The Clinical Outcomes of Percutaneous Coronary Intervention in Chronic Total Coronary Occlusion

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SUMMARY

The objective of the present study was to investigate the effects of percutaneous coronary intervention (PCI) on the development of major cardiac events in patients with chronic total coronary occlusion (CTO). Patients determined to have CTO in at least one coronary artery with stable coronary artery disease were retrospectively enrolled in this study. Among 262 patients (197 males, 65 females), PCI was attempted in 172 while 90 were followed-up conservatively because they had unsuitable angiographic lesions for PCI. PCI was successful in 117 (68.0%) patients. Thirty of the remaining 55 patients, who had multivessel coronary artery disease, underwent coronary artery bypass surgery. The remaining 25 patients were added to the conservative group. Mean follow-up time was 32 ± 12 months. Although a slight degree of development of non-ST elevation acute coronary syndrome was observed in the PCI group (34 [29.1%] versus 21 [18.3%] patients, $P = 0.053$) mostly because of restenosis (14 of 34 patients, [41.2%]), a significant mortality benefit was observed in patients who underwent successful PCI (17 [14.5%] versus 32 [27.8%] patients, $P = 0.013$). This benefit was mainly due to the lower number of deaths from heart failure (7 [6.0%] versus 17 [14.8%] patients, $P = 0.028$) and sudden death (6 [5.1%] versus 12 [10.4%] patients, $P = 0.131$). In conclusion, despite the low success rate and high restenosis rate of PCI for CTO, it is worthwhile to deal with the revascularization of a CTO for its mortality benefit. (Int Heart J 2006; 47: 811-819)

Key words: Heart failure, Mortality, PCI, Total coronary occlusion

THE clinical approach to chronic total coronary occlusion (CTO), a common problem seen in 10-15% of patients¹⁾ undergoing coronary angiography, remains controversial. Despite the development of interventional techniques, many clinicians prefer not to recanalize the CTO by percutaneous coronary intervention (PCI) because of the difficulty and low clinical success of PCI for CTO. The restenosis rate for PCI in CTOs is still higher than stenotic lesions despite the routine usage of stents, which have successfully decreased the restenosis rates²⁻⁷⁾ when compared to only percutaneous transluminal coronary angioplasty (PTCA).

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However, improvements of left ventricular contraction and relaxation in hibernating myocardium,⁸⁻¹⁰⁾ which may decrease mortality¹¹⁾ after recanalization of CTO, are also possible. Moreover, the introduction of drug-eluting stents that prevent restenosis, the major complication limiting late outcomes of PCI in CTOs, seems to be promising.¹²⁻¹⁴⁾

The aim of this study was to assess whether the recanalization of a CTO affected the development of major cardiac events and mortality compared to patients who were treated conservatively due to unsuccessful PCI and/or contraindicated PCI/coronary artery bypass surgery (CABS).

METHODS

Patients determined to have a CTO in at least one coronary artery in an angiographic examination conducted between October 1999 and March 2003 were identified retrospectively from our database. Data on their current health situations were obtained either on the phone or from their last office visit in September 2005.

Coronary angiography was performed because of stable angina pectoris or ischemia detected on any stress test in asymptomatic patients. Patients diagnosed with unstable angina pectoris, myocardial infarction with or without ST segment elevation in the preceding 3 months, and patients who had a history of any revascularization procedure (coronary artery bypass surgery [CABS] or PCI) were excluded.

Either PCI (PTCA or stent implantation) was performed or conservative therapy was applied and these 2 groups were compared to determine whether there was a difference in the occurrence of clinical events until September 2005. The decision for conservative treatment in CTO was based on the following criteria: insufficient symptoms to warrant an invasive revascularization procedure, 2 or more total occlusions, and insufficient myocardium at risk to warrant surgery with no chance of complete revascularization with PCI. Furthermore, if the cardiologist found the procedure unsafe, PCI was not conducted. Patients scheduled to undergo CABS were excluded from the study. CABS was preferred in patients with significant 3-vessel disease with proximal LAD involvement and significant left main coronary artery disease. Lesion related criteria for exclusion was a reference diameter < 2.5 mm by visual estimation. All other patients were candidates for PCI. The patients who underwent unsuccessful PCI were also included in the conservative group. Conventional bare metal stent implantation was attempted for all lesions when possible in the PCI group. Therefore, our aim was to demonstrate any prognostic difference between coronary artery disease patients with successfully performed PCI and those with unsuccessful PCI and/or

contraindicated PCI/CABS.

Procedural technique: Coronary angiography was performed via the femoral or brachial route by using 6F or 7F diagnostic catheters. A CTO was defined as a lesion exhibiting Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 of a native coronary artery. These lesions were estimated to occur during acute coronary syndrome or were documented in coronary angiography performed at least 3 months previously.

PCI procedure: Systemic anticoagulation was achieved by an intravenous bolus of 10,000 units of heparin at the beginning of the procedure. Additional injections of 2500 units were given to keep the activated clotting time above 250 seconds during the procedure. PCI was performed using standard over-the-wire techniques as previously described.¹⁵⁾ Three types of bare metal stents (Jostent [JOMED International AB, Helsingborg, Sweden], ACS MultiLink [Guidant, Advanced Cardiovascular Systems, Santa Clara, California, USA] and Biodiv-Ysio SV stent [Biocompatibles Ltd., Farnham, UK]) were used in the stenting procedure.

Antithrombotic medication consisted of aspirin (100 mg daily) plus ticlopidine (250 mg twice daily) or clopidogrel (300 mg once then 75 mg daily) and was started at the time of stent implantation and continued for a month. Aspirin was given to all patients, except those with a definite aspirin allergy. No glycoprotein IIb/IIIa inhibitors were used because they were not on the market in Turkey at the time of this study. The patients who only underwent PTCA did not receive ticlopidine or clopidogrel.

Endpoints: The primary endpoint of this study was all-cause death; cardiac (due to STEMI, NSTEMI, sudden cardiac death or congestive heart failure) or non-cardiac (cerebrovascular accident, malignancy, etc). The secondary endpoints were admission to hospital due to a nonlethal cardiac event such as acute coronary syndrome (NSTEMI or STEMI), heart failure, or a cerebrovascular accident.

Statistical methods: Data analysis was performed using the SPSS® for Windows® (version 11.5) statistical package. Nominal variables are presented as the number of cases and percentages and continuous variables are expressed as the mean $\pm$ standard deviation. The chi-square test or Fisher's exact test was used for the categorical comparisons. Whether the mean differences between the groups were significant or not was evaluated using Student's *t* test or the Mann-Whitney U test. Survival was determined by Kaplan-Meier analysis and comparisons were made using the log-rank method. A $P < 0.05$ was considered to be statistically significant.

RESULTS

Of a total of 6817 patients who underwent coronary angiography between 1999 to 2003, 304 patients (4.5%) were eligible for inclusion in this study. How-

Table I. Baseline Characteristics and Drug Therapy in the 2 Study Groups

	Treatment group		<i>P</i>
	Successful PCI (<i>n</i> = 117)	Conservative treatment (<i>n</i> = 115)	
Age (years)			
Mean $\pm$ SD	61.1 $\pm$ 10.4	60.3 $\pm$ 10.6	*
Range	41-87	41-84	
Age > 75 years			
Number	12	10	
Mean $\pm$ SD	80.6 $\pm$ 3.4	79.5 $\pm$ 2.9	*
Range	76-87	76-84	
Male sex, <i>n</i> (%)	88 (75.2)	86 (74.8)	*
Medical history, <i>n</i> (%)			
Diabetes	30 (25.6)	27 (23.5)	*
Hypertension	47 (40.2)	49 (42.6)	*
Hyperlipidemia	31 (26.5)	27 (23.5)	*
Prior infarct	47 (40.2)	52 (45.2)	*
Smoking history, <i>n</i> (%)			
Current smoker	41 (35.0)	44 (38.3)	*
Former smoker	40 (34.2)	39 (33.9)	*
Never smoked	36 (30.8)	32 (27.8)	*
Left ventricular ejection fraction (LVEF), %			
Mean $\pm$ SD	50.0 $\pm$ 13.8	49.7 $\pm$ 14.5	*
Range	21-67	22-68	
LVEF $\leq$ 35, %			
Number	27	29	
Mean $\pm$ SD	30.0 $\pm$ 4.0	29.6 $\pm$ 4.1	*
Range	21-35	22-35	
CTO vessel			
Left anterior descending artery	35 (29.9)	34 (29.6)	*
Left circumflex artery	49 (41.9)	44 (38.3)	*
Right coronary artery	33 (28.2)	37 (32.2)	*
Extent of CAD			
Multivessel disease	78 (66.7)	80 (69.6)	*
Single-vessel disease	39 (33.3)	35 (30.4)	*
Drug Therapy			
Aspirin, <i>n</i> (% of patients)	112 (95.7)	109 (94.8)	*
Beta-blocker, <i>n</i> (% of patients)	81 (69.2)	81 (70.4)	*
ACEI or ARB, <i>n</i> (% of patients)	67 (57.3)	68 (59.1)	*
Statin, <i>n</i> (% of patients)	84 (71.8)	85 (73.9)	*
Spironolactone, <i>n</i> (% of patients)	25 (21.4)	25 (21.7)	*
Insulin, <i>n</i> (% of patients)	16 (13.7)	15 (13.0)	*
Clopidogrel or ticlopidine in one month, <i>n</i> (% of patients)	110 (94.0)	6 (5.2)	< 0.001
Clopidogrel or ticlopidine after one month, <i>n</i> (% of patients)	10 (8.5)	6 (5.2)	*

ACEI indicates angiotensin converting enzyme inhibitor and ARB, angiotensin receptor blocker. * Not significant.

Figure. Kaplan-Meier curves for survival in both groups.

Table II. Endpoints Within Follow-up Duration

	Treatment group		<i>P</i>
	Successful PCI (<i>n</i> = 117)	Conservative treatment (<i>n</i> = 115)	
Primary endpoints			
Death from any cause, <i>n</i> (% of patients)	19 (16.2)	37 (32.2)	0.005
Death from cardiac causes, <i>n</i> (% of patients)	17 (14.5)	33 (28.7)	0.009
Secondary endpoints			
STEMI, <i>n</i> (% of patients)	4 (3.4)	6 (5.2)	0.500
NSTEACS, <i>n</i> (% of patients)	34 (29.1)	21 (18.3)	0.053
Heart failure	14 (12)	30 (26.1)	0.006
Cerebrovascular event, <i>n</i> (% of patients)	3 (2.6)	2 (1.7)	0.665
Total	55 (47.0)	59 (51.3)	0.513

STEMI indicates acute ST segment elevation myocardial infarction and NSTEACS, non-ST elevation acute coronary syndrome.

ever, data for only 262 patients (197 males, 65 females) could be obtained in September 2005. PCI was attempted in 172 patients and 90 patients were followed-up conservatively. PCI was performed successfully without any complications in 117 (88 males, 29 females) of the 172 patients. Therefore, the PCI success rate in CTO was 68.0%. Stent implantation was performed in 107 patients (91.5%) in the PCI group. CABS was recommended to 30 of 55 patients who underwent unsuccessful PCI and they were excluded from study. The remaining 25 patients were added to the conservative group, therefore, 115 patients (86 males, 29 females) were examined in the conservative group.

Table III. Causes of Cardiac Mortality in Both Groups

	Treatment group		<i>P</i>
	Successful PCI (<i>n</i> = 117)	Conservative treatment (<i>n</i> = 115)	
Heart failure, <i>n</i> (% of patients)	7 (6.0)	17 (14.8)	0.028
STEMI, <i>n</i> (% of patients)	2 (1.7)	2 (1.7)	0.986
NSTEACS, <i>n</i> (% of patients)	2 (1.7)	1 (0.9)	0.571
Sudden death, <i>n</i> (% of patients)	6 (5.1)	12 (10.4)	0.131
Total deaths, <i>n</i> (% of patients)	17 (14.5)	32 (28.8)	0.013

The baseline characteristics of the 2 groups were similar. There was no significant difference in the medical therapy undertaken between the groups, except for ticlopidine or clopidogrel usage in the month after the diagnosis of CTO. This difference in antiplatelet agent usage disappeared after one month (Table I). Mean follow-up time was 32 ± 12 months. Although the incidence of non-ST elevation acute coronary syndrome (NSTEMI) was slightly higher in the PCI group (34 [29.1%] versus 21 [18.3%] patients, $P = 0.053$), the mortality rate was significantly lower in these patients (19 [16.2%] versus 37 [32.2%] patients, $P = 0.005$). This significant difference was mostly due to the lower incidence of cardiac mortality in the successful PCI group (17 [14.5%] versus 32 [27.8%] patients, $P = 0.013$). The Kaplan-Meier curve for survival showed marked differences between the successful PCI and conservative treatment groups (Figure).

There were no differences between the 2 groups in the rates of acute ST segment elevation myocardial infarction (STEMI) and cerebrovascular events (Table II). In the PCI group, restenosis was found by angiographic examination to be responsible for the development of NSTEMI in 14 (41.2%) patients.

The causes of mortality in both groups are presented in Table III. Heart failure was the major cause of death in both groups and was significantly higher in the conservative group (7 [6.0%] versus 17 [14.8%] patients, $P = 0.028$). The development of heart failure was also significantly higher in the conservative group (Table II). Sudden death was the second most frequent cause of mortality and also tended to be higher in the conservative group (6 [5.1%] versus 12 [10.4%] patients, $P = 0.131$).

Coronary angiography was repeated in 77 patients who were symptomatic in the PCI group during the follow-up period. Restenosis was observed in 38 patients, resulting in a clinical restenosis rate of 32.5% in the PCI group.

DISCUSSION

The results of the present study indicate that recanalization of the CTOs had an improved survival advantage in 3 years, despite the increased risk of development of NSTEMI, mostly caused by restenosis. Several large studies also support the recanalization of CTOs for its mortality benefit. Suero, *et al*⁽¹¹⁾ found a better 10-year survival rate in patients admitted with stable angina pectoris who had undergone successful PCI when compared to unsuccessful PCI (74% versus 65%, $P = 0.002$). Bell, *et al*⁽¹⁶⁾ and Ivanhoe, *et al*⁽¹⁷⁾ also reported similar results.

The mortality benefit of PCI in CTO may be a result of an improved ejection fraction and improvements in both systolic and diastolic functions of myocardium.⁸⁻¹⁰⁾ Also, in this study, heart failure and sudden death were the major causes of mortality in the conservative group, which supported the findings about myocardial function in these recent studies. Additionally, the rate of admission to hospital because of heart failure was significantly higher in the conservative treatment group. Based on these data, it can be speculated that revascularization of CTO, especially in patients with a low ejection fraction, is important for preventing death due to heart failure and arrhythmia.

Restenosis, an important late complication of recanalization of CTO, also caused an increased rate of NSTEMI in the PCI group in our study. Therefore, preventing restenosis appears to be an important component of PCI for CTO. Stent implantation decreased the restenosis rates compared to PTCA, however, the restenosis rates in PCI for CTO are still high compared to PCI for stenotic lesions.²⁻⁷⁾ The introduction of drug-eluting stents can be promising in this era. Nakamura, *et al*⁽¹²⁾ showed that few cardiac events occurred in the 60 patients who underwent implantation of a sirolimus-eluting stent compared to 120 patients in the bare metal stent group after one year ($P < 0.001$). Hoyer, *et al*⁽¹³⁾ also reported a significant reduction in restenosis with sirolimus-eluting stents. In the PACTO study,⁽¹⁴⁾ the results with paclitaxel-eluting stents in PCI for CTO were encouraging. Nevertheless, large, randomized, long-term trials are still needed to determine the effectiveness of drug-eluting stents in PCI for CTO.

It is known that the success rate of PCI for CTO is very low compared to stenotic lesions, which tends to make physicians avoid PCI when treating CTOs. In our study, the success rate was 68.0%, which is comparable to the 60-70% success rates reported in other studies.^{17,18)} The number attained in our study did not appear to represent the real success rate of PCI for CTO because there was a selection bias by the physicians with respect to the decision to perform PCI. For this reason, the success rate of PCI is estimated to be less than 68% when all CTOs are taken into consideration. This difficulty in revascularization of CTOs may be overcome by the development of new interventional techniques and tech-

nologies.^{19,20)}

As already mentioned, this study on the effects of PCI on CTO outcome is not a randomised controlled trial (RCT). Therefore, the possibility of entry-bias can not be ruled out because no randomization was conducted while selecting the patients. However, the clinical characteristics determining the prognosis of the patients were similar in both groups and it is clear that patients with an open artery had a more favorable prognosis.

As a result, despite the low success and high restenosis rates of PCI for CTO, it is worthwhile to deal with the revascularization of a CTO for its mortality benefit. New techniques, technologies, and drug-eluting stents are poised to overcome the disadvantages of PCI in the treatment of CTO.

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