Angioplasty and Coronary Surgery

Coronary Stent Implantation Is Superior to Balloon Angioplasty for Chronic Coronary Occlusions
Six-Year Clinical Follow-Up of the GISSOC Trial

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OBJECTIVES
We investigated whether the benefits of stent implantation over balloon percutaneous transluminal coronary angioplasty (PTCA) for treatment of chronic total coronary occlusions (CTO) are maintained in the long term.

BACKGROUND
Several randomized trials have shown that in CTO, stent implantation confers clinical and angiographic mid-term outcomes superior to those observed after PTCA. However, limited information on the long-term results of either technique is available.

METHODS
Six-year clinical follow-up of patients enrolled in the Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche (GISSOC) trial was performed by direct visit or telephone interview. Major adverse cardiac events (MACE), defined as cardiac death, myocardial infarction, target lesion revascularization (TLR), and anginal status, were recorded.

RESULTS
Freedom from MACE at six years was 76.1% in the stent group, compared with 60.4% in the PTCA group (p = 0.0555). This difference was due mainly to TLR-free survival rates (85.1% vs. 65.5% for the stent and PTCA groups, respectively; p = 0.0165). Eleven patients underwent TLR after the nine-month follow-up visit (stent group: n = 5; PTCA group: n = 6); however, in most cases, restenosis of the study occlusion was evident at nine-month angiography.

CONCLUSIONS
This study represents the longest reported clinical follow-up of patients after percutaneous recanalization of CTO and demonstrates that the superiority of stent implantation over balloon PTCA is maintained in the long term. Stent and PTCA results appear to remain stable after nine-month angiographic follow-up. Stent implantation in CTO that can be recanalized percutaneously is therefore a valuable long-term therapeutic option. (J Am Coll Cardiol 2003;41:1488–92) © 2003 by the American College of Cardiology Foundation

Patients with chronic total coronary occlusions (CTOs) that are successfully recanalized by percutaneous transluminal coronary angioplasty (PTCA) show a higher restenosis rate than that reported for subtotal stenoses (1,2). Several randomized studies (3–9) have demonstrated that stent implantation after successful PTCA of CTO can significantly decrease the incidence of six-month angiographic restenosis and the need for target lesion revascularization (TLR). However, very few data are available on the long-term prognosis of patients treated by balloon PTCA or stent implantation for CTO. In this study, we report the clinical outcomes of 110 patients enrolled in the Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche (GISSOC) trial (5) after a mean follow-up of 6.2 ± 2.1 years. Our aim was to determine whether the benefits of stent implantation over PTCA for treatment of CTO are maintained in the long term.

METHODS

Patient selection and randomization. The study protocol, which has previously been described in detail (5), was approved by the Institutional Review Board at each participating center. Briefly, patients with angina or inducible ischemia thought to be caused by a chronic CTO (>30 days in duration) were selected for the study. A total occlusion was defined as the absence of a discernible luminal channel with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1 (10).

Exclusion criteria included <30 days’ duration of the total occlusion, acute myocardial infarction (MI) within 30 days or chest pain at rest within seven days, contraindication to aspirin or warfarin sodium, ineligibility for bypass surgery, previous PTCA of the occluded vessel, vessel diameter <3 mm, severe vessel tortuosity, and lesion length >13 mm. The target CTO was treated by conventional balloon angioplasty. In case of successful recanalization, defined as

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restoration of anterograde TIMI flow grade 2 or 3 with a residual stenosis <50% of the luminal diameter by visual estimation, the patients were randomized to stent implantation or no additional treatment.

Procedural protocol. All patients received aspirin (150 to 325 mg/day) starting at least 24 h before PTCA. During the procedure, heparin was given to maintain an activated clotting time >250 s. In patients assigned to stent implantation, the articulated Palmaz-Schatz stent (Cordis, Warren, New Jersey) was manually crimped onto a conventional balloon catheter and deployed to the target site. Four to eight hours after hemostasis at the site of arterial access was achieved, oral warfarin and heparin infusions were begun. Heparin infusion was continued until an International Normalized Ratio of 2.5 to 3.5 was obtained. Warfarin was continued for one month and aspirin indefinitely. In patients randomized to PTCA alone, oral aspirin was prescribed, whereas heparin or warfarin was not.

Follow-up. According to the original protocol, a clinical evaluation was performed at three, six, and nine months after the procedure, and coronary angiography was scheduled at nine months. In addition, long-term follow-up was obtained at the time of this analysis, by telephone interview, or by direct visit. If the patient was rehospitalized, hospital records were reviewed to assess the occurrence of clinical events.

Angiographic analysis. Angiographic analysis was performed at a central laboratory by quantitative coronary angiography. Restenosis and reocclusion were respectively defined as stenosis >50% of the lumen diameter at follow-up and recurrence of total occlusion occurring at any time after the procedure. The loss index was calculated as the difference between post-intervention and follow-up minimal luminal diameter divided by the post-intervention minimal luminal diameter.

End points. The primary end point in this study was the occurrence of major adverse cardiovascular events (MACE), defined as cardiac death, any MI, and TLR with either repeat PTCA or coronary artery bypass graft surgery (CABG). Death was considered as cardiac unless otherwise demonstrated. Myocardial infarction was documented by the presence of new pathologic Q waves on the electrocardiogram, according to the Minnesota Code (11), or a rise in creatine kinase of more than twice the upper normal limit. The presence of anginal symptoms at follow-up was a secondary end point. These symptoms were graded according to the Canadian Cardiovascular Society classification. The functional class was evaluated according to the New York Heart Association guidelines (12). All evaluations were performed according to the intention-to-treat principle, and in-hospital events were included in the analysis of follow-up events. When more than one clinical event occurred in a patient, the event occurring first was considered for survival analysis.

Statistical analysis. Categorical variables are expressed as absolute numbers and percentage values. Continuous variables are expressed as the mean ± SD or number (%) of patients. These data were described in detail in the original publication of the GISSOC trial (5). Categorical variables were assessed with the use of a continuity-adjusted chi-square test for categorical variables and with a two-tailed unpaired Student t test for continuous variables. Event-free survival rates were estimated using the Kaplan-Meier method, with differences between the two treatment groups assessed with the use of the log-rank test of significance. A p value <0.05 was considered statistically significant.

RESULTS

There were no significant differences in baseline clinical and angiographic characteristics between the two study groups (Table 1). Bleeding and vascular complications were more frequent in the stent group (4.7% vs. 0%, p = 0.11). At nine months, patients in the PTCA group experienced a signif-
major adverse cardiac events. Table 3 summarizes the events at nine months and six years. Events occurring during the first nine months have been described in detail previously (5). Briefly, the TLR rate was significantly lower in the stent group than in the PTCA group (5.3% vs. 22.2%, \( p = 0.038 \)), whereas the other events were not significantly different when individually analyzed. Events occurring after the nine-month follow-up visit.

In the stent group, six deaths were observed: two were caused by malignancy; two were sudden deaths; one was caused by acute MI; and one patient died during a CABG operation. In the PTCA group, there were two sudden deaths. Two non-fatal MIs were observed in each group; however, these events were not related to the study vessel.

Four patients (three in the stent group and one in the PTCA group) underwent a CABG operation. One CABG in the stent group did not involve the study lesion, which was widely patent, whereas the CABG was a TLR procedure in the other three cases. One of these patients died shortly after the operation, as mentioned already. Repeat PTCA was performed in 11 patients (6 in the stent group and 5 in the PTCA group). Three repeat PTCA procedures in the stent group did not involve the study vessel and were motivated by progression of the disease in other vessels, whereas the other eight were TLR procedures. Seven repeat PTCA procedures (three in the stent group and four in the PTCA group) were completed by stent implantation.

Overall, surgical or percutaneous TLR after nine-month follow-up was performed in 11 patients. In 10 cases, restenosis of the study lesion was evident at nine-month angiography. The decision to perform a new revascularization procedure after nine months was taken on clinical grounds and was generally motivated by reoccurrence or worsening of angina, together with progression of the disease in other coronary vessels. In the remaining patient, the status of the study artery at nine months was uncertain because angiographic follow-up was refused; however, restenosis of the study artery was documented and treated with repeat PTCA three years after enrollment.

The estimated probability of freedom from MACE at six years was 76.1% in the stent group and 60.4% in the PTCA group (\( p = 0.0555 \)). This difference was essentially determined by a higher estimated six-year TLR-free survival rate in the stent group (85.1% vs. 65.5% in the PTCA group, \( p = 0.0165 \)). Kaplan-Meier analyses of freedom from MACE and TLR are shown in Figures 1 and 2.

At the last follow-up interview, 76% of the surviving patients were in New York Heart Association functional class I, whereas the remaining patients (11 in the stent group and 13 in the PTCA group) were in class II. At the same time, 95% of patients had no angina, three patients in the stent group were in angina class I, and one patient in each group was in angina class III.

Table 3. Clinical Events During Follow-Up

<table>
<thead>
<tr>
<th>Event Type</th>
<th>0 to 9-Month Events*</th>
<th>6-Year Follow-Up Events†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stent Group (n = 56)</td>
<td>PTC Group (n = 54)</td>
</tr>
<tr>
<td>Death, all causes</td>
<td>0</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Death, cardiac</td>
<td>0</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>2 (3.6)</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Repeat PTCA</td>
<td>3 (5.3)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>TLR</td>
<td>3 (5.3)</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Cardiac death, MI, or TLR</td>
<td>3 (5.3)</td>
<td>13 (24)</td>
</tr>
</tbody>
</table>

*Data presented as the number (%) of patients. †Data presented as the number of patients (cumulative incidence). Six-year cumulative incidence (%) was estimated according to the Kaplan-Meier product-limit method. In the stent group, three repeat PTCA and one CABG occurring after 9 months did not involve the target lesion. Data on 9-month follow-up were described in detail in the original publication of the GISSOC trial (5).

MACE = major adverse cardiac events (cardiac death, MI, TLR); TLR = target lesion revascularization; other abbreviation as in Table 1.
This study represents the longest reported clinical follow-up of patients treated with percutaneous recanalization of CTO. Six-year follow-up data from the GISSOC trial demonstrate that patients treated by either balloon PTCA or stent implantation for CTO have a good prognosis, with a low event rate. The incidence of cardiac death and the incidence of non-fatal MI were similar in the two study groups. The only significant difference in clinical events was a lower TLR rate in patients assigned to stent implantation. This difference was evident at nine months and remained stable thereafter. The overall good long-term prognosis of the patients in this study may be related to favorable baseline clinical and angiographic characteristics. The patients were relatively young (mean age 58 years), with preserved left ventricular function (mean ejection fraction 55%) and a low prevalence of established risk factors such as diabetes (10%), unstable angina (9.1%), or previous CABG (1.8%). In addition, 70% of patients had single-vessel disease, and the occluded segment was relatively short (<13 mm), suggesting non-extensive coronary atherosclerosis. Moreover, only patients with successful PTCA were included in the study.

During follow-up, four patients experienced a non-fatal MI that was not related to the study artery. The relatively low incidence of MI may be related to the high prevalence of single-vessel disease, together with the fact that reocclusion of recanalized CTO does not cause MI in the great majority of cases (2,13).

**Long-term follow-up of patients treated by balloon PTCA or stent implantation.** In patients with subtotal stenosis treated by either balloon PTCA (14) or stent implantation (15), repeated angiographic follow-up demonstrated that the restenosis process generally takes place in the first six months after the procedure and is very rare thereafter. Consequently, the reported incidence of TLR between one and five years is low, ranging between 2.1% and 8.6% (15–18).

However, there are only limited data on long-term clinical outcomes after percutaneous recanalization of CTO. An early study (13) suggested that after balloon PTCA of CTO, the detection of restenosis did not plateau at six months, unlike that observed in subtotal stenosis, but increased during two-year follow-up. This finding is inconsistent with our results and those of Sirnes et al. (19), who reported follow-up after 2.7 years in patients treated with PTCA or stent implantation for CTO. They found a 6.0% rate of TLR procedures performed between 8 months and 2.7 years. Interestingly, all late TLRs occurred in patients in the PTCA group, whereas none were observed in the stent group (11.9% vs. 0%), although the reason for this difference is unclear.

These rates of late TLR, as well as those reported in patients with subtotal stenosis (15–18), seem to be somewhat lower than those observed in our study (10.9% in the stent group and 11.3% in the PTCA group between 9 months and 6 years). However, in our study, almost all restenoses were already detected on the nine-month angiogram. Therefore, late TLR events are not the consequence of a delayed restenotic process but the result of a clinical decision based on both coronary angiography and symptomatic status. In addition, a higher rate of TLR in our study may be related to the longer follow-up in comparison to other studies (15–19).

**Study limitations.** Because of the small sample size and low rate of clinical events occurring during late follow-up, this study does not have the power to detect potential differences in the incidence of MACE between the two study groups. In addition, only patients with a successful balloon PTCA of CTO were included in the study, and baseline clinical and angiographic characteristics indicated that the study population was at relatively low risk.

The patients assigned to stent implantation were treated...
with a first-generation stent, with a low rate of high-pressure stent expansion, which in turn led to a high residual stenosis. In addition, they followed a suboptimal antithrombotic regimen (aspirin plus warfarin). These results may not apply to a less selected population of patients treated with more recent techniques, including the use of newer guide wires for CTO, extensive reconstruction of occluded vessels with long or multiple stents, high-pressure stent implantation, and aspirin plus ticlopidine therapy.

Conclusions. This study demonstrates that the major benefit of stent implantation over balloon PTCA—a reduced need for TLR—is maintained in the long term. Both the PTCA and stent results appear to remain stable after nine-month angiographic follow-up. Thus, stent implantation in CTO treated by percutaneous recanalization is a valuable long-term therapeutic option.

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REFERENCES