Impact of Drug-Eluting Stents on Distal Vessels

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Background—Previous studies have not addressed vessel response >5 mm distal to the stent edge. Therefore, we investigated the impact of paclitaxel-eluting stents (PES) versus bare metal stents (BMS) on distal vessels in the serial intravascular ultrasound substudies of TAXUS IV, V, and VI.

Methods and Results—TAXUS IV, V, and VI were double-blind, randomized, multicenter, controlled trials comparing PES with BMS. In their intravascular ultrasound substudies, 103 patients (54 BMS, 49 PES) had intravascular ultrasound data ≥10 mm distal to the stent both postprocedure and at 9 months follow-up. Baseline characteristics were similar between the 2 groups. Multilevel modeling was used to account for the variation between patients and within patients among distal segments. Effect of stent type, time, and their interaction was tested using a mixed effect model controlling for distal segments. Postprocedure lumen and vessel were not significantly different between PES versus BMS; however, lumen ($P=0.006$) and vessel ($P=0.0001$) were significantly reduced for BMS at 9-month follow-up but not for PES. Conversely, there was a significant plaque increase from postprocedure to 9-month follow-up for PES ($P=0.0008$) but not for BMS. These vessel responses were statistically consistent among 0- to 5-mm versus 5- to 10-mm versus 10- to 15-mm segments distal to the stent in both groups.

Conclusions—PES use was associated with plaque increase from baseline to 9-month follow-up >5 mm distal to the stent along with positive remodeling, whereas BMS use was associated with negative remodeling and no plaque increase. These vessel responses were consistent in 5-mm long subsegments: 0 to 5 mm versus 5 to 10 mm versus 10 to 15 mm distal to the stent.


Key Words: distal vessel ■ drug-eluting stent ■ vessel response

Compared with bare metal stents (BMS), drug-eluting stents (DES) have a lower incidence of target lesion revascularization and less neointimal hyperplasia.1,2 There is, however, a potential toxic effect of DES on arterial tissue due to delayed endothelialization and persistent inflammation.3–6 Furthermore, there is considerable evidence that patients who receive DES have endothelial dysfunction in segments distal to the DES.7–17 Serial intravascular ultrasound (IVUS) studies have reported intrastent and proximal and distal edge responses of DES. In general, proximal edge effects were similar, but distal edge effects were different between DES and BMS with positive (or less negative) remodeling causing lumen enlargement (or less lumen reduction) in DES compared with BMS.18–22 However, previous serial IVUS studies did not evaluate vessel responses >5 mm distal to the DES. We therefore integrated the serial IVUS substudies from the various TAXUS trials (TAXUS IV, TAXUS V, and TAXUS VI)23–25 to study the vessel responses >5 mm distal to a paclitaxel-eluting stent (PES) compared with the equivalent BMS. These IVUS substudies used a standardized IVUS acquisition protocol and a single-core IVUS laboratory.
WHAT IS KNOWN

• The comparative effects of BMS and DES on changes in coronary plaque and wall dimensions at the site of treatment are well described.

WHAT THE STUDY ADDS

• The response of a coronary artery distal to a stent differs according to whether the stent is drug-eluting or bare metal.
• Distal to a BMS, there is luminal narrowing with progressive negative remodeling.
• Distal to a DES, there is positive remodeling but increase in plaque volume.

Methods

Protocol Design

The TAXUS IV, TAXUS V, and TAXUS VI trials were prospective, double-blind, randomized controlled trials of the polymer-based PES in single, 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).

PES was the commercially available slow-release formulation in the TAXUS IV and V studies and the moderate release formulation in TAXUS VI (not commercially available). TAXUS IV consisted of 73 investigative sites and enrolled 1314 patients; TAXUS V enrolled 1156 patients at 66 sites; and TAXUS VI enrolled 446 patients at 44 sites. IVUS substudies included 268, 509, and 179 patients, respectively. Prospective IVUS subanalyses were prespecified in each trial; sites were selected based on their IVUS experience, volume, and willingness to enroll all study patients in the substudy until the prespecified numbers were obtained. All IVUS studies were performed immediately after stent implantation, and patients were scheduled for repeat IVUS at 9 months follow-up.

All patients provided written informed consent. The individual committees of the respective institutions and the studies complied with the Declaration of Helsinki. The primary end point for the 3 trials was the rate of target vessel revascularization 9 months after the index procedure. IVUS substudy end points included the absolute neointimal volume and in-stent percent net volume obstruction at follow-up. Further details of the individual trial study designs and clinical results have been published previously.

IVUS Imaging and Analysis

IVUS imaging was performed after intracoronary administration of 0.1 to 0.2 mg nitroglycerin using a motorized pullback system (0.5 mm/s) and contemporary, commercial scanners. All images were recorded onto sVHS videotape or digital media and sent to the MedStar Health Research Core Laboratory at Washington Hospital Center (Washington, DC), which was blinded to the treatment arm. Fourteen patients, 29 frames of 4 patients could not be contoured (0.5 mm/s) or significant calcification that precluded measurement of the EEM. This volumetric index was used to compare EEM, plaque and media, and lumen volumes between PES versus BMS within each of these 3 subsegments. Randomization to PES or BMS, risk factors, and procedure characteristics were blinded in all IVUS measurements.

Statistical Analysis

Statistical analyses were performed with SPSS Version 17.0 (SPSS Inc, Chicago, IL). Categorical variables were summarized as frequencies and percentages and were compared between groups using χ² statistics or Fisher exact test, as appropriate. Continuous variables were presented as mean±1 SD and compared between groups using 2-tailed, unpaired t tests or, if parameters were not normally distributed, using the Mann-Whitney test. Continuous variables were compared between postprocedure and follow-up using 2-tailed, paired t tests or, if parameters were not normally distributed, then using Wilcoxon test. All patient data were included in the 0- to 5-mm and 5- to 10-mm volume analyses. Patients with >50% of the slices (ie, with at least 12.5 mm of vessel imaged distal to the stent) were included in the 10- to 15-mm volume analysis. Analysis of variance or Kruskal-Wallis test was used to assess the difference among 0- to 5-mm, 5- to 10-mm, and 10- to 15-mm segments appropriately.

IVUS substudies of the 3 TAXUS trials included 956 patients. Paired postprocedure and follow-up IVUS studies were available in 547 patients; among them, 443 did not have IVUS imaging >10 mm distal to the stent in both studies or had technically inadequate image quality, and 1 patient had inconsistent transducer pullback speed. Thus, 103 patients fit the current inclusion protocol: 54 BMS and 49 PES (Figure 1). Among 1404 paired frames in the overall cohort of 103 patients, 29 frames of 4 patients could not be contoured because of calcium; those frames were excluded. Fourteen patients had a significant side branch (>2 mm) in the segment distal to the stent; in them, 27 frames containing a side branch were excluded.

Results

Baseline Characteristics

Clinical characteristics and multiple stent use in the present study were similar to the entire cohort (n=2916), IVUS substudy (n=956), and IVUS nonsubstudy (n=1960). As shown in Table 1, baseline clinical, demographic, and angiographic characteristics were similar between BMS-treated and PES-treated patients in the present study population. There were no statistically significant differences in the baseline IVUS measurements in the15-mm-long distal refer-
At follow-up within 0 to 5 mm distal to the stent, only the BMS group showed significant lumen reduction \( (P = 0.076 \text{ and } P = 0.088, \text{ respectively}) \). These data are shown in Table 2 and Figure 3.

At follow-up, at 5 to 10 mm distal to the stent, the BMS group did not show any difference in plaque mass \( (P = 0.034) \), whereas the BMS group showed significant plaque increase at 9 months \( (P = 0.007) \) associated with negative vascular remodeling \( (P = 0.012) \), whereas the PES group still did not show any differences \( (P = 0.42 \text{ and } P = 0.57, \text{ respectively}) \); Table 2). The PES group showed significant plaque increase at 9 months \( (P = 0.034) \), whereas the BMS group did not show any difference in plaque mass \( (P = 0.57) \). There were insufficient data for a meaningful analysis of the 5-mm long subsegment 15 to 20 mm distal to the stent edge.

Changes in EEM, plaque, and lumen volumes were comparable among 0 to 5 mm versus 5 to 10 mm versus 10 to 15 mm in the BMS group \( (P = 0.60, P = 0.20, \text{ and } P = 0.56, \text{ respectively}) \). Similarly, changes in EEM, plaque, and lumen volumes were comparable among 0 to 5 mm versus 5 to 10 mm versus 10 to 15 mm in the PES group \( (P = 0.98, P = 0.88, \text{ and } P = 0.93, \text{ respectively}) \). This indicated a consistent vessel response from the distal stent edge to 15 mm distal to the stent.
studies.19,20,23–25

These results were similar to those from previous

P22.8% versus 23.2%
diameter stenosis (37.6% versus 14.0%

10–15 mm Control (n=54) PES (n=49) P Value

<table>
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<tr>
<th>Vessel VI, mm²/mm</th>
<th>Postprocedure</th>
<th>Control (n=54)</th>
<th>PES (n=49)</th>
<th>P Value</th>
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<tr>
<td>Lumen VI</td>
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<td>9-mo follow-up</td>
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<td>P value</td>
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<td>0.27</td>
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</table>

| 5–10 mm Control (n=54) PES (n=49) P Value |
|-----------------------------------------|-----------|-------|
| Vessel VI                               |           |       |
| Postprocedure                            | 9.8±3.7   | 10.4±4.4 | 0.40 |
| 9-mo follow-up                           | 9.2±3.7   | 10.5±4.5 | 0.14 |
| P value                                 | 0.004     | 0.78   |       |
| Plaque VI                               | 4.3±2.5   | 4.7±2.9 | 0.39 |
| 9-mo follow-up                           | 4.4±2.6   | 4.9±3.1 | 0.31 |
| P value                                 | 0.40      | 0.019  |       |
| Lumen VI                                | 5.5±2.0   | 5.6±2.4 | 0.70 |
| 9-mo follow-up                           | 4.8±1.9   | 5.5±2.5 | 0.15 |
| P value                                 | <0.001    | 0.37   |       |

| 10–15 mm Control (n=29) PES (n=30) P Value |
|------------------------------------------|------------|-------|
| Vessel VI                                |            |       |
| Postprocedure                             | 9.9±4.1    | 10.8±4.3 | 0.46 |
| 9-mo follow-up                            | 9.1±3.9    | 10.9±4.1 | 0.094|
| P value                                  | 0.012      | 0.57   |       |
| Plaque VI                                | 3.9±2.5    | 4.8±2.8 | 0.23 |
| 9-mo follow-up                            | 3.8±2.1    | 5.2±3.1 | 0.049|
| P value                                  | 0.57       | 0.034  |       |
| Lumen VI                                 | 6.0±2.3    | 6.0±2.5 | 0.96 |
| 9-mo follow-up                            | 5.3±2.4    | 5.7±2.1 | 0.51 |
| P value                                  | 0.007      | 0.42   |       |

IVUS indicates intravascular ultrasound; PES, paclitaxel-eluting stents; VI, volume index.

Overall, percent in-stent net volume obstruction at 9 months was higher in BMS than in PES (31.6±17.2% versus 14.0±13.6%, P=0.001) as was percent in-stent diameter stenosis (37.6±22.8% versus 23.2±22.3%, P=0.001). These results were similar to those from previous studies.19,20,23–25

There was a moderate correlation between percent in-stent net volume obstruction and remodeling (Δvessel), but only within the 0- to 5-mm segment distal to BMS (r=−0.37, P=0.012). There was no correlation between percent in-stent net volume obstruction and Δvessel in the 5- to 10-mm (r=−0.15, P=0.32) or 10- to 15-mm (r=−0.29, P=0.18) segments distal to BMS or within any of the segments distal to PES (0–5 mm, r=−0.22, P=0.17; 5–10 mm, r=−0.19, P=0.24; 10–15 mm, r=−0.26, P=0.22). Furthermore, there was no correlation between percent in-stent net volume obstruction and plaque progression (Δplaque and media) within any of the 3 segments distal to BMS (0–5 mm, r=−0.14, P=0.36; 5–10 mm, r=0.04, P=0.81; 10–15 mm, r=−0.07, P=0.76) or PES (0–5 mm, r=0.16, P=0.43; 5–10 mm, r=−0.12, P=0.46; 10–15 mm, r=−0.10, P=0.62). Finally, there was no correlation between remodeling and baseline plaque and media.

After excluding patients with a side branch, this analysis was repeated in the remaining 89 patients (BMS n=50, PES n=39). The results observed in this subanalysis were not significantly different from the analyses done for the entire population (data not shown).

Examples of the distal segments 15 mm beyond the BMS and PES at baseline and at follow-up are shown (Figure 4).

Mixed Effect Model

As seen in Table 2 and Figure 3, the effects of stent and time on lumen, vessel, and plaque were consistent across the distal groups (0–5 mm, 5–10 mm, and 10–15 mm). Postprocedure, lumen and vessel were not significantly different between BMS and PES. Lumen and vessel were significantly reduced (by 0.7 mm² and 0.6 mm², respectively) for the BMS group at 9-month follow-up (P=0.0006 and P=0.0001, respectively), whereas changes in lumen and vessel (−0.2 mm² and 0.1 mm², respectively) from postprocedure to 9-month follow-up were not significant for PES. There was a significant plaque increase (0.3 mm²) from postprocedure to 9-month follow-up for PES (P=0.0008); however, there was no significant plaque increase (0.1 mm²) from postprocedure to 9-month follow-up for BMS.

Although the effects of stent and time were consistent, lumen, vessel, and plaque varied significantly among distal subsegments 0 to 5 mm, 5 to 10 mm, and 10 to 15 mm. Compared with the 0- to 5-mm distal subsegment, the lumen area significantly decreased by 0.3 mm² for the 5- to 10-mm subsegment (P=0.02), but not for the 10- to 15-mm subsegment. Compared with the 0- to 5-mm subsegment, vessel area significantly decreased for both the 5- to 10-mm subsegment and the 10- to 15-mm subsegment by 0.9 mm² and 1.3 mm², respectively (P<0.0001 for both). Compared with the 0- to 5-mm subsegment, plaque area significantly decreased for both the 5- to 10-mm subsegments and the 10- to 15-mm subsegments by 0.6 mm² and 1.1 mm², respectively (P<0.0001 for both).

Discussion

In the present study we evaluated the behavior of the distal vessel >10 mm distal to the stent with some patients having serial IVUS imaging as much as 20 mm distal to the stent. The major findings of the present study are as follows: (1) the use of PES has a beneficial effect on the distal vessel with significantly less lumen reduction when compared with BMS;
(2) positive vessel remodeling caused less lumen reduction distal to the PES, whereas negative remodeling was observed in BMS; these vessel responses were consistent from the distal stent edge to 15 mm distal vessel; and (3) significant plaque increase was observed in 5- to 10-mm and 10- to 15-mm distal vessel of PES from baseline to 9 months follow-up, whereas little plaque increase was detected in BMS.

**Effect of DES on Distal Vessels**

Previous studies have reported that BMS implantation has an impact on the distal edge segment with progressively more vessel decrease and progressively less plaque increase at greater distances from the edge of the stent.18–20,26–29 Lumen reduction due to negative remodeling was consistent from 3 to 10 mm distal to the stent.27 The present study showed similar findings in the 0- to 10-mm segment distal to a BMS that continued into the more distal vessel segments (Figures 2 and 3C).

Detailed analysis of the effects of BMS and PES on proximal and distal stent edges (0–5 mm) have been published previously.18–20 TAXUS II18 was a randomized, double-blind trial that compared PES with BMS. At 6 months follow-up, patients treated with PES had significantly less lumen reduction at the distal edge (0–5 mm) compared with patients treated with BMS due to the occurrence of positive remodeling ($P<0.0005$). Using a relatively large cohort ($n=547$) from the TAXUS IV, V, and VI trials, Weissman et al20 showed less lumen reduction due to less negative remodeling (or actual positive remodeling) at the distal edge of PES compared with BMS, especially in the image slices closest to the stent; conversely, proximal edge changes were similar comparing PES and BMS. Similar findings have been observed in other types of DES both in sirolimus-eluting stents (SES)21,30 and in zotarolimus-eluting stents.29 These findings at 0 to 5 mm distal to the stent were consistent with the present study by showing less lumen reduction with less negative remodeling compared with BMS (Figures 2 and 3A). In this article, we expanded the observations beyond the 5-mm segment distal to the stent edge.

The present study found less lumen reduction with positive vascular remodeling at the 5- to 15-mm distal vessel to PES compared with BMS during 9 months of follow-up (Figures 2 and 3B–C). Surprisingly, significant plaque increase was observed in the 5- to 10-mm and 10- to 15-mm distal vessel of PES from baseline to 9 months follow-up, whereas little plaque increase was detected in BMS (Table 2). At follow-up, patients treated with PES tended to have more plaque increase compared with BMS (Figure 3B–C). Vessel response post-PES implantation among 0 to 5 mm versus 5 to 10 mm versus 10 to 15 mm was similar (Figure 3A–C). Although less lumen reduction seems beneficial, these vessel responses post-PES implantation could be recognized as a side effect of the drug.

Only 1 serial IVUS study reported data on the segment 5 to 10 mm distal to the stent but in SES implanted in the setting of an acute myocardial infarction (SES $n=20$, BMS $n=20$).22
In that study, patients treated with SES had lumen enlargement, whereas patients treated with BMS had lumen reduction (change of mean lumen area 0.2±0.8 versus −0.8±1.6 mm²; P=0.04) due to vessel remodeling (change of vessel volume 0.5±3.9 versus −5.6±12.5 mm³; P=0.08). These findings support our results (Figure 3B) although the type of DES is different. It has recently been reported that similar, the PES group had less lumen reduction and positive vascular remodeling (P=0.055, P=0.015) and more plaque increase (P=0.071) compared with the BMS group in the 10- to 15-mm segment distal to the stent (C). Δvessel, Δplaque, and Δlumen volume were comparable between 0 to 5 mm versus 5 to 10 mm versus 10 to 15 mm in the BMS group (P=0.60, P=0.20, and P=0.56, respectively) and in the PES group (P=0.98, P=0.88, P=0.93, respectively). This indicated a consistent vessel response from the distal stent edge to 15 mm distal to the stent. BMS indicates bare metal stents; PES, paclitaxel-eluting stents.

**Possible Mechanisms**

Paclitaxel, a lipophilic molecule derived from the Pacific yew tree Taxus brevifolia, is capable of inhibiting cellular division, motility, activation, secretory processes, and signal transduction. A stent coated with such a cell-cycle inhibitor suppresses neointimal hyperplasia growth that consists of smooth muscle cells and extracellular matrix within the stent. DES implantation causes delayed endothelialization, persistent inflammatory status, hypersensitivity, apoptosis, necrosis, and positive remodeling in local segments leading to atherosclerosis progression. Clinical evidence indicates that patients who receive DES more frequently have positive remodeling in stented segments than do patients treated with BMS, thereby resulting in more late-acquired stent malapposition. The present study demonstrates that positive remodeling continues into the far distal vessel after DES implantation (Figure 2). The mechanism underlying positive vessel remodeling post-DES implantation is still unclear; however, inflammation is thought to be involved. It is also plausible that the drug itself may affect the distal vessel tissue resulting in positive remodeling. The potential role of the polymer and the inflammation caused by it cannot be ruled out. 

Endothelial shear stress is an important factor contributing to plaque progression and vascular remodeling. For example, abnormal endothelial shear stress due to in-stent
Restenosis could affect the vessel wall changes within the segments distal to the stent; however, endothelial shear stress was not assessed in the present study. Finally, the distribution of atheroma in the nonstented distal segments might be associated with flow-mediated compensatory enlargement. However, there was no correlation between remodeling and baseline plaque burden.

Increasing evidence indicates that DES implantation causes endothelial dysfunction at stent edge segments and distal vessel segments (10 or 15–20 mm distal to DES) as late as 12 months after stent implantation compared with BMS. Plaque progression is initiated by endothelial dysfunction that allows increased permeability of lipoproteins and upregulation of adhesion molecules. A previous angiographic study indicates that SES promotes the formation of new atherosclerotic yellow lesions within the stented segment at 10 months follow-up. Furthermore, positive vessel remodeling usually accompanies plaque increase to preserve lumen size early in the atherosclerotic process. These previous studies support the results of the present study; significant plaque increase with positive vessel remodeling was observed in the distal vessel to a PES, whereas little plaque increase with negative vessel remodeling was detected in BMS. Thus, it is plausible that DES might induce progression of atherosclerosis in the vessel distal to the stent.

Limitations

Previous animal studies have shown that vascular effects of DES are different among the different types of DES pathologically, although all types of DES provoked late inflammation, whereas BMS did not. Furthermore, it has been reported that biological responses to shear stress might be different among the types of DES. Thus, the impact of DES on distal vessels might differ among DES types. Despite the fact that the TAXUS IV, V, and VI are the largest IVUS multicenter trials, potential selection bias cannot be excluded. Serial IVUS interrogations were performed only in a subset of the patients enrolled in the TAXUS trials, which may have introduced selection bias. Like with all IVUS studies, it is impossible to attain 100% follow-up. Low-density lipoprotein, C-reactive protein, HbA1, and other similar data that might have contributed to these findings were not collected after patient discharge. The reduced sample size for the distal 10- to 15-mm subsegment limited its power; this might be the reason why differences in some parameters were not significant for the 10- to 15-mm subsegment. Finally, only patients who had IVUS data after patient discharge were included in the present study. Nonetheless, baseline clinical, demographic, angiographic characteristics, and IVUS measurements postprocedure were well balanced between the 2 groups.

Conclusions

The use of PES was associated with significant plaque increase from baseline to 9 months follow-up from >5 mm distal to the stent along with positive remodeling. Significant negative remodeling and no plaque increase were observed in BMS. These vessel responses were consistent in 5-mm long subsegments: 0 to 5 mm versus 5 to 10 mm versus 10 to 15 mm. However, a word of caution is in order; and further studies are required to determine whether the findings after PES implantation are favorable or deleterious.

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References


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