Impact of percutaneous intervention compared to pharmaceutical therapy on complex arrhythmias in patients with chronic total coronary occlusion. Rationale and design of the CTO-ARRHYTHMIA study

Christensen, Martin Kirk; Eftekhari, Ashkan; Raungaard, Bent; Steigen, Terje Kristian; Kumsaars, Indulis; Riahi, Sam; Søgaard, Peter; Thuesen, Leif

Published in:
Cardiovascular Revascularization Medicine

DOI (link to publication from Publisher):
10.1016/j.carrev.2023.04.001

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Cardiovascular Revascularization Medicine 54 (2023) 69–72

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Impact of Percutaneous Intervention Compared to Pharmaceutical Therapy on Complex Arrhythmias in Patients With Chronic Total Coronary Occlusion. Rationale and Design of the CTO-ARRHYTHMIA Study☆

Martin Kirk Christensen [a,*], Ashkan Eftekhari [a], Bent Raungaard [a], Terje Kristian Steigen [b], Indulis Kumsaars [c], Sam Riahi [a], Peter Søgaard [a], Leif Thuesen [a]

[a] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[b] Department of Cardiology, Tromsø University Hospital, Tromsø, Norway
[c] Latvian Center of Cardiology, Paul Stradins Clinical University Hospital, Riga, Latvia

ARTICLE INFO

Article history:
Received 1 December 2022
Received in revised form 22 March 2023
Accepted 3 April 2023
Available online 10 April 2023

Keywords:
CTO
Arrhythmias
Chronic total occlusion
Ventricular tachycardia

ABSTRACT

Chronic total coronary occlusions (CTO) occur in up to 50 % of patients with coronary artery disease by angiography. In CTO-patients, clinically significant arrhythmia is potentially important and insufficiently investigated. Therefore, the purpose of the CTO-ARRHYTHMIA study was to investigate the incidence of loop recorder detected clinically significant arrhythmias and the effect on arrhythmias of revascularization by CTO-PCI.
The study is an independent sub-study of the NOrdic-Baltic Randomized Registry Study for Evaluation of PCI in Chronic Total Coronary Occlusion (NOBLE-CTO); ClinicalTrials.gov Identifier **NCT03392415**. NOBLE-CTO prospectively collects procedural data, quality of life measures, echocardiographic and cardiac MRI findings before and after treatment as well as clinical outcomes in all CTO patients that may be treated by PCI.

1. Introduction

In angiographic registries, a chronic total coronary occlusion is present in approximately 15–25 % of all patients and in 25–50 % of those with significant coronary disease [1,2]. Until recently, due to increased risks of complications and low procedural success, the benefit of percutaneous coronary intervention was dubious. Currently, dedicated CTO PCI operators using contemporary CTO techniques and equipment have made CTO revascularization by PCI a promising treatment option with high likelihood of procedural success.

In CTO patients, clinically significant arrhythmia is a potentially important clinical problem, albeit scarcely investigated [3,4]. The arrhythmia prevalence in an all-comer CTO-population is unknown, but in ICD-populations with ischemic heart disease, a CTO may be found in approximately 30 % of patients at the time of implantation and associated with an increased risk of appropriate ICD therapy [5,6]. Further, in patients with ischemic heart disease receiving an ICD as primary prevention, presence of a CTO was an independent predictor of occurrence of ventricular arrhythmias, and in survivors of out-of-hospital cardiac arrest, the risk of ventricular arrhythmias was found to be increased in patients with a chronic total coronary occlusion [5,7]. CTO-patients with at least one occluded coronary artery are older and have additional risk factors such as hypercholesterolemia, diabetes and lower left ventricular ejection fraction (LVEF) [6]. Although LVEF is reduced in patients with a CTO, <1/3 are potential ICD candidates with an LVEF <35 % [8]. However, a recent study in consecutive post-AMI survivors documented the highest incidence of sudden cardiac death in patients with a relatively preserved LVEF [9].

The purpose of the CTO-ARRHYTHMIA study was to investigate the incidence of clinically significant arrhythmias in CTO patients using an implantable loop recorder. Furthermore, we intended to identify predictors for arrhythmias as well as the impact on arrhythmia of optimized pharmacological treatment and revascularization by PCI in these patients. CTO patients with failed PCI may represent individuals with a particularly high risk of life-threatening arrhythmias.

The study is an independent sub-study of the NOrdic-Baltic Randomized Registry Study for Evaluation of PCI in Chronic Total Coronary Occlusion (NOBLE-CTO) ClinicalTrials.gov Identifier **NCT03392415**. In this study, all patients with a PCI-treatable CTO lesion supplying a major myocardial territory are randomized to an initial conservative treatment of optimal medical therapy (OMT) or OMT and attempted

Abbreviations: CCS, Canadian Cardiovascular Society Angina Grading System; CMR, Cardiac magnetic resonance; CTO, Chronic total occlusion; LVEF, Left ventricular ejection fraction; MACCE, Death, myocardial infarction, stroke and revascularization; PCI, Percutaneous coronary intervention.

☆ ClinicalTrials.gov Identifier **NCT04542460**

* Corresponding author.
E-mail address: m.kirk@rn.dk (M.K. Christensen).

https://doi.org/10.1016/j.carrev.2023.04.001

CTO-PCI. In the NOBLE-CTO study, data is prospectively collected and include quality of life questionnaires, echocardiography and cardiac magnetic resonance perfusion studies as well as clinical outcomes at inclusion and after 6 months. This ongoing trial is a multicenter trial currently including in Denmark and Latvia.

The NOBLE-CTO study has few exclusion criteria and is intended as an all-comer CTO-PCI study including all patient that may be treated by PCI to provide real world data in the treatment of CTO by PCI. The study is currently enrolling, and a total of 134 patients have been included. CTO-ARRHYTHMIA differs from NOBLE-CTO in two ways; the patients are implanted with a loop recorder at randomization, and patients with LVEF <35 % or already treated by an ICD are excluded because of existing indication for ICD treatment.

2. Study design and population

The trial is an investigator driven study with a 1:1 randomized open label design with assessment of pre-specified subgroups including patients with failed CTO PCI. Randomization occurs after informed consent between OMT and OMT plus attempted CTO PCI. For study workflow please see Fig. 1. All patients included will receive an implantable loop recorder. For list of in- and exclusion criteria please see Table 1.

2.1. 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. The study is approved by the ethical committee (**N-20190058**) in the North Denmark Region, and the local ethical committee in future participating sites.

2.2. Study related investigations

Following randomization, all patients are characterized according to the Canadian Cardiovascular Society classification and symptoms of heart failure in New York Heart Association functional classification. For quality-of-life assessment, the Seattle Angina Questionnaire and Short Form-12 item (version 2) health survey are used. Echocardiography is performed for evaluation of left ventricular and atrial volumes, left ventricular systolic and diastolic function including global longitudinal strain and tissue doppler. Perfusion CMR imaging is optional but highly recommended according to the protocol with focus on inducible myocardial perfusion defect size and left ventricular size. At baseline, a CMR compatible loop recorder Biotronik Biomonitor III will be implanted. For overview and timing of investigations see Table 2. In case of worsening symptoms, the occurrence of a significant arrhythmia or increasing burden of a known arrhythmia, an echocardiography and clinical evaluation will be performed and coronary angiography and revascularization will be considered. The management of specific arrhythmias is described in Appendix A. Arrhythmias are monitored on a daily basis using the Biotronic Home Monitoring system and evaluated by a skilled electrophysiologist.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
≥1 CTO lesion amenable to PCI. Stable or stabilized coronary artery disease. Angiographic/echocardiographic signs of reversible perfusion. CTO lesion in a coronary vessel supplying a significant myocardial territory (vessel diameter usually ≥3 mm).	• Expected survival <1 year. • Patients with an indication of ICD due to EF < 35 or previous ventricular tachycardia. • Patients with a cardiac device i.e. ICD, pacemaker or cardiac resynchronizing treatment device. • Renal failure on dialysis. • Indication for coronary artery bypass grafting. • Lesions treated with PCI within one month. • Significant valvular heart disease. • Declined informed consent. Regarding CMR: allergy to contrast medium, severe obesity, claustrophobia and certain metallic implants.

2.3. Endpoints

The endpoints are outlined in Table 3. The primary endpoint used for power calculation is atrial fibrillation and/or ≥8 runs of ventricular premature beats. Endpoints will be assessed by an independent endpoint committee. The endpoint committee will consist of experienced clinical and interventional cardiologists.

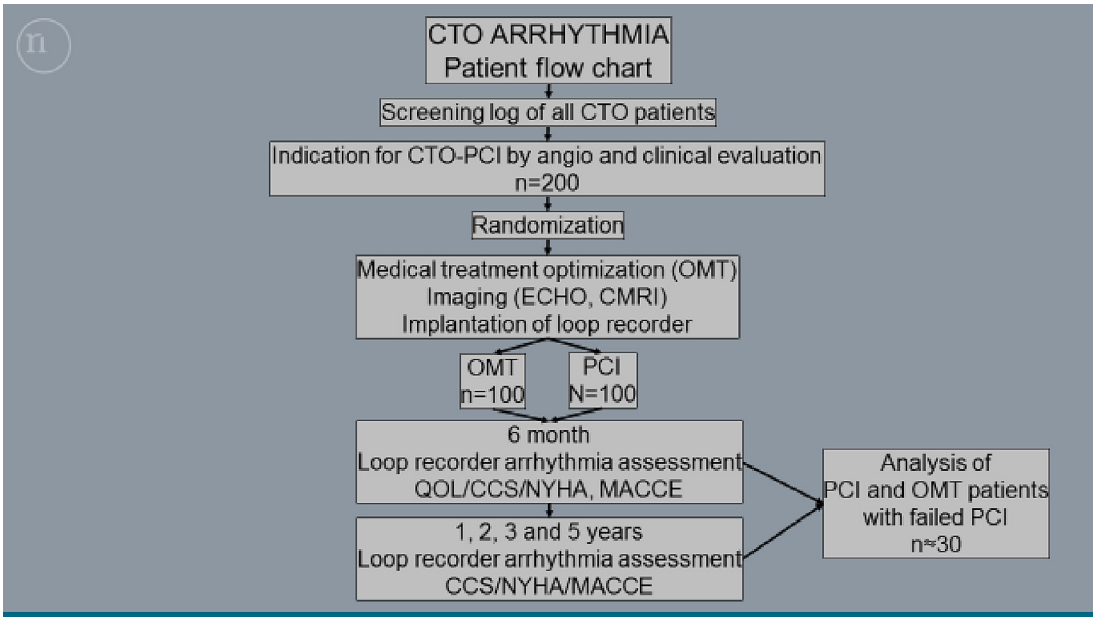

Fig. 1. overview of study workflow.

Table 2
Overview and timing of study related investigations.

	Index	1 month	6 months	12 months	24 months	36 months	60 months
Quality of life evaluation	x		x	x	x	x	X
Echocardiography	x		x				
Cardiac MRI	x		x				
Implantation of loop recorder	x						
MACCE assessment		X	x	x	x	x	x
Optimization of medical therapy[a]	x	X					
Arrhythmia detection[b]							

[a] And as needed according to doctor in charge of optimization.
[b] Arrhythmia detection will be on daily basis via home monitoring system.

2.4. Statistics and power calculation

Continuous variables will be compared with the two-sample *t*-Test or the Mann-Whitney *U* test. Categorical variables will be analyzed with the χ^2-test. Endpoints will be analyzed until occurrence of an endpoint event or loss to follow-up using Kaplan-Meier time-to-event curves. A two-sided *p*-value of <5 % will indicate significance. At present, we have no valid data on prevalence of clinically significant arrhythmias and of the effect of revascularization in CTO-patients. By the loop-recorder assessment, we anticipate a rate of clinically significant arrhythmias (atrial fibrillation and/or ≥8 runs of ventricular premature beats) of 26.5 %. After 36 months, we expect this rate to be unchanged in non-revascularized and reduced to 11 % in revascularized individuals. With alpha of 5 % and power (1-beta) 80 %, and a 2-sided test a total of 196 patients will be needed to detect this treatment effect difference. To account for a minor loss-to follow-up 200 patients (100 in each group) will be included in the CTO-Arrhythmia study. A total of about 30 patients from both study groups with failed PCI will be analyzed separately. The results will be analyzed according to the intention-to-treat principle.

2.5. Randomization

After written informed consent, the patients will be randomized in blocks according to center. Randomization will be performed using REDCap electronic data capture tools hosted at Aalborg University Hospital.

2.6. Data management

The study has been 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 using REDCap [10] hosted at Aalborg University Hospital. Data management is conducted according to GDPR rules.

Table 3
Primary and secondary endpoints.

• Primary endpoints: clinically significant arrhythmias	• Secondary endpoints
• Bradycardia <40 bpm	• All-cause mortality
• Pauses >5 s	• Indication for pacemaker or ICD
• 2nd (type 2) and 3rd degree AV--block	• Major adverse cardiac or cerebral events
• Atrial fibrillation (>4 min)	• Quality of life parameters
• Non-sustained VT (>8 beats)	• Echocardiographic changes
• Sustained VT	• CMR changes
• Polymorphic VT/VF	

AV: atrioventricular, CMR: cardiac magnetic resonance imaging, ICD: implantable cardioverter-defibrillator, VT: ventricular tachycardia, VF: ventricular fibrillation.

2.7. Monitoring of the study

The study will be monitored according to the good clinical practice rules and monitored by data safety monitoring board (DSMB).

2.8. Organization and management

The CTO-ARRHYTHMIA study is organized and run by PCI Research, Aalborg University Hospital. All experienced centers with a CTO program are invited to participate. Each center must include ≥10 patients per year.

2.9. Steering committee

Participating centers will be invited to participate in the steering committee. All steering committee members will have full access to the database and will participate in interpretation of data.

2.10. Progress of the study

We are currently (since November 1, 2020) including at Aalborg University Hospital and have included 66 patients. Pandemic COVID-19 has delayed the patient inclusion and participation of other centers. Centers in Latvia and Norway have obtained ethical approval for participation, and the study is still open for inclusion of new centers.

2.11. Economy

The CTO-ARRHYTHMIA study is an academic conceived study conducted by interventional and non-interventional cardiologists in the Nordic/Baltic countries. The study is supported by an unrestricted grant from the Novo Nordic Foundation and the Danish Heart Foundation. The loop recorder will be supplied as an unrestricted grant from Biotronik (Berlin, Germany). 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.

2.12. Pre-specified sub-studies

The main results are to be published in an international peer-reviewed journal. In addition, pre-specified sub-studies are planned including CMR and echocardiographic data.

3. Discussion

Improved PCI techniques, devices and operator skills in recent years have changed the CTO treatment scenario [11]. In dedicated centers, CTO-PCI may now be characterized by high success rates and acceptable risk of complications [12]. Therefore, it is technically and ethically possible to perform all comers CTO PCI studies.

At present, 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. Two recent conventional randomized clinical trials on PCI vs. OMT; the EUROCTO [13] and the DECISION [14] trials, were hampered by slow and selective patient inclusion. Both studies were terminated prematurely and consequently results may not be applicable for all CTO patients. In the present randomized study, the OMT patients are offered PCI after a 6-months period of optimal medical therapy. Therefore, the study design is expected to be acceptable to most CTO patients and treating physicians. So far, the inclusion rate has been acceptable (72 %) of eligible patients in our single center experience in the NOBLE-CTO study.

At present, the incidence of significant arrhythmias in a population of unselected CTO patients to be treated by PCI is unknown. Also, the possible effect of PCI treatment on significant arrhythmias as well as the relation to PCI procedural success, chronic ischemia and overall cardiac function remains to be evaluated in an all-comers CTO PCI population. The design of the CTO-ARRHYTHMIA study using loop recorder arrhythmia detection, MRI ischemia evaluation, echocardiographic description of cardiac function, and meticulous clinical assessment intended to quantify the clinical problem of arrhythmia and the possible effect of revascularization by PCI.

CRediT authorship contribution statement

Martin Kirk Christensen: Conceptualization, Investigation, Writing – original draft, Project administration. **Ashkan Eftekhari:** Writing – review & editing, Supervision. **Bent Raungaard:** Investigation, Writing – review & editing. **Terje Kristian Steigen:** Investigation, Writing – review & editing. **Indulis Kumsaars:** Investigation, Writing – review & editing. **Sam Riahi:** Conceptualization, Investigation, Writing – review & editing. **Peter Søgaard:** Conceptualization, Writing – review & editing, Supervision. **Leif Thuesen:** Conceptualization, Investigation, Supervision, Writing – original draft, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Leif Thuesen reports equipment, drugs, or supplies was provided by BIOTRONIK SE und Co KG.

Appendix A

Therapy and diagnostic procedures for arrhythmias detected:

Atrial fibrillation:

-DC cardioversion, if appropriate.

-Oral anticoagulation/antithrombotic treatment.

-Plan for either a rhythm or frequency management strategy. A rhythm management strategy is encouraged unless it is contraindicated, or the patient has other preferences.

Radiofrequency ablation is preferred to drug treatment as long-term rhythm management.

-Optimize antihypertensive treatment.

Atrial flutter:

-Direct current cardioversion, if appropriate.

-Radiofrequency ablation is encouraged as first line treatment.

High degree AV-block and sinus bradycardia:

-Pacemaker implantation is recommended for high-degree av-block and sinus bradycardia with nightly heart rhythm <30 bpm persisting after adjustment of medication.

-If left ventricular ejection fraction ≤35 % a cardiac resynchronized therapy device (CRT) is recommended in patients with an expected right ventricular pacing burden >50 %.

Non-sustained ventricular tachycardia:

-If left ventricular ejection fraction <40 %, an electrophysiological study is recommended.

-If the patient is symptomatic after beta blocker treatment and frequent NSVT is detected and eps should be performed.

Sustained ventricular tachycardia and ventricular fibrillation:

-Implantation of implantable cardioverter-defibrillator or CRT-D.

-Radiofrequency ablation is preferred to drug treatment as long-term rhythm management.

References

[1] Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH, Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. Am J Cardiol. 2005;95(9):1088–91.

[2] Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009 Mar;360(10):961–72.

[3] di Marco A, Anguera I, Nombela-Franco L, Oloriz T, Teruel L, Rodriguez Mañero M, et al. Revascularization of coronary chronic total occlusions in an infarct-related artery and recurrence of ventricular arrhythmias among patients with secondary prevention implantable cardioverter defibrillator. Catheter Cardiovasc Interv. 2021;97(1):E1-11.

[4] Assaf A, Diletti R, Hoogendijk MG, van der Graaf M, Zijlstra F, Szili-Torok T, et al. Vulnerability for ventricular arrhythmias in patients with chronic coronary Total occlusion. Expert Rev Cardiovasc Ther. 2020;18(8):487–94. https://doi.org/10.1080/14779072.2020.1793671. Available from:.

[5] Nombela-Franco L, Mitroi CD, Fernández-Lozano I, García-Touchard A, Toquero J, Castro-Urda V, et al. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention. Circ Arrhythm Electrophysiol. 2012 Feb;5(1):147–54.

[6] van Dongen IM, Yilmaz D, Elias J, Claessen BEPM, Delewi R, Knops RE, et al. Evaluation of the impact of a chronic total coronary occlusion on ventricular arrhythmias and long-term mortality in patients with ischemic cardiomyopathy and an implantable cardioverter- defibrillator (the eCTOpy-in-ICD study). J Am Heart Assoc. 2018;7(10):1–14.

[7] Yap SC, Sakhi R, Theuns DAMJ, Yasar YE, Bhagwandien RE, Diletti R, et al. Increased risk of ventricular arrhythmias in survivors of out-of-hospital cardiac arrest with chronic total coronary occlusion. Heart Rhythm. 2018;15(1):124–9.

[8] Suero JA, Marso SP, Jones PG, Laster SB, Huber KC, Giorgi LV, et al. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic Total occlusion in native coronary arteries : a 20-year experience. JACC. 2001;38(2):409–14.

[9] Wellens HJJ, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J. 2014;35(25):1642–51.

[10] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.

[11] Werner GS, Gitt AK, Zeymer U, Juenger C, Towae F, Wienbergen H, et al. Chronic total coronary occlusions in patients with stable angina pectoris: impact on therapy and outcome in present day clinical practice. Clin Res Cardiol. 2009;98(7):435–41.

[12] Brott BC. The safety and outcomes of chronic Total occlusion interventions. JACC Cardiovasc Interv. 2013;6(2):137–8.

[13] Club EC. A randomized multicentre trial to evaluate the utilization of revascularization or optimal medical therapy for the treatment of chronic total coronary occlusions (EuroCTO) [internet]. [cited 2017 Jun 12]. Available from. https://clinicaltrials.gov/ct2/show/NCT01760083; 2016.

[14] Park SJ. Drug-eluting stent implantation versus optimal medical treatment in patients with chronic total occlusion (DECISION-CTO) [internet]. Available from:. https://clinicaltrials.gov/ct2/show/NCT01078051; 2017 Jun 12.