Chronic Arterial Responses to Polymer-Controlled Paclitaxel-Eluting Stents
Comparison With Bare Metal Stents by Serial Intravascular Ultrasound Analyses: Data From the Randomized TAXUS-II Trial

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Background—Polymer-controlled paclitaxel-eluting stents have shown a pronounced reduction in neointimal hyperplasia compared with bare metal stents (BMS). The aim of this substudy was to evaluate local arterial responses through the use of serial quantitative intravascular ultrasound (IVUS) analyses in the TAXUS II trial.

Methods and Results—TAXUS II was a randomized, double-blind study with 536 patients in 2 consecutive cohorts comparing slow-release (SR; 131 patients) and moderate-release (MR; 135 patients) paclitaxel-eluting stents with BMS (270 patients). This IVUS substudy included patients treated with one study stent who underwent serial IVUS examination after the procedure and at 6-month follow-up (BMS, 152 patients; SR, 81; MR, 81). The analyzed stented segment (15 mm) was divided into 5 subsegments in which mean vessel area (VA), stent area (SA), lumen area (LA), intrastent neointimal hyperplasia area (NIHA), and peristent area (VA-SA) were measured. NIHA was significantly reduced in SR (0.7±0.9 mm², \(P<0.001\)) and MR (0.6±0.8 mm², \(P<0.001\)) compared with BMS (1.9±1.5 mm²), with no differences between the two paclitaxel-eluting release formulations. Longitudinal distribution of neointimal hyperplasia throughout the paclitaxel-eluting stent was uniform. Neointimal growth was independent of peristent area at postprocedure examination in all groups. There were progressive increases in peristent area from BMS to SR to MR (0.5±1.7, 1.0±1.8, and 1.4±2.0 mm², respectively; \(P<0.001\)). The increase in peristent area was directly correlated with increases in VA.

Conclusions—Both SR and MR paclitaxel-eluting stents prevent neointimal formation to the same degree compared with BMS. However, the difference in peristent remodeling suggests a release-dependent effect between SR and MR.

Key Words: stents ■ restenosis ■ drugs ■ angioplasty

Stent-based local drug delivery with a number of different types of pharmacological agents has been demonstrated to reduce neointimal hyperplasia within the stent.1-3 However, late chronic arterial responses to drug-eluting stents have not yet been fully characterized. Even the arterial responses to bare metal stents remain controversial as to whether peristent remodeling occurs after stent implantation.4-8 Furthermore, in studies detecting peristent remodeling, its relation to the amount of neointimal hyperplasia is controversial.5,6

Paclitaxel interferes with microtubule function, which leads to the inhibition of cell division and migration, thereby...
interrupting the restenotic cascade. Early clinical feasibility trials suggested paclitaxel-eluting stents as a safe and potentially efficacious way to treat de novo lesions and in-stent restenosis. These promising preliminary results were confirmed by the randomized, double-blind, TAXUS II trial, which showed significant improvement in clinical, quantitative angiography and intravascular ultrasound (IVUS) parameters of restenosis. The aim of this study was to evaluate the arterial responses to paclitaxel-eluting stents through the use of serial quantitative IVUS analyses in the TAXUS II trial.

Methods

Patient Selection
Between June 2001 and January 2002, the TAXUS II trial at 38 sites enrolled 536 patients who were randomly assigned (1:1) into 2 consecutive and independent cohorts. Patients in the first cohort received either the TAXUS-NIRx slow-release formulation (SR) paclitaxel-eluting stent or the control bare metal stent (BMS). Those in the second cohort were randomly assigned to either the TAXUS-NIRx moderate-release formulation (MR) paclitaxel-eluting stent or the BMS. Patients were eligible if they had a single de novo target lesion of a native coronary artery with an estimated stenosis between 50% and 99%, lesion length <12 mm, and vessel diameter between 3.0 and 3.5 mm. The current IVUS substudy included patients who received a study stent and underwent serial IVUS examination following the procedure and at 6-month follow-up. The study protocol was approved by the ethics review committees for all participating centers. All patients gave written informed consent before enrollment.

Study Device and Procedure

The stent used in this study was the NIR Conformer stent (Boston Scientific Corporation and Medinol Ltd). All stents were 15 mm long and 3.0 or 3.5 mm in diameter. The paclitaxel-eluting stent (TAXUS NIRx) was identical to the BMS except that it was coated with a total load of 1.0 μg/mm² of paclitaxel incorporated into a proprietary polymer (Translute) that provides controlled biphasic release. For both stents, the initial burst release over the first 48 hours after implantation is followed by a low-level release phase for approximately 10 days. The difference between both stents is a 5-fold higher release rate in the initial burst of the TAXUS-MR stent when compared with the TAXUS-SR stent.

The balloon predilation procedure was performed followed by study stent implantation, with the use of standard techniques. A postdilation procedure was performed if necessary. There were no objective angiographic or IVUS criteria for ensuring optimal stenting. During the procedure, intravenous heparin was given to maintain an activated clotting time ≥250 seconds. All patients received a 300-mg clopidogrel loading dosage followed by 75 mg daily (or 250 mg ticlopidine twice daily) for 6 months and 75 mg aspirin daily indefinitely.

Quantitative Angiographic and IVUS Analysis

Quantitative coronary angiographic (QCA) and IVUS analyses were performed by an independent core laboratory that continues to be blinded to patient allocation (Cardialysis). IVUS was performed with an automated pullback at 0.5 mm/s to examine the stented vessel segments. The lumen, stent, and external elastic membrane (EEM) contours were detected with the use of CURAD QCU analysis software (Curad BV), applying 3-D reconstruction, as described elsewhere. If the EEM could not be detected (because of extensive calcification with acoustic shadowing), that patient was excluded from this substudy. For the analysis of the longitudinal distribution, the stented segment was arbitrarily divided into 5 subsegments, each 3 mm long, as previously described. In the stented segment and in each subsegment, mean total vessel area (VA), mean stent area (SA), and mean lumen area (LA) were measured. Mean neointimal hyperplasia area (NIHA) and percent area (PSA) were derived by SA−LA and VA−SA, respectively. Percentage of NIHA and PSA were calculated as NIHA/SA×100 and PSA/VA×100, respectively.

Statistical Analysis

Pooling of the BMS groups of the two cohorts were combined because the baseline and 6-month follow-up data showed no significant differences. 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 tested with Fisher’s exact test. Continuous variables are expressed as mean±SD. General analyses were performed on a per-patient basis; if indicated, analyses were performed on a per-segment basis. Delta values (Δ) for each measurement were calculated as follow-up minus postprocedure values. When comparing 3 groups, overall probability values were derived from 1-way ANOVA. Comparisons between postprocedure and 6-month follow-up were performed with a 2-tailed paired t test. Comparisons between 2 groups were performed with Fisher’s least significant difference test. Linear regression was performed on a per-segment basis to assess the correlation between IVUS indexes. A value of P<0.05 was considered statistically significant.

Results

Baseline Characteristics

Of the 536 randomly assigned patients, 314 with serial and analyzable IVUS entered this substudy (BMS, 152; SR, 81; MR, 81). There were 5 subsegments analyzed per patient yielding a total of 1570 subsegments. The patients’ baseline clinical and procedural characteristics are shown in Table 1. In this subgroup, the left circumflex coronary artery was more frequent as a target vessel in the TAXUS-MR group compared with the BMS (P=0.015). The other baseline characteristics were comparable among the 3 groups.

| TABLE 1. Baseline Clinical and Procedural Characteristics |
|----------------|----------------|----------------|
|                | BMS            | Taxus SR       | Taxus MR       |
| No. of patients| 152            | 81             | 81             |
| Age            | 59.2±9.8       | 60.5±10.2      | 59.1±10.2      |
| Male, %        | 78.9           | 71.6           | 74.1           |
| Current smoker, %| 26.3          | 25.9           | 25.9           |
| Diabetes mellitus, %| 13.8        | 11.1           | 14.8           |
| Hypertension, %| 60.5           | 61.7           | 58.0           |
| Hypercholesterolemia, %| 73.0       | 80.2           | 72.8           |
| Unstable angina, %| 32.2         | 32.1           | 31.3           |
| Prior MI, %    | 44.7           | 42.0           | 35.8           |
| Target vessel, %|               |                |                |
| LAD            | 48.7           | 37.0           | 42.0           |
| LCx            | 11.8           | 19.8           | 24.7*          |
| RCA            | 39.5           | 43.2           | 33.3           |
| Balloon artery ratio | 1.1±0.2   | 1.1±0.2        | 1.1±0.2        |
| Maximal inflation pressure, atm | 12.1±2.6     | 12.4±2.8       | 12.0±3.0       |
| Stent size, mm | 3.2±0.25       | 3.3±0.25       | 3.22±0.25      |
| Reference vessel diameter, mm | 2.71±0.38     | 2.81±0.43      | 2.72±0.43      |

Values are presented as relative percentages or mean±SD. LAD indicates left anterior descending artery; RCA, right coronary artery; and LCx, left circumflex artery. *P<0.05 vs BMS group.
Quantitative IVUS Data

Table 2 summarizes quantitative IVUS parameters analyzed on a per-patient basis. IVUS parameters at postprocedure examination were comparable among the 3 groups. At 6-month follow-up, both the TAXUS-SR (0.7 ± 0.9 mm²) and the TAXUS-MR (0.6 ± 0.8 mm²) groups showed a significant reduction in mean NIHA compared with the BMS (1.9 ± 1.5 mm²; \( P < 0.001 \)). As shown in Figure 1, there was a statistically significant increase in mean VA in all groups between postprocedure and follow-up (BMS < TAXUS-SR < TAXUS-MR, ANOVA \( P < 0.001 \)). Second, there was an increase in PSA showing the same ranking (ANOVA \( P < 0.001 \)). Finally, there were decreases in LA between baseline and follow-up for all groups. This decrease was significantly larger in the BMS (1.7 ± 1.7 mm²) than in the SR (0.6 ± 1.1 mm²; \( P < 0.001 \)) and MR (0.5 ± 1.3 mm²; \( P < 0.001 \)). However, there were no release-dependent differences in lumen reduction between the SR and the MR groups.

Table 2. Quantitative IVUS Data

<table>
<thead>
<tr>
<th></th>
<th>BMS</th>
<th>Taxus SR</th>
<th>Taxus MR</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>152</td>
<td>81</td>
<td>81</td>
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<tr>
<td>Postprocedure</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean VA, mm²</td>
<td>16.3 ± 3.4</td>
<td>16.9 ± 3.6</td>
<td>16.2 ± 3.7</td>
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<tr>
<td>Mean SA, mm²</td>
<td>8.2 ± 1.6</td>
<td>8.6 ± 1.8</td>
<td>8.4 ± 1.9</td>
</tr>
<tr>
<td>Mean LA, mm²</td>
<td>8.2 ± 1.6</td>
<td>8.6 ± 1.8</td>
<td>8.4 ± 1.9</td>
</tr>
<tr>
<td>Mean PSA, mm²</td>
<td>8.1 ± 2.5</td>
<td>8.3 ± 2.3</td>
<td>7.8 ± 2.4</td>
</tr>
<tr>
<td>% PSA, %</td>
<td>48.9 ± 7.7</td>
<td>48.5 ± 6.3</td>
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<td>6-mo follow-up</td>
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<tr>
<td>Mean VA, mm²</td>
<td>16.9 ± 3.4</td>
<td>18.0 ± 4.0</td>
<td>17.7 ± 4.2</td>
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<tr>
<td>Mean SA, mm²</td>
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<td>8.7 ± 1.9</td>
<td>8.5 ± 2.0</td>
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<tr>
<td>Mean LA, mm²</td>
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<td>8.1 ± 1.9*</td>
<td>7.8 ± 2.1*</td>
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<td>Mean PSA, mm²</td>
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<td>Mean NIHA, mm²</td>
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<td>0.6 ± 0.8*</td>
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<tr>
<td>% NIHA, %</td>
<td>22.8 ± 17.4</td>
<td>7.4 ± 9.6*</td>
<td>7.7 ± 9.8*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. 
* \( P < 0.05 \) vs BMS group.

Figure 1. Changes of quantitative intravascular parameters between postprocedure examination and 6-month follow-up.

Distribution of Neointimal Hyperplasia

The distribution of neointimal hyperplasia among the 5 subsegments at follow-up in each group is shown in Figure 2A. There was no predilection for neointimal growth to occur within any 3-mm subsegments either in the TAXUS-SR or the TAXUS-MR group nor in the BMS (ANOVA; \( P = 0.95, 0.80, \) and \( 0.35 \), respectively). As shown in Figure 2B, the distribution of PSA at postprocedure was not uniform. Therefore, the correlation between IVUS indexes including PSA and VA was analyzed on a per-segment basis.

Correlation Between IVUS Parameters

Table 3 summarizes regression analyses performed between IVUS parameters. In all groups, there was no significant correlation between PSA before the procedure and NIHA at follow-up, suggesting that residual plaque burden after the procedure does not affect neointimal formation. There was a significant positive correlation between \( \Delta VA \) and \( \Delta PSA \) in all groups (\( P < 0.0001 \)). \( \Delta VA \) did not correlate with NIHA in either group.

Discussion

The major findings of this study are the following: (1) Both SR and MR paclitaxel-eluting stents inhibit neointimal growth to the same degree when compared with BMS. (2) Persistent remodeling occurs in BMS as well as the TAXUS groups. There are progressive increases in PSA from BMS to
SR to MR. (3) The degree of persistent remodeling (change in PSA) is not quantitatively related to the amount of neointimal hyperplasia. (4) Finally, there is no correlation between plaque burden after the procedure and subsequent neointimal hyperplasia.

**Inhibitory Effect of Paclitaxel on Neointimal Hyperplasia**

The SR and MR stents showed a significant reduction in neointimal area compared with the BMS by 73% and 79%, respectively, and this inhibition was uniformly distributed along the stent (Figure 2A), indicating the homogeneous longitudinal diffusion pattern of paclitaxel from the stent. Paclitaxel has been shown to exert dose-dependent, antiproliferative effects on smooth muscle cells in vitro and in in vivo models. In the standard-risk, de novo lesions treated in the TAXUS II, there was no difference in the neointimal reduction between the two release formulations with differing kinetic profiles. The comparable reduction in neointimal hyperplasia suggests that the critical paclitaxel threshold to interrupt the restenotic cascade had been reached with the SR formulation in this low-risk lesion subset. These two release formations differ in that the polymer matrix regulates the amount of paclitaxel that is released in the early burst phase (first 48 hours), with an 8-fold increase in MR compared with SR.

**Effect of Paclitaxel on Stented Tissue Growth (Intrastent and Peristent)**

Paclitaxel may allow an increase in cells or matrix behind the stent, while preventing smooth muscle cells from proliferating and migrating into the stent. Figure 3 shows the comparison of the value of ΔPSA + NIHA among the 3 groups. This measure of stented tissue growth (intrastent and peristent) increased from SR to MR compared with control. This suggests that the increase in cells and/or matrix is less pronounced in the SR formulation. Ongoing studies (TAXUS V and VI) will address the issue of whether different release profiles will alter restenosis outcomes in higher risk lesions.

**Peristent Remodeling After Stent Implantation**

There is controversy as to whether persistent remodeling occurs after bare stent implantation. In 3 retrospective studies evaluating a total of 121 patients, Mudra et al,4 Koyama et al,7 and König et al8 independently reported that remodeling did not occur. Conversely, the presence of remodeling was reported by 2 groups (Hoffmann et al9 and Nakamura et al10) from an aggregate of ≈100 patients. In this TAXUS II IVUS substudy with more than 300 patients, we establish unequivocally that persistent remodeling occurs in BMS as well as TAXUS stents, and there were increases in PSA from BMS to SR to MR.

**Relation Between Peristent Remodeling and Neointimal Hyperplasia**

In the previous studies in which persistent remodeling was detected, the relation to the amount of neointimal hyperplasia is conflicting. Nakamura et al10 reported an inverse correlation, whereas Hoffmann et al9 demonstrated a positive correlation. In our large, randomized, blinded study with core laboratory analysis, the IVUS data establishes that neointimal hyperplasia is not quantitatively correlated with persistent remodeling in either BMS or TAXUS stents.

**Impact of Plaque Burden at Baseline on Neointimal Hyperplasia**

Initial plaque burden, referred to as persistent areas (PSAs) in this study, has been suggested to be important in restenosis because it correlated with neointimal hyperplasia in previous IVUS studies. However, there are more recent reports showing contrasting results. Plaque burden may play any number of roles in tissue responses within and out of the stent. On the one hand, it may serve as a source for cells and growth factors involved in the restenotic process; on the other, it may be a physical barrier that buffers the medial injury caused by stent struts and thus it may attenuate neointimal formation. These opposite facets may counteract each other, leading to the disparity in IVUS findings. The TAXUS II data set establishes the absence of a relation
between plaque burden and neointimal growth in the BMS group.

It is of paramount importance to investigate whether plaque burden affects the efficacy of drug-eluting stents. The size and composition of the plaque may effect drug diffusion, penetration, and activity. We found that for both the SR and MR, there was no relation between plaque burden and neointimal hyperplasia. Since the plaque has no predictive value with respect to neointimal hyperplasia, IVUS assessment of the plaque burden will have no decision-making utility in customizing drug-eluting stents with differing potencies.

Study Limitations
First, the analyses were limited to the patients with serial IVUS, in which the EEM could be well visualized, raising the possibility of selection bias in IVUS sampling. However, this is a randomized, blinded study with a large IVUS sample size compared with previous IVUS studies, which minimizes this bias. Second, patients had relatively low risk profiles and simple lesions related to the inclusion criteria of the TAXUS II trial. Therefore, the results cannot be extrapolated to a general population of diverse patients. Third, this represents a time frame of only 6 months that may not predict subsequent findings or relations identified in this data set.

Conclusions
This study strongly supports the notion that there is no quantitative relation between plaque burden and neointimal hyperplasia after stent implantation. This would argue that the amount of postprocedural plaque burden has no predictive value for the anticipated restenosis rate in the long-term follow-up. By using the sensitivity of IVUS technology in a large cohort of patients, we show that both slow and moderate release of paclitaxel-eluting stents reduce neointimal hyperplasia to the same degree. However, by studying persistent remodeling, we demonstrate release-dependent effects on the global vessel wall response within and around the stent.

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References
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