

## Randomized Study to Assess the Effectiveness of Slow- and Moderate-Release Polymer-Based Paclitaxel-Eluting Stents for Coronary Artery Lesions

Antonio Colombo, MD; Janusz Drzewiecki, MD; Adrian Banning, MD; Eberhard Grube, MD; Karl Hauptmann, MD; Sigmund Silber, MD; Dariusz Dudek, MD; Stephen Fort, MD; Francois Schiele, MD; Krysztof Zmudka, MD; Giulio Guagliumi, MD; Mary E. Russell, MD for the TAXUS II Study Group



**Background**—Early clinical studies demonstrated the feasibility of local paclitaxel delivery in reducing restenosis after treatment of de novo coronary lesions in small patient populations.

**Methods and Results**—We conducted a randomized, double-blind trial of 536 patients at 38 medical centers evaluating slow-release (SR) and moderate-release (MR) formulations of a polymer-based paclitaxel-eluting stent (TAXUS) for revascularization of single, primary lesions in native coronary arteries. Cohort I compared TAXUS-SR with control stents, and Cohort II compared TAXUS-MR with a second control group. The primary end point was 6-month percent in-stent net volume obstruction measured by intravascular ultrasound. Secondary end points were 6-month angiographic restenosis and 6- and 12-month incidence of major adverse cardiac events, a composite of cardiac death, myocardial infarction, and repeat revascularization. At 6 months, percent net volume obstruction within the stent was significantly lower for TAXUS stents (7.9% SR and 7.8% MR) than for respective controls (23.2% and 20.5%;  $P < 0.0001$  for both). This corresponded with a reduction in angiographic restenosis from 17.9% to 2.3% in the SR cohort ( $P < 0.0001$ ) and from 20.2% to 4.7% in the MR cohort ( $P = 0.0002$ ). The incidence of major adverse cardiac events at 12 months was significantly lower ( $P = 0.0192$ ) in the TAXUS-SR (10.9%) and TAXUS-MR (9.9%) groups than in controls (22.0% and 21.4%, respectively), predominantly because of a significant reduction in repeat revascularization of the target lesion in TAXUS-treated patients.

**Conclusions**—Compared with a bare metal stent, paclitaxel-eluting stents reduced in-stent neointimal formation and restenosis and improved 12-month clinical outcome of patients with single de novo coronary lesions. (*Circulation*. 2003;108:788-794.)

**Key Words:** coronary disease ■ drugs ■ stents ■ restenosis

Drug-eluting stents have been heralded as a way to provide local drug delivery at the time of coronary stent implantation to prevent restenosis. Paclitaxel is a microtubule-stabilizing drug that blunts many cellular pathways<sup>1</sup> thought to contribute to the restenotic cascade. Early clinical feasibility studies (TAXUS I and TAXUS III)<sup>2,3</sup> conducted with a polymer-based paclitaxel-eluting stent provided promising safety data. The purpose of the present study was to evaluate the safety and efficacy of 2 different release formulations of paclitaxel-eluting stent in a large group of

patients. In addition, this report addresses 4 key issues associated with drug-eluting stents: stent thrombosis, edge restenosis, incomplete apposition, and aneurysm formation.

### Methods

#### Patient Selection

This randomized, double-blind trial was conducted at 38 sites (see Appendix). The protocol was approved by the Ethics Review Committees of participating institutions. Patients provided written informed consent before enrollment.

Received June 18, 2003; revision received July 8, 2003; accepted July 8, 2003.

From Ospedale San Raffaele, Milano, Italy (A.C.); PSK No 7 Zaklad Kardiologii, Katowice, Poland (J.D.); John Radcliffe Hospital, Oxford, Great Britain (A.B.); Krankenhaus Siegburg, Siegburg, Germany (E.G.); Krankenhaus der Barmherzigen Brüder, Trier, Germany (K.H.); Internistische Klinik Dr. Müller, Munich, Germany (S.S.); Jagiellonian University, Krakow, Poland (D.D.); Sunnybrook & Women's College Health Sciences Center, Toronto, Canada (S.F.); Centre Hospitalier Universitaire Jean Minjot, Besancon, France (F.S.); Jan Pawel II Hospital, International Cardiology Clinic, Krakow, Poland (K.Z.); Ospedali Riuniti di Bergamo, Bergamo, Italy (G.G.); and Boston Scientific Corporation, Natick, Mass (M.E.R.).

**This article originally appeared Online on August 4, 2003 (*Circulation*. 2003;108:r36-r42).**

Dr Banning has received fees for speaking at interventional cardiology meetings. Dr Fort has received funds from Boston Scientific, the study sponsor and the manufacturer of the stents that are the subject of this article, to cover the costs of enrolling patients in this study; Dr Fort also has a preceptor role with Boston Scientific. Dr Russell is a full-time employee of Boston Scientific. Dr Guagliumi has a consultant agreement with Boston Scientific.

Correspondence to Antonio Colombo, MD, Director, Cardiac Catheterization Laboratory, EMO Centro Cuore Columbus S.r.l., Sede Operativa c/o Casa Cura Columbus, Via M. Buonarroti, 48 20145 Milano, Italy. E-mail colombo@emocolumbus.it

© 2003 American Heart Association, Inc.

*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000086926.62288.A6

Eligible patients had stable or unstable angina or silent ischemia, were at least 18 years of age, and were acceptable candidates for percutaneous coronary intervention or CABG. Angiographic inclusion criteria specified a single de novo target lesion with estimated stenosis  $\geq 50\%$  and  $\leq 99\%$ , estimated length  $\leq 12$  mm, and location in a native coronary vessel  $\geq 3.0$  mm and  $\leq 3.5$  mm in diameter. Exclusion criteria included recent coronary intervention ( $\leq 30$  days), left ventricular ejection fraction  $< 30\%$ , evolving myocardial infarction (MI), unprotected left main coronary disease, or prespecified need to implant more than one 15-mm stent for full lesion coverage.

### Polymer-Based Paclitaxel-Eluting Stent

The TAXUS stent was a slotted-tube stainless steel stent (NIR, Medinol Ltd) coated with a proprietary polymer (Translute) designed to control paclitaxel release with an initial burst phase over the first 48 hours after implantation followed by a low-level release phase for  $\approx 10$  days.<sup>4</sup> Paclitaxel-eluting stents were coated with a total loaded dose of  $1 \mu\text{g}/\text{mm}^2$ . Two paclitaxel-eluting release formulations were evaluated, TAXUS-SR (slow release) and TAXUS-MR (moderate release), which has an 8-fold higher 10-day drug release. Of the total loaded dose, approximately 90% remains sequestered within the SR polymer formulation and 75% within the MR formulations without further measurable paclitaxel release. The control stent was the uncoated NIR stent. Study stents included diameters of 3.0 and 3.5 mm and 15-mm length, premounted on 20-mm balloon delivery catheters.

### Study Procedures

A first cohort of patients was randomized to TAXUS-SR or control. After clearance by a data monitoring committee, a second cohort of patients was randomized to TAXUS-MR or control.

To maintain blinding, TAXUS and control stents were indistinguishable by physical and radiographic appearance. The intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) core laboratories and the independent Clinical Events Committee were blinded to treatment allocation.

Twenty-four hours before catheterization or, alternatively, at least 4 hours before placement of the randomly assigned stents, patients received 300 mg of clopidogrel (unless treatment was initiated previously) and 75 mg of aspirin. Patients meeting angiographic inclusion criteria were randomized and treated in accordance with standard interventional techniques. Heparin was administered to maintain an activated clotting time  $\geq 250$  seconds during the procedure. Use of additional stents was permitted if patency of the stented vessel was compromised. Second stents were of the same type as those originally assigned. Third stents, if necessary, could be of any type considered appropriate by the investigator, except for study stents. After stent placement, patients received clopidogrel 75 mg/d (or ticlopidine 250 mg twice daily) for at least 6 months and aspirin 75 mg/d, maintained indefinitely.

### Follow-Up

Clinical status was assessed at hospital discharge and 1, 6, and 12 months after the procedure. The patients will be followed up annually to year 5. These results will be presented in future reports. IVUS and QCA assessments were performed after the procedure and at 6-month follow-up as described previously.<sup>2</sup>

### IVUS and QCA

Quantitative IVUS and angiography analyses (QCA) were performed by a core laboratory (Cardialysis BV, Rotterdam, the Netherlands) according to established methodology.<sup>5,6</sup> IVUS analysis presented in the present report was performed within the stented segment. QCA was performed within the stented segment and the total analysis segment. The total analysis segment was defined as the stented segment plus the regions 5 mm proximal and distal to the stent. In-stent analysis included the length of all stents used to treat the target lesion during the procedure. Incomplete stent apposition was identified by IVUS and defined as separation of 1 or more stent struts from the vessel wall with evidence of blood flow behind the strut.

### Study End Points

The primary end point was the percent of the stent volume obstructed by neointimal proliferation measured by IVUS at 6 months. Secondary end points included major adverse cardiac events (MACE), including cardiac death, Q-wave MI, non-Q-wave MI, and target-vessel revascularization at 1, 6, and 12 months. Non-Q-wave MI was defined as elevation of creatine kinase levels  $> 2$  times normal with detectable creatine kinase-MB in the absence of pathological Q-waves. Target-vessel revascularization included all CABG and percutaneous coronary intervention performed on the target vessel. Target lesion revascularization was performed to treat restenosis of the analysis segment (stent plus the 5-mm regions from the stent border). QCA measurements at 6 months included binary restenosis (defined as  $\geq 50\%$  diameter stenosis), reference vessel diameter, minimum lumen diameter, percent diameter stenosis, and late lumen loss.

An independent clinical events committee adjudicated MACE. An independent data monitoring committee reviewed data for potential safety concerns.

### Statistical Analysis

The primary study hypothesis was that paclitaxel elution would diminish in-stent net volume obstruction at 6 months compared with bare control stents. A mean net volume obstruction of  $26 \pm 17\%$  was estimated for the uncoated control stent.<sup>7</sup> To obtain 80% power to detect an absolute difference of 25% between treatment groups within each cohort with a 35% 6-month attrition rate for IVUS, 133 patients per group were required. This sample size was calculated for a 2-group *t* test of equal means. Safety and efficacy variables were analyzed for intention-to-treat populations. TAXUS-SR and TAXUS-MR cohorts were compared with their respective controls. Continuous variables are expressed as mean  $\pm$  SD and compared with 2-tailed probability values from an overall F test from a 1-way ANOVA and pairwise comparisons with Fisher's test of least significant difference. Discrete variables are displayed as percentages and evaluated with 2-tailed probability values from Fisher's exact test, overall and pairwise. Kaplan-Meier estimates were compared by the Wilcoxon test. A probability value of less than 0.05 was considered statistically significant.

## Results

### Patient Characteristics

Between June 2001 and January 2002, 536 patients were randomized into 2 consecutive and independent cohorts: 267 patients in the SR cohort (TAXUS-SR  $n=131$ ; control  $n=136$ ) and 269 in the MR cohort (TAXUS-MR  $n=135$ ; control  $n=134$ ). Treatment and control groups in both cohorts were well matched for baseline demographics and clinical characteristics (Table 1).

### Procedural Characteristics

Baseline lesion characteristics were comparable among all groups (Table 1). Clinical procedural success rates, defined as achievement of an in-lesion diameter stenosis  $< 30\%$  of the target lesion without the occurrence of in-hospital MACE, were comparable between cohorts and between treatment and control arms (TAXUS-SR 95%; SR control 93%; TAXUS-MR 96%; MR control 94%). Use of single or double study stents and implanted stent sizes were also similar among all groups. One study stent was implanted in 93% of TAXUS-SR patients and in 94% of SR controls, TAXUS-MR patients, and MR controls. Furthermore, the groups did not differ with regard to use of glycoprotein IIb/IIIa inhibitors (TAXUS-SR 11.5% versus SR controls 12.5%; TAXUS-MR 20.7% versus MR controls 23.9%).

**TABLE 1. Baseline Patient Characteristics\***

| Characteristic                | TAXUS-SR<br>(n=131) | SR Control<br>(n=136) | TAXUS-MR<br>(n=135) | MR Control<br>(n=134) |
|-------------------------------|---------------------|-----------------------|---------------------|-----------------------|
| Age, y                        | 61.5±10.5           | 60.4±9.3              | 59.3±10.1           | 59.3±10.0             |
| Male                          | 70                  | 79                    | 76                  | 77                    |
| Current smoker                | 21                  | 25                    | 24                  | 29                    |
| Diabetes mellitus             | 11                  | 16                    | 17                  | 14                    |
| Hypertension                  | 63                  | 67                    | 60                  | 56                    |
| Angina pectoris               |                     |                       |                     |                       |
| Stable                        | 57                  | 56                    | 67                  | 58                    |
| Unstable                      | 35                  | 33                    | 30                  | 40                    |
| Previous MI                   | 36                  | 43                    | 39                  | 42                    |
| Previous revascularization    | 12                  | 17                    | 17                  | 13                    |
| Target coronary vessel        |                     |                       |                     |                       |
| LAD                           | 40                  | 44                    | 42                  | 52                    |
| LCx                           | 22                  | 16                    | 25                  | 15                    |
| RCA                           | 38                  | 40                    | 33                  | 33                    |
| Reference vessel diameter, mm | 2.8±0.4             | 2.8±0.5               | 2.7±0.5             | 2.7±0.5               |
| Target lesion length, mm      | 10.6±3.9            | 10.5±4.1              | 10.2±4.8            | 10.7±4.1              |

LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

Plus-minus values are mean±SD; all other values are percentages.

\*There were no significant differences between TAXUS-SR or TAXUS-MR and control ( $P<0.05$ ).

### Primary End Point

IVUS imaging for the primary end point, percent in-stent net volume obstruction at 6 months, was available for 91% and 88% of patients in the SR and MR cohorts 6 months after the procedure, respectively. As shown in Table 2, the primary end point was met with a significant reduction in percent in-stent net volume obstruction at 6 months in the TAXUS-SR (7.8% versus 23.2%;  $P<0.0001$ ) and TAXUS-MR (7.8% versus 20.5%;  $P<0.0001$ ) groups compared with their respective control groups.

### Coronary Angiography

Six-month coronary angiography was performed in 98% and 96% of all patients in the SR and MR cohorts, respectively. Compared with control, 6-month angiographic parameters (Table 2) were significantly improved in the TAXUS groups, with larger minimum lumen diameter, lower percent diameter stenosis, and reduced late loss. This translated into a significant improvement in binary restenosis rates in the total analysis segment for the TAXUS groups, with reductions from 20.1% to 5.5% in the SR cohort ( $P=0.0004$ ) and from 23.8% to 8.6% in the MR cohort ( $P=0.001$ ). Among the 18 restenoses identified in TAXUS patients, 5 occurred in adjacent bare metal, nonstudy stents (1 in SR, 4 in MR).

As shown in Table 3, reductions in late loss extended beyond the stented segment to the 5 mm proximal and distal to the stent edges, with significantly lower late loss at the edges in both the TAXUS-SR and TAXUS-MR stents than in the control stents. In total, 8 aneurysms were identified by QCA in this study (3 in the TAXUS-SR group, 1 in the SR control group, 1 in the TAXUS-MR group, and 3 in the MR control group). Differences in aneurysm rates between TAXUS and control groups were not significant, and aneu-

rysm formation was not correlated with clinical adverse events.

### Intravascular Ultrasound

IVUS was also used to assess vessel, stent, and lumen volume and the presence of incomplete apposition of stent struts after stent implantation and at 6 months. As shown in Table 2, vessel volume within the stented segment and stent volume were not different between the TAXUS-SR and -MR groups and their respective controls either at baseline or at 6-month follow-up. Lumen volume was also comparable between groups within each cohort at baseline. However, at follow-up, the lumen area was significantly larger in the TAXUS-SR and TAXUS-MR groups than in their respective controls ( $P=0.0002$  and  $0.0004$ ).

The incidence of incomplete apposition did not differ between groups in either cohort at baseline (TAXUS-SR 11.1% versus SR control 9.3%,  $P=0.68$ ; TAXUS-MR 3.1% versus MR control 7.9%,  $P=0.10$ ) or at 6 months (TAXUS-SR 12.5% versus SR control 7.9%,  $P=0.29$ ; TAXUS-MR 9.9% versus MR control 9.2%,  $P=1.00$ ).

### Major Adverse Cardiac Events

Periprocedural and in-hospital MACE rates were comparable in all groups, without significant differences (TAXUS-SR 1.5% versus SR control 4.4%; TAXUS-MR 2.2% versus MR control 4.5%). There was 1 in-hospital death related to periprocedural retroperitoneal bleeding and multiple organ failure and 1 Q-wave MI, both in control patients. One periprocedural stent thrombosis occurred in a TAXUS-SR patient. Thirty-day MACE rates were low and comparable among groups (2.3% TAXUS-SR versus 4.4% SR control

TABLE 2. Quantitative Analysis of the Stented Segment by IVUS and QCA

|   | TAXUS-SR<br>(n=131) | SR Control<br>(n=136) | P       | TAXUS-MR<br>(n=135) | MR Control<br>(n=134) | P       |
|---|---------------------|-----------------------|---------|---------------------|-----------------------|---------|
| <b>IVUS</b>                             |                     |                       |         |                     |                       |         |
| Percent in-stent net volume obstruction |                     |                       |         |                     |                       |         |
| After procedure                         | 0.03±0.18           | 0.08±0.57             | 0.37    | 0.17±0.76           | 0.20±1.05             | 0.77    |
| After 6 months                          | 7.84±9.87           | 23.17±18.19           | <0.0001 | 7.84±9.66           | 20.54±16.68           | <0.0001 |
| Vessel volume, mm <sup>3</sup>          |                     |                       |         |                     |                       |         |
| After procedure                         | 255±68              | 249±63                | 0.52    | 234±71              | 249±64                | 0.17    |
| After 6 months                          | 267±90              | 254±72                | 0.24    | 274±98              | 263±81                | 0.41    |
| Stent volume, mm <sup>3</sup>           |                     |                       |         |                     |                       |         |
| After procedure                         | 131±41              | 130±36                | 0.76    | 127±49              | 126±42                | 0.96    |
| After 6 months                          | 129±42              | 129±40                | 0.24    | 132±49              | 132±42                | 0.93    |
| Lumen volume, mm <sup>3</sup>           |                     |                       |         |                     |                       |         |
| After procedure                         | 131±41              | 130±36                | 0.90    | 126±49              | 126±43                | 0.96    |
| After 6 months                          | 119±41              | 99±38                 | 0.0002  | 121±41              | 104±33                | 0.0004  |
| <b>QCA</b>                              |                     |                       |         |                     |                       |         |
| Reference vessel diameter, mm           |                     |                       |         |                     |                       |         |
| Before procedure                        | 2.78±0.44           | 2.77±0.49             | 0.92    | 2.72±0.46           | 2.73±0.45             | 0.77    |
| After procedure                         | 2.85±0.34           | 2.88±0.41             | 0.50    | 2.85±0.39           | 2.87±0.38             | 0.56    |
| After 6 months                          | 2.78±0.42           | 2.62±0.44             | 0.004   | 2.74±0.41           | 2.66±0.45             | 0.16    |
| Minimum lumen diameter, mm              |                     |                       |         |                     |                       |         |
| Before procedure                        | 1.02±0.30           | 1.03±0.34             | 0.65    | 0.95±0.32           | 0.91±0.36             | 0.38    |
| After procedure                         | 2.53±0.29           | 2.58±0.37             | 0.21    | 2.53±0.36           | 2.52±0.34             | 0.87    |
| After 6 months                          | 2.23±0.47           | 1.79±0.54             | <0.0001 | 2.24±0.47           | 1.76±0.57             | <0.0001 |
| Diameter stenosis, %                    |                     |                       |         |                     |                       |         |
| Before procedure                        | 63.3±9.6            | 62.8±9.9              | 0.68    | 64.9±10.3           | 66.6±11.9             | 0.20    |
| After procedure                         | 10.9±6.5            | 10.2±5.9              | 0.37    | 11.0±6.1            | 12.0±6.3              | 0.18    |
| After 6 months                          | 19.5±12.7           | 31.8±17.1             | <0.0001 | 18.2±12.3           | 33.9±18.0             | <0.0001 |
| Late loss, mm                           |                     |                       |         |                     |                       |         |
|   | 0.31±0.38           | 0.79±0.45             | <0.0001 | 0.30±0.39           | 0.77±0.50             | <0.0001 |
| Binary (>50%) restenosis, %             |                     |                       |         |                     |                       |         |
| Total analysis segment                  | 5.5                 | 20.1                  | 0.0004  | 8.6                 | 23.8                  | 0.001   |
| Stented segment                         | 2.3                 | 17.9                  | <0.0001 | 4.7                 | 20.2                  | 0.0002  |

and 2.2% TAXUS-MR versus 4.5% MR control), with non-Q-wave MIs being the dominant events.

Clinical follow-up at 6 and 12 months (shown in Table 4) was available for 99% and 96% of all patients in the SR and MR cohorts, respectively. At 6 months, MACE rates were significantly lower for TAXUS-SR (8.5%) and for TAXUS-MR (7.8%) than for their respective control groups (19.5%,  $P=0.01$  and 20.0%,  $P=0.006$ , respectively). This reduction in MACE was attributable to lower rates of target-lesion revascularization in the TAXUS groups (4.6% SR, 3.1% MR) than in the control groups (12.0% and 14.6%). This clinical benefit was maintained at 12 months, with lower target-lesion revascularization rates in the TAXUS groups (4.7% SR and 3.8% MR) than in the control groups (12.9% and 16.0%). This translated into 12-month MACE rates of 10.9% for TAXUS-SR ( $P=0.02$ ) and 9.9% for TAXUS-MR ( $P=0.02$ ) compared with 22.0% and 21.4% for the corresponding control groups.

Two patients treated with TAXUS stents (1 SR and 1 MR) presented with ST-elevation MIs between 6 and 12 months.

Subsequent angiography after treatment with thrombolytic therapy revealed widely patent study stents. Because of the absence of other explanatory coronary stenoses, these were adjudicated as "presumed stent thromboses" that accounted for the late stent thrombosis rate of 0.7%.

As shown in the Figure, MACE-free survival at 6 months in the TAXUS-SR (93.9%) and TAXUS-MR (93.3%) groups was significantly higher than in their respective controls (86.0% and 83.6%). This benefit was sustained up to 12 months, with a MACE-free survival rate of 89.2% in the TAXUS-SR group and 89.5% in the TAXUS-MR group compared with 78.7% ( $P=0.01$ ) and 79.1% ( $P=0.008$ ) in their respective control groups.

## Discussion

The TAXUS II trial shows that polymer-controlled slow and moderate release of paclitaxel reduces neointimal obstruction within the stent by 64% as measured by IVUS, angiographic restenosis by 73% and 74%, respectively, and 6- and 12-month MACE rates by 50% and 54% because of reductions in

**TABLE 3. Six-Month Results of QCA Edge Analysis**

|                              | Proximal Edge |          | Stented Segment |          | Distal Edge |          |
|------------------------------|---------------|----------|-----------------|----------|-------------|----------|
|                              | Result        | <i>P</i> | Result          | <i>P</i> | Result      | <i>P</i> |
| Percent diameter stenosis, % |               |          |                 |          |             |          |
| TAXUS-SR                     | 17.0±11.4     | 0.77     | 19.5±12.7       | <0.0001  | 17.7±11.1   | 0.85     |
| SR control                   | 17.5±14.2     |          | 31.8±17.1       |          | 18.0±12.4   |          |
| TAXUS-MR                     | 17.0±12.8     | 0.10     | 18.2±12.3       | <0.0001  | 16.0±10.9   | 0.22     |
| MR control                   | 19.8±14.0     |          | 33.9±18.0       |          | 18.0±14.3   |          |
| Late loss, mm                |               |          |                 |          |             |          |
| TAXUS-SR                     | 0.17±0.37     | <0.0001  | 0.31±0.38       | <0.0001  | 0.05±0.34   | 0.0002   |
| SR control                   | 0.38±0.40     |          | 0.79±0.45       |          | 0.23±0.40   |          |
| TAXUS-MR                     | 0.21±0.40     | 0.004    | 0.30±0.39       | <0.0001  | 0.08±0.34   | 0.0003   |
| MR control                   | 0.36±0.44     |          | 0.77±0.50       |          | 0.27±0.48   |          |
| Binary (≥50%) restenosis, %  |               |          |                 |          |             |          |
| TAXUS-SR                     | 1.6           | 1.00     | 2.3             | <0.0001  | 1.6         | 0.68     |
| SR control                   | 2.2           |          | 17.9            |          | 3.0         |          |
| TAXUS-MR                     | 2.3           | 0.33     | 4.7             | 0.0002   | 2.3         | 1.00     |
| MR control                   | 4.7           |          | 20.2            |          | 3.1         |          |

target-lesion revascularizations of 64% and 76%, respectively. These concordant improvements in IVUS, angiographic, and clinical indices provide proof of principle that polymer-based delivery of paclitaxel reduces restenosis after coronary stent implantation.

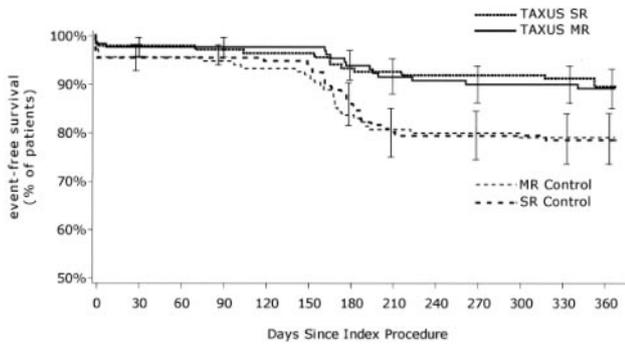
These beneficial antirestenotic effects are balanced against concerns about potential vascular cytotoxicity and its associated clinical correlates. First, discontinuation of thienopyridine after 6 months was not associated with a significant increase in late stent thrombosis rates in TAXUS compared

**TABLE 4. Cumulative MACE Rates During 12 Months of Follow-Up**

| Nonhierarchical Events          | TAXUS-SR<br>(n=131) | SR Control<br>(n=136) | <i>P</i> | TAXUS-MR<br>(n=135) | MR Control<br>(n=134) | <i>P</i> |
|---------------------------------|---------------------|-----------------------|----------|---------------------|-----------------------|----------|
| 6-Month MACE                    |                     |                       |          |                     |                       |          |
| Overall                         | 8.5 (11/130)        | 19.5 (26/133)         | 0.01     | 7.8 (10/129)        | 20.0 (26/130)         | 0.006    |
| Death                           | 0 (0/130)           | 0.8 (1/133)           | 1.00     | 0 (0/129)           | 0 (0/130)             | N/A      |
| MI                              |                     |                       |          |                     |                       |          |
| Q-wave                          | 0 (0/130)           | 1.5 (2/133)           | 0.50     | 0 (0/129)           | 0 (0/130)             | N/A      |
| Non-Q-wave                      | 1.5 (2/130)         | 3.8 (5/133)           | 0.45     | 2.3 (3/129)         | 5.4 (7/130)           | 0.33     |
| Target-vessel revascularization | 7.7 (10/130)        | 14.3 (19/133)         | 0.11     | 6.2 (8/129)         | 17.7 (23/130)         | 0.007    |
| Target lesion                   | 4.6 (6/130)         | 12.0 (16/133)         | 0.04     | 3.1 (4/129)         | 14.6 (19/130)         | 0.002    |
| Nontarget lesion                | 3.1 (4/130)         | 2.3 (3/133)           | 0.72     | 2.3 (3/129)         | 3.1 (4/130)           | 1.00     |
| CABG                            | 0.8 (1/130)         | (1/133)               | 1.00     | 0.8 (1/129)         | 0.8 (1/130)           | 1.00     |
| 12-Month MACE                   |                     |                       |          |                     |                       |          |
| Overall                         | 10.9 (14/129)       | 22.0 (29/132)         | 0.02     | 9.9 (13/131)        | 21.4 (28/131)         | 0.017    |
| Death                           | 0 (0/129)           | 1.5 (2/132)           | 0.50     | 0 (0/131)           | 0 (0/131)             | N/A      |
| MI                              |                     |                       |          |                     |                       |          |
| Q-wave                          | 0.8 (1/129)         | 1.5 (2/132)           | 1.00     | 1.5 (2/131)         | 0.8 (1/131)           | 1.00     |
| Non-Q-wave                      | 1.6 (2/129)         | 3.8 (5/132)           | 0.45     | 2.3 (3/131)         | 4.6 (6/131)           | 0.50     |
| Target-vessel revascularization | 10.1 (13/129)       | 15.9 (21/132)         | 0.20     | 6.9 (9/131)         | 19.1 (25/131)         | 0.005    |
| Target lesion                   | 4.7 (6/129)         | 12.9 (17/132)         | 0.03     | 3.8 (5/131)         | 16.0 (21/131)         | 0.002    |
| Nontarget lesion                | 3.1 (4/129)         | 3.0 (4/132)           | 1.00     | 1.5 (2/131)         | 3.1 (4/131)           | 0.68     |
| CABG                            | 3.1 (4/129)         | 0.8 (1/132)           | 0.21     | 1.5 (2/131)         | 1.5 (2/131)           | 1.00     |

Numbers are % (event rates). Event rates are number of patients who experienced the outcome divided by number of patients eligible for the outcome.

Overall target-vessel revascularization numbers do not add up to 100% because some patients had >1 target-vessel revascularization event.



Kaplan-Meier estimates of survival free of MACE (death, MI, and target-vessel revascularization) among patients who received TAXUS-SR, TAXUS-MR, or control stent. Rate of MACE-free survival was significantly higher in TAXUS-SR and TAXUS-MR groups than in their respective control groups (TAXUS-SR vs SR control,  $P=0.01$ ; TAXUS-MR vs MR control,  $P=0.008$ ).

with control. The rate of 0.7% was comparable to the 0.76% reported by Uretsky and coauthors<sup>8</sup> for bare metal stents. Second, angiographic evaluation of the stent edges showed that the beneficial effect of TAXUS within the stent was associated with low rates of edge stenosis comparable to control stents, which eliminates concern about aggravated edge stenosis. In fact, the QCA measurements showed that late lumen loss at the proximal and distal edges was significantly lower in both TAXUS groups than in their controls. Third, use of paclitaxel-eluting stents was not associated with an increased incidence of incomplete stent apposition at baseline or at follow-up. Fourth, rates of aneurysm were comparable between TAXUS and control stents. Taken together, the improvements in restenosis are accompanied by an acceptable safety profile.

These findings contrast with other studies assessing the effects of local paclitaxel delivery that used different doses and delivery systems. High-capacity delivery (up to 4000  $\mu\text{g}$ ) of a paclitaxel derivative through 4 or 5 high-capacity acrylate polymer sleeves for up to 6 months (Quanam QuaDDS stent system) was associated with an increased incidence of acute, subacute, and late stent thrombosis (SCORE trial).<sup>9</sup> Paclitaxel delivery with non-polymer-based delivery systems resulted in a significant reduction in neointimal formation; however, angiographic improvements did not translate into clinical benefit.<sup>10</sup> With the TAXUS system, biphasic, polymer-controlled delivery of low concentrations of paclitaxel resulted in significant reductions in neointimal proliferation that translated into clinical benefit. Persistence of these benefits in incidence of MACE and target-lesion revascularization from 6 to 12 months indicates that polymer-based paclitaxel-eluting stents may indeed inhibit rather than merely delay restenosis. Of the 4 patients who required operative revascularization between 6 and 12 months, all had patent study stents with diffuse progression of the underlying arteriosclerosis outside the stent. One patient had restenosis proximal to the patent study stent but within the analysis segment.

The present findings are in line with recent reports on a stent system that used polymer-based delivery of sirolimus.<sup>11</sup> Both stent systems provide significant reductions in in-stent

neointimal hyperplasia, which translates into a reduced need for repeat interventions and a reduced incidence of MACE. One major differentiator between these 2 systems appears to be the amount of angiographic late loss seen 6 months after stent implantation. The 60% reduction in mean late loss at 6 months to 0.31 mm in TAXUS-SR and 0.30 mm in TAXUS-MR occurred without a shift toward negative late loss. These results are in contrast to findings with a sirolimus-eluting stent (RAVEL),<sup>11</sup> in which a mean 6-month late loss of  $-0.01$  mm was reported. A negative mean late loss suggests the presence of positive vascular remodeling with vessel distension in a subgroup of patients. Future studies will have to prospectively determine the optimum amount of late loss, combining sufficient antirestenotic properties and adequate healing after stent implantation.

TAXUS II suggests that TAXUS-SR is the minimum effective paclitaxel formulation for standard-risk, de novo lesions. The slow- and moderate-release formulations studied in TAXUS II are loaded with the same dose density of paclitaxel (85  $\mu\text{g}$  per 15-mm stent). The major distinction between the 2 formulations is the 8-fold greater amount of drug released from the TAXUS-MR stent over 10 days, even though the total loaded dose is the same. This pharmacological difference did not translate into differences in IVUS, angiographic, or clinical outcomes given that the study was not designed to detect differences between formulations. The similar efficacy profiles of the 2 formulations may indicate that the dosing threshold to interrupt the restenotic cascade in low-risk lesions had been reached with the slow-release formulation. It is unclear, however, whether the same threshold applies for higher-risk patient populations (diabetic patients) or more complex lesions (small diameter, long lesions, or in-stent restenosis), where much of the unmet need currently lies.

Limitations of the present study evaluating polymer-based paclitaxel elution are the need for longer-term follow-up and the focus on standard-risk, focal, de novo lesions that may not reflect the more complex lesions and patients encountered in real-world practice. The next step in assessing the utility of this promising technology is to expand to studies in more challenging lesion sets and to evaluate optimum dosing strategies.

## Appendix

### Clinical Sites

The following investigators and institutions participated in the TAXUS II study: Antonio Colombo, Ospedale San Raffaele, Milano, Italy; Janusz Dzrewiecki, PSK No. 7 Zaklad Kardiologii, Katowice, Poland; Adrian Banning, John Radcliffe Hospital, Oxford, Great Britain; Karl Hauptmann, Krankenhaus der Barmherzigen Brüder, Trier, Germany; Eberhard Grube, Krankenhaus Siegburg GmbH, Siegburg, Germany; Dariusz Dudek, Jagiellonian University, Krakow, Poland; Stephen Fort, Sunnybrook & Women's College Health Sciences Center, Toronto, Canada; Francois Schiele, Centre Hospitalier Universitaire Jean Minjot, Besancon, France; Sigmund Silber, Internistische Klinik Dr. Müller, Munich, Germany; Krzysztof Zmudka, Jan Pawel II Hospital, International Cardiology Clinic, Krakow, Poland; Giulio Guagliumi, Ospedali Riuniti di Bergamo, Bergamo, Italy; Charles Chan, Singapore General Hospital, Singapore; Thomas Muenzel, Universitätsklinikum Eppendorf, Medizinische Klinik, Hamburg, Germany; Jorge Belardi, Instituto Cardio-

vascular de Buenos Aires, Buenos Aires, Argentina; Witold Ruzyllo, National Institute of Cardiology, Warsaw, Poland; Luc Bilodeau, Montreal Heart Institute, Montreal, Canada; Henning Kelbaek, Heart Center, Copenhagen, Denmark; John Ormiston, Mercy and Greenlane Hospitals, Auckland, New Zealand; Keith Dawkins, Southampton General Hospital, Southampton, Great Britain; John Webb, St. Paul's Hospital, Vancouver, Canada; Louis Roy, Hospital Laval Institute de Cardiologie de Quebec, Quebec, Canada; Bradley Strauss, St. Michael's Hospital, Toronto, Canada; Jaap Hamburger, Vancouver General Hospital, Vancouver, Canada; Wolfgang Rutsch, Universitätsklinikum Charite, Berlin, Germany; Matthias Pfisterer, Cardiology, University Hospital Basel, Basel, Switzerland; Robert Whitbourn, St. Vincent's Hospital, Melbourne, Australia; Edoardo Camenzind, Hospital Cantonal Universitaire, Geneva, Switzerland; Ian Meredith, Cardiovascular Research Center, Victoria, Australia; Francois Reeves, CHUM Notre-Dame Hospital, Montreal, Canada; Christoph Nienaber, Universitätsklinikum Rostock, Rostock, Germany; Edouard Benit, Virga Jesse Ziekenhuis Dienst Hartcatheterisatie, Hasselt, Belgium; Wilhelm Urbaszek, Medizinische Klinik Weisser Hirsch, Dresden, Germany; Edouard Bonnier, Catherina Ziekenhuis Eindhoven, Eindhoven, Netherlands; Jean-Michel La-blanche, Hospital Cardiologique, Lille, France; Tomasz Siminiak, J. Strus Hospital, Proznan, Poland; Jan Nordrehaug, Haukeland Hospital, Bergen, Norway; and Hans Figulla, Friedrich Schiller Universität, Jena, Germany.

### Acknowledgments

This study was supported by Boston Scientific Corporation. We thank Dr Jörg Koglin (Boston Scientific Corporation) for his help in writing the manuscript.

### References

1. Sollott SJ, Cheng L, Pauly RR, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest*. 1995;95:1869–1876.
2. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: 6 and 12 month results from a randomized, double blind trial on a slow release paclitaxel eluting stent for de novo coronary lesions. *Circulation*. 2003;107:38–42.
3. Tanabe K, Serruys PW, Grube E, et al. TAXUS III trial: in-stent restenosis treated with stent based delivery of paclitaxel incorporated in a slow release polymer formulation. *Circulation*. 2003;107:559–564.
4. Silber S, Grube E. The Boston Scientific Antiproliferative, paclitaxel eluting stents (TAXUS). In: Serruys P, Kutryk M, eds. *Handbook of Coronary Stents*. 4th ed. London, UK: Martin Dunitz Publishers Ltd; 2001:311–319.
5. Serruys P, Foley DP, de Feyter PJ. *Quantitative Coronary Angiography in Clinical Practice*. Dordrecht, the Netherlands: Kluwer Academic; 1994.
6. Hamers R, Bruining N, Knook M, et al. A novel approach to quantitative analysis of intravascular ultrasound images. *Comp Cardiol*. 2001;28:589–592.
7. Costa MA, Sabate M, Kay IP, et al. Three-dimensional intravascular ultrasonic volumetric quantification of stent recoil and neointimal formation of two new generation tubular stents. *Am J Cardiol*. 2000;85:135–139.
8. Uretsky BF, Rosanio S, Lerakis S, et al. A prospective evaluation of angiography-guided coronary stent implantation with high versus very high balloon inflation pressure. *Am Heart J*. 2000;140:804–812.
9. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology. Drug-eluting stents: part II. *Circulation*. 2003;107:2383–2389.
10. Park S-J, Shim WH, Ho DS, et al. Paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med*. 2003;348:1537–1545.
11. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773–1780.