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FOCUS ISSUE: DRUG-ELUTING STENTS: TAXUS-IV

Polymer-Based Paclitaxel-Eluting Stents Reduce In-Stent Neointimal Tissue Proliferation

A Serial Volumetric Intravascular Ultrasound Analysis From the TAXUS-IV Trial

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OBJECTIVES The aim of this study was to use serial volumetric intravascular ultrasound (IVUS) to evaluate the effects of polymer-based, paclitaxel-eluting stents on in-stent neointima formation and late incomplete stent apposition.

BACKGROUND The TAXUS-IV trial demonstrated that the slow-release, polymer-based, paclitaxel-eluting stent reduces angiographic restenosis and the need for repeat revascularization procedures. Serial IVUS studies reveal details of the pattern of vascular responses provoked by stent implantation that provide insight into device safety and efficacy.

METHODS In the TAXUS-IV trial, patients were randomized to the slow-release, polymer-based, paclitaxel-eluting TAXUS stent or a bare-metal EXPRESS stent (Boston Scientific Corp., Natick, Massachusetts). As part of a formal substudy, complete volumetric IVUS data were available in 170 patients, including 88 TAXUS patients and 82 controls, at implantation and at nine-month follow-up.

RESULTS No baseline differences were present in the clinical characteristics or IVUS parameters between the control and TAXUS groups. At nine-month follow-up, IVUS lumen volumes were larger in the TAXUS group (123 ± 43 mm^3 vs. 104 ± 44 mm^3, $p = 0.005$), due to a reduction in neointimal volume (18 ± 18 mm^3 vs. 41 ± 23 mm^3, $p < 0.001$). Millimeter-by-millimeter analysis within the stent demonstrated uniform suppression of neointimal growth along the entire stent length. Late lumen loss was similar at the proximal edge of the stent between the two groups, and reduced with the TAXUS stent at the distal edge ($p = 0.004$). Incomplete stent apposition at nine months was observed in only 3.0% of control and 4.0% of TAXUS stents ($p = 0.12$).

CONCLUSIONS Polymer-based, paclitaxel-eluting TAXUS stents are effective in inhibiting neointimal tissue proliferation, and do not result in late incomplete stent apposition. (J Am Coll Cardiol 2005;45:1201–5) © 2005 by the American College of Cardiology Foundation

Recent studies of paclitaxel-eluting and sirolimus-eluting stents have reported dramatic reductions of in-stent restenosis for de novo lesions compared to comparable bare-metal stents based on angiographic assessments (1–4). However, two-dimensional angiographic parameters provide insight limited to luminal characteristics. Volumetric intravascular ultrasound (IVUS) provides complementary information regarding the extent and distribution of neointima, arterial remodeling, vascular responses at the edges, and stent apposition (3,4); the TAXUS-IV is the largest prospective, randomized, multicenter trial of the polymer-based, slow-release paclitaxel-eluting TAXUS stent (2). In the current prospective study, we performed serial IVUS studies in a subset of patients enrolled in the TAXUS-IV trial to evaluate vascular responses after TAXUS stent implantation.

METHODS

In the TAXUS-IV trial, 1,314 patients at 73 U.S. centers undergoing stent implantation of single de novo lesion (2.5

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Abbreviations and Acronyms
EEM = external elastic membrane
IVUS = intravascular ultrasound

to 3.75 mm in diameter and 10 to 28 mm in length by visual estimation) were randomized to receive either the polymer-based, paclitaxel-eluting TAXUS stent or an identical bare-metal EXPRESS stent (Boston Scientific Corp., Natick, Massachusetts). Details of the overall study design and clinical results have been published previously (2). The study was approved by the institutional review board of each participating institution. Eligible patients provided written informed consent.

The current IVUS analysis represents the results of a formal prespecified substudy of 268 patients at 28 centers, designed to recruit a representative cohort. Clinical sites were selected based on their IVUS experience, volume, and willingness to enroll all study patients. Intravascular ultrasound was performed immediately after stent implantation and at nine-month follow-up in all patients at the IVUS substudy sites until the prespecified enrollment was obtained.

IVUS imaging and analysis. Intravascular ultrasound imaging was performed after intracoronary administration of 0.1 to 0.2 mg nitroglycerin using motorized pullback (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. Images were recorded onto SVHS videotape or digitally onto CD or MO disc and analyzed at an independent core laboratory at the Washington Hospital Center (Washington, DC). All IVUS core lab analyses were performed blinded to treatment arm (TAXUS vs. bare-metal stent), and adequacy of the image for analysis was determined before unblinding the data.

Using computerized planimetry (Tapemeasure, Indec Inc., Mountain View, California), the reference segment external elastic membrane (EEM), stent, and lumen were measured every millimeter within the stent and 5 mm proximal and distal to each stent edge. Neointima was calculated as stent minus lumen measures. To correct for different stent lengths, because all stents were at least 16 mm in length, the proximal and distal 7 mm of each stent (14 mm total) were aligned and reported. Volumes were calculated using Simpson's rule, and baseline and follow-up images were aligned using the stent edge. Volumes were calculated only if the vascular interface was visualized every millimeter throughout the stent. Incomplete stent apposition was defined as a separation of at least one stent strut from the intimal surface of the arterial wall; incomplete apposition at nine months was considered "late-acquired" if it was not present after implantation (5). The primary prespecified end point of this analysis was the comparison of intrastent neointimal volume at follow-up between control and TAXUS stents.

Statistical analysis. Anticipating neointimal hyperplasia of 21.3 mm^3 ($\pm$10.7 mm^3) in the control group, 200 patients enrolled provided 80% power to detect a 4.3-mm^3 absolute decrease in neointimal volume in the TAXUS group, a relative 20% reduction. Thus, 268 patients were prespecified for enrollment to allow for 25% attrition due to noncompliance with invasive follow-up procedures, IVUS technical failures, and suboptimal IVUS quality.

Data are presented as frequencies or mean $\pm$ 1 SD. Comparisons between control and TAXUS 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 exact test for categorical variables. Significance was set at alpha of 0.05.

RESULTS

Of the 268 patients in the IVUS substudy, 199 (74.4%) returned for the nine-month angiographic follow-up and had IVUS performed. Volumetric analysis was performed only on IVUS images with a consistent pullback and adequate image quality for every millimeter throughout the stent. After excluding 29 patients for inadequate pullback or poor image quality, volumetric analysis was possible in 170 patients, including 88 and 82 patients receiving TAXUS and control stents, respectively. There were no significant differences in key baseline clinical characteristics between patients in and not in the IVUS substudy, or between the TAXUS and control groups within the IVUS substudy (Table 1). Lesion and stent length were shorter in the

Table 1. Selected Baseline Clinical and Angiographic Characteristics

	Entire Study Population			IVUS Volumetric Analysis Population		
	IVUS Subgroup (n = 268)	Not in IVUS Subgroup (n = 1,046)	p Value	TAXUS (n = 88)	Control (n = 82)	p Value
Age (yrs)	62.5 ± 10.9	62.5 ± 11.1	1.00	63.1 ± 11.8	60.3 ± 9.9	0.10
Male gender	71.6%	72.2%	0.88	78.4%	70.7%	0.29
Diabetes mellitus	28.0%	23.2%	0.11	29.5%	24.4%	0.49
Reference vessel diameter (mm)	2.76 ± 0.52	2.75 ± 0.47	0.88	2.76 ± 0.49	2.86 ± 0.59	0.24
Maximum stent diameter (mm)	3.01 ± 0.38	3.07 ± 0.35	0.024	3.02 ± 0.39	3.07 ± 0.38	0.39
Lesion length (mm)	11.82 ± 4.80	13.77 ± 6.51	<0.0001	12.45 ± 5.20	11.42 ± 4.25	0.16
Study stent/lesion length ratio	1.84 ± 1.08	1.84 ± 0.88	0.95	1.85 ± 1.02	1.94 ± 1.49	0.63

IVUS = intravascular ultrasound.

Table 2. Volumetric Intravascular Ultrasound Measurements

In-Stent	Control (n = 82)	TAXUS (n = 88)	p Value
Post-implantation			
Vessel (mm^3)	285 ± 125	283 ± 91	0.91
Stent (mm^3)	151 ± 56	155 ± 61	0.66
Lumen (mm^3)	151 ± 56	155 ± 61	0.68
Neointima (mm^3)	0 ± 0	0 ± 0	0.24
Nine-month follow-up			
Vessel (mm^3)	283 ± 97	280 ± 89	0.88
Stent (mm^3)	145 ± 51	142 ± 47	0.70
Lumen (mm^3)	104 ± 44	123 ± 43	0.0051
Neointima (mm^3)	41 ± 23	18 ± 18	<0.0001
Net volume obstruction (%)	29.4 ± 14.1	12.2 ± 12.4	<0.0001

IVUS substudy due to enrollment in the earlier phases of the trial.

In-stent neointimal suppression. Intravascular ultrasound volumetric measures appear in Table 2. Post-implantation vessel, stent, and lumen volumes were similar in the control and TAXUS groups. At nine-month follow-up, vessel and stent volumes were again similar between the control and TAXUS groups, but TAXUS patients had significantly larger lumens and reduction in neointimal volume. As a result, the percent net volume obstruction was reduced from 29.4 ± 14.0% for the bare-metal control stent to 12.2 ± 12.4% with the TAXUS stent ($p < 0.001$). The reduction in neointima was uniform throughout the length of the stent; the mean neointimal area was lower in the TAXUS group for each millimeter of analysis within the stent ($p \leq 0.01$) (Fig. 1). Overall vessel volumes were similar between TAXUS and control both at baseline and follow-up. However, positive remodeling assessed as the absolute increase in the EEM volume over time tended to be slightly more prominent with the TAXUS stent (7.66 ± 48.64 mm^3 vs. −12.29 ± 36.05 mm^3, respectively, $p = 0.064$).

Edge analysis. In the 5-mm segment proximal to the stent, late lumen loss was similar for TAXUS and control for each of the 5 mm evaluated. In contrast, at the distal edge, especially within the first 3 mm outside the stent margin, lumen loss was lower for the TAXUS stent (Fig. 1).

Incomplete apposition. As seen in Figure 2, incomplete stent apposition was infrequent and comparable for TAXUS and control groups. Notably, there was only one case of late-acquired incomplete apposition with the TAXUS stent, which was focal (<1 quadrant in circumference and <1 mm in length), compared to two cases with control stents ($p = 0.62$). No episode of incomplete apposition documented by IVUS was associated with a major adverse cardiac event.

DISCUSSION

The current IVUS substudy from the TAXUS-IV trial demonstrates that polymer-based, slow-release, paclitaxel-eluting stents reduce neointimal tissue proliferation resulting in significantly larger in-stent lumen volumes compared to bare-metal stents. These results are concordant with the clinical and angiographic findings from the TAXUS-IV trial showing enhanced freedom from clinical and angiographic restenosis with the TAXUS stent (2).

The degree of neointimal hyperplasia seen in the control stent (29.4%) is similar to other bare-metal stents, which has ranged from 25% to 35% in prior reports (1,3,6–8). The observed reduction in neointimal net volume obstruction with the TAXUS stent to 12.2% in this study is also consistent with the findings from the TAXUS-I (14.8%)

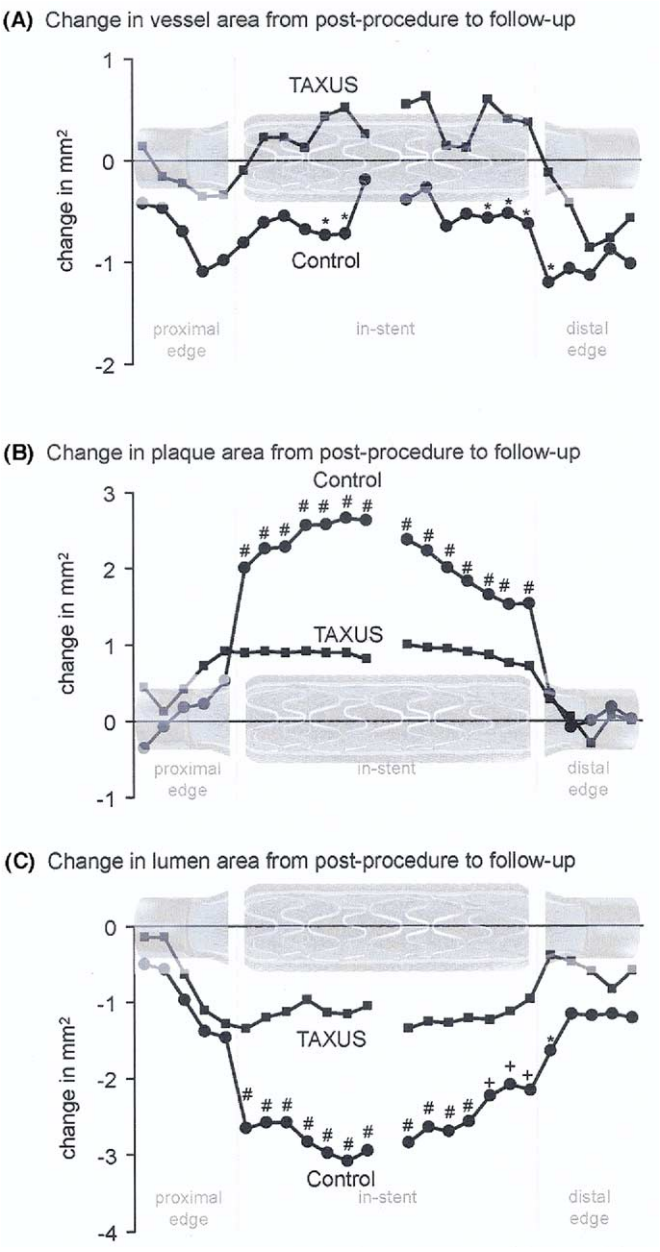

Figure 1. Change in vessel **(A)**, plaque **(B)**, and lumen **(C)** area from post-procedure to nine months for TAXUS and the bare-metal control groups in the stented segments and the edges. Measurements were made every 1 mm, and baseline and follow-up measurements are aligned to the stent edges. Results are reported for the proximal and distal 7 mm of each stent to correct for differences in stent length. Within the stent, neointima growth is displayed in **panel B** rather than plaque outside the stent. *$p < 0.05$; +$p < 0.01$; #$p < 0.001$.

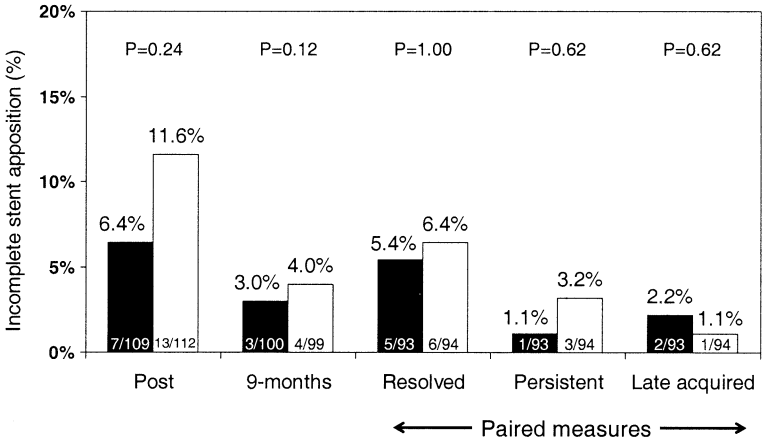

Figure 2. Percentage of patients with incomplete apposition after procedure and at nine-month follow-up. **Solid bars** = control group; **open bars** = TAXUS group.

and TAXUS-II (7.8%) trials, which were completed with different investigator pools and core labs, indicating comparable efficacy in different patient and lesion types (1,7).

In contrast, sirolimus-eluting stents have been characterized in prior IVUS substudies by the near absence of measurable in-stent tissue (3,4). Yet from currently available data, the clinical efficacy (target lesion and vessel revascularization) of paclitaxel- and sirolimus-eluting stents appears roughly comparable, suggesting that accumulation of the small amount of in-stent neointima produced with the TAXUS stent is below the threshold of physiologic significance in most patients.

In the present study, the frequency of late incomplete stent apposition with the TAXUS stent was comparable to the control bare-metal stent, also consistent with prior studies with paclitaxel-eluting stents (1,7). In contrast, the incidence of late incomplete apposition with the sirolimus-eluting stent has ranged from 19% to 21% compared to 4% to 9% for bare-metal stents (3,4,6). The slight excess amount of neointimal hyperplasia with paclitaxel-eluting compared to sirolimus-eluting stents may fill in gaps present either immediately after the procedure, or emerge from positive remodeling during the follow-up period. While the occurrence of late incomplete stent apposition has not been definitively linked to adverse cardiac events (9), patients who develop major adverse events during follow-up often do not undergo routine IVUS follow-up, and optimal patient management when stent malapposition is seen is unsettled.

This study confirms and expands the results from previous studies showing no aggravation of edge stenosis ("candy wrapper" phenomenon) with the TAXUS stent. An attenuated luminal loss was present at the first millimeters of the distal edge with the TAXUS stent compared to controls, similar to that reported from the TAXUS-II trial (7). The absence of a beneficial effect at the proximal edge is at variance with the larger TAXUS-IV angiographic substudy, in which greater angiographic dimensions were present at both stent margins with the TAXUS stent. Possible explanations for the differences between angiographic and IVUS findings may be the smaller sample size and more select nature of patients in the IVUS compared to the angiographic substudy.

Finally, although nine-month vessel volumes were similar when comparing the TAXUS and control stents, a trend was present for slightly more positive remodeling from baseline to follow-up with the TAXUS stent. This pattern was also seen in the TAXUS-II trial, with even more pronounced positive remodeling with the moderate-release formulation. It is possible that paclitaxel may inhibit the inflammatory and or fibrotic responses that affect vessel remodeling. To date, no adverse consequences have been ascribed to this effect, and serial longitudinal IVUS follow-up is being performed in the TAXUS-II trial at two years to evaluate the stability and implications of this observation.

Study limitations. Serial IVUS interrogations were performed in only a small subset of the patients enrolled in the TAXUS-IV trial, which may have introduced selection bias, though IVUS substudy patients had similar baseline characteristics compared to the entire study population. It should also be recognized that IVUS follow-up tends not to be performed in severely obstructive vessels, and in patients with major adverse cardiac events; as such, follow-up IVUS represents a "best-case scenario," providing complementary data to follow-up angiography.

Conclusions. The polymer-based, slow-release, paclitaxel-eluting TAXUS stent attenuates vascular responses that lead to restenosis without adverse edge effects or late incomplete stent apposition.

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