Effect of the polymer-based, paclitaxel-eluting TAXUS Express stent on vascular tissue responses: a volumetric intravascular ultrasound integrated analysis from the TAXUS IV, V, and VI trials


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Aims The TAXUS® Express® stent has been shown to reduce angiographic restenosis, repeat revascularizations, and neointimal hyperplasia when compared with bare metal stent (BMS) control (TAXUS IV, V, and VI) in individual TAXUS trials. Since intravascular ultrasound (IVUS) methodology and core laboratory were consistent among all three TAXUS trials, an integrated analysis of 956 patients across all IVUS cohorts can be performed providing superior power.

Methods and results In the TAXUS randomized trials, patients received an Express BMS or paclitaxel-eluting TAXUS Express stent. Volumetric analysis was performed on a selected subgroup at implantation and 9 months. Compared with BMS control, TAXUS increased 9-month lumen volumes (144 ± 79 vs. 179 ± 95 mm3; P, 0.0001) due to reduced neointimal volume (66 ± 49 vs. 27 ± 30 mm3; P, 0.0001). This corresponded to a 61% decrease in net lumen volume obstruction (31 ± 15 vs. 12 ± 12 mm3; P < 0.0001). Lumen loss was similar between groups for the proximal 5 mm outside the stent but was reduced in TAXUS at the distal edge (P = 0.0056). Neointimal hyperplasia was significantly reduced in the double-strut region of overlapping TAXUS vs. BMS control and in high-risk patients with diabetes, long lesions, multiple stents, and multiple overlapping stents. Late-acquired incomplete apposition (ISA) was more common with moderate-release TAXUS stents. Importantly, there were no major adverse cardiac events or stent thromboses in any late-acquired ISA patient through 2 years. Univariate and multivariable analyses revealed that longer lesion length and previous myocardial infarction are risk factors for late-acquired ISA.

Conclusion Integrated analysis of the TAXUS trials shows that the paclitaxel-eluting TAXUS Express stent effectively inhibits in-stent neointimal proliferation, even in high-risk and overlapping stent patients.

KEYWORDS
Stents; Restenosis; Diabetes mellitus; Revascularization; Ultrasons

Introduction

Individual TAXUS Express randomized, controlled trials have demonstrated the efficacy of the TAXUS® Express® polymer-based, paclitaxel-eluting coronary artery stent in reducing angiographic restenosis and the need for repeat revascularization procedures.1–4 However, compared with angiographic parameters, serial volumetric intravascular ultrasound (IVUS) provides a more detailed analysis of the extent and distribution of in-stent neointimal hyperplasia, incomplete apposition, and vascular responses at the stent edges. IVUS results have been previously reported for TAXUS II and IV;5–7 however, the results from subsequent IVUS substudies in TAXUS V de novo and VI have yet to be reported. The current integrated analysis combines the IVUS data from the TAXUS trials that use the TAXUS Express stent (TAXUS IV, TAXUS V de novo, and TAXUS VI) in order to gain a better understanding of the vascular responses after TAXUS stent implantation. The use of a standardized IVUS acquisition protocol and a single-core IVUS...
laboratory across trials provides consistency conducive to an integrated analysis. The increased sample size afforded by the IVUS integrated analysis is particularly useful in situations where increased statistical power is necessary to study small groups, such as high-risk patient subgroups, overlapping stents, and rare events such as late-acquired incomplete stent apposition (ISA).

Methods

The three TAXUS Express trials that used the polymer-based, paclitaxel-eluting TAXUS Express stent in de novo lesions (TAXUS IV, TAXUS V de novo, TAXUS VI) were included in this integrated analysis and are described individually in Table 1.1,2,4 All three studies were double-blind, randomized, controlled trials of the polymer-based, paclitaxel-eluting stent in de novo coronary artery lesions. Patients were randomized to receive either a bare metal Express® stent or a polymer-based, paclitaxel-eluting TAXUS Express stent (all stents Boston Scientific Corporation, Natick, MA, USA). All patients provided written informed consent. The individual studies were reviewed and approved by the institutional review committees at the respective institutions and the studies complied with the Declaration of Helsinki. The primary endpoint for the three trials was the rate of target vessel revascularization 9 months after the index procedure. Secondary IVUS trial endpoints were the absolute neointimal volume and in-stent per cent net volume obstruction at follow-up. Additional IVUS endpoints included the minimum lumen area (MLA) and neointima area within stent, stent and lumen volume, change in mean vessel area from post-procedure to follow-up, and change in plaque area at both edges from post-procedure to follow-up. Further details of the individual trial study designs and clinical results have been published previously.1,2,4

Intravascular ultrasound imaging and analysis

Clinical sites were selected based on their IVUS experience, volume, and willingness to enroll all study patients. Volumetric IVUS was performed immediately after stent implantation and at 9-month follow-up in all patients at the IVUS substudy sites of each trial until the pre-specified enrolment numbers were obtained.

IVUS imaging was performed after intracoronary administration of 0.1–0.2 mg nitroglycerin using a motorized pullback system (0.5 mm/s) and contemporary, commercial scanners. Images were continuously recorded throughout the stent and at least 5 mm distal and proximal to the stent. All images were recorded onto S-VHS videotape or digitally (DICOM) and sent to an independent core laboratory at the Washington Hospital Center (Washington, DC, USA) that was blinded to the treatment arm. Using computerized planimetry (Tapemeasure, Indec Inc., Mountain View, CA, USA), the reference segment external elastic membrane, plaque, stent, and lumen areas were measured every millimetre within the stent plus 5 mm beyond each stent edge. Neointimal area was calculated as stent area minus lumen area. IVUS images with technically inadequate image quality, inconsistent pullback speed, and those with incomplete visualization of the vascular interface were excluded from the volumetric analysis. Adequacy of the image for analysis was determined in a blinded fashion. Volumes were calculated only if the vascular interface was visualized every millimetre throughout the stent.

ISA was defined as a separation of at least a single stent strut from the intimal surface of the arterial wall post-procedure. Late-acquired ISA was defined as a separation of at least a single strut from the intimal surface of the arterial wall that was not present post-implantation.8 Paired post-procedure and 9-month follow-up films were used to access late-acquired ISA. Further details of the IVUS imaging and analysis method have been previously published.8

Statistical analysis

Individual patient data were integrated from the three TAXUS Express trials (TAXUS IV, TAXUS V de novo, and TAXUS VI) into one common database representing outcomes across two paclitaxel release formulations [slow release (SR) and moderate release (MR)]. For binary data, homogeneity of the odds ratios across the three TAXUS Express studies was assessed with the Breslow-Day test, which tests the null hypothesis that the odds ratios of the treatment effect across studies are equal. P > 0.05 in the test suggests a homogeneous treatment effect across studies, justifying pooling of the results. If the Breslow-Day test indicated a treatment-by-study interaction, then the quantitative interaction with treatment effect in the same direction but of different magnitude was investigated. If there was no evidence to contradict the assumption of homogeneity across different TAXUS Express studies, the treatment effect of drug-eluting stents (DES) over bare metal stent (BMS) control from the pooled data was assessed using a two-sided Fisher’s exact test. Similarly, for continuous data, analysis of variance was used to assess the treatment by study interaction and the treatment effect. Data are presented as frequencies or mean ± 1 standard deviation (SD).

Comparisons between BMS control and TAXUS Express stents were performed with two-tailed, unpaired t-tests for continuous parameters, paired t-tests for change from post-procedure to follow-up, and Fisher’s exact tests for categorical variables. The effect of individual predictors, including patient co-morbidities and lesion characteristics, on late-acquired stent incomplete apposition was assessed by univariate analysis. Multivariable analysis was used to determine predictors on late-acquired stent incomplete apposition and target lesion revascularization (TLR). Standard procedures for multivariable selection using logistic regression model were followed.9 Statistical significance was set at P < 0.05. Continuous variables in the model were checked for linearity assumption and were satisfied. We used both backwards and stepwise selection procedures on the same set of variables to examine the robustness of the results. The following variables were examined: stent type, gender, diabetes, age, procedural GP IIb/IIIa inhibitor use, hyperlipidaemia, hypertension, lesion location, previous MI, unstable angina, current smoking, multiple stents, baseline
aneurysm, post-procedure stent length (IVUS), post-procedure in-stent MLA (IVUS), post-procedure mean reference vessel area (IVUS), post-procedure per cent in-stent net volume obstruction, post-procedure reference vessel diameter by QCA (TLR analysis only), and post-procedure in-stent per cent diameter stenosis by QCA (TLR analysis only).

Results
From 956 patients enrolled in the IVUS substudies [268 (28%) in TAXUS IV, 509 (53%) in TAXUS V de novo, and 179 (19%) in TAXUS VI], post-procedure films were analysed in 633 patients with non-missing, non-excluded data, while 9-month follow-up films were analysed in 566 patients with non-missing, non-excluded data. Breslow–Day testing for homogeneity indicated that the estimated treatment effects (odds ratios) across trials were homogeneous, thus allowing pooling of the data across stent platforms and formulations. Patient flow is outlined in Figure 1.

Baseline and procedural characteristics
As shown in Table 2, patients in the IVUS substudy (n = 956) compared with non-IVUS patients (n = 1960) had a higher incidence of diabetes mellitus (28.6 vs. 25.0%; P = 0.0434), more Type C/ACC/AHA lesions (35.9 vs. 31.2%; P = 0.0129), longer baseline lesion length (16.7 ± 8.7 vs. 15.7 ± 7.9 mm; P = 0.0012), and a higher incidence of multiple stenting (26.0 vs. 20.5%; P < 0.0001). This imbalance was due to the preponderance of the integrated analysis patients drawn from the TAXUS V de novo study (53% of the IVUS subgroup; Figure 1), a US-based trial designed to enroll patients with highly complex lesions. Within the IVUS subgroup, TAXUS Express and BMS control patients were well matched (Table 2). Post-implantation vessel volume, stent volume, and lumen volume were similar in the TAXUS Express and BMS control groups (Table 3).

In-stent neointimal suppression
At 9-month follow-up, vessel volume and stent volume were again similar between the BMS control and TAXUS Express groups (Table 3). However, TAXUS Express patients had a larger lumen volume due to significantly reduced neointima volume. When normalized for the stent volume, the neointima volume occupied 12.4 ± 11.8% (in-stent net volume obstruction) in the TAXUS Express group when compared with 31.3 ± 14.8% for the BMS control group (P < 0.0001), a reduction of 60%.

To assess the uniformity of neointimal suppression across the stent, an in-depth analysis of the entire vessel covered by the stent was conducted on a subset of patients in the
Table 2  Baseline demographics and lesion characteristics

<table>
<thead>
<tr>
<th></th>
<th>Entire TAXUS IV, V, VI population (n = 2916)</th>
<th>IVUS subgroup only (n = 956)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not in IVUS subgroup (n = 1960)</td>
<td>IVUS subgroup (n = 956)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.6 ± 10.9</td>
<td>62.7 ± 10.6</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>28.2 (552)</td>
<td>28.7 (274)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>25.0 (490)</td>
<td>28.6 (273)</td>
</tr>
<tr>
<td>Reference vessel diameter (mm)</td>
<td>2.73 ± 0.52</td>
<td>2.74 ± 0.51</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>15.7 ± 7.9</td>
<td>16.7 ± 8.7</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td>25.57 ± 11.0</td>
<td>27.05 ± 12.06</td>
</tr>
<tr>
<td>Type C lesions (%)</td>
<td>31.2 (609)</td>
<td>35.9 (341)</td>
</tr>
<tr>
<td>Multiple stents (%)</td>
<td>20.5 (402)</td>
<td>26.0 (249)</td>
</tr>
<tr>
<td>Stent overlap length (mm)</td>
<td>5.69 ± 2.53</td>
<td>5.99 ± 2.46</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD.

Table 3  TAXUS IV, V, and VI pooled volumetric intravascular ultrasound measurements

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>TAXUS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-implantation</td>
<td>n = 312</td>
<td>n = 321</td>
<td>0.46</td>
</tr>
<tr>
<td>Stent, mm³ (n)</td>
<td>216 ± 109 (312)</td>
<td>210 ± 101 (321)</td>
<td>0.44</td>
</tr>
<tr>
<td>Lumen, mm³ (n)</td>
<td>216 ± 109 (312)</td>
<td>210 ± 101 (320)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nine-month follow-up</td>
<td>n = 292</td>
<td>n = 292</td>
<td>0.33</td>
</tr>
<tr>
<td>Stent, mm³ (n)</td>
<td>210 ± 105 (274)</td>
<td>204 ± 105 (292)</td>
<td>0.33</td>
</tr>
<tr>
<td>Lumen, mm³ (n)</td>
<td>144 ± 79 (274)</td>
<td>179 ± 95 (291)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neointima, mm³ (n)</td>
<td>66 ± 49 (274)</td>
<td>27 ± 30 (292)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Net volume obstruction</td>
<td>31.3 ± 14.8 (274)</td>
<td>12.4 ± 11.8 (292)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD.

aVolumes were calculated only if the vascular interface was visualized every millimetre throughout the stent.

bP-values are from t-test comparing the difference in mean between the control and TAXUS groups.

TAXUS IV, V, and VI trials (Figure 2). To this end, sequential 1 mm segments were analysed throughout the entire stent length. To account for differing stent lengths, results from individual 1 mm segments were averaged into three areas: (i) proximal stent; (ii) stent centre, and (iii) distal stent. Mean neointimal area (Figure 2) was significantly reduced throughout the stent in the TAXUS Express group relative to the BMS control group (proximal 2.0 ± 1.3 vs. 0.8 ± 1.1 mm²; P < 0.0001; centre 2.5 ± 1.6 vs. 0.8 ± 1.1 mm², P < 0.0001; distal 2.3 ± 1.3 vs. 0.9 ± 1.3 mm², P < 0.0001).

Edge analysis

Stent edge analysis was performed for five 1 mm segments beyond the proximal and distal stent edges (Figure 3). The mean change in plaque area at the proximal stent edge from post-procedure to 9-month follow-up was comparable between BMS control and TAXUS Express (−1.0 ± 0.2 vs. −0.8 ± 0.2; P = 0.32). However, a statistically significant difference in the mean change in plaque area was observed at the distal edge of the stent between BMS control and TAXUS Express (−0.8 ± 0.1 vs. −0.4 ± 0.1; P = 0.0056). At the distal edge, significant reductions were seen in the TAXUS Express group for the first three 1 mm segments closest to the stent (Segments 1, 2, and 3), but not for the most distal two segments (Segments 4 and 5). Lumen loss in the two most distal segments (Segments 4 and 5) was due to a combination of plaque accumulation and negative remodelling, which was observed in both the TAXUS Express and BMS control groups.

Neointimal suppression in overlapping stent segments

To assess the ability of the TAXUS Express stent to suppress neointimal hyperplasia in overlapping stents (n = 80), per millimetre analysis was also done to compare 9-month per cent net lumen volume obstruction in the double-strut region vs. single-strut regions of overlapping stents for TAXUS V de novo and VI (Table 4). The TAXUS Express stent significantly reduced neointimal hyperplasia in both the single- and double-strut region of overlapping stents. In addition, whereas bare metal control stents had significantly more neointimal hyperplasia in the double-strut compared with single-strut regions (P = 0.0109), neointimal hyperplasia was numerically lower in double-strut region of overlapping TAXUS Express stents when compared with single-strut regions (P = 0.31).

Results in high-risk patient subgroups

In bare metal stenting, patients with diabetes, long lesions, and those treated with multiple stents are at a higher risk for restenosis and repeat revascularization events.10–12 The efficacy of the TAXUS Express stent in reducing neointimal hyperplasia in several high-risk subgroups was examined.
Lumen volume obstruction was significantly reduced by 60% or more with TAXUS compared with BMS control in all high-risk subgroups examined which included patients with diabetes (13.7 vs. 34.9%; P, 0.0001), lesions 26 mm in length (13.4 vs. 34.6%; P, 0.0001), multiple stents (13.4 vs. 33.7%; P, 0.0001), and overlapping stents (13.0 vs. 33.8%; P, 0.0001). The ability of the TAXUS Express stent to significantly inhibit neointimal growth in high-risk patients and lesions was very consistent and comparable to the overall IVUS population.

Incomplete apposition
Bare metal control and TAXUS Express patients had comparable rates of post-procedure ISA (6.1 vs. 8.4%; P = 0.25). At 9 months, paired post-procedure and follow-up films were
examined for late-acquired ISA (n = 547). Late-acquired ISA was more common in TAXUS Express patients when compared with BMS control [8.4% (24/287) vs. 3.5% (9/260); P = 0.0189]. This difference was driven primarily by an increase in late-acquired ISA with TAXUS MR stents compared with bare metal MR stents [16.7% (13/78) vs. 3.5% (9/260); P = 0.0001]. The rate of late-acquired ISA with the MR stent was also higher compared with the SR stent [16.7% (13/78) vs. 5.3% (11/209); P = 0.0035]. In contrast to the MR stent, there was no difference in the incidence of late-acquired ISA after implantation of TAXUS SR stents compared with bare metal SR [5.3% (11/209) vs. 3.5% (9/260); P = 0.37]. Additionally, as is shown in Table 5, there were no major adverse cardiac events (MACE) or stent thromboses in any patient with late-acquired ISA between 9 months (when late-acquired ISA was diagnosed) and 2 years (the latest follow-up time point).

**TAXUS slow-release and moderate-release stents**

Besides the higher incidence of late-acquired ISA with the TAXUS MR stent compared with the SR, additional differences existed between the two stent formulations. In the TAXUS VI trial, which used the MR stent, patients had significantly longer lesions (21.3 ± 7.6 mm) than in the SR stent cohort in TAXUS IV and V de novo trials (16.1 ± 8.5, P < 0.0001), which used the SR stent. At 9 months, there was no difference in the percent net volume obstruction between the SR and MR stents (12.82% vs. 10.71%; P = 0.21). There were differences observed in positive remodeling between the SR and MR stents as measured by mean vessel area change from post-procedure to follow-up. With the MR stent, there was a higher degree of positive remodeling observed compared with the SR stent (1.85 ± 1.8 mm² vs. 0.60 ± 1.9 mm²; P = 0.0056).

**Risk factors for late-acquired incomplete stent apposition**

Univariate analysis was performed on the pooled TAXUS and BMS control data to determine the risk factors for late-acquired ISA (Figure 5). Many variables were examined including lesion length, previous MI, gender, diabetes, and age. The analysis revealed that both lesion length (OR 1.05; P = 0.0118) and previous MI (OR 2.42; P = 0.0145) were risk factors for late-acquired ISA. Multivariable analysis was also conducted on the pooled TAXUS and BMS control data to assess the risk factors for late-acquired ISA. On the basis of the multivariable analysis, lesion length is a risk factor for late-acquired ISA with an odds ratio of 1.04 (95% CI 1.00–1.09; P = 0.0396). On the basis of these analyses, longer lesion length increases the risk of late-acquired ISA.

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**Table 4** Per cent net lumen volume obstruction in single- and double-strut regions of overlapping stents in TAXUS V de novo and VI²

<table>
<thead>
<tr>
<th>Per cent net lumen volume obstruction</th>
<th>Control (n = 35)</th>
<th>TAXUS Express (n = 45)</th>
<th>P-value (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-strut regions (%)</td>
<td>33.4 ± 16.6</td>
<td>11.3 ± 10.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Double-strut region (%)</td>
<td>39.0 ± 17.1</td>
<td>9.8 ± 12.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P-value (2)</td>
<td>P = 0.0109</td>
<td>P = 0.31</td>
<td></td>
</tr>
</tbody>
</table>

Data are given as mean ± SD.

²Data from TAXUS V de novo and VI only.

P-value (1) is from an unpaired t-test comparing treatment groups (control vs. TAXUS).

P-value (2) is from a paired t-test comparing single- vs. double-strut regions within treatment groups.

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**Figure 4** Per cent in-stent volume obstruction in high-risk subgroups. Per cent in-stent net volume obstruction area was significantly reduced with the TAXUS Express stent in all high-risk subgroups examined. P-values are from t-test for the treatment difference between the two groups. Values are mean ± standard error.
Risk factors for target-lesion revascularization

Seventy-five of the 633 patients (TAXUS or BMS control) with post-procedure IVUS films had a TLR during the follow-up period (24/321 TAXUS vs. 51/312 BMS control). Multivariable analysis was conducted for numerous clinical, angiographic, and IVUS variables to determine the risk factors for TLR. The analysis revealed that longer stent length by IVUS (OR 1.03; \( P = 0.0044 \)) was a significant risk factor for TLR, whereas TAXUS stent treatment (OR 0.39; \( P = 0.0004 \)) and larger MLA post-procedure by IVUS (OR 0.73; \( P < 0.0001 \)) reduced the risk for TLR.

Discussion

Although individual IVUS analyses have demonstrated that the TAXUS Express polymer-based, paclitaxel-eluting coronary stent effectively inhibits neointimal proliferation,\(^5\)-\(^7\) the relatively small sample sizes of these studies limit their ability to assess vascular tissue responses in high-risk subgroups and to explore the frequency and significance of uncommon effects (e.g. incomplete apposition or edge effects). The present integrated analysis, combining all of the IVUS data from each patient across TAXUS IV, V de novo, and VI, has found the ability of the TAXUS Express stent to suppress neointimal hyperplasia across the entire length of the stent, at the distal stent edge in double-strut regions of overlapping stents, and in several high-risk subgroups. In addition, the incidence and lack of clinical events with ISA was demonstrated.

The patients in this population were at high risk, with diabetes present in 29%, mean lesion length of 17 mm, 36% Type C lesions, and 26% of lesions requiring multiple stents. Across this complex set of lesions, the TAXUS Express stent effectively reduced in-stent neointimal tissue proliferation, resulting in a larger in-stent lumen volume at follow-up compared with an otherwise identical BMS. This reduction in neointimal hyperplasia was seen throughout the entire stented length, as well as in the distal 3 mm beyond the stent. In addition, the ability of the TAXUS Express stent to reduce neointima was preserved in double-strut regions of overlapping stents (in contrast to the BMS in which neointima was increased in the overlap region) and was consistent in patients with diabetes, multiple stents, and long lesions.

Late ISA has been observed after implantation of both BMS and DES,\(^1\)-\(^3\) with an incidence as high as 25% for sirolimus-eluting stents.\(^1\) In our integrated analysis, the rate of late-acquired ISA was 8.4% and was more common with the TAXUS MR than the SR stent. Although there was no difference in the 9-month per cent net volume obstruction between the SR and MR TAXUS stents, vessel area change during the 9-month follow-up was higher in the MR than in the SR stent, suggesting a more pronounced positive remodelling with the MR stent. On the other hand, lesion...
length was found to be a predictor of late-acquired ISA, and since substantially longer lesions were treated with the MR than with the SR stent, the higher incidence of late-acquired ISA in the TAXUS Express MR stent could be independent from the release formulation. Reports of incomplete apposition in randomized trials of DES,\textsuperscript{13,16} as well as this analysis, have indicated that this phenomenon is not associated with an increase in MACE, death, or stent thrombosis. However, the number of patients is too small and the patient follow-up is not sufficient to make definitive conclusions.

This study demonstrated $12.4 \pm 11.8\%$ in-stent net volume obstruction in the TAXUS Express group when compared with $31.3 \pm 14.8\%$ for the bare metal control stent ($P < 0.0001$). The findings in the bare metal control group are similar to most other IVUS stent studies, which have reported 25–35\% in-stent net volume obstruction.\textsuperscript{5,16–19} Similarly, the neointima net volume obstruction in the TAXUS Express stent is similar to findings in other paclitaxel-coated stents.\textsuperscript{16,17} A 12\% net volume obstruction is higher than that reported in most sirolimus-eluting stent trials,\textsuperscript{19,20} which is consistent with the higher degree of late loss by angiography with paclitaxel-eluting stents vs. sirolimus-eluting stents. However, this small degree of neointima was not associated with a difference in clinical events and may allow for complete covering of the stent struts and a lower incidence of late-acquired ISA.

This IVUS integrated analysis demonstrated no negative edge effects in the TAXUS Express stent when compared with the BMS control group, which is consistent with the individually published TAXUS II and TAXUS IV trial results.\textsuperscript{5,6} All stents induce some plaque accumulation and negative remodelling at the stent edges and these effects are more noticeable in stents without neointimal growth. Nonetheless, the TAXUS Express stent appears to have beneficial effects in the first few millimetres beyond the distal stent edge resulting in less lumen loss. Although the mechanism is unknown, this finding may be due to a ‘downstream’ beneficial effect from the drug on the stent.

TLR was more common in the BMS control arm (16.3\%). In fact, 53\% more BMS control patients underwent a TLR compared with TAXUS patients. A multivariable analysis was conducted to determine the predictors of TLR in the IVUS integrated analysis. Clinical, angiographic, and IVUS variables were examined. The multivariable analysis revealed that TAXUS stent treatment reduced the risk for TLR, which further confirmed the TLR event rates observed for the two groups. Shorter stent length and larger MLA post-procedure by IVUS also reduced the risk for TLR. Interestingly, the examined angiographic variables were not identified as significant risk factors for TLR in the stepwise multivariable model suggesting that IVUS provides valuable predictive information for TLR.

Limitations
This analysis is a post hoc study of previous multicentre, randomized, controlled, prospective TAXUS Express trials and is not, in itself, a prospective study and thus it is impossible to evaluate the prognostic value and incremental benefits of IVUS. Additionally, while the individual trials did use the same IVUS acquisition protocol and IVUS core laboratory, differences in dose formulation (SR vs. MR) could theoretically have introduced between-trial variability, although none was detected by a statistical test for homogeneity. As with all IVUS studies, it is not possible to have 100\% follow-up; this may decrease the statistical power. For instance, patients with total occlusions, high-grade lesions and acute myocardial infarctions may not have undergone repeat IVUS. However, this study population remains one of the largest trial-based IVUS data sets with serial long-term follow-up.

Conclusions
This integrated analysis, the largest trial-based IVUS sub-study of the polymer-based, paclitaxel-eluting TAXUS Express stent, shows that this stent is effective in reducing in-stent neointimal proliferation even in double-strut regions of overlapping stents and in high-risk patient populations.

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