Prevention of Lesion Recurrence in Chronic Total Coronary Occlusions by Paclitaxel-Eluting Stents

Gerald S. Werner, MD, FACC, Andreas Krack, MD, Gero Schwarz, MD, Dirk Prochnau, MD, Stefan Bette, MD, Hans R. Figulla, MD

Jena, Germany

OBJECTIVES
The aim of this research was to assess the efficacy of paclitaxel-eluting stents in chronic total coronary occlusions (CTO).

BACKGROUND
Percutaneous coronary interventions for CTOs are characterized by a high target vessel failure rate.

METHODS
In 48 consecutive patients, paclitaxel-eluting stents (Taxus, Boston Scientific Corp., Natick, Massachusetts) were implanted after successful recanalization of a CTO (duration >2 weeks). Patients underwent an angiography after 6 months and were followed clinically for 12 months. They were compared with 48 lesion- and risk-matched patients with CTOs treated with bare metal stents (BMS). Primary clinical end point was the one-year incidence of major adverse cardiac events (MACE) (death, myocardial infarction, repeat revascularization); secondary end points were the rate of restenosis and re-occlusion.

RESULTS
In-hospital MACE was 4.2% with Taxus, and 2.1% with BMS (p = NS). The one-year MACE rate was 12.5% in the Taxus group, and 47.9% in the BMS group (p < 0.001), which was due to a reduced need for repeat revascularization. The angiographic restenosis rate was 8.3% with Taxus versus 51.1% with BMS (p < 0.001). There was only one late re-occlusion with Taxus (2.1%) as compared with 23.4% with BMS (p < 0.005). The late loss was reduced in the Taxus group by 84% as compared with BMS. All nonocclusive restenoses in the Taxus group were focal and successfully treated by implanting an additional Taxus stent.

CONCLUSIONS
The treatment of CTOs with a paclitaxel-eluting stent drastically reduces MACE and restenosis, and almost eliminates re-occlusion, which is typically frequent with BMS in CTOs. Chronic total coronary occlusion should be a preferred indication for drug-eluting stents. (J Am Coll Cardiol 2004;44:2301–6) © 2004 by the American College of Cardiology Foundation

Chronic total coronary occlusions (CTO) represent 10% of lesions treated by percutaneous coronary interventions (PCI) (1). The PCI in CTOs is characterized by a limited primary success rate (2) and a higher target vessel failure rate (TVF) rate even with routine use of coronary stents (3–8). A successfully recanalized CTO can improve left ventricular (LV) function and survival, but this is jeopardized by the high rate of re-occlusions (2,9,10). Diffusely diseased, chronically occluded vessels require longer and multiple stents, which adversely influence TVF (11–13). A solution could be drug-eluting stents, which proved effective in complex nonocclusive lesions (14–16). A registry analysis suggests that drug-eluting stents may also be effective in CTOs (17), but there are no prospective angiographic studies or randomized trials. The present study is the first to prospectively evaluate the safety and efficacy of a paclitaxel-eluting stent in CTOs and its effect on event-free survival and lesion recurrence in comparison with matched patients with CTOs treated with bare metal stents (BMS).

METHODS

Patients. A consecutive cohort of 48 patients with a successfully recanalized CTO of a major coronary branch (diameter >2.0 mm) was enrolled and treated by implantation of one or more polymer-based paclitaxel-eluting stents (Taxus, Boston Scientific Corp., Natick, Massachusetts). The duration of the occlusion (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0 or 1) was >2 weeks (median 6.3 months). Revascularization was indicated by either chest pain or persistent occlusion after a prior myocardial infarction (MI). Exclusion criteria were an LV aneurysm and TIMI flow grade <3 after stenting. The latter lead to the exclusion of one patient. Written informed consent was obtained from all patients. All patients were scheduled for angiography after 6 months and followed clinically for 12 months. No patient was lost to follow-up. Matched pair analysis. The Taxus group was compared with 48 matched patients with CTOs treated with BMS (Coroflex, B. Braun, Melsungen, Germany [18 patients]; Bestent2, Medtronic, Minneapolis, Minnesota [16 patients]; Jostent, Jomed AB, Helsingborg, Sweden [14 patients]). Matching criteria were history of diabetes, prior MI, diameter and number of implanted stents, lesion location, and LV function. This BMS group was drawn.
from 148 consecutive patients treated within four years before availability of the Taxus stent. The matching was done blinded to the angiographic outcome.

**Angioplasty procedure.** The recanalization was done as described previously (13). All patients received aspirin (100 mg) and, additionally, clopidogrel (75 mg) for 4 weeks after BMS and for 6 months after Taxus stents. Glycoprotein IIb/IIIa antagonists were not used. The procedural strategy was to cover the occlusion and adjacent dissections with one or more overlapping stents (Taxus stent length: 18, 24, 28, and 32 mm). A balloon-to-artery ratio of 1.1 with inflation pressures of 12 to 16 atm was chosen. The goal was a residual stenosis <20% within the stent. The creatinine kinase was measured 12 to 24 h after the procedure.

**Quantitative coronary angiography.** The occlusion length was assessed from collateral filling and from the lesion length visible after the first balloon dilation. Quantitative coronary angiography was done with a standard software program (QCA for Research 1.3, PieMedical Imaging, Maastricht, the Netherlands) using the least foreshortening projection with the smallest minimum luminal diameter (MLD). The analysis included both the stent and 5 mm proximal and distal of the stent edges. The late loss was calculated at the site of the MLD at follow-up. The pattern of restenosis was classified according to Mehran et al. (18). An increase of the luminal diameter >25% of the reference diameter at follow-up indicated coronary artery aneurysm (19). Biplane LV angiograms were obtained before PCI and at follow-up and analyzed using a standard software program (LVA 4.0, PieMedical Imaging).

**Study end points.** The primary end point was the incidence of major adverse cardiac events (MACE) within 12 months after PCI, defined as cardiac death, periprocedural and late Q-wave MI, non–Q-wave MI defined by a creatinine kinase elevation above two times the upper reference limit, and target lesion revascularization (TLR). Secondary end points were the binary restenosis rate defined as an MLD <50% of the reference diameter within the analyzed segment, and the incidence of re-occlusion. Target vessel failure was defined as restenosis in the recanalized artery irrespective of the treatment site.

**Statistics.** Data are given as mean values ± SD. Group differences were evaluated by analysis of variance or a chi-square test, as appropriate. A Kaplan-Meier life-table analysis was done with a log-rank test to compare the MACE-free survival between groups. The sample size was calculated to achieve a statistical power of 0.8 with an assumed MACE in BMS of 50% (13) and an expected relative reduction of 50% by the paclitaxel-eluting stent. A level of p < 0.05 was considered significant. All calculations were done with SPSS for Windows (SPSS Version 11.5, SPSS Inc., Chicago, Illinois).

### RESULTS

**Clinical and procedural characteristics.** The clinical characteristics in both groups were comparable (Table 1). One-third of patients had diabetes. The procedural data were well-matched (Table 2). The occlusion duration was >3 months in 70%. The occlusion length was 17 ± 13 mm, and the total stent length was more than double the occlusion length in both groups.

**Quantitative angiographic analysis.** The baseline angiographic parameters were similar in both groups (Table 2). One patient in the Taxus group had died before follow-up angiography. At follow-up after 5.2 ± 1.5 months, the MLD in the Taxus group was significantly larger than in the BMS group (Fig. 1). In the Taxus group, the late loss and the binary restenosis rate were reduced by 84%, and late re-occlusion by 91% as compared with BMS (Table 2). All TVF in the Taxus group occurred with a single stent, unrelated to stent length, whereas, in the BMS group, TVF was 38% with a single stent, and 71% with >2 stents.

In the Taxus group, but not in the BMS group, a moderate enlargement of the lumen within the stent was observed in three patients (4.2%) at follow-up, suggesting positive remodeling. One of these patients had a restenosis at the opposite edge of the stent; after repeat PCI there was no progression of the lumen enlargement at further follow-up (Fig. 2).

**Acute and long-term clinical events.** Elevation of creatinine kinase without symptoms was the only acute MACE (Table 3). No subacute stent thrombosis was observed. Within one year, one patient had died in the Taxus group,
and two in the BMS group. These three patients had severely impaired LV function. The MACE-free survival was higher in the Taxus group (12.4% vs. 47.9%; p < 0.001) due to a reduced TLR (Table 3).

Influence of diabetes mellitus. In diabetic patients treated with BMS, the TVF rate was almost double that in nondiabetic patients (64.3% vs. 35.3%). In contrast, there was no influence of diabetes mellitus on TVF rate in the Taxus group (Table 4). The advantage of the Taxus stents over BMS was significant both in diabetic and nondiabetic patients.

Treatment of lesion recurrence. Target vessel failure in the BMS group was focal in 38%, diffuse in 16%, and occlusive in 46%. In the Taxus group, one patient had re-occlusion, which was treated medically. The three non-occlusive TVFs were focal and located at the stent edge. They received an additional Taxus stent. A subsequent angiography within four to six months showed no recurrent restenosis.

DISCUSSION

The present study was done in a “real world” cohort of patients with CTOs without lesion-related exclusion criteria. They represent lesions with the highest risk of TVF, but they are excluded from recent randomized trials of drug-eluting stents (14–16,20). We could show a considerable clinical benefit of a paclitaxel-eluting stent in CTOs with reduction of MACE and TVF by more than 80% as compared with a matched group treated with BMS.

Risk profile of study group. No selection criteria regarding lesion length and angiographic characteristics were applied including also small vessels of 2.5 mm. This explains the higher TVF rate in the BMS group as compared with previous studies applying more restrictive inclusion criteria (3,4). However, it was comparable with the largest randomized study in CTOs with less restrictive inclusion criteria (5). The comparison with randomized studies of BMS in CTOs (Table 5) underscores that the present study consisted of lesions with a higher risk profile, notably more diabetes, and smaller reference diameters with smaller MLD after the procedure, which are predictors of stent restenosis (21).

Safety and efficacy of paclitaxel-eluting stents in CTOs. The Taxus group showed a substantially improved MACE-free survival due to a reduced TLR without increased risk of
periprocedural MI or subacute stent thrombosis as compared with BMS. The late loss with this paclitaxel-eluting stent was in the range observed in nonocclusive lesions (16), but the clinical benefit was even greater in CTOs. The few focal restenoses at the edges of the stented segment indicate that a liberal stent coverage of the segment adjacent to the original occlusion might be preferred in these diffusely diseased arteries.

Positive remodeling with incomplete stent apposition and development of coronary artery aneurysms has been a concern with drug-eluting stents (22). Recent trials did

**Figure 2.** Examples from the Taxus group. (A) Occlusion location indicated by arrowhead; (B) after stent implantation (stents indicated by arrows); (C) follow-up. Patient 1 (age 59 years, male) right coronary artery (RCA) occlusion (duration nine months), three stents (total length 72 mm). Patient 2 (age 51 years, male) left anterior descending coronary artery (LAD) occlusion (seven months), one 28-mm stent. Moderate positive remodeling at follow-up (C, arrowhead). Patient 3 (age 74 years, female, diabetes) ostial LAD occlusion (eight months), two stents (total length 44 mm). Patient 4 (age 54 years, male, diabetes) RCA occlusion, one 28-mm stent. (C) Irregular moderate positive remodeling at follow-up (arrow) and focal restenosis proximal (arrowhead). After additional Taxus stent, no recurrence four months later, no progression of the negative remodeling (D, arrow).

**Table 3.** Hierarchical Incidence of MACE During Hospitalization and 12-Month Follow-Up in Patients With Successful Recanalization of a CTO

<table>
<thead>
<tr>
<th></th>
<th>Taxus (n = 48)</th>
<th>BMS (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non–Q-wave MI†</td>
<td>4.2 (2)</td>
<td>2.1 (1)</td>
</tr>
<tr>
<td>Subacute stent thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2.1 (1)</td>
<td>4.2 (2)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Repeat PCI</td>
<td>6.3 (3)</td>
<td>31.9 (15)*</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>12.8 (6)</td>
</tr>
<tr>
<td>Total MACE</td>
<td>12.5 (6)</td>
<td>47.9 (23)*</td>
</tr>
</tbody>
</table>

*p*Comparison between the groups: *p* < 0.001; †Non–Q-wave MI defined by elevation of creatine kinase (two times upper limit of normal) within 24 h of recanalization.

Frequency of events (%) with number of patients in parentheses.

BMS = bare metal stent; CABG = coronary artery bypass grafting; CTO = coronary total occlusion; MACE = major adverse cardiac event; MI = myocardial infarction; PCI = percutaneous coronary intervention.

**Figure 3.** Kaplan-Meier curves of major adverse cardiac event (MACE)-free survival; *p* value for log-rank comparison of Taxus and bare metal stent (BMS) groups.
not show an increased risk of coronary artery aneurysm with the Taxus stent (16,20). In our study, 3 of 48 patients (6%) had a moderate increase of luminal diameter at follow-up not reaching the angiographic criteria of coronary aneurysm (19). We did not perform intravascular ultrasound, which could have clarified the morphology. Our observation could be accidental in a limited number of patients, and future studies with intravascular ultrasound could provide a larger database to assess the risk for coronary aneurysms in CTOs.

**Study limitations.** The size of this study is comparable to previous studies of BMS in CTOs (Table 5). The high TVF with BMS provides an adequate statistical power to detect the clinical and angiographic benefit of drug-eluting stents. The comparison with a matched control group is less convincing than a double-blind randomized approach, but it is superior to non-matched registries. Furthermore, the single-center approach ascerts uniform technical performance of the PCI in both study groups. The MACE rate was mainly determined by TLR, and this could be influenced by the fact that we performed an angiographic follow-up not reaching the angiographic criteria of vessel restenosis. However, the issue of more extensive stent coverage versus more selective placement in the area of the occluded lesion and the comparison of different drug-eluting stents should be addressed by a randomized approach.

**Clinical implications.** Our study, together with recent registry data on a sirolimus-eluting stent system (17), supports that drug-eluting stents are a major advancement for the treatment of CTOs. In view of these data and the proven advantage of drug-eluting stents in nonocclusive lesions, a randomized trial of drug-eluting stents versus BMS in CTOs may not be required. However, the issue of more extensive stent coverage versus more selective placement in the area of the occluded lesion and the comparison of different drug-eluting stents should be addressed by a randomized approach.

---

**Table 4.** Target Vessel Failure After Recanalization of a CTO in Patients With and Without Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Patients with diabetes mellitus</th>
<th>Patients without diabetes mellitus</th>
<th>This Study</th>
<th>Taxus</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (%)</td>
<td>6.3 (1)†</td>
<td>6.3 (1)†</td>
<td>48</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>MACE  (n/a)</td>
<td>28</td>
<td>29</td>
<td>46</td>
<td>47</td>
<td>42</td>
</tr>
<tr>
<td>TVF (%)</td>
<td>9.4 (3)†</td>
<td>9.4 (3)†</td>
<td>58</td>
<td>58</td>
<td>35.3 (12)</td>
</tr>
<tr>
<td>TVF (n/a)</td>
<td>100</td>
<td>73</td>
<td>46</td>
<td>48</td>
<td>41.2 (14)</td>
</tr>
</tbody>
</table>

Frequency of events (%) with number of patients in parentheses. Comparison between Taxus and BMS group: *p < 0.001; †p < 0.05.

BMS = bare metal stent; CTO = chronic total coronary occlusion; MACE = major adverse cardiac event; TVF = target vessel failure.
REFERENCES


