

Percutaneous Coronary Intervention Versus Optimal Medical Therapy for Chronic Total Coronary Occlusion With Well-Developed Collaterals

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Background—The impact of percutaneous coronary intervention (PCI) on chronic total occlusion in patients with well-developed collaterals is not clear.

Methods and Results—A total of 640 chronic total occlusion patients with collateral flow grade ≥ 2 were divided into 2 groups; chronic total occlusion patients either treated with PCI (the PCI group; $n=305$) or optimal medical therapy (the optimal medical therapy group; $n=335$). To adjust for potential confounders, a propensity score matching analysis was performed. Major clinical outcomes were compared between the 2 groups up to 5 years. In the entire population, the PCI group had a lower hazard of myocardial infarction (hazard ratio [HR], 0.177; $P=0.039$; 95% confidence interval [CI], 0.03–0.91) and the composite of total death or myocardial infarction (HR, 0.298; $P=0.017$; 95% CI, 0.11–0.80); however, it showed higher hazard of target lesion revascularization (HR, 3.942; $P=0.003$; 95% CI, 1.58–9.81) and target vessel revascularization (HR, 4.218; $P=0.001$; 95% CI, 1.85–9.60). After propensity score matching, a total of 158 matched pairs were generated. Although the PCI group showed a higher hazard of target lesion revascularization (HR, 2.868; $P=0.027$; 95% CI, 1.13–7.31) and target vessel revascularization (HR=2.62; $P=0.022$; 95% CI, 1.15–5.97), it still exhibited a lower incidence of the composite of total death or myocardial infarction (HR, 0.263; $P=0.017$; 95% CI, 0.087–0.790). The mean ejection fraction was improved from 47.8% to 51.6% ($P<0.001$) after PCI.

Conclusions—In our study, successful revascularization by PCI for chronic total occlusion lesions with well-developed collaterals was associated with lower incidence of death and myocardial infarction, improved left ventricular function, but increased repeat revascularization rate. (*J Am Heart Assoc.* 2017;6:e006357. DOI: 10.1161/JAHA.117.006357.)

Key Words: chronic total occlusion • collateral circulation • medical therapy • percutaneous coronary intervention

The success rate of percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) lesions have been increased by the advancement of operator's skill, experience with intervention techniques (anterograde and retrograde approaches, wire manipulations techniques, and so on), and

device technology (improved dedicated CTO guidewires, microcatheters, CTO balloons, and coronary stents).^{1–4} Several studies demonstrated that successful CTO intervention was associated with improved survival rates and angina symptom relief when compared with the failed CTO intervention.^{1,4–6} Despite previous study results, the proportion of patients who underwent PCI for CTO lesions was still lower,^{7,8} and current guidelines recommend that the physicians should consider the clinical benefits regarding clinical, angiographic, and technical parameters when determining whether or not to perform PCI in patients with CTO lesions.^{9,10}

The coronary collateral circulation has been known as an alternative route of blood supply to the occluded segment of the distal myocardium area. Well-developed collateral flow is a positive predictive value for the possibility of myocardium viability, and it has been an important factor for a physician's decision whether or not open up for the CTO lesion, particularly in CTO patients with limited symptoms and preserved left ventricular (LV) function.¹¹ Also, well-developed collateral flow contribute clinical benefits in reducing the

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Clinical Perspective

What Is New?

- In patients who have a chronic total occlusion of a coronary artery with well-developed collaterals, percutaneous coronary intervention for the chronic total occlusion yielded a significantly higher hazard of repeat revascularization than optimal medical therapy alone strategy.
- However, it reduced the composite of death or myocardial infarction, improved left ventricular function, and had particular benefits in certain patient subgroups, such as those with older age (>65 years), non-myocardial infarction, reduced left ventricular ejection fraction ($\leq 50\%$), and diabetes mellitus.

What Are the Clinical Implications?

- When physicians decide the treatment strategy for a chronic total occlusion, our results suggest that chronic total occlusion percutaneous coronary intervention is a more-appropriate treatment strategy for patients with good collateral circulation in whom coronary steal and myocardial viability are likely to exist and cardiac function likely to improve.

incidence of cardiac deaths and cardiovascular events in chronic stable angina patients. Furthermore, it is associated with beneficial effect after acute ischemic status in reducing infarct size and preserving LV function compared with CTO patients with poor-developed collateral flow^{12,13} However, there is limited evidence regarding the impact of PCI in patients with CTO with abundant collateral circulation compared with the optimal medical therapy (OMT) alone. Thus, the purpose of this study is to identify the impact of PCI on long-term clinical outcomes in patients with at least 1 CTO target vessel and well-developed collateral flow compared with OMT alone strategy in the drug-eluting-stent era.

Methods

Study Population

A total of 840 consecutive patients were enrolled in the CTO registry of Korea University Guro Hospital (Seoul, South Korea). In brief, it is a single-center, prospective, all-comer-based data to reflect the “real-world” practice from January 2004 to November 2015. Data were collected by well-trained study coordinators with a standardized case-report form. Participants or their legal guardians were given a thorough literal and verbal explanation of the study procedures before granting a written consent to participate in the study. The study protocol was approved by Medical Device Institutional Review Board of Korea University Guro Hospital. The authors

of this article have certified that the information contained herein is true and correct as reflected in the records of the Medical Device Institutional Review Board (#MD07014).

Among these, a total of 647 patients who had at least 1 CTO lesion in the epicardial vessel and 2 or 3 Rentrop collateral grade flow¹⁴ confirmed by a diagnostic angiography were included in this study. Seven patients who received coronary artery bypass graft were excluded from the present study. We divided them into 2 groups according to the treatment strategy; the PCI group (n=305) and the OMT group (n=335). The OMT group was composed of patients with medical treatment alone (n=267), failed CTO PCI (n=54), and residual CTO lesion despite successful CTO PCI (n=14). The study flow chart is presented in Figure 1.

Study Definitions

The CTO lesion was defined as a complete occlusion of the coronary main vessel with thrombolysis in myocardial infarction flow grade 0 for at least 3 months. Coronary main vessel was defined as having >2.5 mm of the reference vessel diameter. If a patient has CTO lesion in a small vessel (reference vessel diameter, ≤ 2.5 mm) or located on the side branch, the patient is excluded. The Rentrop collateral classification scale was used to grade the coronary collateral flow¹⁴: 0=no collateral filling, 1=filling of side branches without epicardial segment of recipient vessel; 2=partial filling of the recipient epicardial segment through collateral vessels; and 3=complete collateral filling of the epicardial vessel segment to be dilated. Grades 2 or 3 were defined as a well-developed collateral flow.

PCI Procedure and Medical Treatment

Diagnostic angiography and PCI were performed with standardized protocol and techniques by the femoral or radial artery. Before the PCI procedure, unfractionated heparin (50–70 U/kg) and low-molecular-weight heparin (60 mg bid subcutaneously before and after the PCI) was administered. All patients without contraindications were given a loading dose of 200 to 300 mg of aspirin, 300 to 600 mg of clopidogrel, and other adequate antiplatelets by the physician's discretion. Usage of adjunctive Cilostazol to a dual-antiplatelet regimen (aspirin+clopidogrel) was regarded as triple antiplatelets and also depended on the physician's discretion. Cilostazol was administered by 200 mg postloading and then 100 mg bid for at least 1 month. The administration of platelet glycoprotein IIb/IIIa receptor blockers was also based on the physician's discretion. In most cases, atheroablative devices were not utilized. However, when an adequate luminal diameter could not be acquired through predilation, atheroablative devices were utilized for

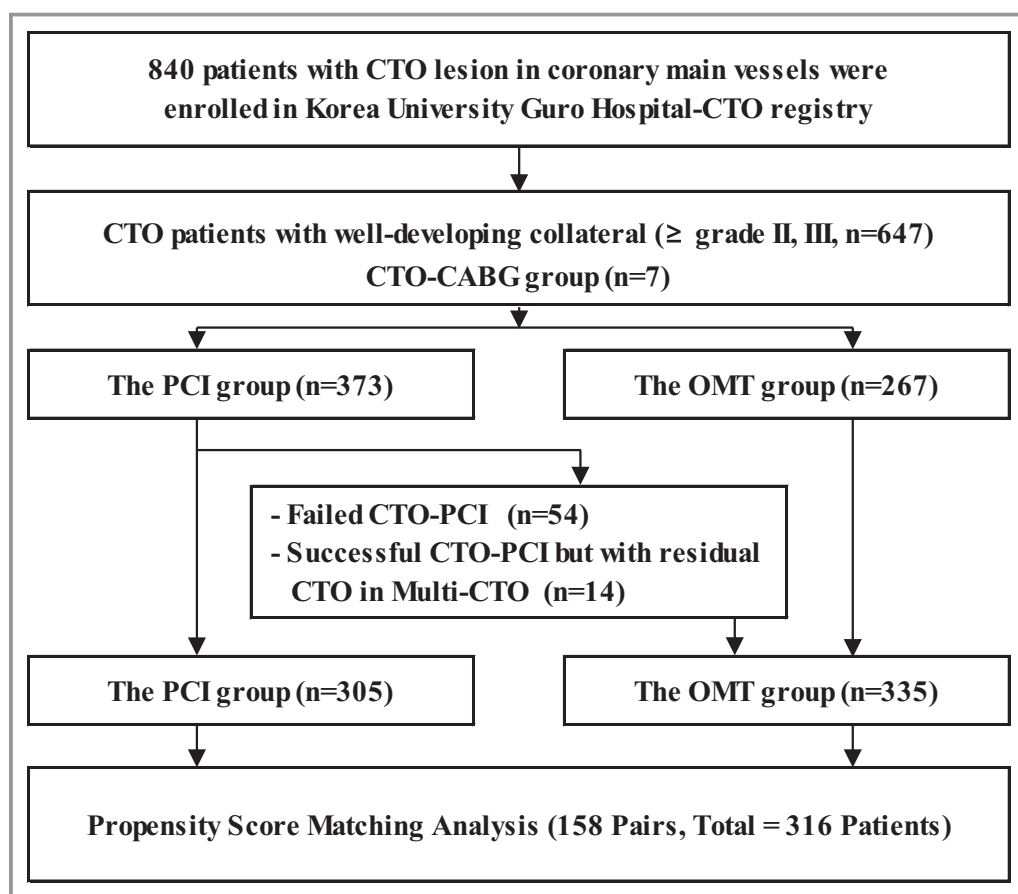


Figure 1. Study flow chart. CTO indicates chronic total occlusion; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

securing the path for optimal stenting. Drug-eluting stents were deployed after preballoon dilatation, and the successful PCI was defined as the achievement of an angiographic residual diameter stenosis of less than 30% with thrombolysis in myocardial infarction grade III flow. After intervention, patients received and maintained dual-antiplatelet therapy for at least 1 year. During the hospitalization period, all patients received appropriate optimal medical treatment, which included β -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, antianginal agents, and statins in addition to antiplatelets. After discharge, patients continued their medication regimen for as long as possible.

Study End Points

In this study, the primary end point was the incidence of major clinical outcomes, including total death, myocardial infarction (MI), revascularization, such as PCI and coronary artery bypass graft, and major adverse cardiovascular events. Major adverse cardiovascular events was defined as the composite of total death, MI, and target vessel

revascularization (TVR). Target lesion revascularization (TLR) indicates revascularization of retreated CTO lesion or identified CTO lesion by PCI or coronary artery bypass graft. TVR indicates revascularization of the identified CTO vessel. Non-TVR indicates revascularization of vessels without CTO lesion. The secondary end point was the level of change for left ventricular ejection fraction (LVEF) before and after CTO PCI during 6 months and 2 years. We acquired the follow-up clinical data of all enrolled patients through face-to-face contacts at outpatient clinic visit, medical chart reviews, and telephone interviews.

Statistical Analysis

Before propensity score matching, we performed statistical analysis in entire population. For continuous data, differences between the 2 groups were analyzed by the Student *t* test or Mann-Whitney rank test. Difference between before and after the procedure of the same group was analyzed by the paired *t* test. Data are expressed as mean $\pm$ SD. For discrete data, differences were analyzed by the chi-square statistics or Fisher's exact test between 2 groups and expressed as counts

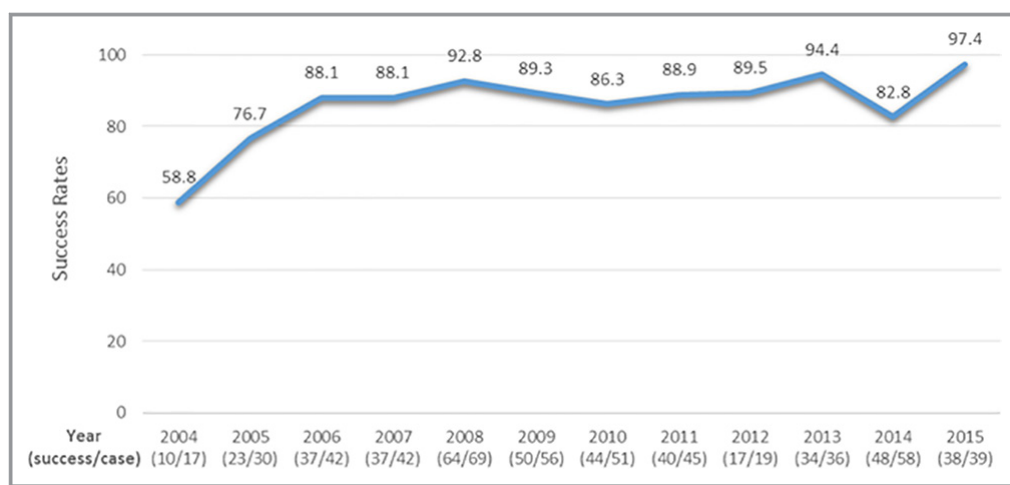


Figure 2. Annual trends in success rate of CTO PCI. CTO indicates chronic total occlusion; PCI, percutaneous coronary intervention.

and percentages. To adjust for any potential confounders, propensity score matching analysis was performed using the logistic regression model. We adjusted all available factors that have been known as confounding variables that could be of potential relevance: age; male; cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease, peripheral artery disease, chronic kidney disease, heart failure, and smoking); and angiographic and procedural characteristics (significant coronary artery lesion, CTO lesion artery, and lesion locations). The PCI group and the OMT group were matched by a 1:1 matching protocol according to propensity scores using the nearest neighbor matching algorithm, with a caliper width equal to 0.05 of the SD of the propensity score. A total of 158 well-matched pairs were generated. A variety of individual and composite clinical outcomes up to 5 years are expressed by the Kaplan–Meier curve, and statistical differences between the groups were performed with the log-rank test before and after propensity score matching. Cox hazard ratio (HR) models were used to assess the HR of the PCI group compared with the OMT group in the matched population. All statistical analyses were performed with SPSS software (version 20.0; SPSS-PC, Inc Chicago, IL). A *P* value less than 0.05 was defined as a significant difference for all statistical analysis.

Results

During the study period, a total of 512 patients were attempted CTO PCI in Korea University Guro Hospital CTO registry. Annual success procedural success rate are shown in Figure 2. Clinical and angiographic baseline characteristics are shown in Table 1. In the entire population, the OMT group was older, had lower LVEF level, and higher prevalence of heart failure than the PCI group, whereas the PCI group had

more-frequent angina symptoms (Canadian Cardiovascular Society class, $\geq$ II). The PCI and OMT groups had some differences in angiographic findings, such as multivessel disease, multivessel CTO, vessels of non-CTO lesion, CTO lesion location, and treated non-CTO lesions. After discharge, The OMT group had a higher prescription rate of nondihydropyridine calcium-channel blocker, diuretics, and nitrate, whereas lower statin rate. After PSM, the clinical and angiographic baseline characteristics were not significantly different between the 2 groups (Table 1).

Clinical outcomes up to 5 years (mean duration, 4.0 ± 1.5 year) were analyzed by the Cox proportional hazard model and estimated by the Kaplan–Meier method. Various clinical outcomes are presented in Table 2. In the entire population, the PCI group had a lower incidence of total death, cardiac death, MI, and the composite of total death or MI; however, the OMT group had a lower incidence of revascularization rates, including TLR and TVR, than the PCI group. In the PSM population, the PCI group demonstrated a lower incidence of total death and the composite of total death or MI than the OMT group, whereas the incidence of TLR and TVR was lower in the OMT group. After Cox proportional hazard model analysis, although the PCI group showed a higher hazard of target lesion (hazard ratio [HR], 2.868; *P*=0.027; 95% confidence interval [CI], 1.13–7.31) and vessel revascularization (HR=2.62; *P*=0.022; 95% CI, 1.15–5.97), it exhibited a lower incidence of the composite of total death or MI (HR, 0.263; 95% CI, 0.087–0.790; *P*=0.017; Table 2 and Figure 3).

The change of LV function after PCI was performed with the paired *t* test. Mean LVEF level in patients who underwent CTO intervention was improved from 47.8% to 51.6% (*P*<0.001) after PCI in the first 1.7 years. Especially, patients with reduced LVEF ($\leq$ 50%) showed a significant improvement

Table 1. Baseline and Angiographic Characteristics in Entire and Propensity-Matched Population

Variables, N (%)	Entire Population				Matched Population			
	PCI (n=305)	OMT (n=335)	P Value	SD	PCI (n=158)	OMT (n=158)	P Value	SD
Sex, male	230 (75.4)	242 (72.2)	0.362	0.37	117 (74.1)	113 (71.5)	0.613	0.30
Age, y	62±11	66±11	<0.01	−0.40	64±9	64±11	0.739	0.04
LV ejection fraction, %	53±11	49±12	<0.01	0.31	50±12	50±12	0.928	−0.01
Myocardial infarction	62 (20.3)	66 (19.7)	0.843	0.14	34 (21.5)	34 (21.5)	> 0.99	0.00
STEMI	23 (7.5)	24 (7.2)	0.855	0.14	11 (7.0)	16 (10.1)	0.314	−1.08
NSTEMI	39 (12.8)	41 (12.2)	0.834	0.16	23 (14.6)	18 (11.4)	0.403	0.88
Hypertension	196 (64.3)	227 (67.8)	0.350	−0.43	107 (67.7)	111 (70.3)	0.627	−0.31
Diabetes mellitus	136 (44.6)	149 (44.5)	0.977	0.02	78 (49.4)	72 (45.6)	0.499	0.55
Dyslipidemia	87 (28.5)	111 (33.1)	0.208	−0.83	51 (32.3)	49 (31.0)	0.809	0.23
Cerebrovascular disease	28 (9.2)	47 (14.0)	0.057	−1.42	21 (13.3)	17 (10.8)	0.489	0.73
Peripheral artery disease	24 (7.9)	40 (11.9)	0.086	−1.29	18 (11.4)	17 (10.8)	0.858	0.19
Chronic kidney disease	19 (6.2)	23 (6.9)	0.745	−0.25	14 (8.9)	13 (8.2)	0.841	0.22
Heart failure	35 (11.5)	57 (17.0)	0.046	−1.47	24 (15.2)	25 (15.8)	0.876	−0.16
Smoking	169 (55.4)	187 (55.8)	0.917	−0.06	79 (50.0)	94 (59.5)	0.090	−1.29
Current	115 (37.7)	124 (37.0)	0.857	0.11	61 (38.6)	57 (36.1)	0.642	0.42
CCS classification			<0.01				0.619	
I	85 (27.9)	207 (61.8)		−5.08	63 (39.9)	74 (46.8)		−1.06
II	69 (22.6)	58 (17.3)		1.19	38 (24.1)	31 (19.6)		0.95
III	70 (23.0)	35 (10.4)		3.06	28 (17.7)	25 (15.8)		0.46
IV	81 (26.6)	35 (10.4)		3.75	29 (18.4)	28 (17.7)		0.15
Serum glucose, mg/dL	139±58	130±56	0.087	0.15	143±63	131±58	0.120	0.20
A1c, %	6.6±1.3	6.6±1.3	0.558	−0.06	6.6±1.3	6.6±1.3	0.967	−0.01
Total cholesterol, mg/dL	167±43	167±41	0.922	0.01	166±43	168±45	0.725	−0.04
Triglyceride, mg/dL	147±92	137±94	0.222	0.11	136±76	138±99	0.829	−0.03
HDL-cholesterol, mg/dL	42±12	42±12	0.993	0.00	42±11	42±11	0.754	0.04
LDL-cholesterol, mg/dL	106±39	104±36	0.657	0.04	107±41	104±37	0.666	0.06
Angiographic and procedural characteristics								
PCI procedure	305 (100.0)	186 (55.5)	<0.01	5.07	158 (100.0)	103 (65.2)	<0.01	3.85
Multivessel disease	181 (59.3)	273 (81.5)	<0.01	−2.65	104 (65.8)	117 (74.1)	0.111	−0.99
No. of vessels	1.8±0.8	2.3±0.8	<0.01	−0.57	2.0±0.8	2.1±0.8	0.227	−0.14
Significant coronary lesion								
LAD	210 (68.9)	241 (71.9)	0.392	−0.37	109 (69.0)	108 (68.4)	0.903	0.08
LCX	162 (53.1)	233 (69.6)	<0.01	−2.11	94 (59.5)	97 (61.4)	0.730	−0.24
RCA	178 (58.4)	268 (80.0)	<0.01	−2.61	105 (66.5)	112 (70.9)	0.396	−0.54
LM	15 (4.9)	33 (9.9)	0.018	−1.82	10 (6.3)	16 (10.1)	0.219	−1.32
RAMUS	7 (2.3)	17 (5.1)	0.065	−1.45	4 (2.5)	9 (5.7)	0.157	−1.56
Coronary CTO lesion								
Multivessel CTO	22 (7.2)	61 (18.2)	<0.01	−3.09	14 (8.9)	13 (8.2)	0.841	0.22
No. of CTO vessels	1.1±0.3	1.2±0.4	<0.01	−0.32	1.1±0.3	1.1±0.3	0.856	0.02
LAD	119 (39.0)	90 (26.9)	0.001	2.12	52 (32.9)	49 (31)	0.717	0.34

Continued

Table 1. Continued

Variables, N (%)	Entire Population				Matched Population			
	PCI (n=305)	OMT (n=335)	P Value	SD	PCI (n=158)	OMT (n=158)	P Value	SD
LCX	85 (27.9)	107 (31.9)	0.262	−0.75	45 (28.5)	43 (27.2)	0.802	0.24
RCA	121 (39.7)	197 (58.8)	<0.01	−2.73	73 (46.2)	78 (49.4)	0.573	−0.46
RAMUS	2 (0.7)	3 (0.9)	0.731	−0.27	2 (1.3)	2 (1.3)	> 0.99	0.00
CTO location			0.029				0.190	
Proximal	152 (49.8)	183 (54.6)		−0.66	80 (50.6)	83 (52.5)		−0.27
Mid	121 (39.7)	102 (30.4)		1.56	62 (39.2)	50 (31.6)		1.28
Distal	32 (10.5)	50 (14.9)		−1.24	16 (10.1)	25 (15.8)		−1.58
Treated non-CTO lesions								
LM	22 (7.2)	32 (9.6)	0.29	−0.80	14 (8.9)	17 (10.8)	0.57	−0.61
LAD	101 (33.1)	153 (45.7)	<0.01	−2.00	64 (40.5)	60 (38)	0.64	0.40
LCx	89 (29.2)	128 (38.2)	0.02	−1.56	56 (35.4)	56 (35.4)	> 0.99	0.00
RCA	73 (23.9)	75 (22.4)	0.64	0.3217	41 (25.9)	41 (25.9)	> 0.99	0.00
Ramus	10 (3.3)	14 (4.2)	0.55	−0.47	4 (2.5)	7 (4.4)	0.36	−1.02
Failed CTO procedure	0 (0.0)	54 (16.1)	<0.01	−5.68	0 (0.0)	32 (20.3)	<0.01	−6.37
Discharge medications								
ACE inhibitors	108 (35.4)	114 (34)	0.71	0.23	50 (31.6)	54 (34.2)	0.63	−0.44
ARBs	89 (29.2)	95 (28.4)	0.82	0.15	53 (33.5)	49 (31)	0.63	0.45
Beta-blockers	146 (47.9)	169 (50.4)	0.51	−0.37	79 (50)	81 (51.3)	0.82	−0.18
CCB DHP	53 (17.4)	50 (14.9)	0.40	0.61	26 (16.5)	23 (14.6)	0.64	0.48
CCB NDHP	119 (39)	90 (26.9)	<0.01	2.12	51 (32.3)	49 (31)	0.81	0.23
Diuretics	61 (20)	96 (28.7)	0.01	−1.76	38 (24.1)	35 (22.2)	0.69	0.40
Nitrate	131 (43)	178 (53.1)	0.01	−1.47	77 (48.7)	76 (48.1)	0.91	0.09
Statin	283 (92.8)	242 (72.2)	<0.01	2.27	139 (88)	142 (89.9)	0.59	−0.20

ACE indicates angiotensin converting enzyme; ARBs, angiotensin receptor blockers; CCB, calcium-channel blocker; CTO, chronic total occlusion; DHP, dihydropyridine; LAD, left anterior descending artery; LCX; left circumflex artery; LV, left ventricular; NDHP, nondihydropyridine; NSTEMI, non-ST-segment-elevation myocardial infarction; OMT, optimal medical therapy; PCI indicates percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment-elevation myocardial infarction.

(mean LVEF from 38.9 to 44.3; $P<0.001$). However, in patients without CTO intervention, LVEF was not improved during the follow-up period (Figure 4).

We performed the subgroup analysis to evaluate the composite of total death or MI through Cox proportional hazard ratio model analysis. PCI was associated with a favorable outcome in patients with older age (>65 years; HR, 0.224; $P=0.017$; 95% CI, 0.07–0.77; $P_{\text{interaction}}$ for age=0.002), non-MI (HR, 0.286; $P=0.042$; 95% CI, 0.09–0.96; $P_{\text{interaction}}$ for MI=0.036), reduced LVEF level ($\leq 50\%$; HR, 0.0134; $P=0.013$; 95% CI, 0.03–0.66; $P_{\text{interaction}}$ for LVEF=0.048), and diabetes mellitus subgroups (HR, 0.243; $P=0.043$; 95% CI, 0.06–0.96; $P_{\text{interaction}}$ for diabetes mellitus=0.036; Figure 5).

Discussion

We utilized PSM to reduce bias for the long-term clinical outcomes and the change of LV function in patients with CTO

and well-developed collateral flow after CTO intervention as compared with CTO patients with OMT alone. The main findings of our present study were: (1) Although the CTO intervention in patients with well-developed collateral flow yielded a significantly higher hazard of repeat revascularization than OMT alone strategy, it reduced composite of as death or MI; (2) improved LV function; and (3) gave benefits in subgroups such as patients with older age (>65 years), non-MI, reduced LVEF level ($\leq 50\%$), and diabetes mellitus.

There were discrepancies in the results regarding survival rates and clinical effect after PCI of the CTO lesion. Several previous observational studies and meta-analysis regarding clinical outcomes in patients with successful CTO PCI have demonstrated its beneficial effect, such as improved survival rates and LV function, compared with failed PCI.^{1,4–6,8,15} In contrast, some observational studies suggest that successful CTO PCI is not associated with improvement of survival rates and cardiovascular events.^{16,17} Thus, these heterogeneous

Table 2. Clinical Outcomes by Cox-Proportional Hazard Ratio Model Analysis and Kaplan–Meier Estimation

	No. of Events Up To 5 Years (%)				
Outcomes	PCI Group	OMT Group	Log Rank	Hazard Ratio (95% CI)	P Value
Entire population					
Total death	5 (1.9)	28 (8.9)	<0.01	0.451 (0.147–1.381)	0.163
Cardiac death	3 (1.1)	13 (4.2)	0.025	0.502 (0.111–2.261)	0.370
Myocardial infarction	2 (0.7)	17 (5.9)	0.002	0.177 (0.034–0.913)	0.039
Revascularization	51 (19.6)	38 (13.0)	0.024	1.687 (0.985–2.889)	0.056
Target lesion (CTO vessel)	28 (10.7)	9 (3.0)	<0.01	3.942 ((1.584–9.810)	0.003
Target vessel (CTO vessel)	35 (13.3)	11 (3.7)	<0.01	4.218 (1.854–9.597)	0.001
Nontarget vessel (non-CTO vessel)	24 (9.2)	34 (11.7)	0.428	0.761 (0.394–1.470)	0.416
Stroke	3 (1.1)	5 (1.6)	0.613	0.892 (0.147–5.405)	0.901
Total MACE	55 (20.8)	65 (20.9)	0.932	1.305 (0.822–2.073)	0.258
Total death or myocardial infarction	6 (2.3)	39 (12.6)	<0.01	0.298 (0.110–0.802)	0.017
Propensity-matched population					
Total death	3 (2.0)	11 (7.9)	0.028	0.305 (0.084–1.102)	0.070
Cardiac death	2 (1.4)	5 (3.6)	0.242	0.408 (0.078–2.124)	0.287
Myocardial infarction	2 (1.4)	7 (5.6)	0.084	0.276 (0.057–1.337)	0.110
Revascularization	30 (22.0)	20 (14.9)	0.139	1.543 (0.873–2.730)	0.135
Target lesion (CTO vessel)	17 (12.5)	6 (4.3)	0.021	2.868 (1.125–7.308)	0.027
Target vessel (CTO vessel)	20 (14.5)	8 (5.8)	0.021	2.615 (1.146–5.965)	0.022
Nontarget vessel (non-CTO vessel)	14 (10.1)	19 (14.5)	0.312	0.711 (0.355–1.424)	0.337
Stroke	2 (1.5)	2 (1.3)	0.974	0.946 (0.132–6.761)	0.956
Total MACE	33 (23.8)	30 (21.3)	0.661	1.165 (0.708–1.917)	0.547
Total death or myocardial infarction	4 (2.8)	16 (11.9)	0.005	0.263 (0.087–0.790)	0.017

CI indicates confidence interval; CTO, chronic total occlusion; MACE, major adverse cardiac event; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

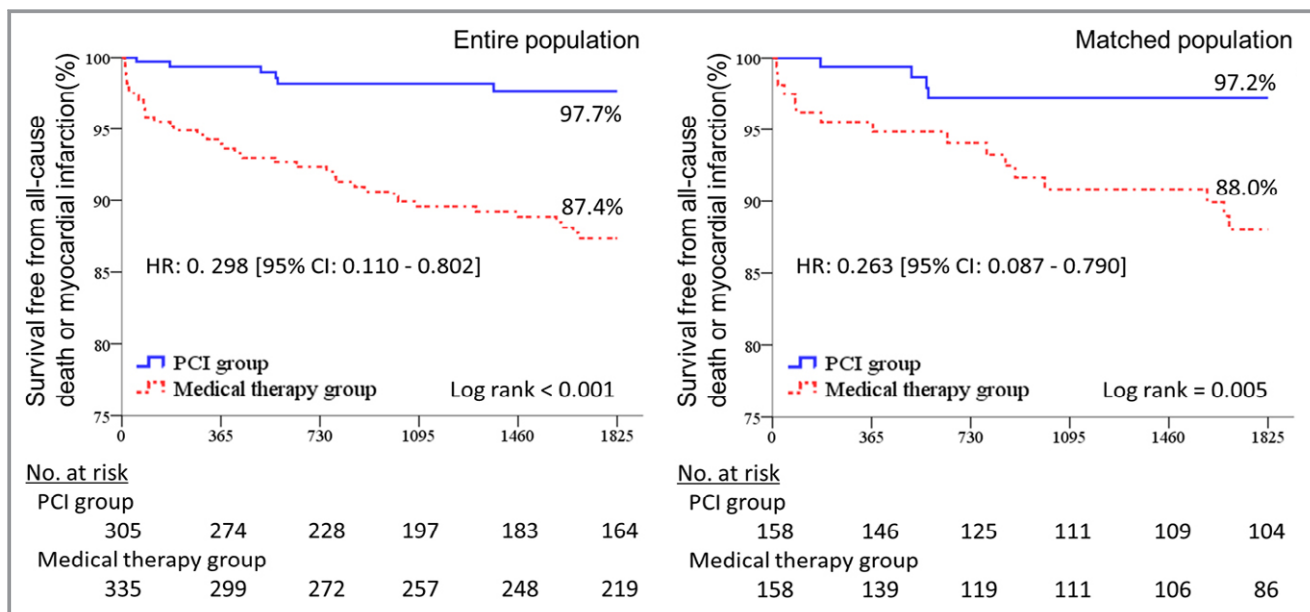


Figure 3. The composite total death and myocardial infarction free survival by Kaplan–Meier curves. CI indicates confidence interval; HR, hazard ratio; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

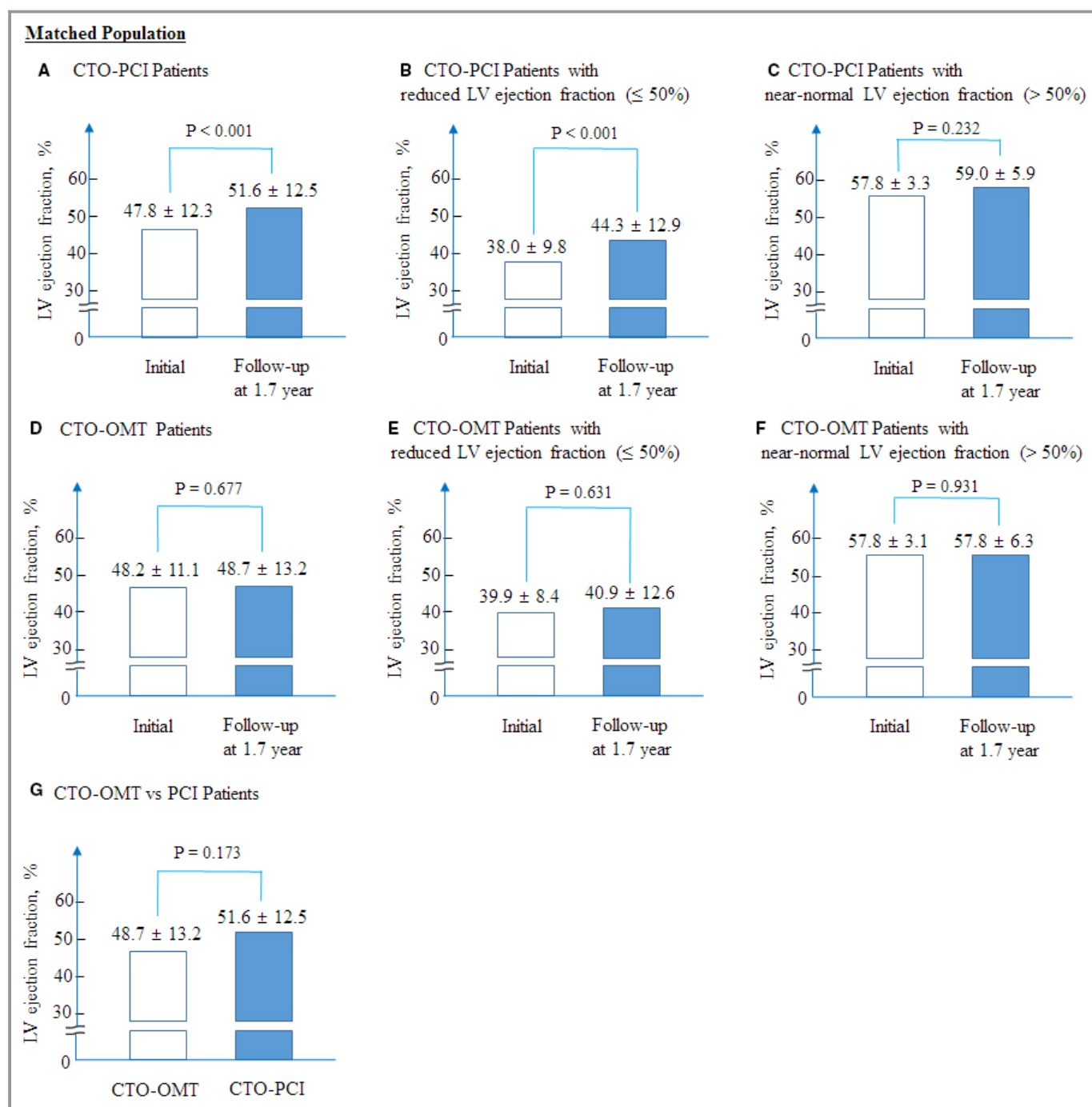


Figure 4. Changes of LVEF using paired *t* test analysis in the first 1.7 years after revascularization. A through C, Change of LVEF in CTO-PCI patients after propensity score matching; all CTO-PCI patients (A), CTO-PCI patients with reduced LVEF (≤50%, B), and CTO-PCI patients with near-normal LVEF (>50%, C). D through F, Change of LVEF in CTO-OMT patients after propensity score matching; All CTO-OMT patients (D), CTO-OMT patients with reduced LVEF (≤50%, E), and CTO-OMT patients with near-normal LVEF (>50%, F). G, Comparison for changed LVEF between CTO-OMT with CTO-PCI patients using Student *t* test. CTO indicates chronic total occlusion; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

data obscure the necessity of PCI for CTO lesion, and thus it is important to assess whether a patient can gain beneficial effects from a CTO intervention before performing PCI. Therefore, the results of our present study would be a supportive evidence for the indication of CTO intervention

when physicians have to make a decision in a real-world setting. Because our data results are originated from an all-comer-based database, it nicely reflects our real-world clinical practice and can be very meaningful, although the treatment strategies are not randomized.

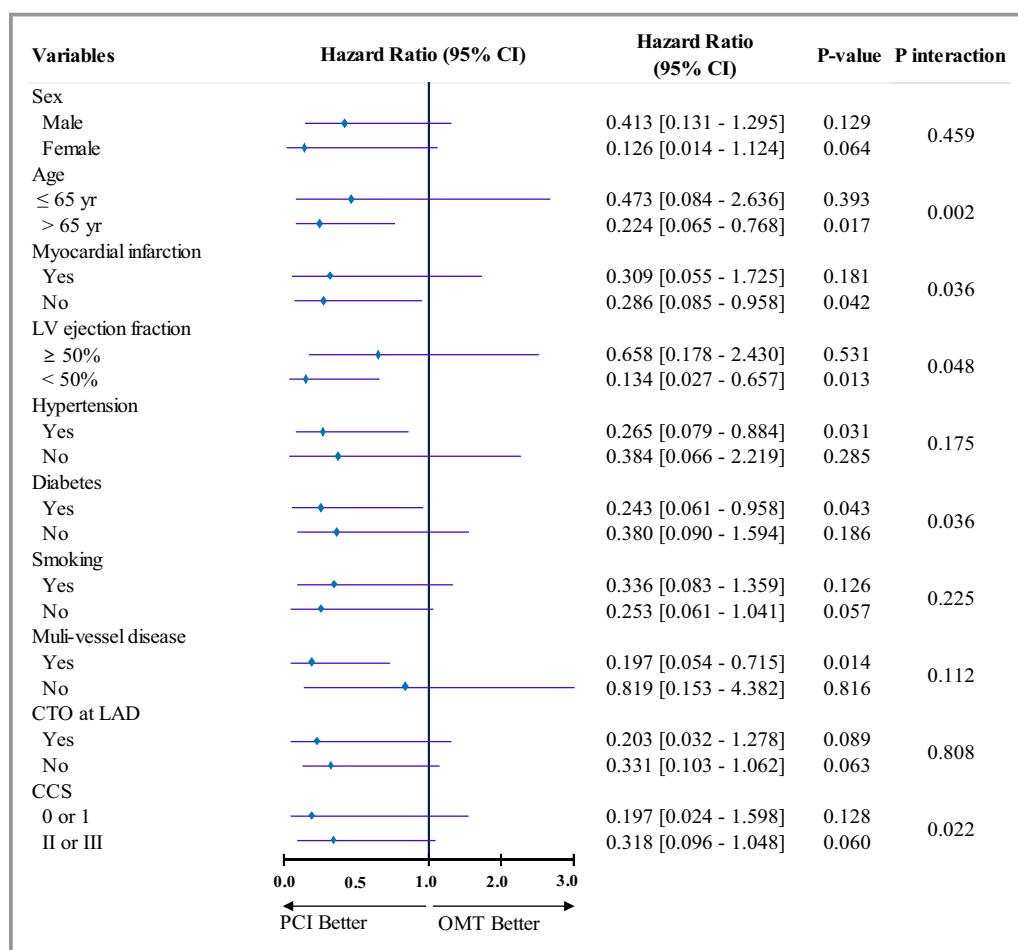


Figure 5. Subgroup analysis of the composite of total death and myocardial infarction. CCS indicates Canadian Cardiovascular Society class; CI, confidence interval; CTO, chronic total occlusion; LAD, left anterior descending artery; LV, left ventricular; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

The collateral circulation provides blood flow to the distal occluded segment and may contribute to maintaining myocardium viability against ischemic status. However, Werner et al¹⁸ reported that physiological function of CTO collaterals in patients without Q-wave MI was limited to only less than 10% of collaterals having a normal functional reserve during adenosine infusion. Furthermore, even with a well-developed collateral flow, at least one third of CTO patients had coronary steal, which is the phenomenon that decreases perfusion flow at the collateral vessel during pharmacological stress.¹⁸ Thus, the myocardium-protecting function of well-developed collateral circulation would be incomplete at rest and during exercise, and therefore it could not protect the myocardium damage thoroughly. On the other hand, these patients are expected to reap more-beneficial effects from a CTO intervention. In our study, main findings and subgroup analysis showed that revascularization by PCI of a CTO lesion reduced major clinical events, such as

the composite of total death or MI, especially in patients with diabetes mellitus. Although multivessel disease and hypertension subgroups did not show statistical significance, we assumed that these populations can affect coronary steal phenomenon. These subgroups were closely related to coronary steal phenomenon, because the multivessel disease group had a higher chance of donor artery stenosis,¹⁹ and the hypertension and diabetes mellitus groups were associated with microvascular dysfunction.^{19–21} According to the results of our study, we suggest that CTO PCI is a more-appropriate treatment strategy for CTO patients with even good collateral circulation in whom coronary steal is more likely to occur.

Previous imaging studies showed that a well-developed collateral circulation in patients with occlusive segments was associated with a predictive value for myocardial viability and indicative factor for revascularization.^{11,22} Previous meta-analysis data demonstrated that preserved myocardial

viability confirmed by imaging studies may reduce considerable risk of death in patients with coronary artery disease and severe LV dysfunction; therefore, successful revascularization further reduced the mortality rate compared with medical therapy alone.²³ In our data, restoration of blood flow through the vessel having CTO lesion improved LVEF, particularly in patients with reduced LVEF before revascularization and it might contribute to improved clinical outcomes. This speculation was confirmed by subgroup analysis that reduced LVEF and non-MI subgroups that underwent CTO PCI presented favorable outcomes compared with OMT alone. Thus, we assumed that patients without previous MI with reduced LVEF may be associated with myocardial viability. Moreover, revascularization of CTO lesion could lead to a beneficial effect of recovering LV function in patients with good collateral circulation as our study results.^{15,24}

One of major disadvantages of CTO PCI is the higher incidence of repeat revascularization at the CTO lesion or CTO vessel. Compared with non-CTO PCI, CTO PCI showed higher incidence of restenosis attributed to variety of adverse factors.²⁵ In our current study, TLR and TVR rates of the PCI group were significantly higher than those of the OMT group. However, with reference to previous studies in the drug-eluting-stent era, our data showed similar TLR and TVR rates,^{4,26} and non-target-vessel revascularization rate was not different between the 2 groups. At the time decided on CTO PCI by physicians, the OMT group was more likely to have ischemic-related lesion in non-CTO vessel and CTO vessel stability was better than that of the PCI group. Although CTO PCI increases the chances for repeat revascularization because of previous stenting in the target CTO lesion and vessel, given that it may improve LV function and long-term clinical outcomes, we carefully suggest that the successful revascularization by CTO intervention would be a more-suitable treatment strategy for CTO patients with well-developed collateral circulation compared with the OMT-alone strategy.

Our present study has some limitations. First, this study was a nonrandomized, observational study. Although we tried PSM analysis to adjust baseline confounding factors, we could not adjust factors perfectly because of underlying limitations of the study design. A prospective, randomized trial is required to clarify the effects of CTO PCI in patients with well-developed collateral circulation. Second, our registry did not have enough of a number of patients to get stronger statistical power. Many patients were not included after PSM, and we failed to determine the survival benefit after CTO PCI, probably attributed to a limited number of patients. Third, The Rentrop collateral grade system only estimates visual epicardial filling through collateral vessels and cannot evaluate functional capabilities and physiological findings. Finally, because of various clinical limitations and cost issues, we

could not perform an imaging study and functional study to assess myocardial function, viability, and presence of ischemia in most of the study subjects.

Conclusion

In conclusion, successful PCI for CTO lesions in patients with well-developed collaterals was associated reduced incidence of the composite of death or MI, improved LV function, and got benefit, especially in certain subgroups of patients compared with OMT alone despite increased incidence of repeat mechanical revascularization for target CTO segment. However, our study results appear to be hypothesis generating, and prospective, randomized trials with larger study population will be essential for further clarifying the present study's results.

Disclosures

None.

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