Paclitaxel-Eluting Stents vs Vascular Brachytherapy for In-Stent Restenosis Within Bare-Metal Stents
The TAXUS V ISR Randomized Trial

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Context Restenosis within bare-metal stents is often treated with repeat percutaneous coronary intervention, although subsequent recurrence rates are high, with vascular brachytherapy (VBT) affording the best results. The effectiveness of drug-eluting stents in this setting has not been established.

Objective To investigate the safety and efficacy of the polymer-based, slow-release paclitaxel-eluting stent in patients with restenotic lesions after prior stent implantation in native coronary arteries.

Design, Setting, and Patients Prospective, multicenter, randomized trial conducted between June 6, 2003, and July 16, 2004, at 37 North American academic and community-based institutions in 396 patients with in-stent restenosis of a previously implanted bare-metal coronary stent (vessel diameter, 2.5-3.75 mm; lesion length, ≤46 mm).

Interventions Patients were randomly assigned to undergo angioplasty followed by VBT with a β source (n=201) or paclitaxel-eluting stent implantation (n=195). Clinical and angiographic follow-up at 9 months was scheduled in all patients.

Main Outcome Measure Ischemia-driven target vessel revascularization at 9 months.

Results Diabetes mellitus was present in 139 patients (35.1%). Median reference vessel diameter was 2.65 mm and median lesion length was 15.3 mm. In the VBT group, new stents were implanted in 22 patients (10.9%) and in the paclitaxel-eluting stent group, multiple stents were required in 57 patients (29.2%), with median stent length of 24 mm. Follow-up at 9 months was complete in 194 patients in the VBT group and 191 patients in the paclitaxel-eluting stent group (96.5% and 97.9%, respectively). For VBT and paclitaxel-eluting stents, respectively, the number of events and 9-month rates for ischemic target lesion revascularization were 27 (13.9%) vs 12 (6.3%) (relative risk [RR], 0.45; 95% confidence interval [CI], 0.24-0.86; P=.01); for ischemic target vessel revascularization, 34 (17.5%) vs 20 (10.5%) (RR, 0.60; 95% CI, 0.36-1.00; P=.046); and for overall major adverse cardiac events, 39 (20.1%) vs 22 (11.5%) (RR, 0.57; 95% CI, 0.35-0.93; P=.02), with similar rates of cardiac death or myocardial infarction (10 [5.2%] vs 7 [3.7%]; RR, 0.71; 95% CI, 0.28-1.83; P=.48) and target vessel thrombosis (5 [2.6%] vs 3 [1.6%]; RR, 0.61; 95% CI, 0.15-2.50; P=.72). Angiographic restenosis at 9 months was 31.2% (53 of 170 patients) with VBT and 14.5% (25 of 172 patients) with paclitaxel-eluting stents (RR, 0.47; 95% CI, 0.30-0.71; P<.001).

Conclusion Treatment of bare-metal in-stent restenotic lesions with paclitaxel-eluting stents rather than angioplasty followed by VBT reduces clinical and angiographic restenosis at 9 months and improves event-free survival.

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bosis and restenosis.13-15 These limitations have resulted in a shift away from VBT for treatment of ISR in daily clinical practice despite the absence of a proven therapeutic alternative.

Drug-eluting stents have been demonstrated in de novo coronary lesions to safely reduce restenosis compared with bare-metal stents.16-20 Whether drug-eluting stents are safe and effective for treatment of ISR, however, has not been established. In a prior small registry series, the safety and potential efficacy of the slow-release, polymer-based, paclitaxel-eluting stent in patients with bare-metal ISR was demonstrated.21 We therefore performed a prospective, multicenter, randomized trial to evaluate the use of paclitaxel-eluting stents compared with VBT in patients with ISR of bare-metal stents.

**METHODS**

**Study Population**

Patients aged 18 years or older with stable or unstable angina or inducible ischemia undergoing percutaneous coronary intervention of a single bare-metal ISR lesion in a native coronary artery were considered for enrollment.

Clinical exclusion criteria included previous or planned use of VBT, external beam radiotherapy, or any anti-restenotic drug-eluting stent in the target vessel; ataxia-telangiectasia or other known genetic radiation sensitivity disorders; myocardial infarction (MI) within 72 hours or creatine kinase-MB level higher than 2 times the upper limit of normal; left ventricular ejection fraction of less than 25%; stroke within 6 months; planned coronary artery bypass graft surgery within 9 months; hemorrhagic diatheses or contraindications or allergy to aspirin, thienopyridines, paclitaxel, stainless steel, or anaphylaxis to iodinated contrast; current or future warfarin use anticipated within 6 months of the procedure; chemotherapy within 12 months, or planned use of paclitaxel, rapamycin, or colchicine within 9 months; serum creatinine level higher than 2.0 mg/dL (176.8 µmol/L), leukocyte count lower than 3500/µL or platelet count lower than 750 × 10^3/µL; woman of child-bearing potential without a recent negative pregnancy test or lactating; man or woman with planned procreation within 3 months; comorbid conditions limiting life expectancy to less than 24 months or that could affect protocol adherence; planned procedure requiring antiplatelet therapy withdrawal within 6 months; and current participation in other investigational trials. There were no specific inclusion or exclusion criteria regarding the duration of the bare-metal stent implant. The study was approved by the institutional review boards at each participating center, and all patients signed written informed consent.
Randomization and Protocol

Telephone randomization was performed in random blocks of 2 to 4 patients before mandatory predilatation. Patients were assigned in 1:1 proportion in an unblinded fashion to treatment with either angioplasty followed by VBT with any FDA-approved β source intracoronary radiation system labeled for treatment of ISR or the slow rate-release polymer-based paclitaxel-eluting TAXUS Express² stent (Boston Scientific Corp, Natick, Mass). 18-20 Brachytherapy was delivered after either noncutting or cutting balloon angioplasty according to standard practice at each clinical site with the oversight of a radiation oncologist, radiation safety officer, or both. The radiation train source length was specified to cover a margin of at least 5 mm beyond each end of the balloon injury zone. Manual stepping (repositioning of radiation source) was permitted in accordance with Nuclear Regulatory Commission guidelines.

A suboptimal angioplasty result after brachytherapy for which stent implantation could be considered was defined as a residual diameter stenosis of more than 50%, a dissection of at least type C refraction to prolonged balloon inflations, or both. However, the implantation of new metal stents was strongly discouraged before or after VBT, and drug-eluting stents were by protocol not permitted in conjunction with VBT. All balloon inflations as well as the position of the VBT source train were graphically recorded to document the extent of the injury and radiation zones.

Paclitaxel-eluting stents were available in 8- to 32-mm lengths and in diameters of 2.5 to 3.5 mm. Coverage of 3 mm of the normal reference segment at both the proximal and distal lesion margins was recommended. The stent was sized 1:1 or 1.1:1 to the distal reference diameter and implanted at 12 atm or higher of pressure. When multiple stents were required, 4 mm of stent overlap was specified. Antiplatelet and glycoprotein IIb/IIIa inhibitor use and performance of postdilatation were at operator discretion.

Patients were administered 325 mg/d of aspirin prior to the procedure and were required to continue taking this dose for a minimum of 9 months postprocedure, with indefinite use recommended. A 300-mg loading dose of clopidogrel was recommended at least 6 hours before the procedure, followed by a dose of 75 mg/d for at least 6 months in all patients; 12 months of clopidogrel therapy was mandated in patients with VBT receiving new stents and recommended in all patients. Clinical follow-up was scheduled at 1, 4, and 9 months and yearly thereafter for 5 years. Follow-up angiography was scheduled in all patients at 9 months.

Data Management and Definitions

Independent study monitors verified all data from case report forms onsite. Major adverse cardiac events and stent thromboses were adjudicated by an independent committee blinded to treatment allocation after review of original source documentation. The clinical and angiographic end point definitions were identical to those in TAXUS IV, as previously described. 19 Target vessel thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within the target vessel, or in the absence of angiographic confirmation, either acute MI in the distribution of the treated vessel or cardiac death within 30 days. Core angiographic laboratory analysis was performed using validated quantitative methods. 22 Measures were reported separately within the stent, in the injury segment (the length over which any balloons were inflated), in the radiation segment (VBT group only), over the entire analysis segment (the radiation segment + 5-mm proximal and distal reference vessel margins in patients receiving VBT, or the stented segment + 5-mm proximal and distal margins in patients receiving paclitaxel-eluting stents), and within the 5-mm proximal and distal margins (FIGURE 1). In-stent measures were not reported for the VBT group as new stents were rarely implanted. The baseline and follow-up pattern of restenosis was described using the Mehran classification. 2

End Points and Statistical Methods

The primary end point was the 9-month incidence of ischemia-driven target vessel revascularization. Target vessel revascularization was considered to be ischemia driven if the target vessel diameter stenosis was at least 50% by quantitative analysis with either electrocardiographic changes at rest or a positive functional study in the distri-
bution of the target vessel, or at least 70% with recurrent symptoms only.

The trial was designed to permit sequential noninferiority and superiority testing. The paclitaxel-eluting stent would be considered noninferior to VBT if the 95% upper 1-sided confidence bound for the difference between the stent and VBT ischemia-driven target vessel revascularization rate was less than a Δ of 10%. With 438 evaluable patients at 9 months, using a 2-group test of equivalence in proportions, with an anticipated 20% event rate for both groups and a Δ of 10% and 1-sided α = .05, the study would have 83% power to reject the null hypothesis of inferiority. For superiority testing (after the noninferiority criterion was met), using a 2-sided test for differences in independent binomial proportions with α = .05, 438 evaluable patients would provide 80% power to detect a difference in the primary end point from an anticipated 20.0% after VBT to 10.0% with the paclitaxel-eluting stent.

The original trial design permitted enrollment of up to 488 patients to allow for 10% attrition. As the trial progressed, extensive use of both sirolimus-eluting and paclitaxel-eluting stents resulted in extremely slow recruitment in the terminal months of the study. Therefore, after discussion with the data and safety monitoring board and FDA (with the executive committee members and sponsor still blinded), the decision was made to terminate enrollment in the randomized trial after 396 patients were randomized. With 385 actual patients with 9-month clinical follow-up, the trial had 78% power to demonstrate noninferiority and 74% power to demonstrate superiority using the original study assumptions. After randomization was terminated and after discussion with FDA, an additional 23 consecutive eligible patients with ISR were treated with the paclitaxel-eluting stent and followed up in a separate registry to accumulate additional safety and efficacy data. These results are presented separately.

Categorical variables were compared with χ² or Fisher exact test. Continuous variables are presented as medians with interquartile ranges (IQRs) and were compared with the nonparametric Wilcoxon rank sum test. Time to event data were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariate logistic regression analysis was performed to adjust for the effect of the baseline differences between groups on the primary end point of ischemic target vessel revascularization. All P values are 2-sided and all analyses are by intention-to-treat, regardless of treatment received. The investigators had unrestricted access to the database. The manuscript was prepared by the principal investigator (G.W.S.) and revised after coauthor review. All statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC).

### RESULTS

#### Baseline Characteristics and Procedural Outcomes

Between June 6, 2003, and July 16, 2004, a total of 396 patients with bare-metal ISR undergoing percutaneous coronary intervention at 37 North American centers were randomly assigned to treatment with either VBT (n = 201) or paclitaxel-eluting stents (n = 195) (Figure 2). Baseline characteristics are shown in Table 1 and are notable for a high frequency of diabetes mellitus (139 patients [35.1%]) and relatively long ISR lesions, mostly with a diffuse or proliferative pattern, with median

#### Table 1. Baseline Characteristics*  

<table>
<thead>
<tr>
<th></th>
<th>Vascular Brachytherapy (n = 201)</th>
<th>Paclitaxel-Eluting Stent (n = 195)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>63 (54-73)</td>
<td>63 (54-70)</td>
<td>.62</td>
</tr>
<tr>
<td>Men</td>
<td>141 (70.1)</td>
<td>121 (62.1)</td>
<td>.09</td>
</tr>
<tr>
<td>Diabetes mellitus (requiring medication)</td>
<td>61 (30.3)</td>
<td>78 (40.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Insulin</td>
<td>21 (10.4)</td>
<td>38 (19.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Noninsulin</td>
<td>40 (19.9)</td>
<td>40 (20.5)</td>
<td>.88</td>
</tr>
<tr>
<td>Hypertension</td>
<td>159 (79.1)</td>
<td>165 (84.6)</td>
<td>.16</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>184 (91.5)</td>
<td>177 (90.8)</td>
<td>.79</td>
</tr>
<tr>
<td>Current smoker</td>
<td>30 (14.9)</td>
<td>27 (13.8)</td>
<td>.76</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>106 (52.7)</td>
<td>101 (51.8)</td>
<td>.85</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>56 (27.9)</td>
<td>55 (28.2)</td>
<td>.94</td>
</tr>
<tr>
<td>Time since bare-metal stent implant, median (IQR), d</td>
<td>316 (177-644)</td>
<td>281 (158-658)</td>
<td>.43</td>
</tr>
<tr>
<td></td>
<td>(n = 201)</td>
<td>(n = 194)</td>
<td></td>
</tr>
<tr>
<td>Target lesion coronary artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>67 (33.3)</td>
<td>76 (39.2)</td>
<td>.23</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>54 (26.9)</td>
<td>45 (23.2)</td>
<td>.40</td>
</tr>
<tr>
<td>Right</td>
<td>78 (38.8)</td>
<td>72 (37.1)</td>
<td>.73</td>
</tr>
<tr>
<td>Left main (protected)</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Diameter, median (IQR), mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference vessel</td>
<td>2.61 (2.32-2.93)</td>
<td>2.68 (2.26-2.94)</td>
<td>.29</td>
</tr>
<tr>
<td>Minimal lumen</td>
<td>0.83 (0.61-1.01)</td>
<td>0.80 (0.56-1.04)</td>
<td>.51</td>
</tr>
<tr>
<td>Stenosis, %</td>
<td>68.0 (69.4-5.4)</td>
<td>68.5 (60.3-77.8)</td>
<td>.25</td>
</tr>
<tr>
<td>Lesion length, median (IQR), mm</td>
<td>15.0 (10.0-23.3)</td>
<td>15.9 (11.8-22.8)</td>
<td>.14</td>
</tr>
<tr>
<td>Restenosis pattern†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>58 (29.0)</td>
<td>36 (18.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Diffuse</td>
<td>94 (47.0)</td>
<td>118 (60.8)</td>
<td>.006</td>
</tr>
<tr>
<td>Proliferative</td>
<td>47 (23.5)</td>
<td>37 (19.1)</td>
<td>.28</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>1 (0.5)</td>
<td>2 (1.0)</td>
<td>.62</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.
*Values are expressed as number (percentage) unless otherwise indicated.
†See Mehran et al.2
reference vessel diameter of 2.65 mm and median lesion length of 15.3 mm. The 2 groups were well matched, except for a higher incidence of insulin-requiring diabetes and diffuse lesions and a lower incidence of focal lesions in the paclitaxel-eluting stent group.

Initial procedural results are shown in Table 2. Vascular brachytherapy was delivered in 193 patients (96.0%); in 8 patients, VBT was unsuccessful due to device malfunction (n = 2) or inability to cross the lesion with the radiation delivery system (n = 6). The β source consisted of Galileo (Guidant, Santa Clara, Calif) in 110 patients (57%) and Betacath (Novoste, Norcross, Ga) in 83 patients (43%). Median radiation activity was 87.8 mCi (IQR, 52.8-167.0) and total dwell time was 198 seconds (IQR, 166-248); the prescribed radiation dose was delivered in all 193 patients. The median length of the radiation source was 30 mm (IQR, 20-40); stepping (manual or automated repositioning of the radiation source) was required in 105 cases (54.4%).

A total of 24 stents (22 bare-metal and 2 paclitaxel-eluting stents) were implanted for suboptimal angioplasty results in 19 of 193 patients (9.8%) who received radiotherapy; an additional 3 patients in whom VBT could not be delivered received 6 stents (3 pacltaxel-eluting and 3 sirolimus-eluting stents). The acute gain and postprocedure minimal luminal diameter were significantly greater and the diameter stenosis smaller in patients assigned to paclitaxel-eluting stent implantation rather than VBT.

Clinical Outcomes at 9 Months
Clinical follow-up was available in 385 patients (97.2%) at 9 months (Figure 2). Paclitaxel-eluting stents were found to be both noninferior and superior to VBT in ISR lesions in terms of reducing the primary end point of ischemic target vessel revascularization at 9 months. The 1-sided upper bound of the 95% confidence interval (CI) for the difference in ischemia-driven target vessel revascularization was −1.3%, less than the prespecified noninferiority margin of 10%, resulting in P < .001, rejecting the hypothesis that the paclitaxel-eluting stent is inferior to VBT.

Implantation of paclitaxel-eluting stents compared with VBT significantly reduced the 9-month rate of ischemic target vessel revascularization by 40% (Table 3). After multivariate adjustment for differences in baseline characteristics between the 2 groups, the reduction in the primary end point of ischemic target vessel revascularization with the paclitaxel-eluting stent compared with VBT remained significant (odds ratio, 0.52; 95% CI, 0.28-0.97; P = .04).

The rate of ischemic target lesion revascularization at 9 months was 6.3% with the paclitaxel-eluting stent compared with 13.9% for VBT, relative reduction of 55%. Target lesion and target vessel revascularization events adjudicated as nonischemic (and thus not counted in the primary efficacy measures) also occurred significantly less frequently with paclitaxel-eluting stents than with VBT. As a result, relative reductions in total target lesion (61%) and target vessel (49%) revascularization events were higher after treatment with the paclitaxel-eluting stent rather than VBT compared with when only ischemic related events were considered.

These benefits were achieved with comparable safety between the 2 groups. The rates of cardiac death or MI at 9 months were similar in the VBT and paclitaxel-eluting stent groups (10 [5.2%] vs 7 [3.7%]; relative risk [RR], 0.71; 95% CI, 0.28-1.83; P = .48), as was the frequency of target vessel thrombosis (5 [2.6%] vs 3 [1.6%]; RR, 0.61; 95% CI, 0.15-2.50; P = .72). As a result, paclitaxel-eluting stents reduced the 9-month composite rate of major adverse cardiac

### Table 2. Procedural Results

<table>
<thead>
<tr>
<th></th>
<th>Vascular Brachytherapy (n = 201)</th>
<th>Paclitaxel-Eluting Stent (n = 195)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 stent implanted</td>
<td>22 (10.9)</td>
<td>191 (97.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients with multiple stents required</td>
<td>6 (3.0)</td>
<td>57 (29.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors used</td>
<td>61 (30.3)</td>
<td>63 (32.3)</td>
<td>.67</td>
</tr>
<tr>
<td>Intervention in nonstudy lesion in nonstudy vessel prior to randomization</td>
<td>38 (18.9)</td>
<td>35 (17.9)</td>
<td>.81</td>
</tr>
<tr>
<td><strong>Median (Interquartile Range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of stents per patient*</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>.89</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>20 (12-33)</td>
<td>24 (20-32)</td>
<td>.14</td>
</tr>
<tr>
<td>Maximum device size (balloon or stent), mm</td>
<td>3.5 (3.0-3.75)</td>
<td>3.0 (3.0-3.5)</td>
<td>.46</td>
</tr>
<tr>
<td>Ratio of maximum balloon to artery</td>
<td>1.21 (1.09-1.30)</td>
<td>1.16 (1.04-1.27)</td>
<td>.03</td>
</tr>
<tr>
<td>Maximum pressure, atm</td>
<td>12 (10-14)</td>
<td>16 (14-18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>QCA measures, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury segment length</td>
<td>19.1 (14.1-28.7)</td>
<td>24.0 (19.6-31.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Radiation segment length</td>
<td>39.1 (31.9-49.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis segment length</td>
<td>52.9 (44.9-64.2)</td>
<td>41.7 (36.0-50.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute gain (paired analysis), mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>1.66 (1.39-1.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury segment</td>
<td>1.14 (0.87-1.47)</td>
<td>1.69 (1.38-2.02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Analysis segment</td>
<td>0.98 (0.71-1.25)</td>
<td>1.62 (1.38-1.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Final minimal luminal diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>2.50 (2.24-2.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury segment</td>
<td>2.04 (1.75-2.38)</td>
<td>2.50 (2.23-2.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Analysis segment</td>
<td>1.84 (1.56-2.13)</td>
<td>2.08 (1.83-2.48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Final diameter stenosis, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>7.5 (4.4-13.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury segment</td>
<td>23.2 (13.1-32.1)</td>
<td>7.6 (0.96-14.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Analysis segment</td>
<td>29.3 (23.4-36.3)</td>
<td>20.6 (13.3-27.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Abbreviation:** QCA, quantitative coronary angiography.

*In patients receiving stents.
events by 43% compared with VBT. The differences between the groups were similar when calculated with time to event methodology (FIGURE 3).

There was only 1 death in the study, a 92-year-old man with a history of prior MI and congestive heart failure who presented with unstable angina due to bare-metal ISR in the right coronary artery. He was randomized to VBT, which was successful, and was discharged to a nursing home. He was subsequently found pulseless and in asystole on day 243. This event was adjudicated as a cardiac death.

Only 1 Q-wave MI occurred in the study in a 52-year-old woman in whom stent thrombosis developed on the third day after successful paclitaxel-eluting stent implantation in a restenotic bare-metal stent in the proximal left anterior descending artery. Non-Q-wave MIs also developed in 6 patients receiving paclitaxel-eluting stents. Two of these MIs occurred in the periprocedural period, both of which were asymptomatic. One was due to a jailed side branch (covered with a stent). The 4 late non-Q-wave MIs were due to stent thrombosis on days 61 and 100 in 2 patients; a perioperative MI on day 175 in 1 patient with diffuse progressive disease; and diabetic ketoacidosis in 1 patient in whom cardiac catheterization was negative. A total of 10 non-Q-wave MIs developed in 9 patients receiving VBT. Three occurred within 30 days. One case was due to procedural cardiac arrest after failure of a commercial (nonstent) angioplasty balloon to deflate; 1 case was an asymptomatic postprocedural cardiac enzyme elevation; and 1 case was due to nontarget lesion stent thrombosis on day 19. The causes of the 7 non-Q-wave MIs between 30 and 270 days in patients after VBT included target vessel thrombosis on days 34, 146, 161, and 194 (n=4); severe restenosis (n=2); and progressive disease in nontarget stenoses (n=1).

### Angiographic Outcomes at 9 Months

Follow-up angiography at 9 months was completed in 342 patients (86.4%). A strong trend was shown for less late loss.
in the analysis segment after paclitaxel-eluting stent implantation compared with VBT, which in concert with greater acute gain resulted in larger minimal luminal diameters and lower binary restenosis rates across the injury zone and analysis segment (Table 4 and Figure 4). Paclitaxel-eluting stent implantation compared with VBT resulted in fewer focal and diffuse restenoses and a trend toward fewer late total occlusions (Table 4). A strong trend was also shown for fewer aneurysms in the paclitaxel-eluting stent group at 9 months.

**Paclitaxel-Eluting Stent Registry Enrollment**

The 9-month clinical and angiographic results for the additional 25 patients with ISR lesions receiving paclitaxel-eluting stents enrolled after randomization was terminated were similar to those of the 195 patients in the randomized cohort, confirming low rates of clinical and angiographic restenosis, as well as death, MI, and stent thrombosis (Table 5).

**COMMENT**

Although drug-eluting stents have been shown to reduce restenosis in simple and moderately complex de novo lesions in native coronary arteries,16-20 bare-metal stents continue to be used in stenoses in which drug-eluting stents have either not been proven to be safe (acute MI23) or cost-effective (focal lesions or large vessels20,24). Bare-metal stent use also continues to be high in many countries because of lack of reimbursement for drug-eluting stents for all but the most complex lesions. In addition, bare-metal stents are preferred in select patients because of expected lack of adherence or inability to tolerate an extended course of dual antiplatelet therapy. However, restenosis occurs in 10% to 50% or more of patients following implantation of bare-metal stents, depending on patient and lesion complexity.25,26

Although the initial success rate is high following repeat percutaneous coronary intervention for ISR lesions, subsequent recurrence rates are further increased and refractory restenosis remains the single most common reason for referral to coronary artery bypass graft surgery after bare-metal stent implantation.1,2,10-12 Identification of the optimal therapy for bare-metal ISR carries significant public health implications.

**Figure 3. Cumulative Event Rates of Ischemic Target Lesion Revascularization, Ischemic Target Vessel Revascularization, and Major Adverse Cardiac Events to 9 Months (N=396)**

Before the drug-eluting stent era, VBT had been proven in numerous randomized trials to be the most effective therapy for bare-metal coronary ISR, with both β and γ sources demonstrating...
ing similar efficacy.10-12 Unresolved concerns with VBT, however, include an increased incidence of edge restenosis at the stent margins, perhaps related to geographic mismatch between the injury zone and radiation coverage; late stent thrombosis, especially when new metal stents are concurrently placed;13; a late “catch-up phenomenon,” which in some studies eliminated the benefit of VBT compared with angioplasty alone within 3 to 5 years after ISR treatment14,15; and the logistical complexity and expense of the procedure. As a result, drug-eluting stents are perceived as an inherently desirable alternative to VBT for bare-metal coronary ISR, assuming at least comparable safety and efficacy (noninferiority). Two previous randomized trials26,29 have been performed in patients with bare-metal ISR lesions in which the superiority of both sirolimus-eluting and paclitaxel-eluting stents compared with balloon angioplasty alone have been demonstrated; however, no study to date has been published comparing drug-eluting stents to the criterion standard therapy of VBT for this application.

In this randomized trial (TAXUS V ISR), the slow-release, polymer-based, paclitaxel-eluting stent was found to be not only noninferior to β source VBT, but also superior in terms of reducing clinical and angiographic restenosis at 9 months after treatment of bare-metal ISR lesions. Because of both greater acute gain and less late loss, luminal dimensions were significantly larger with paclitaxel-eluting stents compared with VBT in the injury zone, at the distal edge, and over the entire analysis segment. Proximal edge luminal dimensions were also numerically larger with the paclitaxel-eluting stent.

The mechanisms underlying the reduction in restenosis with the paclitaxel-eluting stent compared with VBT in ISR lesions would appear to be 3-fold: greater initial acute gain due to the mechanical scaffolding properties of the stent, preservation of this greater initial gain with comparable or less late loss, and mitigation of the radiation-associated edge effect. Notably, whereas late loss is greater after bare-metal stent implantation in ISR compared with de novo coronary lesions,8 the mean in-stent and analysis segment late loss measures with the paclitaxel-eluting stent in the present study (0.36 mm and 0.26 mm, respectively) were less than that after treatment of de novo lesions in the TAXUS V trial (0.49 mm and 0.33 mm, respectively), despite comparable or worse baseline risk factors for restenosis including diabetes (40% in TAXUS V ISR vs 32% in TAXUS V), mean lesion length (18.5 vs 17.3 mm, respectively), and mean reference vessel diameter (2.68 mm in both). Further studies are required to confirm this hypothesis-generating observation. Also, we observed significantly greater efficacy of the slow-release paclitaxel-eluting stent in bare-metal ISR lesions in the present study than in the prior small TAXUS III registry,23 possibly because restenosis in TAXUS III often occurred in bare-metal...
stents placed adjacent to the paclitaxel-eluting stent and in gaps between stents, emphasizing the importance of complete ISR lesion coverage with paclitaxel-eluting stents to minimize restenosis.

The major indicators of safety, including death from any cause, cardiac death, MI, early and late vessel thrombosis, and aneurysm formation after treatment of ISR, occurred with similar frequency in both treatment groups, or numerically favored the paclitaxel-eluting stent group (fewer aneurysms). However, the trial was underpowered to detect small differences in low frequency events, and longer-term follow-up is required to examine the relative safety between these 2 therapies, especially regarding late thrombotic occlusion.

Our results apply to the polymer-based, slow-release, paclitaxel-eluting TAXUS stent only. Whether other drug-eluting stents, such as sirolimus-eluting or zotarolimus-eluting stents, are as or more effective for treatment of bare-metal ISR is unknown. In a recently reported randomized trial, in which 384 patients received sirolimus-eluting stents compared with VBT for ISR, assignment to the drug-eluting stent resulted in a reduction in the primary end point of target vessel failure at 9 months (12.4% vs 21.6%, respectively; P = .02) and a strong trend toward reduced angiographic restenosis at 6 months (19.8% vs 29.5%, respectively; P = .07). Only 1 prior trial has been performed comparing paclitaxel-eluting and sirolimus-eluting stents in patients with bare-metal ISR, which with 200 patients enrolled was underpowered to draw definitive conclusions. Given an approximate 8% target lesion revascularization rate at 9 months with drug-eluting stents in this cohort, approximately 2800 patients would need to be enrolled in a comparative randomized trial to have 80% power to demonstrate a 33% reduction in clinical efficacy with either the sirolimus-eluting or paclitaxel-eluting stent relative to the other.

The TAXUS V ISR study has several limitations. First, it may be argued that the longer analysis zone with VBT than with paclitaxel-eluting stents biased the angiographic analysis in favor of the stent group. This disparity is an accurate reflection of the inherent difference between VBT and drug-eluting stent treatment of ISR, because the longer radiation source exposes more of the artery to potential vascular toxicity. The length of the measured injury segment was actually greater with the paclitaxel-eluting stent and the relative reduction in injury zone binary restenosis with the paclitaxel-eluting stent was nonetheless robust. Most importantly, the reduction in angiographic restenosis paralleled the observed decrease in target lesion and vessel revascularization in the stent group.

Second, longer-term follow-up is necessary to examine relative safety issues and late efficacy. In this regard, the lack of vessel healing after VBT may result in ongoing neointimal hyperplasia with the subsequent need for late revascularization procedures, a finding that thus far has not been observed with the TAXUS stent with follow-up through 3 years.

Third, given the marked differences between VBT and drug-eluting stents, blinding of the investigators was not feasible. Fourth, the results of the present study do not apply to 2 important groups of patients excluded from enrollment, those patients with ISR after drug-eluting stent placement and those with ISR following VBT for a prior recurrence within a bare-metal stent. Few data exist to guide treatment of the former group, whereas emerging studies suggest that drug-eluting stents are often ineffective after VBT failures, with a high frequency of late restenosis and stent thrombosis reported.

Finally, as a result of early trial termination, 9-month data were available for only 385 patients (88% of the 438 patients for which the trial was powered). Consequently, the reduction in the primary end point of 9-month target vessel revascularization was only of borderline statistical significance. However, the reduction in target lesion revascularization (the best clinical surrogate for the antirestenotic efficacy of drug-eluting stents) was more robust and no safety concerns were apparent, making paclitaxel-eluting stents a desirable alternative to the morelogically complex option of VBT.

The results from this trial in concert with other studies indicate that drug-eluting stents should now be considered the treatment of choice for most patients with ISR of previously implanted bare-metal stents. Paclitaxel-eluting stents significantly reduce clinical and angiographic restenosis and improve event-free survival compared with β source in-

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tracoronary radiation. For patients with bare-metal stents who develop in-stent restenosis, the availability of drug-eluting stents represents a safe therapy resulting in a high rate of 9-month event-free survival, a reassuring option for an otherwise difficult-to-treat cohort of patients. Further studies are required to demonstrate the long-term safety and durability of this approach.

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**REFERENCES**


