Successful revascularization improves long-term clinical outcome in patients with chronic coronary total occlusion

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A B S T R A C T

Background: Following the development of breakthrough techniques for percutaneous coronary intervention (PCI) in the treatment of chronic total occlusions (CTO), the initial success rate of PCI in CTO lesions (CTO-PCI) has improved; however, there are few reports regarding the effects of successful CTO revascularization on long-term mortality in Japan. The aim of this study was to compare the long-term clinical outcomes of patients with successful versus failed CTO recanalization and to identify related factors.

Methods and results: From all PCI procedures performed in our hospital between 2006 and 2013, CTO-PCIs were extracted and classified into two groups: PCI success (n = 656 patients) and PCI failure (n = 82 patients). Patients with successful procedures only on a second attempt, CTO-PCI in small branches, or CTOs in more than one vessel were excluded. Survival was determined from a telephone interview or the consultation history in the outpatient clinic. Initial angiographic success was achieved in 88.9% of the patients. A Kaplan–Meier plot with log-rank analysis showed that cumulative all-cause death was significantly lower in the success group than in the failure group (p = 0.0003; average follow-up duration in success group vs. failure group was 1531.3 ± 33.5 vs. 1565.3 ± 97.5 days, p = 0.7). Moreover, the rate of evident cardiac death was significantly lower in the success group than in the failure group (3.5% [23/656] vs. 15.9% [13/82], p < 0.0001).

Conclusions: This study suggests that successful revascularization in patients with CTO improves their long-term clinical outcomes.

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1. Introduction

The technology and techniques for the interventional treatment of chronic total occlusion (CTO) in patients with coronary artery disease have advanced significantly over recent years, and have contributed to the higher initial success rate of percutaneous coronary intervention (PCI) for treating CTO (CTO-PCI) [1,2]. However, the effect of this improvement on the chronic outcomes of patients who undergo CTO-PCI is still unclear. It has been reported that successful CTO-PCI might be associated with symptom relief, a lower rate of subsequent myocardial infarction (MI) and coronary artery bypass graft (CABG) surgery, and improved long-term survival, compared with unsuccessful PCI [3–7]. While the initial success rate of CTO-PCI has also reached an acceptable level in Japan, with an acute result that is widely recognized to be better than in other countries, its long-term outcome has not been fully investigated. Therefore, the aim of this study was to compare the long-term clinical outcomes of patients with successful versus failed CTO recanalization and to identify related factors.

2. Methods

2.1. Study design

Consecutive patients who underwent CTO-PCI were extracted from the database at Toyohashi Heart Center, Toyohashi, Japan, in which data were entered prospectively. The database included relevant patient information as well as angiographic and procedural characteristics. A total of 7353 PCI procedures performed between 2006 and 2013 were screened for this study, of which 848 involved revascularization of a CTO. Any patients with CTOs in more than one vessel or lesions in a small coronary branch vessel, as well as those in whom a repeat procedure succeeded after an initial failure, were excluded from the study, as were 17 patients who were untraceable (Fig. 1). We excluded patients...
with CTO lesions in more than one vessel in order to evaluate the effect of a single CTO-PCI recanalization, while small-branch lesions were excluded because of the known lesser clinical advantage in such cases. The remaining 738 patients represented the total population of this study. These patients were then classified into 2 study groups: those with successful CTO-PCI (success group; 656 patients) and those with failed CTO-PCI (failed group; 82 patients) (Fig. 1). The protocol was approved by the ethics committees in each participating center and all participants gave written informed consent. The PCI and stent implantation were performed in a standard manner. Heparin was administered to maintain an activated clotting time > 250 s. The PCI strategy was left to the discretion of the treating physician. The PCI of the CTO was performed using contemporary techniques as they became available: bilateral injection; specialized hydrophilic, tapered-tip, and stiff wires; parallel wires; micro-catheters; and a retrograde approach. In this study, all the stents deployed were drug-eluting stents (DES). After PCI, all patients were prescribed lifelong aspirin; in addition, clopidogrel was prescribed for at least 6 months after implantation of DES. Demographic and procedural data for all patients undergoing PCI were prospectively entered into a dedicated database. Patients were followed prospectively by telephone interview or on regular outpatient visits.

2.2. Definitions

Coronary CTO is defined as a true total occlusion with complete interruption of antegrade blood flow as assessed by coronary arteriography (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0) and with an estimated occlusion duration of 3 months or more. For the procedural background inherent in this study, we examined the total amount of contrast medium, procedure time, and radiation dose. Procedure time was defined as the total duration for which the patient was in the catheterization room (from entry until exit). Fluoroscopy time and radiation dose were recorded automatically by the cine device. Coronary perforation was examined as a complication during the procedure. The following endpoints were evaluated to compare patients with a failed versus a successful procedure: all-cause death, evident cardiac death, MI, and subsequent coronary artery bypass grafting (CABG). The following definitions were used:

- Evident cardiac death was defined as death within 7 days after MI, death associated with cardiovascular interventions within 30 days after CABG or within 7 days after PCI, or unexpected death presumed to be due to ischemic cardiovascular disease and arrhythmia occurring within 24 h after the onset of symptoms, without clinical or postmortem evidence of another cause, as judged according to the information from the telephone interview. Death from uncertain causes was also classified as cardiac death.
- Double CTO was defined as the presence of a CTO lesion in more than one vessel at the same time.
- Procedural success was defined as residual stenosis less than 50% with TIMI flow grade 3 and without major adverse cardiovascular events.
- MI was diagnosed by an increase in creatine kinase level to twice the upper limit of normal.

2.3. Guidewire crossing strategies

Guidewire crossing strategies were followed in a stepwise manner, as described in our previous report [8]. Briefly, as for antegrade approaches, single wiring, parallel wiring, and wiring techniques guided by intravascular ultrasound (IVUS) were included. For retrograde attempts, retrograde wire cross, kissing wire cross, controlled antegrade and retrograde subintimal tracking (CART), and reverse CART (r-CART) techniques were performed.

2.4. Statistical analysis

Data distribution was assessed by the F-test. Variables that did not follow a normal distribution were expressed as medians and interquartile ranges, whereas other continuous variables were expressed as mean ± standard error. Student’s t-test or the Mann–Whitney U test was used for the comparison of continuous variables, as appropriate. Event rates were estimated using the Kaplan–Meier U test. Follow-up was censored at date of last follow-up or at 7 years, whichever came first. Survival curves with all available follow-up data were constructed for time-to-event variables using Kaplan–Meier methodology.

Fig. 1. Flow diagram of the study population. PCI procedures performed between 2006 and 2013. The flowchart indicates lesions, exclusions, and the composition of the study population. CTO = chronic total occlusion; PCI = percutaneous coronary intervention.
and compared by log-rank test. Data on patients who were lost to follow-up were censored at the time of the last contact. Logistic regression analysis was used to identify the independent predictors for the procedural success of CTO-PCI. The predictors of the multivariate model were entered if their univariate p-value was at the p = 0.1 level. The results are reported as odds ratios (OR) with associated confidence intervals (CI). An OR of <1 indicated better mortality, while that of >1 indicated worse. A value of p < 0.05 was considered statistically significant, and all reported p-values were two-sided. Statistical analysis was performed using SAS software (SAS Institute, Cary, North Carolina).

3. Results

3.1. Patient, lesion and procedural characteristics

Baseline patient characteristics are shown in Table 1. Renal insufficiency requiring hemodialysis after the procedure (serum creatinine level > 2 mg/dL) was observed more often in the failed group than in the success group (12.4% [11/89] vs. 5.8% [38/656]; p = 0.007). Notably, the mean preprocedural creatinine level was significantly higher in the failed group than in the success group (1.4 ± 0.1 vs. 2.0 ± 0.3 mg/dL; p = 0.003). Preprocedural LVEF obtained by echocardiography was lower in the failed patients (50.4 ± 12.5 vs. 45.8 ± 12.8; p = 0.04). Le-}


terstitial edema requiring hemodialysis after the procedure (serum creatinine level > 2 mg/dL) was observed more often in the failed group than in the success group (12.2% [10/82] vs. 5.2% [34/656]; p = 0.001). Regarding the procedural background, the procedure time was significantly longer in the failed group (236.0 ± 10.7 vs. 184.4 ± 3.4 min; p = 0.001). The amount of skin radiation dose measured in frontal view was significantly greater in the failed patients (6.4 ± 0.6 vs. 4.7 ± 0.2 Gy; p = 0.002). Among procedural complications, coronary perforation was observed more frequently in the failed group (31.7% [26/82] vs. 9.0% [59/656]; p < 0.0001).

3.2. Guidewire crossing strategy

The guidewire strategies adopted in all the procedures and in each study group are shown in Table 3. The antegrade wiring strategy was followed more often in the success group than in the failed group, and the frequency of the CART and r-CART techniques was significantly higher in the success group (18.0% vs. 12.1%; p < 0.0001).

3.4. Logistic regression analysis

A Cox proportional-hazards model was used to identify variables independent of all-cause mortality. Prior CABG history and the presence of chronic kidney disease (CKD) were identified as unfavorable independent factors (prior CABG: OR 1.94, 95% CI: 1.10–3.44; p = 0.02; CKD: OR 2.59, 95% CI: 1.67–4.03; p < 0.001), whereas the
success of CTO-PCI was identified as a favorable independent factor for all-cause mortality (OR 0.59; 95% CI: 0.35–0.99; p = 0.04; Fig. 3).

4. Discussion

The results of this study demonstrate that a successful CTO-PCI procedure contributes to a better long-term clinical outcome compared with failed CTO-PCI. Successful CTO-PCI significantly decreased not only all-cause death, but also evident cardiac death. Moreover, successful CTO-PCI significantly decreased the need for subsequent CABG and numerically decreased the presentation of congestive heart failure and stroke. Considering the results of this study, it is possible that successful CTO-PCI contributes not only to lower long-term mortality, but also to a better quality of life. Regarding the lesion background, severe calcified and tortuous lesions were associated with failed procedures. Regarding the procedural factors, a failed CTO-PCI required a much longer time and a greater radiation dose than a successful procedure and was associated with coronary perforation. According to the Cox proportional-hazards model for all-cause death, success of CTO-PCI, age, body mass index, and the presence of CKD were identified as unfavorable independent factors (prior CABG: OR 1.94, 95%: 1.10–3.44, p = 0.02; CKD: OR 2.59, 95% CI: 1.67–4.03, p = 0.001), while the success of CTO-PCI was identified as a favorable independent factor for all-cause mortality (OR 0.59; 95% CI: 0.35–0.99; p = 0.04). CABG = coronary artery bypass grafting; CI = confidence interval; CKD = chronic kidney disease; OR = odds ratio.

Other abbreviations as in Fig. 1.

Fig. 3. Results of logistic regression analysis. A Cox proportional-hazards model was used to identify variables independently associated with all-cause mortality. Prior CABG history and the presence of CKD were identified as unfavorable independent factors (prior CABG: OR 1.94, 95%: 1.10–3.44, p = 0.02; CKD: OR 2.59, 95% CI: 1.67–4.03, p = 0.001), while the success of CTO-PCI was identified as a favorable independent factor for all-cause mortality (OR 0.59; 95% CI: 0.35–0.99; p = 0.04). CTO-PCI = chronic total occlusion procedure; CABG = coronary artery bypass grafting; CI = confidence interval; CKD = chronic kidney disease; OR = odds ratio.

4.1. Characteristics of the CTO-PCI candidate

Compared with the success group, more CKD patients were included in the failed group. This result might reflect the fact that patients on chronic hemodialysis tended to be in the failed group. Heavily calcified coronary lesions are often encountered in chronic hemodialysis patients in daily practice, and it has been reported that heavy calcification can be a major obstacle to the success of CTO-PCI [8,9]. In this study, heavily calcified lesions were found more often in the failed group, as discussed below, which means that this result is consistent with previous reports.

4.2. Lesion and procedural background of CTO-PCI

The CTO was located in the left circumflex artery more often in the failed group than in the success group. It has not been clearly reported whether a lesion location in the left circumflex is a negative factor for procedural success; however, the high angulation from the left main to the left circumflex makes it difficult to cross the lesion. Apart from this issue, once a CTO lesion forms in a severely tortuous vessel it is very difficult to anticipate the trajectory of the vessel. In such a tortuous CTO lesion, preprocedural computed tomography coronary angiography is essential.

Failed CTO-PCI procedures required more time and a higher frontal skin radiation dose than did successful procedures. The total amount of contrast used was numerically greater in the failed patients; however, the difference did not reach statistical significance. These negative factors associated with CTO-PCI were also within a high range even in the patients with successful CTO-PCI. It has been reported that a successful retrograde approach can ameliorate these limitations compared
with failed procedures [11]. Therefore, a retrograde approach can be a good option for patients with CKD as a means of preserving their remaining renal function.

Regarding complications, coronary perforation was observed more frequently in the failed group than in the success group. In this study, the difference between the groups in the incidence of devastating coronary perforation, which leads to an unstable hemodynamic state, did not reach statistical significance; however, the longer procedural time and wiring difficulties in failed procedures can often result in the occurrence of complications such as coronary perforation.

4.3. Effect of guidewire strategy

Despite the higher frequency of retrograde attempts in the failed group compared with the success group, the procedural success was not satisfactory. In the failed group, the retrograde approach was attempted as a final resort; this finding may thus be due to the complexity of the lesions. Heavily calcified lesions were encountered more often in the failed group than in the success group. Heavy calcification often hinders the advance of the catheter via a retrograde approach, leaving no alternative but to use the smallest size of balloon to dilate a greatly calcified lesion. It is probably safe to say that the degree of calcification is the most important factor for the success of retrograde CTO-PCI.

4.4. Results of logistic regression analysis

In the Cox proportional-hazards model analysis, procedural success, prior CABG, and the presence of CKD were the predictors found to be significantly associated with long-term mortality. It has been reported that successful CTO-PCI improved long-term cardiac mortality [7,10]. Consistent with previous reports, our study demonstrates that successful CTO-PCI was effective in improving the cardiac mortality of CTO patients. In our study, patients with double CTO were excluded, so we were able to specifically evaluate the effect of a single CTO lesion on long-term cardiac mortality. It has been reported that the cardiac mortality is better in CTO patients who undergo complete revascularization than in those who undergo partial revascularization [10]. Thus, if patients with double CTO had been included in this study, the evaluation of long-term mortality for each subgroup (partial and complete revascularization) would have been more complicated.

4.5. Study limitations

There are several limitations to our study. First, differences in the performance of the procedures as well as the varied clinical settings involved in the performance of PCI could differ between countries; therefore, the results may also be variable. Second, the success of CTO-PCI is highly dependent on a physician’s skill and experience. Although experience in performing CTO-PCI has accumulated in our hospital, the results concerning acute success may be different under conditions with less experience. Since this is a retrospective observational study, there are also inherent limitations. Finally, it is likely that a previous history of CABG and CKD would reflect the patient’s frailty and general status. In particular, the degree of renal dysfunction needs to be stratified and related to the long-term mortality.

5. Conclusions

The initial success rate of CTO-PCI in Japan has reached a satisfactory level. In line with this development, the long-term mortality among patients who undergo successful CTO-PCI is better than in those in whom CTO-PCI is unsuccessful. Multivariate analysis demonstrated that procedural success, a prior history of CABG, and the presence of CKD were associated with long-term mortality.

Authors’ information

Tomohiko Teramoto MD, PhD is the person who designed this study and wrote the manuscript. Estuo Tsuchikane MD, Masanori Yamamoto MD and Masashi Kimura MD gave me a lot of important comments and suggestions for the design of this study. Hitoshi Matsuo MD, Seiji Kano MD, Tetsuro Shimura MD, and Hirotomo Sato MD discussed the design of this study, and gave me a lot of important comments, and helped data collection. Yoshiaki Kawase MD, Yoriyasu Suzuki MD, Maoto Habara MD, Kenya Nasu MD, Yoshihisa Kinoshita MD, Mitsuaysu Terashima MD, Tetsuo Matsubara MD, and Takahiko Suzuki MD helped make a draft of this manuscript with a lot of important suggestions. Tomohiko Teramoto MD, PhD took charge of the analysis and interpretation of data and approved the final manuscript for the submission.

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Disclosures

None.

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