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TAXUS VI 2-year follow-up: randomized comparison of polymer-based paclitaxel-eluting with bare metal stents for treatment of long, complex lesions

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Aims Drug-eluting stents (DESs) have shown to be effective in reducing in-stent restenosis, although data relating to long-term experience in treating more complex lesion subsets are limited. In order to assess the long-term safety and clinical efficacy of the polymer-based moderate release (MR) paclitaxel-eluting TAXUSTM MR stent in treatment of complex lesion subsets, we evaluated the 2-year follow-up of TAXUS VI.

Method and results TAXUS VI was a randomized multi-centre study enrolling 446 patients with complex lesions, including small vessels in 28% of patients and a mean lesion length of 20.6 mm. At 9-month follow-up, the use of the TAXUS MR stent was highly effective, resulting in a significant 53% reduction of the target vessel revascularization (TVR) rate (primary endpoint) from 19.4% in the control group to 9.1% in the TAXUS group (P = 0.0027). Clinical follow-up at 2 years post-stenting was available in 98.6% of the TAXUS group and 95.6% of the control group. The incidence of major adverse cardiac event at 1- and 2-year follow-up was 16.4% and 21.3% in the TAXUS group when compared with 22.5 and 25.1% in the control group, respectively. A significant difference in TVR was maintained at 2-year follow-up (TAXUS 13.9%; control 21.9%; P = 0.0335). The cumulative 1- and 2-year survival rates free from TVR were, respectively, 91.7 and 90.3% in the TAXUS group vs. 80.0 and 79.0% in the control group (log-rank P < 0.001). The number of patients required to be treated with a TAXUS stent to prevent one re-percutaneous coronary intervention at 2 years was 12.5.

Conclusion Treatment of complex coronary lesions with the polymer-based MR paclitaxel-eluting TAXUS MR stent is associated with a sustained clinical benefit and low rates of TVR up to 2 years after device implantation.

KEYWORDS Paclitaxel; Stent; Follow-up; Coronary artery disease

Introduction Drug-eluting stents (DESs) have proved to be safe and effective in reducing in-stent restenosis, although long-term data are limited and primarily based on populations with 'Benestent'-like lesions with a low risk for restenosis. Using a higher dose release of the active agent paclitaxel, TAXUS VI, a randomized multi-centre study, was specifically designed to assess safety and efficacy of the polymer-based moderate release (MR) paclitaxel-eluting TAXUSTM MR stent in high-risk patients with complex anatomy including small vessels and long lesions often requiring the implantation of longer or multiple overlapping stents. Both factors, small vessels and long lesions, are known predictors of restenotic events. As previously reported,16 TAXUS VI demonstrated a significant reduction in the primary endpoint target vessel revascularization (TVR) rate from 19.4% in the control group to 9.1% in the TAXUS group at 9-month follow-up, confirming the efficacy of this approach. The subgroup analysis revealed a significant benefit in all included lesion types with relative reduction in target lesion revascularization (TLR) rates ranging from 83 to 93%. Given these early
data, there is strong evidence for a striking benefit of DES in high-risk lesions. In order to assess the long-term effects of the TAXUS MR stent for the treatment of complex lesions, we evaluated the clinical outcome of the TAXUS VI population up to 2 years post-stenting.

Methods

Study design

TAXUS VI is a prospective, multi-centre, double-blind, randomized trial assessing clinical and angiographic outcomes of the TAXUS MR paclitaxel-eluting stent in the treatment of long, complex coronary artery lesions. The design and detailed methods of this trial have been published previously. Four hundred and forty-six patients in 44 sites were randomized between a drug-eluting TAXUS Express\textsuperscript{2} stent and an uncoated Express\textsuperscript{2} control stent (TAXUS group: 227 patients and control group 219 patients). The primary endpoint was the rate of TVR 9 months after the study procedure. Patients were treated with a combination of aspirin and clopidogrel for 6 months, followed by aspirin alone thereafter.

Angiographic inclusion criteria included a de novo target lesion located within a single native coronary vessel with a reference vessel diameter between 2.5 and 3.75 mm, a cumulative target lesion length of 18-40 mm, and a diameter stenosis of \(\geq 50\%\). Target lesions randomized to treatment with the study device had to be completely coverable by up to two study stents (maximum allowable stent length of 48 mm). To assure a more ‘real world’ patient population, the study also allowed inclusion of patients with successful treatment of an additional uncomplicated non-study lesion located in a non-target vessel prior to randomization during the same procedure.

Important exclusion criteria included recent acute myocardial infarction, poor left ventricular function, left main coronary artery disease, an ostial target lesion location, total occlusion, or involvement of a bifurcation with a side branch diameter of \(> 2.0\) mm. Treatment with additional devices (e.g. cutting balloons and directional/rotational atherectomy) was not permitted.

The study was reviewed and approved by each participating institution’s Ethics Review Committee, and all patients signed a written informed consent before enrolment.

Study stents

The TAXUS stent consists of a balloon-expandable Express\textsuperscript{2} stent with a triblock copolymer coating containing paclitaxel [1 \(\mu\)g/mm\textsuperscript{2} of paclitaxel (loaded drug/stent surface area)]. The Translute polymer coating serves as a carrier to provide uniform and controlled biphasic release of the drug into the vessel wall once the stent is deployed. The MR polymer formulation used in this study produces a paclitaxel release rate approximately three-fold higher than the slow release formulation based on in vivo pre-clinical measurements. The TAXUS MR stent is pre-mounted on a high-pressure monorail delivery catheter. An uncoated Express\textsuperscript{2} stent served as a control in the study.

Follow-up

The study was considered complete (with regard to the primary endpoint) after all enrolled patients had completed the 9-month angiographic follow-up; these results have been previously reported. However, additional clinical follow-up was conducted at 12 and 24 months post-procedure to assess rates of stent thrombosis and major adverse cardiac events (MACEs). The clinical follow-up consisted of either a telephone interview or a clinic visit. Further clinical follow-up will be conducted at yearly intervals up to 5 years post-stenting.

Definitions

MACEs were defined as cardiac death, Q-wave myocardial infarction, non-Q-wave myocardial infarction, or clinically driven TVR. TVR, but non-TLR, was defined as any clinically driven repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel for a lesion other than the target lesion within the target vessel. Stent thrombosis was defined per protocol as the clinical presentation of an acute coronary syndrome with angiographic evidence of stent thrombosis, acute myocardial infarction in the distribution of the treated vessel, or death within 30 days without other obvious cause.

Data management and statistical analyses

Site monitoring, data management, and analysis were undertaken by an independent organization (PPD Development, D-90402 Nuremberg, Germany); following unblinding, the investigators had unrestricted access to the data. All MACEs were reviewed and adjudicated by an independent committee whose members were unaware of the patients’ treatment allocation. A data monitoring committee periodically reviewed blinded safety data.

All analyses were based on the intention-to-treat principle. For continuous variables, differences between the treatment groups were evaluated by analysis of variance or Wilcoxon’s rank-sum test, as appropriate. For discrete variables, differences were expressed as counts and percentages and were analysed with Fisher’s exact test. Revascularization of the target lesion and the composite of MACEs were also analysed by the Kaplan–Meier method. Differences between the event-free survival curves for the two groups were compared with the use of the log-rank tests. All tests were two-sided and a 5% difference was deemed significant.

Results

The baseline clinical characteristics of the TAXUS VI trial population have been described previously and are summarized in Table 1. Both study groups were similar with respect to all variables examined. Complete data sets were available at 2 years in 98.6% of patients randomly assigned to the TAXUS group and in 95.6% of the control group. Follow-up was by means of a clinic visit or by telephone. The number of patients who experienced a MACE

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline demographics and clinical characteristics\textsuperscript{a}</th>
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<tbody>
<tr>
<td></td>
<td>TAXUS ((N = 219))</td>
</tr>
<tr>
<td>Age</td>
<td>61.8 ± 9.7</td>
</tr>
<tr>
<td>Males, % (n/N)</td>
<td>76.3 (167/219)</td>
</tr>
<tr>
<td>Medically treated diabetes, % (n/N)</td>
<td>17.8 (39/219)</td>
</tr>
<tr>
<td>Insulin requiring, % (n/N)</td>
<td>6.8 (15/219)</td>
</tr>
<tr>
<td>Non-insulin requiring, % (n/N)</td>
<td>11.0 (24/219)</td>
</tr>
<tr>
<td>Medically treated hyperlipidaemia, % (n/N)</td>
<td>70.3 (149/212)</td>
</tr>
<tr>
<td>Medically treated hypertension, % (n/N)</td>
<td>57.5 (126/219)</td>
</tr>
<tr>
<td>Current smoker, % (n/N)</td>
<td>22.5 (47/209)</td>
</tr>
<tr>
<td>Unstable angina, % (n/N)</td>
<td>24.7 (54/219)</td>
</tr>
<tr>
<td>Previous PCI, % (n/N)</td>
<td>17.9 (39/218)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}None of the baseline parameters were statistically different between groups (\(P < 0.05\)).
between 1- and 2-year follow-up is listed in Table 2. There was no significant difference in the incidence of MACE between both study groups during the late follow-up period.

The incidence of MACE at 1- and 2-year follow-up was 16.4 and 21.3% in the TAXUS group when compared with 22.5 and 25.1% in the control group, respectively. Although there was only a trend towards a MACE reduction in the TAXUS group at each time point, the significant difference in TVR events evident at 9 months of follow-up (TAXUS 9.1% control 19.4%; P = 0.0027) was maintained at 2-year follow-up (TAXUS 13.9%; control 21.9%; P = 0.033).

The cumulative 1- and 2-year survival rates free from TLR were, respectively, 91.7 and 90.3% in the TAXUS group vs. 80.0 and 79.0% in the control group (log-rank P < 0.001) (Figure 1). The high-risk subgroup analysis revealed a TLR reduction at 2 years from 72 to 84% by using the TAXUS stent.

Deaths during follow-up

A total of three patients died in the 12–24 months period because of cardiac events (two patients in the control group and one patient in the TAXUS group). The single TAXUS patient died 711 days after the post-procedure because of a sudden cardiac death; no autopsy was undertaken.

Stent thrombosis during follow-up

A total of four stent thromboses occurred in the study population at 2-year follow-up. At 6 months, 94.1% of patients in the TAXUS group and 93.3% of the control group were on dual anti-platelet therapy (P = ns). In three patients, the stent thrombosis was subacute within the first 30 days post-procedure (two patients in the control group and one patient in the TAXUS group). There was no additional event up to 365 days post-procedure. Between 1- and 2-year follow-up, one patient of the TAXUS group developed a stent thrombosis at day 408. This stent thrombosis led to a Q-wave myocardial infarction treated conservatively with low-molecular-weight heparin, without re-intervention. There was no statistical difference in the incidence of stent thrombosis between the two study groups up to 2-year follow-up.

Target vessel revascularization during follow-up

There were a total of 76 revascularizations (TVR/TLR) out to 2 years. The Clinical Events Committee (CEC) determined that 92.1% (n = 70) were confirmed per protocol TVR/TLR, 32.9% (n = 23) in the TAXUS group, and 67.1% (n = 47) in the control group. In 7.9% (n = 6) of patients, the CEC determined that the TVR/TLR was ‘not an event’, four patients in the TAXUS group and two patients in the control group. The number of TVRs in the 12–24 month follow-up period was six in the TAXUS group when compared with four in the control group (P = 0.54). There was no significant difference in late TLR or TVR events between both study groups (Table 2). Only three of the six TAXUS TVRs were related to restenosis within the target lesion. Among the three patients with TLRs beyond 12 months of follow-up, two had focal proximal edge in-segment restenosis without significant in-stent lumen re-narrowing. One patient developed diffuse in-stent restenosis 525 days post-procedure. All TAXUS patients with TVR were treated by PCI. Subgroup analysis for TLR is shown in Table 3.

Discussion

DESs have demonstrated remarkable efficacy in reducing TLR when compared with conventional bare metal stents (BMSs) in low complexity de novo lesions, which led to the market approval of the sirolimus-eluting CYPHER and the paclitaxel-eluting TAXUS stents.6,7 There is now a large body of evidence for the long-term clinical effects of DESs in low-risk coronary lesions. Follow-up results of the first-in-man trials FIM (CYPHER™) and TAXUS I (TAXUS) up to 4 years,17,18 and from the 3-year follow-up of RAVEL, the first randomized multi-centre trial,19 indicate that both safety and efficacy of these stent concepts are durable.

DES approval has resulted in expanded application of the technologies to more complex procedures, lesions, and patients. The TAXUS VI trial was designed as a randomized, controlled study to evaluate expanded utility of DES in truly long lesions requiring complex, multiple stent procedures where the risk benefit of two or more stents had not been examined, thus reflecting real-world practice. As previously reported,16 TAXUS VI studied one of the most complex lesion sets [mean lesion length 20.6 mm, implanted stent covered length 33.4 mm; overlapping stents were used in 27.8%, and complex lesions (ACC/AHA type C)] were
present in 55.6%), formally evaluated. At 9 months, the use of the TAXUS MR stent was highly effective, resulting in a 64% reduction of TLR from 18.9% in controls to 6.8% in the TAXUS MR group (P = 0.0001).15 Furthermore, there was no evidence of any safety differences between groups. At 2-year follow-up, we now demonstrate that this efficacy benefit is maintained in these complex lesions with comparable safety profiles between the two study groups. This 2-year report provides novel insight into natural history of patients with complex lesions treated with both BMS and DES, which has not been previously reported.

There was no significant difference in the incidence of TVR between the two study groups in the second year after implantation, thus confirming the durability of this approach. Furthermore, the subgroup analysis revealed that the benefit was preserved among all study subgroups including small vessels, long lesions, and overlapping stents (Table 3).

Nevertheless, the 5-year results of the WRIST (Washington Radiation for In-stent Restenosis Trial) study20 have shown that adverse events may occur very late after using anti-proliferative techniques. WRIST demonstrated that there is a late catch-up of TVR events following intra-coronary gamma radiation for treatment of in-stent restenosis, with an incidence of 21.6% in the radiation arm compared with 6.1% in the placebo arm, which developed slowly over a 6–60-month period post-procedure. Given the beneficial long-term results of the early experience of treating simple lesions with DES, the presence of a late catch-up phenomenon with DESs appears to be unlikely. The continuing follow-up of TAXUS VI up to 5 years will give further insight into this important question.

Beyond these efficacy findings, the safety results of the TAXUS VI 2-year follow-up are equally important. There was no significant difference in cardiac death, myocardial infarction, or stent thrombosis between the two study groups (Table 2). The trend for an increase in non-Q-wave infarcts in the TAXUS group, which was apparent in TAXUS VI at 9 months of follow-up, was slightly reduced at 2 years. This supports the hypothesis of a peri-interventional event as the most likely origin for these MACEs which might be anticipated in this high-risk patient group.

DES-associated stent thrombosis is currently under intense scrutiny as a potential major safety issue in the long-term follow-up of DESs. Since the SCORE trial, the first randomized DES study evaluating the QP-2 loaded Quanam stent, it became apparent that inappropriate drug dosages and the use of bio-incompatible polymers may lead to an excessive increase in thrombotic events (11.1% in the DES group).21,22 In addition, histopathological examinations have demonstrated delayed endothelialization in DES because of their anti-proliferative properties, which may prolong the risk for thrombotic events.23 By modifying the anti-thrombotic regimen with prolonged dual anti-platelet medication using aspirin and clopidogrel, the rate of DES thrombosis has been similar to conventional control BMSs in all subsequent major DES trials. Meta-analysis of stent studies suggests that there is no increase in subacute stent thrombosis in DES.24–27 Nevertheless, continuing reports of late thrombotic events, even beyond 12 months of post-DES implantation,28,29 raise the question of a late adverse class effect which might require additional prolongation of dual anti-platelet medication. As the stented length has been identified as one of the main predictors of stent thrombosis,24,30 and, in this trial, clopidogrel was discontinued at 6 months, the late follow-up results of TAXUS VI are of particular interest. Up to 365 days post-stenting, there were a total of three stent thromboses, two of them in the control group, and all of them in the subacute phase up to 30 days (P = ns). In the second year of follow-up, there was one additional stent thrombosis in the TAXUS group at day 408 and none in the control arm (P = 1.00). Given these data, there is no evidence from this trial of a significantly higher thrombosis risk in the DES group, even in this complex lesion population up to 2 years post-stent implantation. The single late stent thrombosis (after 365 days) in the TAXUS group might indicate a higher risk for late stent thrombosis in DES, but late stent thrombosis has also been reported with BMSs. A retrospective analysis from Wenaweser et al.31 showed that among 6058 patients with BMS implantation, the overall incidence of stent thrombosis was 1.6%, of which 11% were in the acute phase, 64% subacute, and 25% late, up to 600 days post-stenting. A 2-year stent thrombosis rate of 0.93% in the TAXUS group, compared with 0.93% in the control arm, with similar numbers of cardiac deaths and myocardial infarcts, supports the safe use of the TAXUS MR stent in the treatment of complex lesion subsets.

**Conclusion**

Treatment of complex coronary lesions with the polymer-based MR paclitaxel-eluting TAXUS MR stent is associated with a sustained reduction in TLR up to 2 years after device implantation.

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