Protocol

The NOrdic-Baltic randomized registry study for Long-term clinical Evaluation of adjunction of PCI to optimal medical therapy in Chronic Total coronary Occlusion

NOBLE CTO

The Nordic-Baltic CTO study group

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1. Abbreviations

AMI	Acute Myocardial Infarction
AP	Angina Pectoris
ASA	Acetylsalicylic Acid
CABG	Coronary Artery Bypass Grafting
CCS	Canadian Cardiovascular Society Angina Grading System
CK-MB mass	Creatinine Kinase MB
CMR	Cardiac magnetic resonance
CRF	Case Report Form
CTO	Chronic total occlusion
CV	Curriculum Vitae
DAPT	Dual antiplatelet therapy
DES	Drug Eluting Stents
ECG	Electrocardiogram
EC	Ethical Committee
GCP	Good Clinical Practice
IHD	Ischemic Heart Disease
LAD	Anterior descendant coronary artery
LVEF	Left ventricular ejection fraction
LBBB	Left bundle branch block
MACE	Death, myocardial infarction and revascularization
MACCE	Death, myocardial infarction, stroke and revascularization
PCI	Percutaneous Coronary Intervention
PET	Positron emission tomography
SAQ	Seattle Angina Questionaire
SF-12v2	12-Item Short Form Survey Instrument
SPECT	Single-photon emission computed tomography
TIMI	Thrombolysis In Myocardial Infarction
TNI	Troponin I
TNT	Troponin T
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization

2. Synopsis

The NOrdic-Baltic randomized registry study for Long-term clinical Evaluation of adjunction of PCI to optimal medical therapy in Chronic Total coronary Occlusion

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Version Number	1.3
Date	27. 04. 2018.
National Coordinating investigator	Martin Kirk Christensen, Department of Cardiology, Aalborg University Hospital, Denmark.
Sponsor	Leif Thuesen, Department of Cardiology, Aalborg University Hospital, Denmark.
Investigators	Dedicated Nordic-Baltic chronic total coronary occlusion (CTO) operators. At each site one coordinating investigator.
Protocol authors	Martin Kirk Christensen and Leif Thuesen, Department of Cardiology, Aalborg University Hospital, Denmark.
Study cohort	Patients with CTO-related symptoms or reversible myocardial dysfunction.
CTO lesions for inclusion	Coronary artery supplying a major myocardial territory
Purpose	To assess quality of life, symptoms, cardiac function, cardiac events and survival of adjunction of PCI to optimal medical therapy (OMT) in CTO patients.

Trial Type; randomized registry	In the context of CTO treatment evaluation, the conventional randomized clinical trial is associated with a number of shortcomings: • Unreliable power calculation concerning long-term mortality. • Unknown crossing over rate. • Unknown optimal follow-up time. • Sub-group results problematic. Therefore, we have designed the present study as a randomized registry. Consequently, results will be hypothesis generating. However, the randomization to OMT vs. OMT + PCI will yield an unbiased and clinical relevant evaluation of a relatively conservative therapy vs. a more aggressive CTO approach. The randomization will be 1:1. The OMT-group participants are offered PCI after 6 months. After inclusion of 2000 patients, there will be a decision of continuation of patient inclusion according to clinical results and patient inclusion rate.
Background	• Short and long-term effects of CTO treatment are poorly investigated. • The high procedural success rate of CTO-PCI at dedicated centers permits a randomized comparison of OMT + PCI vs. OMT.

	• In recently published randomized studies CTO PCI did not improve clinical outcomes.
Definitions	• CTO lesion; TIMI 0 antegrade flow for estimated >3 months.
Inclusion criteria	• ≥1 CTO lesion amenable to PCI. • Stable or stabilized coronary artery disease • Symptoms (angina pectoris or shortness of breath) and/or signs of reversible perfusion defect by SPECT, PET or MR and/or angiographic/echocardiographic signs of reversible ischemia. • CTO lesion in a major coronary vessel supplying a significant myocardial territory (vessel diameter usually ≥3mm).
Exclusion criteria	• Expected survival <1 year. • Renal failure on dialysis. • Relative or absolute contraindication to dual antiplatelet therapy • Stable non-CTO lesions treated within one month. • Declined informed consent. • Regarding CMR: allergy to contrast medium, severe obesity, claustrophobia and certain metallic implants
Primary endpoint	• 3-year all-cause mortality • 6-month quality of life (SF-12v2 and SAQ)
Secondary endpoints	• All-cause mortality, cardiac mortality, non-cardiac mortality.

	• Minor and major stroke. • Myocardial infarction (all, type 1-4). • Target vessel and non-target vessel revascularization. • ARC-defined stent thrombosis. • Bleeding (Bleeding Academic Research Consortium Definition for Bleeding; 3a, 3b, 3c, 5a, 5b). • Secondary endpoints will be assessed after inclusion of 100, 250, 500, 1000, 1500 and 2000 patients.
Clinical follow-up	Clinical follow-up as needed to achieve OMT and symptomatic relief. Out-patient clinical control after 6 months. Follow-up by telephone call after 1, 2, 3, 5, 10, 15 and 20 years.
Statistical analysis	Continuous variables will be compared with the two-sample t-test or the Mann-Whitney U-test. Categorical variables will be analysed with the χ^2-test. Endpoints will be analysed until occurrence of and endpoint event or loss to follow-up using Kaplan-Meier time-to-event curves. A two-sided p-value of less than 5% will indicate significance.
Sample size calculation for 3-year all-cause mortality and first published endpoint (6-months quality of life)	There are no randomized clinical trials powered to compare all-cause mortality or symptomatic improvement of OMT vs. OMT and PCI in patients with ≥1 CTO lesion amenable to PCI.

	We expect a 3-year all-cause mortality rate of 4.5% in the PCI group vs. 6.0% in the OMT group. With alpha of 5% and power (1-beta) 80%, a total of 1966 patients will be needed to detect this treatment effect difference. To account for loss-to follow-up 2000 patients will be randomized. We expect symptomatic improvement in 45% of patients after OMT and in 75% of patients after PCI. With alpha of 5% and power (1-beta) 80%, a total of 82 patients will be needed to detect this treatment effect difference. To count for loss to follow-up, a total of 100 patients will be included (50 in each group).
Analysis of the population	The results will be analysed according to the intention-to-treat principle.
Pre-specified subgroups	• Successful/unsuccessful PCI. • 6-month cross-over group. • Permanent OMT group (non-cross-over group) • Female/male gender. • Diabetes/non-diabetes. • Symptomatic/asymptomatic. • Angina/myocardial dysfunction • CTO coronary segment location. • Age ≥/≤ 80 years.
Sub-studies (optional)	• Socio-economic status

	• 6-month CMR evaluation of reversible perfusion defects compared to index CMR before CTO PCI. • 6-month echocardiographic evaluation of systolic and diastolic left ventricular function compared to index echocardiography before CTO PCI. • Evaluation of ventricular arrhythmias by implantation of cardiac monitor

3. Purpose

To assess all-cause mortality and to monitor continuously short- and long-term clinical and socio-economic effects of CTO PCI as adjunction to optimal medical therapy.

4. Hypothesis

In patients with ≥1 CTO lesion amenable to PCI, restoring normal blood flow in the occluded artery will improve short and long-term quality of life, improve and preserve myocardial function, reduce risk of extensive myocardial infarction, reduce cardiac and all-cause death and positively influence socio-economic status.[1,2] At the same time, successful CTO treatment may increase risk of non-extensive myocardial infarction, stent thrombosis and new revascularization.[3,4]

5. Background

Opening of a chronic total coronary occlusion by PCI used to be associated with low procedural successrate and increased risk of procedural complications. Consequently, these patients were primarily medically treated or referred to coronary bypass operation.[1,5,6] Improvements in CTO PCI techniques, devices and operator skills in recent years has changed the CTO treatment scenario.[7] CTO treatments may now be characterized by high success rates and acceptable low risk of complications.[5] However, short and long-term effects of CTO treatment in non-selected CTO patients are poorly investigated and adequately powered randomized clinical trials on symptoms,

quality of life, adverse cardiac events and longevity are non-existent. Consequently, a large-scale randomized clinical CTO vs. OMT trial is a realistic and clinically relevant initiative.

Unfortunately, slow patient inclusion rate and reluctance to include patients have been difficult to overcome in two recent conventional randomized clinical trials on PCI vs. OMT; the EUROCTO[8] and the DECISION[9] trials. Both studies were terminated prematurely. The recently published DECISION trial documented no benefit of PCI as adjunct to OMT in CTO patients. In the present randomized registry, the OMT patients are offered PCI after a 6-month period of optimal medical therapy. The design of the present study is expected to be acceptable to most CTO patients and clinicians. In an all-comers CTO-population it will enable randomized assessment of 6-month quality of life parameters, angina and NYHA scores and imaging indices of myocardial ischemia and function (optional). Furthermore, long-term clinical follow-up with registration of major adverse cardiac events will be possible in cohorts randomized to OMT and PCI vs. OMT, and in non-randomized comparisons of cohorts 1) randomized to PCI, 2) randomized to PCI with unsuccessful/successful procedural results, 3) randomized to OMT without crossover to PCI and 4) randomized to OMT with crossover to PCI.

6. The randomized registry

In the context of CTO treatment evaluation, the conventional randomized clinical trial is associated with a number of shortcomings:

- Unreliable power calculation concerning long-term mortality.
- Unknown cross-over rate.
- Unknown optimal follow-up time.
- Sub-group analyses problematic.

Therefore, we have designed the present study as a randomized registry. Consequently, results will be hypothesis generating. Still, the randomization to OMT vs. OMT + PCI will yield an unbiased and clinical relevant evaluation of a relatively conservative therapy vs. a more aggressive CTO approach. Further, the prospective

and CTO-focused parameter registration will provide high data quality for sub-group analyses.

7. Material and methods

7.1 The index lesion vessel

The present study will focus on CTO lesions in major epicardial vessels that supply a significant myocardial territory (vessel diameter usually ≥3mm).

7.2 Non-CTO lesions

Concomitant non-CTO lesion treatment may invalidate assessment of the clinical effects and paraclinical findings related to a CTO lesion and treatment thereof. Consequently, stable non-CTO lesions should not be treated within one month of the index procedure.

7.3 CTO PCI

A CTO PCI is indicated in patients with angina pectoris/shortness of breath and normal left ventricular function or with demonstrated reversible myocardial perfusion defect by either single-photon emission computed tomography (SPECT), positron emission tomography (PET) or cardiac magnetic resonance (CMR).[10]

Antegrade, retrograde and combined approaches may be used at the discretion of the operator. Coronary stent implantation using 3rd generation DES will be preferred. In case of procedural failure, more attempts should be considered to achieve as high success rate as possible without compromising patient safety. The operators should pay attention to the use of contrast, minimize focal radiation and prioritize patient safety in complex antegrade and retrograde procedures.[1,10]

Bilateral injections should be used routinely. Usually, the initial procedure is carried out by antegrade approach using over-the-wire balloons or dedicated catheters for support and wire exchange. Retrograde wiring through contralateral or ipsilateral collaterals is reserved failed primary attempts and performed either as a secondary procedure or as

a hybrid procedure usually starting by antegrade approach. Antegrade sub-intimal tracking or variants of this procedure may be used in some cases.[11]

Patients will be pre-treated with guideline based dual antiplatelet therapy. Procedural anticoagulation after local standards. Post PCI, lifelong aspirin (75 mg/day) and 6-12 months DAPT.[2]

Uncomplicated cases may be discharged the same or the next day.

7.4 Patients

Consecutive CTO-patients participating in the study will be randomized 1:1 to optimal medical therapy (OMT) vs. OMT and CTO PCI. After inclusion of 2000 patients, it will be decided whether to continue the study considering clinical results and patient inclusion rate.

The patients will be identified after a clinically indicated coronary angiogram. A CTO lesion is defined as absence of antegrade flow (Trombolysis in Myocardial Infarction (TIMI) grade flow 0) and a history suggesting occlusion of the vessel for >3 months. The investigators will not advertise for participants, and the participants will not receive honorarium for participation.

7.5 Inclusion criteria

- ≥1 CTO lesion amenable to PCI.
- Stable or stabilized coronary artery disease.
- Symptoms (angina pectoris or shortness of breath) and/or signs of reversible perfusion defect by SPECT, PET or MR and/or angiographic/echocardiographic signs of reversible ischemia.
- CTO lesion in a major coronary vessel supplying a significant myocardial territory (vessel diameter usually ≥3mm).

7.6 Exclusion criteria

- Expected survival <1 year.
- Renal failure on dialysis.
- Relative or absolute contraindication to dual antiplatelet therapy.
- Allergy relevant to the study treatments.
- Age <18 years.
- Declined informed consent.
- Inability to understand or provide informed consent
- Non-CTO revascularization less than one month prior to the index treatment.
- Regarding CMR: allergy to the contrast medium, severe obesity, claustrophobia and certain metallic implants

8. Schedule of event registration

After 6 months, the routine pre-study assessment of clinical status, quality of life by 12-Item Short Form Survey Instrument (SF-12v2)[1212] and Seattle Angina Questionaire (SAQ)[13], echocardiography (optional) and CMR (optional) will be repeated as an out-patient visit. SF-12v2 and Seattle Angina Questionnaire will be performed as interview. The participants will be contacted by phone after 1, 2, 3, 5, 10, 15 and 20 years. Possible cardiac problems (significant angina, myocardial infarction, new revascularization or death) will be investigated by requisition of relevant hospital files, ECG recordings, angiograms or death certificates. The 15- and 20-year follow-up may be substituted by registry-based event detection.[10] There will be an optional registry-based assessment of socioeconomic status after a relevant follow-up period.

9. Endpoints

9.1 Primary endpoint

All-cause mortality after inclusion of 2000 patients with a minimal follow-up of 6 months.

9.2 Primary co-endpoint

Quality of life assessment by Seattle Angina questionnaire and 12-Item Short Form Survey Instrument (SF-12v2)[12,14] after 6 months. The questionnaires will be performed as interview during an out-patient visit.

9.3 First Published endpoints

After 6 months:

- Quality of life.
- CCS/NYHA status.
- MACCE.
- Echocardiographic parameters (optional).
- Magnetic resonance imaging (CMR) parameters (optional).
- Health economy (optional).
- Socio-economic status (optional).

9.4 Secondary endpoints

After 1, 2, 3, 5, 10, 15 and 20 year's registration of:

- All-cause mortality, cardiac mortality, non-cardiac mortality.
- Minor and major stroke.
- Myocardial infarction (all, type 1-4).
- Target vessel and non-target vessel revascularization.
- ARC-defined stent thrombosis.
- Bleeding (Bleeding Academic Research Consortium Definition for Bleeding; 3a, 3b, 3c, 5a, 5b).

10. Echocardiography

The registration is optional and performed by centre decision.

Endpoints will be

- Systolic function evaluated by left ventricular ejection fraction.
- Systolic longitudinal function evaluated by global longitudinal strain.
- Diastolic and systolic function by tissue Doppler indices.

- Left ventricular and left atrium volume.

11. Cardiac magnetic resonance

The registration is optional and performed by centre decision.

Endpoints will be

- Reduction of inducible myocardial perfusion defect evaluated by CMR perfusion.
- Improvement of left ventricular ejection fraction/regional hypokinesia.
- Correlation of angina and myocardial perfusion defect.

11.1 Health economy and socio-economic aspects

Health economy and socio-economic aspects of the investigation will be assessed and described in a dedicated protocol. The registration is optional and performed by participating countries.

11.2 Evaluation of endpoints

Primary and secondary endpoints will be assessed by an independent endpoint committee. The endpoint committee will consist of experienced clinical and interventional cardiologists.

11.3 Definition of endpoints

11.3.1 All-cause death

All-cause death encompasses cardiac death and other fatal categories, which include cerebrovascular death, death from other cardiovascular diseases (i.e. pulmonary embolism, aortic dissection will be included in this category), death from malignant disease, death from suicide, violence or accident, or death from other causes.[15]

11.3.2 Stroke

- Stroke: duration of a focal or global neurological deficit >24 h; OR <24 h if available neuro-imaging documents a new haemorrhage or infarct; or the neurological deficit results in death.

- Non-disabling stroke: a mRS score of <2 at 90 days or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline.
- Disabling stroke: a mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline.[16]

11.3.3 Cardiac death

Cardiac death encompasses coronary heart disease death 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 a cardiac procedure or surgery within 28 days from the procedure.[15]

11.3.4 Procedure related myocardial infarction

Patients with normal (>99th percentile URL) baseline biomarker concentrations, elevations of cTn >5 x 99th percentile URL occurring within 72 h of the procedure – plus evidence of prolonged ischemia (one of the following):

- Prolonged chest pain (>20 min).
- Ischemic ST changes or new pathological Q waves.
- Angiographic evidence of a flow limiting complication, such as loss of patency of a side branch, persistent slow-flow or no-reflow, embolization.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (MI type 4a).

If the baseline cTn values are elevated and are stable or falling, then a rise of >20% is required for the diagnosis of MI type 4a.[17]

11.3.5 Spontaneous myocardial infarction

Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

1) Rise and/or fall of cardiac biomarkers (preferably troponin) >72 hours after a revascularization procedure with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following (MI types 1 or 2);

- Symptoms of ischemia;

- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block.
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

2) Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

3) Pathological findings of an acute myocardial infarction.[17]

11.3.6 Target lesion revascularization

Coronary artery bypass grafting or PCI of index lesion.[15]

11.3.7 Target vessel revascularization

Coronary artery bypass grafting or PCI of index vessel.[15]

11.3.8 Stent thrombosis

Stent thrombosis is recognized when documented by angiography and/or autopsy and when meeting the criteria for spontaneous myocardial infarction occurring in the territory of the treated vessel. Stent thrombosis is categorized as acute, sub-acute, late and very late and as definite, probable and possible according to the ARC-criteria.[15]

11.4 Recommendations for index lesion re-revascularization

Angina pectoris, CCS >1, related to index lesion, and fractional flow reserve (FFR) ≤ 0.80.

11.5 Study stents

CE-marked 3rd generation drug eluting stent.

11.6 PCI procedure; antithrombotic treatment

Unfractionated Heparin, low-molecular weight Heparin or Bivalirudin and GPIIbIIIa inhibitors are used according to local hospital routine. Dual antiplatelet therapy is administered as recommended by treatment guidelines; usually Acetylsalicylic Acid (ASA) lifelong and an ADP receptor/P2Y12 inhibitor for 1 to 12 months according to clinical presentation and stent characteristics.

11.7 Measurement of biomarkers

After the PCI procedure, Creatinine Kinase MB (CK-MB) and Troponin-T/I will be measured if there is clinical indication; suspicion of procedure-related myocardial infarction.

12. Statistics and sample size

12.1 Primary endpoint

The primary endpoint (all-cause mortality after inclusion of 2000 patients with a median follow-up of 3 years will be analysed for superiority using Kaplan-Meier survival analysis. A p-value ≤5% will indicate significance.

12.2 Primary co-endpoint

The primary co-endpoint of 6-month quality of life by SF36 questionnaire will be analysed for superiority using Kaplan-Meier survival analysis. A p-value ≤5% will indicate significance.

12.3 Secondary endpoints and other variables

For continuous variables, differences between the treatment groups will be evaluated by Wilcoxon's rank-sum test. For discrete variables, differences will be expressed as counts and in percent and will be analysed with the chi-square or Fisher's exact test. Two-sided tests are used and the p-value indicating significance will be ≤5%.

12.4 Sample size calculation (primary endpoint)

There are no randomized data on CTO treatment by PCI vs. OMT. A meta-analysis including 13 studies with 1-10 years of follow-up, found all-cause mortality rates of

14.3% after successful PCI and 17.5% after a failed intervention.[1] Jones DA et al. found a mortality of 4.5% and 17.2% after successful vs. unsuccessful CTO PCI; 836 patients with 2.0 to 5.4 years of follow-up.[18] Jang et al. demonstrated improved survival in CTO patients treated with attempted revascularization and OMT (including CABG and PCI failures) compared to OMT alone even in the presence of well developed collateral circulation. They found a mortality of 3.4% in the combined group compared to 9.7% in OMT during median 40 months of follow up.[19] In the present study, we anticipate a 3-year all-cause mortality rate of 4.5% in the PCI group vs. 6.0% in the OMT group. With alpha of 5% and power (1-beta) 80%, a total of 1966 patients will be needed to detect this treatment effect difference. To count for loss-to follow-up 2000 patients will be randomized (1000 patients in each group).

12.5 Sample size calculation (primary co-endpoint)

We expect symptomatic improvement in 45% of unselected patients after OMT and in 75% of patients after PCI. With alpha of 5% and power (1-beta) 80%, a total of 82 patients will be needed to detect this treatment effect difference. To count for loss to follow-up, a total of 100 patients will be included (50 in each group).

12.6 Analysis of the population

The results will be analysed according to the intention-to-treat principle.

13. Randomization and data management

13.1 Randomization

The patients will be randomized after written informed consent. Randomization by block randomization according to center. Randomization will be performed using REDCap electronic data capture tools hosted at Aalborg University Hospital.

13.2 Data management

The study is reported to The Danish Data Protection Agency (Datatilsynet) through the joint report of the North Denmark Region, and the agency's guidelines for data management will be followed.

Data will be collected and reported using a web-based case report form (CRF) using REDCap[20] hosted at Aalborg University Hospital.

13.3 Monitoring of the study

The study will be monitored according to the good clinical practice (GCP) rules. Study coordinators will have regular contact to the participating departments to ensure that the trial is conducted in compliance with the protocol, GCP and applicable regulatory requirements. The study coordinators will review source documents for verification of consistency with the data recorded in the CRF and provide information and support to the investigator(s).

The investigators must provide a CV or equivalent documentation of suitability to be participate in the trial. All investigators and other responsible personnel will be listed together with their function in the trial on the signature list.

13.4 Data Safety Monitoring Board (DSMB)

The DSMB will receive monthly information on rates of all-cause death, major stroke, procedure related myocardial infarction, spontaneous myocardial infarction, definite stent thrombosis and TLR. The DSMB will have unlimited access to the study database and will independently make decision on continuation or ending the study.

13.5 Direct access to source documentation

The investigators/institutions will permit study-related monitoring, audits, IEC review and regulatory inspections, providing direct access to source data/hospital records. The investigators are responsible and verify that each patient has consented in writing to direct access to the original source data/hospital records by the use of written patient information and signed informed consent.

13.6 Source data verification

The data recorded in the CRF by the investigator will be controlled for consistency and correctness. Any discrepancies of source data/hospital records and CRF data will be described and corrected if possible.

14. Ethical aspects

14.1 Ethical conduct of the study

The study will be 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.

It is the responsibility of the coordinating investigator to obtain approval of the study protocol/protocol amendments, the patient information and the informed consent form from the Ethical Committee for all patients included in the study. The written approval from the Ethical Committee should be dated and have an attached list of those persons present at the IEC meeting.

14.2 Risks, side effects, advantages and disadvantages in study participation

The treatment strategies investigated in the present study, OMT vs. PCI are well known and widely used in routine treatment of CTO lesions. Both treatments may be used according to the international guidelines.

The medical therapy will be based on international standard treatment for angina pectoris. No experimental study drugs will be used.

The PCI treatment is performed in local anaesthesia and may be associated with some discomfort and a less than 5% risk of severe complications, including death, myocardial infarction, stroke, perforation, renal failure and radiation dermatitis.[21,22] After the PCI procedure, the patients will be discharged the same or the following day.

Available data suggest that a successful CTO procedure may be associated with improved quality of life and increased life length. Consequently, study participants randomized to OMT will be offered a PCI procedure after 6 months of OMT.

Before discharge all patients will be seen by a non-invasive cardiologist to optimize medical treatment. Thereafter, study participants will be followed individually according to clinical status to achieve OMT and for the patient acceptable symptomatic relief. In case of failure to achieve acceptable symptomatic relief on OMT or in case of unacceptable side-effects, it will – according to patient wish – be acceptable to change strategy to CTO PCI.

14.3 Ethical considerations

As outlined in earlier, there is considerable uncertainty regarding the optimal treatment of patients with CTO, especially regarding the effect of CTO PCI on mortality, symptom severity and quality of life. Therefore, it is of major clinical interest to examine this problem in a randomized setting. There are no certain advantages related to participating in the study, but participants may appreciate the close contact to the hospital during study period. We perceive a clear advantage for future patients due to the results of this study. There are no disadvantages to participation, but participants may expect spending time for scheduled follow-up visits and examinations. CMR and echocardiography are already used as routine investigations before CTO PCI. The patients will not be exposed to risks beyond that of current standard treatment.

14.4 Informed consent

Patients will only be included in the study only after signing an informed consent form. Written information will be given in sufficient time for the patient to prepare before the oral information provided by either project coordinator or investigator in a quiet environment without disturbances. If the patient so wishes, study participation may be discussed with a third person and a third person may be present during the process of oral information. Amble time for consideration (at least 24 hours is allowed) after initial written and oral information will be provided before signing the consent form. Follow up regarding participation can with the patient’s permission be scheduled as either out of hospital visit or by telephone, but consent form must be signed prior to first study visit.

14.5 Patient information and informed consent

It is the responsibility of the investigator to provide each patient with full and adequate verbal and written information about the objectives, procedures and possible risks and benefits of study participation. The written patient information must not be changed without prior discussion with the coordinating investigator.

The patients will be notified of their voluntary participation and of their right to withdraw from the study at any time and without giving any particular reason. The patients will also be informed that withdrawing from the study does not influence their future treatment. The investigator is responsible for obtaining written informed consent from all patients prior to enrolment in the study.

14.6 Withdrawal

A patient can be withdrawn from the study at any time, if it is the wish of the patient, or if it is medically indicated. If a patient does not show up for a scheduled visit every effort will be made to contact the patient. In any circumstance, every effort will be made to document patient outcome.

A patient's participation in the study will be discontinued if any of the following criteria applies:

- By patient request
- The patient's general condition contraindicates continuing in the study, as judged by the investigator.
- Protocol violation.

If the patient decides to withdraw from the study, he/she will be contacted, if he/she agrees, to obtain information about the reason(s) for discontinuation. The date and reason for the withdrawal will be recorded in the CRF.

14.7 Study termination

Active enrollment in this study will be terminated in case of a statistically significant difference ($p<0.001$) in all-cause mortality by a data and safety monitoring board requested interim analysis after inclusion of 100, 250, 500, 1000, 1500 or 2000 patients.

14.8 Biological material

Biological material will not harvested or stored in relation to the study.

15. Study plan

15.1 Participating centres and operators

Danish/Nordic/Baltic interventional centres with documented interest and experience in treatment of CTO lesions by PCI according to the study protocol may participate. The participating centres should each include ≥10 patients per year.

15.2 Steering committee

The steering committee members will be selected on basis of participation in the study. All steering committee members will have full access to the database and will participate in interpretation of data.

15.3 Progress of the study

The progress of the study will be checked on a monthly basis by the steering committee. The steering committee will receive and evaluate data on inclusion rates and the overall primary endpoint event rate. Further, the steering committee will receive the DSMB assessments and recommendations. The steering committee will receive data by e-mail and answer by e-mail with copy to all members. On basis on comments from the steering committee members, the coordinating investigators will draw preliminary conclusions on study progress. Before decisions on study related issues may be implemented, there should be acceptance from the majority of coordinating investigators.

16. Economy

The NOBLE CTO study is an academic conceived study and conducted by interventional and non-interventional cardiologists in the Nordic/Baltic countries. The study is independent of commercial interests. The study is supported by an unrestricted

grant from the Novo Nordisk Foundation and coordinating investigators will apply for further grants from local and national funds and unrestricted grants from relevant health care companies. All relevant trial documents will be updated with received grants or other changes to funding and the Ethical Committee of Northern Jutland notified. The PCI Research Account, Aalborg University Hospital, will administer the study grants. The participants will not receive any fee for participation. Patients' additional transportation expenses related to the study visits will be covered by the study.

17. Publication

Results, positive as well as negative, will be sought published in an international cardiovascular journal and the protocol is registered online (www.clinicaltrials.gov ID: "*NCT03392415*"). Publication and author issues will be decided by the steering committee on basis of general involvement in the study, number of included patients, drafting of protocol, core laboratory function, etc.

18. References

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