International Randomized Trial on the Effect of Revascularization or Optimal Medical Therapy of Chronic Total Coronary Occlusions with Myocardial Ischemia - ISCHEMIA-CTO Trial - Rationale and Design

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International randomized trial on the effect of revascularization or optimal medical therapy of chronic total coronary occlusions with myocardial ischemia - ISCHEMIA-CTO trial – rationale and design

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Background Chronic total occlusions (CTO) are frequent among patients with coronary artery disease. Revascularization with percutaneous coronary intervention (PCI) is safe and feasible in experienced hands. However, randomized data are needed to demonstrate symptomatic as well as prognostic effect of CTO-PCI compared to optimal medical therapy alone.

Methods This trial aims to evaluate the effect of CTO PCI in patients with a CTO lesion and target vessel diameter ≥ 2.5 mm, and myocardial ischemia in the relevant territory. First, all patients are subjected to optimal medical therapy (OMT) for at least for 3 months and non-CTO lesions are managed according to guidelines. Subsequently, prior to randomization myocardial ischemia and quality of life (Seattle Questionnaire (SAQ)) is assessed. Patients are divided into two cohorts based on their SAQ score and randomized to either OMT alone or OMT and CTO-PCI. Cohort A is defined as Low- or asymptomatic patients with a quality-of-life score > 60 and/or CCS class < 2, and more than 10 % ischemia in the left ventricle (LV). Cohort B is symptomatic patients with a quality-of-life score < 60 or CCS class angina > 1 and at least ischemia in 5% of the LV. The primary end-point in cohort A is a composite of major adverse cardiac and cerebral events, hospitalization for heart failure and malignant ventricular arrhythmias. The primary endpoint in cohort B is difference in quality of life 6 months after randomization.

Implications This trial is designed to investigate if CTO-PCI improves QoL and MACCE. Both positive and negative outcome of the trial will affect future guidelines and recommendations on how to treat patients with CTO. (Am Heart J 2023;257:41–50.)

Background and rationale

A chronic total occlusion (CTO) is observed in up to[1] 30 % of patients undergoing diagnostic coronary angiography.[2,3] The presence of a CTO is associated with worse outcome compared to non-occlusive coronary artery disease.[4,5] Percutaneous Coronary Intervention (PCI) treatment of CTO lesions has gained much attention over the last decade due to introduction of new techniques and devices resulting in high success rates in dedicated centers. However, the scientific evidence is mainly based on observational studies and recent randomized clinical trials. The current European[6] and American[7] guidelines do not provide clear recommendations how to manage

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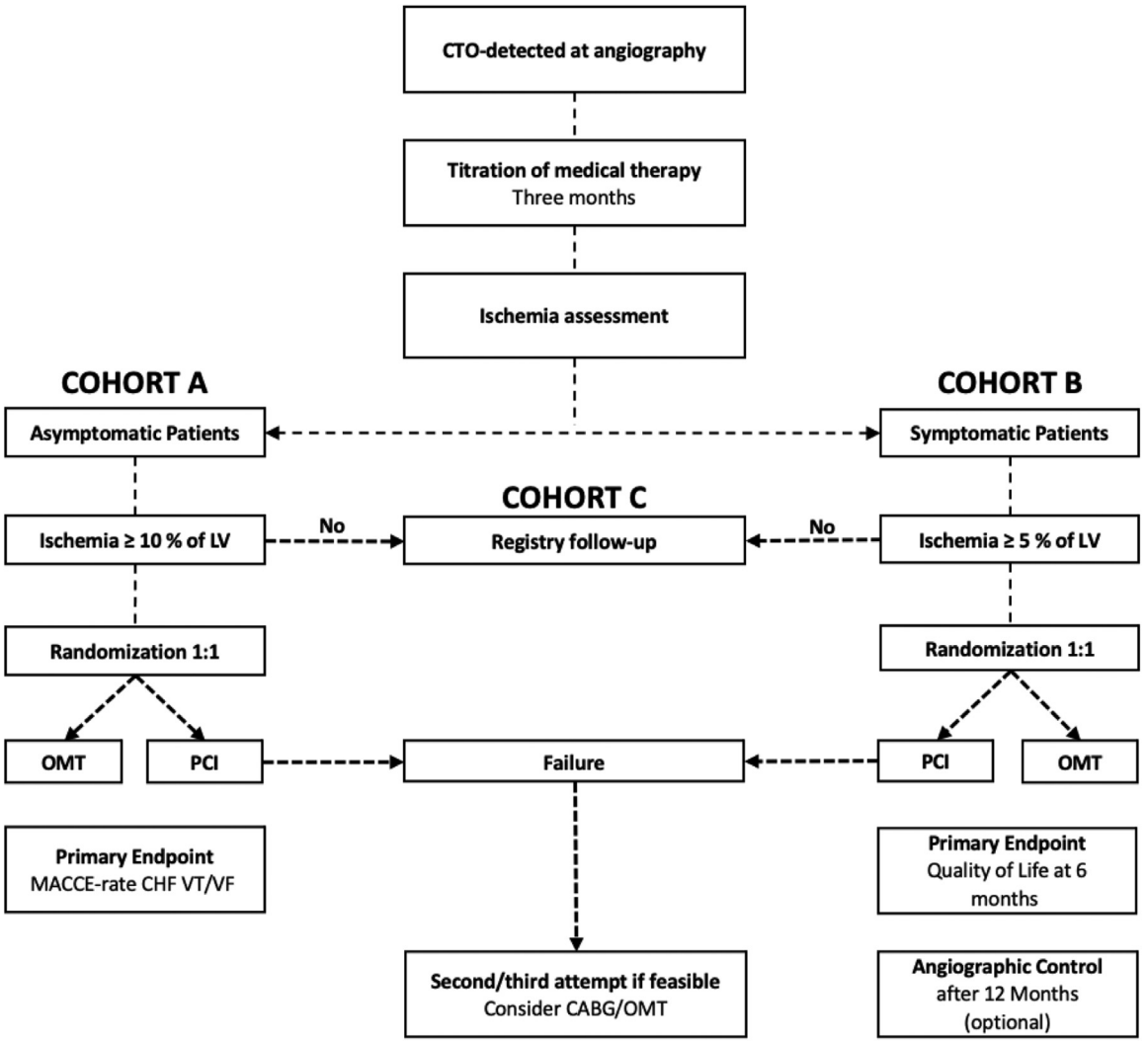
Figure 1



Flow diagram. CABG, coronary artery bypass grafting; CHF, chronic heart failure; LV, left ventricle; MACCE, major adverse cardiac and cerebrovascular events; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; VF, ventricular fibrillation; VT, ventricular tachycardia.

patients with CTO. The indication to revascularize patients with CTO lesions is either to relieve symptoms or improve prognosis. However, to date, there are no randomized clinical trials showing any prognostic benefit from CTO revascularization. In the recent DECISION-CTO study,[8] patients were randomized to PCI vs. OMT, and the study failed to demonstrate a prognostic or symptomatic benefit of PCI vs. OMT. However, the study was prematurely terminated due to slow inclusion rate and had a high crossover rate and a high proportion did not have a quality of life score at follow-up. Results from the EUROCTO-trial[9] demonstrated improvement of quality of life following CTO PCI. The fact that both the DECISION-CTO and the EUROCTO trial failed to include the prespecified number of patients, makes it difficult to draw any conclusions on how to treat these patients. However, both trials indicate that CTO PCI is safe. In the randomized EXPLORE trial, patients with ST-elevation myocardial infarction (STEMI) and a concomitant CTO in a non-infarct related artery were randomized to CTO-PCI or OMT.[10] There was no benefit in terms of improving left ventricular function due to CTO-PCI of the concomitant CTO this is also supported by the findings in the REVASC trial where randomization of 205 stable patients to PCI or OMT found no improvement in indexes of left ventricular functionon on MRI.[11] Meta-analysis of obser-

vational studies[12,13] comparing the prognosis after successful vs. unsuccessful CTO PCI indicate prognostic and symptomatic benefit of successful CTO PCI.[14] However, these studies often lack data regarding ischemia burden and viability. The non-randomized FACTOR trial demonstrated a positive outcome for quality of life, but only in symptomatic patients.[15] In addition to symptomatic improvement, a successful CTO procedure can reduce the amount of myocardium susceptible to ischemia[16] in patients with at least mild to moderate ischemia at baseline and by that the prognosis may be improved (mortality, myocardial infarction, ventricular arrhythmias).

The main purpose of this trial is to evaluate the effect of CTO-PCI on quality of life and prognosis in patients with ischemic burden in the relevant CTO-territory.

Methods and conduct of the study

Study design

The ischemia-CTO trial is an investigator initiated, randomized (1:1), controlled, prospective, superiority, multicenter trial. The trial design compromises 3 separate cohorts (Cohort A, Cohort B and Cohort C). Patients are allocated to the different cohorts depending on symptomatic status after revascularization of significant non-CTO lesions, 3 months of OMT and result of ischemia testing. (Figure 1). The patients will be randomized 1:1 in Cohort A and B to CTO-PCI or OMT. Patients not eligible for randomization in Cohort A or B will be allocated to Cohort C for registry follow-up. We aim to enroll 1200 patients in Cohort A and 360 patients in Cohort B. Enrolment started December 1st 2019. Estimated final enrollment for cohort A is December 1st 2025 and for Cohort B December 1st 2023. We expect to report the result of the primary endpoint in the first quarter 2028 and second quarter 2024 respectively. If the study fail to enroll the patients during the enrollment period it will be prolonged. The study is funded by unrestricted grants from Orbus Neich Corp., Asahi Corp., and Phillips Corp.

Study population

Patients identified with a CTO with possible indication for CTO PCI will enter a dedicated CTO program. All subjects will undergo or have undergone 3 months of initiation and titration of optimal medical therapy and subsequently a mandatory ischemia test according to local practice. The patients are identified 1) when a CTO is detected at coronary angiography, 2) after treatment of the non-CTO lesions during PCI, 3) in an outpatient clinic, or 4) at identification at heart team conference. The eligibility criteria are outlined in Table 1.

Study Cohorts

The study comprises three parallel study cohorts with 1:1 randomization to PCI and optimal medical therapy (OMT) alone in cohort A and B. Patients not eligible for randomization will be subject to registry follow-up in cohort C (Figure 1).

Cohort A

Asymptomatic patients (quality-of-life score $\geq$ 60 and CCS $<$ 2), but with a significant amount of myocardial ischemia ($\geq$10%) in the CTO-territory will be randomized to PCI+OMT vs. OMT.

Cohort B

Symptomatic patients with a quality-of-life score $\leq$ 60 and/or CCS $\geq$ 2, with at least mild to moderate myocardial ischemia ($\geq$ 5 %) will be randomized to PCI+OMT vs. OMT. After final follow-up, the OMT-group will be offered CTO-PCI if clinically indicated.

Optimal medical therapy

Low-dose aspirin (75-150 mg/day) or other guideline directed anti-platelet therapy and statins are mandatory if tolerated. Concomitant diabetes and hypertension must be controlled according to local guidelines. At least two anti-angina drugs with one being rate-limiting must be administered to the maximal tolerated dose. Titration of dose can be conducted at nurse-driven outpatient clinics or according to local practice. All patients where CTO-PCI is performed must be treated with dual-anti-platelet therapy including P2Y12 inhibitors for at least 12 months initiated according to local instructions. All patients are treated with heparin (ACT >250 checked every 30-60 minutes) during PCI procedure.

PCI of non-CTO lesions and CTO-lesions

Prior to randomization it is mandatory to treat all significant lesions no later than one-month prior to randomization if indicated according to guidelines. Culprit lesions in acute coronary syndrome must be treated at index hospitalisation. Ischemic testing and SAQ are performed at least 4 weeks after revascularization of non-CTO lesions.

Ischemia testing

All eligible patients must undergo either rubidium-82 or Oxygen-15 labeled cardiac positron emission tomography imaging, cardiac magnetic resonance imaging, single-photon emission computed tomography, or dobutamine stress echocardiography according to local practice. If LVEF is reduced ($<$ 40%) with hypokinesia or akinesia in the CTO territory demonstration of myocardial viability in the CTO territory with 18F-FDG PET, stress echocardiography, or cardiac MRI is mandatory. Ischemic testing have to be performed after titration of OMT (Table 3).

CTO PCI

The CTO-PCI procedure is conducted only by experienced operators who are familiar with all current techniques and devices, and who have a documented success rate above 85%. Procedures are conducted through

Table 1. Eligibility criteria.

General inclusion criteria

- CTO in native coronary artery
- Age ≥18 yrs.
- Able to provide written informed consent and willing to comply with the specified follow-up contacts.
- Target artery ≥ 2.5 mm

For Cohort A

- Myocardial ischemia (≥ 10% of LV) in a territory supplied by CTO
- Low symptomatic patients (CCS class < 2 and SAQ QoL > 60)

For Cohort B

- Myocardial ischemia (5% of LV) in a territory supplied a CTO
- Symptoms CCS class ≥ II and/or SAQ QoL score ≤ 60 after treating non CTO lesions and after OMT

Exclusion criteria

- NSTEMI or STEMI within 1 month
- Coronary anatomy not suitable for CTO-procedure
- Life expectancy < 2 years
- Severe chronic pulmonary disease (FEV1 < 30 % of predicted value)
- Contraindication to dual anti-platelet therapy
- Pregnancy
- eGFR < 20 mL/min/1.73 m^2
- In multi-vessel disease: if it is deemed unsafe to treat the non-CTO lesion first.
- Severe valvular heart disease

femoral and/or radial access with suitable sheath and catheter size (6-8 French). It is mandatory to use the microcatheters and wires from Asahi company as initial strategy. The drug eluting stent, Combo Plus (Orbus Neich, Wanchai, Hong Kong) is the study stent for all lesions. In the case of failure to revascularize the CTO lesion, a second and third attempt is strongly encouraged.

Intravascular ultrasound

Intravascular ultrasound (IVUS) is mandatory for all patients treated with CTO-PCI. It may be used to identify ambiguous proximal caps and evaluate wire positions during difficult crossing of the CTO. It is mandatory for selection of stent landing zones and stent optimization. After wire crossing IVUS assists lesion preparation by identifying calcifications and sufficient plaque cracking. Stent lengths are selected to cover the entire diseased segment defined as the CTO body and areas with > 50% plaque burden. Stent diameter is selected as an average of two perpendicular measurements of the external elastic membrane and downsized to nearest 0.25 mm (Figure 1) in the distal stent landing zone. If several stents are needed reference diameter is measured at the stent overlap. Post stenting IVUS is performed to secure minimal stent expansion of 80 % of reference diameter and a mean stent area ≥ 5.5mm2. In cases with a distal cap at a bifurcation (Figure 2) two distal references are used.

Primary endpoints and endpoint definitions

The primary endpoint in Cohort A is the composite of major adverse cerebro- and cardiovascular events (MACCE) including 1) death to any cause, 2) myocardial infarction, 3) stroke, 4) clinically driven revascularization, 5) hospitalization for heart failure and, 6) malignant arrhythmias. Patients will be followed yearly for up to 10 years.

In Cohort B the primary endpoint is difference in the Seattle Angina Questionnaire-21 quality of life scale (item 19, 20 and 21) from baseline to 6 months after randomization (Table 2).

All-cause mortality

All-cause mortality includes death of any cause including cardiac deaths and non-natural causes of deaths.

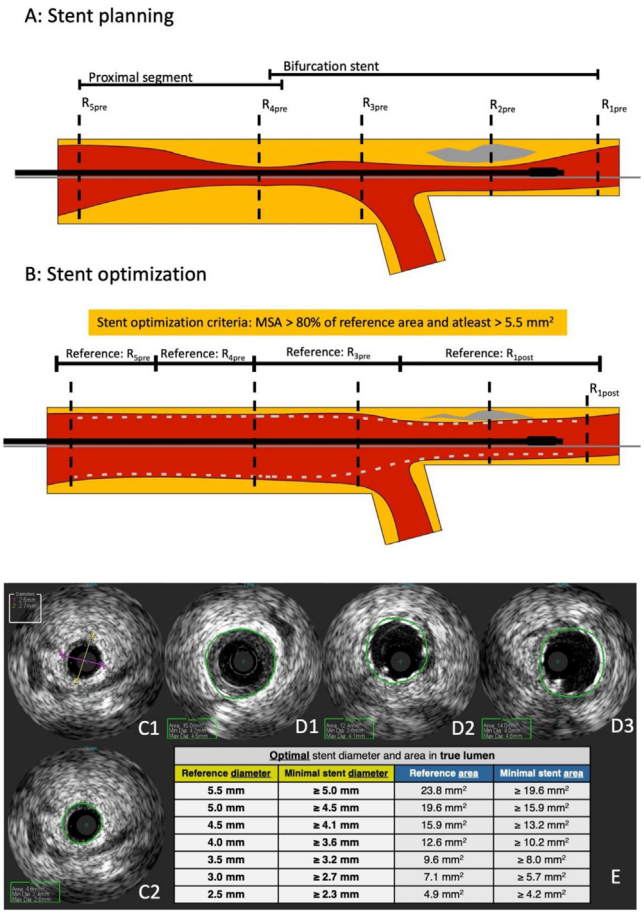
Cardiac death

Encompasses death due to coronary heart disease including fatal myocardial infarction, sudden cardiac death including fatal arrhythmias and cardiac arrest without successful resuscitation, death from heart failure including cardiogenic shock, and death related to the cardiac procedure within 28 days from the procedure. If death is not clearly attributable to other non-cardiac causes it is adjudicated as cardiac death.

Malignant arrhythmias

Include fatal and non-fatal ventricular arrhythmias: sustained ventricular tachycardia, hospitalization due to ap-

Figure 2



Stent sizing and optimization using intravascular ultrasound. **A** indicating the pre specified reference diameters and areas used when performing bifurcation stenting. R1pre is used to size the distal stent which is upsized by 10% and to the nearest 0.25mm platform. R2pre is used to size the distal optimization technique balloon. R3pre is measured proximal to the branching of the side branch and used to size proximal optimization technique balloon. R4pre is measured in the landing zone of the bifurcation stent and used to size the proximal stent. Proximal stent post dilation balloons are sized from R4pre in the distal 50% and R5pre in the proximal 50%. R2pre to R5pre is downsized to nearest 0.25mm. **B** is indicating the stent optimization criteria and which reference that should be used to address it in the different segments. **C1** is showing the measuring of a distal reference with two perpendicular measurements of the external elastic membrane. **C2** showing measurement of the reference area. D) indicating a proximal reference **(D1)** and subsequent stenting **(D2)** with insufficient MSA and finally an optimal expansion in D3. **E** is showing the optimal expansion diameters and areas.

propriate therapy from an implantable cardioverter defibrillator, syncope due to ventricular tachycardia, cardiac arrest due to ventricular tachycardia or fibrillation, data from pacemakers/ICD showing: sustained ventricular tachycardia or fibrillation.

Hospitalization for heart failure

Acute or sub-acute unplanned admission due to decompensated heart failure lasting for >24 hours.[17] New onset of heart failure defined as symptoms + either LVEF < 40% or the combination of LVEF>40% and 1) NT-proBNP > 125 pg/mL and 2) structural heart disease (left ventricular hypertropia or left atrial enlargement) or diastolic dysfunction.[18]

Non-procedure related myocardial infarction

Myocardial infarction is defined by the third universal definition of myocardial infarction including type 1, 2 and 3."[19]

Procedure related myocardial infarction

Procedure related myocardial infarction is based upon the modified SCAI-criteria.[17,20] It is diagnosed in patients with normal baseline biomarkers and elevations of CK-

Table 2. Endpoints.

Primary Endpoint
Cohort A: composite endpoint of MACCE (all-cause mortality, stroke, myocardial infarction, clinically driven revascularization*), hospitalization for heart failure or incidence of malignant arrhythmias.
*CCS class ≥ II and/or QoL score < 60. Same criteria used as for allocation to Cohort B
Cohort B: SAQ Quality of life assessment after 6 months.

Secondary endpoints

- Cerebrovascular events – 12 and 36 months
- Hospitalization due to cardiovascular events (acute coronary syndromes, congestive heart failure, arrhythmias) – 12 and 36 months
- Procedural safety
- cardiac death
- myocardial infarction
- stent thrombosis (definite, possible, probable)
- target lesion myocardial infarction
- target lesion revascularization
- target vessel revascularization
- any revascularization
- CCS angina class
- Quality of life assessment

Table 3. Ischemia test.

SPECT
Cardiac MR
H2-PET
Ammonium-PET
Rb83-PET
Stress-echocardiography

MB > 10 × 99th alone or 5 × 99th percentile plus 1. Evidence of prolonged ischemia > 20 min demonstrated by continuous chest pain, or 2. Ischemic ST changes or new Q-waves, or 3. Angiographic evidence of flow limitation, or 4. Imaging evidence suggesting loss of viable myocardium. In absence of CK-MB, TnT > 70 × 99th percentile plus one of the 4 criterias above may be used. TNI cannot be used for diagnosing procedural myocardial infarction. The modified SCAI-criteria is chosen due to a more robust association to mortality compared to type 4a in the universal definition of myocardial infarction. This will lower the risk of accepting an association that is not a causality.

Stent thrombosis

Stent thrombosis is categorized as acute, sub-acute, late and very late and as definite, probable and possible according to the ARC-criteria.[21]

Revascularization

Any ischemia driven revascularization verified by non-invasive or invasive diagnostics. Revascularization of target CTO-lesion must be symptom driven (CCS ≥ 1 and/or SAQ QoL < 60).

Stroke

Acute neurological deficit of cerebrovascular cause that persists beyond 24 hours.

Seattle angina questionnaire (SAQ)

SAQ-21 is evaluated in all patients and in symptomatic patients following 6 months as primary endpoint assessment. The questionnaire is presented to the patient in the native language by a health professional.

Secondary endpoints

Pre-specified secondary endpoints include the individual component of the primary endpoint, procedural safety, individual components of SAQ-21, and CCS angina class.

Clinical event committee

All events will be evaluated by an independent event committee in the context of the source data, and reported to the investigators.

Non-eligible patients and standard care

Patient not eligible to the study or who are not consenting to participate will receive standard of care treatment according to usual local practice. Patients who are not eligible for randomization following OMT and/or stress-test will be allocated to cohort C.

Notifications

The study is approved by the local or national ethics committees as appropriate and to the Danish Data Protection Agency covering all sites within the European Union. The trial is registered with Clinicaltrials.gov (NCT03563417). The study is conducted in accordance with the protocol, applicable regulatory requirements and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964 and subsequent versions. All products and devices used in the study are CE marked.

Procedural effect measures

Following procedural data are recorded: contrast volume, procedure time, fluoroscopy time, number of stents implanted in target lesion, number of stents implanted in non-target lesion, total stent length in target lesion, total stent length in total, procedural success.

Serious adverse events

Serious adverse events (SAE) are defined as any medical occurrence during the clinical investigation which, directly or indirectly, might lead to or might have led to the death of a patient or to a serious deterioration in their state of health regardless of whether caused by the study treatment or not.

SAE are be reported by the sites to the Sponsor and to the relevant medical ethics committee. A description of the event, including the onset date, duration, whether device related, any action taken and the outcome should be provided. SAE reporing follows good clinical practice guideline ISO 14155 and must be recorded on the case report form (eCRF) provided and submitted to the AUH, within 24 hours of knowledge of the event.

Statistical analysis plan

Cohort A

Distributions of continuous variables between study groups are compared with the two-sample t-test or the Mann-Whitney U test, dependent on whether the data follows a normal distribution. Categorical variables are analyzed with the χ^2-test. Participants will be followed until death, loss to follow-up/emigration, or 120 months after randomization, whichever comes first. Kaplan-Meier curves will be created for the endpoints, which include all-cause mortality (e.g. MACCE). Cumulative incidence curves using Aalen-Johansen estimated will be plotted for the secondary endpoints, where the competing risk of death is taken in account. Groups will be compared by log-rank test. Cox's proportional hazards regression analysis will be used to estimate the hazard ratios and 95% confidence intervals. Risk differences and the belonging 95% confidence intervals for MACCE at median 60 months of follow-up will be calculated. Adjusted hazard ratios will be calculated to assess whether differences between groups detected at baseline have any effects on the result. If significant difference is found in univariate analysis they are included in the multivariate analysis. The proportional hazards assumption will be checked by adding time-dependent covariates and graphing log(-log) plots. If proportional hazards assumptions are found not to fit the data adequately, modified Poisson regression will be used instead. The following subgroup analyses are planned: patients with diabetes, disease-naïve patients, biological sex, age, amount of reversible ischemia, three-vessel disease and jCTO score. Concomitant medication use and quality of treatment (Procedural effect measures): will be summarized and compared between the groups at discharge, and at 12 months by means of a χ^2-test or Fisher's exact. The intention-to-treat principle are used in all analyses and a two-sided p value of less than 0.05 indicates significance. Patients changing treatment strategy during the trial will remain in the allocated treatment group for statistical analysis. An as-treated analysis is planed for the supplementary material to the main publication. Patients treated with at-least one PCI attempt is in the PCI+OMT cohort and patients treated with OMT alone is in the OMT cohort. In cohort B, score in each group at baseline and 6 months follow-up will be reported for the sub group in SAQ-21. The Quality of life scores will be graphically illustrated in the two study arms at baseline and after follow-up. Two-Sample t-test will be used to compare the SAQ scores. Baseline characteristics in cohort C will be reported and compared with the values from Cohort A and Cohort B. Reporting events in this cohort will be optional.

Missing data

5% missing data is expected on the important study variables. Therefore, complete case analyses will be performed if needed. In addition, multiple imputation will be used where needed.

Power calculation

Cohort A. Sample size is event driven. As treatment analysis showed a MACCE-rate after 5 years at 29.3% in the OMT arm vs. 22.3% in PCI arm in the DECISION-CTO trial.[8] Furthermore, an increase in the risk of malignant arrhytmias have been observed with an absolute change from 7.5% to 2.5%.[22] Thus we expect a 30% reduction in MACCE-rate in the PCI-arm. With an alpha of 0.05 and power of 80%, 247 events are needed. To accommodate for the uncertainty of estimates, a PCI success rate of 85%, and lost-to-follow-up the inclusion target is 300 events in total. Inclusion of patients will continue until this total number of events is achieved. Patients will be followed for up to 10 years. With a median follow-up of 5 years we expect 1,200 patients to be included.

Cohort B. The SAQ QoL is expected to increase with 8 points after 6 months following PCI, and standard deviation expected to be 23 in the PCI group and 26 in the OMT group. With an alpha of 0.05 and power of 80%, 260 patients are needed (130 in each group). To accommodate for the uncertainty of estimates and a CTO success rate of 85% and lost-to-follow-up the inclusion target is 360 patients total. In total 1,560 patients are needed for the primary outcome in cohort A and B.

Withdrawal

If the patient decides to withdraw from the study, he/she is contacted in order to, if he/she agrees, obtain information about the reason(s) for discontinuation. The

date and reason for the withdrawal are recorded in the CRF.

Monitoring

The study is monitored according to the Good Clinical Practice (GCP) principles by staff employed at the sponsor organisation. During the study period, monitors will ensure that the trial is conducted in compliance with the protocol, good clinical practice (ISO 14155) and applicable regulatory requirements. All data entries in the eCRF is monitored.

Data management

The safety of the study is monitored by an independent external safety committee (DSMB). DSMB is activated when 50% of the patients are enrolled in each cohort. The DSMB receives information on rates of all-cause death, cardiac death, myocardial infarction, definite stent thrombosis and TLR. The DMSC has unlimited access to the anonymized study database and independently makes decision on continuation, pausing or stopping the study. National MEC or local MEC as appropriate are informed immediately of any changes in the study risk assessment and study status.

Core lab

The raw data comprising the angiograms, imaging files including the ischemia-test will undergo core-lab assessment at random in 10% of cases in order to assure high procedural quality. Proof of ischemic testing, coronary angiography and IVUS recordings are uploaded to the sponsor through a GDPR compliant eCRF.

Study status

Enrollment began January 2019 and 503 patients have been enrolled in the trial. 214 are allocated to cohort C, 107 randomized in cohort A and 147 in Cohort B. Cohort B is expected to be finalized in December 2023 with completion of follow-up second quarter of 2024. Primary endpoint in cohort A is event driven and the trial is terminated when 300 events have occurred. With the current inclusion rate enrollment in cohort A is expected to be finalized first quarter of 2025.

Discussion

The main aims of this CTO-trial are to investigate: 1) the outcome of PCI vs. optimal medical therapy of CTO lesions in patients with significant myocardial ischemia ($\geq$ 10%) *without significant symptoms*, and 2) the outcome of PCI vs. optimal medical therapy of CTO lesions in patients *with symptoms* and at least mild myocardial ischemia ($\geq$5%). The main hypothesis is that CTO-PCI has prognostic and symptomatic benefit given sufficient burden of ischemia.

Hence, the current trial attempts to address the impact of CTO-PCI on symptomatic and/or prognostic indication. These questions have not been sufficiently addressed in the previous trials and we need evidence from randomized clinical trials on how to treat these patients. In order to overcome some of the difficulties in including patients in the previous randomized clinical trials we propose in this trial to include the patients in two different patient cohorts depending on the symptomatic status, i.e. the asymptomatic Cohort A with myocardial ischemia in $\geq$ 10% of the left ventricle, and the symptomatic Cohort B with $\geq$ 5% ischemia. Based upon previous studies, it is probably only patients with at least moderate myocardial ischemia ($\geq$10% of the left ventricle) will benefit of PCI in terms of improving MACCE (17). Accordingly, only CTO patients with $\geq$ 10% ischemia will be included in this cohort (Cohort A). Secondly, the improvement of symptoms and quality of life following CTO PCI can only be expected in patients with moderate to severe symptoms at baseline and symptomatic patients will therefore be randomized to CTO PCI or OMT in Cohort B. The patients randomized to OMT will be offered CTO PCI procedure 6 months after randomization following assessment of Seattle Angina Questionnaire quality of life score(19). Thus, this trial design will reduce the probability of cross-over in patients with symptoms. Moreover, the trial attempts to randomize all eligible patients, by enrolling patients into a dedicated CTO program before randomization.

CTO patients undergoing PCI are at higher risk of in-hospital events compared to non-CTO patients including severe procedural related complications potentially leading to prolonged hospitalizations and serious adverse events. Therefore the trial is also designed to uncover any potential hazards from CTO-PCI by including procedural MI, VT, new onset of HF, and death in the time-dependent primary endpoint. An inherent limitation of the trial is that only experienced high volume CTO centres are included in the trial which might lower the external validity, but previous studies have found that high volume operators and centres yield a higher success rate and therefore potentially better outcome.[23,24] Experienced operators in combination with OMT, ischemic testing and treatment of non-CTO lesions therefore reflects best clinical practice for treating CTO-patients and therefore the implantation of the study results is not only treatment with PCI but implementation of a program dedicated to optimize all aspects of CTO treatment. In conclusion, this is the first randomized study that addresses improvement of prognosis and quality of life following PCI of CTO lesions specifically. The results in cohort A will have an impact on the guidelines on treatment of CTO lesions no matter the if the outcome is negative, positive or neutral. A positive result will have the potential to raise the recommendation and neutral/negative will raise the evidence for OMT alone.

A positive outcome in cohort B, the symptomatic arm, will raise the evidence level for revascularization.

Disclosures

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