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Chronic total occlusion in a non-infarct-related artery is closely associated with increased five-year mortality in patients with ST-segment elevation acute myocardial infarction undergoing primary percutaneous coronary intervention (from the CREDO-Kyoto AMI registry)

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KEYWORDS

- chronic coronary total occlusion
- multivessel disease
- ST-elevation myocardial infarction

Abstract

Aims: We sought to investigate the clinical impact of chronic total occlusion (CTO) in a non-infarct-related artery (IRA) on long-term cardiovascular outcomes in patients with ST-elevation myocardial infarction (STEMI).

Methods and results: Among 5,429 patients enrolled in the CREDO-Kyoto AMI registry, the current study population consisted of 2,045 STEMI patients with multivessel disease (MVD) who underwent primary PCI within 24 hours after symptom onset. The cumulative five-year, 30-day and 30-day to five-year incidences of all-cause death were all significantly higher in the CTO group than in the non-CTO group (37.0% versus 22.0%, log-rank p<0.0001, 12.8% versus 6.3%, log-rank p<0.0001, and 28.2% versus 16.8%, log-rank p<0.0001, respectively). The adjusted risk for all-cause death in the CTO group was significantly higher during the entire five years, during the initial 30 days, and beyond 30 days and up to five years (hazard ratio [HR]: 1.47, 95% confidence interval [CI]: 1.18-1.84, p=0.0009; HR: 1.49, 95% CI: 1.04-2.13, p=0.03; and HR: 1.61, 95% CI: 1.23-2.07, p=0.0006, respectively).

Conclusions: CTO in a non-IRA was associated with increased five-year mortality in STEMI patients with MVD. This was consistently seen even after excluding early deaths within 30 days of the index STEMI event.

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Abbreviations

AMI	acute myocardial infarction
CABG	coronary artery bypass grafting
CI	confidence interval
CTO	chronic total occlusion
HR	hazard ratio
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

Although primary percutaneous coronary intervention (PCI) is currently established as the first-line treatment of acute ST-elevation myocardial infarction (STEMI), there are still some unanswered questions such as the management of non-infarct-related artery (non-IRA) lesions. Several studies have already reported the presence of concurrent chronic total occlusion (CTO) in non-IRA as being an independent risk factor for early and late mortality in STEMI patients with multivessel disease[1-3]. However, these studies were confounded by several limitations such as a relatively small sample size, an insufficiently long follow-up period, and lack of information about the effect of PCI for CTO in non-IRA. In an attempt to overcome these limitations, we sought to investigate the clinical impact of CTO in non-IRA on long-term cardiovascular outcomes using detailed information from a large-scale observational database of AMI patients undergoing primary PCI in Japan.

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Methods

STUDY POPULATION

The Coronary Revascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) AMI registry is a physician-initiated, non-company sponsored, multicentre registry enrolling consecutive AMI patients undergoing coronary revascularisation within seven days of symptom onset among 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. Because of retrospective enrolment, written informed consent from the patients was waived; 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 this registry, the current study population consisted of 2,045 STEMI patients with multivessel disease (MVD) who underwent primary PCI within 24 hours after symptom onset **(Figure 1)**. The patients were classified into two

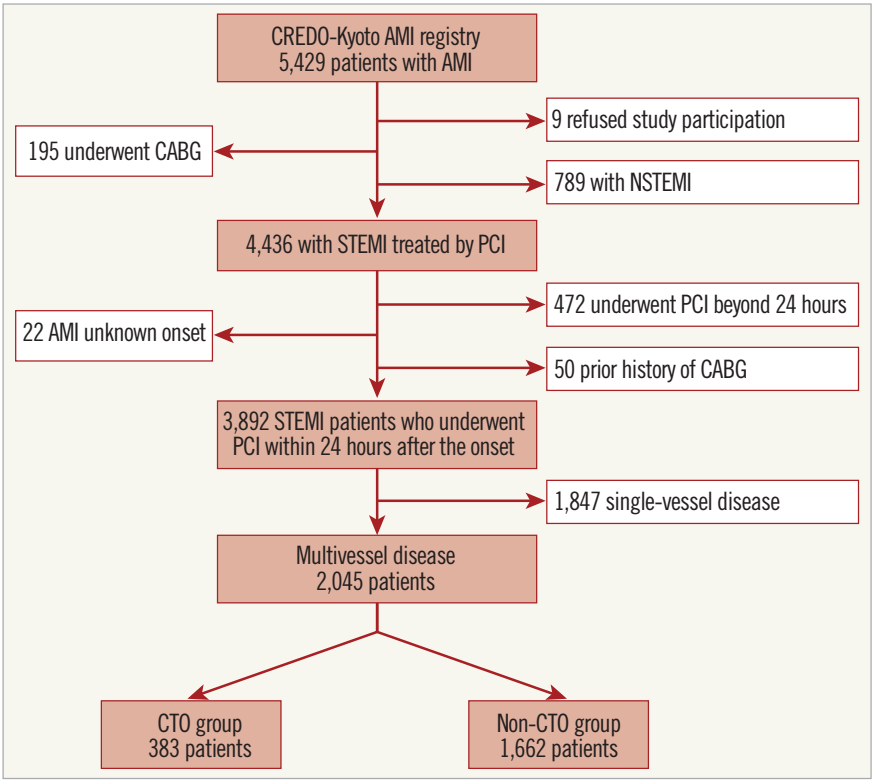


Figure 1. *Study flow chart. CABG: coronary artery bypass grafting; CREDO-Kyoto AMI registry: Coronary Revascularization Demonstrating Outcome Study in Kyoto Acute Myocardial Infarction registry; CTO: chronic total occlusion; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: primary coronary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

groups according to the presence of CTO in a non-IRA (CTO group: 383 patients [18.7%], and non-CTO group: 1,662 patients [81.3%]).

DEFINITIONS AND ENDPOINTS

Definitions of baseline clinical characteristics were previously described[4]. The initial perfusion status of the infarct-related artery was evaluated according to the Thrombolysis In Myocardial Infarction (TIMI) study classification. TIMI 0 referred to the absence of any antegrade flow beyond a coronary occlusion. CTO was defined as complete obstruction of the vessel with TIMI flow of 0 or 1 with an estimated duration of the occlusion >1 month or presence of collateral flow. The duration of occlusion was judged by the investigators in each participating centre on the basis of the interval from the last episode of MI in the target vessel territory, the previous coronary angiography, or changes in electrocardiographic findings. Multivessel disease was defined as the presence of at least one lesion with % diameter stenosis ≥50% by visual estimation in at least one major non-infarct-related epicardial coronary artery or left main coronary artery. The primary outcome measure for the current analysis was all-cause death. Secondary outcome measures included cardiac death, non-cardiac death, myocardial infarction (MI), heart failure hospitalisation, stroke, stent thrombosis (ST), any coronary revascularisation, and CABG. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. MI was defined according to the definition in the Arterial Revascularization Therapy Study[5]. ST was defined according to the Academic Research Consortium (ARC) definition[6]. 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, and 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 1,839 (interquartile range [IQR]: 1,494-2,156) days.

STATISTICAL ANALYSIS

We expressed categorical variables as numbers and percentages, and continuous variables as mean±standard deviation when they followed a normal distribution or as median (interquartile range) when they did not. The distribution appearance was judged by illustrating the listed variables in a histogram. If it was a bell-shaped appearance, the variables were judged to follow a normal distribution. We compared categorical variables with the χ^2 test when suitable; otherwise, we used Fisher's exact test. We compared continuous variables with the Student's t-test or the Wilcoxon rank-sum test based on their distributions. We performed a landmark analysis at 30 days and compared clinical outcomes in each group with early events excluded. We used the Kaplan-Meier method to estimate cumulative incidences of clinical events and evaluated the differences with the log-rank test. Consistent with our previous reports, we used a multivariable Cox proportional hazards model stratified by the participating centres to estimate the impact of CTO in non-IRA on the entire five-year, 30-day and 30-day to five-year all-cause deaths in the two groups by incorporating the presence of CTO in non-IRA together with 15 clinically relevant risk-adjusting variables **(Table 1, Table 2)**. Proportional hazard assumptions for potential independent risk-adjusting variables were assessed on the plots of log (time) versus log (-log[survival]) stratified by the variable. It was confirmed that the assumptions were acceptable for all the variables. We calculated adjusted hazard ratios (HR) and their 95% confidence intervals (CI). In addition, we computed the adjusted event curves of the two groups using the methods described by Ghali et al[7]. Multivariable adjustment could not be performed for several endpoints due to the small number of events observed. As in our previous reports, we dichotomised some continuous variables by using clinically significant reference values or median values. Statistical analyses were performed by a physician (H. Watanabe) and a statistician (T. Morimoto) with the use of JMP 10.0 (SAS Institute Inc., Cary, NC, USA) software. All the statistical analyses were two-tailed. P-values <0.05 were considered statistically significant.

Results

The baseline characteristics were significantly different between the CTO and non-CTO groups in a few important respects **(Table 1)**. On the other hand, the baseline characteristics were not very different between the successful CTO-PCI and the failed CTO-PCI groups **(Appendix Table 1, Appendix Table 2)**.

Throughout the entire five-year follow-up, the cumulative incidence of all-cause death was significantly higher in the CTO group than in the non-CTO group (37.0% versus 22.0%, log-rank p<0.0001). After adjusting for confounders, the excess risk of the CTO group relative to the non-CTO group for all-cause death during the entire five-year follow-up remained significant (HR: 1.47, 95% CI: 1.18-1.84, p=0.0009) **(Table 3, Figure 2)**. During the initial 30 days, the cumulative incidence of all-cause death was significantly higher in the CTO group (12.8% versus 6.3%, log-rank p<0.0001). The adjusted risk of the CTO group relative to the non-CTO group for all-cause death also remained significant (HR: 1.49, 95% CI: 1.04-2.13, p=0.03) **(Table 3, Figure 3)**. By the landmark analysis at 30 days, the cumulative incidence of and the adjusted risk for all-cause death beyond 30 days and up to five years were significantly higher in the CTO group than in the

Table 1. Baseline patient characteristics of the CTO and the non-CTO groups.

Variables	CTO group N=383	Non-CTO group N=1,662	*p*-value
Clinical characteristics			
Age	68.9±12.2	68.6±11.8	0.64
*>75 years	138 (36%)	547 (33%)	0.25
Male	294 (77%)	1,219 (73%)	0.17
Body mass index	23.5±3.5 (352)	23.7±3.3 (1,548)	0.86
<25.0 kg/m^2	252/352 (72%)	1,112/1,548 (72%)	0.96
*Hypertension	299 (78%)	1,294 (78%)	0.93
Diabetes mellitus	138 (36%)	595 (36%)	0.93
*on insulin therapy	26 (6.8%)	88 (5.3%)	0.26
Current smoking	150 (39%)	620 (37%)	0.50
Prior heart failure	17 (4.4%)	24 (1.4%)	0.0007
Mitral regurgitation 3-4/4	19 (5.0%)	53 (3.2%)	0.10
Prior MI	78 (20%)	149 (9.0%)	<0.0001
*Prior stroke	44 (11%)	153 (9.2%)	0.18
Peripheral vascular disease	12 (3.1%)	55 (3.3%)	0.86
Prior PCI	47 (12.3%)	154 (9.3%)	0.08
*eGFR <30, without haemodialysis	25 (6.5%)	75 (4.5%)	0.11
Left ventricular ejection fraction	47±15 (283)	54±13 (1,268)	<0.0001
<40%	95/283 (34%)	191/1,268 (15%)	<0.0001
*Haemodialysis	6 (1.6%)	32 (1.9%)	0.63
*Atrial fibrillation	41 (11%)	146 (8.8%)	0.25
*Anaemia (haemoglobin <11.0 g/dl)	38 (10%)	170 (10%)	0.86
Thrombocytopaenia (platelet <100*10^9/L)	12 (3.1%)	31 (1.9%)	0.14
*COPD	9 (2.4%)	56 (3.4%)	0.29
*Liver cirrhosis	5 (1.3%)	36 (2.2%)	0.25
*Malignancy	38 (10%)	139 (8.4%)	0.34

Variables	CTO group N=383	Non-CTO group N=1,662	*p*-value
Characteristics of STEMI			
Characteristics of STEMI			
Killip class ≤II	253 (66%)	1,350 (81%)	<0.0001
Killip class IV	105 (27%)	271 (16%)	<0.0001
Time from symptom onset to admission (hours)	2.5 (1.1-5.45) (372)	2.5 (1.2-5.7) (1,592)	0.29
Onset-to-balloon time (hours)	4.5 (3-7.7) (343)	4.35 (2.9-7.6) (1,428)	0.48
Door-to-balloon time (hours)	1.7 (1.1-2.5) (335)	1.5 (1-2.2) (1,405)	0.004
Anterior MI	162 (42%)	703 (42%)	0.99
Peak creatinine phosphokinase	2,917 (1,339.5-5,674.5) (376)	2,209 (1,089-4,246) (1,643)	<0.0001
Baseline medications			
Aspirin	374 (98%)	1,634 (98%)	0.39
Thienopyridine	352 (92%)	1,594 (96%)	0.002
Cilostazole	129 (34%)	583 (35%)	0.60
Statin	194 (51%)	917 (55%)	0.11
*ACE-I/ARB	262 (68%)	1,220 (73%)	0.05
*β-blocker	152 (40%)	665 (40%)	0.91
Calcium channel blocker	63 (16%)	358 (22%)	0.02
Nitrate	113 (30%)	517 (31%)	0.54
Nicorandil	114 (30%)	487 (29%)	0.86
Warfarin	37 (9.7%)	153 (9.2%)	0.78
PPI	133 (35%)	548 (33%)	0.51
H2 blocker	114 (30%)	567 (34%)	0.10

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean±SD. * Potential independent variables selected for multivariable analysis. ACE-I/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; CTO: chronic total occlusion; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction

non-CTO group (28.2% versus 16.8%, log-rank p<0.0001, and HR: 1.61, 95% CI: 1.23-2.07, p=0.0006, respectively) **(Table 3, Figure 3)**. The cumulative five-year incidence of and the adjusted risk for cardiac death, heart failure hospitalisation, any coronary revascularisation, and CABG were also significantly higher in the CTO group than in the non-CTO group **(Table 3)**.

As for CTO-PCI groups, the cumulative five-year incidence of all-cause death was not significantly different between the successful CTO-PCI and the failed CTO-PCI groups (23.6% versus 22.5%, log-rank p=0.92) **(Appendix Table 3, Appendix Figure 1)**.

Discussion

The main findings in the current analysis were as follows. 1) CTO in the non-IRA was independently associated with increased risk for mortality in STEMI patients with multivessel disease. 2) The independent increased mortality risk of CTO in the non-IRA was mainly observed beyond 30 days after the index STEMI event. 3) The five-year cumulative incidence of all-cause death was not significantly different between the successful CTO-PCI and the failed CTO-PCI groups.

The current analysis clearly demonstrated that the long-term mortality in STEMI patients with multivessel disease was higher in the presence of CTO in the non-IRA. Regrettably, this study could not provide the exact mechanisms of mortality deterioration by CTO, but some reasons might be inferred from several pieces of evidence. First of all, as many previous studies have suggested, STEMI patients with CTO had a higher prevalence of cardiovascular comorbidities such as prior MI, heart failure, and stroke, and more often presented in shock on admission. Therefore, the adjusted increased mortality of patients with CTO during the initial 30 days could mainly be explained by more unstable haemodynamic characteristics such as cardiogenic shock at the time of the index STEMI event. Hoebers et al reported that multivessel disease with CTO in a non-IRA was an independent risk factor for short-term mortality in STEMI patients[3]. However, the present multivariable analysis indicated an association of CTO in

Table 2. Angiographic and procedural characteristics of the CTO and the non-CTO groups.

Variables		CTO group N=383	Non-CTO group N=1,662	*p*-value
Primary PCI				
Infarct-related artery	Proximal LAD	150 (39%)	608 (37%)	0.35
	LAD	162 (42%)	638 (38%)	0.16
	LCX	52 (14%)	167 (10%)	0.05
	RCA	162 (42%)	775 (47%)	0.12
	Unprotected LMCA	7 (1.8%)	82 (4.9%)	0.003
Initial TIMI flow grade=0		366 (96%)	986 (59%)	<0.0001
BMS use		278 (83%)	1,199 (78%)	0.05
DES use		57 (17%)	331 (22%)	0.05
Number of implanted stents		1 (1-2) (351)	1 (1-2) (1,568)	0.10
Total stent length, mm		38.5 (24-56) (337)	33 (24-48) (1,538)	0.02
>28 mm		133/337 (39%)	517/1,538 (34%)	0.04
Minimal stent diameter, mm		3 (2.75-3.5) (338)	3 (2.5-3.5) (1,538)	0.25
<3.0 mm		100/338 (30%)	423/1,538 (28%)	0.44
Thrombectomy		209 (55%)	982 (59%)	0.11
Distal protection		19 (5.0%)	118 (7.1%)	0.12
IVUS use		81 (21%)	529 (32%)	<0.0001
IABP use		154 (40%)	284 (17%)	<0.0001
PCPS use		27 (7.1%)	55 (3.3%)	0.002
Overall revascularisation procedures				
Two-vessel disease		158 (41%)	1,005 (60%)	<0.0001
Three-vessel disease		216 (56%)	537 (32%)	<0.0001
*Left main disease		22 (5.7%)	155 (9.3%)	0.02
Location of CTO	LAD	124 (32.4%)	–	
	Proximal LAD	96 (25.1%)	–	
	LCX	158 (41.3%)	–	
	RCA	143 (37.3%)	–	
Target of proximal LAD		240 (63%)	938 (56%)	0.03
Target of unprotected LMCA		17 (4.4%)	119 (7.2%)	0.004
Target of LCX		130 (34%)	459 (28%)	0.01
Target of RCA		225 (59%)	988 (59%)	0.80
Attempted PCI of CTO		121 (32%)	–	
**Successful CTO PCI		78 (20%)	–	
Target of bifurcated lesion		125 (33%)	534 (32%)	0.85
Side branch stenting		21 (5.5%)	78 (4.7%)	0.52
DES use		136 (36%)	690 (42%)	0.03
Number of implanted stents		2 (1-3) (346)	2 (1-3) (1,572)	0.22
Total stent length, mm		37 (23-66) (346)	36 (23-57) (1,571)	0.08
>28 mm		208/346 (60%)	943/1,571 (60%)	0.96
Minimal stent diameter, mm		3 (2.5-3) (346)	3 (2.5-3.0) (1,572)	0.13
<3.0 mm		154/346 (45%)	656/1,572 (42%)	0.34

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean±SD. *Potential independent variables selected for multivariate analysis. **The rate of successful CTO PCI was calculated among patients with target of CTO. BMS: bare metal stent; CTO: chronic total occlusion; DES: drug-eluting stent; IABP: intra-aortic balloon pumping; IVUS: intravascular ultrasonography; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LMCA: left main coronary artery; PCPS: percutaneous cardiopulmonary support; RCA: right coronary artery

a non-IRA with increased long-term mortality beyond 30 days. One of the possible mechanisms of increased long-term mortality beyond 30 days in patients with CTO could be a larger infarct size due to the acute occlusion of a donor artery to CTO. The decreased flow of the donor artery might result in myocardial injury and necrosis in the myocardial area in which the myocardial perfusion was dependent on the collateral flow from the infarct-related artery. Lexis et al showed that the size of enzymatic infarct was significantly larger in the CTO group than in the non-CTO group[8]. In the present study, the peak creatinine phosphokinase value was higher in the CTO group than in the non-CTO group. As another explanation, a previous study by Claessen et al demonstrated that the presence of a CTO was associated with reduced residual left ventricular ejection fraction (LVEF) and with a further deterioration of LVEF during follow-up[1]. The CTO group included more patients with LVEF <40% in the present analysis, probably because patients with CTO had silent MI.

Indeed, it is challenging to discern whether CTO in a non-IRA is only a result of multiple cardiovascular comorbidities or whether it exacerbates mortality in STEMI patients, but it might potentially be a modifiable factor in the improvement of mortality. In the current analysis, the five-year cumulative incidence of all-cause death was not significantly different between the successful CTO-PCI and the failed CTO-PCI groups. However, the prevalence of CTO PCI was only around 32% and the success rate was 65%, both of which were relatively low in terms of current CTO PCI. Also, multivariable analysis could not be performed due to the small number of events in the analysis of successful CTO PCI. The robust assessment of the efficacy of successful non-IRA CTO revascularisation is beyond the scope of this study. As discussed previously, the next focus is whether or not the high rate of successful revascularisation of non-IRA CTO ameliorates mortality of STEMI patients. The way of dealing with non-IRA lesions in STEMI patients remains a target of controversy due to a paucity of randomised data and conflicting results in several observational studies. The EXPLORE trial, which randomised 304 STEMI patients to early CTO PCI versus conservative treatment without CTO PCI, assessed the impact of CTO PCI on LVEF and left ventricular end-diastolic volume (LVEDV) at four-month follow-up. The result was that staged PCI of non-IRA CTO within a week of primary PCI was not associated with improvement of LVEF or LVEDV at four-month follow-up[9]. A subgroup analysis suggested a clinical benefit in patients with LAD CTO, which should be investigated in further studies. Limitations in this trial included a lower success rate of CTO PCI and insufficient sample size for evaluation of clinical endpoints.

Concerning the treatment of non-culprit lesions in STEMI patients, two RCTs have suggested the clinical efficacy of preventive PCI of non-culprit lesions in STEMI patients[10,11]. PCI of non-IRA CTO assumes a critical role in the treatment of multivessel disease because the mastery of CTO PCI is imperative for complete revascularisation. The Complete Versus culprit-Lesion only PRimary PCI Trial (CvLPRIT) showed a significant reduction in the

Table 3. Clinical outcomes in the CTO and the non-CTO groups.

During the entire 5-year follow-up	CTO group No. of patients with events (cumulative 5-year incidence) N=383	Non-CTO group No. of patients with events (cumulative 5-year incidence) N=1,662	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
All-cause death	135 (37.0%)	351 (22.0%)	1.87 (1.54-2.26)	<0.0001	1.93 (1.59-2.34)	<0.0001
Cardiac death	102 (27.7%)	203 (12.7%)	2.32 (1.83-2.92)	<0.0001	2.39 (1.89-3.03)	<0.0001
Non-cardiac death	33 (12.8%)	148 (10.6%)	1.26 (0.88-1.75)	0.21	1.26 (0.89-1.79)	0.19
Myocardial infarction	22 (7.7%)	102 (7.1%)	1.04 (0.64-1.59)	0.88	1.02 (0.65-1.61)	0.92
Heart failure hospitalisation	48 (16.9%)	122 (8.6%)	2.08 (1.49-2.86)	<0.0001	2.09 (1.50-2.90)	<0.0001
Stroke	19 (6.6%)	103 (7.0%)	1.04 (0.65-1.60)	0.86	1.00 (0.64-1.57)	1.00
Stent thrombosis	11 (3.6%)	44 (2.9%)	1.15 (0.57-2.15)	0.68	–	–
Any coronary revascularisation	158 (52.6%)	655 (44.5%)	1.34 (1.12-1.59)	0.001	1.37 (1.16-1.63)	0.0003
CABG	35 (10.8%)	77 (5.1%)	2.15 (1.43-3.16)	0.0004	2.73 (1.81-4.10)	<0.0001

A multivariable Cox proportional hazards model was used in adjusted comparisons of all the outcomes except stent thrombosis with 15 clinically relevant risk-adjusting variables (the presence of chronic total occlusion, age >75 years, hypertension, diabetes mellitus requiring insulin therapy, prior stroke, eGFR <30 without haemodialysis, haemodialysis, atrial fibrillation, anaemia, chronic obstructive pulmonary disease, liver cirrhosis, malignancy, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blocker, left main disease). Multivariable analysis was not performed for "stent thrombosis" due to the very small number of events. Cumulative incidence was estimated by the Kaplan-Meier method. CABG: coronary artery bypass grafting; CI: confidence interval; CTO: chronic total occlusion; HR: hazard ratio

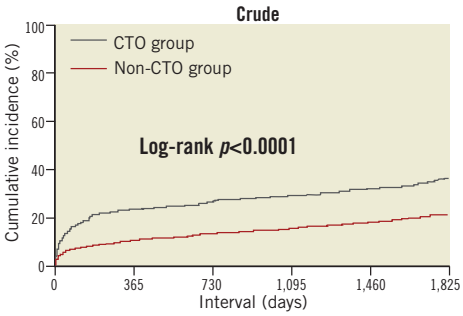
During 30 days	CTO group No. of patients with events (cumulative 30-day incidence) N=383	Non-CTO group No. of patients with events (cumulative 30-day incidence) N=1,662	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
All-cause death	49 (12.8%)	104 (6.3%)	2.10 (1.49-2.94)	<0.0001	2.18 (1.54-3.08)	<0.0001
Cardiac death	49 (12.8%)	103 (6.2%)	2.12 (1.50-2.97)	<0.0001	2.20 (1.55-3.11)	<0.0001
Non-cardiac death	0	1 (0.06%)	–	–	–	–
Myocardial infarction	7 (1.9%)	38 (2.3%)	0.81 (0.33-1.71)	0.61	–	–
Heart failure hospitalisation	2 (0.6%)	2 (0.1%)	4.59 (0.55-38.2)	0.14	–	–
Stroke	7 (2.0%)	34 (2.1%)	0.92 (0.37-1.94)	0.83	–	–
Stent thrombosis	5 (1.4%)	28 (1.7%)	0.79 (0.27-1.87)	0.61	–	–
Any coronary revascularisation	35 (9.8%)	95 (5.9%)	1.67 (1.12-2.44)	0.01	1.80 (1.22-2.66)	0.003
CABG	18 (5.0%)	24 (1.5%)	3.42 (1.83-6.28)	0.0002	-	–

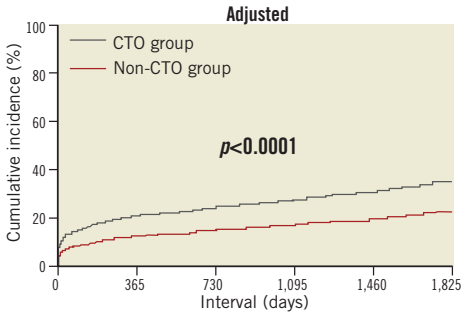
A multivariable Cox proportional hazards model was used in adjusted comparisons of all-cause death, cardiac death and any coronary revascularisation with the 15 clinically relevant risk-adjusting variables as in the analysis of the entire 5-year outcomes. As for the other outcomes, multivariable analysis could not be performed due to the small number of events observed. Cumulative incidence was estimated by the Kaplan-Meier method. CABG: coronary artery bypass grafting; CI: confidence interval; CTO: chronic total occlusion; HR: hazard ratio

Between 30 days and 5 years	CTO group No. of patients with events (cumulative 30-day to 5-year incidence) N=334	Non-CTO group No. of patients with events (cumulative 30-day to 5-year incidence) N=1,557	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
All-cause death	88 (28.2%)	247 (16.8%)	1.81 (1.43-2.27)	<0.0001	1.86 (1.47-2.34)	<0.0001
Cardiac death	55 (17.6%)	100 (7.0%)	2.59 (1.88-3.54)	<0.0001	2.68 (1.95-3.69)	<0.0001
Non-cardiac death	33 (12.8%)	147 (10.6%)	1.26 (0.88-1.76)	0.19	1.27 (0.90-1.80)	0.17
Myocardial infarction	15 (5.9%)	65 (5.0%)	1.17 (0.66-1.96)	0.58	1.16 (0.67-1.99)	0.60
Heart failure hospitalisation	46 (16.4%)	120 (8.4%)	2.04 (1.45- 2.82)	<0.0001	2.05 (1.46-2.86)	<0.0001
Stroke	12 (4.7%)	69 (5.0%)	1.10 (0.62-1.84)	0.72	1.03 (0.60-1.78)	0.91
Stent thrombosis	6 (2.3%)	16 (1.2%)	1.85 (0.67-4.45)	0.22	–	–
Any coronary revascularisation	123 (47.5%)	560 (41.0%)	1.27 (1.05-1.54)	0.017	1.28 (1.05-1.55)	0.01
CABG	17 (6.1%)	53 (3.7%)	1.56 (0.88-2.62)	0.12	1.78 (1.03-3.09)	0.04

A multivariable Cox proportional hazards model was used in adjusted comparisons of all the outcomes except "stent thrombosis" with the 15 clinically relevant risk-adjusting variables. Cumulative incidence was estimated by the Kaplan-Meier method. CABG: coronary artery bypass grafting; CI: confidence interval; CTO: chronic total occlusion; HR: hazard ratio

primary endpoint of mortality, recurrent MI, heart failure, or ischaemia-driven revascularisation at 12 months (10.0% vs. 21.2%; HR: 0.45; p=0.009)[11]. In these two RCTs, CTO in a non-IRA was part of the exclusion criteria. Thus, further prospective randomised trials concerning revascularisation of non-IRA lesions including CTO in STEMI patients are warranted to elucidate this unsolved question.



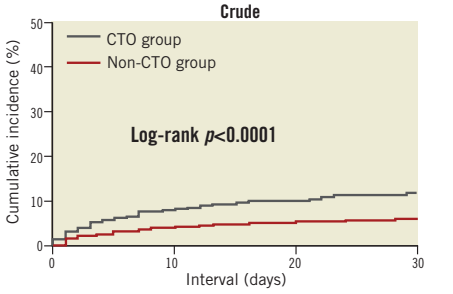


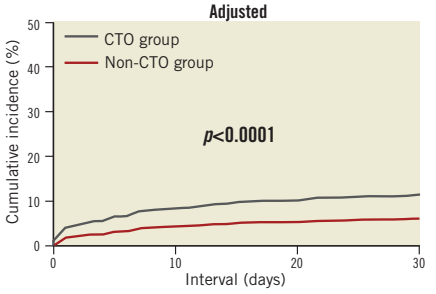
Interval	0 day	1 year	3 years	5 years
CTO group				
Number of patients with at least one event		92	113	143
Number of patients at risk	383	284	256	135
Cumulative incidence		24.2%	29.9%	37.0%
Non-CTO group				
Number of patients with at least one event		189	267	351
Number of patients at risk	1,662	1,452	1,339	838
Cumulative incidence		11.4%	16.2%	22.0%

Interval	1 year	3 years	5 years
CTO group			
Cumulative incidence probability	17.0%	23.0%	29.8%
Non-CTO group			
Cumulative incidence probability	13.0%	17.9%	23.8%

Figure 2. *Crude and adjusted Kaplan-Meier curves for the cumulative incidence of all-cause death in the CTO and the non-CTO groups during the entire five-year follow-up. CTO: chronic total occlusion*

A

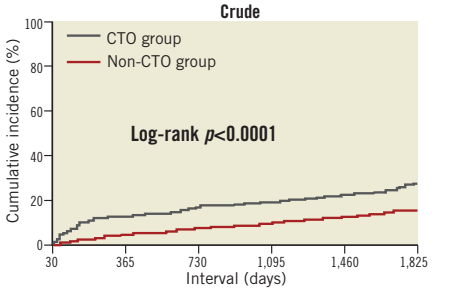


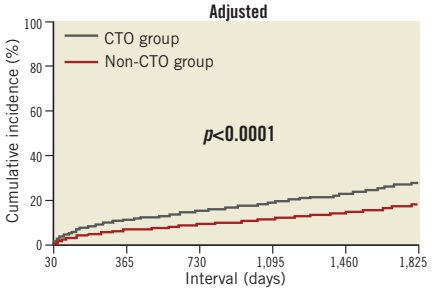


Interval	0 day	10 days	20 days	30 days
CTO group				
Number of patients with at least one event		33	40	49
Number of patients at risk	383	351	343	334
Cumulative incidence		8.6%	10.4%	12.8%
Non-CTO group				
Number of patients with at least one event		78	95	104
Number of patients at risk	1,662	1,585	1,567	1,557
Cumulative incidence		4.7%	5.7%	6.3%

Interval	10 days	20 days	30 days
CTO group			
Cumulative incidence probability	5.3%	6.6%	7.4%
Non-CTO group			
Cumulative incidence probability	5.1%	6.4%	7.2%

B





Interval	30 days	1 year	3 years	5 years
CTO group				
Number of patients with at least one event		45	66	88
Number of patients at risk	334	284	256	143
Cumulative incidence		13.6%	20.1%	28.2%
Non-CTO group				
Number of patients with at least one event		85	163	247
Number of patients at risk	1,557	1,452	1,339	838
Cumulative incidence		5.5%	10.6%	16.8%

Interval	1 year	3 years	5 years
CTO group			
Cumulative incidence probability	9.1%	13.0%	24.0%
Non-CTO group			
Cumulative incidence probability	6.0%	8.7%	17.0%

Figure 3. *Crude and adjusted Kaplan-Meier curves for the cumulative incidence of all-cause death in the CTO and the non-CTO groups during the initial 30 days (A), and beyond 30 days and up to five years (B). CTO: chronic total occlusion*

Limitations

The current study has several potential limitations. First, and most importantly, this is a retrospective observational, but not a prospective randomised study. As differences in baseline patient, angiographic and procedural characteristics between the groups exist, unmeasured confounders cannot be excluded despite robust multivariable analysis. The decision of PCI for non-IRA CTO or non-IRA non-CTO lesions was at the discretion of the operator. Onset-to-balloon time and/or door-to-balloon time were among the strongest factors that could influence mortality in AMI patients. We did not include these factors as adjusting variables in the Cox hazard models because of missing values. We should take into consideration the small but significant difference in door-to-balloon time (but not in onset-to-balloon time) between the two groups in interpreting the present study results. Secondly, we chose 15 clinically relevant adjusting variables according to the number of events for all-cause death during the initial 30 days in the multivariable analysis. Therefore, the models were inevitably overfitted with the 15 adjusters in several endpoints such as myocardial infarction, stroke and CABG. The results for these endpoints should be interpreted cautiously, although the rule of thumb of a minimum of 10 outcome events per predictor variable is not an absolute requirement and can sometimes be relaxed[12]. Finally, this study did not assess detailed angiographic or electrocardiographic findings, such as myocardial blush grade or ST-segment resolution.

Conclusions

CTO in a non-IRA was associated with increased five-year mortality in STEMI patients with MVD. This was consistently seen even after excluding early deaths within 30 days of the index STEMI event.

Impact on daily practice

As with previous studies, our robust analysis in a large cohort demonstrated that CTO in a non-IRA was independently associated with long-term clinical cardiovascular outcomes in STEMI patients with MVD. The assessment of the effect of successful non-IRA CTO PCI was also shown, though this involved many limitations such as small sample size and the lower patient-level CTO success rate. Whether more successful revascularisation of CTO in a non-IRA improves clinical outcomes is the next target of an investigation.

Acknowledgements

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

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Claessen BE, Tijssen JG, van der Schaaf RJ; EXPLORE Trial Investigators. Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI: The EXPLORE Trial. *J Am Coll Cardiol.* 2016;68:1622-1632.

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Supplementary data

Appendix 1. List of participating centres and investigators for the CREDO-Kyoto PCI/CABG Registry Cohort-2.

Appendix 2. List of clinical research coordinators.

Appendix 3. List of clinical events committee members.

Appendix Table 1. Baseline patient characteristics of the successful and the failed CTO-PCI groups.

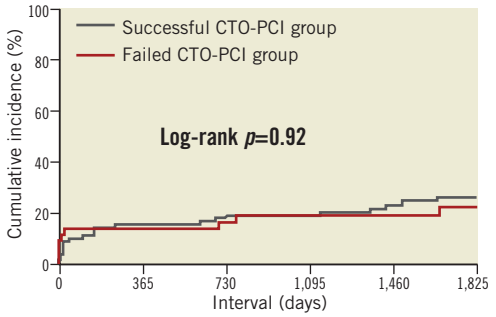
Appendix Table 2. Angiographic and procedural characteristics of the successful and the failed CTO-PCI groups.

Appendix Table 3. Clinical outcomes in the successful and the failed CTO-PCI groups.

Appendix Figure 1. A crude Kaplan-Meier curve for the cumulative incidence of all-cause death in the successful and the failed CTO-PCI groups during the entire five-year follow-up.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/112th_issue/306

Supplementary data



Interval	0 day	1 year	3 years	5 years
Successful CTO-PCI group				
Number of patients with at least one event		12	15	20
Number of patients at risk	78	66	63	37
Cumulative incidence probability		15.5%	19.4%	26.3%
Failed CTO-PCI group				
Number of patients with at least one event		6	8	9
Number of patients at risk	43	37	31	21
Cumulative incidence probability		14.0%	19.1%	22.5%

Appendix Figure 1. *A crude Kaplan-Meier curve for the cumulative incidence of all-cause death in the successful and the failed CTO-PCI groups during the entire five-year follow-up.*

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)*.

Appendix Table 1. Baseline patient characteristics of the successful and the failed CTO-PCI groups.

Variables	Successful CTO-PCI group N=78	Failed CTO-PCI group N=43	*p*-value
Clinical characteristics			
Age	66.1±12.4	67.6±11.3	0.51
>75 years	26 (33%)	12 (28%)	0.54
Male	36 (84%)	62 (79%)	0.57
Body mass index	24.3±3.6 (72)	24.6±3.6 (39)	0.61
<25.0 kg/m²	46/72 (64%)	23/39 (59%)	0.61
Hypertension	57 (73%)	36 (84%)	0.18
Diabetes mellitus	29 (37%)	10 (23%)	0.11
on insulin therapy	5 (6.4%)	1 (2.3%)	0.29
Current smoking	33 (42%)	20 (47%)	0.66
Prior and current heart failure	35 (45%)	20 (47%)	0.86
Mitral regurgitation 3-4/4	2 (2.6)	4 (9.3%)	0.11
Prior MI	8 (10%)	8 (19%)	0.20
Prior stroke	8 (10%)	2 (4.7%)	0.26
Peripheral vascular disease	2 (2.6%)	1 (2.3%)	0.94
Prior PCI	4 (5.1%)	5 (12%)	0.20
eGFR <30, without haemodialysis	1 (1.3%)	2 (4.7%)	0.27
Left ventricular ejection fraction	48±14 (62)	49±14 (29)	0.82
<40%	18/62 (29%)	6/29 (21%)	0.39
Haemodialysis	0	1 (2.3%)	0.15
Atrial fibrillation	8 (10%)	7 (16%)	0.34
Anaemia (haemoglobin <11.0 g/dl)	1 (1.3%)	3 (7.0%)	0.10
Thrombocytopaenia (platelet 100*10⁹/L)	2 (2.6%)	0	0.18
COPD	0	0	–
Liver cirrhosis	2 (2.6%)	0	0.18
Malignancy	4 (5.1%)	2 (4.7%)	0.91
Characteristics of STEMI			
Killip class ≤II	56 (72%)	28 (65%)	0.45
Killip class IV	19 (24%)	11 (26%)	0.88
Time from symptom onset to admission (hours)	1.9 (1.15-5.3) (77)	2.95 (1.25-5.5) (42)	0.36
Onset-to-balloon time (hours)	4.3 (2.85-8.1) (69)	4.1 (3.1-7.6) (36)	0.64
Door-to-balloon time (hours)	1.5 (0.9-2.25) (69)	1.3 (1.0-2.3) (35)	0.65
Anterior MI	35 (45%)	12 (28%)	0.06
Peak creatinine phosphokinase	2,525 (1,329-5,769)	1,718 (953-3,677)	0.08
Medication at discharge			
Aspirin	77 (99%)	40 (93%)	0.10
Thienopyridine	75 (96%)	40 (93%)	0.46
Cilostazole	32 (41%)	11 (26%)	0.09
Statin	45 (58%)	23 (53%)	0.66
ACE-I/ARB	57 (73%)	35 (81%)	0.30
β-blocker	30 (38%)	19 (44%)	0.54
Calcium channel blocker	12 (15%)	9 (21%)	0.45
Nitrate	21 (27%)	14 (33%)	0.52
Nicorandil	21 (27%)	10 (23%)	0.66
Warfarin	6 (7.7%)	7 (16%)	0.15
PPI	31 (40%)	11 (26%)	0.11
H2 blocker	19 (24%)	16 (37%)	0.14

Appendix Table 2. Angiographic and procedural characteristics of the successful and the failed CTO-PCI groups.

Variables		Successful CTO-PCI group N=78	Failed CTO-PCI group N=43	*p*-value
Primary PCI				
Infarct-related artery	Proximal LAD	30 (38%)	11 (26%)	0.15
	LAD	33 (42%)	12 (28%)	0.11
	LCX	11 (14%)	6 (14%)	0.98
	RCA	31 (40%)	24 (56%)	0.09
Unprotected LMCA		3 (3.9%)	1 (2.3%)	0.65
Initial TIMI flow grade=0		75 (96%)	42 (98%)	0.65
BMS use		54 (69%)	34 (79%)	0.24
DES use		17 (22%)	5 (12%)	0.15
Number of implanted stents		1 (1-2)	1 (1-2)	0.14
Total stent length, mm		28 (18-50)	24 (20-41)	0.36
>28 mm		34 (47%)	15 (38%)	0.37
Minimal stent diameter, mm		3 (2.6-3.5)	3 (3-3.5)	0.79
<3.0 mm		78 (100%)	43 (100%)	–
Thrombectomy		42 (54%)	26 (60%)	0.48
Distal protection		5 (6.4%)	2 (4.7%)	0.69
IVUS use		14 (18%)	7 (16%)	0.82
IABP use		32 (41%)	16 (37%)	0.68
PCPS use		6 (7.7%)	2 (4.7%)	0.51
CTO PCI				
Number of CTO		1 (1-1)	1 (1-1)	0.11
Location of target CTO	LAD	26/83 (31%)	12/45 (27%)	0.58
	LCX	30/83 (36%)	20/45 (44%)	0.36
	RCA	27/83 (33%)	13/45 (29%)	0.67
IVUS use		23 (29%)	1 (2.4%)	<0.0001
Interval of CTO PCI after primary PCI (days)		11 (4-17)	7 (0-16.5)	0.14
Staged CTO PCI		64 (82%)	25 (58%)	0.03
DES use		49 (63%)	–	–
Number of implanted stents		1 (1-2)	–	–
Total stent length, mm		34.5 (23-54.5)	–	–
>28 mm		36/66 (55%)	–	–
Minimal stent diameter, mm		2.5 (2.5-3)	–	–
<3.0 mm		42/66 (63%)	–	–

Appendix Table 3. Clinical outcomes in the successful and the failed CTO-PCI groups.

	Successful CTO-PCI group No. of patients with events (cumulative incidence) N=78	Failed CTO-PCI group No. of patients with events (cumulative incidence) N=43	Crude HR (95% CI)	Log-rank *p*-value
All-cause death	20 (23.6%)	9 (22.5%)	1.04 (0.51-2.23)	0.92
Cardiac death	16 (20.9%)	8 (19.1%)	1.05 (0.46-2.58)	0.92
Non-cardiac death	4 (6.9%)	1 (4.2%)	1.01 (0.25-4.95)	0.99
Myocardial infarction	4 (6.9%)	4 (13.9%)	0.50 (0.12-2.12)	0.32
Heart failure hospitalisation	10 (15.1%)	5 (16.4%)	1.09 (0.39-3.49)	0.88
Stroke	4 (6.3%)	4 (10.7%)	0.54 (0.15-1.96)	0.33
Any coronary revascularisation	38 (57.8%)	23 (61.9%)	0.71 (0.43-1.20)	0.19
CABG	3 (4.2%)	4 (12.9%)	0.40 (0.08-1.80)	0.21