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Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion

The DECISION-CTO Trial

Editorial, see p 1684

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BACKGROUND: Procedural results for percutaneous coronary intervention (PCI) in coronary vessels with chronic total occlusion (CTO) have improved in recent years, and PCI strategies have moved toward more complete revascularization with more liberal use of CTO-PCI. However, evidence evaluating CTO-PCI is limited to observational studies and small clinical trials.

METHODS: In this open-label, multicenter, randomized, noninferiority trial, PCI-eligible patients were assigned to receive either 1 of 2 strategies: PCI or no PCI for the qualifying de novo CTO lesion with the option for PCI of obstructive non-CTO lesions at the discretion of the operator. The primary end point was a composite of death, myocardial infarction, stroke, or any revascularization. Health-related quality of life was assessed at baseline and at 1, 6, 12, 24, and 36 months. Because of slow recruitment, the trial was stopped before completion of the 1284 planned enrollments.

RESULTS: Between March 2010 and September 2016, 834 patients were randomly assigned to the CTO-PCI (n=417) or no CTO-PCI (n=398) strategy. Among the patients assigned to the no CTO-PCI strategy, 78 (19.6%) crossed over to receive staged CTO-PCI within 3 days of randomization. The overall CTO-PCI success rate was 90.6%. Serious nonfatal complications associated with CTO-PCI occurred in 3 patients (1 stroke, 1 cardiac tamponade, and 1 patient with recurrent episodes of ventricular tachyarrhythmia induced by intracoronary thrombus). Approximately half of the patients in each group underwent PCI for an average of 1.3 non-CTO lesions, resulting in a comparable residual SYNTAX score (Synergy Between PCI With TAXUS and Cardiac Surgery; 3.7±5.4 versus 4.0±5.9, *P*=0.42) confined to non-CTO vessels. During a median follow-up of 4.0 years (interquartile range, 2.4 to 5.1 years), there was no significant difference between the CTO-PCI and the no CTO-PCI strategies in the incidence of the primary end point (22.3% versus 22.4%, hazard ratio, 1.03; 95% CI, 0.77 to 1.37; *P*=0.86). Both CTO-PCI and no CTO-PCI strategy were associated with significant improvements but without between-group differences in disease-specific health status that was sustained through 36 months.

CONCLUSIONS: CTO-PCI was feasible with high success rates. There was no difference in the incidence of major adverse cardiovascular events with CTO-PCI versus no CTO-PCI, but the study was limited by low power for clinical end points and high crossover rates between groups.

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Clinical Perspective

What Is New?

- Chronic total occlusion (CTO)–percutaneous coronary intervention (PCI) did not reduce the 4-year risk of major adverse cardiovascular events in patients with PCI-eligible, de novo coronary CTOs.
- These findings should be interpreted with the caveats that nearly 20% of patients in the no CTO-PCI group crossed over to CTO-PCI within 3 days after randomization and that the study was stopped early because of slow enrollment.
- Both study groups (CTO-PCI and no CTO-PCI) were associated with substantial quality of life improvements that were sustained through 36 months, with no differences between groups in the primary quality of life analyses.

What Are the Clinical Implications?

- DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion) demonstrates feasibility of CTO-PCI strategy with low procedural complication rates.
- The impact of CTO-PCI on clinical outcomes should be tested in large randomized trials that include higher-risk patients with more complex CTOs.

Chronic total occlusion (CTO) of a coronary artery is relatively common, but strategies for its treatment have been inconsistent.[1,2] Coronary artery bypass surgery has been preferred in patients with severe coronary artery disease (CAD) including a CTO.[3] In contrast, CTO of 1 major epicardial coronary artery without other coronary stenoses has traditionally been treated conservatively because of the uncertain benefits and technical challenges of percutaneous coronary intervention (PCI).[4–6] In patients with multivessel CAD including a CTO, stenting obstructive non-CTO lesions while treating the CTO medically has been an alternative strategy in real-world practice.[5,7]

Advances in devices and treatment algorithms and growing experience have increased technical success of CTO-PCI in recent years.[8–10] In addition, several studies have suggested improved symptoms or survival with CTO-PCI, supporting the theoretical argument that PCI effectively relieves ischemia in myocardium subtended by the CTO vessel.[11–13] Accordingly, the treatment strategy for patients with CTO has moved toward complete revascularization with more liberal use of CTO-PCI. However, most data suggesting a benefit of CTO-PCI were derived from observational studies that compared patients who experienced successful PCI to those who experienced a failed procedure, without a consistent strategy on non-CTO vessels. Indeed, other studies have suggested limited clinical benefit from CTO-PCI.[14–17]

To address this issue, we designed the DECISION-CTO trial (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion) to compare the effect of CTO-PCI versus no CTO-PCI, with a background of medical therapy and PCI of obstructive non-CTO lesions in both groups. The trial was terminated early because of slow patient recruitment.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Overview

The DECISION-CTO trial was an open-label, multicenter, randomized controlled trial that was conducted at 19 sites in the Asian countries of Korea, India, Indonesia, Thailand, and Taiwan. An annual volume of at least 500 PCIs with a presence of a CTO operator was a prerequisite for each study center. Investigators affiliated with the Heart Institute at Asan Medical Center, Seoul, South Korea, designed the study, collected and managed the data, and performed the statistical analyses. The study protocol was approved by the institutional review board at each participating center, and each patient provided written informed consent.

Eligible patients were men and women at least 18 years old who presented with silent ischemia, stable angina, or acute coronary syndrome. Patients with a de novo CTO located in a proximal to midepicardial coronary artery with a reference vessel diameter of ≥2.5 mm were enrolled. CTO was defined as a coronary artery obstruction with Thrombolysis in Myocardial Infarction flow grade 0 of at least 3 months' duration based on the patient's history. When no definite evidence of occlusion duration existed, the diagnosis of CTO was made based on angiographic morphology by at least 2 experienced interventional cardiologists working at each center.[18,19] Patients with a CTO located in a distal coronary artery, 3 different vessel CTOs at any location, 2 proximal CTOs in separate coronary arteries, or a CTO in the left main segment, in-stent restenosis, or graft vessel were excluded. Patients with ST-segment–elevation myocardial infarction (MI) requiring primary PCI, those with complex CAD who were considered more appropriate for bypass surgery, and those who were deemed to have a high procedural risk, including those with a serum creatinine value ≥2.0 mg/dL or left ventricular ejection fraction <30% at baseline, were also excluded.

The DECISION-CTO trial was a noninferiority study, hypothesizing that the efficacy of no CTO-PCI strategy is not inferior to the CTO-PCI strategy for the treatment of CAD accompanied by CTO. For the sample size calculation, we assumed that the 3-year rate of the primary composite end point in the CTO-PCI group would be 17% based on a previously published report.[20] Using a noninferiority margin of 0.7 of the 3-year event rate ratio (rate of the no CTO-PCI group/rate of the CTO-PCI group) for the lower boundary of the 97.5% confidence interval with 5% lost to follow-up, we estimated that with a total of 1284 patients, the study would have 80% power to show noninferiority, with a 1-sided type I error rate

of 0.025. Patient enrollment started in March 2010; however, enrollment was much slower than anticipated, because site participation decreased considerably over time. Because of slow enrollment, the trial was terminated early on September 15, 2016, at the request of the executive committee in agreement with the data and safety monitoring board.

Randomization

After anatomic assessment of CAD by diagnostic coronary angiography, eligible patients were randomized in a 1:1 ratio using an interactive web response system to receive either PCI or no PCI for the qualifying CTO lesion. All patients were to receive guideline-directed medical therapy and PCI for obstructive non-CTO lesions. The allocation sequence was computer-generated and stratified according to the study center, location of CTO, and presence or absence of diabetes mellitus, with random block sizes of 4 or 6.

Procedures and Medications

For patients assigned to the CTO-PCI strategy, CTO-PCI was to be performed within 30 days after randomization. In the case of procedural failure, an additional attempt was allowed within 30 days after the first attempt. The use of specialized devices or techniques and the choice of the drug-eluting stent type were left to the operator's discretion. Successful CTO-PCI was defined as restoration of Thrombolysis in Myocardial Infarction flow grade 3 with residual stenosis <30%, as determined by the operator.

Study patients were not restricted to those who had isolated CTO disease; thus, the trial also involved revascularizations for obstructive non-CTO lesions. For patients with multivessel CAD, regardless of random treatment assignment, PCI was recommended for all obstructive (diameter stenosis ≥50% for left main and ≥70% for nonleft main CAD) non-CTO lesions within a vessel diameter ≥2.5 mm. In the CTO-PCI strategy arm, the treatment sequence of CTO and non-CTO lesions was decided by the operator, taking into consideration the safety of the procedure. Identical types of drug-eluting stent were recommended for all CTO and non-CTO lesions in a single patient at the index treatment and at any revascularization procedures during follow-up.

Pharmacological treatments had to be optimized early after randomization in accordance with the clinical guidelines and established standards of practice.[21,22] Patients were prescribed daily aspirin and statin. β-Blockers, calcium channel blockers, or long-acting nitrates, alone or in combination, were used as anti-ischemic therapy. An angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker was considered for secondary prevention. Patients undergoing stent implantation received a P2Y12 receptor inhibitor for at least 12 months in addition to standard medical therapy. Blood pressure and diabetic control were emphasized. Patients received counseling about smoking cessation, weight control, and regular exercise.

Study End Points and Follow-Up

The primary end point of the trial was a composite of death from any cause, MI, stroke, or any revascularization. Secondary outcomes included the individual components of the primary outcome, as well as bleeding, stent thrombosis, and health-related quality of life (QOL). Detailed definitions of end points and additional secondary end points are listed in the Appendix in the online-only Data Supplement. Any subsequent PCI or bypass surgery after the index procedure performed in both study arms was regarded as a primary end point event. However, cases of patients assigned to the no CTO-PCI strategy who received a staged CTO-PCI early after the study enrollment (all within 3 days in this trial) were considered protocol deviations rather than events. This decision was made because the trial examined the effect of complete (opening the CTO) versus incomplete (leaving the CTO unopened) revascularization intended around the time of the randomization. Study monitors collected source documents of all primary and secondary end point events for adjudication by an independent events committee. The extent of CAD and the SYNTAX score (Synergy Between PCI With TAXUS and Cardiac Surgery) were assessed at the angiographic core laboratory. CTO lesion complexity was evaluated by calculating the Japanese-CTO score for each case.[23] Health-related quality of life was assessed at baseline and at 1, 6, 12, 24, and 36 months with the use of the visual analogue scale of European Quality of Life-5 Dimensions score and the Seattle Angina Questionnaire.[24,25]

Clinical follow-up assessments were performed via clinic visits or telephone interviews at 30 days, 6 and 12 months, and annually thereafter. Data quality was monitored systematically, because the research team in the Data Coordinating Center in the CardioVascular Research Foundation periodically visited all participating centers and performed monitoring through source document verification of the informed consent form, enrollment criteria, and main outcomes in all patients.

Statistical Analysis

Time-to-event outcomes were determined from the date of randomization to the final follow-up date. Cumulative event rates and survival curves were generated using the Kaplan-Meier method. The noninferiority hypothesis was assessed with the use of a z-test. Cox proportional hazards regression analyses were conducted to estimate the risk associated with CTO-PCI strategy relative to that of no CTO-PCI strategy. Secondary analysis for primary outcome was conducted in several clinically relevant subgroups with tests for interactions.

Analyses of QOL data were restricted to patients who had data both at baseline and at each time point of interest. To evaluate the changes in QOL, within-group comparisons for each health status scale were performed between baseline and each follow-up time point using paired Student *t* tests. Differences in QOL measures between CTO-PCI and no CTO-PCI strategy at each time point were estimated using random-effect growth curve models, which accounted for missing data under the missing-at-random assumption. Covariates for the models included treatment group, follow-up time, interactions between treatment and time, and baseline clinical factors (age, sex, hypertension, diabetes mellitus, previous stroke, heart failure, renal dysfunction, clinical presentation, location of CTO, and SYNTAX score category). In addition, quadratic and cubic terms of time along with their interactions with treatment group were included in the models to account for

nonlinear trends. Data analyses were performed using "survival," "cmprsk," and "lme4" packages in R software version 3.2.2 13 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Statistical hypothesis tests with P <0.05 were considered significant.

RESULTS

Patients and Procedures

Between March 2010 and October 2016, 834 patients were randomly assigned to a treatment group. After exclusion of 19 patients who withdrew consent, 417 patients were assigned to the CTO-PCI strategy, and 398 patients were randomly assigned to the no CTO-PCI strategy. Final follow-up status was ascertained between August and September 2017, and the 3-year follow-up was complete in 89.9% and 92.1% of the eligible patients in the CTO-PCI and no CTO-PCI groups, respectively (Figure I in the online-only Data Supplement).

Baseline patient and lesion characteristics were well balanced between the 2 treatment groups (Table 1). The mean patient age was 62.5±10.0 years, and 82.5% of patients were men, 33.1% had diabetes mellitus, and 73.4% had multivessel CAD. CTOs were located in the left anterior descending artery in 43.3% of patients, right coronary artery in 46.3%, and left circumflex artery in 10.4%. The overall mean SYNTAX score was 20.8±9.3, and the mean Japanese-CTO score for CTO lesions was 2.1±1.2, without between-group differences. Averages of 1.24±1.04 and 1.29±0.99 (P=0.49) obstructive non-CTO lesions were present at a total of 427 and 417 non-CTO vessels in the CTO-PCI and no CTO-PCI group, respectively.

Among the 417 patients assigned to the CTO-PCI strategy, PCI for a CTO lesion was attempted in 384 patients at a median time of 1 day (interquartile range, 0 to 7 days). Of those, the procedure was successful in 348 patients (90.6%). Among the 398 patients assigned to the no CTO-PCI strategy, 313 remained in their assigned group, whereas 78 (19.6%) immediately crossed over to CTO-PCI (median 1 day [interquartile range, 1 to 2 days], successful in 73, failed in 5). Details on treatment flow, crossovers, and final treatments are depicted in Figure 1. The most common reason for crossover from no CTO-PCI to CTO-PCI strategy was the investigator's intention to control the patient's symptom (26 patients, 24.3%) (Table I in the online-only Data Supplement). Characteristics of participants who crossed over between groups are shown in Table II in the online-only Data Supplement.

Procedural details for both groups are summarized in Tables III and IV in the online-only Data Supplement. Overall, the retrograde approach was used in 24.6% of the patients who actually underwent attempted CTO-PCI. The overall success rate was 91%, and an average of 2.3 stents with a length of 68.2 mm was used for the target CTO lesion. Serious nonfatal complications associated with CTO-PCI occurred in 3 patients (1 stroke, 1 cardiac tamponade, and 1 patient with recurrent episodes of ventricular tachyarrhythmia induced by intracoronary thrombus). In both groups, about half of the patients underwent PCI, for an average of 1.3 non-CTO lesions. The total number of stents used for non-CTO lesions were higher in the no CTO-PCI group (1.5±0.9

Table 1. Baseline Characteristics of the Study Patients

Characteristic	CTO-PCI (n=417)*	No CTO-PCI (n=398)*	P Value
Age, y	62.2 (10.2)	62.9 (9.9)	0.32
Male sex	344 (83.3)	319 (81.6)	0.59
Body mass index, kg/m^2	25.6 (3.5)	25.5 (3.3)	0.59
Hypertension	262 (63.4)	238 (60.9)	0.50
Diabetes mellitus	132 (32.0)	134 (34.3)	0.54
Hypercholesterolemia	249 (60.3)	217 (55.5)	0.19
Current smoker	125 (30.3)	102 (26.1)	0.22
Previous PCI	64 (15.5)	75 (19.2)	0.20
Previous myocardial infarction	45 (10.9)	34 (8.7)	0.35
Previous bypass operation	4 (1.0)	5 (1.3)	0.93
Congestive heart failure	18 (4.4)	19 (4.9)	0.87
Previous stroke	29 (7.0)	31 (7.9)	0.72
Peripheral vascular disease	16 (3.9)	18 (4.6)	0.74
Chronic lung disease	8 (1.9)	8 (2.0)	>0.99
Renal dysfunction†	6 (1.5)	5 (1.3)	>0.99
Clinical presentation			0.79
Silent ischemia	54 (13.1)	57 (14.6)	
Stable angina	246 (59.6)	236 (60.4)	
Unstable angina	84 (20.3)	76 (19.4)	
Acute myocardial infarction	29 (7.0)	22 (5.6)	
Left ventricular ejection fraction	57.3 (9.8)	57.6 (9.1)	0.68
Location of the CTO			0.67
Left anterior descending artery	185 (44.8)	163 (41.7)	
Left circumflex artery	42 (10.2)	42 (10.7)	
Right coronary artery	186 (45.0)	186 (47.6)	
No. of diseased vessels			0.83
One-vessel disease	111 (26.9)	103 (26.3)	
Two-vessel disease	175 (42.4)	160 (40.9)	
Three-vessel disease	127 (30.8)	128 (32.7)	
SYNTAX score	20.8 (9.2)	20.8 (9.5)	0.99
J-CTO score	2.1 (1.2)	2.2 (1.2)	0.16

The data are presented as n (%) or means (SD), unless otherwise stated. CTO indicates chronic total occlusion; J-CTO, Japanese-chronic total occlusion; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.

*Complete data were available for 413 patients in the CTO-PCI group and 391 patients in the no CTO-PCI group, which were the denominators of the percentages.

†Renal dysfunction was defined as an estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2} of the body surface area.

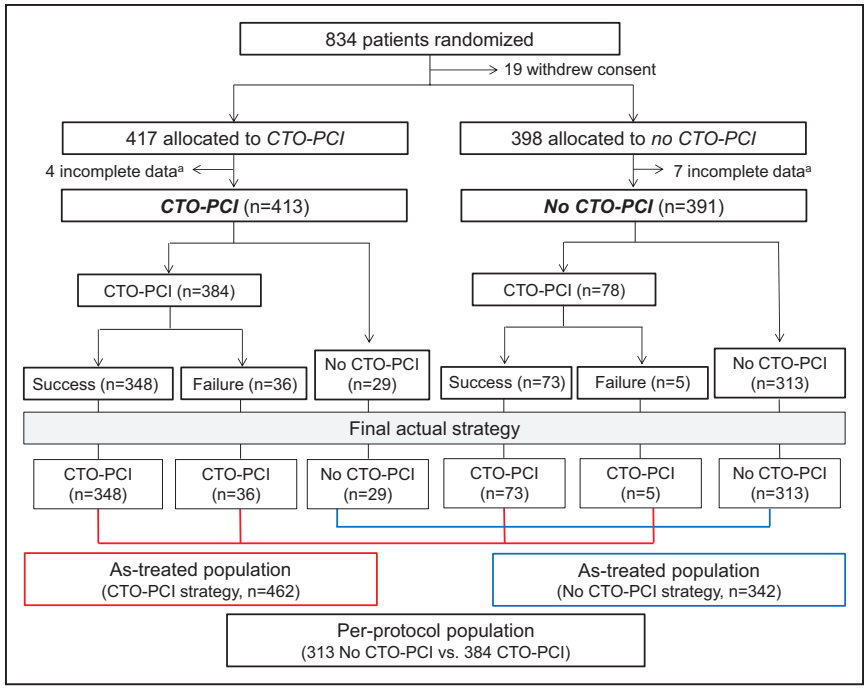

Figure 1. Study flow chart.
[a]Patients with incomplete data were censored at day 0 in the analysis. CTO indicates chronic total occlusion; and PCI, percutaneous coronary intervention.

versus 1.7±1.0, *P*=0.03), whereas the mean stent length (41.1±25.9 versus 44.2±28.0, *P*=0.26) and the diameter (3.2±0.4 versus 3.2±0.4, *P*=0.88) were comparable between the 2 groups. Complete revascularization of non-CTO vessels was achieved in 325 (78.7%) and 302 (77.2%) patients in the CTO-PCI and no CTO-PCI groups, respectively (*P*=0.67). The overall residual SYNTAX score was significantly lower in the CTO-PCI group compared to the no CTO-PCI group (6.3±8.4 versus 14.6±9.4, *P*<0.001). However, the scores confined to non-CTO vessels were comparable between the 2 groups (3.7±5.4 versus 4.0±5.9, *P*=0.42).

The medications that the patients were taking at baseline and during follow-up are summarized in Table V in the online-only Data Supplement. Compared to patients in the no CTO-PCI group, those in the CTO-PCI group were more likely to receive antiplatelet agents, including aspirin or P2Y12 receptor inhibitors. However, the use of other secondary preventive or antianginal medications was similar between the 2 groups.

Primary and Secondary End Points

The median duration of follow-up was 4.0 years (interquartile range, 2.4 to 5.1 years) in both groups. The results of the analyses of the primary and hierarchical secondary end points are provided in Table 2. During follow-up, the primary end point occurred in 93 patients (22.3%) in the CTO-PCI group and 89 patients (22.4%) in the no CTO-PCI group (hazard ratio, 1.03; 95% CI, 0.77 to 1.37; *P*=0.86; 3-year event rate ratio, 1.02; lower limit of 1-sided 97.5% CI, 0.755; *P*=0.014 for noninferiority; Figure 2). The post hoc power of the study given the number of patients enrolled was 63.6%, and it was 94.1% if the observed event rate is taken into consideration. There was no difference between the CTO-PCI and no CTO-PCI groups with regard to individual outcomes of death, MI, stroke, revascularization, or any composite secondary outcomes. The subsequent revascularization rate between the two strategies was not different for both the CTO vessels and the non-CTO vessels. Bleeding, mostly access-site bleeding, was more frequent in the CTO-PCI group than in the no CTO-PCI group (37.4% versus 13.6%; hazard ratio, 3.18; 95% CI, 2.33 to 4.33; *P*<0.001). However, the rate of major bleeding was not significantly different between the two groups (1.8% versus 1.7%; hazard ratio, 1.15; 95% CI, 0.40 to 3.28; *P*=0.80). Definite stent thrombosis occurred in 4 patients: 1 in a stent placed in the CTO segment and 3 in stents placed in non-CTO vessels. The results of secondary and subgroup analysis are shown in Table VI and Figures II through IV in the online-only Data Supplement.

Health-Related Quality of Life

The overall rate of response for QOL assessments among surviving patients was 76.4% at baseline, 65.2% at 1 year, 61.7% at 2 years, and 59.0% at 3 years. Changes in mean scores on the QOL scales at each follow-up time point are summarized in Table VII and Supplemental Figure V in the online-only Data Supplement. At 1 month, the scores had increased substantially from baseline in both groups for all domains of the QOL questionnaire but generally increased to a larger extent in the CTO-PCI arm compared to the no CTO-PCI arm. These improvements in scores in each group were largely maintained by 12 and 36 months.

Table 2. Primary and Secondary Clinical End Points in the Intention-to-Treat Analysis

	CTO-PCI (n=417)	No CTO-PCI (n=398)	Crude HR (95% CI)	*P* Value
Primary end point: death, MI, stroke, or any revascularization	93 (22.3)	89 (22.4)*	1.03 (0.77–1.37)	0.86
Secondary end points				
Death	15 (3.6)	21 (5.3)	0.70 (0.36–1.37)	0.30
Cardiac cause	8 (1.9)	14 (3.5)	0.56 (0.24–1.34)	0.19
Noncardiac cause	7 (1.7)	7 (1.8)	0.99 (0.35–2.82)	0.99
Myocardial infarction	47 (11.3)	34 (8.5)	1.39 (0.90–2.15)	0.14
Periprocedural MI	41 (9.8)	30 (7.5)	1.37 (0.816–2.18)	0.19
Spontaneous MI	7 (1.7)	7 (1.8)	0.88 (0.30–2.57)	0.82
Stroke	6 (1.4)	10 (2.5)	0.61 (0.23–1.65)	0.33
Any revascularization	46 (11.0)	42 (10.6)	1.14 (0.75–1.73)	0.55
CTO vessel	33 (7.9)	30 (7.5)	1.13 (0.69–1.84)	0.63
Non-CTO vessel	29 (7.0)	23 (5.8)	1.34 (0.77–2.31)	0.30
Death, MI, or stroke	66 (15.8)	61 (15.3)	1.07 (0.75–1.51)	0.72
Cardiac death, MI, stroke, or any revascularization	86 (20.6)	82 (20.6)	1.02 (0.76–1.39)	0.88
Death, spontaneous MI, stroke, or any revascularization	64 (15.3)	69 (17.3)	0.91 (0.65–1.30)	0.59

Hazard ratios are for patients with CTO-PCI strategy relative to that of no CTO-PCI strategy. CTO indicates chronic total occlusion; HR, hazard ratio; MI, myocardial infarction; and PCI, percutaneous coronary intervention.
*Number and percentages are crude rates.

Between-group differences in QOL measures over time are summarized in Table 3 and Table VIII in the online-only Data Supplement. Overall, there was no significant difference in the mean scores between the treatment strategies on any of the QOL scales.

DISCUSSION

DECISION-CTO involved patients with PCI-eligible, de novo coronary CTO and compared the effect of 2 treatment strategies: PCI versus no PCI on CTO lesions with the option for PCI of non-CTO lesions. The study was limited by large numbers of protocol violations, with almost 20% crossover from no CTO-PCI to CTO-PCI. The study was also terminated early because of slow enrollment. There was no significant difference between the CTO-PCI and the no CTO-PCI strategy with respect to the composite primary end point of death, MI, stroke, or any revascularization throughout a median of 4-year follow-up period. Both CTO-PCI and no CTO-PCI strategy were associated with significant improvements, but without between-group differences, in disease-specific

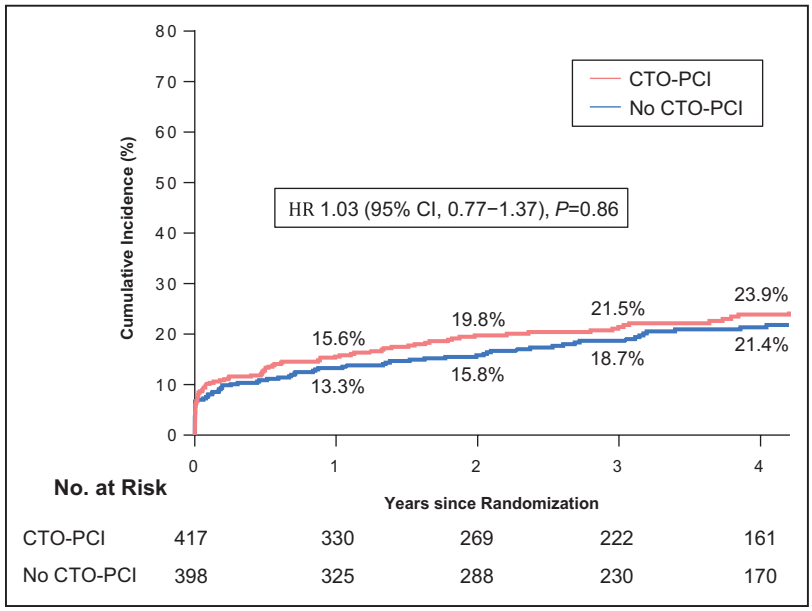

Figure 2. Cumulative incidence of the primary end point in the intention-to-treat population.
CTO indicates chronic total occlusion; HR, hazard ratio; and PCI, percutaneous coronary intervention.

Table 3. Between-Group Differences in Quality-of-Life Measures Over Time

	CTO-PCI	No CTO-PCI	Mean Difference Between CTO-PCI and No CTO-PCI Strategy (95% CI)	*P* Value
EQ-5D, visual analogue scale				
1 mo	77.39±13.76	75.85±15.16	1.55 (–0.99 to 4.08)	0.23
6 mo	79.94±12.64	78.20±13.98	1.74 (–0.74 to 4.22)	0.17
12 mo	81.00±12.58	78.28±13.27	2.72 (0.23 to 5.20)	0.03
24 mo	83.08±11.87	80.10±12.00	2.98 (0.45 to 5.51)	0.02
36 mo	84.56±9.12	80.97±11.05	3.59 (1.18 to 6.00)	0.004
SAQ physical limitation				
1 mo	90.00±15.66	88.38±17.11	1.62 (–1.26 to 4.49)	0.27
6 mo	92.22±13.61	91.80±14.32	0.42 (–2.18 to 3.02)	0.75
12 mo	93.06±11.96	91.77±15.12	1.29 (–1.33 to 3.91)	0.33
24 mo	94.84±12.72	93.69±12.74	1.14 (–1.56 to 3.84)	0.41
36 mo	94.52±12.86	93.54±14.98	0.98 (–2.35 to 4.30)	0.56
SAQ angina frequency				
1 mo	94.63±10.54	93.31±13.78	1.33 (–0.81 to 3.46)	0.23
6 mo	96.00±10.13	95.44±9.98	0.56 (–1.30 to 2.42)	0.56
12 mo	94.55±11.18	95.33±10.19	–0.78 (–2.83 to 1.26)	0.45
24 mo	97.31±7.13	97.18±7.65	0.13 (–1.43 to 1.69)	0.87
36 mo	98.21±5.32	97.38±7.20	0.83 (–0.67 to 2.32)	0.27
SAQ treatment satisfaction				
1 mo	83.07±12.75	80.42±15.03	2.66 (0.23 to 5.09)	0.03
6 mo	83.16±13.29	83.13±14.25	0.02 (–2.53 to 2.57)	0.99
12 mo	83.98±13.19	83.26±14.61	0.72 (–1.94 to 3.39)	0.59
24 mo	84.95±12.62	83.28±13.41	1.67 (–1.07 to 4.42)	0.23
36 mo	87.13±11.89	84.00±11.59	3.13 (0.38 to 5.89)	0.03
SAQ quality of life				
1 mo	66.16±19.87	64.26±19.65	1.90 (–1.55 to 5.35)	0.28
6 mo	72.08±17.54	69.74±17.48	2.34 (–0.90 to 5.58)	0.16
12 mo	72.19±19.06	71.89±16.6	0.30 (–3.12 to 3.71)	0.86
24 mo	77.37±17.43	75.91±17.77	1.45 (–2.25 to 5.16)	0.44
36 mo	78.26±17.39	77.53±16.69	0.73 (–3.26 to 4.72)	0.72

Positive values indicate better outcomes with CTO-PCI strategy. CTO indicates chronic total occlusion; EQ-5D, European Quality of Life Dimensions; PCI, percutaneous coronary intervention; and SAQ, Seattle Angina Questionnaire.

health status that were sustained through 36 months. CTO-PCI was associated with higher overall bleeding rates, but major bleeding was rare and not different between the two groups.

Several features of the trial design and enrolled patients should be acknowledged. First, the trial design involved not only the comparison of an initial strategy for a CTO lesion but also treatment for non-CTO lesions. The trial did not intend to compare the pure treatment effect of PCI versus no PCI for a given CTO. More than 70% of patients had multivessel CAD, and nearly half of patients in both groups received PCI for non-CTO lesions. Although the rate of complete revascularization and residual SYNTAX score in non-CTO vessels was similar for both groups, this complex situation deserves consideration, particularly when interpreting the health status data. Second, patients enrolled in our trial may have had a relatively lower risk of future cardiovascular events (ie, 25% of patients had single-vessel disease comprising only a CTO, SYNTAX score was relatively low, and most patients had a normal left ventricular ejection fraction). Third, the trial was led by high-volume centers with expertise on CTO-PCI, 2 of them actively recruiting >60% of the total patients. The success rate of CTO-PCI was high (≈90%), whereas the rate of associated serious complications was low (<1%). Thus, we acknowledge that the particulars of clinical practice in the institutions in this trial, as well as the specific expertise of the interventional cardiologists who performed the procedures, may differ from those

of other institutions and practitioners, potentially limiting the generalizability of these results in other settings.

In our trial, the rate of the primary end point of death, MI, stroke, or any revascularization was not significantly different between the no CTO-PCI strategy and the CTO-PCI strategy. Given the limitations of study conduct, including high rates of crossover and early study termination, these null findings must be interpreted with caution. Further large-scale randomized trials are needed to address the impact of CTO-PCI on ischemia, clinical outcomes, and quality of life.

Somewhat unexpectedly, there was substantial and rapid improvement in early health status scores among the patients in both groups, potentially limiting the ability of the study to evaluate difference in QOL between the two strategies at later time points in our longitudinal analyses. Because baseline health status assessments were done before any intervention, this observation indicates that PCI for non-CTO lesions may have had considerable influence in both groups. The EURO-CTO trial evaluated QOL among patients whose symptoms were deemed to be truly attributed to CTO and showed superiority of CTO-PCI over no CTO-PCI.[26]

This study had several limitations. First, the early termination of the trial reduced its statistical power, which warrants cautious interpretation of the study results. Under the same assumptions as for the original sample size calculation, the study would retain 64% power for the original primary analysis with our given sample size. Second, the high number of crossovers in the no CTO-PCI group limits conclusions drawn from the intention-to-treat analysis and may have led to an underestimation of the true effect of CTO-PCI strategy. Third, the response rate of the QOL questionnaire was low; thus, the results may have been potentially biased. Also, the lack of sham control may have introduced a chance of a placebo effect in the treatment group. Fourth, a viability test was not mandatory for patient enrollment in our trial. Concerns exist because reopening a CTO vessel supplying nonviable territories would be unlikely to improve prognosis. Nearly 60% of the study patients underwent a noninvasive stress test at baseline in our trial, but only 272 patients underwent a myocardial perfusion scan. However, the majority of patients enrolled in this study had preserved left ventricular function on echocardiography, and 95% of patients who underwent a perfusion scan showed inducible ischemia in the CTO-related territory without between-group differences. The prognosis may differ based on the amount of myocardium at risk that is subtended by the CTO vessel, and this should be a subject of investigation.[27] Higher-risk patients with more complex CTOs must also be tested to define the prognostic role of CTO-PCI in the future, but investigators should be cautious because PCI failures, unexpected complications, and crossovers may occur more frequently.

In conclusion, our trial demonstrated no significant difference in the primary end point of death, MI, stroke, or any revascularization with CTO-PCI versus no CTO-PCI over the course of 4 years. Both the CTO-PCI and no CTO-PCI groups showed substantial QOL improvements that were sustained through 36 months. Future large-scale studies are needed to study the role of CTO-PCI, with careful attention to prevent crossover between groups.

ARTICLE INFORMATION

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REFERENCES

1. Galassi AR, Brilakis ES, Boukhris M, Tomasello SD, Sianos G, Karmpaliotis D, Di Mario C, Strauss BH, Rinfret S, Yamane M, Katoh O, Werner GS, Reifart N. Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. *Eur Heart J*. 2016;37:2692–2700. doi: 10.1093/eurheartj/ehv391
2. Jeroudi OM, Alomar ME, Michael TT, El Sabbagh A, Patel VG, Mogabgab O, Fuh E, Sherbet D, Lo N, Roesle M, Rangan BV, Abdullah SM, Hastings JL, Grodin J, Banerjee S, Brilakis ES. Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. *Catheter Cardiovasc Interv*. 2014;84:637–643. doi: 10.1002/ccd.25264
3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972. doi: 10.1056/NEJMoa0804626
4. Grantham JA, Marso SP, Spertus J, House J, Holmes DR Jr, Rutherford BD. Chronic total occlusion angioplasty in the United States. *JACC Cardiovasc Interv*. 2009;2:479–486. doi: 10.1016/j.jcin.2009.02.008
5. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, Sparkes JD, Wright GA, Strauss BH. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol*. 2012;59:991–997. doi: 10.1016/j.jacc.2011.12.007
6. Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS, Dehmer GJ, Kirtane AJ, Wann LS, Ward RP. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;59:1995–2027. doi: 10.1016/j.jacc.2012.03.003
7. Tomasello SD, Boukhris M, Giubilato S, Marzà F, Garbo R, Contegiacomo G, Marzocchi A, Niccoli G, Gagnor A, Varbella F, Desideri A, Rubartelli P, Cioppa A, Baralis G, Galassi AR. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. *Eur Heart J*. 2015;36:3189–3198. doi: 10.1093/eurheartj/ehv450
8. Brilakis ES, Grantham JA, Rinfret S, Wyman RM, Burke MN, Karmpaliotis D, Lembo N, Pershad A, Kandzari DE, Buller CE, DeMartini T, Lombardi WL, Thompson CA. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. *JACC Cardiovasc Interv*. 2012;5:367–379. doi: 10.1016/j.jcin.2012.02.006
9. Brilakis ES, Banerjee S, Karmpaliotis D, Lombardi WL, Tsai TT, Shunk KA, Kennedy KF, Spertus JA, Holmes DR Jr, Grantham JA. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2015;8:245–253. doi: 10.1016/j.jcin.2014.08.014
10. Harding SA, Wu EB, Lo S, Lim ST, Ge L, Chen JY, Quan J, Lee SW, Kao HL, Tsuchikane E. A new algorithm for crossing chronic total occlusions from the Asia Pacific Chronic Total Occlusion Club. *JACC Cardiovasc Interv*. 2017;10:2135–2143. doi: 10.1016/j.jcin.2017.06.071
11. Hoebers LP, Claessen BE, Elias J, Dangas GD, Mehran R, Henriques JP. Meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome. *Int J Cardiol*. 2015;187:90–96. doi: 10.1016/j.ijcard.2015.03.164
12. George S, Cockburn J, Clayton TC, Ludman P, Cotton J, Spratt J, Redwood S, de Belder M, de Belder A, Hill J, Hoye A, Palmer N, Rathore S, Gershlick A, Di Mario C, Hildick-Smith D; British Cardiovascular Intervention Society; National Institute for Cardiovascular Outcomes Research. Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central Cardiac Audit Database. *J Am Coll Cardiol*. 2014;64:235–243. doi: 10.1016/j.jacc.2014.04.040
13. Sapontis J, Salisbury AC, Yeh RW, Cohen DJ, Hirai T, Lombardi W, McCabe JM, Karmpaliotis D, Moses J, Nicholson WJ, Pershad A, Wyman RM, Spaedy A, Cook S, Doshi P, Federici R, Thompson CR, Marso SP, Nugent K, Gosch K, Spertus JA, Grantham JA. Early procedural and health status outcomes after chronic total occlusion angioplasty: a report from the OPEN-CTO Registry (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures). *JACC Cardiovasc Interv*. 2017;10:1523–1534. doi: 10.1016/j.jcin.2017.05.065
14. Henriques JP, 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 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. doi: 10.1016/j.jacc.2016.07.744
15. de Labriolle A, Bonello L, Roy P, Lemesle G, Steinberg DH, Xue Z, Kaneshige K, Suddath WO, Satler LF, Kent KM, Pichard AD, Lindsay J, Waksman R. Comparison of safety, efficacy, and outcome of successful versus unsuccessful percutaneous coronary intervention in "true" chronic total occlusions. *Am J Cardiol*. 2008;102:1175–1181. doi: 10.1016/j.amjcard.2008.06.059
16. Lee PH, Lee SW, Park HS, Kang SH, Bae BJ, Chang M, Roh JH, Yoon SH, Ahn JM, Park DW, Kang SJ, Kim YH, Lee CW, Park SW, Park SJ. Successful recanalization of native coronary chronic total occlusion is not associated with improved long-term survival. *JACC Cardiovasc Interv*. 2016;9:530–538. doi: 10.1016/j.jcin.2015.11.016
17. Jolicœur EM, Sketch MJ, Wojdyla DM, Javaheri SP, Nosib S, Lokhnygina Y, Patel MR, Shaw LK, Tcheng JE. Percutaneous coronary interventions and cardiovascular outcomes for patients with chronic total occlusions. *Catheter Cardiovasc Interv*. 2012;79:603–612. doi: 10.1002/ccd.23269
18. Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, Moussa I, Teirstein PS, Dangas G, Baim DS, Selmon M, Strauss BH, Tamai H, Suzuki T, Mitsudo K, Katoh O, Cox DA, Hoye A, Mintz GS, Grube E, Cannon LA, Reifart NJ, Reisman M, Abizaid A, Moses JW, Leon MB, Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation*. 2005;112:2364–2372. doi: 10.1161/CIRCULATIONAHA.104.481283
19. Sianos G, Werner GS, Galassi AR, Papafaklis MI, Escaned J, Hildick-Smith D, Christiansen EH, Gershlick A, Carlino M, Karlas A, Konstantinidis NV, Tomasello SD, Di Mario C, Reifart N; EuroCTO Club. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. *EuroIntervention*. 2012;8:139–145. doi: 10.4244/EIJV8I1A21
20. García-García HM, Daemen J, Kukreja N, Tanimoto S, van Mieghem CA, van der Ent M, van Domburg RT, Serruys PW. Three-year clinical outcomes after coronary stenting of chronic total occlusion using sirolimus-eluting stents: insights from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. *Catheter Cardiovasc Interv*. 2007;70:635–639. doi: 10.1002/ccd.21249
21. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; Members AATF. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344-426. doi: 10.1161/CIR.0000000000000134
22. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:3097–3137. doi: 10.1161/CIR.0b013e3182776f83

23. Morino Y, Abe M, Morimoto T, Kimura T, Hayashi Y, Muramatsu T, Ochiai M, Noguchi Y, Kato K, Shibata Y, Hiasa Y, Doi O, Yamashita T, Hinohara T, Tanaka H, Mitsudo K; J-CTO Registry Investigators. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *JACC Cardiovasc Interv*. 2011;4:213–221. doi: 10.1016/j.jcin.2010.09.024
24. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25:333–341.
25. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*. 2001;33:337–343.
26. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, Rumoroso JR, Erglis A, Christiansen EH, Escaned J, di Mario C, Hovasse T, Teruel L, Bufe A, Lauer B, Bogaerts K, Goicolea J, Spratt JC, Gershlick AH, Galassi AR, Louvard Y; EUROCTO trial investigators. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. 2018;39:2484–2493. doi: 10.1093/eurheartj/ehy220
27. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900–2907. doi: 10.1161/01.CIR.0000072790.23090.41