end point was IVUS percent neointimal obstruction assessed at 6-month follow-up.

Before stent implantation, patients who were not on dual antiplatelet therapy received a minimum loading dose of 300 mg of aspirin and/or clopidogrel. Dual antiplatelet therapy was mandated for a minimum of 6 months after the procedure with indefinite use of aspirin. Periprocedural anticoagulation with heparin or bivalirudin was administered according to local hospital practice, and the use of glycoprotein IIb/IIIa inhibitors was left to the operators’ discretion. Approval by each participating institution’s ethics committee and informed consent from all patients were required and obtained.

Device Description

The NEVO SES is a novel balloon-expandable cobalt chromium alloy stent (Figure 2) with nondeformable 100-μm-thick struts containing multiple laser-cut reservoirs. Each reservoir is individually filled with a bioabsorbable PLGA polymer matrix blended with sirolimus, creating discrete sources for drug elution. Because poly-
figure 3. Three-dimensional assessment of neointimal distribution within a stent. A, Neointimal area is divided into 12 circumferential sectors (30° for each sector as referenced from the lumen center). Average neointimal thickness is then obtained from each sector, and the computation is performed for the entire stented segment at 1-mm intervals. B, To visualize the 2D color-mapped image layout, consider an image of the stent surface after having cut it along the longitudinal direction and flattening the stent surface out into a rectangular shape. The angle (sector)-axis represents circumferential variability; the distance-axis indicates longitudinal variability of neointimal thickness. Representative cases are shown for the NEVO SES (C) and the Taxus Liberté PES (D). SES indicates sirolimus-eluting stent, PES, paclitaxel-eluting stent.

Three-Dimensional Assessment of Neointimal Distribution

Because NEVO SES uses focal drug-elution design, nonuniform neointimal suppression is a theoretical concern. To investigate this hypothesis, a 3-dimensional assessment of in-stent neointimal distribution was conducted. First, lumen and stent contours on cross-sectional images at 1-mm intervals were imported into custom-designed morphometric software. This system can partition neointima into 12 equally spaced circumferential sectors (spanning 30 degrees for each sector) per each cross-sectional IVUS image, based on reconstructed images and information on the pixel location represented as pixel coordinates in (x,y) format. (Figure 3) In this process, the lumen center was used as a reference of sector division. Then, neointimal area and average neointimal thicknesses in each sector were automatically computed. Subsequently, the roughness of neointima (variability of neointimal thickness) within a whole stent was evaluated by standard deviation (SD) of neointimal thickness computed from each 30° sector along the entire stented segment.
Clinical Follow-Up
In the NEVO ResElution-I study, clinical follow-up was scheduled at 30 days, 6 months, and annually for 5 years. Death, myocardial infarction (MI, defined according to the WHO definition based on CK and CKMB rise),11 clinically driven target lesion and target vessel revascularization (TLR, defined as repeat PCI or CABG to the target lesion), and the composite end points major adverse cardiac events (MACE: death, MI, or TLR), target vessel-related MI, or clinically driven TLR were adjudicated according to the Academic Research Consortium (ARC) classification12 were evaluated. An independent and blinded clinical events committee adjudicated all deaths, MI, stent thromboses, revascularization procedures, and cerebrovascular events.

Statistical Analysis
Sample size calculation was performed based on recent pivotal randomized trials of second-generation DES and the TAXUS stents, with estimated neointimal reduction of NEVO as at least 40% compared with the control TAXUS stents (6.9% versus 11.2%, SD=6.4). With the 2-tailed test and 5% significance level, 36 patients per group were required for 80% power. Allowing for 25% dropout, final sample size was set at 100 patients. Statistical analysis was performed using StatView 5.0 (SAS Institute, Cary, NC). Categorical variables were compared using $\chi^2$ or Fisher exact test. Continuous variables are expressed as mean±SD. For continuous variables, comparisons between NEVO and TAXUS Libéreté stent were performed with 2-tailed, unpaired t test, and comparisons between baseline and follow-up were done by paired t test. For the subsegment analysis, data were compared between NEVO and TAXUS Libéreté stents by unpaired t test within each segment. Significance was assumed at a value of $P<0.05$.

Results

Study Population and Patient Characteristics
Of the 100 patients enrolled in the IVUS cohort, 2 patients did not have baseline IVUS due to technical reasons and 83 had

<table>
<thead>
<tr>
<th>Table 1. Baseline Clinical Characteristics</th>
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<tbody>
<tr>
<td><strong>NEVO SES</strong> (n=50)</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Male, %</td>
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<td>BMI</td>
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Risk factors, %
- Diabetes: 20.0 vs. 18.0 | 0.80 |
- Hypertension: 64.0 vs. 70.0 | 0.52 |
- Hyperlipidemia: 74.0 | 84.0 | 0.22 |
- Current smoker: 26.0 vs. 20.0 | 0.48 |
- Prior MI: 40.0 vs. 36.0 | 0.68 |
- Prior PCI: 38.0 vs. 28.0 | 0.29 |
- Prior CABG: 0.0 vs. 2.0 | 0.31 |
- Family history of CAD: 44.0 vs. 46.0 | 0.84 |

Angina status, %
- Stable: 68 vs. 58 | 0.57 |
- Unstable: 24 vs. 30 |
- Silent ischemia: 8 vs. 12 |

Values are presented as mean±SD or percent. BMI indicates body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; SES, sirolimus-eluting stent; and PES, paclitaxel-eluting stent.

Quantitative coronary angiography
- Lesion length, mm: 14.1±6.3 vs. 14.1±7.4 | 0.98 |
- Reference diameter, mm: 2.5±0.4 vs. 2.7±0.4 | 0.09 |
- In-stent minimum lumen diameter, mm
  - Before: 0.61±0.27 vs. 0.66±0.27 | 0.34 |
  - After: 2.45±0.31 vs. 2.52±0.43 | 0.38 |
  - Follow-up: 2.28±0.50 vs. 2.10±0.60 | 0.11 |

In-stent % diameter stenosis
- Before: 75.7±9.4 vs. 74.9±9.84 | 0.70 |
- After: 3.55±9.23 vs. 6.47±10.4 | 0.14 |
- Follow-up: 10.8±15.0 vs. 19.3±19.3 | 0.02 |

Procedural characteristics
- Stent length, mm: 19.8±7.2 vs. 19.3±7.7 | 0.71 |
- Stent diameter, mm: 2.8±0.2 vs. 2.9±0.3 | 0.006 |
- After dilatation, %: 56.0 vs. 58.0 | 0.84 |
- Maximum balloon size, mm: 3.0±0.4 vs. 3.2±0.5 | 0.046 |
- Maximum balloon pressure, atm: 16.7±3.6 vs. 17.0±4.0 | 0.66 |

Values are presented as mean±SD or percentages. LAD indicates left anterior descending artery; LCX, left circumflex; RCA, right coronary artery; ACC-AHA, American College of Cardiology–American Heart Association lesion classification; SES, sirolimus-eluting stent; and PES, paclitaxel-eluting stent.

IVUS performed at 6 months (Figure 1). Reasons for not performing IVUS at follow-up were (1) patient refused or withdrew from the study (8 cases); (2) IVUS catheter did not cross the lesion (7 cases); (No.) site investigator forgot to perform the IVUS examination during the 6-month angiography (2 cases). Serial qualitative IVUS analysis was possible in a total of 77 cases (38 NEVO SES: 39 TAXUS Libéreté PES). After excluding cases with inconsistent pullback, follow-up volumetric IVUS analysis was available in 73 cases (35 NEVO SES: 38 TAXUS Libéreté PES), and serial volumetric analysis was possible in 66 cases (32 NEVO SES: 34 TAXUS Libéreté PES) (Figure 1). Among the voided cases, no patient had clinical events or stent thrombosis, except for 1 patient with a Q-wave MI during the index procedure in the TAXUS group.

Patient, lesion, and procedural characteristics are shown in Tables 1 and 2. Except for larger stent diameter and maximal balloon size in the TAXUS Libéreté PES group, there were no significant differences between the 2 groups.

Quantitative Angiographic Findings
Although there was no significant difference in minimum lumen diameter and percent diameter stenosis before and after stenting, 6-month follow-up percent diameter stenosis was significantly smaller in NEVO SES than TAXUS Libéreté.
PES group, due to significantly smaller late loss with NEVO SES (Table 2).

**Qualitative IVUS Findings**
The incidences of baseline edge dissection, intraluminal tissue, and ISA were numerically similar for the 2 stent groups (Table 3). Late-acquired ISA was observed in 4 NEVO SES cases and 3 TAXUS Liberté PES cases. In the relatively few cases of late-acquired ISA, the NEVO SES had numerically less outward vessel remodeling as assessed by serial measurements of the external elastic lamina as compared with the TAXUS Liberté PES at the site of the greatest stent-vessel wall separation (Figures 4 and 5). No stent discontinuity, suggesting strut fracture, was detected in either stent group.

**Suppression of Neointimal Proliferation**
There was significantly less percent neointimal obstruction in the NEVO SES group (NEVO SES: 5.5±11.0% versus TAXUS Liberté PES: 11.5±9.7%, P=0.02), with less maximum %CSN (NEVO SES: 13.9±14.3% versus TAXUS Liberté PES: 28.6±17.7%, P=0.0002) (Table 4). In the subsegment analysis, a greater neointimal suppression with NEVO SES was consistently observed regardless of predefined subsegment locations (Figure 6). There was 1 case with severe narrowing in the NEVO SES group, whereas 3 cases were observed in the TAXUS Liberté PES group. As for the neointimal variability within the stent, absolute variation expressed by SD of neointimal thickness was significantly smaller in the NEVO SES than the TAXUS Liberté PES group (Figure 3 and Table 4).

**Serial Arterial Changes at Stented Segments**
The NEVO stent showed significantly less lumen volume loss and minimum lumen area loss than the TAXUS Liberté PES at 6 months (Table 5). Both stents showed increases in vessel

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**Table 3. Qualitative IVUS Analysis**

<table>
<thead>
<tr>
<th></th>
<th>NEVO SES (n=38)</th>
<th>TAXUS Liberté PES (n=39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edge dissection at baseline</td>
<td>1 (2.6)</td>
<td>0 (0)</td>
<td>0.49†</td>
</tr>
<tr>
<td>Intraluminal tissue* at baseline</td>
<td>2 (5.3)</td>
<td>0 (0)</td>
<td>0.24†</td>
</tr>
<tr>
<td>ISA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISA at baseline</td>
<td>4 (10.5)</td>
<td>6 (15.4)</td>
<td>0.99†</td>
</tr>
<tr>
<td>Resolved ISA</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Persistent ISA</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Late-acquired ISA</td>
<td>4 (10.5)</td>
<td>3 (7.7)</td>
<td>0.71†</td>
</tr>
</tbody>
</table>

Values are presented as n (%).
ISA indicates incomplete stent apposition; SES, sirolimus-eluting stent; and PES, paclitaxel-eluting stent.
*Intraluminal tissue includes thrombus and plaque prolapse.
†By Fisher test.

Figure 5. Intravascular ultrasound images of late-acquired incomplete stent apposition in vessels treated with a NEVO sirolimus-eluting stent (SES) and a TAXUS Liberté paclitaxel-eluting stent. A, The NEVO SES was well apposed at baseline (upper panel), whereas minor stent-vessel detachment (red area) was observed at follow-up (lower panel). There was no vessel outward remodeling at the site of late-acquired incomplete stent apposition. B, The TAXUS Liberté paclitaxel-eluting stent (PES) was well apposed at baseline (upper panel), whereas stent-vessel separation (red area) was observed at follow-up (lower panel) and was associated with significant enlargement of external elastic membrane as compared with that at baseline.

Figure 4. Quantitative analysis of late-acquired incomplete stent apposition (LISA). The NEVO sirolimus-eluting stent (SES) had numerically less outward vessel remodeling than the TAXUS Liberté paclitaxel-eluting stent (PES) as well as less LISA area at the site of the late-acquired incomplete stent apposition in this very limited cohort of patients. *By Mann-Whitney test.
Table 4. Detailed Assessment of Neointimal Proliferation at Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>NEVO SES (n=35)</th>
<th>TAXUS Libérté PES (n=38)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neointimal VI, mm³/mm</td>
<td>0.3±0.7</td>
<td>0.9±0.9</td>
<td>0.003</td>
</tr>
<tr>
<td>%NIV</td>
<td>5.5±11.0</td>
<td>11.5±9.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Max %CSN</td>
<td>13.9±14.3</td>
<td>28.6±17.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>Neointimal thickness, mm</td>
<td>0.04±0.1</td>
<td>0.10±0.09</td>
<td>0.009</td>
</tr>
<tr>
<td>SD of neointimal thickness</td>
<td>0.04±0.04</td>
<td>0.10±0.07</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD.

VI indicates volume index; %NIV, percent neointimal volume; %CSN, percent cross-sectional narrowing; SD, standard deviation; SES, sirolimus-eluting stent; and PES, paclitaxel-eluting stent.

Responses at Adjacent Reference Segments

In adjacent reference segments, there was no significant difference in terms of the baseline IVUS variables between the 2 stent groups, except for a larger lumen volume index at the distal reference segment in the TAXUS Libérté group (Table 6). In the proximal reference segment, a significant lumen decrease was observed in both groups due to the combination of negative vessel remodeling and plaque progression. In the distal reference segment, however, only the TAXUS Libérté PES showed a significant lumen decrease over time, mainly due to plaque progression during follow-up. There was a trend toward a greater lumen decrease in the TAXUS Libérté PES group at the distal reference segment.

Clinical Outcomes at 6 Months

Clinical outcomes at 6 months were collected in all patients enrolled in the IVUS substudy. No death or TLR was observed. There were no significant differences in the rates of MI (2.0% versus 2.0%, P>0.99), TVR (4.0% versus 4.0%, P>0.99), target lesion failure (2.0% versus 2.0%, P>0.99), and MACE (2.0% versus 2.0%, P>0.99) for NEVO SES versus TAXUS Libérté PES, respectively (each tested by Fisher exact test). In this IVUS substudy, no stent thromboses were observed in the NEVO SES group up to 6 months, whereas there was 1 case with ARC-probable stent thrombosis at day 180 in the TAXUS Libérté PES group. This probable stent thrombosis occurred despite dual antiplatelet therapy and resulted in an acute ST-elevation MI that was treated with thrombolysis; angiographic and IVUS examination 9 days before the MI demonstrated no abnormalities.

Discussion

The NEVO SES is a novel DES using reservoir technology with each reservoir acting as a depot into which drug-polymer compositions are loaded. This unique design delivers drug from focal sources rather than from a conformal coating. Because polymer and drug are confined to the reservoirs and each reservoir is only partially filled, the stent surface in contact with the vessel wall is completely polymer-free on stent implantation. Furthermore, after 90 days, only a biologically inert bare metal platform remains in the vessel wall. The current study represents the first in vivo report investigating the detailed arterial response to this new drug-delivery strategy in patients with coronary artery disease.

In this predefined IVUS subset analysis of the multicenter, randomized, controlled NEVO ReElution-I trial comparing the NEVO SES with the TAXUS Libérté PES in de novo native coronary artery lesions, the NEVO SES showed significantly less neointimal proliferation, resulting in less late lumen area loss and smaller maximal cross-sectional narrowing than the TAXUS Libérté PES. Additionally, the NEVO stent demonstrated more uniform suppression of neointima than the TAXUS Libérté PES. The key IVUS findings were also confirmed by the quantitative angiographic analysis of patients in this subgroup in which the NEVO SES showed significantly less percent diameter stenosis and less in-stent late loss during the 6-month follow-up period. These results matched those of the larger angiographic trial that demonstrated superiority of the NEVO SES over the TAXUS Libérté PES for the primary end point of in-stent late loss (0.13±0.31 mm versus0.36±0.48 mm, P<0.001 for noninferiority and superiority).

Neointimal Hyperplasia After NEVO SES Implantation

The present study demonstrated that the NEVO SES provided greater suppression of neointima than TAXUS Libérté PES. The NEVO SES has been designed to release sirolimus with arterial tissue sirolimus concentrations similar to those with
the CYPHER SES. The percent of neointimal obstruction obtained in our study with the NEVO SES (5.5%) is similar to those of the CYPHER SES (3.1% in SIRIUS1) and the Xience V stents (8 and 6.9% in SPIRIT-I14 and -III15) and compares favorably with the Endeavor stent (16.1% in ENDEAVOR-III16).

In addition to the overall neointimal volume suppression, maximum CSN and late lumen area loss, both of which are relevant to focal neointimal proliferation, were significantly less with the NEVO SES stent, again mirroring the findings of the larger NEVO ResElution-I angiographic study. Given the unique formulation strategy that elutes sirolimus focally from each reservoir, nonuniform neointimal suppression is a theoretical concern with the NEVO stents. However, no IVUS-based method has been established to quantitatively evaluate the in vivo variability of neointima distribution in a multidimensional fashion within the implanted stent. Therefore, we developed a 3-dimensional method to assess neointimal distribution to investigate the uniformity of neointima proliferation. Using this method, NEVO SES showed less variability of neointimal thickness within the stent, indicating more homogeneous neointimal suppression by the NEVO SES than by the surface-coated TAXUS Liberté PES. To date, several factors have been suggested as possible contributors to varying neointimal distribution within stents.10,17,18 The type of drug used is one of the important factors that affects not only the total amount of neointima but also the pattern of neointimal distribution.16,19 Indeed, recent clinical

Table 5. Serial Intravascular Ultrasound Variables at the Stented Segment

<table>
<thead>
<tr>
<th></th>
<th>NEVO SES (n=35)</th>
<th>TAXUS Liberté PES (n=38)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
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<td></td>
<td>P</td>
<td></td>
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<tr>
<td>Lumen VI, mm³/mm</td>
<td>6.0±1.7</td>
<td>5.7±1.8</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
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<tr>
<td>Δ Lumen VI, mm³/mm</td>
<td>−0.32±0.80</td>
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<tr>
<td>Vessel VI, mm³/mm</td>
<td>12.4±4.4</td>
<td>12.8±4.4</td>
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<tr>
<td></td>
<td>0.009</td>
<td></td>
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<tr>
<td>Δ Vessel VI, mm³/mm</td>
<td>0.36±0.63</td>
<td></td>
</tr>
<tr>
<td>*Plaque VI, mm³/mm</td>
<td>6.5±2.9</td>
<td>6.9±2.8</td>
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<tr>
<td></td>
<td>0.01</td>
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<tr>
<td>Δ *Plaque VI, mm³/mm</td>
<td>0.37±0.69</td>
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<tr>
<td>MLA, mm²</td>
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<td></td>
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<tr>
<td>Δ MLA, mm²</td>
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Values are presented as mean±SD. 
VI indicates volume index; MLA, minimum lumen area; SES, sirolimus-eluting stent; and PES, paclitaxel-eluting stent. 
*Plaque indicates persistent plaque. 
†P values for NEVO SES versus TAXUS Liberté PES.

Table 6. Serial Intravascular Ultrasound Variables at Reference Segments

<table>
<thead>
<tr>
<th></th>
<th>NEVO SES</th>
<th>TAXUS Liberté PES</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>Proximal reference, mm³/mm</td>
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<tr>
<td>Lumen VI</td>
<td>7.2±2.9</td>
<td>6.5±2.6</td>
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<tr>
<td></td>
<td>−0.69±1.5</td>
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<tr>
<td>Vessel VI</td>
<td>13.8±4.9</td>
<td>13.5±4.8</td>
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<tr>
<td></td>
<td>−0.35±1.6</td>
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<tr>
<td>*Plaque VI</td>
<td>6.5±2.8</td>
<td>6.9±3.4</td>
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<tr>
<td></td>
<td>0.37±1.2</td>
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<tr>
<td>Distal reference, mm³/mm</td>
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<tr>
<td>Lumen VI</td>
<td>4.9±1.8‡</td>
<td>5.0±1.8‡</td>
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<td></td>
<td>0.075±0.72</td>
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<tr>
<td>Vessel VI</td>
<td>8.7±3.3</td>
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<tr>
<td></td>
<td>0.23±0.78</td>
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<tr>
<td>*Plaque VI</td>
<td>3.8±1.9</td>
<td>3.9±2.0</td>
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<tr>
<td></td>
<td>0.16±0.48</td>
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</table>

Values are presented as mean±SD. 
VI indicates volume index; MLA, minimum lumen area; SES, sirolimus-eluting stent; and PES, paclitaxel-eluting stent. Δ indicates the difference between baseline and 6-month values. 
*Plaque indicates persistent plaque. 
†P values for NEVO SES versus TAXUS Liberté PES. 
‡P<0.05 versus TAXUS PES.
studies using optical coherence tomography or angioscopy have demonstrated more heterogeneous neointimal distribution within TAXUS Liberté PES than the CYPHER SES, which is consistent with our findings. Sirolimus and paclitaxel have a number of different properties, in terms of diffusion capacity and distribution in the vascular wall. Therefore, the diffusion properties of sirolimus, allowing for consistent drug distribution across the vessel wall, may be particularly suitable for reservoir-based DES technology.

Another possible explanation for the more uniform distribution of neointima seen with the NEVO SES may be the protection of the drug-polymer component in the reservoir during tracking to and across the lesion. Peeling, webbing, cracking, and wrinkling of the drug-polymer matrix during implantation have been described with surface-coated stents, and this could reduce the uniform effectiveness of drug delivery, especially in tortuous, calcified vessels and/or in complex lesion stenting. It would be of interest to measure uniformity of intimal thickness using this IVUS technique in a wider range of DES and determine if there is a relationship to outcomes.

Vessel Reactions to Bioabsorbable Polymers in Human Patients

Durable surface polymer-based drug-loading technology has been most widely used in the currently available DES. However, durable polymers are considered to be partly responsible for pathological vessel reactions and late adverse clinical events such as very late thrombosis and late angiographic catch-up. In the NEVO SES, the bioabsorbable polymer is restricted to the interior of the reservoirs, thereby eliminating at least initial contact with the arterial vessel wall. Preclinical studies have shown that polymer is absorbed within approximately 3 months after implantation, with complete tissue in-growth into the reservoirs. These distinctive design features of the NEVO SES might limit polymer-induced arterial wall inflammation, reducing the risk of ST and the requirement for prolonged dual antiplatelet therapy. Long-term follow-up of the NEVO ResElution-I trial and further studies comparing long and short regimens of dual antiplatelet therapy after implantation of the NEVO SES are necessary before definite conclusions can be drawn on this important clinical issue.

Compared with the NEVO SES, the TAXUS Liberté PES showed significantly greater increases in persistent plaque and vessel volumes in the stented segment. This phenomenon has been consistently reported in past clinical studies with PES. In contrast, the CYPHER SES has rarely shown positive vessel remodeling in human trials. In this study, although the slight vessel enlargement after NEVO SES implantation reached statistical significance, its magnitude was markedly less than that with the TAXUS Liberté PES. The exact pathological mechanisms of this serial arterial response remain unclear, and larger scale studies with longer-term follow-up may be warranted to clarify the clinical importance of these findings.

Study Limitations

Several limitations should be noted. First, although this IVUS analysis was based on serially enrolled patients, the modest sample size was reduced by technical limitations (such as inconsistent transducer pullback or image distortion) or patient/operator compliance in some cases. Although these issues are common in IVUS studies, they might increase the possibility of selection bias due to small sample size and lack of full data ascertainment, which can lead to low statistical power and precision. Also, due to multiple comparisons with the selected nature of the population, the results of the study and probability values should be interpreted cautiously. Second, the follow-up period was limited to 6 months, a time at which neointimal hyperplasia in response to vessel wall injury from stenting is substantially but not fully complete, and no direct insight into late events such as very late stent thrombosis can be made. These limitations warrant further studies in additional patients receiving longer follow-up.

Conclusion

Detailed IVUS analysis with a randomized, blinded comparison confirmed that the strategy of focal sirolimus delivery from reservoirs with bioabsorbable polymer produced both significantly greater suppression of neointima formation as well as more consistent spatial attenuation of neointima across the full stent length by the NEVO SES compared with the surface-coated TAXUS Liberté PES at 6 months. This superior efficacy of the NEVO SES was associated with less positive vessel remodeling and no increased morphological or morphometric abnormalities surrounding the stent or at the stent margins. Additional trials and longer follow-up in the current study will address the durability of these observations and whether the advanced formulation strategy of the NEVO SES using bioabsorbable polymer recessed within reservoirs will fulfill the potential for improved long-term clinical safety.

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Disclosures

Dr스 Ormiston and Abizaid are members of Boston Scientific and Abbott Vascular Advisory Boards and have received minor honoraria. Dr Abizaid is a member of scientific advisory boards for Cordis and has received minor honoraria. Dr Fitzgerald received institutional research grants from Cordis and Boston Scientific; a consulting fee from Cordis. At the time of the study, Dr Spaulding was a member of scientific advisory boards for Cordis and received minor honoraria. Since June 1, 2010, Dr Spaulding has been a full-time employee of Cordis Corporation; Drs Rogers, Macours, and Cohen are full-time employees of Cordis Corporation.

References


Durable surface polymer-based drug-loading technology has been most widely used in the currently available drug-eluting stents (DES). However, durable polymers are considered to be partly responsible for pathological vessel reactions and late adverse clinical events such as very late thrombosis and late angiographic catch-up. The NEVO sirolimus-eluting stent (SES) is a novel cobalt-chromium stent combining sirolimus release from reservoirs with bioabsorbable polymer to reduce spatial and temporal polymer exposure. We assessed the arterial response to the NEVO SES in a randomized, blinded comparison versus the surface-coated TAXUS Liberte paclitaxel-eluting stent (PES) in human native coronary lesions using serial intravascular ultrasound analysis (baseline and 6-month follow-up). The NEVO SES showed significantly less positive vessel remodeling than the TAXUS Liberte PES up to 6 months. This was associated with greater preservation of vessel wall integrity.
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Hiromasa Otake, Yasuhiro Honda, Brian K. Courtney, Takao Shimohama, Junya Ako, Katsuhisa Waseda, Nathalie Macours, Campbell Rogers, Jeffrey J. Popma, Alexandre Abizaid, John A. Ormiston, Christian Spaulding, Sidney A. Cohen and Peter J. Fitzgerald

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