AsiaIntervention 2017;3:81-89

Clinical impact of revascularisation of chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation acute myocardial infarction undergoing primary percutaneous coronary intervention (from the CREDO-Kyoto AMI registry)

Hiroki Watanabe[1], MD; Takeshi Morimoto[2], MD; Hiroki Shiomi[1], MD; Erika Yamamoto[1], MD; Naritatsu Saito[1], MD; Yutaka Furukawa[3], MD; Yoshihisa Nakagawa[4], MD; Kenji Ando[5], MD; Kazushige Kadota[6], MD; Takeshi Kimura[1]*, MD; on behalf of the CREDO-Kyoto AMI investigators

1. Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 2. Division of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya City, Hyogo, Japan; 3. Division of Cardiology, Kobe City Medical Center General Hospital, Kobe City, Hyogo, Japan; 4. Division of Cardiology, Tenri Hospital, Tenri City, Nara, Japan; 5. Division of Cardiology, Kokura Memorial Hospital, Kitakyushu City, Fukuoka, Japan; 6. Division of Cardiology, Kurashiki Central Hospital, Kurashiki City, Okayama, Japan

KEYWORDS

- chronic coronary total occlusion
- multiple vessel disease
- ST-elevation myocardial infarction

Abstract

Aims: This study aimed to investigate the clinical effect of percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) in a non-infarct-related artery (IRA) on long-term cardiovascular outcomes in ST-elevation myocardial infarction (STEMI) patients.

Methods and results: The study population consisted of 134 STEMI patients undergoing primary PCI who received PCI for CTO in a non-IRA in the CREDO-Kyoto AMI registry. The patients were divided into two groups: 83 patients who underwent successful CTO-PCI (success group) and 51 patients who underwent failed CTO-PCI (failure group). We performed a landmark analysis set at 90 days to compare clinical outcomes in the groups. The cumulative five-year incidence of all-cause death was not significantly lower in the success group than in the failure group (19.8% vs. 15.4%, log-rank p=0.65). Similarly, the adjusted risk for all-cause death was not statistically different between the groups (adjusted hazard ratio: 1.64, 95% confidence interval: 0.63-5.05, p=0.32). No significant difference was observed between the groups in the cumulative incidence of cardiac death, non-cardiac death, myocardial infarction, heart failure hospitalisation, and any coronary revascularisation.

Conclusions: Successful PCI of CTO in non-IRA was not associated with improved five-year mortality in STEMI patients. Further larger studies are warranted to confirm the present findings.

**Corresponding author: Department of Cardiovascular Medicine, Kyoto University, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan. E-mail: taketaka@kuhp.kyoto-u.ac.jp*

SUBMITTED ON 23/09/2016 - REVISION RECEIVED ON 1st 15/12/2016 / 2nd 22/12/2016 - ACCEPTED ON 31/12/2016

DOI: 10.4244/AsiaInterv_V3I1A16

Abbreviations

AMI	acute myocardial infarction
CABG	coronary artery bypass grafting
CI	confidence interval
CTO	chronic total occlusion
HR	hazard ratio
IRA	infarct-related artery
MI	myocardial infarction
MVD	multivessel disease
PCI	percutaneous coronary intervention
RCT	randomised controlled trial
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction

Introduction

ST-elevation myocardial infarction (STEMI) patients with multivessel disease (MVD), particularly with chronic total occlusion (CTO) in a non-infarct-related artery (IRA), have the worst prognosis according to several studies[1-4]. The reason is plausibly explained by several hypotheses, such as the presence of silent myocardial infarction (MI) and greater ischaemia in decreased collateral circulation as in acute coronary syndrome (ACS). However, those observational studies only suggested a close association between the presence of concurrent CTO and increased mortality, but did not prove a cause-and-effect relationship. Although intuitively plausible, it cannot be concluded that CTO in a non-IRA directly increases mortality in STEMI patients. To date, only a few reports are available about whether revascularisation of CTO in the non-IRA improves long-term outcomes in STEMI patients undergoing primary percutaneous coronary intervention (PCI)[5-7]. Hence, to assess the prognostic effect of CTO revascularisation, we sought to elucidate the clinical effectiveness of CTO-PCI in a non-IRA on long-term outcomes of STEMI patients in a large Japanese observational database of STEMI patients undergoing coronary revascularisation.

Methods

STUDY POPULATION

The Coronary Revascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) AMI registry is a physician-initiated, non-company sponsored, multicentre registry. This study enrolled consecutive acute myocardial infarction (AMI) patients undergoing coronary revascularisation within seven days of symptom onset in 26 centres in Japan between January 2005 and December 2007 **(Appendix 1)**. The relevant review boards or ethics committees in all participating centres approved the research protocol. Written informed consent from the patients was waived because of retrospective enrolment. However, we excluded those patients who refused to participate in the study when contacted at follow-up. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

Among 5,429 AMI patients enrolled in the registry, 4,436 STEMI patients were treated by PCI. After excluding 3,935 patients who had no concurrent CTO and 55 patients who had a prior history of coronary artery bypass grafting (CABG), 446 patients had concurrent CTO in a non-IRA. Among the remaining 446 patients with CTO in the non-IRA, the current study population consisted of 134 STEMI patients who received CTO-PCI after excluding 31 patients who underwent CABG within 90 days of the index PCI, and 281 patients who did not receive CTO-PCI **(Figure 1)**. They were divided into two groups according to the status of CTO in the non-IRA: 83 patients who had successful PCI of a CTO in the non-IRA (61.9% initial patient success rate for CTO) (success group) and 51 patients who had failed CTO-PCI (38.1%) (failure group). Moreover, CTO revascularisation was attempted simultaneously with primary PCI for 42 out of the 134 patients (31.3%).

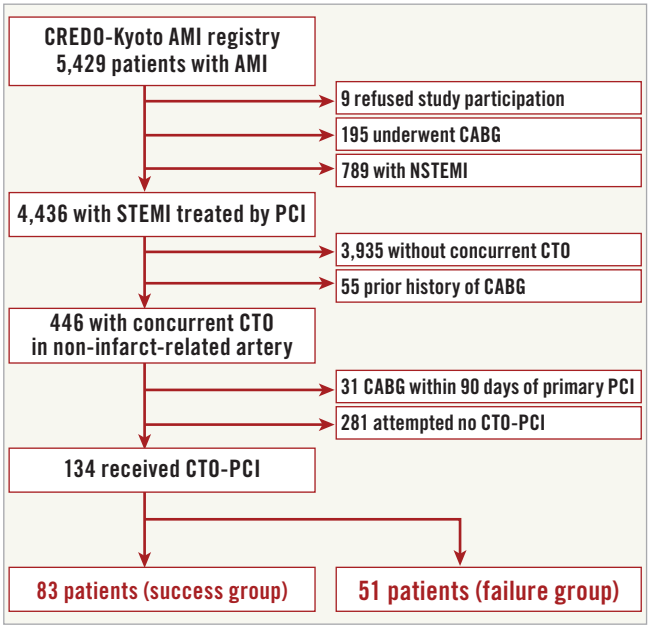


Figure 1. *Study flow chart. CABG: coronary artery bypass grafting; CREDO-Kyoto AMI registry: Coronary Revascularization Demonstrating Outcome Study in Kyoto Acute Myocardial Infarction registry; CTO: chronic total occlusion; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention*

DEFINITIONS AND ENDPOINTS

Definitions of baseline clinical characteristics were previously described in detail[8,9]. The initial perfusion status of the IRA was evaluated according to the Thrombolysis In Myocardial Infarction (TIMI) study classification. CTO was defined as complete obstruction of the vessel with a TIMI flow of 0 or 1 with an estimated duration of the occlusion >1 month or in the presence of collateral flow[10]. The duration of occlusion was evaluated by the investigators in each participating centre based on the interval from the last episode of MI in the target vessel territory, the previous coronary angiography, or changes in electrocardiographic findings. Staged PCI was pre-specified as PCI scheduled during the index hospitalisation and performed within 90 days of the index PCI.

The primary outcome measure for the current analysis was all-cause death. Secondary outcome measures included cardiac death, non-cardiac death, MI, heart failure hospitalisation, and any coronary revascularisation. Death was regarded as cardiac in origin unless evident non-cardiac causes could be identified. MI was defined according to the definition in the Arterial Revascularization Therapies Study[11]. Any coronary revascularisation was defined as either PCI or CABG for any reason.

DATA COLLECTION FOR BASELINE CHARACTERISTICS AND FOLLOW-UP EVENTS

Demographic, angiographic, and procedural data were collected from hospital charts or hospital databases according to the pre-specified definitions by experienced clinical research coordinators from the study management centre (Research Institute for Production Development, Kyoto, Japan) **(Appendix 2)**. In this retrospective cohort study, data collection for follow-up events was performed in 2010 and 2012. Collection of follow-up information was mainly conducted through review of in-patient and out-patient hospital charts by the clinical research coordinators. Additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by sending mail with questions regarding vital status, subsequent hospitalisations, and status of antiplatelet therapy. Death, MI, ST, and stroke were adjudicated by the clinical events committee **(Appendix 3)**. Median follow-up duration was 1,709 (interquartile range [IQR]: 1,092-2,122) days.

STATISTICAL ANALYSIS

Categorical variables were expressed as numbers and percentages, and continuous variables as mean±standard deviation. Categorical variables were compared with the χ^2 test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared with the Student's t-test or the Wilcoxon rank-sum test based on their distributions. The Kaplan-Meier method was used to estimate cumulative incidences of clinical events, and the difference was evaluated with the log-rank test. We performed a landmark analysis at 90 days after primary PCI to compare the clinical outcomes between the success and the failure groups. Consistent with our previous reports, we used a multivariable Cox proportional hazards model to estimate the effect of the success group relative to the failure group for the primary and secondary outcome measures[8,9]. Given the small number of events, we selected the following three clinically relevant risk-adjusting variables for the Cox models: successful CTO-PCI, diabetes mellitus requiring insulin therapy, and haemodialysis. Adjusted hazard ratios (HR) and their 95% confidence intervals (CI) were calculated. Multivariable adjustment could not be conducted for several endpoints due to the small number of events. As in our previous reports, we dichotomised continuous variables by using clinically relevant reference values or median values. Statistical analyses were performed with the use of JMP 10.0 (SAS Institute Inc., Cary, NC, USA) software. All statistical analyses were two-tailed. P-values <0.05 were considered statistically significant.

Results

BASELINE CHARACTERISTICS

Baseline characteristics were very analogous except for only one aspect between the success and failure groups **(Table 1)**. More patients in the failure group received haemodialysis than in the success group. Similarly, few differences were found in the procedural and lesion characteristics between the two groups. In CTO-PCI, intravascular ultrasound was more often used in the success group than in the failure group. Moreover, more patients in the success group received complete revascularisation **(Table 2)**.

LONG-TERM CLINICAL OUTCOMES

Landmark analysis at 90 days showed that the cumulative incidence of all-cause death beyond 90 days and up to five years was not significantly lower in the success group than in the failure group (19.8% vs. 15.4%, log rank p=0.65) **(Table 3, Figure 2)**. Even after adjusting for confounders, no significant difference was observed in the adjusted risk of the success group relative to the failure group for all-cause death beyond 90 days and up to five years (HR 1.64, 95% CI: 0.63-5.05, p=0.32) **(Table 3)**.

The cumulative five-year incidences of cardiac death, non-cardiac death, MI, and heart failure hospitalisation and any coronary revascularisation were not significantly different between the success and failure groups **(Table 3)**. The adjusted risk of the success group as compared to the failure group for any coronary revascularisation was not significantly different **(Table 3)**.

Discussion

The main findings in the current analysis were as follows. First, only approximately two thirds of STEMI patients with CTO in the non-IRA received successful CTO-PCI. Second, successful PCI of CTO in the non-IRA was not associated with improved all-cause mortality in STEMI patients who underwent primary PCI.

Whether revascularisation of a CTO could improve mortality in STEMI patients remains unknown due to a paucity of data. No randomised controlled trials (RCT) have been conducted to assess the clinical effect of staged revascularisation of a CTO in a non-IRA to date. Three observational studies have demonstrated the clinical efficacy of staged PCI for CTO in a non-IRA in AMI patients[5-7]. However, these studies had varied population sizes and were confounded by the small sample size and low patient success rate of CTO-PCI. Yang et al compared successful CTO-PCI and failed CTO-PCI. They reported that successful CTO-PCI (87 patients) improved cardiac mortality in 136 STEMI patients (patient success rate: 64%) at two-year follow-up[5]. Valentine et al compared successful CTO-PCI and failed/non-attempted CTO-PCI. They showed that successful CTO-PCI (58 patients) was statistically significantly associated with improved mortality in 169 AMI patients (patient success rate: 78%) at one-year follow-up[7]. In the current study, the cumulative incidence of all-cause death beyond 90 days and up to five years was not significantly different between the success and the failure groups. Similarly, the adjusted risk for all-cause death was similar between the groups.

Table 1. Baseline patient characteristics.

Variables	Success group N=83	Failure group N=51	*p*-value
Clinical characteristics			
Age (years)	66.4±12.4	66.9±11.6	0.82
>75 years	29 (34.9%)	14 (27.5%)	0.36
Male	66 (79.5%)	42 (82.4%)	0.69
Body mass index (kg/m²)	24.4±3.6	24.9±3.5	0.44
<25.0 kg/m²	54 (65.1%)	29 (56.9%)	0.34
Hypertension	63 (75.9%)	44 (86.3%)	0.14
Diabetes mellitus	32 (38.6%)	14 (27.5%)	0.19
requiring insulin therapy	5 (6.0%)	3 (5.9%)	0.97
Current smoking	35 (42.2%)	24 (47.1%)	0.58
Prior and current heart failure	36 (43.4%)	25 (49.0%)	0.52
Mitral regurgitation 3-4/4	2 (2.4%)	4 (7.8%)	0.15
Prior myocardial infarction	8 (9.6%)	9 (17.7%)	0.18
Prior stroke	9 (10.8%)	2 (3.9%)	0.14
Peripheral vascular disease	2 (2.4%)	2 (3.9%)	0.62
eGFR <30, without haemodialysis	2 (2.4%)	4 (7.8%)	0.15
Haemodialysis	0	2 (3.9%)	0.048
Left ventricular ejection fraction	49.0±13.8 (67)	48.4±13.9 (36)	0.82
<40%	16/67 (23.9%)	9/36 (25.0%)	0.90
Atrial fibrillation	8 (9.6%)	7 (13.7%)	0.47
Anaemia (haemoglobin <11.0 g/dl)	2 (2.4%)	3 (5.9%)	0.31
Thrombocytopaenia (platelet <100*109/L)	2 (2.4%)	0	0.16
Liver cirrhosis	2 (2.4%)	1 (2.0%)	0.86
Malignancy	5 (6.0%)	2 (3.9%)	0.59
Peak creatinine phosphokinase (IU/L)	2,466 (1,312-5,261)	1,683 (828-4,590)	0.12
Presentation of STEMI			
Killip class ≤II	61 (73.5%)	35 (68.6%)	0.55
Killip class IV	19 (22.9%)	12 (23.5%)	0.93
Anterior MI	37 (44.6%)	15 (29.4%)	0.08
Onset-to-presentation time (hours)	1.9 (1.1-5.9) (82)	3.1 (1.5-7.4) (49)	0.12
Onset-to-balloon time (hours)	4.3 (2.8-8.7) (74)	4.7 (3.5-12.3) (43)	0.12
Door-to-balloon time (hours)	1.5 (1.0-2.4) (74)	1.6 (1.1-2.8) (43)	0.59
Medication at discharge			
Aspirin	82 (98.8%)	48 (94.1%)	0.13
Thienopyridine	80 (96.4%)	48 (94.1%)	0.54
Cilostazole	34 (41.0%)	14 (27.5%)	0.11
Statin	47 (56.6%)	27 (52.9%)	0.68
ACE-I/ARB	63 (75.9%)	43 (84.3%)	0.24
ß-blocker	33 (39.8%)	24 (47.1%)	0.41
Calcium channel blocker	14 (16.9%)	11 (21.6%)	0.50
Nitrate	23 (27.7%)	18 (35.3%)	0.36
Nicorandil	23 (27.7%)	15 (29.4%)	0.83
Warfarin	6 (7.2%)	8 (15.7%)	0.13
PPI	34 (41.0%)	18 (35.3%)	0.51
H2 blocker	21 (25.3%)	16 (31.4%)	0.45

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean±SD or median (interquartile range). ACE-I/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; PPI: proton pump inhibitor; STEMI: ST-segment elevation myocardial infarction

Table 2. Angiographic and procedural characteristics.

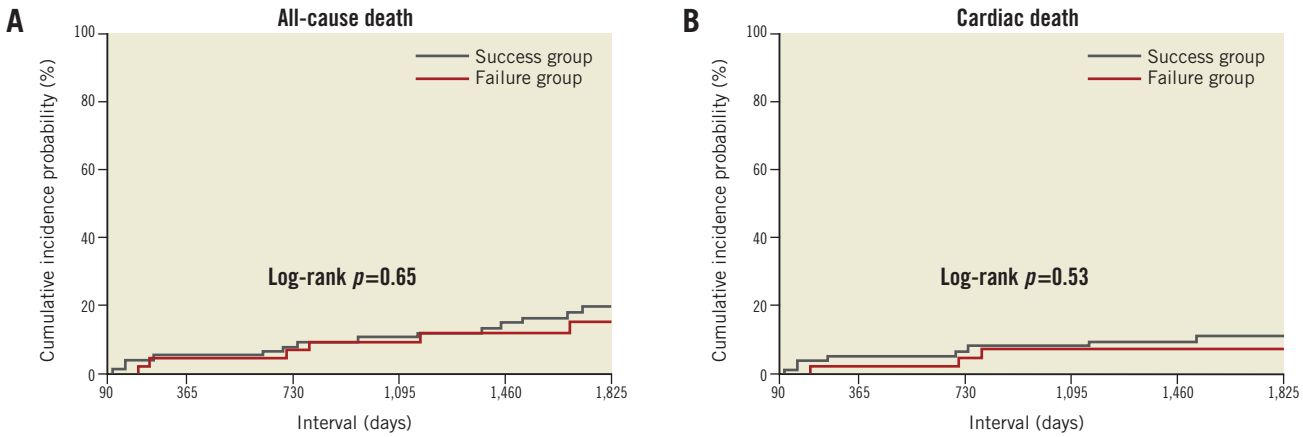
Variables		Success group N=83	Failure group N=51	*p*-value
Primary PCI				
Infarct-related artery	Proximal LAD	32 (38.6%)	14 (27.5%)	0.19
	LAD	35 (42.2%)	16 (31.4%)	0.21
	LCX	11 (13.3%)	7 (13.7%)	0.94
	RCA	34 (41.0%)	27 (52.9%)	0.18
	Unprotected LMCA	3 (3.6%)	1 (2.0%)	0.57
DES use		50 (60.2%)	–	–
Contrast media (ml)		189 (144-266) (70)	200 (132-251) (41)	0.81
Implanted stents		1 (1-2) (77)	1 (1-1) (40)	0.40
Total stent length (mm)		23.5 (18-30.75) (76)	23 (18-30) (39)	0.95
>28 mm		23/76 (30.3%)	11/39 (28.2%)	0.82
Minimal stent diameter (mm)		3.0 (3.0-3.5) (76)	3.0 (3.0-3.5) (39)	0.56
<3.0 mm		16/76 (21.1%)	6/39 (15.4%)	0.46
Thrombectomy		42 (50.6%)	26 (51.0%)	0.97
Distal protection		5 (6.0%)	2 (3.9%)	0.59
IVUS use		15 (18.1%)	8 (15.7%)	0.72
IABP use		33 (39.8%)	19 (37.3%)	0.77
PCPS use		6 (7.2%)	4 (7.8%)	0.90
CTO-PCI				
Number of CTO (interquartile range)		1 (1-1)	1 (1-1)	0.36
Location of CTO	LAD	36 (43.4%)	23 (45.1%)	0.85
	LCX	31 (37.4%)	15 (29.4%)	0.34
	RCA	26 (31.3%)	18 (35.3%)	0.64
Location of target CTO	LAD	31 (37.4%)	22 (43.1%)	0.51
	LCX	28 (33.7%)	13 (25.5%)	0.31
	RCA	25 (30.1%)	17 (33.3%)	0.70
IVUS use		23 (27.7%)	4 (7.8%)	0.003
Contrast media		249±107	234±106	0.49
Interval of CTO-PCI after primary PCI (days)		11 (0-17)	6 (0-16)	0.11
CTO-PCI on Day 0		21(25%)	21(41%)	0.06
DES use		50 (60.2%)	–	–
Implanted stents		1 (1-2) (76)	–	–
Total stent length (mm)		33 (23-56) (65)	–	–
>28 mm		35/65 (53.9%)	–	–
Minimal stent diameter (mm)		2.5 (2.5-3.0) (65)	–	–
<3.0 mm		42/65 (64.6%)	–	–
Procedural complication	Slow flow	3 (3.6%)	0	0.09
	Acute occlusion	1 (1.2%)	0	0.33
	Coronary perforation	0	1 (2.0%)	0.16
Overall procedures				
PCI for LMT		4 (4.8%)	1 (2.0%)	0.38
Non-IRA, non-CTO-PCI		28 (33.7%)	16 (31.4%)	0.78
Complete revascularisation		60 (72.3%)	0	<0.001

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean±SD or median (interquartile range). CTO: chronic total occlusion; DES: drug-eluting stent; IABP: intra-aortic balloon pumping; IRA: infarct-related artery; IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LMCA: left main coronary artery; PCI: percutaneous coronary intervention; PCPS: percutaneous cardiopulmonary support; RCA: right coronary artery

Table 3. Crude and adjusted 5-year clinical outcomes: success group versus failure group.

Variable	Success group No. of patients with events (cumulative incidence) N=83	Failure group No. of patients with events (cumulative incidence) N=51	Crude HR (95% CI)	*p*-value (log-rank)	Adjusted HR (95% CI)	*p*-value
All-cause death	14 (19.8%)	6 (15.4%)	1.23 (0.52-3.23)	0.65	1.64 (0.63–5.05)	0.32
Cardiac death	8 (11.1%)	3 (7.4%)	1.52 (0.44-6.93)	0.53	–	–
Non-cardiac death	6 (9.8%)	3 (8.7%)	1.01 (0.31-3.88)	0.98	–	–
Myocardial infarction	3 (5.2%)	3 (10.0%)	0.53 (0.10-2.87)	0.43	–	–
Heart failure hospitalisation	7 (10.3%)	4 (10.2%)	1.01 (0.30-3.84)	0.99	–	–
Any coronary revascularisation	38 (56.4%)	16 (48.7%)	1.03 (0.59-1.86)	0.93	1.08 (0.61-1.99)	0.79

Cumulative incidence was estimated by the Kaplan-Meier method. CABG: coronary artery bypass grafting; CI: confidence interval; HR: hazard ratio



Interval	90 days	1 year	3 years	5 years
Success group				
No. of patients with at least one event		4	8	14
No. of patients at risk	74	71	67	38
Cumulative incidence probability		5.4%	10.8%	19.8%
Failure group				
No. of patients with at least one event		2	4	6
No. of patients at risk	44	42	36	24
Cumulative incidence probability		4.7%	9.6%	15.4%

Interval	90 days	1 year	3 years	5 years
Success group				
No. of patients with at least one event		4	6	8
No. of patients at risk	74	71	67	38
Cumulative incidence probability		5.4%	8.2%	11.1%
Failure group				
No. of patients with at least one event		1	3	3
No. of patients at risk	44	42	36	24
Cumulative incidence probability		2.3%	7.4%	7.4%

Figure 2. *Crude Kaplan-Meier curves for the cumulative incidence of all-cause death and cardiac death in the success and failure groups.*

The current study mainly focused on the analysis of the long-term effect of successful CTO revascularisation. The effect of CTO revascularisation in STEMI patients should be evaluated according to clinical settings. On the one hand, in the acute setting, emergent multivessel revascularisation was sometimes unavoidable, as in AMI patients complicated by cardiogenic shock (CS). The purpose of this strategy is the restoration of haemodynamic stability because of ongoing large ischaemia, which often involves CTO revascularisation. The clinical efficacy of acute multivessel PCI in the CS setting was assessed in several observational studies, but remains controversial due to inconsistent results[12,13]. On the other hand, in the subacute and chronic phases, the presumed advantage of CTO-PCI was recovery of contraction in hibernating viable myocardium.

Given that low left ventricular ejection fraction (LVEF) was a strong prognostic indicator, CTO revascularisation based on adequate assessment of myocardial viability was expected to result in better clinical outcomes. The EXPLORE trial, assessing the effect of early CTO-PCI on LVEF and left ventricular end-diastolic volume (LVEDV) at a four-month follow-up,

demonstrated that the staged PCI of non-IRA CTO within a week of primary PCI was not associated with improvement of LVEF or LVEDV (44.1±12.2% vs. 44.8±11.9%, p=0.60)[14]. However, a subgroup analysis suggested the clinical benefit from LAD-CTO revascularisation, which was endorsed by previous observational studies[15,16]. Thus, further investigations should be performed on this topic. Staged revascularisation of CTO in the non-IRA was part of a staged multivessel PCI strategy in STEMI patients. Recent RCT have suggested that a multivessel revascularisation strategy is a safe and acceptable alternative compared with a culprit-only PCI strategy[17-19]. Complete revascularisation was the prerequisite of a staged multivessel revascularisation strategy in most previous observational and randomised studies. However, numerous studies with positive results excluded patients with CTO in the non-IRA due to the difficulty in achieving complete revascularisation.

One of the latest randomised studies, CvLPRIT (Complete Versus culprit-Lesion only PRimary PCI Trial), which excluded STEMI patients with CTO in the non-IRA, randomised 296 STEMI patients to complete versus culprit lesion-only revascularisation. It resulted in significant reduction in the primary endpoint of MACE (mortality, recurrent MI, heart failure, or ischaemia-driven revascularisation within 12 months [10.0% vs. 21.2%; HR 0.45; p=0.009])[19].

As the techniques and devices for CTO revascularisation have evolved over time, more data about revascularisation of CTO in the non-IRA should be obtained to elucidate its clinical relevance in STEMI patients with MVD.

Limitations

The current study has several limitations. First, this retrospective observational study could not exclude unmeasured confounders despite multivariable adjustment. Second, compared with the results in CTO revascularisation in stable coronary disease, the procedural success rate of CTO-PCI was very low in this study and does not reflect the contemporary success rate of CTO-PCI. The main strategy of CTO-PCI in the study period was only antegrade wiring. The second-generation DES and other supplementary devices, including newly developed CTO guidewires and channel dilation microcatheters, many of which were not available in the study period, have been widely used in the current CTO-PCI. Therefore, the current study result cannot be directly applied to contemporary CTO-PCI. Finally, the number of study patients was too small to draw solid conclusions. Furthermore, the study population in our current analysis included those who received CTO-PCI simultaneously with primary PCI. Multivessel revascularisation at the primary PCI had a different clinical role because it was often performed due to haemodynamic instability, such as in cardiogenic shock.

Conclusions

Successful PCI of CTO in a non-IRA was not associated with a better five-year mortality rate in STEMI patients who underwent primary PCI.

Impact on daily practice

Our analysis shows real data about the management of non-infarct-related CTO in STEMI patients who underwent primary PCI. When we evaluated the advantage of CTO-PCI in STEMI patients, meticulous discussion was required according to the clinical situation. CTO-PCI should play a pivotal role both in emergency situations such as cardiogenic shock, and in the chronic phase where the recovery of lost LVEF is indispensable. Larger sample-size cohort studies and randomised trials are warranted on this topic.

Appendix 1

LIST OF PARTICIPATING CENTRES AND INVESTIGATORS FOR THE CREDO-KYOTO PCI/CABG REGISTRY COHORT-2

CARDIOLOGY

Kyoto University Hospital: Takeshi Kimura; *Kishiwada City Hospital:* Mitsuo Matsuda, Hirokazu Mitsuoka; *Tenri Hospital:* Yoshihisa Nakagawa; *Hyogo Prefectural Amagasaki Hospital:* Hisayoshi Fujiwara, Yoshiki Takatsu, Ryoji Taniguchi; *Kitano Hospital:* Ryuji Nohara; *Koto Memorial Hospital:* Tomoyuki Murakami, Teruki Takeda; *Kokura Memorial Hospital:* Masakiyo Nobuyoshi, Masashi Iwabuchi; *Maizuru Kyosai Hospital:* Ryozo Tatami; *Nara Hospital, Kinki University Faculty of Medicine:* Manabu Shirotani; *Kobe City Medical Center General Hospital:* Toru Kita, Yutaka Furukawa, Natsuhiko Ehara; *Nishi-Kobe Medical Center:* Hiroshi Kato, Hiroshi Eizawa; *Kansai Denryoku Hospital:* Katsuhisa Ishii; *Osaka Red Cross Hospital:* Masaru Tanaka; *University of Fukui Hospital:* Jong-Dae Lee, Akira Nakano; *Shizuoka City Shizuoka Hospital:* Akinori Takizawa; *Hamamatsu Rosai Hospital:* Masaaki Takahashi; *Shiga University of Medical Science Hospital:* Minoru Horie, Hiroyuki Takashima; *Japanese Red Cross Wakayama Medical Center:* Takashi Tamura; Shimabara Hospital: Mamoru Takahashi; *Kagoshima University Medical and Dental Hospital:* Chuwa Tei, Shuichi Hamasaki; *Shizuoka General Hospital:* Hirofumi Kambara, Osamu Doi, Satoshi Kaburagi; *Kurashiki Central Hospital:* Kazuaki Mitsudo, Kazushige Kadota; *Mitsubishi Kyoto Hospital:* Shinji Miki, Tetsu Mizoguchi; *Kumamoto University Hospital:* Hisao Ogawa, Seigo Sugiyama; *Shimada Municipal Hospital:* Ryuichi Hattori, Takeshi Aoyama, Makoto Araki; *Juntendo University Shizuoka Hospital:* Satoru Suwa.

CARDIOVASCULAR SURGERY

Kyoto University Hospital: Ryuzo Sakata, Tadashi Ikeda, Akira Marui; *Kishiwada City Hospital:* Masahiko Onoe; *Tenri Hospital:* Kazuo Yamanaka; *Hyogo Prefectural Amagasaki Hospital:* Keiichi Fujiwara, Nobuhisa Ohno; *Kokura Memorial Hospital:* Michiya Hanyu; *Maizuru Kyosai Hospital:* Tsutomu Matsushita; *Nara Hospital, Kinki University Faculty of Medicine:* Noboru Nishiwaki, Yuichi Yoshida; *Kobe City Medical Center General Hospital:* Yukikatsu Okada, Michihiro Nasu; *Osaka Red Cross Hospital:* Shogo Nakayama; *University of Fukui Hospital:* Kuniyoshi Tanaka, Takaaki Koshiji, Koichi Morioka; *Shizuoka City Shizuoka Hospital:*

Mitsuomi Shimamoto, Fumio Yamazaki; *Hamamatsu Rosai Hospital:* Junichiro Nishizawa; *Japanese Red Cross Wakayama Medical Center:* Masaki Aota; *Shimabara Hospital:* Takafumi Tabata; *Kagoshima University Medical and Dental Hospital:* Yutaka Imoto, Hiroyuki Yamamoto; *Shizuoka General Hospital:* Katsuhiko Matsuda, Masafumi Nara; *Kurashiki Central Hospital:* Tatsuhiko Komiya; *Mitsubishi Kyoto Hospital:* Hiroyuki Nakajima; *Kumamoto University Hospital:* Michio Kawasuji, Syuji Moriyama; *Juntendo University Shizuoka Hospital:* Keiichi Tanbara.

Appendix 2

LIST OF CLINICAL RESEARCH COORDINATORS

RESEARCH INSTITUTE FOR PRODUCTION DEVELOPMENT

Kumiko Kitagawa, Misato Yamauchi, Naoko Okamoto, Yumika Fujino, Saori Tezuka, Asuka Saeki, Miya Hanazawa, Yuki Sato, Chikako Hibi, Hitomi Sasae, Emi Takinami, Yuriko Uchida, Yuko Yamamoto, Satoko Nishida, Mai Yoshimoto, Sachiko Maeda, Izumi Miki, Saeko Minematsu.

Appendix 3

LIST OF CLINICAL EVENTS COMMITTEE MEMBERS

Mitsuru Abe, *Kyoto Medical Center*; Hiroki Shiomi, *Kyoto University Hospital*; Tomohisa Tada, *Kyoto University Hospital*; Junichi Tazaki, *Kyoto University Hospital*; Yoshihiro Kato, *Kyoto University Hospital*; Mamoru Hayano, *Kyoto University Hospital*; Akihiro Tokushige, *Kyoto University Hospital*; Masahiro Natsuaki, *Kyoto University Hospital*; Tetsu Nakajima, *Kyoto University Hospital*.

Acknowledgements

We appreciate the collaboration of the co-investigators in the CREDO-Kyoto PCI/CABG Registry Cohort-2.

Funding

The CREDO-Kyoto AMI registry was supported by the Ministry of Health, Labor and Welfare, and the Pharmaceuticals and Medical Devices Agency in Japan.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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