Design and rationale of the drug-coated balloon coronary angioplasty versus stenting for treatment of disease adjacent to a chronic total occlusion (Co-CTO) trial

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ABSTRACT

Background Percutaneous coronary intervention (PCI) of chronic total coronary occlusions (CTOs) typically involves extensive drug-eluting stent (DES) implantation. As a result, patients undergoing CTO PCI are exposed to a relatively high risk of in-stent restenosis and target lesion revascularization. While the application of drug-coated balloons (DCBs) may improve patient outcome by reducing stent burden, randomized controlled trials investigating the use of DCB in CTO PCI are lacking.

Methods The Co-CTO trial (NCT04881812) is a single-blind, noninferiority randomized controlled trial enrolling 144 patients undergoing CTO PCI. A hybrid strategy (stenting of the CTO body and DCB treatment of adjacent disease) will be compared to a complete stenting strategy. The primary study endpoint is in-segment percentage diameter stenosis at 1 year follow-up determined by intravascular ultrasound. Secondary endpoints include major adverse cardiovascular events (a composite of cardiac death, nonfatal myocardial infarction, and ischemia-driven target lesion revascularization) at 1 year, angiographic outcomes, and cardiac symptoms (Canadian Cardiovascular Society Grading Scale, New York Heart Association Classification of Dyspnea).

Conclusion The Co-CTO trial is the first randomized controlled trial exploring a hybrid strategy (DES + DCB) in patients undergoing CTO PCI.

Trial registration Registered at ClinicalTrials.Gov under registration number: NCT04881812 (https://clinicaltrials.gov/study/NCT04881812?cond=cto&intr=drug-coated%20balloon&rank=1). (Am Heart J 2025;288:65–76.)

Introduction

Percutaneous coronary intervention (PCI) of chronic total coronary occlusions (CTOs) was historically characterized by a relatively low technical success rate, even in selected cases.[1] With the introduction of the retrograde approach and dissection re-entry techniques, success rates increased to over 90% with acceptable complication rates in experienced centers.[2-5] This improvement was partly driven by the introduction of the hybrid algorithm: a framework which allows the operator to rapidly and effectively alternate between techniques.[6] Although the field of CTO PCI has undergone many changes over the years it has consistently involved implantation of a higher number of drug-eluting stents (DES) with longer total stent lengths compared to non-CTO lesions.[7] Factors predisposing to an increased stent length are omnipresent in CTOs, including severe disease in the distal landing zone and heavy calcification.[2,8] Importantly, longer total stent length is directly related to worse outcome, due to its association with in-stent restenosis (ISR), target lesion revascularization (TLR), and major adverse

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cardiovascular events (MACE).[9-12] A viable alternative to DES has emerged in the form of drug-coated balloons (DCBs). DCBs embody the "leave-nothing-behind'' strategy by facilitating effective transfer of an antiproliferative agent to the coronary vessel wall through a balloon.[13] Evidence from randomized controlled trials have shown comparable outcomes with DCB and DES in ISR and small vessel de novo lesions, yet contemporary clinical practice reflects a more widespread adoption of DCBs in selected populations.[14-17] The benefit of DCBs in CTO PCI may be found in the application of a hybrid strategy, in which DCBs act as a complement to DES. Retrospective analyses have suggested that a hybrid strategy may reduce stent burden and is possibly associated with a lower MACE rate compared to a DES-only treatment in patients with diffuse and multivessel disease (including CTO lesions).[18-20] In addition to these data, a prospective study including long lesions and true bifurcation lesions suggested a hybrid approach to be a safe and effective alternative to DES-only angioplasty.[21] At present, data on the use of DCB in CTO PCI are scarce and lack a randomized comparison to DES.

Methods

Primary objective

The drug-coated balloon coronary angioplasty vs stenting for treatment of disease adjacent to a chronic total occlusion (Co-CTO) trial aims to investigate the value of DCB treatment in residual disease of a CTO artery after successful recanalization and stenting of the CTO body (Figure 1). The primary aim of this study is to demonstrate noninferiority of a hybrid strategy (minimal DES combined with DCB) compared with a complete stenting strategy in patients undergoing CTO PCI, with regard to in-segment percentage diameter stenosis (%DS) as determined with intravascular ultrasound (IVUS) at 1 year.

Study design and population

The Co-CTO trial (NCT04881812) is an investigator-initiated, single-center, single-blind (patients are masked), randomized, noninferiority clinical trial. Figure 2 depicts the study flow. Patients with a clinical indication for CTO revascularization as determined by the local heart team (based on symptoms, documented ischemia, and viability[22]) will be eligible for inclusion after successful recanalization of the CTO body with residual disease adjacent (proximal and/or distal) to the CTO body. The inclusion and exclusion criteria are listed in Table 1. Patients who meet the eligibility criteria but decline participation, will be approached for inclusion in a parallel CTO registry.

Study procedures

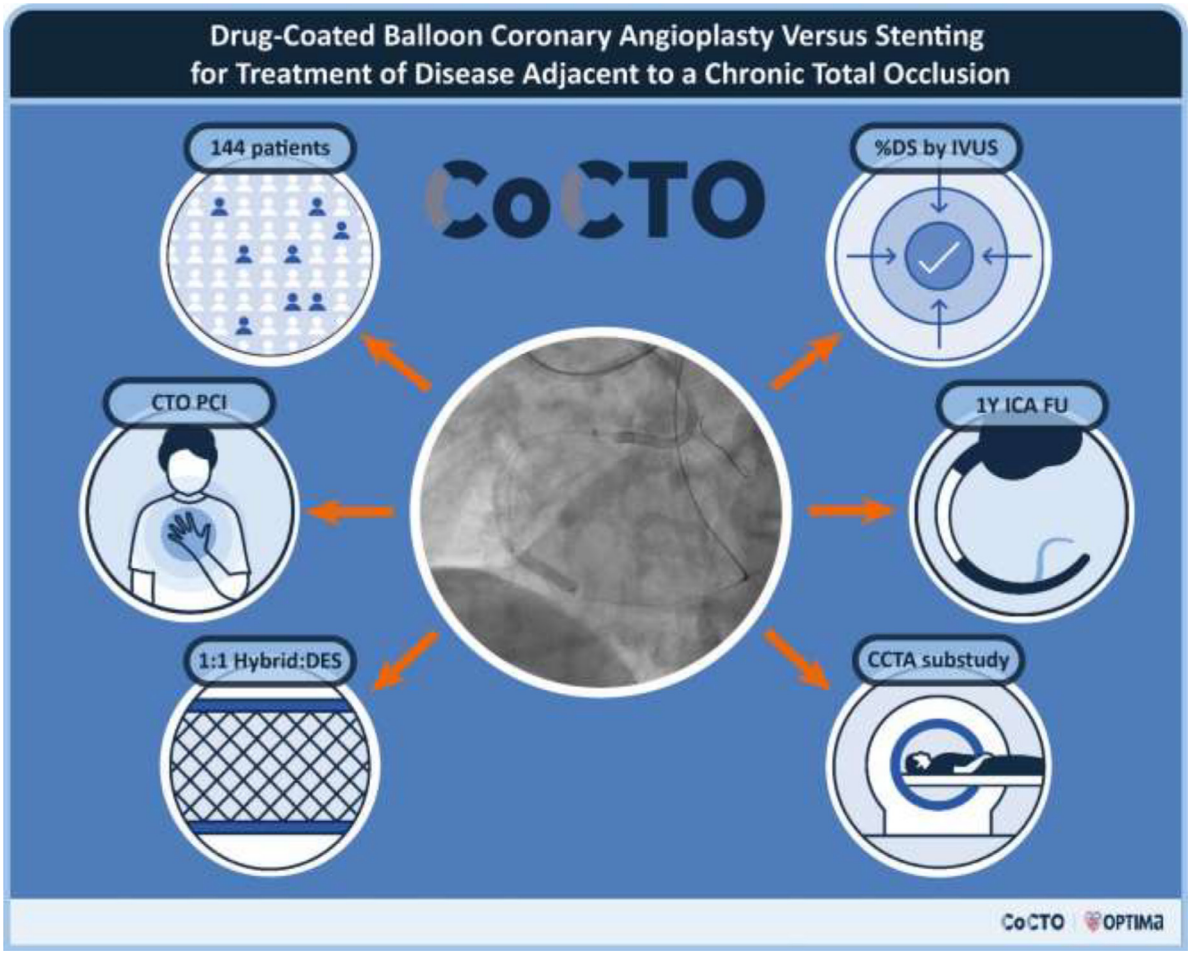
CTO procedure and randomization

After obtaining written informed consent, the patient will be planned for CTO PCI according to standard practice and in adherence with international guidelines. Patients are treated by expert CTO operators (AN and PK) according to the hybrid algorithm.[6] This algorithm utilizes several angiographic characteristics to guide strategical planning of the procedure, using 4 complementary techniques to cross a CTO: antegrade wire escalation, antegrade dissection and re-entry, retrograde wire escalation and retrograde dissection and re-entry. Technical CTO PCI success is defined as <30% residual stenosis and TIMI flow III to the distal vascular bed.[23] Only patients meeting the angiographic eligibility criteria are randomized. Angiographic eligibility criteria consist of: (1) successful crossing of the CTO lesion, (2) successful recanalization and predilation of the entire target vessel, and (3) the presence of a significant stenosis on angiography (diameter stenosis ≥70%) with IVUS confirmation of atherosclerosis beyond the CTO body which requires treatment of the downstream vessel. Patients meeting the angiographic eligibility criteria are subsequently randomly assigned in a 1:1 ratio to either a hybrid stenting strategy (minimal DES combined with DCB) or a complete stenting strategy. In case of a modification procedure, randomization will be postponed to the follow-up procedure. Randomization is performed using an interactive Web-based randomization platform in Castor (Castor Electronic Data Capture, Amsterdam, The Netherlands). Randomization is conducted using block sizes of 4 and 6. A visual representation of both treatment arms is illustrated in Figure 3. To ensure blinding of the patients, the randomized treatment is not revealed to the patient until completion of the trial. During the inclusion period, a detailed screening log of all patients screened for eligibility will be captured. These data will be published upon completion of the trial, and may provide valuable insight into the proportion of CTO lesions eligible for a hybrid approach.

DCB procedure

Allocation to the hybrid strategy entails stenting of the CTO body, with additional DCB treatment of adjacent disease according to the German consensus group criteria.[24] First, the CTO body will be treated with DES, followed by DCB-angioplasty of the adjacent segments (distal to proximal). The DCB may overlap with DES at the edges of the implanted stent, but the operator aims to limit overlap of DCB with the stented segment(s). The ratio of the DCB diameter to the nominal diameter of the target vessel is recommended to be between 0.8 and 1.0. The present trial excludes vessels with unfavorable characteristics for DCB treatment, including flow-limiting dissection (thrombolysis in myocardial infarction (TIMI) flow <3), significant recoil (≥30%), or coronary perforation following predilation. If needed due to the length

Figure 1. Central illustration. The drug-coated balloon coronary angioplasty vs stenting for treatment of disease adjacent to a chronic total occlusion (Co-CTO) trial is the first randomized controlled trial to compare a hybrid strategy (minimal DES with DCB) to a complete DES-strategy in patients undergoing CTO PCI. The trial includes 144 patients scheduled for elective CTO treatment, during which they are randomized in a 1:1 fashion to a hybrid (DES + DCB) or DES-only strategy. The primary endpoint is defined as %DS at 1 year follow-up, as measured by IVUS. Patients are voluntarily included in the explorative CCTA substudy, which aims to compare CCTA-derived plaque characteristics with repeat ICA and IVUS imaging. Abbreviations as previously described.



of the lesion or adjacent disease, the use of >1 DCB is allowed. The length of the balloon should cover 2 to 3 mm beyond both ends of the lesion. The duration of balloon inflation is at least 30 seconds, but optimally 60 seconds. If a patient has ≥1 CTO vessel appropriate for the study protocol, the operator will perform the assigned randomization protocol in both vessels (thus, the study subject will have ≥1 target vessel). If a flow-limiting dissection occurs following DCB-angioplasty, bail-out treatment with DES will be performed. A case example of a Co-CTO patient is provided in Figure 4.

Study devices

During index PCI, IVUS will be performed at 2 time points: (1) after crossing (recanalization) of the CTO, and (2) at the end of the procedure. Care will be taken in cases using dissection re-entry techniques, in which IVUS will guide the minimal stent length required to cover the entire dissection plane. All IVUS images will be obtained using OptiCross coronary imaging catheters (Boston Scientific Corporation, Marlborough, USA), or a commercially available CE-marked equivalent, with the transducer pulled back automatically at a speed of 0.5 mm/s to 1.0 mm/s. The IVUS images will be digitally recorded and stored at the baseline and at 1-year follow-up procedures. The CTO vessels will be treated with the Synergy XD everolimus-eluting Stent System either alone or in combination with the Agent paclitaxel-eluting Drug-Coated Balloon (Boston Scientific Corporation, Marlborough, USA). Alternatively, CE-marked equivalent devices may be used if deemed appropriate by the operator. All

Figure 2. Study flow. Flowchart of the Co-CTO trial. Abbreviations: FU, follow-up, ITT, intention-to-treat, other abbreviations as previously described.

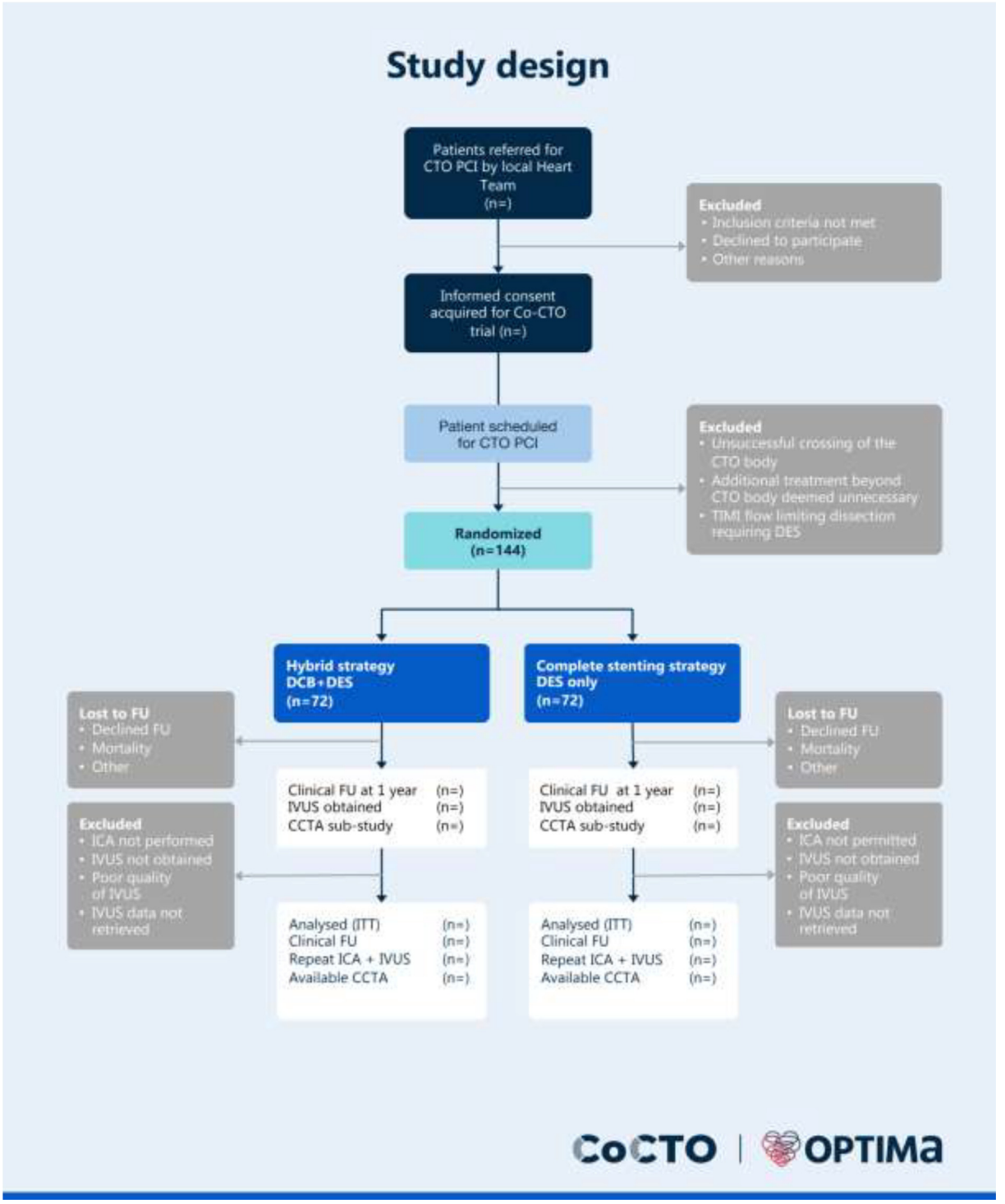


Figure 3. Treatment arms. Visual illustration of both randomization arms, depicting a hybrid strategy (DES + DCB) vs a complete stenting strategy (DES-only). Prior to randomization, the operator achieves successful recanalization and predilation of the CTO vessel. Subsequently, the patient is randomized to a hybrid strategy vs complete stenting strategy in a 1:1 fashion. In the hybrid strategy arm, the CTO body is stented, followed by DCB-angioplasty of adjacent disease. Abbreviations as previously described.

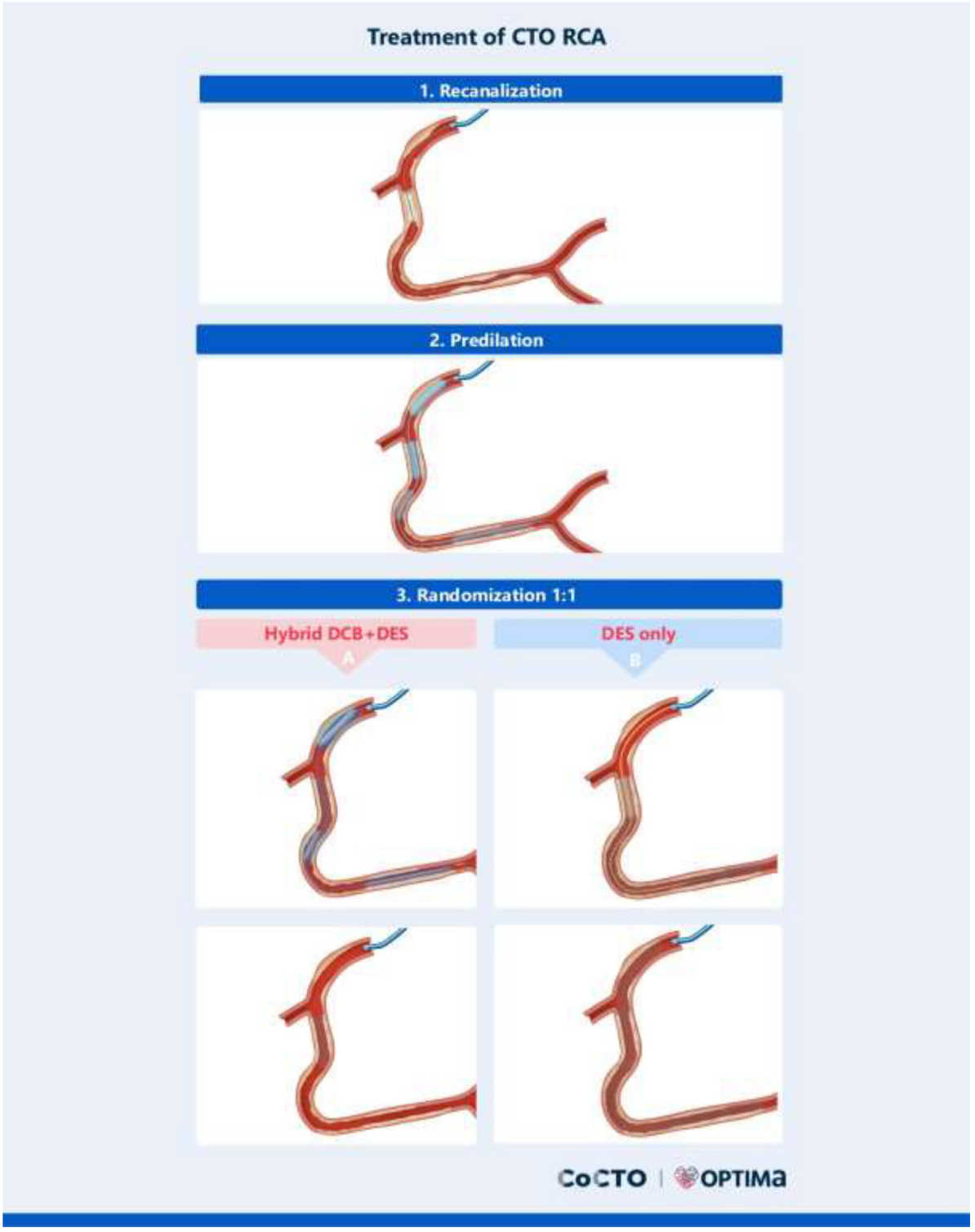


Figure 4. Case example of a calcified CTO RCA. Patient was a 59 year old male with a history of diabetes mellitus type II and ambulant myocardial infarction in the inferior territory. ICA revealed a CTO of the distal RCA, J-CTO score = 2 (calcification, length ≥20 mm). Due to refractory symptoms under optimal medical therapy, the patient was accepted and planned for CTO PCI. (A-B) Primary set-up shots with dual catheter injection of the RCA, revealing ample retrograde filling by the LAD (Rentrop III, CCS 2) via septal collaterals. (C) Successful recanalization of the CTO via antegrade wire escalation**.** **(**D) After wiring of the CTO vessel, the entire coronary artery was predilated at high pressure (20 atm). After predilation, the patient was randomized to a hybrid strategy. (E-F) Pre-PCI intravascular ultrasound (IVUS) was performed from the right posterior descending artery (RPD) to the ostium, in accordance with the Co-CTO protocol. Besides extensive adjacent disease in all segments of the RCA (proximal, mid, distal, RPD, and posterolateral branch (RPL)), IVUS also revealed almost 360° calcium ring. (G) PCI was performed with a short drug-eluting stent (SYNERGY, 3.5 × 38 mm, left upper corner) to cover the CTO body, followed by 4 paclitaxel-DCBs (AGENT, twice 2.75 × 30 mm in RPL and RPD (with kissing balloon inflation), 4.0 × 30 mm mid-RCA, 4.0 × 20mm in proximal RCA). A second DES (3.5 × 8 mm) was deployed at the distal stent edge because of edge dissection. (H-J) Final result with good stent expansion (confirmed by IVUS), and nonflow limiting dissection in the proximal RCA, mid-RCA, RPL, and RPD. (K-L) Follow-up at 12 months was planned according to protocol, and demonstrated late lumen enlargement in the proximal RCA, mid-RCA, RPL and RPD, with a good stent result.

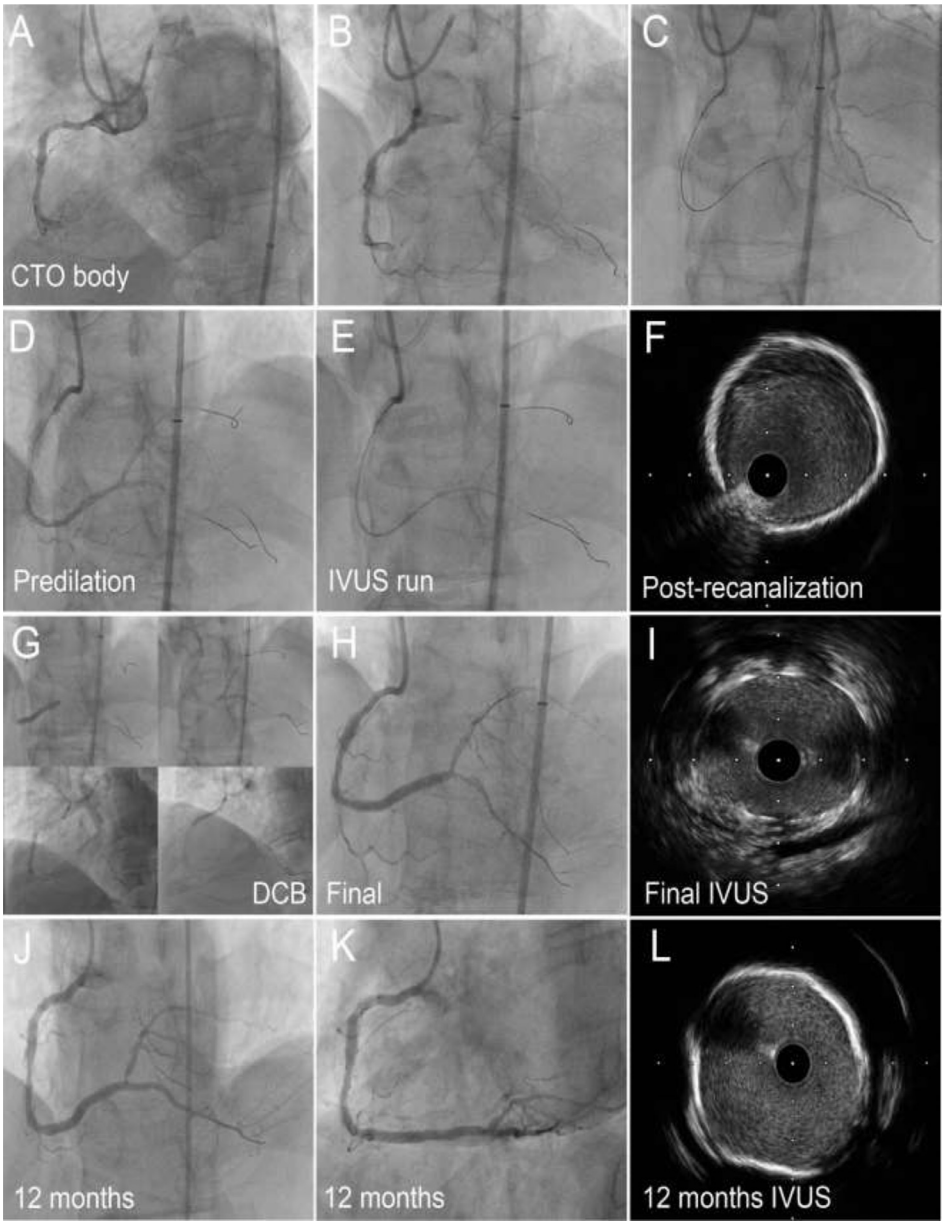


Table 1. Eligibility criteria.

Inclusion criteria	
1	Age ≥18 y
2	Clinical indication for revascularization of the CTO as determined by the local heart team (based on symptoms, documented ischemia, and viability)
3	Successful recanalization of the CTO with residual disease adjacent to the initial lesion
Exclusion criteria	
1	Dissection affecting the flow (TIMI flow grade <3), significant recoil (>30%) or coronary perforation after predilation
2	Reference diameter of the vessel is <2.5 mm or >4.0 mm
3	Bifurcation lesion requiring the stenting of the side branch
4	Prior extensive stent-placement (presence of a continuous segment of intracoronary stenting >60 mm or "full metal jacket"[37])
5	Left main lesion
6	Acute coronary syndrome
7	Cardiogenic shock
8	Severe kidney disease defined as an eGFR <30 ml/min
9	Pregnancy
10	Life expectancy <12 mo
11	Inability to give written consent

Abbreviations: CTO, chronic total coronary occlusion; eGFR, estimated glomerular filtration rate; TIMI, thrombolysis in myocardial infarction.

products have a CE-mark and will be used according to their intended purpose.

Standard procedural protocols

All patients receive a loading dose of 300 mg aspirin and 300 to 600 mg of clopidogrel prior to PCI. An intravenous bolus of 10,000 international units of unfractionated heparin is administered at the start of the procedure. Additional heparin is administered during the procedure based on a target activated clotting time of >300 seconds, which is checked every 30 minutes. Before IVUS, 100 to 300 mg of intracoronary nitroglycerin is administered. Following PCI, and in accordance with current clinical guidelines,[22] patients receive life-long aspirin 80 to 100 mg daily and clopidogrel 75 mg daily for 12 months. Patients on long-term anticoagulation therapy receive 1 month of aspirin and 12 months of clopidogrel. Postprocedure, all patients are hospitalized for at least 6 hours, with same-day discharge pursued in accordance with standard hospital policy.[25]

Clinical and angiographic follow-up

For the identification and verification of clinical endpoints, patient follow-up will be performed by telephone calls at 30 days (± 15 days) and 1 year (± 3 months) after the index procedure. The use of medication and the occurrence of cardiac symptoms will also be recorded. Follow-up invasive coronary angiography (ICA) and IVUS is planned at 1 year (±3 months) in all patients. All clinical endpoints will be documented prior to performing the follow-up angiogram. Any clinically indicated coronary angiogram performed before 1-year follow-up is considered unplanned. If an unplanned angiogram is followed by target lesion or target vessel revascularization, a planned follow-up angiogram will not be performed at 1 year. Of note, IVUS will be performed prior to any intervention to capture the primary endpoint. If no revascularization is performed during an unplanned angiogram within 6 months after the index procedure, the planned 1-year angiogram will still be performed. If unplanned angiography is performed beyond 6 months, the 1-year follow-up angiogram is omitted. Importantly, because angiographic follow-up in clinical trials is known to increase the incidence of repeat revascularization,[26] the IVUS run performed prior to any intervention will be considered as the primary endpoint. Significant late luminal loss may be treated with either additional DCB or DES at the discretion of the operator. These revascularization events (occurring after the follow-up IVUS run) will be documented. Finally, some patients may require multivessel revascularization (in a staged procedure) or further PCI for optimization following a modification procedure. Therefore, patients who have an additional PCI (for either a CTO or non-CTO lesion) that is both documented as planned and scheduled at the time of their index PCI will not be classified as a repeat revascularization endpoint. It is anticipated that these procedures will occur within 4 months of the index (enrolling) PCI.

Co-CTO trial endpoints

The primary endpoint of the study is in-segment %DS at 1 year follow-up as determined by IVUS. In-segment %DS is defined as the difference between the reference vessel diameter (mm) and the minimal lumen diameter (mm), divided by the reference diameter and multiplied by 100.[27] From the acquired IVUS images, the reference vessel diameter is measured in disease-free proximal segments (excluding ectatic areas). In vessels where there is no proximal reference (i.e. ostial stent implantation), the largest lumen diameter will be used as the reference. The segment to be evaluated includes the treated area plus 5 mm margins proximal and distal to it (in-segment).

In the hybrid strategy arm, %DS will be assessed in segments treated with both DES and DCB. Secondary endpoints include the following parameters measured with IVUS: minimal lumen diameter (MLD), late luminal loss ($MLD_{baseline}$ – $MLD_{follow\text{-}up}$), late lumen change (loss or increase), length of adjacent disease (mm), length of CTO body (mm), (edge) dissection burden (dissection length, maximum arc, and depth), presence and location of stent under-expansion, calcium burden (maximum arc, length, and depth), plaque burden (determined for CTO segment and treated adjacent segment(s)), and wire tracking (subintimal vs intraplaque, including length (mm)). Quantitative coronary angiography (QCA) will be performed to evaluate %DS, MLD, length of adjacent disease (mm), length of CTO body (mm), reference vessel diameter, Japanese CTO score, in-segment binary restenosis, and target vessel re-occlusion (defined in Table 2). Secondary clinical endpoints include MACE and its components at 1 year follow-up. Clinical events are defined according to the Academic Research Consortium.[28] MACE is defined as a composite of cardiac death, nonfatal myocardial infarction, and ischemia-driven target lesion revascularization. Prior to PCI, at 30 days, and at 1 year follow-up, cardiac symptoms are assessed using the Canadian Cardiovascular Society Scale for the degree of angina, and the New York Heart Association Classification of Dyspnea for the presence of dyspnea at exertion.

Co-CTO trial primary endpoint assessment

All baseline and follow-up angiographic and IVUS imaging will be assessed by an independent corelab (Cardiovascular Research Foundation, New York, United States of America). The corelab will be blinded to the patient characteristics and clinical events. Importantly, complete blinding of the corelab to the randomization arm is not feasible, as it will be possible to deduce whether patients have been treated with a complete stenting or hybrid strategy.

CCTA substudy

Coronary computed tomography angiography (CCTA) has already been shown to be a useful noninvasive imaging tool for strategic planning and assessing procedural risk and outcome in CTO PCI.[29-31] However, its use in assessing the vessel once treated may be hampered due to its limited spatial and temporal resolution in the presence of extensive calcification or long stents.[32] This substudy is explorative in nature, and aims to compare CCTA-derived plaque characteristics with repeat ICA and IVUS imaging. All patients providing informed consent for the trial are requested to participate in the substudy. The CCTA will be performed at 1 year postindex procedure (±3 months), and will precede the 1 year angiogram. The CCTA scanner characteristics and scanning protocol are described in detail in the Supplemental Material.

Statistical considerations

Statistical analysis plan

In order to prove noninferiority, the null hypothesis describes that a hybrid strategy (DES + DCB) is noninferior to a complete stenting strategy in terms of in-segment %DS by IVUS at 1 year follow-up. The noninferiority margin (Δ) has been set at an absolute difference of 5%, which constitutes the direct difference (in percentages) between both arms. Importantly, we preferred %DS over late luminal loss due to the potential for higher acute gain following stenting (resulting in increased late luminal loss), although both treatment options might produce comparable results.[33] Furthermore, using minimal lumen area as a primary endpoint may lead to under- or overestimation of the true disease severity, as this metric does not incorporate a healthy reference segment.[34]

We based the noninferiority margin on previous trials and current clinical insights. Baan et al.[35] showed noninferiority of DEB vs DES in ISR lesions in terms of MLD at 6 months. The absolute difference between in-segment %DS at follow-up between DEB and DCB was 2.3%. Equally, Byrne et al.[33] demonstrated noninferiority of the paclitaxel eluting balloon vs paclitaxel eluting stent in terms of %DS in an ISR population. The absolute difference and concomitant 1-sided confidence interval were well within the predefined noninferiority margin of 7% (absolute difference 0.6%, 1-sided 95% CI 4.9%). In the BELLO study, Latib et al.[36] reported a statistically comparable in-segment %DS in small coronary vessels treated with paclitaxel eluting balloons vs paclitaxel eluting stents (absolute difference of 1.7% at 6 months angiographic follow-up). In our study, the limit of inferiority was set at 5%, which captures the noninferiority margins and concomitant absolute percentage differences of the aforementioned studies. As such, noninferiority of a hybrid strategy will be established if the upper limit of the 2-sided 95% confidence interval for the absolute difference in %DS is less than 5%, which would indicate that the hybrid strategy does not result in an absolute difference in %DS greater than 5% between both groups. We consider this threshold to be clinically acceptable, as it represents a minimal difference in %DS that is unlikely to have a significant impact on patient outcomes. Noninferiority testing will be performed in the intention-to-treat population by computing the Student's t-test for the difference in (in-segment) %DS at 1 year. If noninferiority can be demonstrated, superiority testing may follow. All randomized patients that adhere to the study protocol will be included in the per-protocol analysis. Secondary categorical endpoint p-values will be computed by means of the Fisher's exact test in case of categorical variables and Student-t-test for normally distributed variables. A P-value of $< .05$ is considered to be statistically significant. Statistical analysis will be carried out using SPSS software (IBM SPSS Statistics, Chicago, IL).

Table 2. Co-CTO study definitions.

Variable	*Description*
Clinical definitions	
CTO	Angiographic evidence of a total occlusion with complete interruption or minimal penetration of anterograde blood flow (TIMI flow grade 0-1) with an estimated duration of ≥3 months (based on previous angiograms, angina symptoms, and a history of myocardial infarction)[38]
MACE	Composite of cardiac death, nonfatal myocardial infarction and ischemia-driven target lesion revascularization
Cardiac death	Death due to myocardial infarction, cardiac perforation or tamponade, arrhythmia, stroke within 30 days of the procedure or related to the procedure, death due to a complication of the procedure, and any death in which a cardiac cause cannot be excluded*
Nonfatal MI	PCI-related myocardial infarction or a myocardial infarction during follow-up and >48 h after PCI
PCI-related MI	According to the SCAI definition[39]: 1. In patients with normal baseline CK-MB: a. The peak CK-MB measured within 48 h of the procedure rises to ≥10 x the local laboratory ULN, or to ≥5 x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70 x the local laboratory ULN, or ≥35 x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB 2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: a. The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent preprocedure levels 3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: a. The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension
MI >48 h after PCI	According to the fourth universal definition of myocardial infarction[40]: Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL, and one of the following elements: (1) symptoms of acute myocardial ischaemia, (2) new ischaemic ECG changes, (3) development of pathological Q-waves, (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic etiology, (5) identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy
Revascularization definitions	
Target lesion	The treated segment between 5 mm proximal and 5 mm distal to the treated area*
ID-TLR	Any repeat PCI of the target lesion performed for restenosis or other complication of the target lesion. Evidence of ischemia is required either by noninvasive testing (stress or perfusion imaging) or by pressure wire measurement (iFR/FFR) during coronary angiography
Clinically driven revascularization	Any repeat PCI in a stenotic lesion ≥50% of the luminal diameter on the basis of quantitative coronary angiography and in the presence of ischemic signs and/or symptoms, or any repeat PCI of a diameter stenosis ≥70% irrespective of the presence or absence of ischemic signs or symptoms*
TVR	Revascularization in the entire coronary vessel proximal and distal of the target lesion, incl. side branches*
TLR	Revascularization due to a stenosis within a 5-mm border proximal or distal to the treated segment(s) (with either DES or DCB)*
TVF	Composite of cardiac death, myocardial infarction, clinically driven target vessel revascularization, binary angiographic in-stent restenosis and target vessel re-occlusion
Target vessel re-occlusion	Recurrent total occlusion at the previously treated segment(s)
Repeat revascularization	Any further PCI that is not documented as planned and scheduled at the time of index PCI will be classified as a repeat revascularization endpoint
Bail-out stenting	Implantation of ≥1 stent(s) in the DCB arm
Cross-over	Re-allocation of a study subject to the other randomization group during the index procedure. Cross-over can only occur *prior* to the implantation of any medical devices
IVUS and angiographic definitions	
Percentage diameter stenosis	Difference between the reference vessel diameter (mm) and the minimal lumen diameter (mm), divided by the reference diameter and multiplied by 100
Late lumen loss	Difference between the minimal lumen diameter at the end of the PCI procedure and the minimal lumen diameter at 1 year follow-up
In-segment binary restenosis	At least 50% residual diameter stenosis located in the treated segment including 5 mm proximal or 5 mm distal of the treated segment(s)

*Defined according to the academic research consortium document.[28] Abbreviations: CABG, coronary artery bypass grafting; CK-MB, creatine kinase MB; cTn, cardiac troponin I; DCB, drug-coated balloon; DES, drug-eluting stent; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; ULN, upper limit of normal; URL, upper reference limit.Other abbreviations as previously described.

Sample size calculation

For the sample size calculation, we assumed that under the alternative of noninferiority the mean %DS would be equal in both treatment groups, with a common standard deviation of 10%. Assuming a 2-sided significance level of 5%, a statistical power of 80%, and estimated dropout rate of 10%, 72 patients are needed for each treatment arm. Based on these assumptions, 144 patients will be included in this study.

Ethical considerations

This study is conducted in full accordance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, and Johannesburg), with ICH-GCP, and with the laws and regulations of the Netherlands. It is the responsibility of the investigators to obtain written informed consent.

Study funding and data management

The Co-CTO trial is an investigator-initiated clinical trial with funding provided by Boston Scientific Corporation (Marlborough, USA). The sponsor is responsible for conducting the trial, the protocol and amendments, and monitoring the progression of the study. Additional safety and data management monitoring will be performed by an independent clinical research organization appointed by the Medical Ethical Committee of the local institute. The monitor will be responsible for surveilling accurate data management (including the timely documentation of serious adverse events), trial conduct, and the occurrence of study protocol deviations. All data will be stored for up to 15 years after completion of the study. The appointed storage location will be located at the medical center of the study sponsor. The principal investigators and the monitor will have access to the study data. Finally, the authors of the Co-CTO trial carry responsibility for the design and conduct of the study, future study analyses, drafting and editing of the manuscript and its final contents.

Conclusions

Treatment of CTOs is often accompanied by long and multiple DES implantation, which is associated with an increased risk of in-stent restenosis and target lesion revascularization. The potential of DCBs to reduce stent burden presents an attractive alternative option. The Co-CTO trial is an investigator-initiated, randomized controlled trial investigating the application of DCB in the treatment of disease adjacent to the CTO segment during CTO PCI. The study aims to assess whether a hybrid strategy (DES combined with DCB) is noninferior to a complete stenting strategy. This trial has the potential to drive a significant shift in clinical practice and improve patient outcomes following CTO PCI.

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Declaration of competing interest

Nothing to disclose.

CRediT authorship contribution statement

Yvemarie B.O. Somsen: Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Ruben W. de Winter:** Writing – review & editing, Conceptualization. **Jiawei Wu:** Writing – review & editing, Formal analysis. **Roel Hoek:** Writing – review & editing. **Ralf W. Sprengers:** Methodology. **Niels J. Verouden:** Writing – review & editing. **Bimmer E.P.M. Claessen:** Writing – review & editing, Supervision. **Sebastiaan A. Kleijn:** Writing – review & editing. **Jos W.R. Twisk:** Methodology. **José P. Henriques:** Writing – review & editing, Supervision. **James C. Spratt:** Methodology. **Tuomas T. Rissanen:** Writing – review & editing, Methodology. **Margaret B. McEntegart:** Writing – review & editing, Supervision, Methodology. **Akiko Maehara:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Alexander Nap:** Writing – review & editing. **Paul Knaapen:** Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2025.03.023.

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