One-Year Clinical Results With the Slow-Release, Polymer-Based, Paclitaxel-Eluting TAXUS Stent

The TAXUS-IV Trial

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Background—The safety and efficacy of the slow-release, polymer-based, paclitaxel-eluting stent after implantation in a broad cross section of de novo coronary lesions at 1 year are unknown.

Methods and Results—In the TAXUS-IV trial, 1314 patients with single de novo coronary lesions 10 to 28 mm in length, with reference-vessel diameter 2.5 to 3.75 mm, coverable by a single study stent, were prospectively randomized to the slow-release, polymer-based, paclitaxel-eluting TAXUS stent or an identical-appearing bare-metal EXPRESS stent. By actuarial analysis, the TAXUS stent compared with the bare-metal stent reduced the 12-month rates of target-lesion revascularization by 73% (4.4% versus 15.1%, P < 0.0001), target-vessel revascularization by 62% (7.1% versus 17.1%, P < 0.0001), target-vessel failure by 52% (10.0% versus 19.4%, P < 0.0001), and composite major adverse cardiac events by 49% (10.8% versus 20.0%, P < 0.0001). The 1-year rates of cardiac death (1.4% versus 1.3%), myocardial infarction (3.5% versus 4.7%), and subacute thrombosis (0.6% versus 0.8%) were similar between the paclitaxel-eluting and control stents, respectively. Between 9 and 12 months, there were significantly fewer myocardial infarctions (0% versus 1.1%, P = 0.007), target-vessel revascularizations (2.4% versus 5.8%, P = 0.002), and major adverse cardiac events (2.4% versus 6.3%, P = 0.0009) in the paclitaxel-eluting stent than in the control stent group, respectively.

Conclusions—The relative efficacy reported at 9 months for the polymer-based, paclitaxel-eluting TAXUS stent compared with the EXPRESS stent is preserved and continues to increase at 1 year, with no safety concerns apparent. (Circulation. 2004;109:1942-1947.)

Key Words: stents ■ paclitaxel ■ hyperplasia ■ restenosis

N eointimal hyperplasia resulting in restenosis after coronary stent placement frequently results in recurrent angina, necessitating repeat percutaneous and surgical revascularization procedures. The polymer-regulated delivery of both paclitaxel and sirolimus at the site of arterial injury has been shown to reduce clinical and angiographic restenosis rates after stent implantation in de novo coronary lesions.1–7 Specifically, in the pivotal TAXUS-IV trial, slow-release paclitaxel-elution from the TAXUS stent resulted in lower 9-month rates of target-lesion revascularization (TLR), target-vessel revascularization (TVR), and binary restenosis than bare-metal control stents.7 Longer-term follow-up from this trial has not been reported, nor have clinical TLR rates been examined in subgroups known to affect restenosis. The purpose of the present analysis is to examine the 1-year clinical outcomes from this trial and to determine the clinical and angiographic correlates of freedom from TLR after implantation of the TAXUS stent.

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Methods

Patient Population and Protocol

The TAXUS-IV study design has been described previously.7 In brief, 1314 patients with single de novo lesions visually estimated to be between 10 and 28 mm in length, with reference-vessel diameter 2.5 to 3.75 mm, coverable by a single study stent, were prospectively randomized to the slow-release, polymer-based, paclitaxel-eluting TAXUS stent or an identical-appearing bare-metal EXPRESS stent. By actuarial analysis, the TAXUS stent compared with the bare-metal stent reduced the 12-month rates of target-lesion revascularization by 73% (4.4% versus 15.1%, P < 0.0001), target-vessel revascularization by 62% (7.1% versus 17.1%, P < 0.0001), target-vessel failure by 52% (10.0% versus 19.4%, P < 0.0001), and composite major adverse cardiac events by 49% (10.8% versus 20.0%, P < 0.0001). The 1-year rates of cardiac death (1.4% versus 1.3%), myocardial infarction (3.5% versus 4.7%), and subacute thrombosis (0.6% versus 0.8%) were similar between the paclitaxel-eluting and control stents, respectively. Between 9 and 12 months, there were significantly fewer myocardial infarctions (0% versus 1.1%, P = 0.007), target-vessel revascularizations (2.4% versus 5.8%, P = 0.002), and major adverse cardiac events (2.4% versus 6.3%, P = 0.0009) in the paclitaxel-eluting stent than in the control stent group, respectively.

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Continuous variables are presented as mean ± SD or median with 25% and 75% interquartile ranges and were compared by Student’s t test or the Wilcoxon 2-sample test. Time-to-event data are summarized and displayed as Kaplan-Meier estimates and compared with the log-rank test. The influence of baseline variables on the 12-month rates of TLR was evaluated with Cox proportional hazards regression analysis, with entry and stay criteria of <0.20 and <0.10, respectively. The following baseline clinical, angiographic, and procedural variables were entered into the multivariate models: age, gender, smoking status, diabetes, hypertension, hyperlipidemia, prior myocardial infarction, unstable angina, creatinine clearance, left ventricular ejection fraction, epicardial vessel, lesion length, reference-vessel diameter, baseline minimal luminal diameter, study stents implanted (yes versus no), bailout stents used (yes versus no), total stent length, maximum device pressure, maximum device diameter, balloon:artery ratio, stent:lesion length ratio, vessel tortuosity, ostial location, angulation ≥45°, lesion calcification, and randomization arm. All probability values are 2-sided, and statistical significance was set at the 0.05 level.

Results

Patient Population and Follow-Up Events

As previously reported, 1314 patients were randomized to either the paclitaxel-eluting TAXUS stent (n=662) or a bare-metal control EXPRESS stent (n=652). As shown in Table 1, the key baseline demographic, angiographic and procedural features that affect clinical restenosis were well matched between the 2 groups. Follow-up at 12 months was available in 1272 patients (97%), including 639 TAXUS patients and 633 control patients. The 12-month event rates appear in Table 2. The frequency of TLR was reduced from 15.1% with the bare-metal stent to 4.4% with the TAXUS stent (relative risk 0.27, 95% CI 0.18 to 0.41, P<0.0001), and TVR was reduced from 17.1% to 7.1% (relative risk 0.38, 95% CI 0.27 to 0.54, P<0.0001). The need for subsequent percutaneous coronary intervention or bypass graft surgery procedures was reduced with the TAXUS stent (Table 2). As a result, the rates of composite target-vessel failure and major adverse events were reduced by 52% and 49%, respectively. The rates of cardiac death, myocardial infarction, and stent thrombosis at 12 months were similar between the 2 groups. Of note, all stent thromboses in both study arms occurred within the first 6 months of the study, with no such events occurring between 6 and 12 months.

Adverse event rates between 9 and 12 months appear in Figure 1. There were significantly fewer TLR and TVR events between 9 and 12 months in the TAXUS arm than in the control arm. In addition, patients assigned to the TAXUS stent had significantly fewer myocardial infarctions between 9 and 12 months than patients assigned to the bare-metal stent (7 [1.1%] versus 0, respectively). Of the 7 myocardial infarctions in the control arm that occurred between 9 and 12 months, 5 developed after repeat revascularization procedures for restenosis in the bare-metal study stent, 1 occurred after stent thrombosis of a nonstudy stent in a nonstudy vessel, and 1 occurred in a diabetic with hyperglycemia, renal failure, and a new left bundle-branch block. As a result of fewer myocardial infarction and TVR events, the differences in the rates of freedom from TLR and composite major adverse cardiac events in favor of the TAXUS-assigned group continued to grow between 9 and 12 months (Figure 2).

Impact of Routine Angiographic Follow-Up

Protocol angiographic follow-up was completed in 559 patients, 43% of the total study population. In the TAXUS group, TLR by 12 months was performed in 5.7% of the 292 patients in the prespecified angiographic cohort compared with 3.3% of the 370 patients without prespecified angiographic follow-up (a relative 73% increase, P=0.18). In the control group, TLR by 12 months was performed in 18.4% of
the 267 patients in the prespecified angiographic cohort compared with 12.8% of the 385 patients without prespecified angiographic follow-up (a relative 44% increase, \( P < 0.04 \)).

**Predictors of TLR at 12 Months**

As seen in Figure 3, the relative reduction in TLR rates at 12 months with the TAXUS stent compared with the bare-metal stent was independent of vessel location, reference-vessel diameter, lesion length, and diabetic status. By multivariate analysis (Table 3), randomization to the TAXUS stent was the strongest independent predictor of freedom from 12-month TLR (OR 0.29, 95% CI 0.19 to 0.45, \( P < 0.0001 \)). Among patients assigned to the TAXUS stent, the only independent predictors of 12-month TLR were lack of use of a TAXUS stent, lesion length, female gender, and no prior myocardial infarction.

**Discussion**

The main conclusions from this report detailing the 12-month TAXUS-IV results are as follows: (1) The relative benefits of the polymer-based, slow-release, paclitaxel-eluting stent in reducing TLR, TVR, and major adverse cardiac events...
previously reported at 9 months are preserved and continue to increase at 1 year. (2) Between 9 and 12 months, not only were further reductions apparent in the rates of repeat revascularization procedures in patients treated with the TAXUS stent compared with the bare-metal control stent, but as a result, there were also significantly fewer myocardial infarctions. (3) TLR rates were reduced significantly with the TAXUS stent across a broad spectrum of complex patient and lesion types, including large and small vessels, short and long lesions, and in patients with and without diabetes. (4) No safety concerns became apparent in patients treated with the paclitaxel-eluting stent during this extended follow-up period.

As reported previously from the 9-month angiographic substudy of the TAXUS-IV trial,7 angiographic restenosis at 9 months was reduced from 26.6% with the bare-metal EXPRESS stent to 7.9% with the TAXUS stent (a 70% relative reduction, P<0.0001). As a result, TLR, the clinical correlate of angiographic restenosis within the analysis segment, was markedly reduced at 9 months in patients treated with the TAXUS stent. Because of delays in symptom recurrence, patient presentation to the healthcare provider, performance of stress tests, referral to the invasive cardiologist, and scheduling of angiographic studies, there is a well-documented lag period between the time of angiographic restenosis and repeat revascularization.8 As a result, events continued to accrue between 9 and 12 months in both study arms. Of note, whereas the difference in absolute TLR event rates between treatment arms continued to grow from 9 to 12 months (from 8.4% to 10.7%, as seen in Figure 2), the relative TLR risk reduction for the paclitaxel-eluting stent versus the control stent remained constant (from 77% at 9 months to 75% at 12 months).

As seen in the freedom-from-TLR curves, an increment in the number of repeat revascularization procedures occurred at 9 months, the time at which follow-up angiography was mandated by protocol in a subset of patients. Although only 43% of the study population underwent protocol-specified follow-up angiography, concern may thus be expressed that the so-called occlusion reflex influenced the relative results between the treatment and control groups in favor of the TAXUS stent.9 However, in patients in whom 9-month angiographic follow-up was prespecified compared with those followed up only clinically, the relative increase from 9 to 12 months in the rates of TLR was 73% in the TAXUS arm compared with 44% in the control arm. Thus, although some incremental degree of revascularization may have been prompted by routine follow-up angiography in both groups, this phenomenon does not explain the marked benefit of the paclitaxel-eluting stent in reducing TLR; indeed, TLR rates with the TAXUS stent were reduced in both the angiographic follow-up and non–follow-up cohorts. These data do reinforce, however, that for a trial to accurately reflect true clinical event rates, routine angiographic follow-up should be kept to a minimum. Such a decision, however, must be made with due consideration to the scientific information routine angiographic follow-up provides.

By multivariate analysis, randomization to the TAXUS stent was the strongest independent predictor of freedom from TLR. The TAXUS stent markedly reduced the requirement for repeat revascularization procedures in patients and lesions at both low and high risk for restenosis,10–14 which suggests that cost considerations aside, optimum patient benefit will result from the application of this new device to

| Table 2. Cumulative Adverse Event Rates at 12 Months |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Cardiac death                  | 1.4             | 1.3             | 1.11 (0.43–2.87) | 0.83            |
| Myocardial infarction          | 3.5             | 4.7             | 0.76 (0.44–1.30) | 0.31            |
| Stent thrombosis               | 0.6             | 0.8             | 0.79 (0.21–2.93) | 0.72            |
| TLR                            | 4.4             | 15.1            | 0.27 (0.18–0.41) | <0.0001         |
| Repeat percutaneous coronary intervention | 3.7          | 12.2            | 0.28 (0.18–0.45) | <0.0001         |
| Bypass graft surgery           | 0.8             | 3.7             | 0.20 (0.08–0.53) | 0.0003          |
| TVR (nontarget lesion)         | 2.9             | 3.2             | 0.89 (0.47–1.68) | 0.72            |
| TVR                            | 7.1             | 17.1            | 0.38 (0.27–0.54) | <0.0001         |
| Repeat percutaneous coronary intervention | 5.5          | 13.9            | 0.38 (0.25–0.56) | <0.0001         |
| Bypass graft surgery           | 1.8             | 4.0             | 0.41 (0.20–0.83) | 0.01            |
| Target-vessel failure          | 10.0            | 19.4            | 0.48 (0.36–0.65) | <0.0001         |
| Major adverse cardiac events   | 10.8            | 20.0            | 0.51 (0.38–0.68) | <0.0001         |

Figure 1. Major adverse event rates occurring between 9 and 12 months.
all patients who meet the entry criteria for the present trial. Indeed, among patients randomized to receive the TAXUS stent, not receiving this device (which occurred in only 1.7% of patients) was the strongest predictor of TLR. Lesion length was also an independent predictor of TLR among patients assigned to the TAXUS stent (as is true with the sirolimus-eluting stent4), and thus, even though long lesions benefited greatly from the paclitaxel-eluting stent (with a 77% reduction in TLR in lesions >20 mm long compared with a bare-metal stent), there may be a role for additional strategies (eg, intravascular ultrasound guidance, plaque modification, or other adjunctive antiproliferative approaches) for very long lesions treated with drug-eluting stents. The relationship between TLR and female gender and the absence of prior myocardial infarction in TAXUS-treated patients may relate to altered pain perception or thresholds15–17 and deserves further study.

With similar rates of cardiac death, myocardial infarction, and stent thrombosis at 12 months in the treatment and control arms, the present study provides reassurance that no safety concerns are evident 1 year after implantation of the polymer-based, slow-release, paclitaxel-eluting stent. Importantly, no episodes of late stent thrombosis occurred 6 months after clopidogrel discontinuation. Moreover, the reduction in TLR and TVR procedures with the TAXUS compared with the control stent between 9 and 12 months resulted in fewer myocardial infarctions, which suggests that by preventing restenosis, drug-eluting stents offer the potential to reduce long-term rates of myocardial infarction, especially if adjunctive pharmacological strategies can curtail periprocedural adverse events. Finally, as a consequence of the late reduction in myocardial infarctions and TLR and TVR events in the TAXUS arm, the difference from 9 to 12 months in both the absolute (from 6.6% to 9.2%) and the relative (from a 45% reduction to a 49% reduction) rates of composite major adverse events increased in patients assigned to the paclitaxel-eluting stent. Despite the encouraging safety profile to date with the TAXUS stent in this trial, follow-up for several more years and in greater numbers of patients is required to alleviate all concerns about any late hazards. Furthermore, additional studies are required to demonstrate

<table>
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<th>Combinatory</th>
<th>Hazard Ratio (95% CI)</th>
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<td>Randomization to control stent</td>
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<td>Total stent length (longer)</td>
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<td>No prior myocardial infarction</td>
<td>1.61 (1.03–2.56)</td>
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<td>No study stents implanted</td>
<td>5.86 (1.36–25.27)</td>
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<tr>
<td>No prior myocardial infarction</td>
<td>3.70 (1.11–12.50)</td>
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<td>Female gender</td>
<td>2.33 (1.08–5.00)</td>
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<td>1.85 (1.18–2.94)</td>
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Figure 2. Kaplan-Meier survival curves displaying cumulative rates of freedom from adverse events in 2 groups over 12-month follow-up period. Top, Freedom from TLR. Bottom, Freedom from major adverse cardiac events.

Figure 3. Twelve-month TLR rates in 2 groups, stratified by selected variables known to influence restenosis. Vertical lines indicate relative risk ratio, and horizontal lines indicate 95% CI. RR indicates relative risk; meds, medications; LAD, left anterior descending artery; and RVD, reference-vessel diameter.
the safety and efficacy of this device in more complex and high-risk lesions excluded from enrollment in the present study.

In conclusion, the 1-year results of the TAXUS-IV trial provide strong evidence that the polymer-based, paclitaxel-eluting stent represents a major advance in the treatment of patients with obstructive coronary artery disease. In concert with other studies demonstrating durability in efficacy without apparent late toxicity,5,18 Food and Drug Administration–approved polymer-based drug-eluting stents should be considered the standard of care for stent implantation in the majority of de novo atherosclerotic lesions as studied in the pivotal randomized trials.

References
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