A Randomized Trial of Elective Stenting After Balloon Recanalization of Chronic Total Occlusions

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OBJECTIVES
The aim of this study was to assess the role of Wiktor stent implantation after recanalization of chronic total coronary occlusions with regard to the clinical and angiographic outcome after six months.

BACKGROUND
Beside the common use of stents in clinical practice, the number of stent indications proven by randomized trials is still limited.

METHODS
Eighty-five patients with a thrombolysis in myocardial infarction grade 0 chronic coronary occlusion were examined. After standard balloon angioplasty, the patients were randomly assigned to stent implantation, or percutaneous transluminal coronary angioplasty (PTCA) alone (no further intervention). Quantitative coronary angiography was performed at baseline and after six months.

RESULTS
The minimal lumen diameter did not differ immediately after recanalization (stent group 1.61 ± 0.30 mm vs. PTCA group 1.65 ± 0.36 mm), and increased after stent implantation to 2.51 ± 0.41 mm. After six months, the stent group still had a significantly greater lumen (1.57 ± 0.59 vs. 1.06 ± 0.90 mm; p < 0.01) and a significantly lower restenosis and reocclusion rate (32% and 3%) compared with the PTCA group (64% and 24%); restenosis analysis according to treatment was 72% (PTCA) versus 29% (stent, p < 0.01). Late loss was equal in both groups. At follow-up, the stent patients had a better angina class (p < 0.01), and fewer cardiac events (p < 0.03). A meta-analysis including this trial and three other controlled trials with the Palmaz-Schatz stent showed concordant results.

CONCLUSIONS
Stent implantation after reopening of a chronic total occlusion provides a better angiographic result, corresponding to a better clinical outcome with fewer recurrence of symptoms and reinterventions after six months. (J Am Coll Cardiol 1999;34:722–9) © 1999 by the American College of Cardiology

The long-term success after percutaneous transluminal coronary angioplasty (PTCA) for chronic total occlusions is hampered by a high rate of subacute reocclusion and late restenosis. However, after successful recanalization of a total occlusion (provided the vessel remains patent), the patients had relief from symptoms, improvement of left ventricular function, fewer cardiac events and fewer requirements for bypass surgery (1,2). Successful primary recanalization can be achieved in more than 70% (3,4) at low risk (5), however, recurrence rates are as high as 77% (6). So far, stents are the only clinically applicable tool succeeding in a remarkable reduction of restenosis rate, as demonstrated by the Belgium Netherlands Stent Trial (BENESTENT) and the Stent Restenosis Study (STRESS) trials (7,8). Yet, these investigations are only applicable on focal nonocclusive lesions in patients with symptomatic single-vessel disease. Though there are some strong suggestions that stenting in chronic total occlusions may be useful in preventing restenosis and reocclusion, a randomized trial was not available at the onset of our study. Recently, three other controlled trials (9–11) have shown a reduction of restenosis in chronic coronary occlusions with the Palmaz-Schatz stent. The aim of the present study was to evaluate if there is an advantage of elective Wiktor stent implantation after successful angioplasty of a chronic total occlusion with regard to the clinical and angiographic outcome after six months.

METHODS
Study design and patient selection. The SPACTO study (Stent versus PTCA after recanalization of chronic total...
Abbreviations and Acronyms

BENESTENT = Belgium Netherlands Stent Trial
CCS = Canadian Cardiovascular Society
GISSOC = Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche
LAD = left anterior descending artery
MLD = minimal luminal diameter
PTCA = percutaneous transluminal coronary angioplasty
RCA = right coronary artery
RD = reference diameter
SICCO = Stenting in chronic coronary occlusion
SPACTO = Stent versus PTCA after recanalization of chronic total occlusions
STRESS = Stent Restenosis Study
TIMI = thrombolysis in myocardial infarction

Oclusions) was directed in two centers (Ulm and Göttingen, Germany).

From July 1994 to January 1997, a total of 223 patients were scheduled for recanalization of a total coronary occlusion and screened for this study. Patients were included if the event causative for the occlusion occurred at least 28 days earlier, ischemia in the supplied area was proven by either exercise electrocardiography or myocardial scintigraphy and online quantitative coronary angiography revealed a reference diameter (RD) of at least 2.7 mm (for deployment of a 3-mm stent). Total occlusion was defined as thrombolysis in myocardial infarction (TIMI) grade 0 flow (12). Exclusion criteria were the presence of any contraindications for anticoagulation with phenprocoumon, ticlopidine or acetylsalicylic acid, renal failure and recent cerebrovascular events. The study protocol was approved by the local ethics committee in both centers, and written informed consent was obtained from every patient.

PTCA/stent implantation procedure and randomization.

After successful recanalization with standard balloon angioplasty resulting in an RD of at least 2.7 mm in on-line quantitative coronary angiography, the patients were randomly assigned either to PTCA (no further intervention) or implantation of one or more Wiktor stents. All patients were pretreated with at least 500 mg acetylsalicylic acid orally or intravenously. They received a 10,000-U bolus of heparin before recanalization adjusted by the activated clotting time. Afterwards, they were treated with acetylsalicylic acid 100 mg/day throughout the study. The stent group additionally received phenprocoumon (initial 40% of the stented patients), or ticlopidine 2 × 250 mg/day, and acetylsalicylic acid 300 mg/day (60% of the patients) for three months according to recent recommendations for poststent treatment (13). The Wiktor-GX stent (Medtronic, San Diego, California) consists of a single tantalum wire formed as a sinusoidal wave and wound into a helical coil. It is obtainable mounted on 3-, 3.5- and 4-mm balloon catheters. Its prominent properties are a high radio-opacity and flexibility.

Follow-up. Coronary events during and after the procedure were recorded, and exercise testing was performed after the recanalization procedure. Clinical controls were done in the cardiology clinic four and 12 weeks after the procedure, including physical examination, stress test and history taking of cardiac complaints. Six months after recanalization, the patients were hospitalized for reangiography, and again a stress test was performed and all events were recorded. For evaluation of cardiac symptoms, the Canadian Cardiovascular Society (CCS) classification of angina (14) was used. Coronary angiography was required six months after the procedure. If an angiographic study was performed earlier than six months due to recurrent symptoms and repeated revascularization was carried out, this one was used for quantitative coronary angiography.

Quantitative coronary angiography. The Kontron Cardio 500 system (Kontron Instruments, Tokyo, Japan) was used for quantitative analysis. Intracoronary glyceroltrinitrate was administered before all angiographic assessments. To assess the minimal luminal diameter (MLD), the most severe stenosis in two orthogonal views was measured post-PTCA/prestent, poststent and at follow-up. The RD was interpolated by the computer algorithm using a proximal and a distal reference in a “normal” looking vessel area adjacent to the stenosis. Percent stenosis was calculated as [(1 – MLD/RD) × 100], and numerically negative stenoses (e.g., due to stent oversizing) were counted as 0%. Biplane left ventricular analysis was performed to assess the ejection fraction and the ventricular size.

End points and statistics. Primary end points were restenosis and reocclusion rates six months after stent implantation versus conventional balloon angioplasty. Restenosis was defined as at least 50% stenosis on the follow-up angiogram. Major cardiac events including death (related to PTCA/stent or heart disease), myocardial infarction, further revascularization and recurrence of angina during follow-up were considered as secondary end points.

Continuous data are presented as means ± standard deviation or median (range). For analysis of differences between the two treatment groups, the two-tailed Student t test was used in case of standard distribution (tested with the Kolmogorov–Smirnov test); otherwise, the Mann–Whitney U test was applied. Categorical data were compared by the chi-square test. To account for differences in angiographic baseline data, multiple analysis of covariance was performed. Risk factor analysis for restenosis or reocclusion was done by multivariate logistic regression and Cox proportional regression. A statistical probability of p < 0.05 was considered to be significant.
RESULTS

Patients. Out of the 223 screened patients with chronic total occlusions, 139 (62%) were successfully recanalized. From these, 20 patients refused to take part in the study, 23 had a vessel size below 2.5 mm and another 11 had contraindications against the anticoagulation protocol. Finally, 85 patients with a median age of 62 years were randomized. There was no difference in demographic data between the patients from Ulm and Göttingen, except for hypertension being more frequent in the Ulm subgroup (70% vs. 38%, p = 0.04).

Baseline characteristics of the two treatment groups are shown in Table 1. Apart from a significantly higher rate of women in the stent group, the PTCA and the stent group did not differ in age, risk factors, extent of disease and angiographic data.

Procedural outcome. From the 85 patients, 42 were randomized to the stent group and 43 to the PTCA group. There were seven crossovers with stent implantation in the PTCA group due to dissection (n = 2), acute vessel closure (n = 1) or deterioration of the initial result after randomization (n = 4). Thus, a total of 49 patients received one (69%) or multiple (31%) Wiktor stents (49% 3 mm, 24% 3.5 mm, 6% 4 mm in diameter). However, the data were analyzed by intention to treat.

Postprocedure, all patients received antiplatelet treatment with acetylsalicylic acid (95%) and/or ticlopidine (38%). The patients in the stent group received ticlopidine (57% vs. 19%, p = 0.01) and phenprocoumon (43% vs. 16%, p = 0.01) more frequently compared with the PTCA group. Subacute stent thrombosis occurred in one case (2.4%); this patient did not take his medication. One stent implantation was unsuccessful because the stent could not be advanced to the lesion site due to extreme vessel tortuosity. Bleeding complications or femoral aneurysms were nonsignificantly higher in the stent group (11.6%) compared with the PTCA group (4.8%). Excluding the patients with phenprocoumon therapy, only 5.6% of the stent patients had a bleeding complication.

Angiographic results. Angiographic follow-up at six months was performed in 79% of all patients. Eighteen patients without follow-up angiography were excluded from further analysis due to their unknown restenosis status, although clinical follow-up was free from myocardial infarction or death.

Restenosis rate at follow-up defined as 50% stenosis was 32.4% in the stent group and 63.6% in the PTCA group (p = 0.01; intention-to-treat analysis). All patients with restenosis had an increase in percent stenosis by at least 17 percentage points. Reocclusion rate was 2.9% in the stent group and 24.2% in the PTCA group (p = 0.01; Fig. 1). Analysis based on therapy received revealed an even stronger difference: 28.9% restenosis rate in the stent group versus 72.4% (p < 0.01) in the PTCA group, and 2.6% reocclusion in the stent group versus 27.6% (p < 0.01) in the PTCA group. Restenosis rate in the left anterior descending artery (LAD) occlusion subgroup was 75% with conventional
PTCA, while there was no stent-treated patient with restenosis \( (p < 0.01) \). In the right coronary artery (RCA) subgroup, restenosis rate was 83.3% in the PTCA group versus 33.3% in the stent group \( (p < 0.01) \), respectively.

The results of the quantitative coronary angiography are shown in Table 2. At randomization, RD and percent stenosis were significantly higher in the stent group, but the mean MLD did not differ. After stent implantation, the MLD had significantly improved. At follow-up after six months, the stent group still had a larger mean luminal diameter \( (1.57 \text{ vs. } 1.06 \text{ mm}, p < 0.01) \). The mean reduction in the luminal diameter during follow-up (late loss) was equal in both groups \( (0.93 \text{ vs. } 0.85 \text{ mm}) \).

These data are illustrated in Figure 2. Figures 3 and 4 show the difference in MLD between the stent and the PTCA treatment group analyzed according to treatment (Fig. 3) and intention to treat (Fig. 4).

Multiple covariance analysis revealed that the significantly higher MLD of the stent group at follow-up was independent from the baseline differences of RD and/or percent stenosis mentioned above. Subgroup analysis with respect to the higher restenosis rate of the RCA compared with the LAD showed no difference of the RD and MLD at randomization. The postinterventional MLD was even slightly higher (analysis of variance, \( p = 0.094 \)) in the RCA \( (\text{PTCA } 2.01 \pm 0.69 \text{ mm}; \text{stent } 2.55 \pm 0.40 \text{ mm}) \) compared with the LAD \( (\text{PTCA } 1.82 \pm 0.47 \text{ mm}; \text{stent } 2.25 \pm 0.34 \text{ mm}) \). However, in patients with stent implantation, the mean number of stents was significantly higher in the RCA compared with the LAD \( (1.9 \text{ vs. } 1.1; p < 0.01) \).

**Events and clinical outcome.** Clinical follow-up data were available from 80 of the 85 patients (94%). One asymptomatic patient in the stent group died from postoperative complications after rectum cancer surgery.
patient in the stent group and three patients in the PTCA group were lost to follow-up. In the stent group, there were significantly more event-free patients with a significantly better clinical outcome. Cardiac events analyzed by intention to treat are shown in Table 3. The higher event-free survival of the stent group (70%) in contrast to the PTCA group (42.5%) was also significant by solely clinical follow-up based on anginal status and stress test (p = 0.013).

Patients with stent had a significant greater improvement of their CCS class angina (1.3 vs. 0.3 classes; p < 0.01; see Fig. 5). Stress test and left ventricular function data analysis revealed a strong tendency towards a better outcome in patients with stent. In terms of the lower percentage of patients with positive stress test in the stent group (40.9% vs 13.6%), this difference was statistically significant. While there was no significant difference in the median hospital stay for recanalization (9 days for stent patients vs. 9.5 days for PTCA alone), the larger number of revascularization procedures in the stent group resulted in a significantly shorter stay at follow-up: median three days compared with seven days in the PTCA group.

Risk factors for restenosis and reocclusion. By univariate analysis, two biologically linked variables emerged as statistical risk factors for restenosis: recanalization of the right coronary artery versus the left coronary artery (p = 0.03) and a previous posterior myocardial infarction versus a previous anterior myocardial infarction (p = 0.01). Diabetes mellitus was the only cardiovascular risk factor more frequent in the restenosis group, and all diabetics in the PTCA group had restenosis. Multivariate regression analysis did not reveal a significant independent risk factor for restenosis.

Multivariate significant risk factors for reocclusion were a lower CCS angina class before recanalization (p = 0.03) and less residual stenosis after recanalization (p = 0.04; significance of the logistic model p = 0.004).

Table 3. Events and Clinical data

<table>
<thead>
<tr>
<th>Events</th>
<th>All Patients</th>
<th>PTCA</th>
<th>Stent</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (cardiac)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>3 (3.8%)</td>
<td>2 (5%)</td>
<td>1 (2.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>New/recurrent</td>
<td>13 (16.3%)</td>
<td>9 (22.5%)</td>
<td>4 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>(un)stable angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTCA repeated</td>
<td>26 (32.5%)</td>
<td>16 (40%)</td>
<td>10 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Event-free patients</td>
<td>46 (57.5%)</td>
<td>18 (45%)</td>
<td>28 (70%)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

n = 80. Stent implantation resulted in a significant reduction of new onset of angina and repeated revascularization, analysis by intention to treat. PTCA = percutaneous transluminal coronary angioplasty.
Recent meta-analysis with three other controlled trials. Recently, three similar trials were published showing a significant benefit of the Palmaz-Schatz stent after recanalization of chronic coronary occlusions: Gruppo Italiano di Studio sullo Stent Nelle Occlusioni Coronariche (GISSOC) (11), Stenting in Chronic Coronary Occlusion (SICCO) (9) and Mori et al. (10). Despite the usage of different stents and the fact that the three other trials also included nontotal occlusions (TIMI 1), it seems to be reasonable to combine the results of all three studies in order to achieve a more general conclusion about stent implantation after recanalization of chronic total occlusions. All three studies showed a convincing correspondence: in this collective of 374 patients, the stent implantation reduced restenosis and reocclusion rate by more than 50% (Table 4), and the stent group had a larger vessel lumen both directly after procedure and after six months compared with the PTCA group (Table 5).

In terms of basic patient data, there are three significant differences between GISSOC, SICCO, the trial from Mori et al. (10) and the present (SPACTO) study: there were more women in SPACTO compared with GISSOC, SICCO and Mori et al. (10) (30.6% female patients vs. 15.5%, 17.9% and 14.6%; p < 0.01). In SICCO, 74.4% of the patients had an occlusion existing longer than 3 months, compared with 38.8% in SPACTO and 36.5% in the trial of Mori et al. (10). In the Mori Study and the GISSOC trial, most (58.3%, and 52.7%) of the occlusions were located in the LAD compared with 41.9% LAD occlusions in SICCO and 31.8% in SPACTO, respectively.

**DISCUSSION**

Stenting has become very popular in combination with almost all angioplasty procedures, but there are only few indications based on randomized trials [proximal focal LAD stenoses (7,8) saphenous vein graft lesions (15), bail-out-stenting].

The aim of this study was to examine whether there is an advantage of elective Wiktor stent implantation after reopening of chronic total occlusions. Similar to the results of STRESS (7) and BENESTENT (8) for focal nonocclusive lesions, we found a significant and even greater reduction of restenosis, and remarkably of reocclusions, in the stent group compared with PTCA alone. The difference was mainly due to the stent’s ability to provide and maintain a greater postprocedural lumen. This angiographical improvement was translated into a better clinical outcome of the stent patients with fewer recurrences of symptoms and reinterventions after six months.

**Risk factors for restenosis and reocclusion.** There was no independent risk factor for restenosis beside treatment with stent or PTCA. The higher incidence of restenoses in the RCA is probably due to minor distribution differences including the greater length of the stented segments in the RCA. Correspondingly, the patients with restenosis had more likely posterior than anterior previous myocardial infarction.

Risk factors for reocclusion in our study were a lower angina class before the intervention and less residual stenosis after recanalization. Yet, this is a small subgroup, and almost all reocclusions (eight out of nine) occurred in the balloon group, which had a trend towards a lower angina class at baseline. A biological explanation could be a better collateral flow reflected by the lower angina before recanalization and resulting in concurrent blood flow after reopening of the vessel. The lower residual stenosis as a statistical risk factor for reocclusion might occur by chance. However, because we tried to avoid crossovers from the balloon to the

### Table 4. Pooled End Points of the Four Stenting for Chronic Occlusion Trials SPACTO, SICCO (9), Mori et al. (10) and GISSOC (11), analysis by intention to treat

<table>
<thead>
<tr>
<th></th>
<th>PTCA</th>
<th>Stent</th>
<th>p Value</th>
<th>PTCA</th>
<th>Stent</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirnes et al. (9)</td>
<td>114</td>
<td>42 (73.7%)</td>
<td>18 (31.6%)</td>
<td>&lt; 0.001</td>
<td>15 (26.3%)</td>
<td>7 (12.3%)</td>
</tr>
<tr>
<td>Mori et al. (10)</td>
<td>96</td>
<td>30 (56.6%)</td>
<td>12 (27.9%)</td>
<td>0.005</td>
<td>6 (11.3%)</td>
<td>3 (7.0%)</td>
</tr>
<tr>
<td>Rubartelli et al. (11)</td>
<td>97</td>
<td>32 (68.1%)</td>
<td>16 (32.0%)</td>
<td>&lt; 0.001</td>
<td>16 (34.0%)</td>
<td>4 (8.0%)</td>
</tr>
<tr>
<td>SPACTO</td>
<td>67</td>
<td>21 (63.6%)</td>
<td>11 (32.4%)</td>
<td>0.010</td>
<td>8 (24.2%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Pooled</td>
<td>374</td>
<td>125 (65.8%)</td>
<td>57 (31.0%)</td>
<td>&lt; 0.001</td>
<td>45 (23.7%)</td>
<td>15 (8.2%)</td>
</tr>
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</table>

Patients (408) were randomized and 374 had angiographic follow-up (92%).

PTCA = percutaneous transluminal coronary angioplasty.
stent group, a higher mechanical vessel wall damage in patients with less residual stenosis cannot be excluded.

Comparison with other stent trials. In contrast to findings of elective stenting of stenoses (e.g., BENESTENT), we found no significant increase in late lumen loss of the stent group in this trial. A possible explanation is that intimal proliferation after recanalization of chronic total occlusions is already activated to a maximum level (as indicated by the high restenosis rate after conventional balloon recanalization), so that stent implantation does not result in any further substantial activation. Furthermore, the larger lumen maintained by the stent leads to a better flow and an increase in vessel wall shear stress, which inhibits intimal proliferation (16) and might foster endothelialization by inhibiting endothelial apoptosis (17).

Study limitations. A potential limitation of our study is the small sample size. The same is true for the three other randomized trials dealing with stents in chronic occlusions (9–11). Yet, all the four studies, SICCO, Mori et al. (10) and GISSOC, and now SPACTO, showed convincingly parallel results. Combining them into a meta-analysis of 374 patients shows a conclusive advantage of elective stent implantation after recanalization of chronic total occlusions. All three studies are limited to one certain stent type. Due to the small sample size, we did not try to perform a comparison of the stents.

The major advantages of the Wiktor stent are its excellent visibility, the high flexibility and the easy access to small branch vessels through the stent wire loops (18). On the other hand, the low surface covered by the stent represents a disadvantage in irregular lesions with protruding dissectional flaps (19). Despite the low mass of the stent, it is sufficiently resistant to the collapsing pressure of a coronary segment (20,21). In the present study, we found that Wiktor stent implantation is easy to perform, including crossing of the stent by another stent, and had a low rate of stent thrombosis or other complications.

Due to our study design, the evidence of a positive effect of elective stent implantation after recanalization of chronic total occlusions is limited to vessels >2.5 mm. Other studies (22,23) demonstrated a higher stent restenosis rate in smaller vessels, so that there might be no benefit of stent implantation after recanalization of total occlusions in very small vessels.

Summary and conclusion. Primary implantation of the Wiktor stent after recanalization of chronic total occlusions resulted in a significant reduction of the restenosis and reocclusion rate, as well as a reduction of repeated PTCA and a new onset of unstable angina. In terms of angiographical data, elective stenting resulted in a significantly larger vessel lumen both acutely and at six months follow-up. The better angiographic result corresponded to a better clinical outcome of the stent patients with less recurrence of symptoms and reinterventions after six months.

<table>
<thead>
<tr>
<th>Table 5. Corresponding Quantitative Angiographic Data of SPACTO, SICCO (9), Mori et al. (10) and GISSOC (11), analysis by intention to treat</th>
</tr>
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<tr>
<td></td>
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<tr>
<td>Pooled</td>
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<tr>
<td>PTCA</td>
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<td>Stent</td>
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<tr>
<td>Mori et al.</td>
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<tr>
<td>PTCA</td>
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<td>Stent</td>
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<td>Rubartelli et al.</td>
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<tr>
<td>SPACTO</td>
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<tr>
<td>PTCA</td>
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<tr>
<td>Stent</td>
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</table>

Data are in millimeters except diameter stenosis given in %. MLD = minimal luminal diameter; PTCA = percutaneous transluminal coronary angioplasty; RD = reference diameter.
In contrast to other stent applications, stenting of chronic total occlusions is not associated with an increased late lumen loss.

Based on the pooled data from this trial with the results of SICCO, Mori et al. (10) and GISSOC, we conclude that elective stenting after recanalization of a chronic total occlusion improves the angiographic and clinical outcome and thus represents a proven stent indication.

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REFERENCES