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**CLINICAL RESEARCH**
*Interventional cardiology*

# A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions

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**Aims** The clinical value of percutaneous coronary intervention (PCI) for chronic coronary total occlusions (CTOs) is not established by randomized trials. This study should compare the benefit of PCI vs. optimal medical therapy (OMT) on the health status in patients with at least one CTO.

**Method and results** Three hundred and ninety-six patients were enrolled in a prospective randomized, multicentre, open-label, and controlled clinical trial to compare the treatment by PCI with OMT with a 2:1 randomization ratio. The primary endpoint was the change in health status assessed by the Seattle angina questionnaire (SAQ) between baseline and 12 months follow-up. Fifty-two percent of patients have multi-vessel disease in whom all significant non-occlusive lesions were treated before randomization. An intention-to-treat analysis was performed including 13.4% failed procedures in the PCI group and 7.3% cross-overs in the OMT group. At 12 months, a greater improvement of SAQ subscales was observed with PCI as compared with OMT for angina frequency [5.23, 95% confidence interval (CI) 1.75; 8.71; $P = 0.003$], and quality of life (6.62, 95% CI 1.78–11.46; $P = 0.007$), reaching the prespecified significance level of 0.01 for the primary endpoint. Physical limitation ($P = 0.02$) was also improved in the PCI group. Complete freedom from angina was more frequent with PCI 71.6% than OMT 57.8% ($P = 0.008$). There was no periprocedural death or myocardial infarction. At 12 months, major adverse cardiac events were comparable between the two groups.

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† For full list of participating centers, see Supplementary material online.

**Conclusion** Percutaneous coronary intervention leads to a significant improvement of the health status in patients with stable angina and a CTO as compared with OMT alone.

**Trial registration** NCT01760083.

**Keywords** Chronic coronary occlusion • Percutaneous transluminal intervention • Optimal medical therapy • Seattle angina questionnaire • EQ-5D

# Introduction

Chronic coronary total occlusions (CTOs) are found in 15–25% of patients with stable angina pectoris.[1] Recent advancements in the treatment of coronary CTOs have resulted in improved procedural success in this lesion subset.[2] Still, treatment of a CTO constitutes less than 5% of percutaneous coronary interventions (PCIs) in contemporary interventional practice.[3]

One obstacle to a wider adoption of CTO recanalization is the absence of robust evidence on the benefits of this treatment. Longitudinal series in several thousand patients have established the distinct negative effect of CTOs on prognosis, most prominently in patients with an acute coronary syndrome, but also among patients with stable angina pectoris.[4] Additionally, non-randomized comparative studies also showed a beneficial effect of CTO recanalization on symptoms, left ventricular function, and even survival.[5] However, these data are observational comparing patients with successful and unsuccessful PCI. Despite also physiological evidence that collaterals are not sufficient to prevent ischaemia in CTOs,[6] the lack of randomized studies lead to a low level of recommendation for CTO-PCI in myocardial revascularization guidelines.[7]

The primary benefit that should be expected from CTO revascularization is symptomatic improvement.[8,9] Accordingly, the EUROCTO trial was designed to evaluate the benefit of PCI, as compared with optimal medical therapy (OMT), on patients' symptomatic status, as objectively assessed by the Seattle angina questionnaire (SAQ).

# Methods

## Trial design

The EUROCTO trial was a prospective randomized, multicentre, open-label, and controlled clinical trial to assess in a 2:1 allocation whether PCI with a Biolimus-eluting stent (Biomatrix; Bisoensors Europe SA, Morges, Switzerland) plus OMT was superior to OMT alone with respect to health status at 12-month follow-up. Patients with both single- and multi-vessel disease were recruited at 28 European centres with high expertise for CTO-PCI.

The trial was managed and overseen by an independent Clinical Research Organization (Cardiovascular European Research Centre, Massy, France) and the data were assessed and adjudicated by a Clinical Events Committee and a Data and Safety Monitoring Board. The study protocol was approved by the relevant authorities, and all patients signed an approved informed consent form. The trial was registered on clinicaltrials.gov (NCT01760083).

## Participants

Symptomatic patients with at least one CTO, defined as a complete occlusion (TIMI 0 flow) of at least 3 months duration, in a major coronary artery with a vessel diameter of at least 2.5 mm (American Heart Association site map 1–3, 6, 7, and 11) were enrolled. The operator had to judge the CTO lesion as suitable for PCI. In patients with a CTO and regional myocardial dysfunction, a non-invasive imaging test was requested to assess myocardial viability in the territory of the CTO. Patients with a prior acute coronary syndrome were included only, if this event was related to a non-CTO lesion successfully treated more than 4 weeks before enrolment. Patients were not enrolled if they had any exclusion criteria for implantation of a drug-eluting stent (e.g. patients not tolerating dual antiplatelet therapy or need for elective non-cardiac surgery within 6 months).

## Study intervention

Patients with a single-vessel CTO were treated according to randomization. Patients with multi-vessel disease received first treatment of any other significant non-CTO lesions >4 weeks before baseline assessment and randomization. If the operator deemed that treating the non-CTO lesion before the CTO lesion would carry an increased risk for the patient, the patient was excluded.

The procedural strategy to open the CTO followed recent technical recommendations including the retrograde approach if feasible collateral connections were identified.[2,10] In case of initial PCI failure, an additional attempt was encouraged, else medical or surgical therapy was chosen according to the clinical need.

Angiographic success was defined as a final angiographic residual stenosis of <20% by visual estimate and TIMI III flow after implantation of biolimus-eluting stents.[11] Patients were preloaded with clopidogrel 600 mg. Post-procedure patients received aspirin 75–100 mg per day and clopidogrel 75 mg per day for 6 to 12 months according to operator's preference. Equivalent doses of prasugrel or ticagrelor could be used at the operator's discretion.

Full anti-angina medication was pro-actively prescribed at the start of the trial in both patient groups. During follow-up, efforts were made to adapt and if necessary to escalate anti-angina therapy in both groups, and specifically within the OMT group to prevent unplanned revascularization of the CTO.

## Health status assessment

The disease-specific health status was assessed by SAQ, a 19-item questionnaire that measures five domains related to coronary artery disease: angina frequency, physical limitations, quality of life, angina stability, and treatment satisfaction.[12] Scores range from 0 to 100, with higher scores indicating fewer symptoms and better health status. Significant improvement in each subscale are predefined for physical limitation (≥8 points), angina frequency (≥20 points), and quality of life (≥16 points).[12,13] General health status was assessed with the use of the European Quality of Life–5 Dimensions (EQ-5D) instrument.[14] The EQ-5D is a five-item measure of mobility, self-care, usual activity, pain or discomfort, and anxiety or depression. Written questionnaires were collected at baseline and at 12 months. The questionnaires were

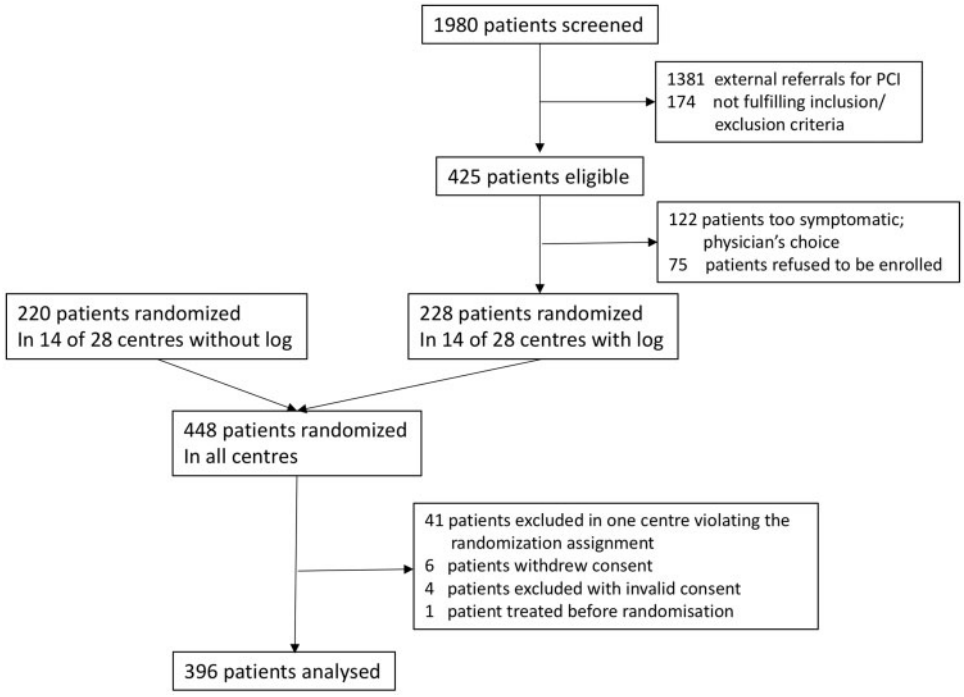


**Figure 1** Consort diagram of patient enrolment.

administered in each patient's native language, and centrally evaluated by the clinical trial organization, examples in English can be found in the Supplementary material online.

## Primary and secondary study endpoints

The primary endpoint was a change in health status subscales as assessed by SAQ between the treatment groups. Secondary endpoints were changes from baseline to 12 months of EQ-5D and the Canadian Cardiology Society (CCS) classification, and major cardiac adverse events, stent thrombosis, cerebrovascular events, hospitalization for cardiac reasons, all evaluated at 12 months. The study will be continued for 36 months to assess the long-term safety of PCI as compared with OMT.

## Adverse event definition and assessment

Major adverse cardiac events were defined as cardiac death, non-fatal myocardial infarction (MI), and ischaemia-driven premature target lesion revascularization during follow-up. Criteria for acute MI followed up the new universal definition of MI[15]: detection of a rise of cardiac biomarker values [preferably cardiac troponin with at least one value above the 99th percentile upper reference limit (URL)] combined with either symptoms of ischaemia, new or presumed new significant ST-segment T-wave changes, new left bundle branch block, development of pathological Q-waves in the electrocardiogram (ECG), new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy. In-hospital procedural complications were death, periprocedural MI (Type 4a), pericardial tamponade, need for blood transfusion, urgent coronary bypass graft (CABG), contrast induced nephropathy, proven periprocedural cerebrovascular events. Stent thrombosis was defined according to the Academic Research Council criteria.[16]

## Study size calculation and randomization

The goal was to enrol all consecutive patients presenting at the study centres with a CTO fulfilling the criteria for inclusion. Taking loss-to-follow-up and 20% expected unsuccessful PCIs into account, about 600 patients would still yield 95% power to detect a score difference in SAQ subscales of more than eight at a one-sided significance level of 0.01. Details on the original sample size calculation can be found in the Supplementary materials online.

Randomization was stratified by study site and assigned by a web-based electronic data capture form. The algorithm used when building a randomization list was based on the standard algorithm of blocked randomization with randomly selected block sizes. In the PCI group, the intervention was scheduled within 4 weeks after randomization.

## Statistical analysis

The analysis is based on the intention-to-treat population. Mean and standard deviation are reported for continuous variables, and numbers and percentages for categorical variables. Concomitant medication was summarized and compared between the groups at discharge, and at 12 months by means of a $\chi^2$ test or Fisher's exact test, whichever was appropriate. The total number of anti-anginal drugs was compared by means of a Wilcoxon rank-sum test.

The analysis of the primary endpoint was performed as follows. Each component of the SAQ was analysed by means of an analysis of covariance (ANCOVA) analysis with the score at 12 months as a response and the baseline score, and a treatment group indicator as independent covariate. A Bonferroni correction for multiple testing of the five components was applied. Hence, a two-sided significance level of 0.01 was used. *Post hoc* defined dichotomized scores were reported for comparison with the literature. For all other endpoints, a two-sided significance level of 0.05 without correction for multiple testing was applied. The EQ-5D visual health

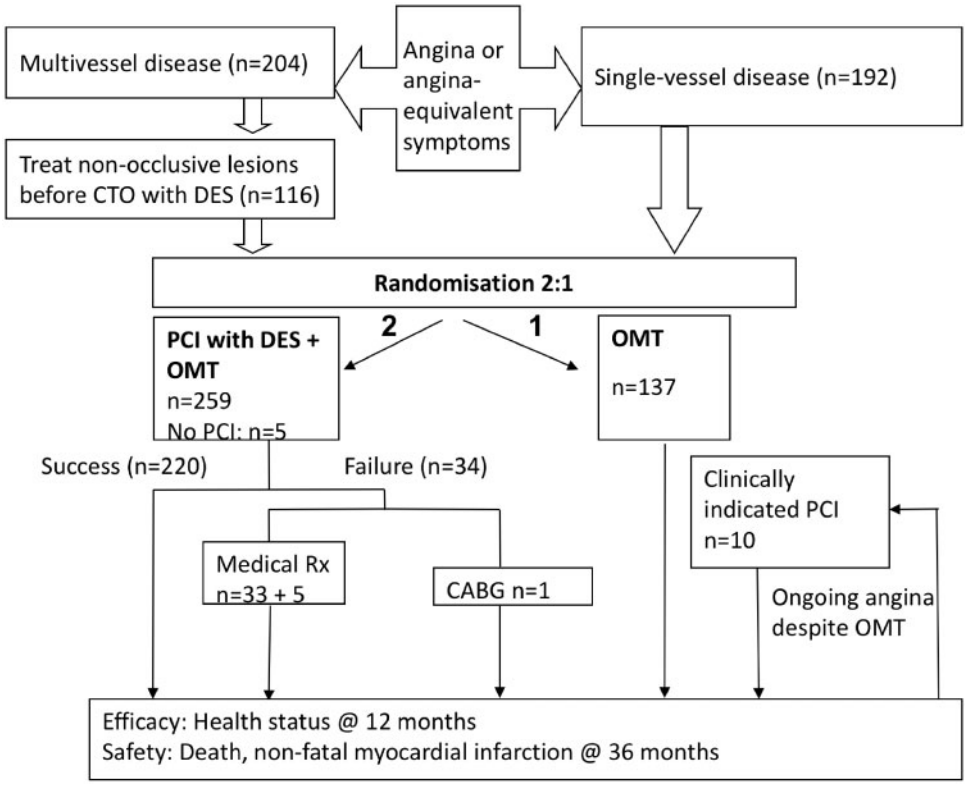


**Figure 2** Study flowchart of the EUROCTO trial.

state was analysed similarly as the primary endpoint. Changes in the EQ-5D subscores and in the CCS scores were compared by means of a Wilcoxon rank-sum test. The number of adverse events with a percentage, determined from a Kaplan–Meier curve, are reported per group and compared between groups by means of a $\chi^2$ test on the Kaplan–Meier estimates. All analyses were performed with the use of SAS, version 9.4.

# Results

## Enrolment

The enrolment period was from March 2012 to May 2015. The median time of enrolment for the sites was 19 months (range 1–39). The funding was limited and therefore enrolment could not be extended to achieve the target of 600 patients. A log of screened patients was available in 14 of 28 centres. *Figure 1* shows the patient flow in these 14 centres in which 53.6% of eligible patients were enrolled. Total enrolment was 448 patients of whom 52 were excluded due to lack of respect for the randomization assignment in a fraudulent centre (41 patients) or because of other protocol violations, leaving a study population of 396 patients.

Follow-up of 12 months was completed for all patients. Of the 137 patients randomized to OMT, 10 (7.3%) patients underwent CTO-PCI during the first 12 months of follow-up. Of the 259 randomized to PCI, five did not undergo PCI and received OMT only, and 34 (13.4%) were not successfully recanalized, one of them was referred to CABG (*Figure 2*).

## Patient and lesion characteristics

Patients were aged 65.0 ± 9.7 years, 84% were male with typical risk factors (*Table 1*), 31.6% were diabetic, of these 27.2% were insulin-dependent. There were less two-vessel patients and more three-vessel disease in the PCI group as compared with OMT, with almost twice as many post-CABG patients (*Table 1*). Study related non-CTO-PCI was performed in 27.0% in the OMT group, and in 30.5% in the PCI group with an interval of at least 4 weeks before randomization and SAQ assessment.

Most CTOs were in the right coronary artery (61.5%), followed by the left anterior descending (26.0%) and circumflex artery (12.5%). The lesion characteristics were similar between both groups except for slightly longer lesions in the PCI group (*Table 1*).

## Procedural data from the percutaneous coronary intervention group

A recanalization was attempted in 254 patients in the PCI group. Percutaneous coronary intervention was successful by the first attempt in 83.1%. Further attempts in 19 patients were successful in 9 leading to a final success rate of 86.6%. The retrograde approach was applied in 35.8% of procedures. The average number of stents used was 2.0 ±1.32, with a mean total length of 65.9 ± 28.9 mm (*Table 2*).

In-hospital complications occurred in 2.9%, which included pericardial tamponade ($n = 4$), vascular surgical repair ($n = 2$), and need for blood transfusion ($n = 5$). There was no periprocedural death.

**Table 1 Patient and lesion characteristics of patients with a coronary total occlusion randomized to optimal medical therapy or percutaneous coronary intervention**

| | OMT (*N* = 137) | PCI (*N* = 259) |
|---|---|---|
| Patient characteristics | | |
| Age (years) | 64.7 ± 9.9 | 65.2 ± 9.7 |
| Male, *n* (%) | 118 (86.1) | 215 (83.0) |
| Body mass index (kg/m$^2$) | 28.3 ± 5.2 | 28.4 ± 4.9 |
| Hypertension, *n* (%) | 98 (71.5) | 189 (73.0) |
| Insulin-dependent diabetes, *n* (%) | 12 (8.8) | 22 (8.5) |
| Non-Insulin-dependent diabetes, *n* (%) | 28 (20.4) | 63 (24.3) |
| Hypercholesterolaemia, *n* (%) | 111 (81.0) | 210 (81.1) |
| History of smoking, *n* (%) | 92 (67.2) | 190 (73.4) |
| Family history, *n* (%) | 36 (26.3) | 81 (31.3) |
| Previous myocardial infarction, *n* (%) | 25 (18.3) | 59 (22.8) |
| Previous bypass surgery, *n* (%) | 10 (7.3) | 34 (13.1) |
| Previous PCI unrelated to study, *n* (%) | 71 (51.8) | 145 (56.0) |
| Previous PCI to facilitate study entry, *n* (%) | 37 (27.0) | 79 (30.5) |
| In-stent CTO, *n* (%) | 10 (7.3) | 26 (10.0) |
| Left ventricular ejection fraction | 55.7 ± 10.8 | 54.5 ± 10.8 |
| Reversible ischaemia demonstrated, *n* (%) | 85 (62.0) | 167 (65.0) |
| Myocardial viability demonstrated, *n* (%) | 117 (85.4) | 223 (86.1) |
| Number of diseased vessels, *n* (%) | | |
| Single vessel | 62 (45.3) | 130 (50.2) |
| Two vessels | 51 (37.2) | 63 (24.3) |
| Three vessels | 24 (17.5) | 66 (25.5) |
| Lesion characteristics | | |
| Target vessel | 141 | 259 |
| Right coronary artery, *n*/*N* (%) | 81/141 (57.4) | 165/259 (63.7) |
| Left anterior descending artery, *n*/*N* (%) | 38/141 (27.0) | 66/259 (25.5) |
| Left circumflex artery, *n*/*N* (%) | 22/141 (15.6) | 28/259 (10.8) |
| Visual reference vessel diameter (mm) | 3.0 ± 0.41 | 2.9 ± 0.44 |
| Visual length of occlusion (mm) | 26.5 ± 16.0 | 31.4 ± 20.5 |
| Lesion calcifications (moderate or severe), *n*/*N* (%) | 51/141 (36.2) | 96/258 (37.2) |
| Proximal cap tapered, *n*/*N* (%) | 65/131 (49.6) | 119/220 (54.1) |
| J-CTO score | 1.67 ± 0.91 | 1.82 ± 1.07 |

Numbers are represented as mean ± standard deviation or counts. All differences were non-significant with the exception of the number of diseases vessels ($P = 0.02$) and visual length of occlusion ($P = 0.04$).

There were six incidences of a creatinine kinase (CK) increase >three times URL, but only four had a positive troponin, and none of them experienced pain, ECG changes or wall motion abnormalities, and therefore were not categorized as Type 4a MI.

## Medical therapy in the study groups

Cardiac medication is shown in *Table 3*. In the OMT group, 64.2% of patients were discharged with adenosine diphosphate antagonists because of previous PCI in a non-CTO lesions and 91.1% in the PCI group. At follow-up, this difference was no longer significant with 43.7% in the OMT group and 51.2% in the PCI group. Nitrates and alternative antianginal medication were prescribed more often in the OMT group both at discharge and at follow-up. The total number of antianginal medications was higher in the OMT group at discharge and the difference increased at follow-up.

## Clinical and health status changes in the study groups

The five subscales of the SAQ questionnaire all showed numerically but not statistically higher scores in the OMT group as compared with the PCI group at baseline (*Table 4*). At follow-up, the angina frequency ($P = 0.003$) and quality of life ($P = 0.007$) improved significantly more in the PCI group than in the OMT group, both reaching the prespecified statistical level for the primary endpoint of 0.01 (*Figure 3*). There was a numerical improvement in the subscales of physical limitation in the PCI group, and no difference in angina stability and treatment satisfaction. More patients in the PCI group showed a significant improvement of the subscales physical limitation, angina frequency, and quality of life, and more patients had complete freedom from angina (*Figure 4*).

**Table 2 Procedural characteristics in patients randomized to coronary total occlusion percutaneous coronary intervention**

| | PCI |
|---|---|
| Total number of procedures | 274 |
| Radial approach for PCI, *n/N* (%) | 94/274 (34.3) |
| Contralateral injection, *n/N* (%) | 224/274 (81.8) |
| Retrograde approach, *n/N* (%) | 98/274 (35.8) |
| Intravascular ultrasound used, *n/N* (%) | 37/214 (17.3) |
| First procedure successful, *n/N* (%) | 211/254 (83.1) |
| Final procedure success per lesion, *n/N* (%) | 220/254 (86.6) |
| Drug-eluting stents used | |
| Biomatrix, *n/N* (%) | 185/203 (91.1) |
| Others, *n/N* (%) | 18/203 (8.9) |
| Total length of stent used (mm) | 65.9 ± 28.9 |
| Width of largest stent (mm) | 3.3 ± 2.49 |
| Number of stents used | 2.0 ± 1.32 |
| Procedure duration (min) | 121.2 ± 67.8 |
| Fluoroscopy time (min) | 49.6 ± 34.9 |
| Contrast volume (mL) | 285 ± 198 |
| Patient dose (mGy) | 3685 ± 3058 |
| Dose area product (cGy*cm$^2$) | 21 464 ± 19 056 |

Numbers are represented as mean ± standard deviation with number of procedures with information available between brackets. Results are based on 254 of 259 patients who received a PCI, 19 with two PCIs and one with three PCIs.

The EQ-5D index improved by 0.07 in the PCI group and 0.04 in the OMT group ($P = 0.037$ for difference at 12 months). The EQ-5D categories mobility ($P = 0.005$), activity ($P < 0.001$), and pain/discomfort ($P = 0.001$) improved at follow-up significantly in the PCI group. Self-care and anxiety/depression were rated similar in both groups (Supplementary material online, Table S1). The CCS classification improved considerably more in the PCI group than in the OMT group (*Figure 5*).

## Clinical events during follow-up

The cardiovascular event rate at 12 months was comparable with 6.7% in the OMT group and 5.2% in the PCI group (*Table 5*). The main events in the OMT group were ischaemia-driven revascularization and cardiac hospitalization. In the PCI group, two (0.8%) patients have died from a cardiovascular cause, and five (1.9%) sustained a MI, four (1.6%) of which were non-Q-wave MI. Both patients with cardiac death in the PCI group during follow-up had previously been randomized to PCI but had not undergone the procedure because of advanced heart failure developed during hospitalization. Two out of five MIs happened late after unsuccessful procedures, and one in a patient who had not undergone a PCI.

# Discussion

In this trial of patients with stable angina pectoris and at least one CTO we found, that, compared with medical treatment alone,

**Table 3 Medication at discharge and at 12 months follow-up in patients with a coronary total occlusion randomized to optimal medical therapy or percutaneous coronary intervention**

| | OMT (*N* = 137) | PCI (*N* = 259) | *P*-value |
|---|---|---|---|
| Aspirin baseline, *n/N* (%) | 130/137 (94.9) | 252/259 (97.3) | 0.217 |
| Follow-up, *n/N* (%) | 125/135 (92.6) | 241/258 (93.4) | 0.761 |
| ADP receptor inhibitors baseline, *n/N* (%) | 88/137 (64.2) | 236/259 (91.1) | <0.001 |
| Follow-up, *n/N* (%) | 59/135 (43.7) | 132/258 (51.2) | 0.160 |
| Beta-blocker baseline, *n/N* (%) | 112/137 (81.8) | 197/259 (76.1) | 0.193 |
| Follow-up, *n/N* (%) | 104/135 (77.0) | 192/258 (74.4) | 0.568 |
| ACE-inhibitor baseline, *n/N* (%) | 75/137 (54.7) | 143/259 (55.2) | 0.929 |
| Follow-up, *n/N* (%) | 69/135 (51.1) | 134 258 (51.9) | 0.876 |
| AT1-antagonist baseline, *n/N* (%) | 26/137 (19.0) | 39/259 (15.1) | 0.316 |
| Follow-up, *n/N* (%) | 27/135 (20.0) | 43/258 (16.7) | 0.412 |
| Calcium antagonist baseline, *n/N* (%) | 37/137 (27.0) | 64/259 (24.7) | 0.618 |
| Follow-up, *n/N* (%) | 44/135 (32.6) | 69/258 (26.7) | 0.224 |
| Statin baseline, *n/N* (%) | 125/137 (91.2) | 235/259 (90.7) | 0.867 |
| Follow-up, *n/N* (%) | 118/235 (87.4) | 229/258 (88.8) | 0.692 |
| Non-statin lipid-lowering drugs baseline, *n/N* (%) | 14/137 (10.2) | 22/259 (8.5) | 0.570 |
| Follow-up, *n/N* (%) | 15/135 (11.1) | 18/258 (7.0) | 0.161 |
| Nitrate baseline, *n/N* (%) | 44/137 (32.1) | 59/259 (22.8) | 0.044 |
| Follow-up, *n/N* (%) | 39/135 (28.9) | 44/258 (17.1) | 0.006 |
| Other anti-anginal drug baseline, *n/N* (%) | 22/137 (16.1) | 28/259 (10.8) | 0.135 |
| Follow-up, *n/N* (%) | 27/135 (20.0) | 27/258 (10.5) | 0.009 |
| Total number antianginal drugs baseline, median (Q1–Q3) | 2 (1–2) | 1 (1–2) | 0.038 |
| Follow-up, median (Q1–Q3) | 2 (1–3) | 1 (0–2) | 0.009 |

ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate; AT-1, angiotensin-1; Q1, first quartile; Q3, third quartile.

**Table 4 Seattle angina questionnaire health status changes at 12 months in patients with a coronary total occlusion randomized to optimal medical therapy or percutaneous coronary intervention**

| | OMT (*N* = 137) | PCI (*N* = 259) | *P*-value |
|---|---|---|---|
| Angina frequency | | | |
| Baseline | 80.6 ± 24.2 [133] | 77.2 ± 23.8 [254] | |
| Follow-up | 87.6 ± 18.7 [128] | 91.8 ± 16.3 [232] | |
| Follow-up after correction for baseline | 86.8 (83.1–90.5) [125] | 92.0 (89.3–94.8) [230] | 0.003 |
| Physical limitation | | | |
| Baseline | 71.2 ± 24.7 [133] | 67.1 ± 24.9 [240] | |
| Follow-up | 76.6 ± 22.9 [121] | 80.2 ± 22.4 [215] | |
| Follow-up after correction for baseline | 75.9 (71.3–80.5) [119] | 81.1 (77.6–100) [205] | 0.022 |
| Quality of life | | | |
| Baseline | 59.8 ± 26.2 [131] | 55.3 ± 24.9 [251] | |
| Follow-up | 71.8 ± 25.5 [125] | 76.6 ± 23.0 [230] | |
| Follow-up after correction for baseline | 70.5 (65.4–75.6) [123] | 77.1 (73.3–80.9) [225] | 0.007 |
| Anginal stability | | | |
| Baseline | 53.4 ± 23.4 [133] | 52.0 ± 22.7 [253] | |
| Follow-up | 56.2 ± 20.2 [125] | 57.7 ± 19.6 [231] | |
| Follow-up after correction for baseline | 55.9 (51.2–60.5) [122] | 57.8 (54.4–61.2) [228] | 0.386 |
| Treatment satisfaction | | | |
| Baseline | 88.2 ± 13.7 [132] | 84.1 ± 17.6 [253] | |
| Follow-up | 89.2 ± 13.9 [125] | 90.0 ± 15.3 [230] | |
| Follow-up after correction for baseline | 88.5 (85.2–91.8) [123] | 90.5 (88.0–92.9) [227] | 0.219 |

Baseline and follow-up report mean ± standard deviation with number of patients within brackets '[]'. Follow-up after correction for baseline reports mean and a 95% confidence interval determined from an ANCOVA analysis with baseline and treatment indicator as independent variables.

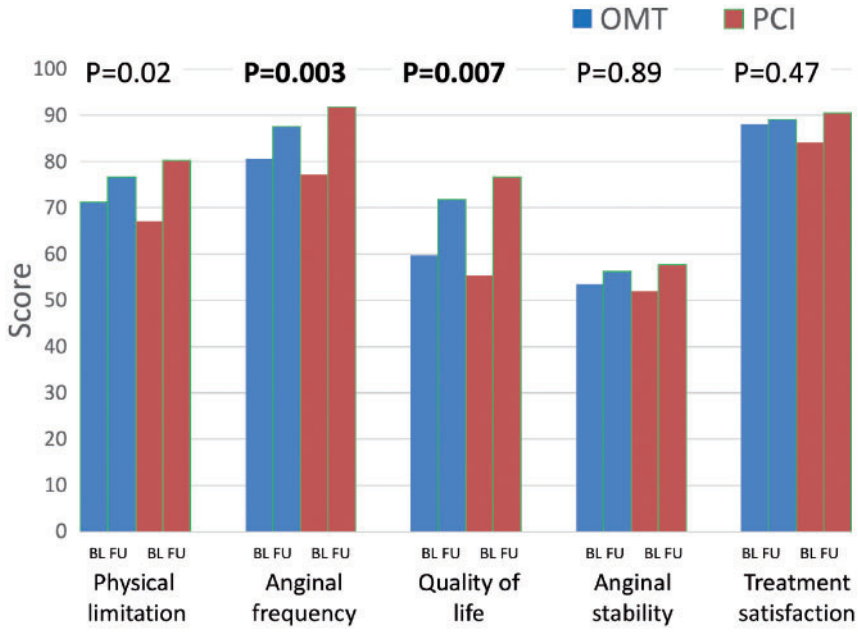


**Figure 3** Comparison of Seattle angina questionnaire subscale changes between optimal medical therapy and percutaneous coronary intervention.

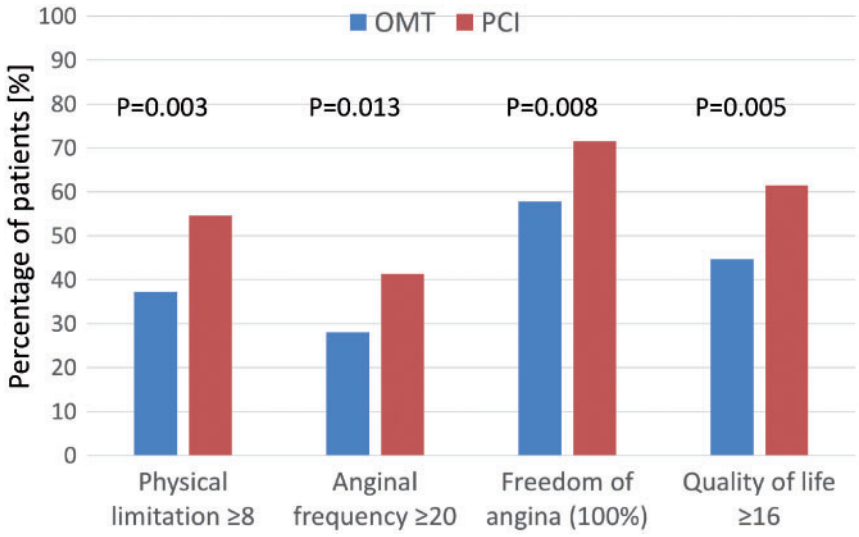


**Figure 4** Comparison of significant changes in the Seattle angina questionnaire categories from baseline to follow-up between optimal medical therapy and percutaneous coronary intervention.

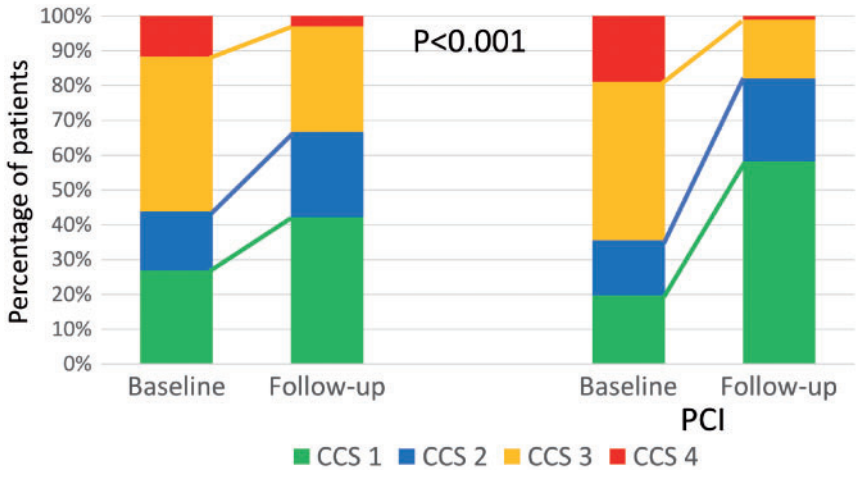


**Figure 5** Comparison of changes in CCS classification from baseline to follow-up between optimal medical therapy and percutaneous coronary intervention. CCS: Canadian Cardiology Society.

recanalization of a CTO lead to better symptom control and quality of life. These results support also the high procedural success rate and safety of contemporary PCI for CTO.

## Health status modification in patients with a coronary total occlusion

The use of the SAQ and EQ-5D tools allowed us to identify the facets of patient's life that were most modified by CTO revascularization. The benefit of PCI was observed as an improvement in angina frequency and quality of life, which reached the prespecified significance level of 0.01 for the primary endpoint in an intention-to-treat analysis. The EQ-5D self-assessment also showed more improvement in three of five categories in the PCI arm.

Our findings are consistent with two prior registries finding significantly greater improvement of physical limitation, angina frequency, and quality of life in patients with successful PCI of a CTO as opposed to failed procedures.[8,9] The comparison with medical management in a Canadian registry showed a considerable benefit of revascularizing a CTO either by PCI or surgery, especially in multi-vessel patients.[17] In the recent OPEN-CTO registry, the health status assessment showed a significant improvement of the SAQ subscales.[18] The comparison of the baseline scores in this registry and the EUROCTO trial shows about a 3–7 point

**Table 5 Adverse events at 12 months follow-up in patients with a coronary total occlusion randomized to optimal medical therapy or percutaneous coronary intervention**

| | OMT (*N* = 137) | PCI (*N* = 259) | *P*-value |
|---|---|---|---|
| Major cardiovascular and cerebrovascular events during follow-up, *n* (%) | 9 (6.7) | 13 (5.2) | 0.55 |
| All-cause death, *n* (%) | 0 | 2 (0.8) | NC |
| Cardiac death | 0 | 2 (0.8) | NC |
| Myocardial infarction, *n* (%) | 0 | 5 (1.9) | NC |
| Non-Q-wave | 0 | 4 (1.6) | NC |
| Q-wave | 0 | 1 (0.4) | NC |
| Ischaemia-driven revascularization, *n* (%) | 9 (6.7) | 7 (2.9) | 0.11 |
| Ischaemia-driven target revascularization, *n* (%) | 9 (6.7) | 5 (2.0) | 0.04 |
| Stent thrombosis (definite or probable), *n* (%) | 0 | 1 (0.4) | NC |
| Cerebrovascular event, *n* (%) | 1 (0.7) | 2 (0.8) | 0.97 |
| Hospitalization cardiac, *n* (%) | 8 (5.9) | 15 (5.9) | 0.98 |

The percentages for the events are determined from a Kaplan–Meier curve.
NC, not calculated.

difference, underscoring a bias to exclude severely symptomatic patients in a randomized trial.

## Procedural safety and adverse events during follow-up

The success rate in our study was 86.6% due to modern interventional techniques including 36% of retrograde approach.[10] This success rate is identical to that obtained in CTO lesions included in SYNTAX II (87%), performed over the same period as our study,[19] which also included the participation of proficient CTO operators and contemporary recanalization techniques.

Coronary total occlusion percutaneous coronary intervention entails the risk of specific complications which occur with a higher frequency even in expert hands.[3,20] Furthermore, enzyme leaks with increase of troponin and creatinine kinase isoenzyme (CK-MB) are observed more frequently after CTO-PCI but their clinical significance below a tenfold increase seems limited.[21,22] In this trial, the periprocedural complication rate was low, with a small number of pericardial effusions requiring drainage, access site repair, and blood transfusion. The percentage of subsequent PCI was higher in the OMT group because of cross-over after failure to control symptoms with antianginal medication.

## Limitation of this study

When applying the SAQ in an open-label design there is a chance of a placebo effect in the treatment group, but as the reassessment was done 12 months after the procedure, this should minimize such an influence. There was a slight difference in response rates to the SAQ and EQ-5D questionnaires which could lead to a response bias. The number of randomized patients did not reach the prespecified target. One of the reasons of this failure was the limitation to expert centres chosen to avoid low procedural success rates. Non-expert centres would have affected the assessment of the procedural benefit as failed procedures carry a higher complication rate and would bias results in terms of persistence of symptoms.[23] The limitation to expert centres also lead to bias against enrolment of highly symptomatic patients, as the operator was convinced of the benefit of PCI for CTOs based on available clinical evidence.[24] This bias is evident from the higher baseline SAQ scores in this study as compared with a non-randomized CTO population.[18]

Despite the lower than planned study size, the health status assessment showed a significant advantage of PCI vs. OMT in patients with a CTO. Under the same assumptions as for the original sample size calculation, our given sample size would yield 81% power.

## Comparison with DECISION-CTO study

Recently the DECISION-CTO study was presented (American College of Cardiology Annual conference 2017). This trial observed no difference between PCI and OMT as both groups showed a similar improvement of SAQ subscales. However, the trial design was completely different to our trial. We had all non-CTO lesions treated before randomization and baseline assessment, so only the difference in CTO treatment would affect SAQ changes. In contrast, with 77% of patients having multi-vessel disease in DECISION-CTO, non-CTO lesions were treated after randomization and baseline assessment. Effectively this meant, that about 70% of patients in the OMT arm of DECISION-CTO received PCI, which explains an improved SAQ even in the OMT group.

## Clinical relevance

Health status assessment is a valid study endpoint in patients with a low mortality risk from their underlying cardiovascular disease.[13] This study is the first randomized study to demonstrate the clinical benefit of PCI over OMT in patients with stable angina pectoris related to a CTO, at the cost of a numerical higher number of death or MI. As in many randomized trials, there is a bias to include less symptomatic patients than in registries, but despite this fact and the limitations of a small sample size, this study shows that symptomatic patients with a CTO benefit from PCI provided that a high success rate can be achieved. The long-term safety of this strategy remains to be explored with longer follow-up in this study.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

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**Conflict of interest:** G.S.W. reports speaker honoraria from ASAHI Intecc Co. Ltd; K.B. reports consulting fees for the trial analysis from

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