Long-Term Outcomes after Percutaneous Coronary Intervention for Chronic Total Occlusion (From the CREDO-Kyoto registry Cohort-2)

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Short title: Outcomes after PCI for CTO

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Abstract

Despite improving success rate of percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) lesions, the clinical benefit of recanalization of CTO is still a matter of debates. The purpose of this study is to elucidate the impact of successful PCI for CTO on cardiovascular outcome in a large Japanese observational database of patients who underwent first coronary revascularization. Among 13087 patients who underwent PCI in the CREDO-Kyoto registry Cohort-2, 1524 patients received PCI for CTO. Clinical outcomes were compared between 1192 patients with successful CTO-PCI and 332 patients with failed CTO-PCI. In-hospital death tended to occur less frequently in the successful CTO-PCI group than in the failed CTO-PCI group (1.4% vs. 3.0%, P=0.053). Through 3-year follow-up, the cumulative incidence of all-cause death was not significantly different between the successful and failed CTO-PCI groups (9.0% vs. 13.1%, p=0.18), while the cumulative incidence of cardiac death was significantly lower in the successful CTO-PCI group than in the failed CTO-PCI group (4.5% vs. 8.4%, P=0.03). However, after adjusting confounders, successful PCI for CTO was not associated with lower risk for all-cause death (Hazard ratio [HR]: 0.93, 95% confidence interval [CI]: 0.64-1.37, P=0.69) nor for cardiac death (HR: 0.71, 95% CI: 0.44-1.16, P=0.16). The cumulative incidence of coronary artery bypass grafting (CABG) was remarkably lower in patients with successful PCI compared to those with failed PCI (1.8% vs. 19.6%, P<0.0001). In conclusion, successful PCI for CTO as compared with failed PCI was not associated with lower risk for 3-year mortality.

Key words: chronic total occlusion, percutaneous coronary intervention, coronary artery disease, prognosis.

Text

Percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) has dramatically changed in recent years. The improvement of devices such as the guidewires, microcatheters, as well as low-profile balloon catheters and refinement of operator techniques such as parallel wire technique and retrograde approach have contributed to the improved success rate for CTO-PCI, although the penetration rates of parallel wire technique and retrograde approach might be different between Japan and outside Japan.[1] Furthermore, introduction of drug-eluting stent (DES) has significantly reduced the restenosis and reocclusion rates in the CTO lesions.[2-3] Successful CTO-PCI has been reported to be associated with less subsequent coronary artery bypass grafting (CABG), improvement of left ventricular function and relief of symptoms.[4-6] There are several reports that successful CTO-PCI improved the long-term survival outcomes after revascularization.[7-8] Recently, Mehran and Jones also reported successful PCI for CTO was independently associated with lower cardiac morality.[9-10] However, many previous studies were associated with relatively low procedural success rates. Procedural success rate itself might have significant influence in analyzing the effect of successful CTO-PCI on survival outcome. Survival outcome after CTO-PCI should also be investigated in a population with relatively high procedural success rates. Therefore, we analyzed the impact of successful PCI for CTO on cardiovascular outcomes in a large Japanese observational database of patients who underwent first coronary revascularization.

Methods

The CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome study in Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) registry cohort-2 is a multi-center registry

enrolling consecutive patients undergoing first coronary revascularization procedures among 26 centers in Japan between January 2005 and December 2007 (Supplementary 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 participation in the study when contacted for follow-up. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

The design and patient enrollment of the CREDO-Kyoto PCI/CABG registry cohort-2 has been described previously.[11] Among a total of 15263 patients, 13087 patients underwent PCI as their first coronary revascularization procedure during the 3 years of enrollment period. Among 2491 patients (19%) with at least 1 CTO lesion, 1524 patients underwent attempt of PCI for CTO lesions. PCI for at least one CTO lesion was successful in 1192 patients (successful CTO-PCI group), while PCI for CTO lesions was unsuccessful in 332 patients (failed CTO-PCI group) (78% initial patient success rate for CTO) (Figure 1). The number of cases and initial success rate of CTO-PCI in each participating center were illustrated in Supplemental Figure 1. In the successful PCI group, 1230 lesions out of 1245 CTO lesions in 1192 patients were successfully treated (1154 patients had 1 treated CTO lesion and 38 patients had 2 treated CTO lesions). A total of 2032 stents were used in the successful CTO-PCI group; 1589 were drug-eluting stents (78%) and 443 were bare-metal stents (22%). In the failed PCI group, no CTO lesion among 339 CTO lesions in 332 patients was successfully treated, while 262 non-CTO lesions were successfully treated in 177 patients. In the current pre-specified substudy of the

CREDO-Kyoto PCI/CABG registry cohort-2, we compared 3-year clinical outcome between the successful and failed CTO-PCI groups.

Definitions of baseline clinical characteristics were described previously.[11] *CTO* was defined as complete obstruction of the vessel with Thrombolysis In Myocardial Infarction (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 myocardial infarction (MI) in the target vessel territory, the previous coronary angiography, or changes in electrocardiographic findings. *Procedural success* was defined as a final diameter stenosis of <50% and a TIMI flow of 2 or 3.

All-cause death was regarded as the primary outcome measure in the current analysis. Cardiac death, MI, stroke, stent thrombosis (ST), CABG and any coronary revascularization were also assessed as endpoints. *Death* was regarded as *cardiac in origin* unless an obvious non-cardiac cause could be identified. Any death during the index hospitalization was regarded as *cardiac death*. *MI* was defined according to the definition in the Arterial Revascularization Therapy Study.[12] Within 1 week of the index procedure, only Q-wave MI was adjudicated as MI. *Stroke* was defined as ischemic or hemorrhagic stroke either occurring during the index hospitalization or requiring hospitalization with symptoms lasting >24 hours. *ST* was defined according to the Academic Research Consortium (ARC) definition.[13] ARC definite ST was used as the end point for ST in this study. The recommend antiplatelet regimen was aspirin (≥81 mg daily) indefinitely and thienopyridine (200 mg ticlopidine or 75 mg clopidogrel daily) for at least 3 months. Duration of antiplatelet therapy was left to the discretion of each attending physician.

Demographic, angiographic, and procedural data were collected from hospital charts or databases according to the pre-specified definitions by the experienced clinical research coordinators in the independent clinical research organization (Research Institute for Production Development, Kyoto, Japan) (Supplementary Appendix B). Follow-up data were collected also by the experienced clinical research coordinators from hospital charts or by contacting patients, or referring physicians. Death, MI, stroke and ST were adjudicated against original source documents by a clinical event committee (Supplementary Appendix C). Median follow-up duration was 934 (inter-quartile range [IQR]: 669-1243) days.

Categorical variables were compared with the chi-square test. Continuous variables were expressed as mean value ± standard deviation or median and IQR. Continuous variables were compared using the Student's *t*-test or Wilcoxon rank sum test based on their distributions. Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed with the log-rank test. We used Cox proportional hazard models to estimate the risk of the successful CTO-PCI group relative to the failed CTO-PCI group adjusting for the differences in patient characteristics and procedural factors as well as medications. In consistent with our previous reports, we selected 34 clinically relevant factors shown in Table 1 as potential independent risk-adjusting variables.[11,14] Independent correlates for all-cause death were identified by a backward elimination procedure (Supplemental Table 1). The final model incorporated the successful CTO-PCI together with 8 variables remaining after the backward procedure. Adjusted analysis for the other endpoints was performed by using the same 8 risk-adjusting variables as used in the analysis for all-cause death. The continuous variables were dichotomized by clinically meaningful reference values or median values. The effect of the successful CTO-PCI (the successful CTO-PCI

group compared to the failed CTO-PCI group) was expressed as hazard ratios (HR) and their 95% confidence intervals (CI). Post-hoc subgroup analysis was also conducted for an exploratory purpose in several clinically relevant subgroups. Statistical analyses were conducted by two physicians (Yamamoto E and Natsuaki M) and by a statistician (Morimoto T) with the use of JMP 10.0 (SAS Institute Inc, Cary, NC) and SAS 9.2 (SAS Institute Inc, Cary, NC) softwares. All the statistical analyses were two-tailed. P values <0.05 were considered statistically significant.

Results

At baseline, acute myocardial infarction, shock at presentation, multivessel disease, moderate to severe mitral regurgitation and dialysis were more prevalent in the failed CTO-PCI group than in the successful CTO-PCI group, while prior MI was more common in the successful CTO-PCI group. Regarding lesion and procedural characteristics, right coronary artery was more frequently targeted in the failed CTO-PCI group than in the successful PCI group. Aspirin and thienopyridine were more frequently used in the successful CTO-PCI group than in the failed CTO-PCI group, while nitrates were more often used in the failed CTO-PCI group (Table 1).

Regarding the procedural complications, coronary perforation was significantly more frequent in the failed CTO-PCI group than in the successful CTO-PCI group. However, there was no significant difference in the incidences of coronary dissection, cardiac tamponade and pericardial drainage between the 2 groups (Table 2). Regarding the in-hospital adverse events, incidence of death and MI tended to be lower in the successful CTO-PCI group. However, there was no significant difference in the incidence of stroke between the 2 groups (Table 2).

The median follow-up durations were 942 (IQR: 679-1245) days in the successful PCI group and 907

(IQR: 635-1235) days in the failed PCI group. The median duration of dual anti-platelet therapy (DAPT) was significantly different between the successful and failed PCI groups (475 [IQR: 91-874] days vs. 35 [IQR: 1-543] days, P<0.0001) (Supplemental Figure 2). Through 3-year follow-up, the cumulative incidence of all-cause death was not significantly different between the successful and failed CTO-PCI groups, while the cumulative incidence of cardiac death was significantly lower in the successful CTO-PCI group than in the failed CTO-PCI group (Table 3, and Figure 2). After adjusting confounders, however, the risks of successful PCI relative to failed PCI for both all-cause death and cardiac death were not significant (Table 3). There was no significant difference in the incidences of MI, stroke and definite ST between the 2 groups (Table 3, and Figure 3). The adjusted risks of successful PCI relative to failed PCI for MI, stroke and definite ST were also not significant (Table 3). Cumulative incidence of CABG was remarkably lower in the successful PCI group than in the failed PCI group. The cumulative incidence of any coronary revascularization was also lower in the successful PCI group than in the failed PCI group (Figure 3). Even after adjusting confounders, the lower risk of successful PCI relative to failed PCI for CABG and any coronary revascularization remained significant (Table 3).

In the post-hoc subgroup analysis, successful PCI was not associated with lower risk for all-cause death in any of the subgroups evaluated. However, successful PCI was associated with lower risk for cardiac death in several subgroups including patients with treated CTO lesion located in left anterior descending artery, patients with single vessel disease, patients without history of heart failure, and patients without diabetic mellitus (Table 4).

Discussion

The main findings of the current study are as follows: (1) Successful PCI for CTO as compared with failed

PCI for CTO was not associated with lower risk for 3-year mortality; (2) However, successful PCI for CTO was associated with significantly lower risk for subsequent CABG. CTO-PCI was one of the most challenging fields in the interventional cardiology in the past decade. In the early 2000s, the success rate of CTO-PCI was 60%-70%.[9,15] Recently, the reported success rate of CTO-PCI has reached >80% owing to the development of devices such as tapered wires or micro-catheters as well as advances in operators' techniques such as parallel wire technique and retrograde approach.[16-19] In consistent to these reports, initial patient success rate of CTO-PCI was 78% in this study. Successful CTO-PCI is reported to be associated with less subsequent CABG, improvement in left ventricular function and relief of symptoms, which are the main reasons for physicians to perform CTO-PCI.[4-6] However, the impact of successful PCI for CTO on long-term prognosis is still a matter of debates.[8,20-23] Most of previous studies evaluating the impact of successful CTO-PCI on long-term outcome adopted the methodology comparing the long-term mortality after successful CTO-PCI with that after failed CTO-PCI. Suero and Hoye reported successful revascularization of CTO were independent predictors of all-cause death.[7,15] Recently, Mehran reported that successful PCI for CTO was an independent predictor of all-cause death and cardiac death.[9]

In this study, successful PCI for CTO was not associated with lower risk for all-cause death and cardiac death. This result is not consistent to previous reports and there might be several reasons for this discrepancy. First, complications of CTO-PCI might have some influence on the mortality after PCI. Coronary perforation was significantly higher in the failed CTO-PCI group than in the successful CTO-PCI group in this study. However, there were no significant differences in the frequency of severe complications such as cardiac tamponade or pericardial drainage. In contrast, severe complications were more frequent in the failed PCI group than in the

successful PCI group in previous reports. Mehran et al. reported rate of coronary perforation and residual dissection was 7.4% and 9.4% respectively in failed group, and 1.7% and 4.3% in success group.[9] Olivari reported that 2.3% of patients in the failed CTO-PCI group underwent emergent CABG (no emergent CABG in our study).[4] Additionally, some reports reported that the incidence of in-hospital MACE was significantly high in failed CTO-PCI group.[7,15] Second, the difference in the rate of subsequent revascularization after the index PCI might be related to the difference in the outcome. Valenti reported that the incidence of CABG at 1 year was 9.1% in the failed PCI group, which was remarkably lower compared with current study (17.9%).[23] Additionally, among 332 patients in the failed CTO-PCI group, 167 patients underwent repeated revascularization procedures for CTO during 3 years and 113 patients got successful revascularization (PCI: 53 patients, CABG: 60 patients). Subsequent coronary revascularization in patients with failed CTO-PCI might heve attenuated the possible long-term mortality benefit of successful CTO-PCI. Third, the differences in background patient characteristics between the success and failed CTO-PCI groups should be taken in consideration. Fefer et al reported that only 10% of patients who have CTO lesions underwent CTO-PCI in Canadian multicenter chronic total occlusion registry.[24] In contrast, 1524 patients out of 2491 patients with CTO lesions (61%) underwent CTO-PCI in this study. Patients' backgrounds in this study seemed to be worse compared to those reported in previous studies. Additionally, due to relatively high initial success rate, successful CTO-PCI group included many patients with complex clinical and procedural characteristics, who are deemed to have poor long-term prognosis. The success rates of CTO-PCI reported in previous studies suggesting better survival outcome after successful CTO-PCI were lower than the success rate in our study (Mehran: 68.5%, Jones: 69.6%, Aziz: 69.4%).[9,10,25] It might be postulated that many complex patients

included in the successful CTO-PCI group in our study could be included in the failed CTO-PCI group in these previous reports, leading to worse survival outcome in the failed CTO-PCI group. Indeed, the failed CTO-PCI group in these previous reports included more patients with older age,[23] lower left ventricular ejection fraction, and previous MI[10] than the successful CTO-PCI group, while in the current study, there was no significant difference between the successful and failed CTO-PCI groups with regard to these factors.

There is no randomized controlled trial comparing PCI plus medical therapy with medical therapy alone in patients with CTO. Given the discrepancy between the current and previous studies in terms of long-term mortality benefit of successful CTO-PCI, it is currently unclear whether successful CTO-PCI could improve long-term mortality. Recently, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME-2) study demonstrated that in patients with stable coronary artery disease (CAD) and functionally significant stenosis, PCI guided by fractional flow reserve plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the need for urgent revascularization.[26] However, the benefit of avoiding the need for urgent revascularization could not be expected in stable CAD patients with CTO. A significant proportion of stable CAD patients with CTO are asymptomatic and therefore, we also could not expect symptomatic relief in this patient population. Furthermore, recent prospective randomized trials comparing PCI using DES with CABG in patients with complex multivessel CAD clearly demonstrated better long-term survival with less MI during follow-up with CABG.[27-28] Therefore, most of the complex multivessel CAD patients with CTO should be referred to CABG surgery, although the above mentioned randomized controlled trials included relatively small number of patients with CTO (6-24%). According to these recent observations, the appropriate indications for CTO-PCI

seemed to be limited.

In the exploratory subgroup analysis of this study, successful PCI was associated with lower risk for cardiac death in several subgroups. Safley also reported that successful PCI for CTO was a multivariable predictor for long-term survival in patients with treated LAD CTO lesion.[29] Therefore, it is possible that successful CTO-PCI could be associated with improved survival outcome in some selected subgroups of patients. However, we should be very careful in interpreting the results of the subgroup analysis in the overall negative study.

Prospective randomized trials comparing PCI plus medical therapy with medical therapy alone in patients with CTO, adequately powered for evaluating long-term mortality, are absolutely required to define the indication of PCI for CTO. Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION-CTO) trial is currently ongoing.

There are several limitations in this study. This is an observational study and the baseline patient characteristics were significantly different between the 2 groups. Despite statistical adjustment, it was not certain whether the mortality outcome was related to the successful CTO-PCI itself or was related to the presence of unmeasured confounders. Second, the current analysis was obviously underpowered in evaluating long-term mortality, although we enrolled relatively large number of patients with CTO as compared with previous studies. Third, there were no criteria to perform PCI for CTO lesions and the decision was left to each attending physician. Therefore, the conclusions of the current study could not be extrapolated to CTO-PCI in general. Fourth, patients with failed CTO-PCI are not equivalent to those patients with CTO who were managed with medical therapy alone. Fifth, the skill for CTO-PCI is demanding and therefore, procedural outcome as well as long-term outcome could

be different according to the centers or operators. Sixth, the low treatment rate of statins, beta blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers may have significant impact on the overall event rates at follow-up. Seventh, successful intervention of non-CTO lesions may lead to difficulty in detecting a difference between the 2 groups. Furthermore, high rate of subsequent coronary revascularization in patients with failed CTO-PCI might have attenuated the possible long-term mortality benefit of successful CTO-PCI in this study. Eighth, the duration of DAPT was different between the successful and failed PCI group, which might have influenced the long-term outcome. Finally, there was no information about the viability or ischemia in the myocardial territory subtended by the targeted lesions in this study.

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Disclosures

None

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Figure legends

Figure 1.

Study flow chart.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CTO, chronic total occlusion.

Figure 2.

Cumulative incidences of (A) all-cause death and (B) cardiac death: the success PCI vs. failed PCI group.

PCI, percutaneous coronary intervention;

Figure 3.

Cumulative incidences of (A) myocardial infarction, (B) stroke, (C) CABG and (D) any coronary revascularization: the success PCI vs. failed PCI group.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 1. Baseline Characteristics: Successful versus Failed PCI for Chronic Total Occlusion

Variable	Success (N=1192)	Failure (N=332)	P value
(A) Clinical characteristics			
Age (years)	66.9±10.8	66.2±10.7	0.32
Age >= 75*	324 (27%)	80 (24%)	0.26
Male*	926 (78%)	253 (76%)	0.57
BMI (kg/m^2)	24.2±3.6	24.3±3.6	0.82
BMI < 25.0**	762 (64%)	205 (62%)	0.47
Acute myocardial infarction*	101 (8.5%)	63 (19%)	<0.0001
Hypertension*	989 (83%)	290 (87%)	0.055
Diabetes mellitus	498 (42%)	141 (42%)	0.82
on insulin therapy*	114 (9.6%)	32 (9.6%)	0.97
Current smoker*	389 (33%)	118 (36%)	0.32
Heart failure**	258 (22%)	81 (24%)	0.29
Shock at presentation*	25 (2.1%)	19 (5.7%)	0.001
Multivessel coronary disease**	853 (72%)	277 (83%)	<0.0001
Mitral regurgitation grade 3/4*	65 (7.1%)	31 (13%)	0.005
Ejection fraction (%)	55.4 ±13.4	54.3 ±14.6	0.23
Prior myocardial infarction*	381 (32%)	80 (24%)	0.006
Prior stroke*	178 (15%)	56 (17%)	0.39
Peripheral vascular disease*	93 (7.8%)	27 (8.1%)	0.84
eGFR < 30, not on dialysis**	45 (3.8%)	13 (3.9%)	0.91
Dialysis**	43 (3.6%)	27 (8.1%)	0.0005
Atrial fibrillation*	99 (8.3%)	26 (7.8%)	0.78
Anemia (hemoglobin < 11 g/dl)**	131 (11%)	40 (12%)	0.59
Platelet < $100*10^9/L$*	17 (1.4%)	4 (1.2%)	0.76
Chronic obstructive pulmonary disease*	35 (2.9%)	11 (3.3%)	0.72
Liver cirrhosis*	27 (2.3%)	8 (2.4%)	0.88
Malignancy*	80 (6.7%)	26 (7.8%)	0.48
(B) Procedural characteristics			
Number of target lesions	1.8±0.9	1.8±0.9	0.96
Number of target vessels	1.6±0.7	1.6±0.7	0.88
Number of CTO vessels	1.1±0.4	1.2±0.4	0.4
Number of target CTO vessels	1.0±0.2	1.0±0.1	0.053
Location of target CTO			

Left anterior descending	505 (42%)	121 (36%)	0.053
Proximal left anterior descending*	458 (38%)	111 (33%)	0.1
Left circumflex	346 (29%)	88 (27%)	0.37
Right	507 (43%)	176 (53%)	0.0007
Unprotected left main*	1 (0.1%)	0	0.6
Contrast media volume	211 (150-303)	207 (146-300)	0.26
(C) Baseline medication			
Antiplatelet therapy			
Thienopyridine	1172 (98%)	303 (91%)	<0.0001
Ticlopidine	1058 (91%)	279 (92%)	0.42
Clopidogrel	110 (9.4%)	24 (7.9%)	
Aspirin	1181 (99%)	322 (97%)	0.004
Cilostazol*	140 (12%)	48 (14%)	0.18
Other medications			
Statin**	633 (53%)	160 (48%)	0.11
Beta-blockers*	379 (32%)	124 (37%)	0.06
ACE-I / ARB**	678 (57%)	195 (59%)	0.55
Nitrates*	475 (40%)	155 (47%)	0.03
Calcium channel blockers*	488 (41%)	140 (42%)	0.69
Nicorandil*	303 (25%)	93 (28%)	0.34
Warfarin*	99 (8.3%)	28 (8.4%)	0.94
Proton pump inhibitors*	278 (23%)	71 (21%)	0.46
H2-blockers*	267 (22%)	86 (26%)	0.18

Values are expressed as mean ± SD or median (inter-quartile range).

BMI indicated body mass index; eGFR, estimated glomerular filtration rate; CTO, chronic total occlusion; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

* Potential independent variables selected for Cox proportional hazard models.

** Risk-adjusting variables.

Table 2. Procedural Complications and In-hospital Adverse Events

Variable	Success (N=1192)	Failure (N=332)	P value
Procedural Complications			
Coronary dissection	12 (1.0%)	5 (1.5%)	0.44
Coronary perforation	7 (0.6%)	10 (3.0%)	0.0002
Cardiac tamponade	3 (0.3%)	2 (0.6%)	0.32
Pericardial drainage	0	1 (0.3%)	0.06
In-hospital adverse events			
Death	17 (1.4%)	10 (3.0%)	0.053
Myocardial infarction	10 (0.8%)	7 (2.1%)	0.053
Stroke	5 (0.4%)	2 (0.6%)	0.66
Coronary bypass	0	1 (0.3%)	0.06
Any coronary revascularization	13 (1.1%)	8 (2.4%)	0.07

Table 3. Unadjusted and Adjusted Risk for Clinical Events

Variable	Success N of events /N of patients (Incidence)	Failure N of events /N of patients (Incidence)	Unadjusted HR (95%CI)	P value	Adjusted HR (95%CI)	P value
All-cause death	92/1192 (9.0%)	35/332 (13.1%)	0.77 (0.53-1.30)	0.18	0.93 (0.64-1.37)	0.69
Cardiac death	46/1192(4.5%)	24/332 (8.4%)	0.58 (0.37-0.95)	0.03	0.71 (0.44-1.16)	0.16
Myocardial infarction	30/1192 (3.2%)	15/332 (5.5%)	0.54 (0.30-1.01)	0.052	0.60 (0.33-1.13)	0.11
Stroke	52/1192 (5.0%)	19/332 (6.3%)	0.71 (0.43-1.21)	0.2	0.81 (0.49-1.40)	0.45
Coronary bypass	20/1192 (1.8%)	60/332 (19.6%)	0.08 (0.05-0.13)	<0.0001	0.09 (0.06-0.15)	<0.0001
Any coronary revascularization	389/1192 (35.5%)	60/332 (55.7%)	0.46 (0.38-0.55)	<0.0001	0.50 (0.41-0.60)	<0.0001

Cumulative incidence was estimated by the Kaplan-Meier method.

HR indicated hazard ratio; CI, confidence interval.

Table 4. Subgroup Analysis for All-cause Death and Cardiac Death at 3 Years

Variable	Success N of events /N of patients (Incidence)	Failure N of events /N of patients (Incidence)	Unadjusted HR (95%CI)	P value
All-cause death				
Multivessel coronary disease	79/853 (10.8%)	30/277 (13.7%)	0.92 (0.62-1.40)	0.69
Single vessel coronary disease	13/399 (4.6%)	5/55 (9.9%)	0.40 (0.15-1.23)	0.06
History of heart failure	50/258 (22.1%)	16/81 (24.5%)	1.01 (0.60-1.84)	0.98
No history of heart failure	42/934 (5.4%)	19/251 (9.5%)	0.63 (0.29-1.07)	0.07
Left anterior descending	35/505 (8.3%)	14/121 (13.3%)	0.67 (0.38-1.28)	0.19
Non-left anterior descending	57/687 (9.6%)	21/211 (13.0%)	0.83 (0.52-1.37)	0.45
Diabetes mellitus	48/498 (11.4%)	14/141 (11.3%)	0.99 (0.57-1.82)	0.97
Non-diabetes mellitus	44/694 (7.4%)	21/191 (14.5%)	0.62 (0.38-1.04)	0.06
Cardiac death				
Multivessel coronary disease	40/853 (5.6%)	19/277 (8.1%)	0.76 (0.45-1.30)	0.3
Single vessel coronary disease	6/399 (1.8%)	5/55 (9.9%)	0.20 (0.06-0.68)	0.01
History of heart failure	35/258 (15.6%)	12/81 (17.6%)	0.94 (0.51-1.88)	0.86
No history of heart failure	11/934 (1.5%)	12/251 (5.5%)	0.32 (0.16-0.68)	0.004
Left anterior descending	15/505 (3.7%)	10/121 (9.2%)	0.43 (0.21-0.97)	0.04
Non-left anterior descending	14/687 (5.1%)	14/211 (8.0%)	0.70 (0.39-1.33)	0.27
Diabetes mellitus	26/498 (6.2%)	11/141 (8.4%)	0.71 (0.38-1.45)	0.33
Non-diabetes mellitus	20/694 (3.3%)	13/191 (8.4%)	0.47 (0.24-0.95)	0.04

Figure 1.

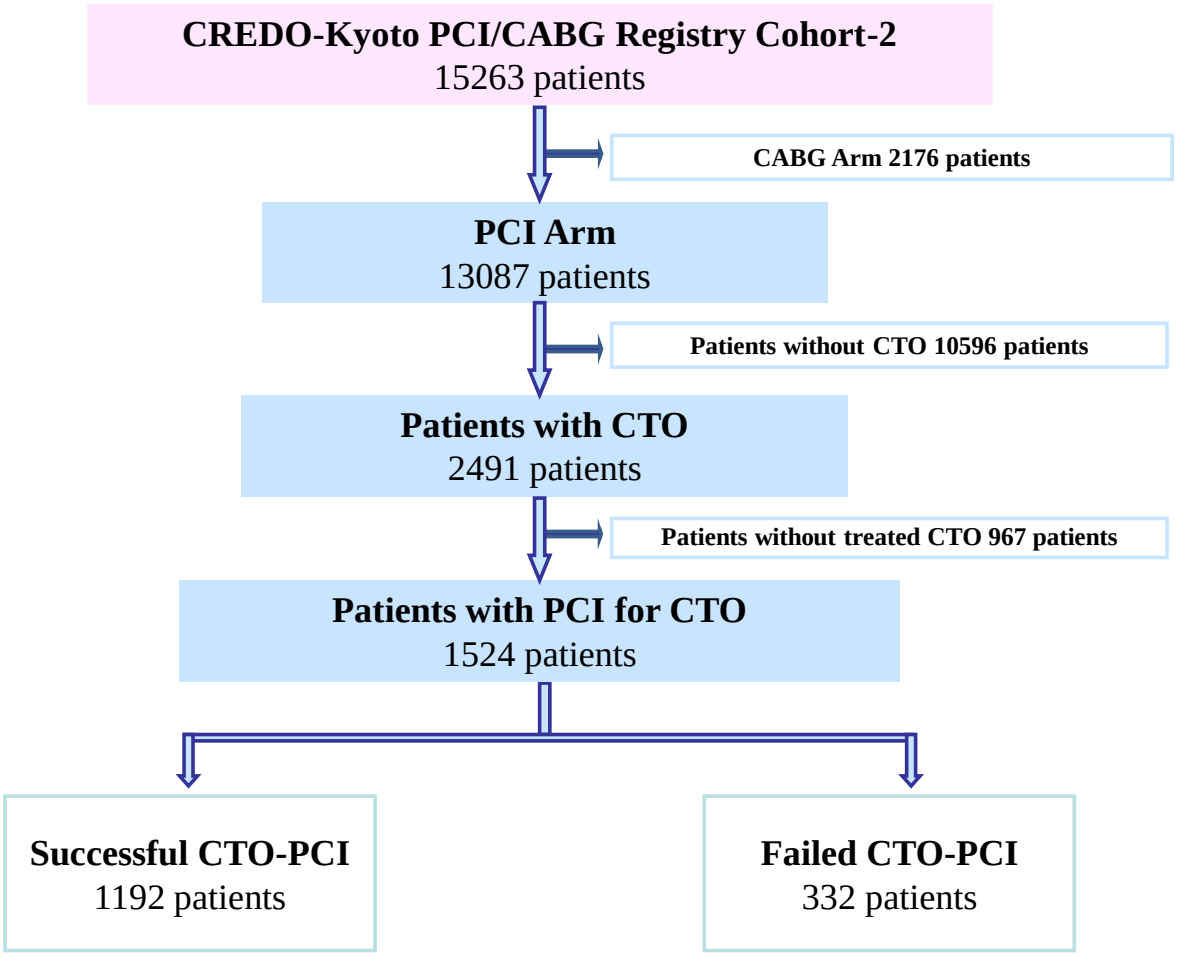
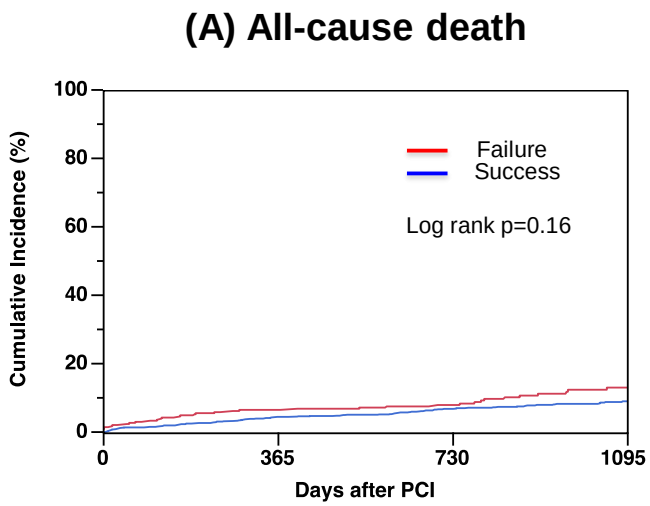
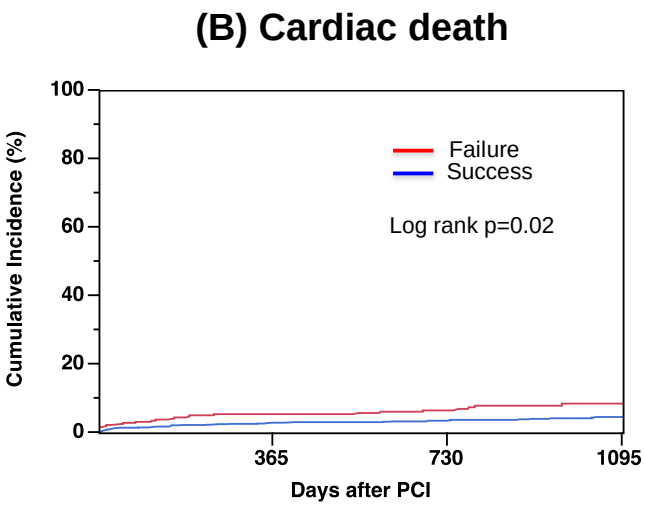

CREDO-Kyoto PCI/CABG Registry Cohort-2
15263 patients
CABG Arm 2176 patients
PCI Arm
13087 patients
Patients without CTO 10596 patients
Patients with CTO
2491 patients
Patients without treated CTO 967 patients
Patients with PCI for CTO
1524 patients
Successful CTO-PCI
1192 patients
Failed CTO-PCI
332 patients

Figure 2.



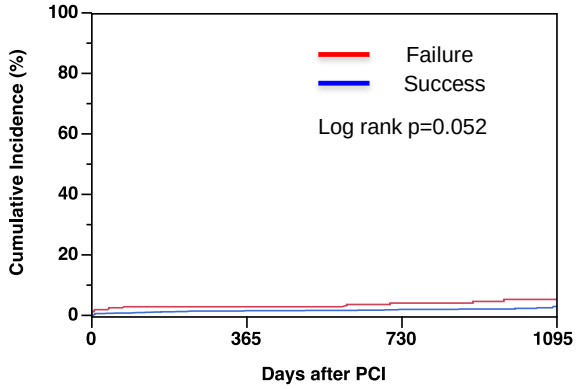
Interval	0days	30days	1year	2years	3years
Success					
Cumulative incidence		1.3%	4.5%	6.8%	9.0%
N of patients with event		15	53	77	92
N of patients at risk	1192	1175	1108	825	453
Failure					
Cumulative incidence		2.4%	6.5%	8.0%	13.1%
N of patients with event		8	21	25	35
N of patietns at risk	332	315	289	222	128



Interval	0days	30days	1year	2years	3years
Success					
Cumulative incidence		1.2%	2.8%	3.4%	4.5%
N of patients with event		14	33	39	46
N of patients at risk	1192	1175	1108	825	453
Failure					
Cumulative incidence		2.4%	5.3%	6.4%	8.4%
N of patients with event		8	17	20	24
N of patients at risk	332	315	289	222	128

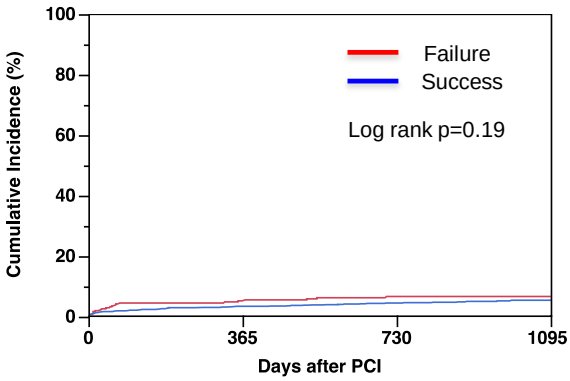
Figure 3.

(A) Myocardial infarction



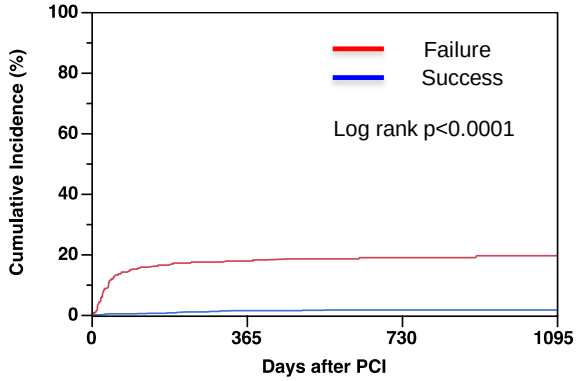
Interval	0days	30days	1year	2years	3years
Success					
Cumulative incidence		0.8%	1.8%	2.2%	3.2%
N of patients with event		10	21	25	30
N of patients at risk	1192	1166	1089	808	442
Failure					
Cumulative incidence		2.2%	3.1%	4.3%	5.5%
N of patients with event		7	10	13	15
N of patients at risk	332	309	281	215	124

(B) Stroke



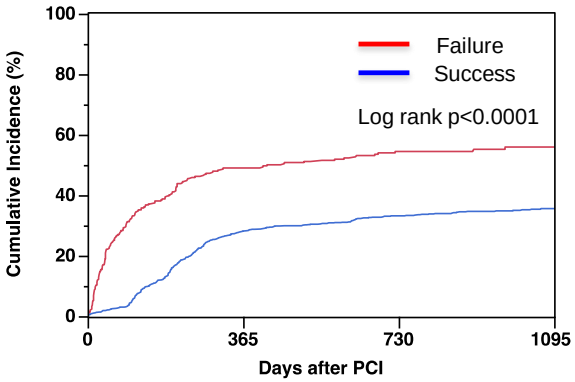
Interval	0days	30days	1year	2years	3years
Success					
Cumulative incidence		1.2%	3.0%	4.1%	5.0%
N of patients with event		14	35	46	52
N of patients at risk	1192	1163	1085	803	439
Failure					
Cumulative incidence		1.9%	5.1%	6.3%	6.3%
N of patients with event		6	16	19	19
N of patients at risk	332	310	278	209	121

(C) CABG



Interval	0days	30days	1year	2years	3years
Success					
Cumulative incidence		0.3%	1.6%	1.8%	1.8%
N of patients with event		3	18	20	20
N of patients at risk	1192	1172	1089	808	444
Failure					
Cumulative incidence		8.5%	17.9%	19.0%	19.6%
N of patients with event		27	56	59	60
N of patients at risk	332	289	236	174	97

(D) Any revascularization



Interval	0days	30days	1year	2years	3years
Success					
Cumulative incidence		1.5%	28.1%	33.1%	35.5%
N of patients with event		18	321	373	389
N of patients at risk	1192	1159	798	570	307
Failure					
Cumulative incidence		15.1%	48.8%	54.2%	55.7%
N of patients with event		48	151	165	167
N of patients at risk	332	268	146	97	50

SUPPLEMENTAL MATERIAL

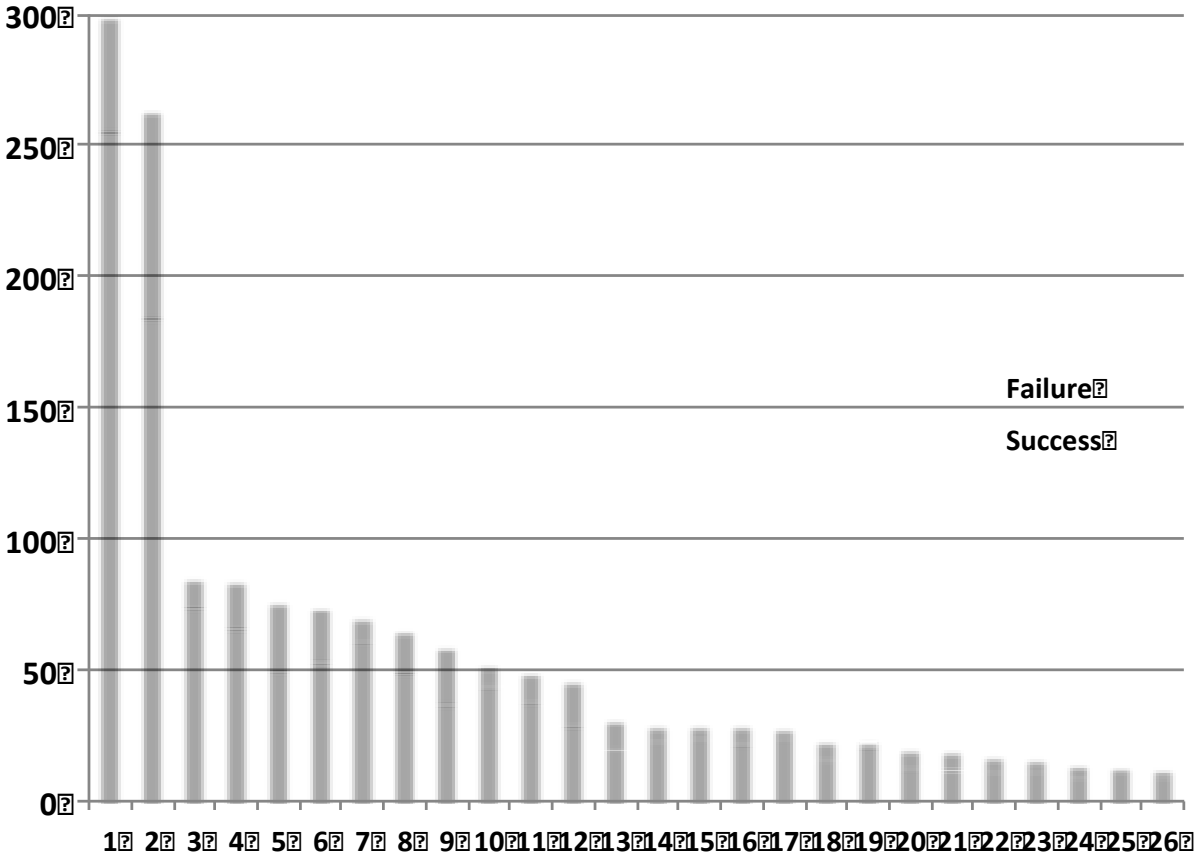
Supplemental Table 1. Unadjusted and Adjusted Analysis for All-cause Death

Variable	Unadjusted HR (95%CI)	P value	Adjusted HR (95%CI)	P value
CTO Success	0.77 (0.53-1.13)	0.18	0.93 (0.64-1.37)	0.69
Age >=75	2.55 (1.83-3.54)	<0.0001		
Male	1.17 (0.79-1.81)	0.44		
BMI <25.0	2.85 (1.89-4.49)	<0.0001	2.09 (1.37-3.33)	0.0005
Acute myocardial infarction	2.29 (1.50-3.39)	0.0003		
Hypertension	1.02 (0.67-1.64)	0.92		
Diabetes mellitus on insulin therapy	2.03 (1.29-3.07)	0.003		
Current smorker	0.80 (0.55-1.14)	0.21		
Heare failure	3.79 (2.73-5.27)	<0.0001	3.27 (2.32-4.59)	<0.0001
Shock at presentation	6.91 (4.08-11.03)	<0.0001		
Multivessel coronary disease	2.32 (1.47-3.88)	0.0002	2.69 (1.69-4.52)	<0.0001
Mitral regurgitation grade 3/4	1.99 (1.10-3.33)	0.02		
Prior myocardial infarction	1.37 (0.97-1.91)	0.07		
Prior stroke	1.73 (1.15-2.52)	0.009		
Peripheral vascular disease	2.12 (1.30-3.29)	0.0037		
eGFR<30, not on dialysis	4.21 (2.54-6.88)	<0.0001	2.92 (1.68-4.83)	0.0003
Dialysis	5.39 (3.39-8.21)	<0.0001	3.24 (1.92-5.31)	<0.0001
Atrial fibrillation	2.45 (1.54-3.73)	0.003		
Anemia (hemoglobin <11 g/dl)	4.61 (3.23-6.49)	<0.0001	2.09 (1.39-3.10)	0.0005
Platelet < $100*10^9$/L	2.71 (0.96-5.95)	0.06		
Chronic obstructive pulmonary disease	0.91 (0.28-2.14)	0.84		
Liver cirrhosis	0.91 (0.23-2.41)	0.87		
Malignancy	1.92 (1.11-3.09)	0.02		
Target of proximal LAD	1.20 (0.86-1.69)	0.29		
Target of unprotected LMCA	1.31 (0.40-3.10)	0.61		
Cirostazole use	0.95 (0.56-1.51)	0.83		
Statins use	0.43 (0.30-0.60)	<0.0001	0.62 (0.42-0.89)	0.0092
Beta-blockers use	0.90 (0.62-1.27)	0.55		
ACE-I/ARB use	0.66 (0.48-0.92)	0.01	0.62 (0.44-0.87)	0.0062
Nitrate use	0.88 (0.63-1.23)	0.46		
Calcium chanel blockers use	0.87 (0.62-1.22)	0.43		

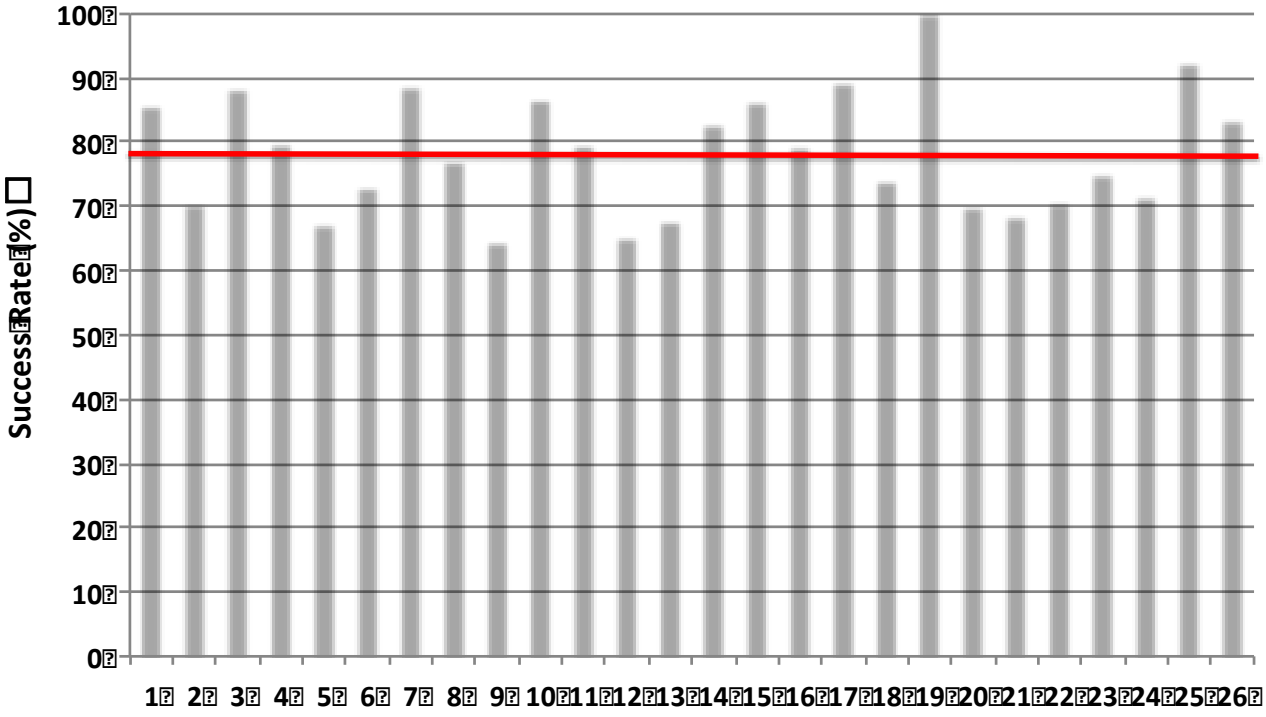
Nicorandil use	0.97 (0.66-1.40)	0.87
Warfarin use	1.33 (0.76-2.16)	0.3
Proton pump inhibitors use	1.86 (1.30-2.3)	0.001
H2-blockers use	0.92 (0.61-1.35)	0.67

CTO indicated chronic total occlusion; BMI, body mass index; eGFR, estimated glomerular filtration rate; LAD, left anterior descending artery; LMCA, left main coronary artery; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

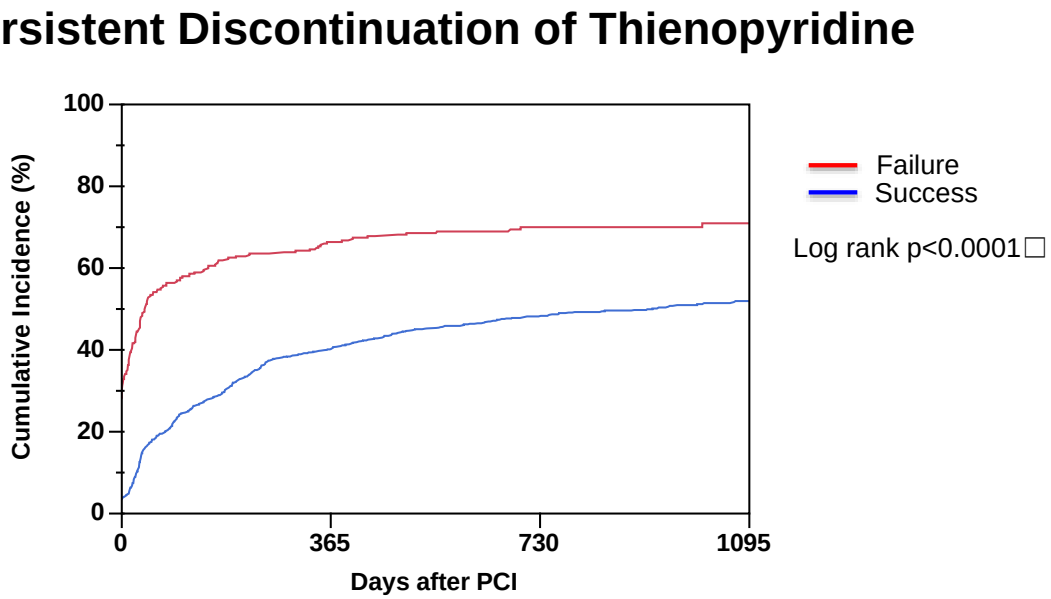
Supplemental Figure 1
(A)Number of patients underwent CTO-PCI in 26 centers



(B) Success rate of CTO-PCI in 26 centers

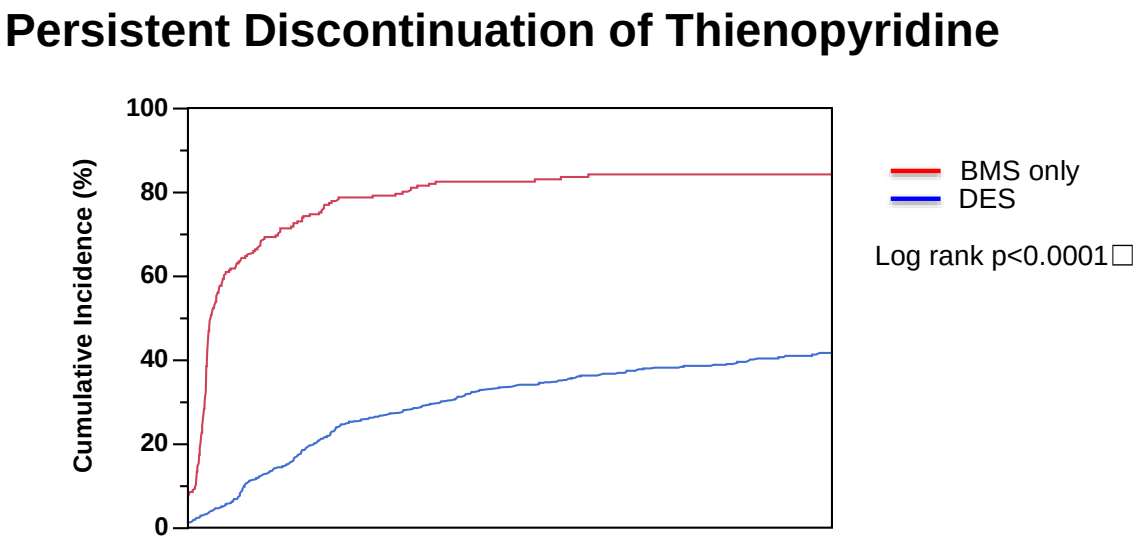


Supplemental Figure 2
(A) Persistent Discontinuation of Thienopyridine



Interval	0days	30days	1year	2years	3years
Success					
Cumulative incidence		10%	40%	48%	52%
N of patients with event		122	456	538	558
N of patients at risk	1192	1042	653	402	175
Failure					
Cumulative incidence		45%	66%	70%	71%
N of patients with event		146	212	221	222
N of patients at risk	332	176	95	54	27

(B) Persistent Discontinuation of Thienopyridine



Interval	0days	30days	1year	2years	3years
DES					
Cumulative incidence		2.8%	27%	37%	41%
N of patients with event		26	234	305	325
N of patients at risk	900	852	601	374	161
BMS only					
Cumulative incidence		29%	79%	84%	84%
N of patients with event		73	194	203	203
N of patients at risk	256	177	45	25	14

Supplemental Appendix A: List of participating centers 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 Medica 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 Medica 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

Supplemental Appendix B: 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.

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).