Peristent Remodeling and Neointimal Suppression 2 Years After Polymer-Based, Paclitaxel-Eluting Stent Implantation

Insights From Serial Intravascular Ultrasound Analysis in the TAXUS II Study

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Background—The purpose of this study was to evaluate long-term vascular responses as long as 2 years after implantation of polymer-based, paclitaxel-eluting stents, providing a unique opportunity to evaluate serial intravascular ultrasound (IVUS) changes over time.

Methods and Results—TAXUS II is a randomized, double-blind trial comparing slow-release (SR) and moderate-release (MR) TAXUS stents with bare-metal control stents (BMSs). One hundred sixty-one event-free patients (SR, 43; MR, 41; and BMS, 77) underwent serial intravascular ultrasound (IVUS) analysis after the procedure and at 6 months and 2 years. At 2 years, neointimal responses continued to be significantly suppressed in the SR and MR groups when compared with the BMS group (BMS, 1.49±1.12 mm²; SR, 0.94±0.76 mm² [P=0.004]; and MR, 1.06±0.90 mm² [P=0.02]). Between 6 months and 2 years, the BMS group showed compaction of the neointima (Δ, −0.22±0.105 mm² [P=0.08]). In contrast, both the SR and MR groups exhibited an increase (Δ SR, 0.30±0.76 mm² [P=0.01]; MR, 0.41±0.94 mm² [P=0.009]). Between 6 months and 2 years, the initial increase in plaque outside the stent regressed in the BMS and SR groups to levels comparable to those after the procedure, whereas expansive remodeling partially regressed in the MR group (Δ between after the procedure and 2 years BMS, −0.34±1.28 mm² [P=0.05]; SR, −0.02±1.40 mm² [P=0.93]; MR, 0.32±1.56 mm² [P=0.27]).

Conclusions—The 2-year follow-up demonstrates that neointimal suppression was dose independent and that this effect was still sustained at 2 years. However, the increase in area outside the stent seen at 6 months regressed to different extents in a dose-dependent manner at 2 years. (Circulation. 2005;112:3876-3883.)

Key Words: stents ■ remodeling ■ restenosis

Both slow-release (SR) and moderate-release (MR) polymer-based, paclitaxel-eluting stents prevent in-stent neointimal growth compared with bare-metal stents (BMSs).1 In the patient population studied in TAXUS II, these antirestenotic effects were comparable for both dose formulations. However, at 6 months, this inhibition was associated with expansive, persistent remodeling.2 The extent of persistent remodeling was more pronounced with the MR formulation, implying dose-dependent differences in vascular responses outside but not inside the stent.

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In animal studies, the mechanism of action of drug-eluting stents on neointimal proliferation after stent implantation seems to be partially explained by a delay in vascular responses. For polymer-based, paclitaxel-eluting stents, inhibition of in-stent neointimal growth is associated with a delay in intimal healing up to 28 days, as indicated by initially increased fibrin deposition, inflammation, and delayed endothelialization.3 By 90 days, peristrut changes associated with paclitaxel were resolving, but in-stent neointimal growth suppression was no longer present.

TAXUS II is an international study of 2 consecutive cohorts designed to evaluate 2 formulations of a polymer-based, paclitaxel-eluting stent. The primary end point in the original protocol was the percent net volume obstruction, providing a unique opportunity to evaluate serial intravascular ultrasound system (IVUS) changes over time.

The objective of this study was to evaluate long-term arterial responses both inside and outside the stent as long as 2 years after implantation of polymer-based, paclitaxel-eluting stents by using serial quantitative IVUS analysis in event-free patients.

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Methods

Patient Selection
The original study design, procedure, and IVUS results have been described previously. The design of the TAXUS II study is a randomized, double-blind, controlled trial. In brief, 536 patients with single de novo coronary lesions (>50% stenosis on visual assessment) treatable with a single stent (3.0- or 3.5-mm diameter and 15 mm long) were randomly assigned to 2 consecutive, independent cohorts. The first cohort of patients was randomized to be treated with either a control BMS or a TAXUS-NIRx SR formulation stent. A second cohort of patients was randomized to control BMSs versus a TAXUS-NIRx MR formation. The primary end point was met with a significant 66% (SR) and 62% (MR) reduction in 6-month percent net volume obstruction as assessed by IVUS in both groups, without an apparent difference between the SR and MR groups.

To further evaluate the natural history of vascular responses to TAXUS, the study protocol was amended to include a 2-year IVUS long-term follow-up. Of the initial 536 patients, 161 patients without any clinical events through the 2-year follow-up and with serial (procedure, 6 months, and 2 years) and analyzable IVUS data were selected for this substudy (BMS, 77; SR, 43; and MR, 41). This patient population represents a highly selected subgroup of patients successfully treated with either a BMS, a TAXUS SR stent, or a TAXUS MR stent. Because the 2-year quantitative coronary angiography (QCA) and IVUS substudy was added as an amendment to the original study protocol, it required additional approval from the local regulatory agencies and ethics committees before being implemented at the sites. The 2-year substudy was not approved by the appropriate regulatory authorities or ethics committees at 9 of the 38 sites. As a result, of the original 536 intent-to-treat patients, 154 were not eligible to participate in the 2-year substudy. Additionally, 122 patients did not consent to the 2-year substudy, whereas 30 patients were excluded for clinical reasons, resulting in 230 patients who were eligible to participate in the substudy. In 34 of the 230 patients, IVUS either was not performed or was not of adequate quality to be included in the qualitative and quantitative analysis. An additional 23 patients were excluded because they had either a target-vessel revascularization before 6 months or had a target-vessel revascularization after 6 months but did not have IVUS before the target-vessel revascularization. Finally, 12 patients were excluded from this analysis because paired IVUS data were not available at all 3 time points (postprocedure, 6-month, and 2-year data). Written, informed consent was obtained from all patients.

TAXUS Stent System
The 15-mm NIR Conformer stent of 3.0- or 3.5-mm diameter was used in this study (Boston Scientific Corp and Medinol Ltd). All TAXUS NIRx stents were coated with 1.0 μg/mm² paclitaxel in an SR or MR formulation as previously described. The SR and MR dose formulations are characterized by differences in the amount of drug released during the initial 48-hour burst phase as well as the amount of drug remaining embedded in the polymer at 30 days.

Study Procedure
Stents were implanted after balloon predilatation as described in the initial reports. Per study protocol, all patients were to receive 75 mg/d aspirin indefinitely. Clopidogrel (300 mg) was administered, preferably 48 hours before the procedure, followed by 75 mg once daily for 6 months.

Quantitative IVUS and Angiographic Analysis
The quantitative IVUS and QCA analyses were performed by an independent core laboratory that remains blinded to treatment allocation during the ongoing 5-year follow-up (Cardialysis). Serial IVUS (postprocedure, 6-month, and 2-year follow-up) procedures were performed after administration of 200 μg intracoronary nitroglycerin with an automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotape, and images were digitized for analysis. A computer-based contour-detection program was used for automated 3-dimensional reconstruction of the stented segment. Reconstruction and quantification of 3-dimensional IVUS images have been validated previously. In brief, a series of tomographic images is continuously acquired during an IVUS pullback procedure. With use of a 40-MHz ultrasound probe, 25 frames per second are available from a motorized pullback procedure recorded on videotape. In this study, an average of 714 sections in the stented lesion were obtained per patient. All acquired cross-sectional frames were analyzed by semiautomatic contour tracing in several reconstructed, longitudinally cut planes, as developed and tested in cooperation with Guard B.V. The applied approach focuses on the tracing of contours in the reconstructed, longitudinally cut planes (L-mode view). The number of L-mode contours to be traced is independent of the number of frames in the analysis. As many as 72 L-mode views at 5° intervals can be selected for display and subsequent analysis. Contours of vessel, lumen, and stent structures can then be traced. Instead of trying to find the structures completely automatically, the program uses starting points as defined by the user, followed by autotracing of the contour segment in either of 2 possible directions. Pieces of the contours can be retraced in a semiautomatic procedure to optimize the interaction between operator and algorithm. In this way, all cross-sectional areas are analyzed, and the 3-dimensional nature of the data set is fully used. The interobserver correlation coefficients for lumen, stent, and vessel volumes resulted in R² values of 0.96, 0.99, and 0.99, respectively.

In the stented segment, mean peristent area and mean neointimal area were calculated. Incomplete stent apposition (ISA) was defined as 1 or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut without overlapping side branches. ISA was classified into 3 groups. Resolved ISA was defined as ISA that disappeared during follow-up. Persistent ISA was defined as ISA that was evident both after the procedure and at follow-up. Late acquired ISA was defined as ISA that was absent after the procedure but present at follow-up.

Statistical Analysis
The BMS groups of the 2 cohorts were combined because the baseline and 6-month follow-up data showed no significant differences, as previously described. Therefore, 3 groups are reported in this study: The combined BMS, the TAXUS-SR, and the TAXUS-MR groups. Discrete variables are displayed as percentages and were tested with Fisher’s exact test. Continuous variables are expressed as mean±SD. When 3 groups were compared, overall probability values were derived from 1-way ANOVA or Fisher’s exact test. Comparisons between postprocedure and follow-up data were performed with a 2-tailed, paired t test, whereas comparisons between 2 groups were performed with Fisher’s least significant difference test. Linear regression was performed to assess the correlation between different IVUS outcomes. A value of P<0.05 was considered statistically significant.

Results

Patients and Procedural Characteristics
Table 1 presents the patient and procedural characteristics for the group that had serial (after the procedure, at 6 months, and at 2 years) IVUS examinations compared with the entire TAXUS II study cohort. Comparable baseline demographic and angiographic data with the exception of the prevalence of males (P=0.03) indicate that the data in the serial IVUS cohorts are representative of the overall randomized study population.

Area Inside the Stent (Neointimal Area)
As shown in Table 2, the neointimal area at 6 months was significantly suppressed in the SR and MR groups, as detected by serial IVUS when compared with the BMS group (1.71±1.38 mm² in the BMS group versus 0.64±0.81 mm² in
the SR group, \( P < 0.0001 \); 0.66±0.83 mm\(^2\) in the MR group, \( P < 0.0001 \). This reduction relative to the BMS group was also present at 2 years (1.49±1.12 mm\(^2\) in the BMS group versus 0.94±0.76 mm\(^2\) in the SR group, \( P = 0.004 \); 1.06±0.90 mm\(^2\) in the MR group, \( P = 0.02 \)). When relative changes within the 3 groups were compared, the BMS group showed compaction of the neointima between 6 months and 2 years, as demonstrated by a trend toward a decrease in neointimal area (\( \Delta, -0.22±1.05 \) mm\(^2\), \( P = 0.08 \)). In contrast, the SR and MR groups both exhibited a significant increase in neointimal area between 6 months and 2 years when compared with controls (SR \( \Delta, 0.30±0.76 \) mm\(^2\), \( P = 0.01 \) versus BMS; MR \( \Delta, 0.41±0.94 \) mm\(^2\), \( P = 0.009 \) versus BMS; Table 2). However, according to QCA analyses, the average minimal lumen diameter (MLD) in the SR and MR groups did not decrease from 6 months to 2 years (2.30±0.33 to 2.36±0.28 mm in the SR group; 2.30±0.38 to 2.31±0.35 mm in the MR group; Table 3).

### TABLE 1. Baseline and Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>BMS (n=77)</th>
<th>SR (n=43)</th>
<th>MR (n=41)</th>
<th>( P )</th>
<th>All Randomized Patients (N=536)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.2±9.0</td>
<td>59.4±1.3</td>
<td>57.5±10.9</td>
<td>0.50</td>
<td>60.1±10.0</td>
</tr>
<tr>
<td>Male, %</td>
<td>85.7</td>
<td>65.1</td>
<td>73.2</td>
<td>0.03</td>
<td>75.6</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>29.9</td>
<td>14.0</td>
<td>24.4</td>
<td>0.14</td>
<td>25.0</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>13.0</td>
<td>9.3</td>
<td>9.8</td>
<td>0.85</td>
<td>14.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>46.8</td>
<td>62.8</td>
<td>51.2</td>
<td>0.24</td>
<td>61.4</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>72.7</td>
<td>83.7</td>
<td>80.5</td>
<td>0.35</td>
<td>75.9</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>27.3</td>
<td>27.9</td>
<td>16.6</td>
<td>0.26</td>
<td>34.3</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>50.7</td>
<td>41.9</td>
<td>51.2</td>
<td>0.63</td>
<td>39.7</td>
</tr>
<tr>
<td>Target vessel, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>52.0</td>
<td>41.9</td>
<td>39.0</td>
<td>0.34</td>
<td>44.6</td>
</tr>
<tr>
<td>LCX</td>
<td>11.7</td>
<td>20.9</td>
<td>16.5</td>
<td>0.31</td>
<td>19.6</td>
</tr>
<tr>
<td>RCA</td>
<td>36.4</td>
<td>37.2</td>
<td>41.5</td>
<td>0.89</td>
<td>35.8</td>
</tr>
<tr>
<td>RVD, mm</td>
<td>2.73±0.50</td>
<td>2.78±0.38</td>
<td>2.76±0.45</td>
<td>0.88</td>
<td>2.75±0.46</td>
</tr>
<tr>
<td>Target lesion length, mm</td>
<td>10.5±4.15</td>
<td>10.0±3.69</td>
<td>11.0±6.27</td>
<td>0.68</td>
<td>10.4±4.23</td>
</tr>
<tr>
<td>Stent size, mm</td>
<td>3.29±0.25</td>
<td>3.31±0.24</td>
<td>3.32±0.25</td>
<td>0.31</td>
<td>3.26±0.25</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; and RVD, reference vessel diameter. Other abbreviations are as defined in text. Values are mean±SD or percentages.

*ANOVA among the 3 groups.

### TABLE 2. Quantitative IVUS Data

<table>
<thead>
<tr>
<th></th>
<th>BMS (n=77)</th>
<th>SR (n=43)</th>
<th>MR (n=41)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neointimal area, mm(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>1.71±1.38</td>
<td>0.64±0.81</td>
<td>0.66±0.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 Years</td>
<td>1.49±1.12</td>
<td>0.94±0.76</td>
<td>1.06±0.90</td>
<td>0.006</td>
</tr>
<tr>
<td>Difference 2 years–6 months</td>
<td>-0.22±1.05</td>
<td>0.30±0.76</td>
<td>0.41±0.94</td>
<td>0.001</td>
</tr>
<tr>
<td>Plaque area outside the stent (persistent area), mm(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After procedure</td>
<td>7.97±2.00</td>
<td>8.18±2.11</td>
<td>8.38±2.52</td>
<td>0.71</td>
</tr>
<tr>
<td>Difference 6 months–after</td>
<td>0.68±1.19</td>
<td>1.18±1.66</td>
<td>1.52±1.68</td>
<td>0.04</td>
</tr>
<tr>
<td>Difference 2 years–6 months</td>
<td>-1.02±0.92</td>
<td>-1.21±1.39</td>
<td>-1.18±1.56</td>
<td>0.74</td>
</tr>
<tr>
<td>Difference 2 years–after</td>
<td>-0.34±1.28</td>
<td>-0.02±1.40</td>
<td>0.32±1.56</td>
<td>0.11</td>
</tr>
<tr>
<td>Vessel area, mm(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After procedure</td>
<td>16.43±3.07</td>
<td>17.25±2.93</td>
<td>16.79±3.36</td>
<td>0.50</td>
</tr>
<tr>
<td>Difference 6 months–after</td>
<td>1.03±1.41</td>
<td>1.21±1.84</td>
<td>1.60±1.94</td>
<td>0.34</td>
</tr>
<tr>
<td>Difference 2 years–6 months</td>
<td>-1.18±1.23</td>
<td>-1.33±1.74</td>
<td>-1.38±1.78</td>
<td>0.50</td>
</tr>
<tr>
<td>Difference 2 years–after</td>
<td>-0.15±1.49</td>
<td>-0.12±1.76</td>
<td>0.21±1.80</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text. Values are mean±SD.

*ANOVA among the 3 groups.
TABLE 3. QCA Data

<table>
<thead>
<tr>
<th></th>
<th>After Procedure</th>
<th>6 Months</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS (n=77)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVD, mm</td>
<td>2.89±0.39</td>
<td>2.64±0.49</td>
<td>2.64±0.46</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.61±0.35</td>
<td>1.91±0.45</td>
<td>2.05±0.40</td>
</tr>
<tr>
<td>DS, %</td>
<td>9.50±5.45</td>
<td>27.19±13.36</td>
<td>21.49±11.41</td>
</tr>
<tr>
<td>SR (n=43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVD, mm</td>
<td>2.87±0.30</td>
<td>2.81±0.40</td>
<td>2.78±0.33</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.59±0.29</td>
<td>2.30±0.33</td>
<td>2.36±0.28</td>
</tr>
<tr>
<td>DS, %</td>
<td>9.53±5.44</td>
<td>17.63±8.78</td>
<td>14.64±6.96</td>
</tr>
<tr>
<td>MR (n=41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVD, mm</td>
<td>2.89±0.38</td>
<td>2.75±0.37</td>
<td>2.79±0.42</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.58±0.33</td>
<td>2.30±0.38</td>
<td>2.31±0.35</td>
</tr>
<tr>
<td>DS, %</td>
<td>10.24±5.25</td>
<td>16.05±9.59</td>
<td>16.24±9.56</td>
</tr>
</tbody>
</table>

RVD indicates reference vessel diameter; DS, diameter stenosis. Other abbreviations are as defined in text. Values are mean±SD.

Area Outside the Stent (Persistant Area)

Changes up to 6 Months
In the first 6 months, significant increases in mean persistant area (calculated as mean vessel area minus mean stent area), consistent with expansive vessel remodeling, were observed in all 3 groups (Table 2). In the BMS group, the persistant area increased by 8.5%, from 7.97±2.00 to 8.65±1.91 mm² (P<0.0001). This contrasted with an increase by 14.4% in the SR group (8.18±2.11 mm² after the procedure versus 9.37±2.79 mm² at 6 months; P<0.0003) and by 18.1% in the MR group (8.38±2.52 mm² after the procedure versus 9.90±2.45 mm² at 6 months; P<0.0001).

Changes From 6 Months to 2 Years
From 6 months to 2 years, a significant regression of the persistant area was observed in all 3 groups. In the BMS group, the persistant area decreased by 11.8% from 8.65±1.91 to 7.63±1.56 mm² (P<0.0001). Similarly, the persistant area decreased by 12.9% in the SR group (9.37±2.79 mm² versus 8.16±2.09 mm²; P<0.0001) and by 12.0% in the MR group (9.90±2.45 mm² versus 8.70±2.20 mm²; P<0.0003).

At 2 years, this regression in the BMS and SR groups resulted in absolute persistant areas that were comparable to those observed after the procedure (difference between post-procedure and 2-year measurements, −0.34±1.28 mm² in the BMS group and −0.02±1.40 mm² in the SR group). In the MR group, regression of the initial increase was incomplete, with a remaining net increase at 2 years with respect to the postprocedure value of 0.32±1.56 mm² (Table 2).

Assessment of the persistant area showed that the expansive vessel remodeling observed at 6 months regressed from 6 months to 2 years in all 3 groups. The incidence of this vessel remodeling observed at 6 months regressed from 6 months to 2 years in all 3 groups (Table 2). In the BMS group, the persistant area increased by 11.8% from 7.97±2.00 to 8.65±1.91 mm² (P<0.0001). This contrasted with an increase by 14.4% in the SR group (8.18±2.11 mm² after the procedure versus 9.37±2.79 mm² at 6 months; P<0.0003) and by 18.1% in the MR group (8.38±2.52 mm² after the procedure versus 9.90±2.45 mm² at 6 months; P<0.0001).

Correlation Between Area Inside the Stent (Neointimal Area) and Area Outside the Stent (Persistant Area)
Figure 2 presents the changes of the area inside the stent versus the correlating changes outside the stent for 2 years to illustrate the natural history of vascular responses around and within the stent. This graph illustrates that for the BMS, there was a reduction in neointimal area as well as a reduction in the persistant area between 6 months and 2 years. For the SR group, the neointimal area increased, yet there was a reduction in persistant area, similar to that seen with the BMS. Finally, for the MR group, the neointima significantly increased between 6 months and 2 years, with a partial decrease in persistant area.

For all 3 groups, there were no correlations between persistant area and neointimal area at 6 months (R=-0.016, P=0.70 in the BMS group; R=-0.021, P=0.55 in the SR group; and R=-0.037, P=0.93 in the MR group) and 2 years (R=-0.011, P=0.51 in the BMS group; R=0.11, P=0.037 in the SR group; and R=-0.036, P=0.88 in the MR group). In addition, there were no correlations between relative changes in persistant area and changes in area for 2 years. Probability values for persistant area from after the procedure to 6 months are 0.0001 for BMS, 0.0003 for SR, and <0.0001 for MR. Probability values for persistant area from 6 months to 2 years are <0.0001 for BMS, <0.0001 for SR, and 0.0003 for MR. The probability value for neointimal area from after the procedure to 6 months is <0.0001 for all 3 groups, whereas probability values for neointimal area from 6 months to 2 years are 0.08 for BMS, 0.01 for SR, and 0.009 for MR. Abbreviations are as defined in text.
neointimal area over time at 6 months ($R = -0.013, P=0.57$ in the BMS group; $R=0.028, P=0.18$ in the SR group; and $R = -0.018, P=0.48$ in the MR group) and 2 years ($R = -0.017, P=0.72$ in the BMS group; $R = -0.021, P=0.54$ in the SR group; and $R = 0.021, P=0.22$ in the MR group).

Incomplete Stent Apposition

As shown in Figure 3, the incidences of ISA at 2 years were similar among the 3 groups (10.4% in the BMS group, 7.0% in the SR group, and 7.3% in the MR group; $P=0.82$). The incidences of late acquired ISA at 2 years in all groups were lower than at 6 months (2.6% versus 6.5% in the BMS group, 0% versus 9.3% in the SR group, and 2.4% versus 9.8% in the MR group).

Discussion

This article presents the first long-term (up to 2 years) serial IVUS analysis after deployment of BMSs or drug-eluting stents in a series of 161 patients. To assess long-term IVUS outcomes in response to the original study stent implanted during the index procedure, neointimal area analyses had to exclude patients with target-lesion revascularization before the follow-up IVUS examination. Thus, neointimal hyperplasia in the overall population might be underestimated when compared with this analysis. The major findings of this study are as follows: (1) Neointimal suppression is maintained for as long as 2 years in both the SR and MR groups when compared with the BMS group. (2) Whereas the BMS group showed compaction of the neointima over time, there were very modest increases in neointima in the SR and MR groups between 6 months and 2 years, with significant reductions relative to the control. (3) The initial increase in persistent area that coincides with neointimal suppression in both TAXUS groups during the first 6 months regressed completely in the SR group and partially in the MR group during the following 18 months to 2 years.

Change in Plaque Area Outside the Stent

In both paclitaxel groups, a significantly increased persistent area was observed at 6 months. This expansive remodeling regressed at 2 years, resulting in comparable levels of persistent area to the BMS group. One might hypothesize that this could be a result of the “drug effect” associated with a potentially delayed healing process. The mode of action of polymer-based, paclitaxel-eluting stents is believed to be associated with a delay in cellular processes within the vessel wall. This effect is exemplified in animal models by later endothelialization, reduced smooth muscle cell proliferation, and increased fibrin disposition around the stent struts.3 Long-term follow-up beyond 2 years may provide more insight regarding the possibility of a continued delay versus a persistent alteration of the remodeling processes outside the stent.

Mean persistent area is driven by vessel area minus stent area. Thus, ISA area influences persistent area. The occurrence of late acquired ISA at 6 months that was resolved at 2 years can also explain the plaque remodeling pattern outside the stent in this study. However, the incidences of late acquired ISA at 6 months that were resolved at 2 years were low (1.3% in the BMS, 4.7% in the SR, and 4.9% in the MR groups). In addition, because the change in vessel area was similar to the change in persistent area, plaque remodeling outside the stent can be mainly accounted for by changes in plaque area, not ISA.

The current in vivo findings are limited to areal comparisons between groups and do not account for potentially different cellular compositions of the areas inside and outside the stent among the groups. New IVUS technologies, such as computer-assisted gray-scale value analysis and virtual hist-
Long-Term Effect of Inhibition of Neointimal Growth

Both neointimal area from IVUS analyses and the change in MLD from QCA analyses are parameters of neointimal growth. In the present study, there are apparent discrepancies between the change in neointimal area and the change in MLD from 6 months to 2 years, especially in the TAXUS groups. Although average neointimal area increased in both TAXUS groups from 6 months to 2 years, average MLD did not decrease during the same time period. Neointimal area is calculated by considering neointimal growth in the entire stented segment. The change in MLD is calculated by considering the worst region, regardless of axial location. Thus, MLD does not account for diffuse neointimal growth over the entire length of the stent. These differences demonstrate that neointimal area is a better index of the magnitude and distribution of neointimal growth within the stent segment and may account for some of the discrepancies between the change in neointimal area and the change in MLD in this study.

Carter et al\(^1\) reported that the inhibition of neointimal hyperplasia after deployment of polymer-coated, sirolimus-eluting stents was not sustained at 90 and 180 days owing to delayed cellular proliferation associated with increased levels of proliferative cell nuclear antigen. Farb et al\(^2\) reported that neointimal suppression after deployment of chondroitin sulfate– and gelatin-coated, paclitaxel-eluting stents was also not maintained at 90 days. In this human IVUS study, from 6 months to 2 years, there was a small but significant increase in neointima of unclear clinical significance observed in the TAXUS group. At variance with the animal studies mentioned earlier, the present study of a distinctly different polymer and dose-release formulation shows that a significant effect on neointimal suppression was still present at the 2-year follow-up when compared with the BMS.

In this large IVUS 2-year substudy, neointimal regression in the BMS group confirmed findings previously reported from other long-term follow-up assessments of the natural healing process after stent implantation. Kimura et al\(^3\) reported that mean in-stent luminal diameter as measured by serial QCA analysis was improved from 1.95 to 2.09 mm between 6 months and 3 years. This observation is in agreement with a postmortem human coronary artery analysis. A hypercellular neointima, rich in type III collagen, versican, and hyaluronan but relatively little type I collagen, was observed as long as 18 months after BMS implantation in humans. After 18 months, neointimal tissue regressed because of the replacement of water-trapping proteoglycans (hyaluronan and versican) by decorin and type I collagen. After drug-eluting stent implantation, this pathological change may be delayed owing to chronic vessel responses induced by the presence of a durable polymer that still contains the drug. The histological findings of atherectomy specimens of neointimal tissue after implantation of a paclitaxel derivative–eluting polymer stent showed persistent fibrin accumulation with smooth muscle cells and a proteoglycan- and type III collagen–rich matrix associated with inflammation at 12 months.\(^4\)

Although long-term follow-up after drug-eluting stent implantation has shown a sustained clinical benefit in several randomized trials, little is known about neointimal growth beyond the first 6 to 9 months.\(^5,6\) The longest available angiographic follow-up after drug-eluting stent implantation (sirolimus-eluting stents) is 4 years. From 2 to 4 years, neointimal growth was still observed.\(^6\) When neointimal growth after drug-eluting stent implantation begins to subside is unknown. The issue of a “late catch-up phenomenon” (delayed restenosis), which was observed after brachytherapy, has not been fully investigated with drug-eluting stents.\(^7,8\) Longer follow-up with serial angiographic and IVUS analyses are needed to resolve this issue.

Interestingly enough, this phenomenon of long-term compaction of the neointima was not observed in the TAXUS arm of this substudy up to 2 years. One might argue that this can also be attributed to the mode of action of paclitaxel, as discussed earlier, resulting in a general delay in vascular responses. In contrast to the findings outside the stent, no potential dose-dependent differences could be identified inside the stent. This raises the interesting question of different dose thresholds and time kinetics for paclitaxel-induced effects on different cellular compartments. Longer-term follow-up studies will be needed to further understand these phenomena.

Change of Plaque Area Outside the Stent and Neointimal Growth

The relation between persistent remodeling and neointimal growth after BMS implantation has been a controversial topic. Nakamura et al\(^9\) reported an inverse correlation between percent persistent volume change and percent intrasistent neointimal volume change \((r=-0.517, P<0.0001)\), whereas Hoffman et al\(^10\) reported a weak positive correlation \((r=0.282, P=0.058)\). However, the remodeling of the persistent area observed in the present study had no relation to neointimal growth inside the stent in all groups.

Incomplete Stent Apposition

Regional expansive remodeling has been established as the cause of late ISA after BMS implantation.\(^11\) In this study, plaque outside the stent shrank from 6 months to 2 years. As a result, the incidence of late acquired ISA at 2 years was lower than at 6 months. After drug-eluting stent implantation, the multiple effects of the eluted drugs also influence the phenomenon of ISA; the antiproliferative effect may preclude the growth of tissue in the void between the struts, and the antimetabolic effect may induce either necrosis or apoptosis, which may generate a new empty space between the struts.\(^12,13\) However, the incidences of ISA in both the SR and MR paclitaxel stent groups for 2 years were similar to those observed in the BMS group. In other words, the antiproliferative and antimetabolic effects of the drug did not affect the incidence of ISA at 2 years, and the clinical relevance of ISA is dubious.\(^14\) Previously, one case of ISA at 6 months that
evolved into a coronary aneurysm at 18 months after sirolimus-eluting stent implantation was reported. However, such a phenomenon was not observed in this study.

Limitations
The virtual impossibility of analyzing exactly the same ultrasonic cross sections is a major limitation in serial ultrasound studies. To minimize this limitation, the 3-dimensional IVUS reconstruction with semiautomatic contour tracing in several reconstructed, longitudinally cut planes was adapted for this study.

In addition, this study is a substudy of the TAXUS II trial, which is analyzing outcomes in a highly selected subgroup of event-free patients with focal, de novo lesions, and serial 2-year data were obtained in approximately half of the original 6-month cohort of 314 patients. Although the serial data at 6 months were comparable to the original 6-month cohort data, this selection might theoretically limit transferability to the overall patient cohort.

Conclusions
Increased plaque outside the stent 6 months after paclitaxel-eluting stent implantation regressed completely in the SR group and partially in the MR group by 2 years. Neointimal suppression with both SR and MR paclitaxel-eluting stents was sustained for as long as 2 years. Whereas neointima decreased in the BMS group between 6 months and 2 years, neointima continued to increase in the SR and MR groups without effect on clinical events. Although plaque outside the stent began to shrink by 2 years, longer-term follow-up will be required to establish the natural history of local paclitaxel delivery.

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Disclosure
Dr Russell is a full-time employee of and stockholder in Boston Scientific Corp. Dr Koglin is a full-time employee of Boston Scientific Corp. Dr Dudek has a consultant/advisory board position with Boston Scientific Corp and has received fees for speaking at interventional cardiology meetings from Boston Scientific Corp. Dr Drzewiecki has received a research grant from Boston Scientific Corp. Dr Dudek has a consultant/advisory board position with Boston Scientific Corp and has received fees for speaking at interventional cardiology meetings from Boston Scientific Corp. Dr Russell is a full-time employee of and stockholder in Boston Scientific Corp. Dr Guagliumi has received a research grant from Boston Scientific Corp. The other authors report no conflicts.

References
Although long-term follow-up after drug-eluting stent implantation has shown a sustained clinical benefit in several randomized trials, little is known about neointimal and plaque growth beyond the first 6 to 9 months. In the IVUS analyses of the TAXUS II study, neointimal suppression with both SR and MR paclitaxel-eluting stents was sustained for as long as 2 years. Whereas neointima decreased in the BMS group between 6 months and 2 years, neointima continued to increase in the SR and MR groups without affecting clinical events. Although plaque outside the stent began to shrink by 2 years, a longer-term follow-up will be required to establish the natural history of local paclitaxel delivery. The issue of delayed restenosis, which has been observed after brachytherapy, has not been thoroughly evaluated with drug-eluting stent.
Peristent Remodeling and Neointimal Suppression 2 Years After Polymer-Based, Paclitaxel-Eluting Stent Implantation: Insights From Serial Intravascular Ultrasound Analysis in the TAXUS II Study

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