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의학박사 학위논문

다혈관 관상동맥 만성폐색병변의 경피적 관상동맥 중재술에 있어 치료 전략에 따른 시술 전후 합병증과 시술 적절성 및 장기 임상 경과에 대한 분석

Periprocedural complication and feasibility and long-term clinical outcomes about percutaneous coronary intervention (PCI) of multivessel-chronic total occlusion (MV-CTO) according to the treatment strategies

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의학과

조상철

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이 논문을 의학박사 학위논문으로 제출함

2021 년 2 월

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Abstract

Objective: To evaluate periprocedural complication and feasibility and long-term clinical outcomes about percutaneous coronary intervention (PCI) of multivessel-chronic total occlusion (MV-CTO) according to the treatment strategies.

Background: Limited data are available on PCI for MV-CTO, which is rarely identified in CTO patients.

Methods: In total, 164 consecutive patients who underwent 232 PCIs for MV-CTO at single tertiary cardiac center in South Korea were included. MV-CTO was defined as the identification of CTO lesions in more than two coronary arteries. The periprocedural complication and feasibility and long-term clinical outcome were analyzed according to CTO PCI strategies.

Results: 96 patients underwent just one CTO PCI (96 cases) and 68 patients had two CTO PCIs (136 cases). The mean Japanese Multicenter CTO Registry (J-CTO) score was 2.0 ± 1.7. Of the 232 CTO procedures, 198 cases were successful in 85.3% and the success rate of all two CTO PCI was 75.5%. The staged PCI seemed to be more successful than the simultaneous second PCI (94.5% vs 80.5%, p = 0.156). The incidence of periprocedural complication and the target vessel failure, mainly driven by target vessel revascularization did not differ according to PCI strategies.

Conclusion: PCI for MV-CTO showed a high success rate with an acceptable periprocedural complication and long-term rate of target-vessel failure. If the patient is stable and the CTO lesion is anatomically suitable for PCI, it is recommended to revascularize completely.

Key words: Chronic coronary total occlusion, Multiple vessel disease, Percutaneous coronary intervention

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INTRODUCTION

Chronic coronary total occlusions (CTOs) are found in 15-25% of patients with stable angina pectoris and multivessel-chronic coronary total occlusion (MV-CTO) were observed in 17-24% of CTO patients, with no established treatment strategy[1,2]. Still, treatment of a CTO constitutes less than 5% of percutaneous coronary interventions (PCIs) in contemporary interventional practice[3,4]. Recent advances in devices and treatment strategies and growing experience of technical success of CTO-PCI have moved toward complete revascularization with more liberal use of PCI in patients with CTO[5-9]. In addition, several studies have suggested improved symptoms or survival with complete revascularization in patients with stable angina or ST elevation myocardial infarction[10-13]. The clinical benefits of complete revascularization along with acceptable complication risk and technical feasibility of CTO-PCI allows the therapeutic approach of PCI to MV-CTO.

Since MV-CTO is generally accepted to perform surgical treatment with CABG[14, 15], an algorithmic approach for the PCI treatment of MV-CTO has not been fully described. Since only limited data have been made available for the features and results of PCI for MV-CTO lesions, we evaluated the 'real-word' practice of PCI for MV-CTO in terms of periprocedural complication and feasibility and long-term clinical outcomes about PCI of MV-CTO according to the treatment strategies based on a single center registry.

Methods

Study Population and Data Collection

The study cohort included data on consecutive patients who underwent PCI for Multivessel-CTO involving the treatment of just one CTO lesion or the treatment of two CTO lesions at one tertiary cardiac center with two highly experienced operators with more than 50 CTO-PCI cases per year[7] in South Korea between July 2003 and June 2018. The patients enrolled in the registry were required to have either angina or evidence of ischemia, presumably attributable to the CTO lesions. The use of devices and techniques and the choice of PCI strategy were at the operator's discretion. Clinical, procedural, and outcome data were obtained by medical record and periodic outpatient follow-up was done. The extent of coronary artery disease and the CTO lesion complexity was assessed by calculating the Japanese Multicenter CTO Registry (J-CTO) score[16]. We also obtained details of the location of lesions, the extent of the lesion and the pattern of collateral flow through analyzing coronary angiographic imaging.

Definitions and Endpoints

CTO was defined as a coronary artery obstruction with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0 on angiography that lasted at least 3 months based on clinical history and previous angiography. When no definite evidence of occlusion duration existed, the diagnosis of CTO was made according to angiographic morphology suggested by the Euro CTO Club consensus document[17]. Multivessel-CTO was defined as the identification of CTO lesions in more than two coronary arteries.

The primary outcome of interest was target vessel failure (TVF), defined as the composite of cardiac death, spontaneous myocardial infarction (MI), and target-vessel revascularization (TVR). Cardiac death was regarded as death from a cardiac event, or if there was no definite identifiable noncardiac cause. Periprocedural MI was defined as peak elevations of the creatine kinase–myocardial band > 10-fold the upper reference limit within 48 hours of the procedure according to the 3rd definition of the Society of Cardiac Angiography and Interventions (SCAI)[18]. The spontaneous MI included any creatine kinase–myocardial band or troponin increase above the upper limit of the normal range with ischemic symptoms or signs during follow-up after discharge. TVR was defined as any repeat revascularization in the previously treated CTO lesions using either PCI or bypass surgery.

The intra-procedural complication included the thrombus, coronary perforation, recoil, no reflow and shock during the procedure. The procedural complication was assessed for adverse events, which included any of the following events after PCI and prior to hospital discharge: hematoma, contrast induced nephropathy, periprocedural MI, in-hospital TVR, cardiac tamponade requiring intervention, stroke and

death.

Statistical Analysis

Continuous variables are presented as mean values with standard deviation and categorical variables as numbers with percentages. For comparison among groups, the $\chi 2$-test for categorical variables and unpaired Student's test or one-way analysis of variance for continuous variables were applied as required. Nonparametric tests were applied in those non-normally distributed variables. The time-to-event outcomes were determined from the date of intervention to the final follow-up. Cumulative event rates and survival curves were generated using the Kaplan-Meier method. Multivariable logistic regression analysis with backward stepwise elimination was performed to identify the predictors of procedural failure. The following clinical, anatomical and procedural predictors were selected based on clinical importance with respect to CTO-PCI: age, sex, BMI, current smoking, hypertension, diabetes, history of CABG, ejection fraction, presence of calcification within the CTO segment, CTO length ≥ 20 mm, stent length and stent diameter. P-values were two-sided, and $P < 0.05$ was considered significant. Data analyses were performed using SPSS 24 (IBM Rochester, Minnesota, USA).

RESULTS

Clinical and angiographic characteristics

A total of 164 patients underwent 232 PCI cases for Multivessel-CTO during the study period. 96 patients underwent just one CTO PCI and 68 patients had two CTO PCIs. The clinical and angiographic characteristics are listed in **Table 1**. The mean patient age was 60.5 ± 11.0 years, and 84.8% of patients were men and 37.8% had diabetes. The mean left ventricular ejection fraction was 55.0 ± 9.3%. Among the coronary vessels, RCA CTO was the most common and LCX and RCA CTO combination were most frequently observed. The mean CTO length was 15.3 ± 9.4 mm, and the total lesion length incorporating the CTO was 41.4 ± 18.6 mm. The mean J-CTO score was 2.0 ± 1.7, and the major components contributing to the score were blunt entry and CTO length > 20 mm. The patients with two CTO PCIs tended to be younger, more past MI history, less LM disease, and less RCA CTO lesion than those with only one CTO PCI, but most other clinical and anatomical features were similar.

Table 1. Clinical and Angiographic Characteristics

Demographic and clinical characteristics	Total (N = 164, 232 lesions)	One CTO (N=96, 96 lesions)	Two CTO (N=68, 136 lesions)	p-value
Age (years)	60.5 ± 11.0	63.3 ± 11.3	58.6 ± 10.5	0.001
Men	139 (84.8%)	80 (83.3%)	59 (86.8%)	0.467
BMI	25.6 ± 2.8	25.6 ± 2.8	25.6 ± 2.9	0.997
Hypertension	104 (63.4%)	58 (60.4%)	46 (67.6%)	0.309
Diabetes mellitus	62 (37.8%)	35 (36.5%)	27 (39.7%)	0.616
Current smoker	44 (26.8%)	26 (27.1%)	18 (26.5%)	0.917
Dyslipidemia	117 (71.3%)	67 (65.6%)	50 (72.8%)	0.241
Prior CABG	17 (10.4%)	11 (11.5%)	6 (8.8%)	0.508
Prior myocardial infarction	17 (10.4%)	5 (5.2%)	12 (17.6%)	0.007
Prior PCI	52 (31.7%)	33 (34.4%)	19 (27.9%)	0.295
Peripheral vascular disease	5 (3.0%)	4 (4.2%)	1(2.2%)	0.235
Chronic kidney disease*	8 (4.9%)	5 (5.2%)	3 (4.4%)	0.572
Clinical presentation				0.682
stable angina	133 (81.1%)	79 (82.3%)	54 (79.4%)	
Acute coronary syndrome	31 (18.9%)	17 (17.7%)	14 (20.6%)	
Atrial fibrillation	4(2.4%)	2 (2.1%)	2 (2.9%)	0.596
Left ventricular ejection fraction (%)	55.0 ± 9.3	55.3± 8.9	54.8±9.6	0.680
Angiographic characteristics				
Left main disease	4(2.4%)	4(4.2%)	0(0.0%)	0.028
LAD CTO	91 (55.5%)	52 (54.2%)	39 (57.4%)	0.771

LCX CTO	123 (75.0%)	76 (79.2%)	47 (69.1%)	0.088
RCA CTO	130 (79.3%)	71 (74.0%)	59 (86.8%)	0.021
CTO location				0.126
LAD & LCX CTO	44 (19.0%)	25 (26.0%)	20 (14.7%)	
LAD & RCA CTO	62 (26.7%)	20 (20.8%)	42 (30.9%)	
LCX & RCA CTO	103 (44.4%)	44 (45.8%)	58 (42.6%)	
Triple CTO	23 (9.9%)	7 (7.3%)	16 (11.8%)	
CTO length (mm)	15.3 ± 9.4	14.3 ± 6.7	16.5 ± 11.8	0.261
Lesion length (mm)	41.4 ± 18.6	41.1 ± 18.4	41.9 ± 19.1	0.827
In stent restenosis	28 (12.1%)	12 (12.5%)	16 (11.8%)	0.866
Visible interventional collateral	75 (32.6%)	30 (31.3%)	45 (33.6%)	0.710
Japanese CTO score	2.0 ± 1.7	2.0 ± 1.1	2.0 ± 1.1	0.852
Blunt stump	136 (59.1%)	58 (60.4%)	78 (58.2%)	0.737
Calcification at CTO	96 (41.7%)	40 (41.7%)	56 (41.8%)	0.985
Bending > 45°	88 (38.3%)	38 (39.6%)	50 (37.3%)	0.727
Occlusion length ≥20 mm	111 (48.3%)	45 (46.9%)	66 (49.3%)	0.722
Retry lesion	22 (9.5%)	9 (9.4%)	13 (9.6%)	0.962

Values are presented as mean ± standard deviation or numbers (%).

*Chronic kidney disease was defined as an estimated glomerular filtration rate < 60mL/min/1.73 m^2.

CTO: Chronic total occlusion, BMI: body mass index, CABG: Coronary artery bypass graft, PCI: Percutaneous coronary intervention, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery.

Procedural Sequence and Results

A detailed presentation of the procedures and results is shown in **Table 2 and Figure 1**. Of the 232 CTO procedures, 198 cases were successful in 85.3% and the success rate of all two CTO PCI was 75.5% (102/136 cases). The success rate of second CTO PCI [82.4% (56/68 cases)] was similar to that of the first CTO PCI [86.6% (142/164 cases)], and staged second PCI [94.5% (18/19 cases)] seemed to be more successful than the simultaneous second PCI [80.5% (38/49 cases), p = 0.156]. The PCI success rate for the RCA CTO was the highest and the PCI of LCX CTO lesion was more successful in cases of just one CTO PCI than two CTO PCI.

The antegrade-only approach was used in the majority of cases (87.5%) for final CTO-crossing technique and wire escalation (89.1%) was the most frequently used wiring technique, following parallel wire (9.2%) for the success of the antegrade-only approach procedure. The primary retrograde or rescue retrograde approach was used in 12.5% of cases, and the rescue antegrade approach was used after the failure of the retrograde approach in 4.3% of cases. The success rate of the retrograde approach was 82.8%, similar to that of the anterograde approach (85.7%, p = 0.674). In the retrograde approach, the wire escalation (52.6%) was the most successful, followed by reverse CART (42.1%).

In most PCI, IVUS (78.9%) was used, with about 80% being treated with stents. In patients with procedural success, the mean stent length was 68.9 ± 26.7 mm, and the average number of implanted stents was 2.3 ± 0.8. In the two CTO PCI group, more stents and longer stents were used and the procedure

time and fluoroscopy time were longer and contrast was used more. However, POBA was performed more in the only one CTO PCI group.

Table 2. Procedural characteristics

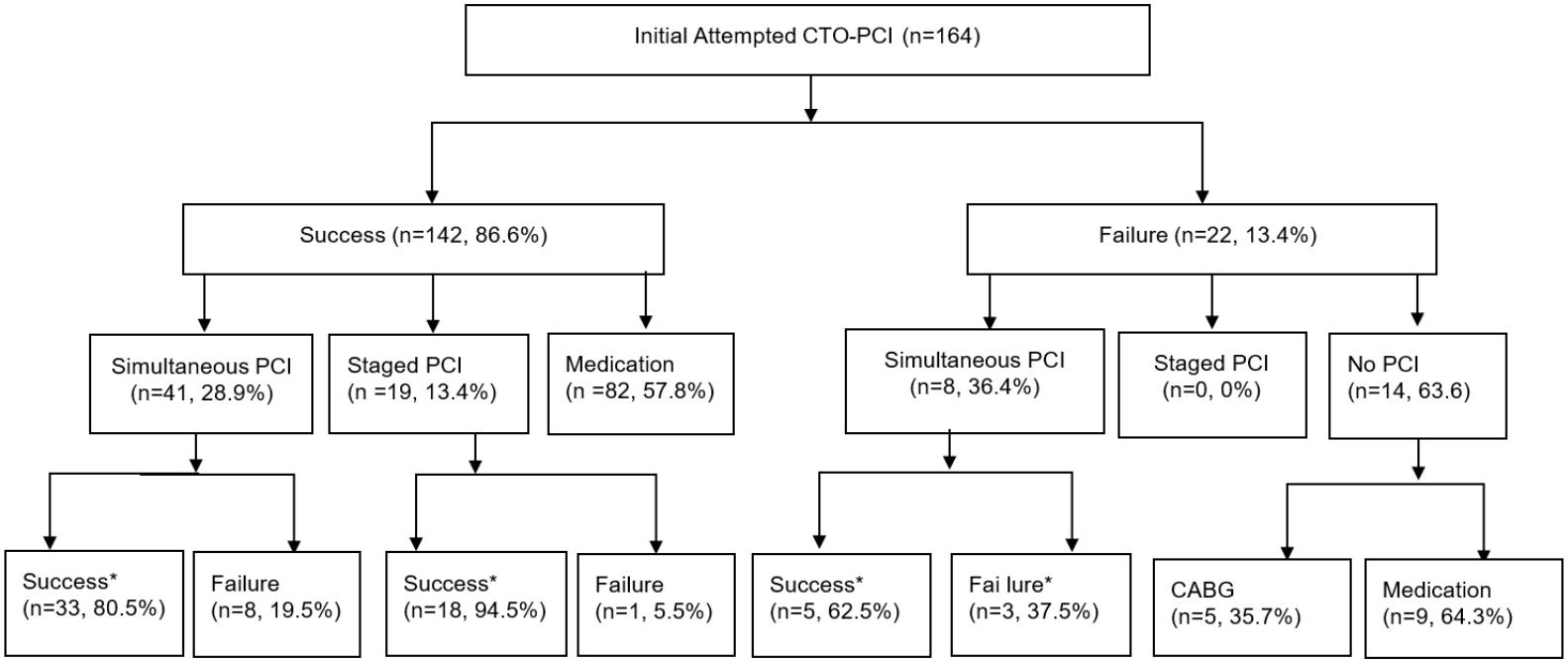
Variable	Total (N = 164, 232 lesions)	One CTO (N=96, 96 lesions)	Two CTO (N=68, 136 lesions)	p-value
Technical success				
Success	198 (85.3%)	82 (85.4%)	116 (85.3%)	0.979
All two CTO success		NA	102 (75.0%)	
All two CTO failure		NA	6 (4.4%)	
CTO success				
LAD CTO	68(86.1%)	32(80.0%)	36(92.3%)	0.193
LCX CTO	46(75.4%)	19(95.0%)	27(65.9%)	0.013
RCA CTO	84(91.3%)	31(86.1%)	53(94.6%)	0.255
Bilateral injection	108(46.6%)	43 (44.8%)	65 (47.8%)	0.652
Microcatheter	162(69.8%)	64 (66.7%)	98 (72.1%)	0.378
Wiring strategy				
Antegrade-only	203(87.5%)	85 (88.5%)	118 (86.8%)	0.687
Anterograde success*	174 (85.7%)	74(87.1%)	100 (84.7%)	0.642
Retrograde approach	29(12.5%)	11 (11.5%)	18 (13.2%)	0.687
Primary retrograde	18(62.1%)	6(54.5%)	12(66.7%)	0.514
Retrograde success*	24(82.8%)	8(72.7%)	16(88.9%)	0.339
Final CTO-crossing technique				
Antegrade approach				0.120
Wire escalation	155(89.1%)	70 (94.6%)	85 (85.0%)	
Parallel wire	16(9.2%)	3 (4.1%)	13 (13.0%)	
IVUS-guided rewiring	3(1.7%)	1 (1.4%)	2 (2.0%)	

Retrograde approach				0.342
Reverse CART	8(42.1%)	2 (28.6%)	6 (50.0%)	
CART	1(5.3%)	0 (0.0%)	1 (8.3%)	
Wire escalation	10 (52.6%)	5 (71.4%)	5 (41.7%)	
IVUS use	183(78.9%)	74 (77.1%)	109 (80.1%)	0.573
Total procedural time(min)	115.9 ± 149.5	88.8 ± 61.8	134.9 ± 186.0	0.009
Total fluoroscopy time(min)	52.1 ± 67.4	39.6 ± 28.1	60.9 ± 83.8	0.008
Contrast amount(mL)	467.2 ± 223.6	402.0 ± 197.4	512.7 ± 230.1	<0.001
Number of stents (mm)	2.3 ± 0.8	1.7 ± 0.9	3.2 ± 0.9	0.004
Average stent diameter (mm)	3.0 ± 0.7	2.7 ± 1.1	2.8 ± 1.0	0.688
Length of stent (mm)	68.9 ± 26.7	50.3 ± 27.7	95.2 ± 29.8	0.006
Stent	185 (79.7%)	77 (80.2%)	108 (79.4%)	0.946
BMS	5 (2.7%)	3 (3.9%)	2 (1.9%)	0.522
1st generation	48 (25.9%)	22 (28.6%)	26 (24.1%)	
2nd generation	132 (71.4%)	52 (67.5%)	80 (74.1%)	
DCB	1(0.4%)	1 (1.0%)	0 (0.0%)	0.414
POBA	23(9.9%)	14 (14.6%)	9 (6.6%)	0.046

Values are presented as mean ± standard deviation or numbers (%).

CTO: Chronic total occlusion, LAD: Left anterior descending, LCX: Left circumflex artery, IVUS: Intravascular ultrasound, CART: Controlled antegrade and retrograde tracking, DCB: Drug-coated balloon, POBA: Plain old balloon angioplasty.

*Comparison between anterograde success and retrograde success(p=0.674)



*Comparison between success and failure of 2nd stage CTO PCI(p=0.156)

Figure 1. Algorithmic approach for the PCI treatment of MV-CTO. Among initial attempted CTO-PCIs in the 164 CTO patients, 142 cases were successful in 86.6% and the success rate of all two CTO PCI was 75.5% (102/136 cases). 96 patients had only one CTO PCI and 68 patients had PCI of two CTOs. Of the two CTO PCI, 49 cases were done simultaneously and 19 cases was treated sequentially. The success rate of second CTO PCI [82.4% (56/68 cases)] was similar to that of the first CTO PCI [86.6% (142/164 cases)], and staged second PCI [94.5% (18/19 cases)] seemed to be more successful than the simultaneous second PCI [80.5% (38/49 cases), p = 0.156]. CTO; chronic total occlusion, PCI; percutaneous coronary intervention, MV; multi-vessel, CABG; coronary artery bypass graft.

Periprocedural complication

Table 3 and Table 4 shows periprocedural complication. Serious procedural complication after CTO-PCI occurred in 15 patients (6.5%); these included 9 intra-procedural complications (3.9%), 1 cerebrovascular event (0.4%). 4 in-hospital TVR (1.7%), which was related to 3 failed procedure and 1 acute stent thrombosis after PCI. All TVR patients were treated by emergent open-heart surgery. In addition, there were 3 cases (1.1%) of cardiac tamponade that required pericardiocentesis.

The incidence of periprocedural complication did not differ between the only one CTO PCI group and the two CTO PCI group. Cardiac Tamponade occurred more in one CTO PCI group, but there was no statistical significance, and contrast induced nephropathy was rarely identified in both groups (**Table 3**). In the second CTO PCI, the procedural time and fluoroscopy time were longer and more contrast were used in staged procedures, however there was no significant difference between complications occurring between two strategies. (**Table 4**) Moreover, the contrast was used more in staged PCI group, but the incidence of contrast induced nephropathy was similar between the two groups and rarely occurred.

Regardless of the success or failure of the first CTO PCI, the periprocedural complications and the procedure burdens were similar. Even in the second CTO PCI, there was no difference in the periprocedural complications and the procedure burdens regardless of the success or failure of both the simultaneous and staged PCI.

Table 3. Periprocedural complications in patients with only one CTO PCI and patients with two CTO PCI

	Total (N = 232)	One CTO PCI (N=96)	Two CTO PCI (N=136)	p-value
Procedural complication [1]	68 (29.3%)	24 (25.0%)	44 (32.4%)	0.226
Procedural complication [2]	15 (6.5%)	6 (6.3%)	9 (6.6%)	0.911
Intra-procedural complication	9 (3.9%)	3 (3.1%)	6 (4.4%)	0.749
In-hospital CVA	1 (0.4%)	1 (1.0%)	0 (0.0%)	0.414
In-hospital TVR	4 (1.7%)	2 (2.1%)	2 (1.5%)	1.000
Urgent CABG	4 (1.7%)	2 (2.1%)	2 (1.5%)	1.000
Cardiac tamponade	3 (1.3%)	3 (3.1%)	0 (0.0%)	0.070
Contrast induced nephropathy	2 (1.4%)	1 (1.0%)	1 (0.7%)	1.000
Periprocedural MI	17 (7.3%)	7 (7.3%)	10 (7.4%)	0.986
Hematoma	43 (18.5%)	14 (14.6%)	29 (21.3%)	0.193

Procedural complication[1]: intra-procedural complication, cerebrovascular event, coronary artery bypass graft, cardiac tamponade including hematoma and periprocedural myocardial infarction (MI),

Procedural complication[2]: Not including hematoma and periprocedural MI, intra-procedural complication; coronary perforation or dissection, recoil, no reflow, thrombus, shock etc.

CTO; chronic total occlusion, PCI; percutaneous coronary intervention, CVA; cerebrovascular event, TVR; target vessel revascularization, CABG: coronary artery bypass graft.

Table 4. Periprocedural complications and procedure burden according to simultaneous or staged revascularization of second CTO PCI

	Total (N = 136 cases)	Simultaneous (N= 98 cases)	Staged (N=38 cases)	p-value
Procedural complication	44 (32.4%)	34 (34.7%)	10 (26.3%)	0.349
Intra-procedural complication	6 (4.4%)	3 (3.1%)	3 (3.1%)	0.348
Contrast induced nephropathy	1 (0.7%)	0 (0.0%)	1 (2.6%)	0.279
Periprocedural MI	10 (7.4%)	10 (10.2%)	0 (0.0%)	0.062
Hematoma	29 (21.3%)	22 (22.4%)	7 (18.4%)	0.067
Total procedural time(min)	134.9 ± 186.0	132.4 ± 96.3	328.1 ± 321.7	0.008
Total fluoroscopy time(min)	60.9 ± 83.8	59.1 ± 43.4	146.8 ± 144.8	0.006
Contrast amount(mL)	512.7 ± 230.1	539.0 ± 200.0	838.5 ± 286.1	0.015

PCI; percutaneous coronary intervention, MI; myocardial infarction.

Clinical Outcomes

The median follow-up period was 5.2 years (interquartile range, 2.5–9.2 years). During follow-up period, the primary endpoint occurred in 30 patients (18.3%). Target vessel failure (TVF), mainly driven by target vessel revascularization (TVR), was not statistically different in only one CTO PCI group and two CTO PCI group (**Table 5 and Figure 2**), and individual component TVF was also similar between groups. All cause death, cerebrovascular event and major bleeding occurred also similar between groups. In the two CTO PCI group, there was no difference in both TVF and its components in the simultaneous or staged CTO PCI patients (**Table 6 and Figure 3**). Even when only the successful CTO procedures was analyzed, TVF and its components showed no difference between successful two CTO PCI group and successful one CTO PCI group.

Cox proportional multivariable analysis showed that male (HR: 5.018, 95 % CI: 1.04-24.19, p = 0.044), acute coronary syndrome (HR: 4.076, 95 % CI: 1.63-10.23, p = 0.003), stent length (HR: 1.023, 95 % CI: 1.01-1.04, p = 1.019) and stent diameter (HR: 0.395, 95 % CI: 0.23-0.68, p = 0.001) was associated independently with the occurrence of target vessel failure . However, the strategy of CTO PCI (HR: 1.034, 95 % CI: 0.39-2.71, p = 0.946) was not a predictor of target vessel failure.

Table 5. Multivariate analysis of clinical outcomes between one CTO PCI and two CTO PCI

	One CTO PCI (n = 96)	Two CTO PCI (n = 68)	Univariate			Multivariate		
	Total number of events (%)		HR	95% CI	p-value	HR	95% CI	p-value
Target vessel failure	18(18.8%)	12(17.6%)	0.828	0.40-1.73	0.617	1.034	0.39–2.71	0.946
Cardiac death	4 (4.2%)	3(4.4%)	1.079	0.24–4.83	0.920	1.692	0.25–11.38	0.588
Target vessel revascularization	14(14.6%)	8(11.8%)	0.668	0.28–1.61	0.368	0.875	0.30–2.56	0.807
Spontaneous myocardial infarction	3(3.1%)	2(2.9%)	0.776	0.13–4.69	0.782	0.837	0.10–6.82	0.868
All-cause death	17(17.7%)	7(10.3%)	0.627	0.26–1.53	0.303	0.765	0.26–2.25	0.627
Target lesion revascularization	14 (14.6%)	8 (11.8%)	0.668	0.28–1.61	0.368	0.875	0.30–2.56	0.807
Cerebrovascular accident	2 (2.1%)	2(2.9%)	1.410	0.20–10.03	0.731	1.112	0.13–9.28	0.922
Major bleeding	2(2.1%)	1(1.5%)	0.736	0.07–8.12	0.803	0.739	0.07–8.25	0.806

Variables =age, sex, BMI, clinical diagnosis, current smoking, hypertension, DM, history of CABG, ejection fraction, stent length, stent diameter, calcification, CTO length ≥ 20mm. CTO; chronic total occlusion, PCI; percutaneous coronary intervention, CI; confidence interval, HR; hazard ratio.

Table 6. Multivariate analysis of clinical outcomes between simultaneous PCI and staged PCI

	Simultaneous (n = 49)	Staged (n = 19)	Univariate			Multivariate		
	Total number of events (%)		HR	95% CI	p-value	HR	95% CI	p-value
Target vessel failure	9 (18.4%)	3 (15.8%)	1.186	0.34–4.42	0.800	0.364	0.03–4.30	0.422
Cardiac death	2 (4.1%)	1 (5.3%)	0.800	0.07–8.84	0.856	1.575	0.09–29.20	0.760
Target vessel revascularization	7 (14.3%)	1 (5.3%)	2.661	0.32–21.85	0.362	3.173	0.36–28.17	0.300
Spontaneous myocardial infarction	1 (2.0%)	1 (5.3%)	0.271	0.02–4.46	0.361	0.040	0.00–5.43	0.198
All-cause death	5 (10.2%)	2 (10.5%)	0.952	0.18–4.91	0.953	1.253	0.20–7.83	0.809
Target lesion revascularization	7 (14.3%)	1 (5.3%)	2.661	0.32–21.85	0.362	3.173	0.36–28.17	0.300
Cerebrovascular accident	1 (2.0%)	1 (5.3%)	0.403	0.03–6.45	0.520	0.371	0.02–5.99	0.371
Major bleeding	0 (0.0%)	1 (5.3%)	NA	NA	NA	NA	NA	NA

Variables =age, sex, BMI, Current smoking, hypertension, DM, hyperlipidemia, CKD, history of CABG, history of MI, stent length, stent diameter, calcification. PCI; percutaneous coronary intervention, CI; confidence interval, HR; hazard ratio.

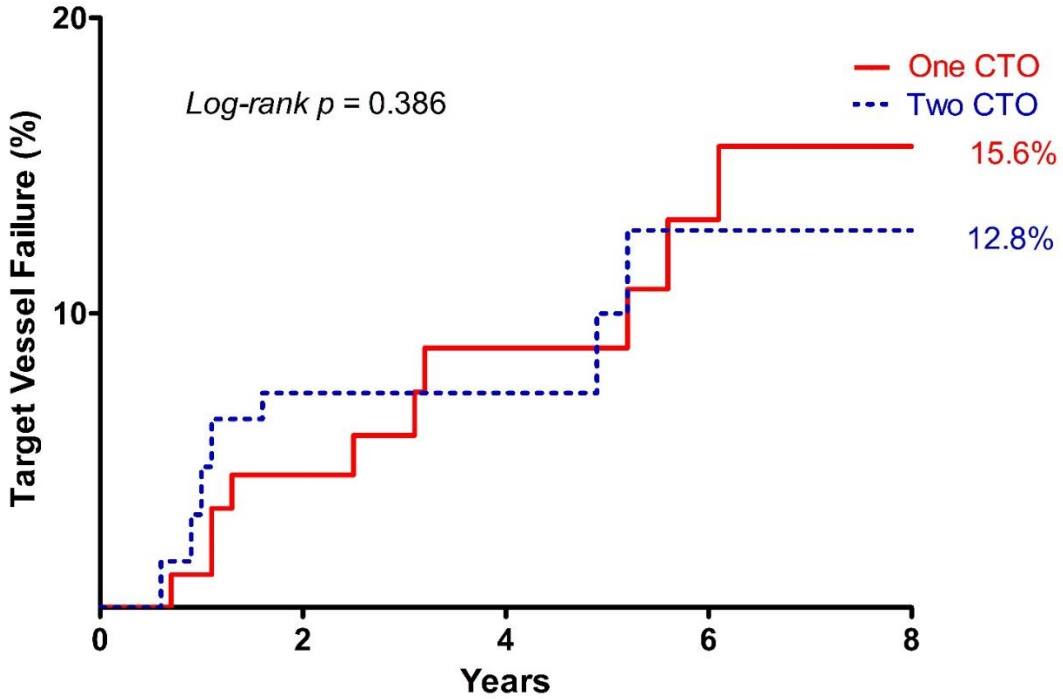


Figure 2. Survival curve of Target vessel failure between one CTO PCI and two CTO PCI. Target vessel failure (TVF), mainly driven by target vessel revascularization (TVR), was not statistically different in only one CTO PCI group and two CTO PCI group (15.6 % vs 12.8 %, p = 0.386)

CTO; chronic total occlusion, PCI; percutaneous coronary intervention.

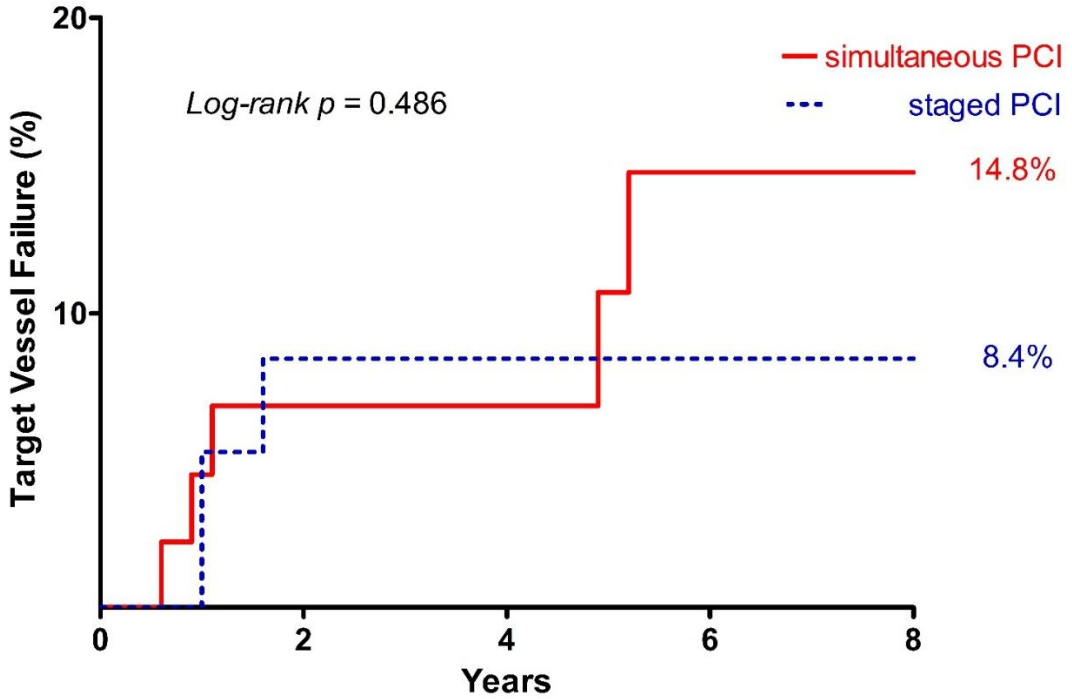


Figure 3. Survival curve of Target vessel failure between simultaneous PCI and staged PCI. In the two CTO PCI group, there was no difference in target vessel failure (TVF) between the simultaneous and the staged CTO PCI patients. (14.8% vs 8.4%, p = 0.486)

CTO; chronic total occlusion, PCI; percutaneous coronary intervention.

DISCUSSION

To the best of our knowledge, this is the largest study to date to report on PCI practices for Multivessel-CTO. The current study demonstrates a high technical success rate (85.3%) in either only one CTO PCI or two CTO PCI with an acceptable periprocedural complications rate between the two groups when performed by experienced operators mainly using the wire-based CTO-PCI approach. If two CTOs are to be treated, clarifying the treatment strategy and staged PCI can increase the two CTO PCI success rate. However, due to the acceptable periprocedural complications and procedural burdens, simultaneous PCI can be performed if the patient is stable and has low comorbidities depending on the discretion of operator and selection of patient. Based on the acceptable long-term rate of TVF that was observed after successful stenting regardless of only one CTO PCI or two CTO PCI, our study suggests that PCI may be a safe and effective treatment for Multivessel-CTO lesions.

Although randomized trials failed to demonstrate the prognostic benefit of CTO-PCI over no CTO-PCI[19, 20], PCI can lead to a significant improvement of quality of life in patients with CTO as compared with optimal medical therapy alone[21, 22]. Several observational studies showed a higher adverse events and poorer clinical outcomes in patients with multivessel CTO PCI and comprehensive evaluation of several observational studies and guidelines suggests that multivessel CTO may be appropriately treated with CABG treatment[14, 15, 23, 24]. On the other hand, there are several studies that survival might be better in the group with successful multiple CTO PCI[25] and in the group with successful CTO PCI in multivessel

disease[26]. With little information on multivessel CTO PCI, our study focused on more clearly showing the feasibility and long-term clinical outcome of multivessel-CTO PCI.

CTOs are challenging lesion to approach using PCI. The success rate, defined as achieving <50 percent stenosis with TIMI3, is known as very low (50 to 70%) compared with non-CTO PCI (approximately 95%)[27, 28]. However, technical advances have increased the success rate without increasing rate of complication[4]. Some studies report a success rate of 85 to 90% in experienced centers[5-7]. As highly experienced center, our center's CTO PCI success rate was 85.3% and all two CTOs PCI success rate was also high as 75.0%. Even though the J-CTO score was close to "difficult CTO" with 2.0 ± 1.7 due to many blunt sumps and occlusion length exceeding 20mm, with proper use of computed tomography or intravascular ultrasound to guide wire-based techniques, our investigators were able to achieve acceptable rates of technical success and clinically relevant complications.

Even though, two CTO PCI requires long procedure time, long fluoroscopy time and large amount of contrast agents, periprocedural complications was not significantly different from those of only one CTO PCI. The two CTO PCI is feasible because of the high procedural success rate and acceptable periprocedural complications. Moreover, considering that the cumulative TVF rates shown in our study, regardless of only one CTO PCI or two CTO PCI, were similar to that of numerous contemporary stent studies targeting non-CTO lesions[29, 30], PCI may be regarded as a viable option to treat multivessel-CTO.

There is lots of evidence that complete revascularization in both stable angina and ST elevation myocardial infarction improves the patient's symptom and survival[10-13]. Although the effect of complete

revascularization on multivessel-CTO has not been clarified, the successful revascularization of two CTOs is close to complete revascularization, which might give a favorable clinical outcome when reflecting the effect of complete revascularization on stable angina. If CTO PCI is technically feasible and has low likelihood of complications during procedure, it would be desirable to treat all CTO lesions as much as possible.

Through this study result, we can present an algorithm for multiple CTO treatment (**Figure 1**). After considering the patient's symptom and comorbidities and analyzing the angiographic finding thoroughly, the extent of CTO PCI should be determined with the discussion with the patient. If the revascularizations of two CTO are decided, it is recommended to treat easily accessible CTO lesion first. The staged PCI seems to have a higher success rate than the simultaneous PCI ($p = 0.156$), so it is recommended to perform the staged PCI whenever possible. If the patient is stable with low comorbidities and the next CTO PCI is expected to be feasible, second CTO PCI can be performed simultaneously. Since the anterograde approach has a tendency to be more successful and safer than the retrograde approach, the anterograde approach such as wire escalation or parallel wire technique is recommended first. If the anterograde approach fails and there is a visible interventional collateral flow, the retrograde approach such as rewiring cross or reverse CART can be tried. If the CTO PCI fails, CABG or medication should be chosen depending on the patient's symptoms and serious complications.

Study Limitations

Our study has a number of limitations. First, our study was retrospective observational in nature and included just one tertiary cardiac center with relatively small sample size, and is therefore, inherently subject to bias. The procedural results and clinical outcomes are likely to be affected by the patient's characteristics and the operator's disposition. Future prospective studies with a larger population are warranted. Second, a progressive improvement in the devices and procedural techniques throughout the long study period should be taken into consideration when interpreting our study results. Although the majority of patients (70%) in our cohort were recruited after 2010, it is undeniable that the case selection strategies and concepts of CTO-PCI have changed significantly over time. Thus, extrapolating our findings to any CTO-PCI procedure should be performed with caution. Third, as there was no difference in the primary outcome of both complete revascularization or incomplete revascularization and only one CTO PCI or two CTO PCI, the symptom improvement is an important parameter in determining the effect of CTO PCI. However, the objective indicators on the improvement of the symptoms of the patients could not be checked, and thus the effect of the CTO PCI could not be presented in detail.

Conclusions

Our study involving a large number of patients undergoing PCI for Multivessel-CTO demonstrated high technical success rate, acceptable complication rates, and favorable long-term outcomes regardless of only one CTO PCI or two CTO PCI. If the patient is stable, has low comorbidity and the CTO lesion is anatomically suitable for PCI, it is recommended to treat two CTOs if possible. If two CTOs are planned to be treated, it is better to treat them sequentially than simultaneously.

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국문요약

목표: 다혈관 관상동맥 만성폐색병변의 경피적 관상동맥 중재술에 대한 치료 전략 따른 임상 경과에 대한 자료는 부족한 실정이다. 다혈관 관상동맥 만성폐색병변의 경피적 관상동맥 중재술에 대한 치료 전략에 따른 임상 경과를 비교 분석하여 상황에 따른 다혈관 관상동맥 만성폐색질환의 적합한 치료 전략을 찾고자 한다.

연구방법: 일년에 50 개 이상의 관상동맥 만성폐색병변을 시술하는 두명의 이상의 경험이 풍부한 중재시술 전문의가 있는 3 차 의료기관에서 2003 년 7 월부터 2018 년 6 월 까지 다혈관 관상동맥 만성폐색 병변이 있는 환자에서 한 개 이상의 만성폐색변에 대하여 경피적 관상동맥 중재시술을 받은 164 명의 환자, 232 건의 경피적 관상동맥 중재시술에 대하여 분석한다. 이들 시술에 대하여 치료 전략에 따른 시술간 합병증, 시술 성공 가능성, 장기간 임상 결과를 비교하여 상황에 따른 적합한 치료 전략을 찾는다. 일차 종말점(primary endpoint)은 목표혈관실패(target vessel failure)로 설정하고, 이는 심인성 사망, 자발적 심근경색, 목표혈관 재개통(target vessel revascularization)으로 한다.

결과: 한 개의 만성 관상동맥 폐색에 대하여 관상동맥 중재술을 시행한 환자는 96 명으로 96 개의 증례였고, 두 개의 만성 관상동맥 폐색에 대하여 관상동맥 중재술을 시행한 환자는 68 명으로 136 개의 증례였다. 평균 J-CTO 점수는 2.0±1.7 이었다. 232 개의 만성 관상동맥 폐색 병변에 대한 시술에서, 198 개의 시술에서 성공하여 85.3%의 성공률을 보였으며, 두 개의 만성 관상동맥 폐색에 대한 시술에서 두 개의 병변에 대한 시술이 모두 성공한 경우는 75.5% 이었다. 순차적 시술(staged PCI)이 동시적 시술(simultaneous PCI)보다 시술 성공률이 높아 보이나 통계학적으로 유의한 차이는

없었다. (94.5% vs 80.5%, p=0.156) 시술간 합병증(periprocedural complication)과 주로 목표혈관 재개통(target vessel revascularization)으로 발생한 목표혈관실패(target vessel failure)는 관상동맥 중재술의 전략에 따라 차이를 보이지 않았다.

결론: 다혈관 만성 관상동맥 폐색에 대한 관상동맥 중재술은 높은 성공률을 보였고, 수용 가능한 시술간 합병증 (periprocedural complication)이 발생하였고, 목표혈관실패(target vessel failure)로 대표되는 장기간 임상 경과가 양호하였다. 만약 환자가 안정적이고, 만성 관상동맥 폐색 병변이 해부학적으로 관상동맥 중재술에 적합하다면, 모든 관상동맥 폐색 병변을 치료하는 것이 추천된다.

중심단어: 만성 관상동맥 폐색(Chronic coronary total occlusion), 다혈관 질환(Multiple vessel disease), 관상동맥 중재술 (Percutaneous coronary intervention)