

Title page

Title: Chronic total occlusion in 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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Short running title: Clinical impact of CTO in non-IRA in STEMI patients

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Conflict of interest statement

The authors have nothing to disclose concerning the current study.

The total word count: 4997 words

Abstract

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

Methods and Results: Among 5429 patients enrolled in the CREDO-Kyoto AMI registry, the current study population consisted of 2045 STEMI patients with multi-vessel disease (MVD) who underwent primary PCI within 24 hours after the symptom onset. The cumulative 5-year, 30-day and 30-day-to-5-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 $P<.0001$, 12.8% versus 6.3%, log-rank $P<.0001$, and 28.2% versus 16.8%, log-rank $P<.0001$). The adjusted risk for all-cause death in the CTO group was significantly higher during the entire 5 years, during the initial 30 days, and beyond 30-day and up to 5-year, and (hazard ratio[HR]: 1.47, 95% confidence interval [CI]: 1.18-1.84, $P=0.0009$, and HR: 1.49, 95%CI: 1.04-2.13, $P=0.03$, HR: 1.61, 95%CI: 1.23-2.07, $P=0.0006$).

Conclusions: CTO in non-IRA was associated with increased 5-year mortality in STEMI patients with MVD, which was consistently seen even after excluding early deaths within 30-day of the index STEMI event.

Key words: STEMI, multiple vessel disease, chronic coronary total occlusion

Condensed Abstract

We compared 5-year cardiovascular outcomes between STEMI patients with and without CTO in non-IRA using our large registry in addition to performing 30-day landmark analysis to exclude early events. The cumulative 5-year, 30-day and 30-day-to-5-year incidences of all-cause death were all significantly higher in the CTO group than in the non-CTO group. The adjusted risk for all-cause death in the CTO group was significantly higher during the initial 30 days, beyond 30-day and up to 5-year and during the entire 5 years than that in the non-CTO group.

Abbreviations

AMI = acute myocardial infarction

CABG = coronary arterial bypass grafting

CI = confidence interval

CTO = chronic total occlusion

HR = hazard ratio

MI = myocardial infarction

MVD = multi-vessel disease

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

STEMI = ST-elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Text

Introduction

Although primary percutaneous coronary intervention (PCI) is currently established as the first-line treatment of ST-elevation acute myocardial infarction (STEMI), there are still some unanswered questions such as the management of non-infarct-related artery (non-IRA) lesions. Several studies already reported the presence of concurrent chronic total occlusion (CTO) in non-IRA was an independent risk factor of early and late mortality in STEMI patients with multi-vessel disease¹⁻³. However, these studies were confounded with several limitations such as relatively small sample, insufficiently short 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.

Methods

Study population

The Coronary Revascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) AMI registry is a physician-initiated, non-company sponsored, multi-center registry enrolling consecutive AMI patients undergoing coronary revascularization within seven days of symptom onset among 26 centers in Japan between January 2005 and December 2007 (Supplemental Appendix A). The relevant review boards or ethics committees in all participating centers approved the research protocol. Because of retrospective enrollment, written informed consents from the patients were 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 5429 AMI patients enrolled in this registry, the current study population consisted of 2045 STEMI patients with multi-vessel disease (MVD) who underwent primary PCI within 24 hours after the symptom (Figure 1). The patients were classified into 2 groups according to the presence of CTO in the non-IRA (CTO group: 383 patients [18.7%], and non-CTO group: 1662 patients [81.3%]).

Definitions and endpoints

Definitions of baseline clinical characteristics were previously described⁴. 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 center 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. Multi-vessel disease was defined as the presence of at least 1 lesion with % diameter stenosis $\geq$ 50% by visual estimation in at least 1 major non-infarct-related epicardial coronary arteries 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 hospitalization, stroke, stent thrombosis (ST), any coronary revascularization, 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 Study⁵. ST was defined according to the Academic Research Consortium (ARC) definition⁶. Any coronary revascularization was defined as either PCI

or CABG for any reasons.

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 center (Research Institute for Production Development, Kyoto, Japan) (Supplemental Appendix B). 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 hospitalizations, and status of antiplatelet therapy. Death, MI, ST, and stroke were adjudicated by the clinical event committee (Supplemental Appendix C). Median follow-up duration was 1839 (inter-quartile range [IQR]: 1494-2156) days.

Statistical analysis

We expressed categorical variables as numbers and percentages, and continuous variables as mean $\pm$ standard deviation when they followed normal

distribution or as median (interquartile range) when they didn't. The appearance of distribution was judged by illustrating the listed variables in histogram. If it was a bell-shaped appearance, the variables were judged to follow 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 groups 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 centers to estimate the impact of CTO in non-IRA on the entire 5-year, 30-day and 30-day-to-5-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 as listed in Table1 and Table2. 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 and 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 2 groups using the methods

described by Ghali et al⁷. Multivariable adjustment could not be performed for several endpoints due to the small number of events observed. As in our previous reports, we dichotomized some continuous variables by using clinically significant reference values or median values. Statistical analyses were performed by a physician (Watanabe H), and a statistician (Morimoto T) with the use of JMP 10.0 (SAS Institute Inc, Cary, NC) 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 but important aspects (Table 1). On the contrary, the baseline characteristics were not very different between the successful CTO-PCI and the failed CTO-PCI groups (Supplemental Table 1, Supplemental Table 2).

Through the entire 5-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 $P<.0001$). After adjusting for confounders, the excess risk of the CTO group relative to the non-CTO group for all-cause death during the entire 5-year follow-

up remained significant (HR: 1.47, 95%CI: 1.18-1.84, P=0.0009) (Table 3 and 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<.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 and Figure 3). By the landmark analysis at 30-day, the cumulative incidence of and the adjusted risk for all-cause death beyond 30-day and up to 5-year were significantly higher in the CTO group than in the non-CTO group (28.2% versus 16.8%, log rank P<.0001, and HR: 1.61, 95%CI: 1.23-2.07, P=0.0006, respectively) (Table 3 and Figure 3). The cumulative 5-year incidence of and the adjusted risk for cardiac death, heart failure hospitalization, any coronary revascularization, 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 5-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) (Supplemental Table 3, Supplemental Figure).

Discussion

The main findings in the current analysis were: (1) CTO in the non-IRA was independently associated with increased risk for mortality in STEMI patients with multi-vessel disease; (2) This independent increased mortality risk of CTO in the non-IRA was mainly observed beyond 30-day after the index STEMI event; (3) The 5-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 multi-vessel 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 evidence. First of all, as many previous studies 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-day could mainly be explained by more unstable hemodynamic characteristics as in cardiogenic shock at the time of the index STEMI event. Hoebers et al. reported multi-vessel disease with CTO in non-IRA was an independent risk factor of short-term mortality in STEMI patients³. However, the present multivariable analysis indicated an association of CTO in non-IRA with increased long-

term mortality beyond 30-day. One of the possible mechanisms of increased long-term mortality beyond 30-day 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 group⁸. 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 the presence of a CTO was associated with reduced residual LVEF and with a further deterioration of LVEF during follow-up¹. 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 the non-IRA is only a result of multiple cardiovascular comorbidities or it exacerbates mortality of STEMI patients, but it might potentially be a modifiable factor in the improvement of mortality. In the current analysis, the 5-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 from the current situation of CTO PCI. The multivariable analysis could also 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 revascularization is beyond the scope of this study. As discussed previously, the next focus is whether the high rate of successful revascularization of non-IRA CTO ameliorates mortality of STEMI patients or not. The way of dealing with non-IRA lesions in STEMI patients has still been a target of controversy due to a paucity of randomized data and conflicting results in several observational studies. The EXPLORE trial, which randomized 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 4-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 nor LVED at 4-month follow-up⁹. A subgroup analysis suggested 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 suggested the clinical efficacy of preventive PCI of non-culprit lesions in STEMI

patient^{10,11}. PCI of non-IRA CTO assumes a critical role in the treatment of multi-vessel disease because the mastery of CTO PCI is imperative for complete revascularization. Among them, CvLPRIT (Complete Versus culprit-Lesion only PRimary PCI Trial) showed a significant reduction in the primary endpoint of mortality, recurrent MI, heart failure, or ischemia-driven revascularization with 12 months (10.0% vs. 21.2%; hazard ratio:0.45; p=0.009)¹¹. In these two RCTs, CTO in non-IRA was part of the exclusion criteria. Thus, further prospective randomized trials about revascularization of non-IRA lesions including CTO in STEMI patients should be warranted to elucidate the unsolved question.

Limitation

The current study involves several potential limitations. First, most importantly, this is a retrospective observational, but not a prospective randomized 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 didn't include

these factors as adjusting variables in the Cox hazard models because of missing values. We should take the small but significant difference in door-to-balloon time (but not in onset-to-balloon time) between the 2 groups into consideration in interpreting the present study results. Secondly, we chose clinically relevant 15 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 over-fitted 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 relaxed¹². Finally, this study didn't assess detailed angiographic or electrocardiographic findings such as myocardial blush grade or ST-segment resolution.

Conclusions

CTO in non-IRA was associated with increased 5-year mortality in STEMI patients with MVD, which was consistently seen even after excluding early deaths within 30-day of the index STEMI event.

Acknowledgements

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

Funding

This study was supported by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

Impact on daily practice

As with previous studies, our robust analysis in a large cohort demonstrated CTO in the 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, which involved many limitations such as small sample size and the lower patient-level CTO success rate. Whether more successful revascularization of CTO in the non-IRA improves clinical outcomes is the next target of an investigation.

Conflict of interest statement

The authors have no conflict of interest to declare.

Reference

1. Claessen BE, van der Schaaf RJ, Verouden NJ, Stegenga NK, Engstrom AE, Sjaauw KD, Kikkert WJ, Vis MM, Baan J, Koch KT, de Winter RJ, Tijssen JGP, Piek JJ, Henriques JPS. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2009;2:1128–1134.
2. Claessen BE, Dangas GD, Weisz G, Witzenbichler B, Guagliumi G, Möckel M, Brener SJ, Xu K, Henriques JPS, Mehran R, Stone GW. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J.* 2012;33:768–775.
3. Hoebers LP, Vis MM, Claessen BE, van der Schaaf RJ, Kikkert WJ, Baan J, de Winter RJ, Piek JJ, Tijssen JGP, Dangas GD, Henriques JPS. The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. *Eur J Heart Fail.* 2013;15:425–432.
4. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T,

- Shirotani M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Tatami R, Suwa S, Takizawa A, Takatsu Y, Takahashi M, Kato H, Takeda T, Lee JD, Nohara R, Ogawa H, Tei C, Horie M, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther*. 2011;26:234–245.
5. Serruys PW, Ong ATL, Van Herwerden LA, Sousa JE, Jatene A, Bonnier JJRM, Schönberger JPMA, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol*. 2005;46:575–581.
 6. Mauri L, Hsieh W, Massaro JM, Ho KKL, D’Agostino R, Cutlip DE. Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents. *N Engl J Med*. 2007;356:1020–1029.
 7. Ghali WA, Quan H, Brant R, van Melle G, Norris CM, Faris PD, Galbraith PD, Knudtson ML, APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) Investigators. Comparison of 2 methods for calculating

- adjusted survival curves from proportional hazards models. *JAMA*. 2001;286:1494–7.
8. Lexis CPH, Van Der Horst ICC, Rahel BM, Lexis MAS, Kampinga MA, Gu YL, De Smet BJGL, Zijlstra F. Impact of chronic total occlusions on markers of reperfusion, infarct size, and long-term mortality: A substudy from the TAPAS-trial. *Catheter Cardiovasc Interv*. 2011;77:484–491.
 9. Henriques JPS, Hoebers LP, Råmunddal T, Laanmets P, Eriksen E, Bax M, Ioanes D, Suttorp MJ, Strauss BH, Barbato E, Nijveldt R, van Rossum AC, Marques KM, Elias J, van Dongen IM, Claessen BEPM, Tijssen JG, van der Schaaf RJ. Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI. *J Am Coll Cardiol*. 2016;68:1622–1632.
 10. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115–1123.
 11. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McCann GP. Randomized trial of complete versus lesion-only revascularization in patients

undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *JACC*. 2015;65:963–972.

12. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol*. 2007;165:710–718.

Figure titles and legends

Figure 1: Study flow chart

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

Figure 2: Crude and adjusted Kaplan-Meier curves for the cumulative incidence of all-cause death in the CTO and the non-CTO group during the entire 5-year follow-up.

CTO=chronic total occlusion

Figure 3: Crude and adjusted Kaplan-Meier curves for the cumulative incidence of all-cause death in the CTO and the non-CTO group (A) during the initial 30-day, and (B) beyond 30-day and up to 5-year.

CTO=chronic total occlusion

Tables

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

Variables	CTO group N=383	Non-CTO group N=1662	P value
Clinical characteristics			
Age	68.9±12.2	68.6±11.8	0.64
*>75years	138(36%)	547(33%)	0.25
Male	294(77%)	1219(73%)	0.17
Body mass index	23.5±3.5(352)	23.7±3.3(1548)	0.86
<25.0kg/m2	252/352(72%)	1112/1548(72%)	0.96
*Hypertension	299(78%)	1294(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%)	<.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 hemodialysis	25(6.5%)	75(4.5%)	0.11
Left ventricular ejection fraction	47±15(283)	54±13(1268)	<.0001
<40%	95/283(34%)	191/1268(15%)	<.0001
*Hemodialysis	6(1.6%)	32(1.9%)	0.63
*Atrial fibrillation	41(11%)	146(8.8%)	0.25
*Anemia(hemoglobin<11.0g/dl)	38(10%)	170(10%)	0.86
Thrombocytopenia(Platelet < 100*109/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
Characteristics of STEMI			

Killip class≤2	253(66%)	1350(81%)	<.0001
Killip class4	105(27%)	271(16%)	<.0001
Time from symptom onset to admission(hours)	2.5(1.1-5.45)(372)	2.5(1.2-5.7)(1592)	0.29
Onset-to-balloon time(hours)	4.5(3-7.7)(343)	4.35(2.9-7.6)(1428)	0.48
Door to balloon time(hours)	1.7(1.1-2.5)(335)	1.5(1-2.2)(1405)	0.004
Anterior MI	162(42%)	703(42%)	0.99
Peak creatinine phosphokinase	2917(1339.5-5674.5)(376)	2209(1089-4246)(1643)	<.0001

Baseline medications

Aspirin	374(98%)	1634(98%)	0.39
Thienopyridine	352(92%)	1594(96%)	0.002
Cilostazole	129(34%)	583(35%)	0.60
Statin	194(51%)	917(55%)	0.11
*ACE-I/ARB	262(68%)	1220(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.

Table 2: Angiographic and procedural characteristics of the CTO and the non-

CTO groups

Variables	CTO group N=383	Non-CTO group N=1662	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%)	<.0001
BMS use	278(83%)	1199(78%)	0.05
DES use	57(17%)	331(22%)	0.05
Number of implanted stents	1(1-2)(351)	1(1-2)(1568)	0.10
Total stent length	38.5(24-56)(337)	33(24-48)(1538)	0.02
>28mm	133/337(39%)	517/1538(34%)	0.04
Minimal stent diameter	3(2.75-3.5)(338)	3(2.5-3.5)(1538)	0.25
< 3.0mm	100/338(30%)	423/1538(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%)	<.0001
IABP use	154(40%)	284(17%)	<.0001
PCPS use	27(7.1%)	55(3.3%)	0.002
Overall revascularization procedures			
Two-vessel disease	158(41%)	1005(60%)	<.0001
Three-vessel disease	216(56%)	537(32%)	<.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)(1572)	0.22
Total stent length	37(23-66)(346)	36(23-57)(1571)	0.08
>28mm	208/346(60%)	943/1571(60%)	0.96
Minimal stent diameter	3(2.5-3)(346)	3(2.5-3.0)(1572)	0.13
< 3.0mm	154/346(45%)	656/1572(42%)	0.34

Categorical variables are expressed as number (%) unless otherwise indicated.

Continuous variables are shown as mean $\pm$ 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.

Table 3: Clinical outcomes in the CTO and the non-CTO groups**(A) 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=1662	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)	<.0001	1.93 (1.59-2.34)	<.0001
Cardiac death	102(27.7%)	203(12.7%)	2.32 (1.83-2.92)	<.0001	2.39 (1.89-3.03)	<.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 hospitalization	48(16.9%)	122(8.6%)	2.08 (1.49-2.86)	<.0001	2.09 (1.50-2.90)	<.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 revascularization	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)	<.0001

A multivariable Cox proportional hazard models 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>75years, hypertension, diabetes mellitus requiring insulin therapy, prior stroke, eGFR< 30 without hemodialysis, hemodialysis,

atrial fibrillation, anemia, 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.

CTO=chronic total occlusion; HR=hazard ratio; CI=confidence interval;

CABG=coronary artery bypass grafting

(B) 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=1662	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)	<.0001	2.18 (1.54-3.08)	<.0001
Cardiac death	49(12.8%)	103(6.2%)	2.12 (1.50-2.97)	<.0001	2.20 (1.55-3.11)	<.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 hospitalization	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 revascularization	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 hazard model was used in adjusted comparisons of all-cause death, cardiac death and any coronary revascularization 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.

CTO=chronic total occlusion; HR=hazard ratio; CI=confidence interval; CABG=coronary artery bypass grafting

(C) 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=1557	Crude HR (95%CI)	P value	Adjusted HR (95%CI)	P value
All-cause death	88(29.2%)	247(16.8%)	1.81 (1.43-2.27)	<.0001	1.86 (1.47-2.34)	<.0001
Cardiac death	55(17.6%)	100(7.0%)	2.59 (1.88-3.54)	<.0001	2.68 (1.95-3.69)	<.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 hospitalization	46(16.4%)	120(8.4%)	2.04 (1.45-2.82)	<.0001	2.05 (1.46-2.86)	<.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 revascularization	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 hazard 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.

CTO=chronic total occlusion; HR=hazard ratio; CI=confidence interval;

CABG=coronary artery bypass grafting

Figure1: Study population chart

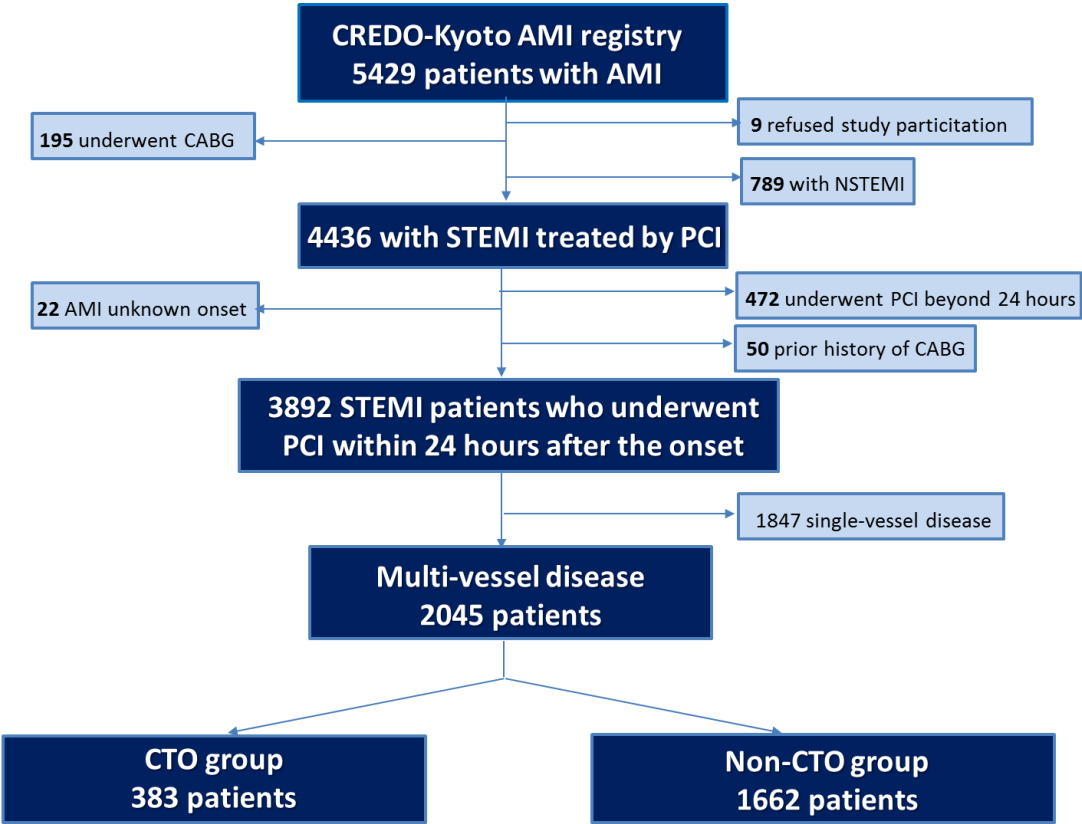


Figure 2.

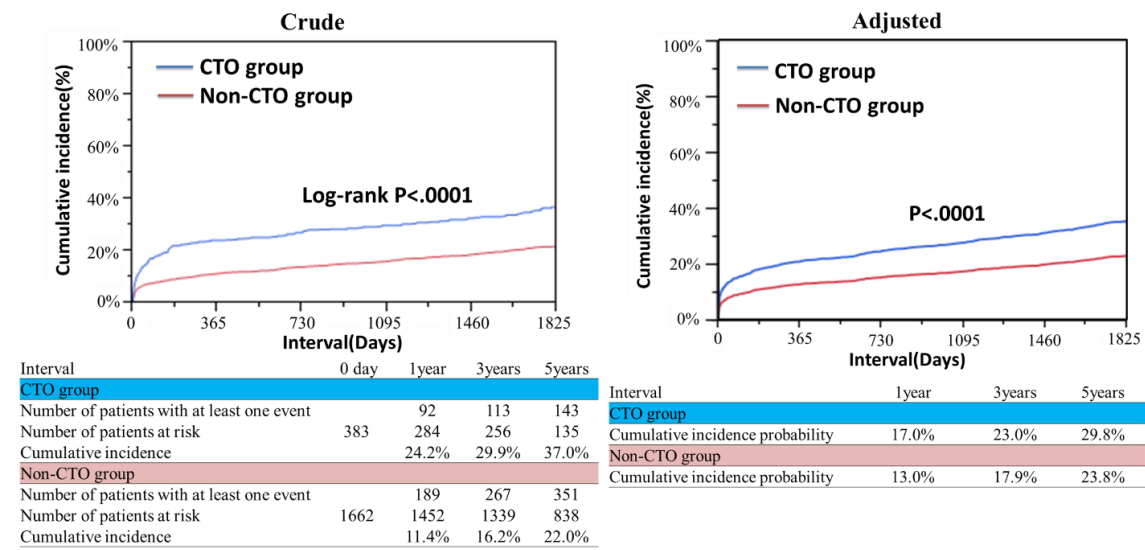
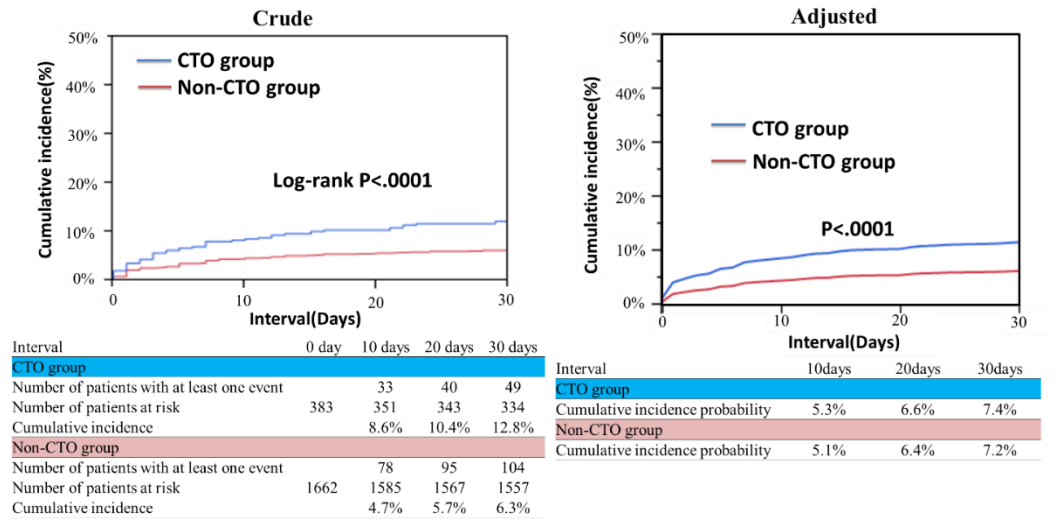
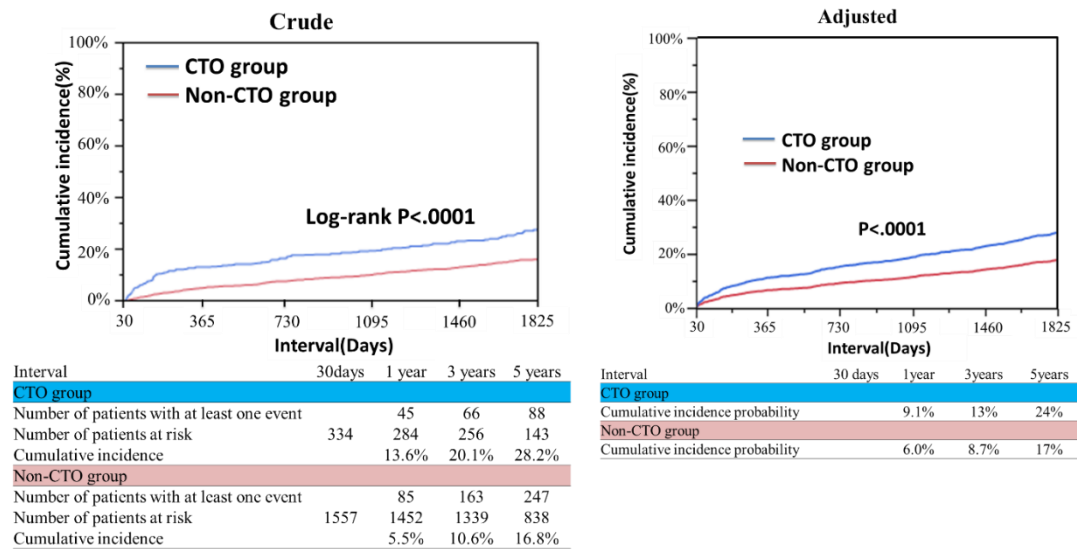


Figure 3.

(A) During the initial 30-day



(B) Beyond 30-day and up to 5-year



Supplemental 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
>75years	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
<25.0kg/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 hemodialysis	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
Hemodialysis	0	1(2.3%)	0.15
Atrial fibrillation	8(10%)	7(16%)	0.34
Anemia(hemoglobin<11.0g/dl)	1(1.3%)	3(7.0%)	0.10
Thrombocytopenia(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≤2	56(72%)	28(65%)	0.45
Killip class4	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	2525(1329-5769)	1718(953-3677)	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

Supplemental Table 2: Angiographic and procedural characteristics of the successful and the failed CTO-PCI groups

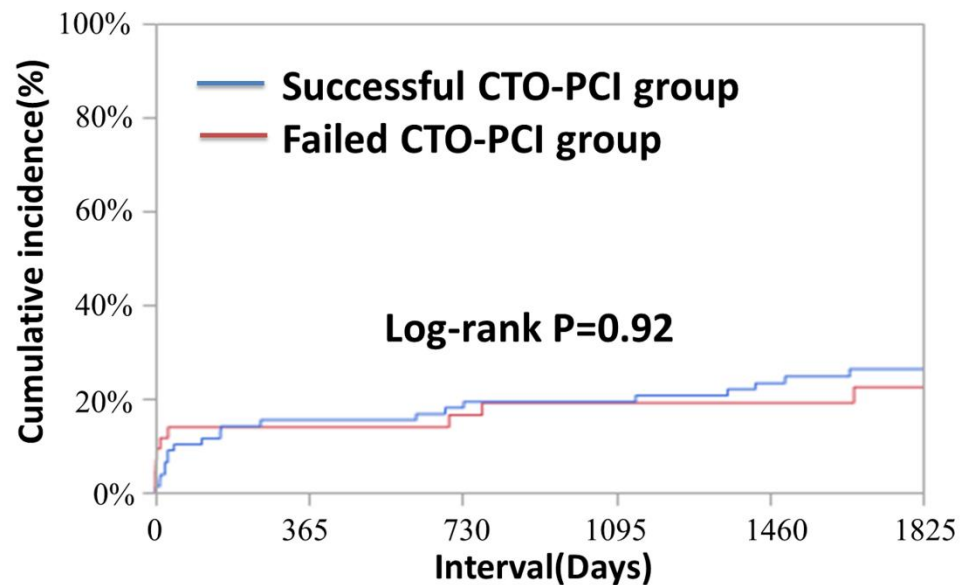
Variables	Successful CTO-PCI group N=78	Failed CTO-PCI group N=43	P value
<u>Primary PCI</u>			
Infarct-related artery			
Proximal LAD	30(38%)	11(26%)	0.15
LAD	33(42%)	12(28%)	0.11
LCX	11(14%)	6(14%)	0.98
RCA	31(40%)	24(56%)	0.09
Unprotected LMCA	3(3.9%)	1(2.3%)	0.65
Initial TIMI flow grade=0	75(96%)	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	28(18-50)	24(20-41)	0.36
>28mm	34(47%)	15(38%)	0.37
Minimal stent diameter	3(2.6-3.5)	3(3-3.5)	0.79
< 3.0mm	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
<u>CTO PCI</u>			
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%)	<.0001
Interval of CTO-PCI after primary PCI(day)	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	34.5(23-54.5)	-	-
>28mm	36/66 (55%)	-	-
Minimal stent diameter	2.5(2.5-3)	-	-
< 3.0mm	42/66 (63%)	-	-

Supplemental 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
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%)	0.5 (0.12-2.12)	0.32
Heart failure hospitalization	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 revascularization	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

Supplemental Figure: 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 5-year follow-up.



Interval	0 day	1 year	3 years	5 years
Successful CTO-PCI group				
No of patients with at least one event		12	15	20
No of patients at risk	78	66	63	37
Cumulative incidence probability		15.5%	19.4%	26.3%
Failed CTO-PCI group				
No of patients with at least one event		6	8	9
No of patients at risk	43	37	31	21
Cumulative incidence probability		14.0%	19.1%	22.5%

Supplemental Appendix A: List of Participating Centers and Investigators for the CREDO-Kyoto AMI Registry

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Hyogo Prefectural Amagasaki Hospital: Hisayoshi Fujiwara, Yoshiki Takatsu, Nobuhisa Ohno

Kitano Hospital: Ryuji Nohara

Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

Kokura Memorial Hospital: Masakiyo Nobuyoshi, Masashi Iwabuchi, Michiya Hanyu

Maizuru Kyosai Hospital: Ryoza Tatami, Tsutomu Matsushita

Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani, Noboru Nishiwaki

Kobe City Medical Center General Hospital: Toru Kita, Yutaka Furukawa, Yukikatsu Okada

Nishi-Kobe Medical Center: Hiroshi Kato, Hiroshi Eizawa

Kansai Denryoku Hospital: Katsuhisa Ishii

Osaka Red Cross Hospital: Masaru Tanaka, Shogo Nakayama

University of Fukui Hospital: Jong-Dae Lee, Akira Nakano, Takaaki Koshiji, Koichi Morioka

Shizuoka City Shizuoka Hospital: Akinori Takizawa, Mitsuomi Shimamoto, Fumio Yamazaki

Hamamatsu Rosai Hospital: Masaaki Takahashi, Junichiro Nishizawa

Shiga University of Medical Science Hospital: Minoru Horie, Hiroyuki Takashima

Japanese Red Cross Wakayama Medical Center: Takashi Tamura, Masaki Aota

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Shimada Municipal Hospital: Ryuichi Hattori, Takeshi Aoyama, Makoto Araki

Juntendo University Shizuoka Hospital: Satoru Suwa, Keiichi Tanbara

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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.

Supplemental Appendix C: List of clinical event 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).