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CORONARY

Determinants and Prognostic Significance of Periprocedural Myocardial Injury in Patients With Successful Percutaneous Chronic Total Occlusion Interventions

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ABSTRACT

OBJECTIVES This study sought to evaluate the determinants and prognostic implications of periprocedural myocardial injury (PMI) in successful percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs).

BACKGROUND There are limited studies addressing the risk factors and clinical implication of PMI in patients undergoing CTO-PCI.

METHODS We examined 1,058 consecutive CTO patients who underwent successful drug-eluting stent implantation and serial measurements of creatine kinase-myocardial band (CK-MB) values between March 2003 and August 2014. PMI was defined as elevations of CK-MB >3 times the upper reference limit (URL).

RESULTS PMI occurred in 121 patients (11.4%). Multivariable analysis revealed that the presence of renal failure (odds ratio [OR]: 4.25; 95% confidence interval [CI]: 1.59 to 11.35; p = 0.004), attempted retrograde approach (OR: 2.27; 95% CI: 1.34 to 3.84; p = 0.002), concomitant non-target lesion intervention (OR: 1.74; 95% CI: 1.17 to 2.59; p = 0.006), and stent number (OR: 1.38; 95% CI: 1.08 to 1.77; p = 0.011) were predictors associated with PMI. During a median follow-up of 4.4 years, PMI was associated with an increased risk of mortality (adjusted hazard ratio: 1.86; 95% CI: 1.09 to 3.17; p = 0.02). These findings were also consistent when higher CK-MB cutoff was used to define PMI. Although there was a trend toward higher all-cause mortality with increasing peak CK-MB levels, in multivariable analyses, this association was statistically significant only for peak CK-MB levels of >10 times the URL.

CONCLUSIONS PMI was associated with an increased risk of long-term mortality after successful CTO-PCI. Patients with renal insufficiency, those who require more stents, multiple lesion treatment, and retrograde approach have a higher likelihood of having PMI. (J Am Coll Cardiol Intv 2016;9:2220–8) © 2016 by the American College of Cardiology Foundation.

Previous studies showed that successful recanalization of coronary artery chronic total occlusion (CTO) could provide considerable clinical benefits (1,2). Although percutaneous coronary intervention (PCI) for CTO is 1 of the most complex percutaneous procedures, the worldwide procedural success rate has recently improved after the introduction of dedicated devices and increased

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operators' clinical experience, and thereby, the threshold for performing PCI for more complex CTOs has been lowered (3,4). However, the potential for a relatively higher likelihood of undesirable procedural complications compared with non-CTO PCI is still problematic (5).

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Periprocedural myocardial injury (PMI) is one of the known complications of PCI and is observed in a considerable proportion of patients undergoing otherwise successful procedures (6,7). Given the complex nature of the procedure, the high atherosclerotic burden, and the need for multiple overlapping stents, patients undergoing PCI for CTO may be particularly susceptible to PMI. Previous studies have shown that the occurrence of PMI was associated with a higher risk of mortality and adverse cardiac events in unselected populations or in patients with acute coronary syndrome who underwent PCI (6–13). However, the clinical implications of PMI in patients undergoing CTO-PCI have not yet been systematically evaluated (14). Therefore, in our study, we attempted to evaluate: 1) the determinants of PMI during CTO-PCI; and 2) the long-term prognostic implication of PMI in patients who received successful drug-eluting stent (DES) implantation for coronary CTOs.

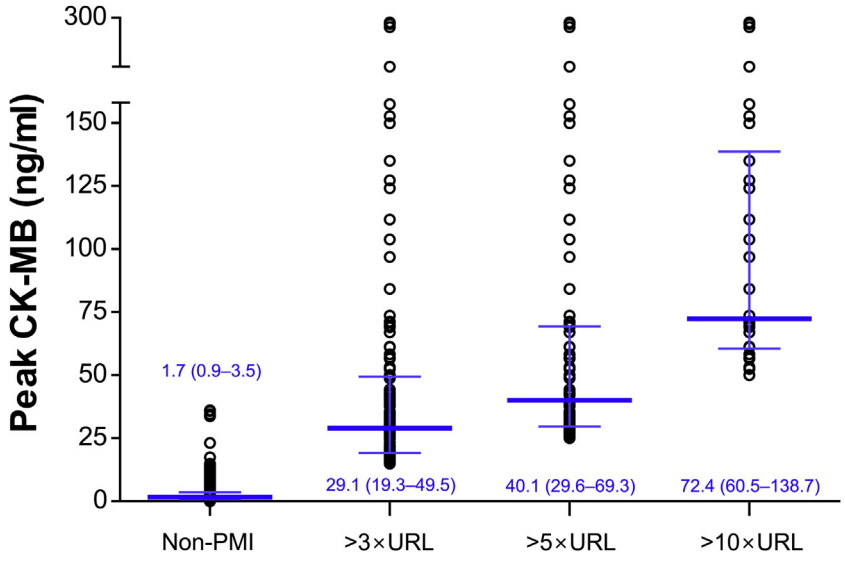
METHODS

STUDY POPULATION. The CTO registry database, which involves prospective recruitment of consecutive patients undergoing attempted PCI for CTO at the Asan Medical Center in Seoul, South Korea, was used for the current retrospective analysis. All patients who underwent successful PCI for at least 1 CTO lesion between March 2003 and June 2014 were included in this study. Because DES represents the standard device for CTO-PCI over the study period, patients who received bare-metal stent were excluded from analyses. A CTO was defined as a coronary artery obstruction with Thrombolysis In Myocardial Infarction flow grade 0 determined on angiography and which was estimated to be of at least 3 months' duration on the basis of the patient's clinical history (i.e., demonstrated with the last episode of myocardial infarction in the same target vessel territory or the gap between diagnoses made based on the previous angiogram) (15,16). If there was no definite evidence allowing estimating of the occlusion duration, at least 2, clinically experienced, interventional cardiologists made the diagnosis of CTO based on the angiographic morphology (i.e., the degree of

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CK-MB = creatine kinase-myocardial band
CTO = chronic total occlusion
DES = drug-eluting stent(s)
HR = hazard ratio
IQR = interquartile range
PCI = percutaneous coronary intervention
PMI = periprocedural myocardial injury
URL = upper reference limit

FIGURE 1 Distribution of the Peak CK-MB Values After CTO-PCI



The non-periprocedural myocardial injury (PMI) group refers to the study patients who did not meet the criteria for the PMI definition. **Blue lines** and **numbers** represent the median and interquartile range of each category. CK-MB = creatine kinase-myocardial band; CTO = chronic total occlusion; PCI = percutaneous coronary intervention; URL = upper reference limit.

TABLE 1 Demographics and Clinical Characteristics

	All Patients (N = 1,058)	PMI (n = 121)	Non-PMI (n = 937)	p Value
Age, yrs	59.5 ± 10.5	60.7 ± 10.7	59.3 ± 10.5	0.16
Male	873 (82.5)	98 (81.0)	775 (82.7)	0.73
Body mass index, kg/m^2	25.5 ± 3.1	25.3 ± 2.6	25.5 ± 3.2	0.35
Hypertension	637 (60.2)	80 (66.1)	557 (59.4)	0.19
Diabetes	322 (30.4)	35 (28.9)	287 (30.6)	0.78
Diabetes using insulin	50 (4.7)	7 (5.8)	43 (4.6)	0.50
Hypercholesterolemia	686 (64.8)	77 (63.6)	609 (65.0)	0.85
Current smoker	273 (25.8)	31 (25.6)	242 (25.8)	1.00
Prior PCI	270 (25.5)	33 (27.3)	237 (25.3)	0.72
Prior CABG	31 (2.9)	6 (5.0)	25 (2.7)	0.16
History of MI	105 (9.9)	13 (10.7)	92 (9.8)	0.87
History of heart failure	105 (9.9)	13 (10.7)	92 (9.8)	0.87
History of stroke	66 (6.2)	15 (12.4)	51 (5.4)	0.008
Peripheral vascular disease	20 (1.9)	4 (3.3)	16 (1.7)	0.27
Chronic lung disease	26 (2.5)	5 (4.1)	21 (2.2)	0.21
Renal dysfunction*	20 (1.9)	7 (5.8)	13 (1.4)	0.005
Clinical diagnosis				<0.001
Stable angina	787 (74.4)	73 (60.3)	714 (76.2)	
NSTE-ACS	271 (25.6)	48 (39.7)	223 (23.8)	
Atrial fibrillation	19 (1.8)	3 (2.5)	16 (1.7)	0.47
Left ventricular ejection fraction, %	57.8 ± 8.3	57.6 ± 8.7	57.9 ± 8.2	0.76
Antiplatelet therapy at discharge				
Aspirin	1,057 (99.9)	121 (100)	936 (99.9)	1.00
Clopidogrel	1,053 (99.5)	120 (99.2)	933 (99.6)	0.46
Cilostazol	273 (25.8)	31 (25.6)	242 (25.8)	1.00

Value are mean ± SD or n (%). *Renal dysfunction was defined as serum creatinine ≥2.0 mg/dl or dialysis.

CABG = coronary artery bypass grafting; EF = ejection fraction; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PMI = periprocedural myocardial injury.

calcification, bridging collaterals, nontapered stump, or angiographic filling from collaterals) (1).

PROCEDURE AND CLINICAL DATA. The revascularization procedure and the DES implantation were performed in a standard manner. The use of specialized devices or techniques and the choice of the type of DES were left to the operator's discretion. All patients received aspirin (a loading dose of 200 mg followed by 100 or 200 mg/day indefinitely) and clopidogrel (a loading dose of 300 or 600 mg, followed by 75 mg/day for at least 12 months). Further use of cilostazol after the procedure was left to the discretion of the attending physician. Restoration of TIMI flow grade 3 with residual stenosis <30%, as determined on visual assessment, was achieved in all stented lesions.

The clinical, laboratory, and outcome data were determined by careful analysis of the medical records of all patients performed by independent research personnel. The CTO length and lesion length of the target vessel were determined by analyses of digital angiograms using an automated edge detection system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). To ensure accurate assessment of the clinical end points, additional follow-up information was obtained during visits or telephone contacts with living patients or family members and from medical records obtained from other hospitals, as necessary. The cause and date of a patient's death were confirmed by information from the National Population Registry of the Korea National Statistical Office using a unique personal identification number for each patient.

DEFINITIONS AND STUDY ENDPOINT. The absolute levels of creatine kinase-myocardial band (CK-MB) isoenzyme were measured by sandwich immunoassay (Bayer Corporation, Tarrytown, New York) normal range <5 ng/ml at the baseline (1 to 3 h before PCI) and at 6 h after the PCI. In cases of CK-MB value elevation or chest pain, further remeasurement was performed at 12 h after PCI. These measurements of CK-MB levels are performed in all patients undergoing elective PCI according to the standard policy of our medical institution and are maintained by specific order sets since 2002. Additional measurements were optionally performed at the discretion of the attending physician, and the peak CK-MB value could be determined in all study cases. Cardiac troponin measurements were not mandatory for our study. PMI was defined as elevations of CK-MB >3 times the upper reference limit (URL) in cases of normal baseline CK-MB values. If the baseline CK-MB value was elevated, a CK-MB increase >3 times the URL as well as a rise of CK-MB >20% relative to the baseline was required with documentation that the values were decreasing or at nadir before PCI. Renal dysfunction was defined as a baseline serum creatinine ≥2.0 mg/dl or a need for dialysis.

The primary study endpoint was patient death during the follow-up duration, and death was defined as death due to any cause. Deaths were considered cardiac related unless an unequivocal, noncardiac cause was established. All events were adjudicated by an independent group of clinicians.

STATISTICAL ANALYSIS. Continuous variables are summarized as mean ± SD or median (interquartile range [IQR]) and categorical variables as numbers with percentages. Continuous variables were compared using the Student *t* test or the Wilcoxon rank sum test and categorical variables using chi-square statistics or Fisher exact test, as appropriate. The cumulative probability and survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Multivariable logistic regression analysis was conducted to identify the predictors of PMI. The following candidate predictors were selected based on clinical importance and special interest associated with CTO-PCI: patient age

(per-year increment), gender, presence of diabetes mellitus, presence of renal dysfunction, clinical diagnosis of acute coronary syndrome, concomitant non-target lesion intervention, collateral grade, attempted retrograde approach, total stent number, total stent length, and use of double coronary injection. To identify the predictors of long-term mortality and examine the clinical impact of PMI on it, we performed Cox proportional hazards regression analysis. Candidate predictors were patient age (per-year increment), presence of diabetes mellitus (with or without insulin), presence of renal dysfunction, history of heart failure, clinical diagnosis of acute coronary syndrome, left ventricular ejection fraction (per 5% decrement), CTO located in the left anterior descending artery, and the occurrence of PMI. Missing data of pre-PCI left ventricular ejection fraction (36 cases) were imputed using single imputation with a Markov chain Monte Carlo approach. The final models were determined by backward stepwise elimination procedures in which the least significant variables were discarded 1 by 1 from the full model. The proportional hazards assumption was confirmed by examination of log (-log [survival]) curves and partial (Schoenfeld) residuals. All data analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina) software. A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS. Among the 4,518 patients with at least 1 CTO identified during the study period, 1,816 patients were referred for

TABLE 2 Lesion and Procedural Characteristics

	All Patients (N = 1,058)	PMI (n = 121)	Non-PMI (n = 937)	p Value
Multivessel disease	576 (54.4)	85 (70.2)	491 (52.4)	<0.001
Left main disease	43 (4.1)	7 (5.8)	36 (3.8)	0.320
Multiple CTOs	82 (7.8)	12 (9.9)	70 (7.5)	0.440
Restenotic CTO*	68 (6.3)	6 (4.9)	62 (6.5)	0.690
CTO location*				0.230
Left anterior descending artery	482 (44.8)	48 (39.3)	434 (45.5)	
Left circumflex artery	151 (14.0)	16 (13.1)	135 (14.2)	
Right coronary artery	439 (40.8)	57 (46.7)	382 (40.0)	
Left main	2 (0.2)	0 (0.0)	2 (0.2)	
Saphenous vein graft	2 (0.2)	1 (0.8)	1 (0.1)	
Collateral flow, Rentrop scale*				0.820
0/1	226 (21.0)	27 (22.1)	199 (20.9)	
2	407 (37.8)	48 (39.3)	359 (37.6)	
3	443 (41.2)	47 (38.5)	396 (41.5)	
CTO length, mm*	13.8 ± 9.2	16.7 ± 11.7	13.5 ± 8.7	0.005
Lesion length, mm*	39.4 ± 19.4	45.0 ± 22.3	38.7 ± 18.9	0.005
Stent type*				0.870
First-generation DES	491 (45.6)	57 (46.7)	434 (45.5)	
Second-generation DES	585 (54.4)	65 (53.3)	520 (54.5)	
Number of stents*	1.78 ± 0.78	1.98 ± 0.87	1.76 ± 0.76	0.003
Length of stent, mm*	50.7 ± 23.3	55.9 ± 25.3	50.1 ± 23.0	0.009
Average stent diameter, mm*	3.15 ± 0.33	3.17 ± 0.28	3.14 ± 0.33	0.340
Retrograde attempt*	124 (11.5)	26 (20.5)	99 (10.4)	0.002
Retrograde success*	93 (8.6)	21 (17.2)	72 (7.5)	0.001
Double coronary injection*	362 (33.6)	44 (36.1)	318 (33.3)	0.620
Intravascular ultrasound use*	948 (88.1)	106 (86.9)	842 (88.3)	0.770
Contrast volume, ml	400 (300-520)	460 (310-655)	400 (300-510)	0.002
Fluoroscopy time, min	33 (19-53)	56 (27-89)	31 (19-49)	<0.001
Non-target lesion intervention	358 (33.8)	54 (44.6)	304 (32.4)	0.010

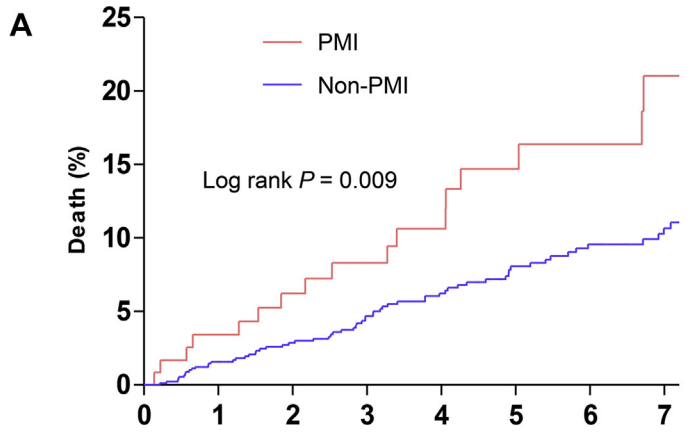
Values are n (%), mean ± SD, or median (interquartile range). *Values apply to 1,076 chronic total occlusion (CTO) lesions (122 vs. 954) in which successful percutaneous coronary intervention was performed.
DES = drug-eluting stent(s); PMI = periprocedural myocardial injury.

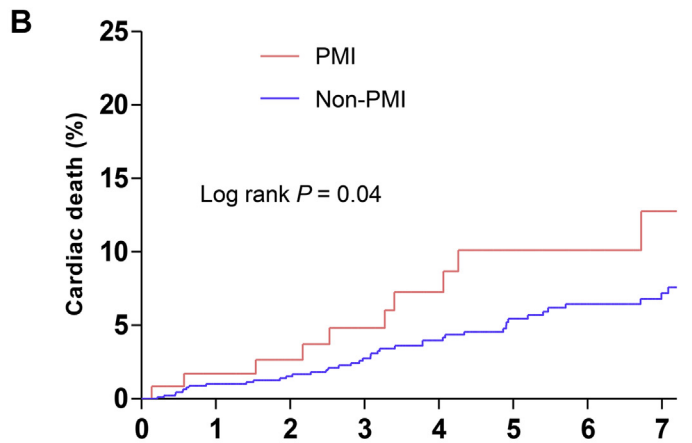
TABLE 3 Predictors of Periprocedural Myocardial Injury

	Univariate	p Value	Multivariate*	p Value
Age (per-year increment)	1.013 (0.995-1.032)	0.160	NA	
Female	1.123 (0.692-1.823)	0.640	NA	
Diabetes mellitus	0.922 (0.608-1.398)	0.700	NA	
Renal dysfunction*	4.364 (1.706-11.164)	0.002	4.251 (1.592-11.348)	0.004
Clinical presentation of ACS†	2.105 (1.420-3.122)	<0.001	2.181 (1.447-3.286)	<0.001
Collateral flow (per 1 Rentrop scale)	0.927 (0.724-1.188)	0.550	NA	
Double coronary injection	1.115 (0.750-1.657)	0.590	NA	
Stent length of the target vessel (per 1-mm increment)	1.010 (1.002-1.018)	0.011	NA	
Stent number of the target vessel	1.409 (1.117-1.777)	0.004	1.379 (1.075-1.769)	0.011
Retrograde attempt	2.229 (1.370-3.629)	0.001	2.267 (1.338-3.840)	0.002
Non-target lesion intervention	1.678 (1.144-2.463)	0.008	1.741 (1.171-2.587)	0.006

Values are odds ratio (95% confidence interval). *Renal dysfunction was defined as serum creatinine ≥2.0 mg/dl or dialysis. †Hazard ratios are for patients with clinical presentation of acute coronary syndrome (ACS), compared with those with stable angina.
CTO = chronic total occlusion; NA = not applicable.

FIGURE 2 Incidence of Death or Cardiac Death In Patients With and Without PMI





(A) The cumulative incidence of death during a median of 4.4 years was higher among patients who had PMI after CTO-PCI than in those who did not. **(B)** Cumulative incidence of cardiac death. Abbreviations as in Figure 1.

coronary artery bypass grafting, 1,253 underwent PCI, and 1,449 received medical treatment alone as an initial therapy. The overall initial success rate of CTO-PCI was 86.1% during the study period. Excluding patients who received bare-metal stent implantation or failed PCI (n = 173), a total of 1,058 consecutive patients successfully underwent DES implantation in 1,076 CTO lesions and were included in the present analysis. The cohort comprised 873 (82.5%) men with a mean age of 60 years. Stable angina was the clinical presentation in the majority of the patients, whereas CTO was discovered incidentally and recanalized in 25.6% of patients who presented with acute coronary syndrome. The left anterior descending artery was the most frequently targeted vessel. A retrograde approach was attempted in 124 (11.5%) CTO lesions and succeeded in 75% (92 of 124) of cases. Concomitant, non-target lesion PCI (either CTO or non-CTO) was performed in 33.8% of the patients. In 88.1% of the CTO lesions, stent implantation was guided by intravascular ultrasound.

DETERMINANTS OF PMI. PMI occurred in 121 patients (11.4%) during PCI for 122 CTOs. The median baseline and peak CK-MB levels were 1.1 ng/ml (IQR: 0.7 to 1.8 ng/ml) and 29.1 ng/ml (IQR: 19.3 to 49.5 ng/ml), respectively (Figure 1). Of the 1,058 study patients, 48 had elevated baseline CK-MB (>5 ng/ml): 15 of these 48 patients had peak post-PCI CK-MB >3 times the URL and 8 patients finally met the definition criteria and were categorized as having PMI. Among patients with PMI, peak CK-MB values of 3 to 5 times the URL, 5 to 10 times the URL, and >10 times the URL were reported in 44 (36.4%), 47 (38.8%), and 30 (24.8%) patients, respectively. New Q waves developed in 9 patients (0.9%) after PCI. Baseline characteristics of the study patients according to the occurrence of PMI are shown in Table 1. Compared with the patients without PMI, those with PMI had a higher prevalence of renal dysfunction, history of stroke, and clinical presentation of recent acute coronary syndrome. Detailed data regarding the angiographic and procedural characteristics in the groups are listed in Table 2. The CTO length and the total lesion length incorporating CTO were significantly longer in the PMI group. Accordingly, patients with PMI received longer stent implantation with the use of a greater number of stents. Furthermore, those patients had more frequent multivessel disease and underwent more concomitant PCIs for nontarget lesions. Technically, a retrograde approach was more often used to treat CTOs in patients with PMI. Multivariable analysis revealed that the presence of renal failure, clinical presentation of acute coronary syndrome, attempt of retrograde approach, concomitant nontarget lesion intervention, and stent number were key predictors associated with PMI (Table 3).

PMI AND CLINICAL OUTCOMES. The median follow-up time was 4.4 (IQR: 2.1 to 7.0) years. During follow-up, death occurred in 89 (8.4%) patients, of whom 59 died of a cardiac cause. Thirteen patients suffered a Q-wave myocardial infarction and 8 suffered a stroke. Any repeat revascularization was performed in

74 patients, of whom 45 underwent target vessel revascularization. Seven patients underwent coronary artery bypass graft surgery. Definite or probable stent thrombosis occurred in 11 patients.

The Kaplan-Meier curves for the clinical endpoints are shown in **Figure 2**. Patients with PMI during CTO-PCI had a significantly higher unadjusted rate of mortality (hazard ratio [HR]: 1.96; 95% confidence interval [CI]: 1.17 to 3.28; p = 0.01) and cardiac mortality (HR: 1.92; 95% CI: 1.02 to 3.63; p = 0.04) compared to those who did not. Similar tendencies were found regarding a higher incidence of mortality when patients were categorized by peak CK-MB cut-off values of 5 times the URL (HR: 1.77; 95% CI: 0.95 to 3.31; p = 0.07) and 10 times the URL (HR: 2.36; 95% CI: 1.02 to 5.46; p = 0.04). The univariate predictors of cumulative death are shown in **Table 4**. All factors associated with death in our patient cohort were clinical factors except for PMI, which was related to the complications regarding CTO-PCI. In adjusted analyses using a Cox proportional hazards model (**Figure 3**, Online Table 1), PMI continued to be associated with an increased risk of mortality (HR: 1.86; 95% CI: 1.09 to 3.17; p = 0.02).

The relationship between intermediate levels of CK-MB elevation and mortality is shown in **Figure 4**. During follow-up, 55, 15, 6, 7, and 6 patients died in the group with peak CK-MB levels of <1 times the URL, 1 to 3 times the URL, 3 to 5 times the URL, 5 to 10 times the URL, and >10 times the URL, respectively. Overall, there was a trend toward increased rate of cumulative death with higher peak CK-MB ratios (Online Table 2). However, the association between peak CK-MB and increased mortality was statistically significant only for peak CK-MB levels of >10 times the URL.

PROCEDURE-RELATED MYOCARDIAL INJURY AFTER FAILED CTO-PCI. The incidence of PMI based on the definition of CK-MB elevations >3 times and >5 times URL in our 173 failed CTO-PCI cohort were 15.6% and 14.5%, respectively. During a median follow-up of 4.6 years, patients with PMI during failed CTO-PCI showed a numerically higher cumulative rate of mortality (for CK-MB >3 times URL, HR: 2.13; 95% CI: 0.68 to 6.68; p = 0.19; for CK-MB >5 times URL, HR: 1.69; 95% CI: 0.48 to 5.99; p = 0.41) but failed to reach statistical significance.

DISCUSSION

In this study, we demonstrated that PMI was determined by clinical and procedural factors including renal dysfunction, clinical presentation of acute coronary syndrome, the number of stents used, attempted retrograde approach, and concomitant, non-target lesion intervention. PMI was also associated with an increased risk of long-term mortality even in patients who underwent successful CTO-PCI. These findings might be helpful when planning a treatment strategy for patients with complex coronary artery disease including CTO.

The underlying pathophysiological mechanisms of periprocedural myonecrosis during PCI have been previously investigated and are known to be multifactorial (17). However, there are limited studies addressing the risk factors predisposing patients to PMI during CTO-PCI: particularly in those undergoing successful PCI. The results of our analysis

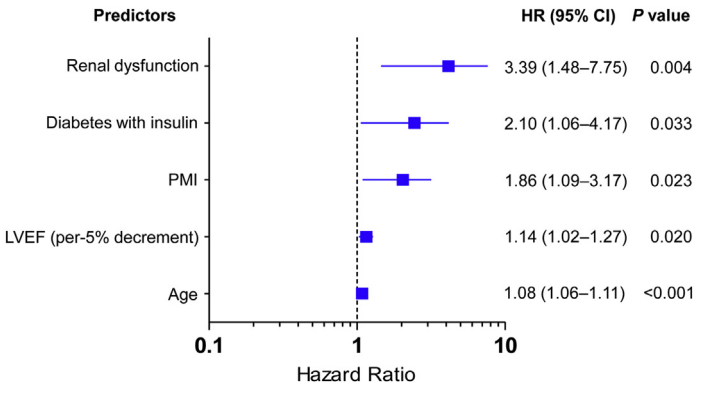
TABLE 4 Univariate Predictors of Cumulative Death

	Incidence of Death		Hazard Ratio (95% CI)	p Value
	Variable Present	Variable Absent		
Categorical variables				
Diabetes	39/322 (12.1)	50/736 (6.8)	1.837 (1.208–2.794)	0.004
Diabetes using insulin	10/50 (20.0)	79/1,008 (7.8)	3.062 (1.574–5.960)	0.001
Renal dysfunction*	7/20 (35.0)	82/1,038 (7.9)	6.610 (3.044–14.352)	<0.001
History of heart failure	18/105 (17.1)	71/953 (7.5)	2.482 (1.478–4.169)	0.001
Clinical presentation of ACS†	31/271 (11.4)	58/787 (7.4)	1.397 (0.903–2.163)	0.130
CTO located in left anterior descending artery	41/476 (8.6)	48/582 (8.2)	1.009 (0.663–1.536)	0.970
PMI	19/121 (15.7)	70/937 (7.5)	1.960 (1.172–3.279)	0.010
Continuous variables				
Age (per-year increment)	66.7 ± 10.5	58.8 ± 10.3	1.089 (1.064–1.115)	<0.001
LVEF (per 5% decrement)	55.0 ± 10.0	58.1 ± 8.1	1.198 (1.073–1.337)	0.001

Values are n/N (%) or mean ± SD. *Renal dysfunction was defined as serum creatinine ≥2.0 mg/dl or dialysis. †Hazard ratio is for patients with clinical presentation of acute coronary syndrome (ACS), compared with those with stable angina.

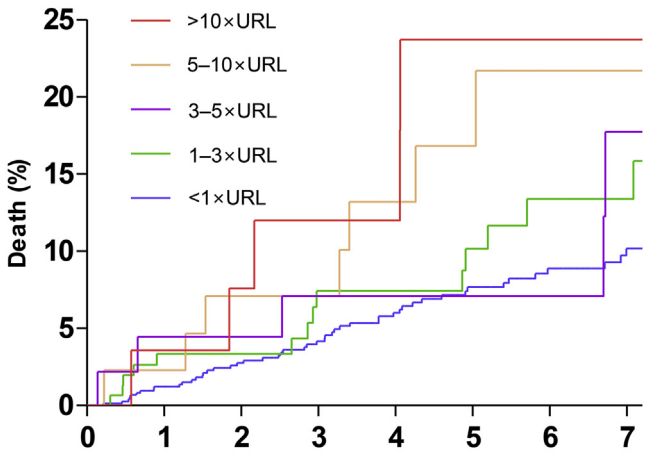
CI = confidence interval; CTO = chronic total occlusion; LVEF = left ventricular ejection fraction; PMI = periprocedural myocardial infarction.

FIGURE 3 Adjusted HRs for Independent Predictors of Cumulative Death



CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; PMI = periprocedural myocardial injury.

FIGURE 4 Incidence of Death According to Intermediate Levels of Peak CK-MB Values



No. of patients at risk				
>10×URL	30	23	16	12
5–10×URL	47	39	28	23
3–5×URL	44	34	26	13
1–3×URL	159	112	80	46
<1×URL	778	600	425	279

Abbreviations as in Figure 1.

are consistent with those of non-CTO PCI studies (11,17-19) in that the procedure-related and clinical risk factors, such as the number of stents used, treatment of multiple lesions, and renal dysfunction, were independently associated with PMI during CTO-PCI. CTOs constitute the most advanced form of atherosclerotic disease and are frequently accompanied by diffuse, long segment lesions and site calcifications. Therefore, reopening a CTO commonly requires multiple, overlapping stent deployment with high-pressure balloon inflation to achieve a satisfactory angiographic result. Moreover, nontarget lesions (i.e., CTO or non-CTO lesions) are often concomitantly treated with target CTOs and all of these factors can lead to side branch compromise or distal embolization and subsequent PMI. Renal dysfunction is associated with negative plaque characteristics, heightened states of arterial inflammation, and antiplatelet resistance, which may have a critical role in the development and perpetuation of coronary microvascular obstruction following PCI (20,21). In particular, in line with previous reports, the use of a retrograde technique was revealed as a key predictor of PMI in our study (3,14). Although the introduction of this unique technique has improved success rates for more complex CTO lesions, it may potentially cause unexpected complications such as dissection or perforation of collateral arteries during device delivery or channel dilation. Also, placing microcatheters or balloons in small collateral vessels for a considerable amount of time may result in myocardial injury along the index territory (22,23). Taken together, our analysis indicates that a more complex procedure entails a greater risk of PMI, which is among the most common but unrecognized complications of CTO-PCI (24). This observation can also explain the higher frequency of PMI in our study cohort (11.4%) compared to what is generally seen in non-CTO PCI procedures (~7%) (17).

The prognostic relevance of PMI after CTO-PCI has been studied less often. To date the only published study was conducted by Lo et al. (14) in which evaluation of serial cardiac biomarkers was routinely performed in all 325 study patients to assess the clinical implications of PMI. Although this study demonstrated a numerically higher incidence of major adverse events among patients who developed PMI, the small numbers of their study population (28 PMI patients) and the clinical events precluded further statistical analysis to draw any definite conclusion. Furthermore, patients who underwent failed PCI were included in their analysis. Because failed CTO-PCI itself has significant influence on the frequency of major complications and short- or long-term mortality (24,25), it would act as an important confounder in analyses of the association between PMI and patient mortality. Our study aimed to evaluate the prognostic relevance of PMI in a patient population that underwent successful CTO-PCI, which would be of greater clinical interest. In our study, along with well-known clinical factors, PMI was an independent predictor of the long-term risk of mortality. These findings were also consistent when higher CK-MB cutoff (>5 or >10 times URL) were used to define PMI. Our results are similar to those of previous, non-CTO PCI studies using the same CK-MB criteria (9-12,26,27) and they may not be surprising as theoretically, the prognostic value of PMI would depend on the presence and severity of irreversible myocardial injury. Accordingly, the correlation between periprocedural biomarker release and irreversible myocardial damage has been validated based on several studies using contrast-enhanced magnetic resonance imaging (28,29). However, in reality, the majority of patients with PMI do not develop symptoms and are not accompanied by electrocardiographic or echocardiographic changes suggesting relatively limited areas of affected myocardium (14). Therefore, whether PMI is a direct cause of mortality or it functions as a simple marker of an

atherosclerotic burden and the procedural complexity is uncertain, which is also evidenced by no relationship of CK-MB elevation 3 to 5 times the URL subgroup with mortality and somewhat weaker relationship of PMI to subsequent mortality in failed CTO-PCI procedure compared with successful ones in our cohort. The mechanism linking PMI and patient mortality should be determined by further dedicated investigations (17,19). So far, from the clinical point of view, given the adverse prognostic implications, it will be important to develop treatment strategies to prevent PMI, such as careful selection of candidates for CTO-PCI and providing alternative treatments for those in whom complex procedures are expected.

STUDY LIMITATIONS. Our study has limitations inherent to its retrospective and observational design. Although statistical adjustments for confounding factors were performed, hidden confounders or a selection bias cannot be eliminated. Second, as detailed angiographic data was not entered in the registry, the exact angiographic mechanisms of PMI could not be assessed. Third, the relatively small sample size of patients with failed CTO-PCI and intermediate levels of peak CK-MB leads to the possibility of a lack of sufficient statistical power. PMI in the setting of failed CTO-PCI procedure may have different determinants and prognostic significance, which needs further investigation. Fourth, the 1% stent thrombosis rate at 4 years is lower than expected in this complex cohort. The high rate of intravascular ultrasound use may have contributed to avoiding stent underexpansion, contributing to this low rate of stent thrombosis. However, we cannot exclude under-reporting of events as a possible cause. In addition, reocclusion after CTO-PCI may be clinically silent. Follow-up angiography in ~50% of patients demonstrated reocclusion in 31 cases, 14 of which were asymptomatic. Finally, as we did not have complete information regarding the serial cardiac troponin values, comparison of the level of 2 biomarkers and its prognostic implication was not feasible. Although cardiac troponin is the preferred biomarker for myocardial necrosis, there is less clinical experience using this biomarker and its oversensitivity for discriminating the prognostic impact has been suggested (30). Given the large burden of clinical evidence using CK-MB as an indicator of PMI, we believe that our study will be of clinical value.

CONCLUSIONS

In patients undergoing CTO-PCI, those who require a greater number of stents, multiple lesion treatment, and a retrograde approach have a higher likelihood of having PMI. From a clinical perspective, PMI was associated with an increased risk of long-term mortality after successful CTO-PCI. This finding may have important implications for therapeutic decision making for patients with CTO, and should be confirmed through further large-scale clinical investigations.

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PERSPECTIVES

WHAT IS KNOWN? Given the complex nature of the procedure, patients undergoing PCI for CTO may be particularly susceptible to PMI. However, the risk factors predisposing patients to PMI during successful CTO-PCI and the clinical implications of PMI in this situation have not yet been systematically evaluated.

WHAT IS NEW? In patients undergoing successful PCI for CTO, those with renal insufficiency and who require a greater number of stents, multiple lesion treatment and a retrograde approach entail a greater risk of PMI, which is associated with an increased risk of long-term mortality.

WHAT IS NEXT? The mechanism linking PMI and patient mortality should be determined by further investigations. It will be also important to define optimal strategies to prevent PMI for those in whom complex procedures are expected.

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KEY WORDS chronic total occlusion, drug-eluting stent, periprocedural myocardial injury, prognosis, retrograde

APPENDIX For supplemental tables, please see the online version of this article.