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A Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion

The REVASC Trial

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ABSTRACT

OBJECTIVES The aim of this study was to investigate whether percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) improves left ventricular function.

BACKGROUND The benefit of PCI in CTOs is still controversial.

METHODS Patients with CTOs who were candidates for PCI were eligible for the study and were randomized to PCI or no PCI of CTO. Relevant coexisting non-CTO lesions were treated as indicated. Patients underwent cardiac magnetic resonance imaging at baseline and at 6 months. The primary endpoint was the change in segmental wall thickening (SWT) in the CTO territory. Secondary endpoints were improvement of regional wall motion and changes in left ventricular volumes and ejection fraction. Furthermore, major adverse coronary events after 12 months were assessed.

RESULTS The CTO PCI group comprised 101 patients and the no CTO PCI group 104 patients. The change in SWT did not differ between the CTO PCI (4.1 [−14.6 to 19.3]) and no CTO PCI (6.0 [−8.6 to 6.0]) groups ($p = 0.57$). Similar results were obtained for other indexes of regional and global left ventricular function. Subgroup analysis revealed that only in patients without major non-CTO lesions (basal SYNTAX [Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery] score ≤13) was CTO PCI associated with larger improvement in SWT than no CTO PCI (p for interaction = 0.002). Driven by repeat intervention, major adverse coronary event rates at 12 months were significantly lower in the CTO PCI group (16.3% vs. 5.9%, $p = 0.02$).

CONCLUSIONS No benefit was seen for CTO PCI in terms of the primary endpoint, SWT, or other indexes of left ventricular function. CTO PCI resulted in clinical benefit over no CTO PCI, as evidenced by reduced major adverse coronary event rates at 12 months. (J Am Coll Cardiol Intv 2018;■:■-■) © 2018 by the American College of Cardiology Foundation.

The benefit of percutaneous coronary intervention (PCI) of chronically occluded coronary arteries is still controversial. Recent randomized trials such as DECISION (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion) and EURO-CTO (A Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) did not show a

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

cMRI = cardiovascular magnetic resonance imaging

CTO = chronic total occlusion

LV = left ventricular

LVEF = left ventricular ejection fraction

PCI = percutaneous coronary intervention

rSS = residual SYNTAX score

SWT = segmental wall thickening

TEI = transmural extent of infarction

significant reduction in major cardiovascular events (1,2). In the EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) trial, evaluating patients with ST-segment elevation myocardial infarction, additional PCI of chronic total occlusions (CTOs) did not result in improvement in left ventricular ejection fraction (LVEF) and lower left ventricular (LV) end-diastolic volume as assessed by cardiovascular magnetic resonance imaging (cMRI) at follow-up of 4 months compared with patients without CTO PCI (3). However, several studies demonstrated relief of symptoms after CTO PCI (4-6), and 2 recent studies described improvement in maximal oxygen consumption upon revascularization of a last remaining CTO vessel (7,8). Furthermore, some studies demonstrated that segmental wall thickening (SWT) in the CTO territory, assessed by cMRI, may improve after interventional revascularization (9-12). However, most of these studies were retrospective or did not include control groups of optimal medical therapy.

The REVASC (Recovery of Left Ventricular Function After Stent Implantation in Chronic Total Occlusion of Coronary Arteries) trial evaluated whether PCI of CTO, in addition to PCI of relevant coexisting non-CTO vessels, improves LV function.

TABLE 1 Baseline Characteristics

	OMT ± Non-CTO PCI (n = 104)	OMT + CTO PCI (n = 101)	p Value
Age (yrs)	68 (61-74)	65 (57-72)	0.02
Male	90 (86.5)	91 (90.1)	0.43
Body mass index (kg/m^2)	27.7 (25.7-31.2)	27.9 (25.7-29.7)	0.57
Diabetes	31 (29.8)	32 (31.6)	0.77
Hypertension	93 (89.4)	81 (80.2)	0.08
Family history of coronary artery disease	35 (33.7)	41 (40.6)	0.30
Current smoker	21 (20.2)	23 (22.8)	0.65
Peripheral arterial occlusive disease	26 (25.0)	23 (22.8)	0.75
Previous stroke	9 (8.6)	5 (5.0)	0.41
Previous myocardial infarction	38 (36.5)	39 (38.6)	0.76
Previous bypass operation	14 (13.5)	12 (11.9)	0.73
Previous PCI	33 (31.7)	28 (27.7)	0.53
Coronary artery disease			0.55
1-vessel disease	10 (9.6)	14 (13.9)	
2-vessel disease	33 (31.7)	34 (33.7)	
3-vessel disease	61 (58.7)	53 (52.5)	
SYNTAX score	16 (11-21)	14 (9-22)	0.33
Residual SYNTAX score	11 (8-16)	2 (0-7)	<0.01
Additional PCI of coexisting non-CTO lesions	63 (60.1)	16 (15.8)	<0.01
Additional PCI of the donor vessel artery	43 (41.3)	7 (6.9)	<0.01
CTO territory			0.15
Left anterior descending coronary artery	17 (16.3)	23 (22.8)	
Left circumflex coronary artery	16 (15.4)	20 (19.8)	
Right coronary artery	71 (68.3)	58 (57.4)	
J-CTO score	2 (1-2)	2 (1-3)	0.43
Blunt stump	36 (34.6)	37 (36.6)	
Bending	18 (17.3)	26 (25.7)	
Calcification	40 (38.5)	32 (31.7)	
Occlusion length ≥20 mm	88 (84.7)	82 (81.2)	
Reattempt	8 (7.7)	22 (21.8)	

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METHODS

PATIENT SELECTION. The REVASC trial was a prospective, randomized, single-center trial at the University Heart Center Bad Krozingen. We screened patients undergoing coronary angiography with a potential indication for myocardial revascularization on the basis of symptoms and/or noninvasive functional testing. Patients with diagnostic angiographic results showing CTO were eligible for the study, if PCI was the preferred treatment option. In patients with equivocal indication for PCI as opposed to coronary artery bypass grafting, the choice of treatment modality was based on discussion by the local heart team. As target CTO vessels, we accepted vessels with 100% stenosis and TIMI (Thrombolysis In Myocardial Infarction) flow grade 0 of putatively >3 months' duration, with an estimated reference vessel diameter of 2.5 to 4.0 mm (13). Patients with LVEF <25%, acute coronary syndromes within 72 h preceding the index procedure, and contraindications to cMRI were excluded from the study. Previous PCI and a previous attempt at CTO PCI were not defined as exclusion criteria.

The study was approved by the ethics committee of the medical faculty of the University of Freiburg. All patients gave written informed consent before any study procedure. This trial was registered at ClinicalTrials.gov (NCT01924962).

STUDY PROTOCOL. Following diagnostic angiography and additional PCI in case of relevant coexisting non-CTO vessels, patients were randomly assigned to no CTO PCI or CTO PCI in a 1:1 fashion using sealed, opaque envelopes on the basis of a computer-generated sequence. All procedures were performed by dedicated CTO operators. The technique of the CTO PCI procedure was left to the operator's discretion without any restrictions, except for protocol-mandated "olimus"-eluting stent use. In case of a failed CTO attempt, a second attempt was performed within 30 days after the index procedure, to achieve

the highest possible success rate in the CTO PCI arm. For patients with multiple CTOs, the main CTO was defined as the CTO supplying the largest amount of myocardium. PCI of relevant coexisting non-CTO vessels was staged before CTO PCI.

Before CTO PCI and at 6-month follow-up, patients underwent cMRI. All cardiovascular magnetic resonance images were sent to an independent core laboratory (Department of Cardiology, Robert-Bosch-Krankenhaus, Stuttgart, Germany) for quality control and blinded central analysis.

cMRI PROTOCOL. cMRI was performed on a 1.5-T scanner (Magentom Sonata, Siemens Healthcare, Erlangen, Germany) and a 3-T scanner (Somatom Skyra, Siemens Healthcare) using a dedicated phased-array cardiac receiver coil. For LV function imaging, electrocardiographically gated balanced steady-state free precession cine images were obtained during repeated breath holds in short-axis orientation covering the left ventricle from base to apex and in 2-, 3-, and 4-chamber view. For the assessment of myocardial scar, 10 min after contrast injection of intravenous gadolinium (at a dose of 0.2 mmol/kg), delayed contrast-enhanced images were acquired using inversion recovery gradient-echo sequences in identical slice position (14).

cMRI ANALYSIS. cMRI analysis was performed by the external core laboratory using dedicated cMRI evaluation software (Medis Suite 2.1, Medis, Utrecht, the Netherlands). LV diameter, quantitative LV volumes, LVEF, and LV mass were assessed using the steady-state free precession cine images. For wall motion analysis, the myocardium was divided into 17 segments (according to the American Heart Association model), and the regional wall movement of all segments was graded as follows: as 0 (normal), 1 (mildly hypokinetic), 2 (severely hypokinetic), 3 (akinetic), or 4 (dyskinetic) (15). The extent of scar (0% to 25%, 25% to 50%, 50% to 75%, or >75%) was additionally expressed for all 17 segments. SWT was defined as a percentage increase of LV wall thickness during systole compared with diastole and was considered dysfunctional if wall thickening was <45% (16). After tracing the endocardial and epicardial borders of the left ventricle, late enhancement was semi-automatically marked (signal intensity >5 SDs exceeding the mean signal intensity of remote myocardium) and expressed as a percentage of the left ventricle and mass. Transmural extent of infarction (TEI) was used to assess viability, which was calculated by dividing the hyperenhanced area by the total area in each of the 17 segments and expressed as a percentage.

TABLE 1 Continued

	OMT ± Non-CTO PCI (n = 104)	OMT + CTO PCI (n = 101)	p Value
PROGRESS score	0 (0-1)	1 (0-1)	<0.01
Medication			
Acetylsalicylic acid	100 (96.2)	98 (97.0)	0.73
$P2Y_{12}$ receptor antagonist	73 (70.2)	101 (100.0)	<0.01
Beta-blocker	79 (76.0)	84 (83.2)	0.20
ACE inhibitor or angiotensin receptor blocker	80 (76.9)	83 (82.2)	0.35
Statin	103 (99.0)	99 (98.0)	0.54
Laboratory characteristics			
Serum creatinine (mg/dl)	1.0 (0.9-1.1)	0.9 (0.8-1.1)	0.54
Triglycerides (mg/dl)	145 (104-199)	142 (100-196)	0.96
Total cholesterol (mg/dl)	180 (148-212)	194 (155-216)	0.31
HDL cholesterol (mg/dl)	48 (38-58)	45 (38-53)	0.27
LDL cholesterol (mg/dl)	109 (82-141)	116 (90-144)	0.24
C-reactive protein (mg/dl)	0.20 (0.16-0.40)	0.25 (0.16-0.48)	0.44

Values are median (interquartile range) or n (%).

ACE = angiotensin-converting enzyme; CTO = chronic total occlusion; HDL = high-density lipoprotein; J-CTO = Japanese Multicenter CTO Registry; LDL = low-density lipoprotein; OMT = optical medical therapy; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

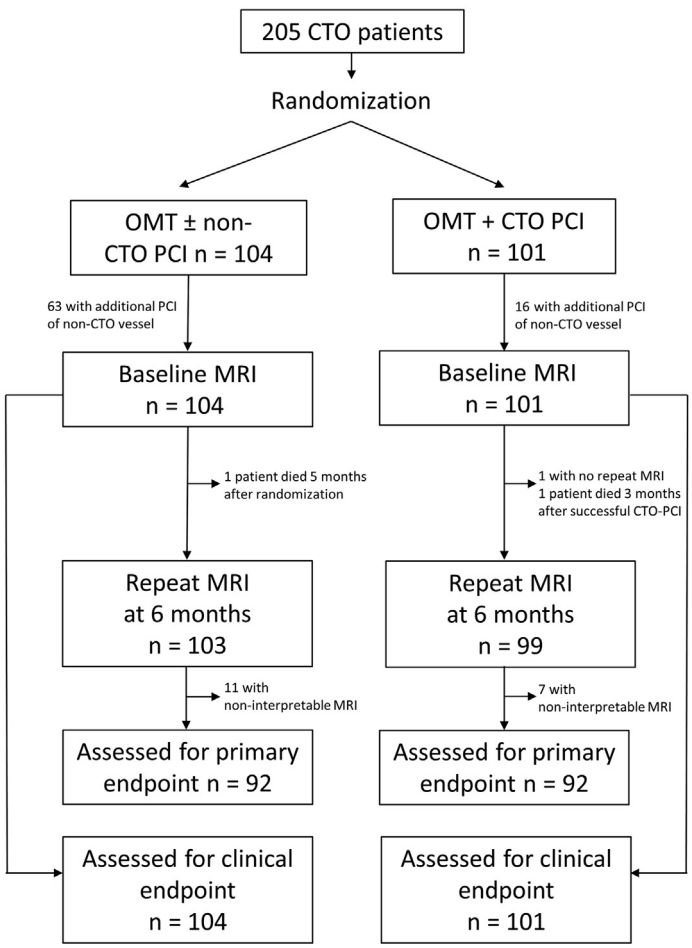
TABLE 2 Procedural Characteristics in Patients With Optimal Medical Therapy Plus Chronic Total Occlusion Percutaneous Coronary Intervention (n = 101)

	OMT + CTO PCI
Multiple CTO arteries treated	2 (2.0)
CTO recanalization technique	
Antegrade only	61 (60.4)
Retrograde	40 (39.6)
Septal crossing	28 (27.7)
Epicardial crossing	12 (11.8)
Technical success on first attempt	87 (86.1)
Technical success including second attempts	100 (99.0)
Procedural success including second attempts	89 (88.1)
Guiding catheter size used for initial approach (F)	
6	90 (89.1)
7	11 (10.9)
Size of second catheter (F)	
6	67 (66.3)
7	1 (1.0)
Procedure time (min)	96 (65-149)
Fluoroscopy time (min)	37 (20-76)
Radiation dose ($\mu Gy \cdot cm^2$)	10,322 (5,725-17,539)
Contrast volume (ml)	280 (200-400)
Number of stents used	2 (2-3)
Stent length (mm)	75 (48-94)
Periprocedural adverse events	
Type 4a myocardial infarction	11 (10.9)
Recurrent angina requiring TVR	
Emergency CABG operation	0
Stroke	0
Tamponade	0
Periprocedural death	0

Values are median (interquartile range) or n (%).

CABG = coronary artery bypass grafting; TVR = target vessel revascularization; other abbreviations as in Table 1.

FIGURE 1 Flowchart of the Study Population



CTO = chronic total occlusion; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention.

CORONARY SEGMENTAL ANALYSIS. All coronary angiograms were classified according to their coronary arterial dominance to ensure correct assignment of CTO territory. The coronary tree was considered right dominant when the posterior descending artery and posterolateral branches originated from the right coronary artery and left dominant when they both originated from the left circumflex coronary artery. A balanced coronary circulation was defined when the posterior descending artery originated from the right coronary artery and all posterolateral branches from the left circumflex coronary artery.

For assessment of the primary endpoint, a 16-segment model, excluding the apex, was used to analyze the myocardial wall in each patient (15). According to prior findings, segments 12, 15, and 16 were used to analyze the myocardium supplied from the left anterior descending coronary artery territory (17). In patients with left-dominant systems, segments 4, 5, 6, 10, 11, and 12 were assigned to the left circumflex coronary artery, and in those with right-dominant system, segments 3, 4, 9, 10, 11, and 15 were categorized to the right coronary artery (18).

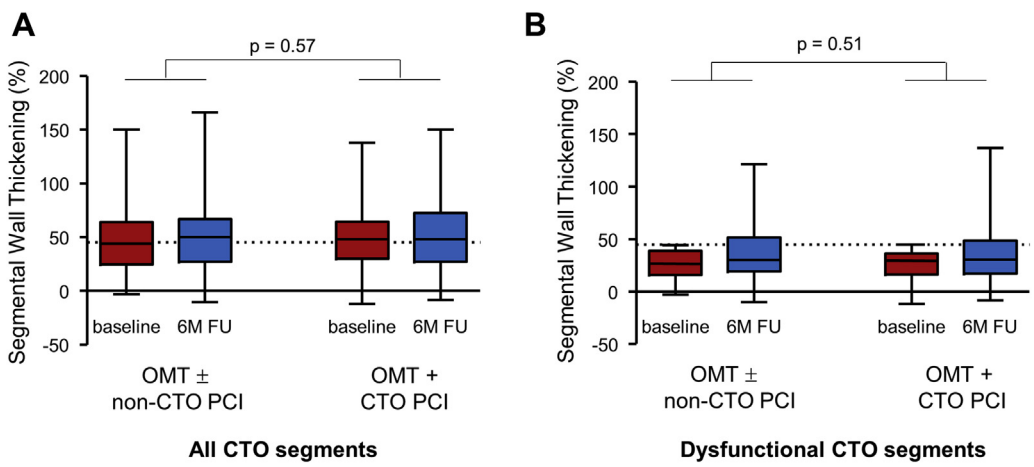
ENDPOINTS AND DEFINITIONS. The primary endpoint was the change in SWT in the CTO territory between baseline and follow-up at 6 months. Secondary endpoints were improvement of regional wall motion in the CTO territory according to the 17-segment model and changes in LV end-diastolic and end-systolic volume indexes and LVEF. In addition, we assessed clinical outcomes at 12 months. Technical success was defined as a residual stenosis <30% with antegrade TIMI flow grade 3 in the CTO target vessel (19).

Procedural success was defined as technical success in the absence of in-hospital adverse events (all-cause death, type 4a myocardial infarction, stroke, recurrent angina requiring target vessel revascularization with PCI or coronary artery bypass graft, tamponade requiring pericardiocentesis or surgery). Periprocedural myocardial infarction was defined according to the third universal definition of myocardial infarction (20). Major adverse coronary events at 12 months were defined as all-cause death, myocardial infarction (20), and any clinically driven repeat revascularization. Clinically indicated reintervention was defined as coronary artery bypass surgery or repeat PCI performed for symptoms or signs of ischemia in the presence of angiographic stenosis. We determined the incidence of stent thrombosis according to the Academic Research Consortium criteria (21).

STATISTICAL ANALYSIS. The study was designed to detect 15% recovery of SWT with CTO PCI versus 2% recovery with no CTO PCI at a common standard deviation of 30% (22). To detect this difference with power of 80%, a minimum sample size of 85 per group was required. To account for loss to follow-up, we intended to recruit 200 patients.

For continuous variables, the Mann-Whitney *U* test was used for statistical comparisons between the groups. For categorical variables, the Fisher exact test was performed. All p values were 2-sided, and p values <0.05 were considered to indicate statistical significance. Linear regression analyses were used to derive regression coefficients with 95% confidence intervals and to detect interactions with pre-specified subgroups. For the analysis of major adverse cardiac events, Kaplan-Meier curves were derived for 12-month follow-up.

FIGURE 2 Primary Magnetic Resonance Imaging Endpoint



Segmental wall thickening in territories of chronic total occluded coronary arteries. Baseline **(red boxes)** and 6-month follow-up (FU) **(blue boxes)** values are shown for **(A)** all chronic total occlusion (CTO) territories and **(B)** CTO segments with dysfunctional baseline segmental wall thickening (<45%). Whiskers indicate minimal and maximal values, boxes with internal lines show median and interquartile range. P values are calculated for comparison of differences between baseline and follow-up. PCI = percutaneous coronary intervention.

Comparison between both treatment arms was performed using the log-rank statistic. All analyses were performed using SPSS Statistics version 23 (IBM, Armonk, New York).

RESULTS

Between August 2007 and September 2015, 205 patients were enrolled. One hundred four patients were randomized to the no CTO PCI group and 101 patients to the CTO PCI group. Baseline characteristics of the study population (Table 1) were well balanced except for a minor difference in age. Most patients had triple-vessel coronary artery disease (n = 114 [56%]) with median basal SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score of 15 (10 to 21.5) (Table 1). The prevailing CTO territory was the right coronary artery (n = 129 [63%]). Relevant viability in the CTO area, defined as TEI <50%, was present in 158 patients (77%). Technical success of the first CTO attempt was 86% (Table 2). When including a second attempt within 30 days of the index procedure, only 1 patient could not be revascularized. Because of 2 periprocedural Q-wave myocardial infarctions, the overall procedural success rate of CTO PCI was 97%. Residual SYNTAX score (rSS) remained significantly higher in the no CTO PCI group (11 [8 to 16] vs. 2 [0 to 7], p < 0.01).

FUNCTIONAL OUTCOMES. Follow-up cMRI was not available in 21 patients, leaving 184 patients for assessment of the primary endpoint (Figure 1). Change of median SWT in the CTO territory was not significantly different between the no CTO PCI and the CTO PCI group (p = 0.57) (Figure 2). When restricting the analysis to CTO segments that showed dysfunctional SWT (<45%) at baseline, similar improvement was observed in both groups (p = 0.51) (Figure 2). Baseline wall motion in the CTO territory was impaired in 61 patients in the no CTO PCI group (66.3%) and in 64 patients in the CTO PCI group (69.6%) (p = 0.43). Improved regional wall motion in the CTO territory was observed in similar proportions in both groups (18.5% vs. 19.6%, p = 0.85) (Table 3). Secondary cMRI endpoints of global LV function, LVEF and LV end-diastolic volume index, showed improvement, which was similar in both groups (p = 0.79 and p = 0.54, respectively) (Table 3).

Restriction of the analysis to the 158 patients with relevant viability in the CTO area also showed no difference in SWT between the 2 groups. Additional subgroup analyses in all patients are shown in Figure 3. The lack of effect of CTO PCI on change in SWT was consistent across various subgroups, expect for the subgroup with baseline SYNTAX score below the median (≤13). This subgroup was associated with a significant improvement in SWT with CTO PCI but not with no CTO PCI (p for interaction = 0.002).

CLINICAL EVENTS. Clinical follow-up at 12 months was complete for all patients (Table 4). One patient in

TABLE 3 Magnetic Resonance Imaging Endpoints

	OMT ± Non-CTO PCI (n = 92)	OMT + CTO PCI (n = 92)	p Value
SWT in CTO territory			
Baseline	43.9 (24.9 to 63.9)	48.2 (30.1 to 64.3)	0.71
6-month follow-up	50.3 (27.3 to 67.3)	48.2 (27.3 to 72.4)	0.95
Change of SWT in CTO territory	6.0 (−8.6 to 6.0)	4.1 (−14.6 to 19.3)	0.57
SWT in dysfunctional CTO territories (n = 49 resp. 44)			
Baseline	27.0 (15.7 to 38.8)	29.6 (16.3 to 36.3)	0.91
6-month follow-up	30.0 (19.4 to 51.3)	30.6 (17.2 to 48.8)	0.64
Change of SWT in dysfunctional CTO territories	10.0 (−4.3 to 23.1)	5.9 (−6.0 to 20.7)	0.51
LVEF (%)			
Baseline	59.6 (45.8 to 64.3)	54.7 (42.9 to 65.1)	0.48
6-month follow-up	61.0 (51.3 to 66.8)	57.0 (45.0 to 65.5)	0.21
Change in LVEF	0.7 (−1.0 to 3.7)	0.9 (−1.3 to 4.1)	0.79
LVEDV index (ml/m^2)			
Baseline	79 (59 to 92)	78 (61 to 100)	0.51
6-month follow-up	72 (60 to 90)	73 (62 to 89)	0.58
Change in LVEDV index	−2 (−12 to 7)	−3 (−13 to 6)	0.54
LVESV index (ml/m^2)			
Baseline	32 (22 to 45)	33 (23 to 54)	0.46
6-month follow-up	30 (20 to 42)	31 (22 to 47)	0.31
Change in LVESV index	−2 (−8 to 4)	−2 (−8 to 4)	0.95
Improved regional wall motion status in CTO territory	17 (18.5)	18 (19.6)	0.85
TEI in CTO territory <50%			
Baseline	84 (91.3)	82 (89.1)	0.62
6-month follow-up	85 (92.4)	82 (89.1)	0.45
Myocardial mass (g)			
Baseline	99.3 (80.5 to 115.4)	103.0 (84.8 to 114.8)	0.37
6-month follow-up	91.6 (80.6 to 109.6)	97.0 (82.5 to 116.1)	0.13
Change in myocardial mass	−0.9 (−9.2 to 5.2)	−1.5 (−8.8 to 4.5)	0.78
Area of late gadolinium enhancement (g)			
Baseline	8.1 (2.9 to 18.2)	8.4 (2.6 to 19.3)	0.73
6-month follow-up	7.8 (2.1 to 18.1)	7.8 (2.9 to 17.1)	0.83
Change in late gadolinium enhancement	−0.1 (−1.0 to 0.0)	0.0 (−1.1 to 0.1)	0.44

Values are median (interquartile range) or n (%).

LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; SWT = segmental wall thickening; TEI = transmural extent of infarction; other abbreviations as in Table 1.

the CTO PCI group died, and 2 patients in the no CTO PCI group died. Sixteen patients in the no CTO PCI group and 5 patients in the CTO PCI group underwent clinically driven repeat revascularization during the follow-up period (**Figure 4**). Periprocedural myocardial infarction occurred in 11 patients undergoing CTO PCI and 11 patients treated by PCI of the coexisting non-CTO lesion in the no CTO PCI arm (20) (**Table 2**). In the CTO PCI group, 1 patient died of unknown cause. In the no CTO PCI group, 1 patient died of cardiac death and 1 patient of myocardial infarction due to definite stent thrombosis. Otherwise, there were no definite or probable stent thromboses in either group.

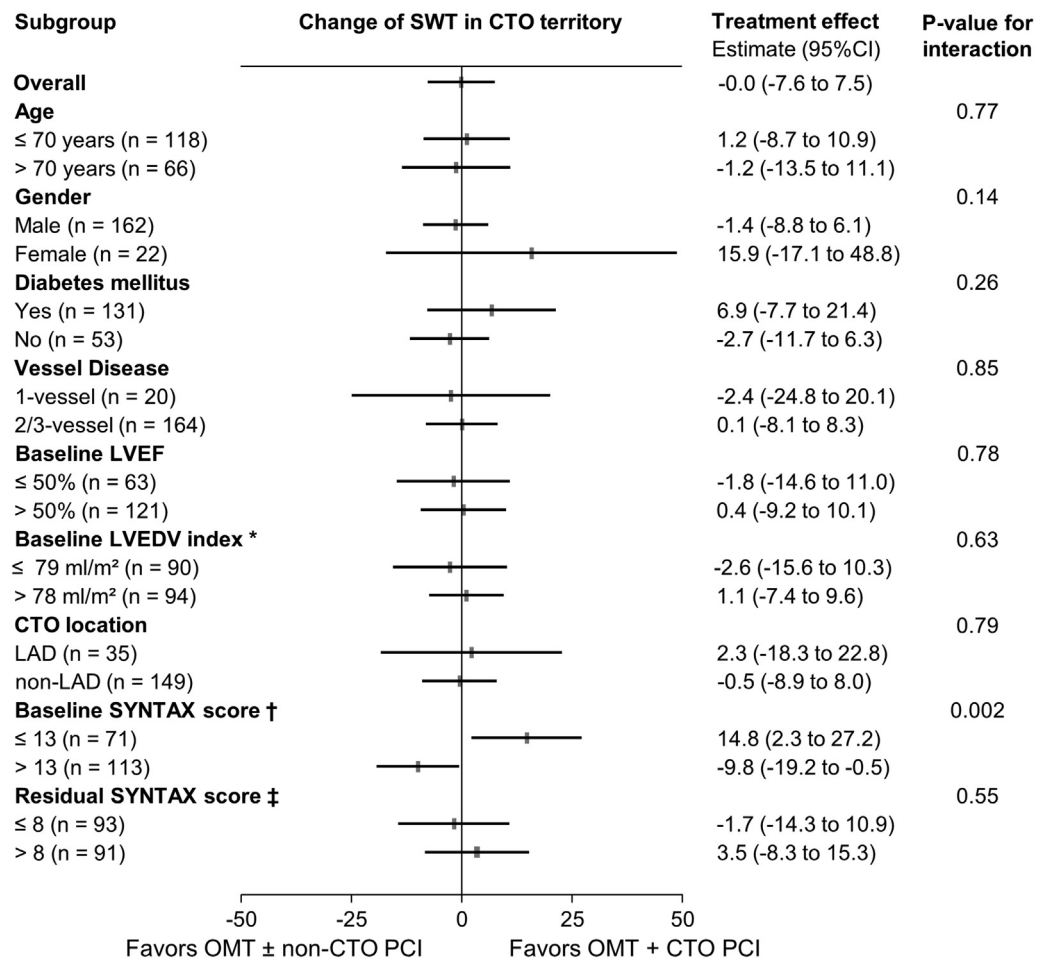
DISCUSSION

REVASC was a randomized clinical, single-center trial, investigating the impact of CTO PCI in comparison with no CTO PCI on functional and clinical endpoints. In an unselected cohort of patients undergoing coronary angiography and additional PCI in case of relevant coexisting non-CTO lesions and optimal medical therapy, withholding CTO PCI had no adverse effect on primary or secondary cMRI outcomes after 6 months. Specifically, the REVASC trial showed no difference in SWT in the myocardium supplied by the CTO artery, whether or not CTO PCI was performed. This finding was corroborated by other indexes of LV function assessed by cMRI.

Thus, contrary to our expectations, we were unable to show a beneficial effect of CTO PCI on recovery of regional wall motion. There are 2 potential reasons for this finding. To start with, a substantial proportion of patients did not show relevant dysfunction of the CTO segment. Hence, there was little room for improvement. Only when we restricted the analysis to patients with dysfunctional CTO segments at baseline did we find the expected recovery of SWT after CTO PCI. Second, even without CTO PCI, the recovery of SWT after PCI of other relevant lesions was similar to that in the CTO PCI group. Thus, improvement of collateral flow might have contributed to the recovery of hibernating myocardium. In this respect, the findings in patients with less complex coronary artery disease at baseline (SYNTAX score ≤13) are noteworthy. In these patients, the SYNTAX score is driven almost exclusively by the CTO lesion itself, and collateral flow cannot be improved. Accordingly, this subset did not show an improvement of SWT in the CTO territory without CTO PCI. There was, however, a significant benefit after CTO PCI (p for interaction = 0.002). Given the hypothesis-generating nature of our subgroup analysis, further studies aiming to prove benefit of CTO PCI may focus on patient cohorts with ischemia limited to CTO territories.

Likewise, a number of previous studies showed improvement of regional wall motion after CTO PCI (11,22-27). Two of these studies assessed viability by cMRI as it was performed in REVASC (22,24). In patients with inducible myocardial perfusion deficit and viability in the CTO territory, significant improvements in LVEF and LV end-systolic volume were demonstrated (24). A significant increase in LVEF after successful CTO PCI was also recently demonstrated by Galassi et al. (28) in patients with

FIGURE 3 **Subgroup Analysis for the Primary Magnetic Resonance Imaging Endpoint**



Forest plots indicate estimated treatment effect (95% confidence interval [CI]). *The median baseline left ventricular end-diastolic volume (LVEDV) index was 78 ml/m^2. The median †baseline and ‡residual SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores were 13 and 8, respectively. LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction.

LVEF ≤35%, which was associated with improved symptoms at 6-month follow-up and mid-term clinical outcomes.

Concerning regional LV function, Baks et al. (22) showed that SWT improved significantly only in segments with 25% to 75% TEI, whereas segments with TEI >75% did not improve (22). Our observation that significant improvement of SWT in the CTO PCI group was limited to dysfunctional segments at baseline is largely in line with these findings. Of interest, we observed a similar improvement of global and regional LV function in the no CTO PCI control arm of REVASC. In these patients, additional PCI was in more than two-thirds of cases undertaken in the donor vessel artery. The observed recovery of regional LV function in the non-CTO PCI group could therefore be attributed to concomitant therapy reducing ischemic burden to a last remaining CTO.

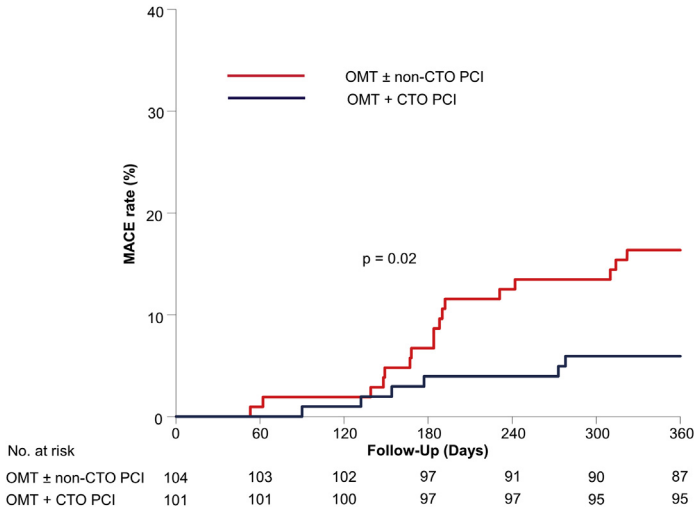
The recently published EXPLORE trial was the first randomized trial evaluating patients with ST-segment elevation myocardial infarction and concurrent CTO (3). Additional CTO PCI within 1 week after primary PCI for ST-segment elevation myocardial infarction was feasible and safe, although mean LVEF and major adverse coronary event rate did not differ between the 2 groups after 4 months. A subgroup cMRI analysis of EXPLORE delineated that the

TABLE 4 Major Adverse Cardiac Events at 6 and 12 Months

	OMT ± Non-CTO PCI (n = 104)	OMT + CTO PCI (n = 101)
MACE at 6 mo	6 (5.8)	4 (4.0)
Death of any cause at 6 mo	1 (1.0)	1 (1.0)
Clinically driven repeat revascularization at 6 mo	5 (4.8)	3 (3.0)
Target vessel revascularization (CTO)	5 (4.8)	3 (3.0)
Treated with drug-eluting balloon	0 (0.0)	0 (0.0)
Treated with drug-eluting stent	4 (3.8)	2 (2.0)
Sent to CABG	1 (1.0)	1 (1.0)
De novo stenosis	0 (0.0)	1 (1.0)
Treated with drug-eluting balloon	0 (0.0)	0 (0.0)
Treated with drug-eluting stent	0 (0.0)	1 (1.0)
Sent to CABG	0 (0.0)	0 (0.0)
Definite or probable stent thrombosis	0 (0.0)	0 (0.0)
Acute myocardial infarction	0 (0.0)	0 (0.0)
MACE at 12 mo	17 (18.2)	6 (5.9)
Death of any cause at 12 mo	2 (2.0)	1 (1.0)
Clinically driven repeat revascularization at 12 mo	16 (15.4)	5 (5.0)
Target vessel revascularization (CTO)	14 (13.5)	3 (3.0)
Treated with drug-eluting balloon	0 (0.0)	0 (0.0)
Treated with drug-eluting stent	13 (12.5)	2 (2.0)
Sent to CABG	1 (1.0)	1 (1.0)
De novo stenosis	3 (2.9)	3 (3.0)
Treated with drug-eluting balloon	1 (1.0)	1 (1.0)
Treated with drug-eluting stent	2 (1.9)	2 (2.0)
Sent to CABG	0 (0.0)	0 (0.0)
Definite or probable stent thrombosis	1 (1.0)	0 (0.0)
Acute myocardial infarction	1 (1.0)	0 (0.0)

Values are n (%).

FIGURE 4 Major Adverse Cardiac Events at 12-Month Follow-Up



Major adverse cardiac events consisted of death, clinically driven revascularization, and stroke. CTO = chronic total occlusion; PCI = percutaneous coronary intervention.

recovery of SWT in the CTO territory was not significantly better in the CTO PCI group compared with the no CTO PCI group. Only in dysfunctional segments with TEI <50% in the CTO territory did CTO PCI result in significantly better recovery of SWT compared with no CTO PCI (10).

REVASC is the first randomized, prospective trial to evaluate whether PCI of CTO improves LV function in patients with stable coronary artery disease. There was no additional effect on SWT in the CTO territory in comparison with the no CTO PCI group after 6 months.

In contrast to the EXPLORE trial, REVASC showed a reduction in the combined clinical endpoint favoring CTO PCI, which was driven largely by a reduced need for clinically driven revascularization, with no difference in fatal outcomes. After additional PCI of relevant coexisting non-CTO vessels, the rSS was significantly reduced after CTO PCI in comparison with the no CTO PCI group. Farooq et al. (29) reported that an rSS >8 is associated with adverse outcomes and is a powerful indicator of 5-year mortality. Généreux et al. (30) also suggested that an rSS <8 had adequate discriminatory power for risk prediction of 1-year ischemic outcomes after PCI. A recently published observational study showed that an rSS ≤12 after PCI may reduce the risk for cardiac mortality and could be a measure of reasonable incomplete revascularization in patients with CTO and multivessel coronary artery disease (31). Therefore, lower rSS after CTO PCI might have contributed to the observed lower need for clinically driven revascularization.

STUDY LIMITATIONS. A major limitation of the present study was that the trial was not powered to detect differences in clinical endpoints, such as death or myocardial infarction. Moreover, as in most randomized controlled trials, selection of patients was on the basis of inclusion and exclusion criteria. The study was not blinded, and no sham procedures were performed in the no CTO PCI arm, because of ethical aspects.

SWT as an imaging parameter has high dispersion and was measured at rest. Yet all cMRI endpoint analyses were performed by an independent core laboratory blinded to randomized treatment assignment. A further limitation was that the inclusion of CTO patients was not based on prior cMRI perfusion deficiency and viability. Thus, 26 patients with relevant TEI in the CTO territory were randomized. However, excluding these patients from the analysis had no impact on the reported results.

CONCLUSIONS

For the majority of patients with CTO lesions, the recovery of impaired wall motion in the CTO territory with PCI of relevant coexisting non-CTO lesions is similar irrespective of CTO PCI. Nevertheless, analysis of the subset of patients without relevant coronary disease outside the CTO lesion suggests a small beneficial effect of CTO PCI on wall motion. In patients with more extensive coronary disease, this effect may be blurred by the overall effect of improved flow to the myocardium due to PCI of other lesions. Apart from its equivocal effect on LV function, CTO PCI appears to reduce the risk for major adverse coronary events during 1-year follow-up because of a lower need for clinically driven target vessel revascularization.

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PERSPECTIVES

WHAT IS KNOWN? Previous nonrandomized cMRI studies showed an improvement of SWT after CTO PCI.

WHAT IS NEW? REVASC is the first randomized trial investigating the improvement of SWT in a CTO territory. In case of PCI of relevant coexisting non-CTO lesions, CTO PCI does not afford an additional benefit on SWT within in 6 months.

WHAT IS NEXT? Further studies are needed on the long-term effect of CTO PCI on regional and global LV function, particularly in patients with impaired LV function.

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