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Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI

The EXPLORE Trial

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ABSTRACT

BACKGROUND In 10% to 15% of patients with ST-segment elevation myocardial infarction (STEMI), concurrent coronary chronic total occlusion (CTO) in a non-infarct-related artery is present and is associated with increased morbidity and mortality.

OBJECTIVES The EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) trial evaluated whether patients with STEMI and concurrent CTO in a non-infarct-related artery benefit from additional percutaneous coronary intervention (PCI) of CTO shortly after primary PCI.

METHODS From November 2007 through April 2015, we enrolled 304 patients with acute STEMI who underwent primary PCI and had concurrent CTO in 14 centers in Europe and Canada. A total of 150 patients were randomly assigned to early PCI of the CTO (CTO PCI), and 154 patients were assigned to conservative treatment without PCI of the CTO (no CTO PCI). Primary outcomes were left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume (LVEDV) on cardiac magnetic resonance imaging after 4 months.

RESULTS The investigator-reported procedural success rate in the CTO PCI arm of the trial was 77%, and the adjudicated success rate was 73%. At 4 months, mean LVEF did not differ between the 2 groups (44.1 ± 12.2% vs. 44.8 ± 11.9%, respectively; $p = 0.60$). Mean LVEDV at 4 months was 215.6 ± 62.5 ml in the CTO PCI arm versus 212.8 ± 60.3 ml in the no-CTO PCI arm ($p = 0.70$). Subgroup analysis revealed that patients with CTO located in the left anterior descending coronary artery who were randomized to the CTO PCI strategy had significantly higher LVEF compared with patients randomized to the no-CTO PCI strategy (47.2 ± 12.3% vs. 40.4 ± 11.9%; $p = 0.02$). There were no differences in terms of 4-month major adverse coronary events (5.4% vs. 2.6%; $p = 0.25$).

CONCLUSIONS Additional CTO PCI within 1 week after primary PCI for STEMI was feasible and safe. In patients with STEMI and concurrent CTO, we did not find an overall benefit for CTO PCI in terms of LVEF or LVEDV. The finding that early CTO PCI in the left anterior descending coronary artery subgroup was beneficial warrants further investigation. (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Segment Elevation Myocardial Infarction; NTR1108) (J Am Coll Cardiol 2016;68:1622-32) © 2016 by the American College of Cardiology Foundation.

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Patients with acute ST-segment elevation myocardial infarction (STEMI) are effectively treated with immediate percutaneous coronary intervention (PCI) to restore blood flow to the acutely occluded infarct-related coronary artery (1–4). Approximately one-half of these patients are identified with additional flow-limiting stenoses in non-infarct-related coronary arteries, often referred to as multivessel coronary artery disease. These patients have 2-fold higher morbidity and mortality rates compared with patients with single-vessel disease (5,6). The most severe expression of coronary artery disease is chronic total occlusion (CTO). A growing body of evidence suggests that the excess morbidity and mortality findings in patients with multivessel coronary artery disease compared with patients with single-vessel disease are mainly explained by the presence of concurrent CTO (7,8). Concurrent CTO lesions are found in 10% to 15% of patients with STEMI (7,8). Several observational studies suggested that percutaneous revascularization of CTO lesions leads to higher left ventricular ejection fraction (LVEF), a reduced need for coronary artery bypass graft (CABG) procedures, and improved survival (9,10). Because of the procedural complexity and below-average success rate, PCI is attempted only in 10% of all CTO lesions, commonly in an elective setting (11).

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The EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Segment Elevation Myocardial Infarction) trial is a randomized clinical trial powered to investigate functional outcome after percutaneous treatment of CTO found during primary PCI for STEMI. There are 2 main mechanisms in the hypothesis of the EXPLORE trial. First, recanalization of the CTO may restore the contractile function of the hibernating myocardium. Second, recanalization of the CTO may improve healing of the infarct border zone, especially where the perfusion area of the infarct-related coronary artery and the CTO are adjacent or overlapping. We hypothesize that early revascularization of CTO improves myocardial perfusion in these overlapping territories and protects against negative remodeling.

In the EXPLORE trial, we test the hypothesis that early, routine PCI of concurrent CTO found during primary PCI for STEMI improves LVEF and reduces left ventricular end-diastolic volume (LVEDV), as measured by cardiac magnetic resonance (CMR) after 4 months.

METHODS

STUDY DESIGN. The EXPLORE study was an investigator-initiated, prospective, multicenter, international, randomized, 2-arm trial with blinded evaluation of endpoints. European and North American high-volume primary PCI centers with a 1.5-Tesla cardiac magnetic resonance (CMR) facility participated in this global trial. The trial protocol, as approved in Amsterdam by a central ethics committee, has previously been published (12). Ethics committee approval was received in all participating centers, according to local regulations.

The study was conducted in accordance with the Declaration of Helsinki. The EXPLORE trial was registered on October 30, 2007 at Nederlands Trial Register, with the trial number NTR1108. A steering committee provided oversight of the trial, and a data and safety monitoring board advised on whether the trial should be stopped because of clear evidence of benefit or harm.

PARTICIPANTS. After electrocardiographic confirmation of STEMI, patients presenting within 12 h of symptom onset were considered for the trial if they fulfilled all inclusion criteria and did not fulfill any exclusion criteria. Patients were eligible if concurrent CTO in a non-infarct-related artery was found during successful primary PCI for STEMI. Successful primary PCI was defined as a residual stenosis of the culprit lesion <30% and a Thrombolysis In Myocardial Infarction (TIMI) flow classification ≥2. For the purpose of this trial, CTO was defined as a 100% luminal narrowing without antegrade flow or with antegrade or retrograde filling through collateral vessels. The CTO should be located in a coronary

ABBREVIATIONS AND ACRONYMS

ARC = Academic Research Consortium

CABG = coronary artery bypass graft

CTO = chronic total occlusion

LAD = left anterior descending coronary artery

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

PCI = percutaneous coronary intervention

RCA = right coronary artery

STEMI = ST-segment elevation myocardial infarction

of Amsterdam, in combination with a research grant from Abbott Vascular. Dr. Henriques has received grants from Abbott Vascular during the conduct of the study; and has received grants from BBraun, Abiomed, and Biotronik outside the submitted work. Dr. van der Schaaf has received grants from Abbott Vascular, Biotronik, and Biosensors; has received personal fees from Biotronik and Boston Scientific; has been a consultant for Biotronik; and has received speakers fees from OrbusNeich, Boston Scientific, and Asahi Intecc outside the submitted work. Dr. Råmunddal has been a proctor for Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Henriques and Hoebers contributed equally to this work. William Lombardi, MD, served as Guest Editor for this paper.

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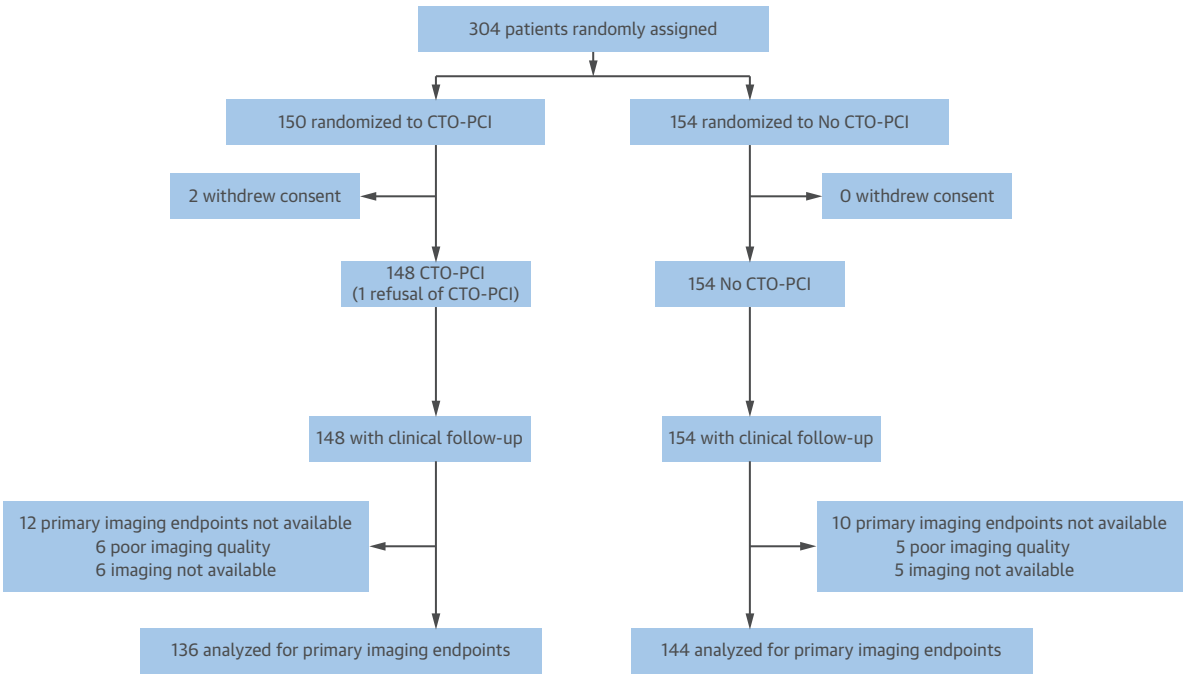
FIGURE 1 Trial Profile



CTO = chronic total occlusion; PCI = percutaneous coronary intervention.

vessel with a reference diameter of at least 2.5 mm. Among the exclusion criteria were hemodynamic instability persisting for >48 h after primary PCI and factors precluding reliable CMR imaging such as persistent or permanent atrial fibrillation, severe renal insufficiency, and indications for pacemaker or implantable cardioverter-defibrillator insertion. Full inclusion and exclusion criteria are summarized in Online Appendix A and B, respectively. The study protocol mandated a screening echocardiogram to exclude valvular disease requiring surgical treatment. All patients were eligible only after local heart team approval, including decision making on PCI of any non-CTO lesions. **Figure 1** shows the flow chart of the trial.

RANDOMIZATION. After written informed consent had been obtained, patients were randomized to a strategy of additional PCI of the CTO (CTO PCI) within 7 days after primary PCI or to a conservative strategy for at least 4 months (no CTO PCI). In patients randomized to no CTO PCI, intervention of the CTO within the first 4 months was permitted only when clinically driven in the presence of severe symptoms requiring invasive treatment. Randomization was done in an open-label manner with an electronic Internet-based system in permuted blocks of varying size in each participating center.

PCI OF CTO. The technique of the CTO PCI procedure was left to the operator without any restrictions, except for protocol-mandated everolimus-eluting stent use. Successful CTO PCI was defined as a residual stenosis of the CTO lesion <30% and TIMI flow ≥2 to at least 50% of the territory supplied by the CTO. In patients with multiple CTO lesions, success was defined if at least 1 CTO was successfully treated. For patients with multiple CTOs, the CTO supplying the largest amount of myocardium was defined as the main CTO.

PCI OF NON-CTO COEXISTING CORONARY LESIONS. The protocol recommended a conservative approach for non-CTO coexisting lesions, except for those requiring intervention as decided by the local heart team. In patients randomized to CTO PCI, these lesions were treated during the CTO PCI procedure. In patients randomized to no CTO PCI, an extra procedure was scheduled within 1 week after randomization.

FOLLOW-UP, DATA COLLECTION, AND CMR IMAGING. Clinical follow-up information was obtained at the outpatient clinic where all patients were seen at 1 and 4 months. At 4 months, CMR was performed on a 1.5-T scanner using a dedicated phased-array cardiac receiver coil. For functional imaging,

electrocardiogram-gated steady-state free-precession cine images were obtained during repeated breath holds in short-axis orientation covering the left ventricle from base to apex. At least 10 min after administration of a gadolinium-based contrast agent, the late gadolinium-enhanced images were acquired using an inversion recovery gradient-echo pulse sequence with slice locations identical to the cine images to identify the size and extent of myocardial infarction. All CMR images were sent to an independent core laboratory (ClinFact Corelab, Leiden, the Netherlands) for quality control and blinded central analysis using dedicated software (QMass MR analytical software version 7.6, Medis BV, Leiden, the Netherlands).

Data were gathered electronically and were stored on a dedicated, secure server by Med-Base, Zwolle, the Netherlands. Trial data were independently monitored by Cordinamo, Wezep, the Netherlands. All baseline coronary angiograms, (non)CTO PCI procedural characteristics, complications, and success rates were adjudicated by a dedicated blinded core laboratory, and calculation of SYNTAX scores was performed by Cardialysis, Rotterdam, the Netherlands.

OUTCOMES. The 2 co-primary endpoints were LVEF and LVEDV, assessed by CMR at 4 months. The short axis cine images were used to measure LVEDV and were indexed for body surface area. LVEF was calculated from the LVEDV and left ventricular end-systolic volume. Patients who died before the 4-month endpoint were attributed the lowest LVEF and the largest LVEDV. If CMR was not available, primary endpoint parameters were obtained from alternative imaging modalities, preferably from nuclear-based imaging or echocardiography. Assessment of primary endpoints using alternative imaging modalities was performed by an independent core laboratory blinded to other trial data and randomization outcome.

Secondary CMR endpoints were infarct size and regional myocardial function. Infarct size was determined on the late gadolinium-enhanced images as previously described using a standardized definition of hyperenhancement (13). Regional myocardial function was assessed by dividing each short-axis slice into 12 equiangular segments to calculate wall thickening (in millimeters) of each segment by subtracting end-diastolic from end-systolic wall thickness. Myocardial segments were considered dysfunctional if segmental wall thickening was <3 mm (14). Transmurality of scar tissue of the myocardium in the territory supplied by the coronary artery in which the non-infarct-related artery CTO

TABLE 1 Baseline Characteristics and Discharge Medication

	CTO PCI (n = 148)	No CTO PCI (n = 154)
Age, yrs	60 ± 10	60 ± 10
Men	131 (89)	126 (82)
Diabetes	22 (15)	25 (16)
Hypertension	59 (40)	69 (45)
Family history of coronary artery disease	66 (45)	64 (42)
Hypercholesterolemia or receiving statin therapy	51 (35)	52 (34)
Current smoker	77 (52)	76 (49)
Previous myocardial infarction	19 (13)	24 (16)
Previous PCI	9 (6)	16 (10)
Previous stroke	5 (3)	6 (4)
Primary PCI		
Infarct-related artery		
Right coronary artery	46 (31)	47 (31)
Left circumflex artery	30 (20)	43 (28)
Left anterior descending artery	72 (49)	64 (42)
TIMI flow pre-PCI 0/1	101 (68)	97 (63)
TIMI flow post-PCI 2/3	148 (100)	154 (100)
Stent placement	146 (99)	154 (100)
Drug-eluting stent	88 (59)	103 (67)
Triple-vessel disease (>70% stenosis)	62 (42)	67 (44)
MI SYNTAX score I (pre-PCI)	29 ± 8	29 ± 10
MI SYNTAX score II (wiring/balloon/aspiration)	27 ± 8	27 ± 10
Infarct size		
Peak CK-MB	130 (39–272)	111 (43–256)
Peak troponin T	3.1 (1.1–7.8)	3.3 (0.9–6.0)
LVEF before randomization*	41 ± 11	42 ± 12
CTO characteristics during primary PCI (adjudicated)		
Patients with multiple CTOs†	13 (9)	22 (14)
CTO-related artery		
Right coronary artery	64 (43)	78 (51)
Left circumflex artery	48 (32)	37 (24)
Left anterior descending artery	36 (24)	39 (25)
TIMI flow		
0	132 (89)	139 (90)
1	15 (10)	14 (9)
2	1 (1)	1 (1)
Total J-CTO score	2 ± 1	2 ± 1
Previously failed lesion	2 (1)	4 (3)
Blunt stump	33 (22)	45 (29)
Bending	98 (66)	108 (70)
Calcification	115 (78)	132 (86)
Occlusion length ≥20 mm	60 (41)	68 (44)
Discharge medication		
Aspirin	148 (100)	152 (99)
Clopidogrel, prasugrel, or ticagrelor	148 (100)	154 (100)
Beta-blocker	138 (93)	139 (90)
ACE inhibitor or ARB	133 (90)	121 (79)
Lipid-lowering drugs	144 (97)	147 (96)

Values are mean ± SD, n (%), or median (interquartile range). *Imaging modality is MRI only; data available in n = 201 patients. †For patients with multiple CTOs, the CTO supplying the largest amount of myocardium was defined as the main CTO.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CK-MB = creatine kinase-MB isoenzyme; CTO = chronic total occlusion; J-CTO = Multicenter CTO registry of Japan; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 2 Procedural Characteristics in Patients Undergoing CTO PCI

CTO Treatment	CTO PCI (n = 147*)
Number of days from primary PCI to CTO PCI	5 ± 2
Number of days from randomization to CTO PCI	2 ± 2
Multiple CTO arteries treated	6 (4)
Technique CTO procedure	
Antegrade only	124 (84)
Retrograde	23 (16)
CrossBoss or Stingray	5 (3)
PCI successful (investigator reported)	113 (77)
PCI successful (core laboratory adjudicated)	106 (73)
Stent usage (in patients with successful CTO PCI, n = 106)	
Everolimus-eluting stent	97 (90)
Other drug-eluting stent	11 (10)
Number of stents used	2 (1–3)

Periprocedural Adverse Events	CTO Vessel	Donor Artery
Dissection	12	1
Occlusion side branch	2	0
Thrombus	1	0
Tamponade	1	0
Major arrhythmia†	2	–
Resuscitation	4	–
Periprocedural myocardial infarction		–
Third universal definition of myocardial infarction	4	–
Study protocol‡	13	–
Emergency CABG operation	0	–
Stroke	0	–
Periprocedural death	0	–

Values are mean ± SD, n (%), median (interquartile range), or n. *1 patient refusal of PCI CTO. †Ventricular fibrillation or sustained ventricular tachycardia. ‡Data available in n = 71.
CABG = coronary artery bypass graft; other abbreviations as in Table 1.

was located was assessed in patients who underwent baseline CMR of sufficient quality. The left ventricle was divided into 16 segments according to the American Heart Association model (15). Whether a segment was supplied by the CTO coronary artery was assessed by the CMR core laboratory based on the baseline coronary angiogram.

Periprocedural myocardial infarction was assessed according to the original protocol definition, which was identical to the 2007 Academic Research Consortium (ARC) criteria (16). Additionally, periprocedural myocardial infarction was also adjudicated according to the third universal definition of myocardial infarction (17).

Major adverse coronary events (MACE) were defined as the composite of cardiac death, myocardial infarction, and CABG. Cardiac death was defined according to the ARC criteria, and myocardial infarction was defined according to the third universal definition of myocardial infarction criteria. PCI was characterized as repeat PCI of the treated CTO lesion, PCI of non-CTO lesions in the CTO vessel, and PCI in non-CTO vessels according to ARC criteria. Stent thrombosis was defined according to ARC criteria. Stent thromboses were assigned to the CTO unless they could unequivocally be associated with a non-CTO lesion.

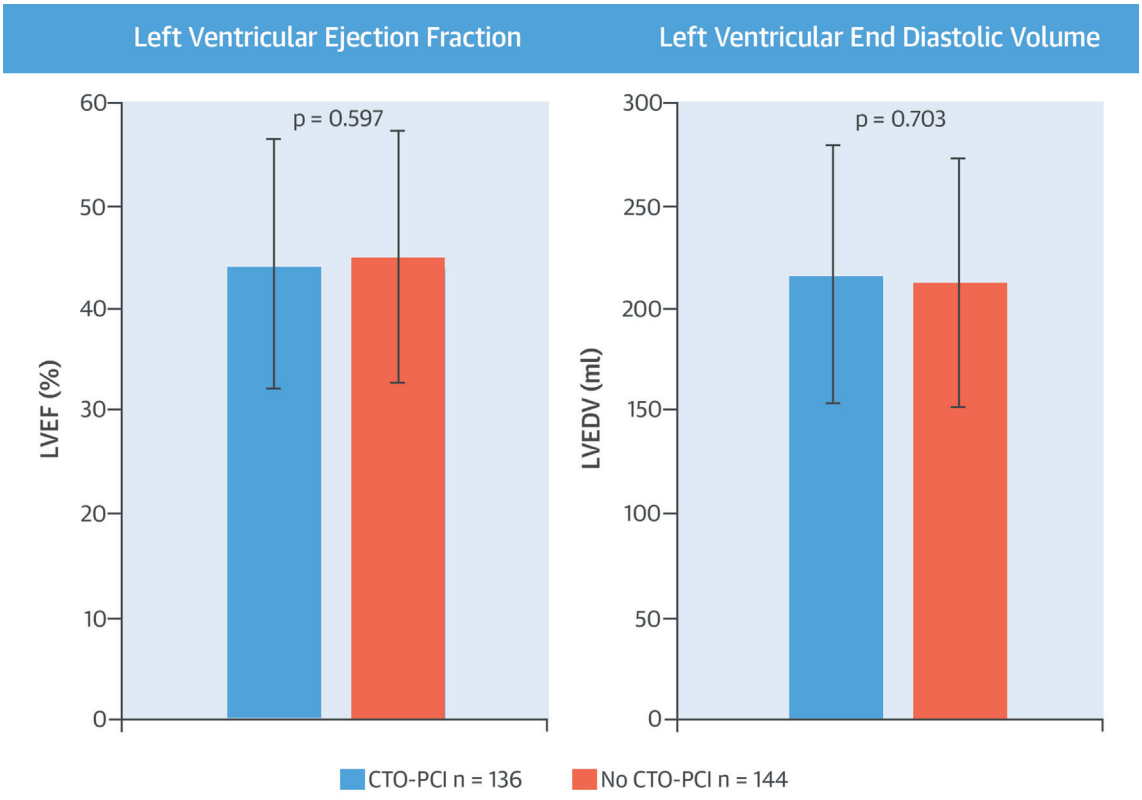
An independent clinical events committee adjudicated all potential cases of periprocedural myocardial infarction, MACE, repeat PCI, stent thrombosis, and all other periprocedural complications.

TABLE 3 Imaging Outcomes

	CTO PCI	No CTO PCI	Difference (95% CI)	p Value
Primary endpoint	136	144		
Left ventricular ejection fraction, %	44.1 (12.2)	44.8 (11.9)	−0.8 (−3.6 to 2.1)	0.60
Left ventricular end-diastolic volume, ml	215.6 (62.5)	212.8 (60.3)	2.8 (−11.6 to 17.2)	0.70
MRI or other imaging	132	143		
Left ventricular ejection fraction, %	45.1 (10.9)	45.1 (11.6)	0.1 (−2.7 to 2.7)	1.00
Left ventricular end-diastolic volume, ml	209.9 (53.8)	211.5 (58.3)	−1.6 (−14.9 to 11.8)	0.82
Left ventricular end-diastolic volume index, ml/m^2	102.9 (23.9)	104.3 (25.4)	−1.4 (−7.3 to 4.4)	0.63
Left ventricular end-systolic volume index, ml/m^2	57.9 (22.6)	58.9 (24.8)	−1.1 (−6.7 to 4.6)	0.71
MRI only	124	135		
Left ventricular ejection fraction, %	45.0 (10.6)	45.2 (11.5)	−0.2 (-2.9 to 2.5)	0.88
Left ventricular end-diastolic volume, ml	213.8 (51.8)	214.8 (56.4)	−1.0 (−14.2 to 12.3)	0.89
Left ventricular end-diastolic volume index, ml/m^2	104.9 (22.6)	105.9 (24.2)	−1.0 (−6.7 to 4.7)	0.73
Left ventricular end-systolic volume index, ml/m^2	59.0 (22.4)	59.7 (24.5)	−0.7 (−6.5 to 5.0)	0.81
Left ventricular end-diastolic mass index, g/m^2*	51.6 (9.2)	52.4 (12.0)	−0.8 (−3.5 to 2.0)	0.58
Dysfunctional segments, %*	58.0 (26.6)	61.5 (27.0)	−3.6 (−10.4 to 3.2)	0.30
Total infarct size, g†	7.6 (6.0)	7.2 (5.6)	0.4 (−1.1 to 2.0)	0.59

Values are n or n (%), unless otherwise indicated. *Data available in n = 113/n = 130. †Data available in n = 95/n = 114.
CI = confidence interval; MRI = magnetic resonance imaging; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Left Ventricular Function at 4-Month Follow-Up in STEMI Patients Undergoing CTO PCI Versus no CTO PCI**



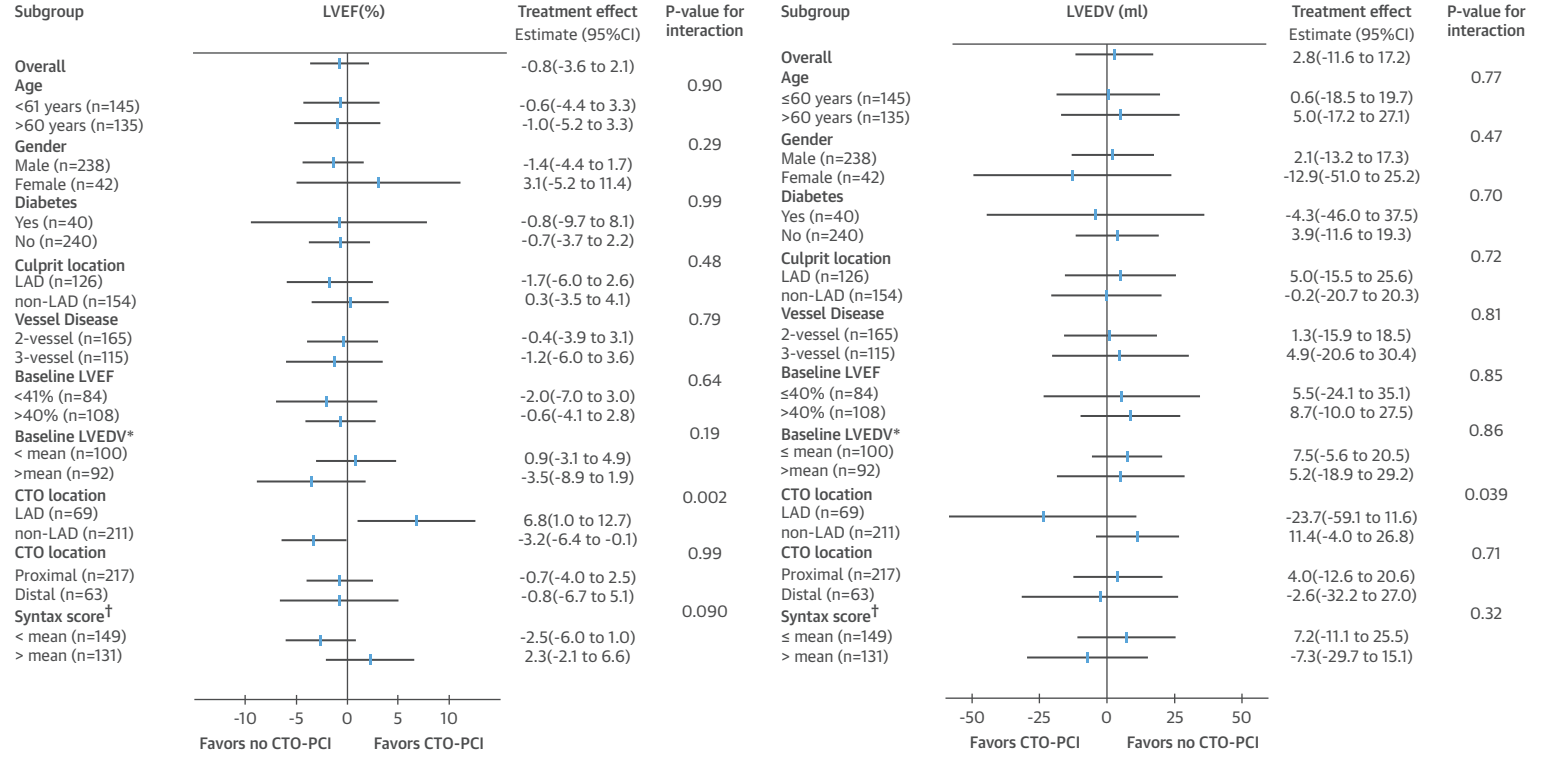
Henriques, J.P.S. et al. J Am Coll Cardiol. 2016;68(15):1622–32.

Left ventricular ejection fraction (LVEF) **(left)** and left ventricular end-diastolic volume (LVEDV) **(right)** at 4-month follow-up. All analyses were performed on an intention-to-treat basis: core-laboratory–reported success rates of chronic total occlusion percutaneous coronary intervention were 73%; and operator-reported success rates were 77%. **Whiskers** indicate standard deviation. CTO = chronic total occlusion; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

STATISTICAL ANALYSIS. The trial was powered to detect differences between the 2 groups in CMR-assessed LVEF and LVEDV at 4 months after STEMI (Online Appendix C). With 2 × 150 randomized patients, there was 80% power to detect absolute differences of 4% in LVEF and 15 ml in LVEDV in favor of PCI of the CTO with a 2-sided alpha of 5%. We assumed that CTO PCI would be successful in 80% of cases. The mean global LVEF in patients randomized to the no-CTO strategy was assumed to be 36% versus 41% in patients randomized to the CTO PCI strategy with a common standard deviation of 12%. Consequently, the expected global ejection fraction was 40% (0.8 × 41% + 0.2 × 36%) in patients randomized to CTO PCI versus 36% in patients randomized to no CTO PCI. The calculation for the second primary endpoint was made on the basis of the assumption of a net mean LVEDV of 185 ml for patients randomized to CTO PCI and 200 ml for patients randomized to no CTO PCI. The standard deviation for LVEDV was assumed to be 45 ml. The primary endpoint was analyzed on an intention-to-treat basis.

Because this study had 2 primary endpoints, the Hochberg extension of the Bonferroni method for multiple comparisons was used to test for statistical significance with an overall type I error rate ≤0.05 (18). The statistical comparisons of the treatment arms of the trial with respect to the primary and secondary endpoints were performed using the independent-samples Student *t* test, or the Fisher exact probability test in case of binary endpoints. All p values were 2 sided. For the incidence of MACE,

FIGURE 2 Forest Plots of Subgroup Analyses for the Primary Outcomes



*The mean left ventricular end-diastolic volume was 210.5 ml. †The mean SYNTAX score was 26.5. CI = confidence interval; LAD = left anterior descending coronary artery; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; other abbreviations as in Figure 1.

Kaplan-Meier curves displaying the pattern of events over the 4-month follow-up period were constructed; the log-rank statistic was used to calculate statistical significance.

RESULTS

From November 2007 through April 2015, 304 patients were enrolled at 14 sites (Online Appendix D). A total of 150 patients were randomly assigned to the CTO PCI arm of the trial, and 154 patients were randomized to the no-CTO PCI arm. Two patients randomized to the CTO PCI arm withdrew informed consent before CTO PCI, thus reducing the CTO PCI group to 148 patients.

BASELINE AND PROCEDURAL CHARACTERISTICS. The study populations in both trial arms were well balanced, without any significant differences in baseline characteristics (Table 1). The most common infarct-related coronary artery was the left anterior descending coronary artery (LAD) (n =136; 45%), followed by the right coronary artery (RCA) (n = 93; 31%) and the circumflex artery (n = 73; 24%). Triple-vessel disease was present in 43% of the study population (n = 129). Most concurrent CTOs were located in the RCA (n = 142; 47%), followed by the circumflex artery (n = 85; 28%) and the LAD (n = 75; 25%). Transmurality of scar tissue in the myocardial territory supplied by the CTOs was assessed in 149 patients (49.0%), and >75% transmurality in the CTO territory was present in none of the patients.

Patients randomized to a CTO PCI strategy underwent the procedure on average on day 5.0 ± 1.9. One patient randomized to the CTO PCI arm refused the procedure. The investigator-reported procedural success rate in the CTO PCI arm was 77%, and the adjudicated success rate was 73%. Procedural characteristics including procedural complications are presented in Table 2. No periprocedural death or emergency CABG procedures occurred during CTO PCI.

PRIMARY AND SECONDARY CMR ENDPOINTS. A total of 136 patients were analyzed for the primary endpoints in the CTO PCI arm and 144 in the no-CTO PCI arm, as elucidated in the flow chart (Figure 1). At 4 months, mean LVEF was 44.1 ± 12.2% in the CTO PCI arm and 44.8 ± 11.9% in the no-CTO PCI arm (p = 0.597). Mean LVEDV was 215.6 ± 62.5 ml in the CTO PCI arm versus 212.8 ± 60.3 ml in the no-CTO PCI arm (p = 0.703) (Central Illustration). A subgroup analysis showed a strongly significant interaction between randomized treatment assignment and 4-month LVEF in patients with CTO located in the LAD (p < 0.002) (Figure 2). In patients with concurrent CTO in the LAD, LVEF was significantly higher in the CTO PCI arm compared with the no-CTO PCI arm (47.2 ± 12.3% vs. 40.4 ± 11.9%; p = 0.02). For the co-primary endpoint of LVEDV, there was also a significant interaction between CTO location and randomized treatment assignment (p = 0.039) (Figure 2). Additional subgroup analyses revealed no other significant interactions. Left ventricular function at 4 months follow-up in both study arms is presented in Table 3.

CLINICAL EVENTS. Clinical follow-up at 4 months was complete in all patients and is presented in Table 4. At 4 months, MACE rates were 5.4% in the

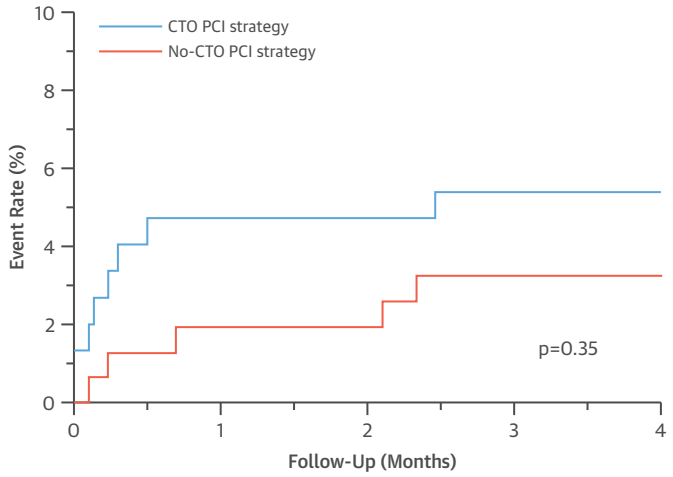
TABLE 4 Adjudicated Clinical Outcomes From Randomization to 4-Month Follow-Up

	CTO PCI (n = 148)	No CTO PCI (n = 154)	p Value
Major adverse cardiac events			
Cardiac death	4 (2.7)	0 (0.0)	0.056
Myocardial infarction	5 (3.4)	3 (1.9)	0.49
Periprocedural*	4 (2.7)	1 (0.6)	–
Spontaneous or recurrent	2 (1.4)	2 (1.3)	–
CABG operation	–	1 (0.6)	–
MACE	8 (5.4)	4 (2.6)	0.25
Other events			
PCI	39 (26.4)	20 (13.0)	0.004
CTO PCI	–	5 (3.2)	–
Repeat CTO PCI	2 (1.4)	0 (0.0)	–
Non-CTO PCI in CTO vessel	10 (6.8)	0 (0.0)	0.001
Before initial CTO procedure	1 (0.7)	–	–
During initial CTO procedure	9 (6.1)	–	–
Post-initial CTO procedure	–	–	–
PCI in non-CTO vessel	31 (20.9)	17 (11.0)	0.027
Before initial CTO procedure	0 (0.0)	–	–
During initial CTO procedure	26 (17.6)	–	–
Post-initial CTO procedure	5 (3.4)	–	–
Total stent thrombosis	5 (3.4)	3 (1.9)	0.49
Stent thrombosis CTO lesion	2 (1.4)	0 (0.0)	–
Definite	1 (0.7)	0 (0.0)	–
Probable	1 (0.7)	0 (0.0)	–
Timing of stent thrombosis CTO lesion			
Acute	0 (0.0)	0 (0.0)	–
Subacute	2 (1.4)	0 (0.0)	–
Stent thrombosis non-CTO lesion	4 (2.7)	3 (1.9)	0.72
Definite	3 (2.0)	3 (1.9)	–
Probable	1 (0.7)	0 (0.0)	–
Timing of stent thrombosis non-CTO lesion			
Acute	0 (0.0)	1 (0.6)	–
Subacute	3 (2.0)	2 (1.3)	–
Stroke†	0 (0.0)	2 (1.3)	–
Bleeding according to GUSTO-criteria	5 (3.4)	2 (1.3)	0.28
Mild	1 (0.7)	1 (0.6)	–
Moderate	3 (2.0)	1 (0.6)	–
Severe or life-threatening	1 (0.7)	0 (0.0)	–

Values are number of events (%). The first event per patient is listed. *Periprocedural myocardial infarction was defined according to the third universal definition of myocardial infarction criteria. †1 patient had a fatal stroke; there were no other noncardiac deaths.

GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; MACE = a composite of cardiac death, myocardial infarction, and coronary artery bypass graft; other abbreviations as in Tables 1 and 2.

FIGURE 3 Major Adverse Cardiac Events Event Rates at 4-Month Follow-Up



Major adverse cardiac events consisted of cardiac death, myocardial infarction, and coronary artery bypass graft operation. Abbreviations as in Figure 1.

CTO PCI arm versus 2.6 % in the no-CTO PCI arm ($p = 0.25$) (Figure 3). Repeat CTO PCI occurred in only 2 patients in the CTO PCI arm (1.4%). A total of 5 patients in the no-CTO PCI arm underwent clinically driven CTO PCI before the 4-month endpoint. There was a higher rate of additional revascularization in non-CTO vessels in the CTO PCI arm (20.9% vs. 11.0%; $p = 0.03$). Definite or probable stent thrombosis occurred in 5 patients in the CTO PCI arm compared with 3 patients in the no-CTO PCI arm (3.4% vs. 1.9%; $p = 0.49$). Two cases of stent thrombosis in the CTO PCI arm were related to the treated CTO lesion: 1 case of angiographically confirmed definite stent thrombosis in the CTO lesion occurring 8 days after the CTO PCI; and 1 case of probable stent thrombosis in a patient who died after hospital discharge on day 7 after CTO PCI. The other 3 definite stent thrombosis cases in the CTO PCI arm were related to the culprit lesion of the STEMI.

DISCUSSION

EXPLORE was a randomized clinical trial investigating the impact of CTO PCI on functional and clinical outcome. The EXPLORE trial showed that routine CTO PCI did not result in higher LVEF and lower LVEDV at 4 months when compared with a no-CTO PCI strategy in an unselected cohort of patients with STEMI and concurrent CTO. We found similar MACE rates in the 2 treatment groups. Periprocedural myocardial infarction (third universal definition) occurred in only 4 patients. There were no periprocedural deaths or emergency CABG operations. A subgroup analysis showed that CTO PCI in patients with a concurrent CTO in the LAD was associated with a significantly higher LVEF after 4 months compared with no CTO PCI (47.2 ± 12.3% vs. 40.4 ± 11.9%; $p = 0.02$), a finding suggesting that CTO PCI can still improve outcomes in high-risk patients. To be able to make any firm conclusion on this topic, further research is needed.

The CTOs were mostly located in the RCA, in agreement with large registries (19,20). The mean multicenter CTO registry of Japan (J-CTO) score of 2 ± 1 in EXPLORE is comparable to the mean J-CTO score in a contemporary registry study of CTO PCI in patients with stable coronary artery disease, thereby illustrating the complexity of the patients enrolled (21). The study protocol did not mandate use of a specific protocol or technique for CTO PCI, but rather left the technical approach to CTO PCI at the discretion of the operator; this approach resulted in the use of various techniques, as shown in Table 2. The investigator-reported procedural success rate of 77% was similar to success rates from large CTO registry studies (22,23). The strict core laboratory-adjudicated success rate of 73% was slightly lower.

The PRAMI (Multi Centre Open Label Randomised Controlled Parallel-Group Three Arm Trial to Compare the Use of Fractional Flow Reserve Guided and Angiographically Guided Revascularization to the Treatment of Infarct Related Artery Only in Patients With STEMI and Multivessel Disease), CULPRIT (Complete Versus Lesion-Only Primary PCI trial), and PRIMULTI (Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization) trials studied the value of additional PCIs of other flow-limiting stenoses after primary PCI for STEMI. All 3 studies excluded patients with concurrent CTOs (24–26). The presence of CTO resulted in a higher degree of complex coronary artery disease in the study cohort. In EXPLORE, 43% of patients had triple-vessel disease despite the use of a strict definition (luminal stenosis >70%). This percentage was higher than in the PRAMI, CULPRIT, and PRIMULTI trials (24–26). In the CULPRIT study, 23% of all patients had 3-vessel disease (25). In the PRAMI and PRIMULTI studies, multivessel coronary artery disease was defined as a luminal stenosis >50%, and 3-vessel disease was reported in 36% and 31% of the 465- and 627-patient cohorts, respectively (24,26). In EXPLORE, the extent of coronary artery disease, including concurrent CTO and expressed in an overall high SYNTAX score, also resulted in a lower baseline LVEF

(41%) compared with the CULPRIT (45%) and PRIMULTI (50%) studies (baseline LVEF was not reported in the PRAMI study).

The body of evidence of a potential benefit of CTO recanalization has been derived from retrospective analyses and greatly focused on differences in clinical outcome between patients with failed and successful CTO PCI (9). Studies focusing on potential improvement of left ventricular function are scarce and lack an adequate control group because of their nonrandomized study designs (10). A meta-analysis of observational studies in elective patients showed that successful CTO PCI was associated with an improvement of 4.4% absolute LVEF points (10). Subgroup analyses in EXPLORE revealed a significant interaction between the location of the CTO and randomized treatment allocation in terms of LVEF at 4 months; patients with a CTO located in the LAD who were randomized to the CTO PCI strategy had significantly higher LVEF with a similar favorable trend for LVEDV. On the one hand, this finding in a subgroup of the study cohort should be interpreted with caution, but on the other hand, the interaction terms for LVEF and LVEDV were highly significant and marginally significant, respectively. Moreover, earlier large registry studies already reported a survival benefit after successful versus failed CTO PCI in the LAD, but not in the RCA or the circumflex artery (27,28).

STUDY LIMITATIONS. A major limitation of the current study is that it was not powered to detect differences in hard clinical endpoints such as death, myocardial infarction, and stroke. Moreover, as in most randomized controlled trials, selection of patients was on the basis of inclusion and exclusion criteria. Patients with high-risk characteristics (e.g., shock, ventricular arrhythmias, out-of-hospital resuscitation) were not suitable for inclusion in EXPLORE. Moreover, patients expected to have an indication for an implantable cardioverter-defibrillator and patients with severe concomitant valvular disease and/or arrhythmias such as atrial fibrillation were not eligible for inclusion. Unfortunately, a screening log was not prospectively collected for each participating site. The results of our study apply only to patients who are hemodynamically stable during the first week after primary PCI. Our results cannot be applied to acutely ill hemodynamically compromised patients. Further studies focusing on very high-risk patients are needed.

Furthermore, there was no uniform protocol-specified technique for CTO PCI; however, this resulted in a "real-world" approach to CTO PCI. For ethical reasons, the study was not blinded, and no sham procedures were performed in the no-CTO PCI arm, but all primary endpoint analyses were performed by an independent core laboratory blinded to randomized treatment assignment. Finally, the CTO PCI success rate was lower (73%) than expected (80%), and this outcome negatively affected the power of the study. However, given that the LVEF and LVEDV were numerically similar in the CTO PCI and no-CTO PCI groups, it is unlikely that an 80% success rate would have led to significant differences between both groups.

CONCLUSIONS

The EXPLORE trial showed that additional CTO PCI within 1 week after primary PCI for STEMI was feasible and safe. In patients with STEMI and concurrent CTO, we did not find an overall benefit for CTO PCI in terms of LVEF or LVEDV. However, a subgroup analysis suggests that patients with CTO in the LAD may benefit from early additional CTO PCI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Up to 15% of patients with acute STEMI have concurrent CTO of a non–infarct-related coronary artery, and this is associated with higher mortality rates.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Routine additional PCI of a concurrent CTO within 1 week after successful primary PCI of the infarct related artery does not improve LVEF or LVEDV at 4-month follow-up.

TRANSLATIONAL OUTLOOK: Further studies are needed to verify whether the subgroup of patients with CTO of the non–infarct-related LAD gain benefit from PCI of this vessel as reflected in improved left ventricular function or survival.

REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.

2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:485–510.

3. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.

4. Widimsky P, Wijns W, Fajadet J, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J 2010;31:943–57.

5. Park DW, Clare RM, Schulte PJ, et al. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. JAMA 2014;312:2019–27.

6. van der Schaaf RJ, Timmer JR, Ottervanger JP, et al. Long-term impact of multivessel disease on cause-specific mortality after ST elevation myocardial infarction treated with reperfusion therapy. Heart 2006;92:1760–3.

7. Claessen BE, van der Schaaf RJ, Verouden NJ, et al. 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. J Am Coll Cardiol Intv 2009;2:1128–34.

8. Claessen BE, Dangas GD, Weisz G, et al. 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;33:768–75.

9. Christakopoulos GE, Christopoulos G, Carlino M, et al. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. Am J Cardiol 2015;115:1367–75.

10. 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;187:90–6.

11. Grantham JA, Marso SP, Spertus J, House J, Holmes DR Jr., Rutherford BD. Chronic total occlusion angioplasty in the United States. J Am Coll Cardiol Intv 2009;2:479–86.

12. van der Schaaf RJ, Claessen BE, Hoebers LP, et al. Rationale and design of EXPLORE: a randomized, prospective, multicenter trial investigating the impact of recanalization of a chronic total occlusion on left ventricular function in patients after primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. Trials 2010;11:89.

13. Bondarenko O, Beek AM, Hofman MB, et al. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. J Cardiovasc Magn Reson 2005;7:481–5.

14. Nijveldt R, Beek AM, Hirsch A, et al. Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury. J Am Coll Cardiol 2008;52:181–9.

15. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–42.

16. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

17. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

18. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289–300.

19. Ramunddal T, Hoebers LP, Henriques JP, et al. Chronic total occlusions in Sweden: a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). PloS One 2014;9:e103850.

20. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol 2012;59:991–7.

21. Nombela-Franco L, Urena M, Jerez-Valero M, et al. Validation of the J-chronic total occlusion score for chronic total occlusion percutaneous coronary intervention in an independent contemporary cohort. Circ Cardiovasc Interv 2013;6:635–43.

22. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. Am Heart J 2010;160:179–87.

23. Galassi AR, Brilakis ES, Boukhris M, et al. Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. Eur Heart J 2015 Aug 7 [E-pub ahead of print].

24. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115–23.

25. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963–72.

26. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386:665–71.

27. Claessen BE, Dangas GD, Godino C, et al. Impact of target vessel on long-term survival after percutaneous coronary intervention for chronic total occlusions. Catheter Cardiovasc Interv 2013;82:76–82.

28. Safley DM, House JA, Marso SP, Grantham JA, Rutherford BD. Improvement in survival following successful percutaneous coronary intervention of coronary chronic total occlusions: variability by target vessel. J Am Coll Cardiol Intv 2008;1:295–302.

KEY WORDS chronic total occlusion percutaneous coronary intervention, ST-segment elevation myocardial infarction

APPENDIX For a complete list of the EXPLORE study investigators, inclusion and exclusion study criteria, an expanded explanation of the calculations used to determine the power of this study, and an additional table showing the study sites and numbers of study participants at each site, please see the online version of this article.