ULTRA-CTO STUDY

USE OF PHYSIOLOGY TO EVALUATE PROCEDURAL RESULT AFTER PCI CTO

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Version 2.0

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PROTOCOL SIGNATURE SHEET

I have read the protocol and agree to conduct this trial in accordance with all stipulations of the protocol, with applicable laws and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

Name	Signature	Date
Principal Investigator:		

HISTORY OF CHANGES

Revision	Release date	Change
1.0	31-12-2020	Initial release
1.1	10-03-2021	Additional information objectives, endpoints, co-investigator and sample size calculation
2.0	04 December 2023	Adjustments: - Sponsor - CRO - Co-principal investigator - Secondary objectives - Inclusion criteria: deletion of inclusion criterion 'Presence of at least one intermediate (angiographically 30-90%) stenosis in the non-CTO vessel or major side branch of the CTO vessel with diameter ≥ 2mm, for which FFR is clinically indicated'. - Study design and study procedures: • Staged OCT vs direct OCT (based on clinical judgement and local practice) • Repeat post-PCI FFR and RFR after additional PCI is now compulsory instead of recommended.

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1. LIST OF ABBREVIATIONS

CCS	Canadian Cardiovascular Society
CFR	Coronary flow reserve
CTO	Chronic total occlusion
FFR	Fractional flow reserve
IMR	Index of microcirculatory resistance
IVUS	Intravascular ultrasound
MACE	Major adverse cardiovascular events
NYHA	New York Heart Association
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
Pd/Pa	Pressure-distal / pressure-aorta = ratio of mean resting distal coronary pressure to aortic pressure
POBA	Plain old balloon angioplasty
RFR	Resting full-cycle ratio
SSR	Suboptimal stent result
ST	Stent thrombosis
TLR	Target lesion revascularization
TVF	Target vessel failure

2. SUMMARY

Rationale:
Post-percutaneous coronary intervention (PCI) intra-coronary physiology emerges as a useful tool to assess acute stent results. After PCI of non-chronic total occlusions (CTOs), several previous studies suggested a relationship between low post-PCI fractional flow reserve (FFR) and future adverse cardiac events [1, 2]. Non-hyperemic pressure ratio is a new category of resting indices, such as resting full-cycle ratio (RFR), that is calculated by measuring a resting pressure gradient across a coronary lesion under resting conditions (i.e. without pharmacologic hyperemia, as opposed to FFR) to assess the hemodynamic significance of a stenosis [3]. A non-hyperemic pressure ratio, such as RFR, is theoretically less subject to the factors influencing FFR after PCI of a CTO, such as total stent length or acutely smaller diameters of the newly reperfused CTO vessel. However, the usefulness of post-PCI RFR in these patients remains to be elucidated. The ULTRA-CTO study will primarily evaluate both the value of post-PCI RFR and post-PCI FFR for detecting suboptimal stent result (SSR) in the acute phase. The components of SSR are depicted in figure 1.
Hypothesis: The hypothesis is that the area under the curve (AUC) of post-PCI RFR is non-inferior to the AUC of post-PCI FFR in CTO patients with regard to prediction of suboptimal stent result (SSR).
Primary objective: To assess the predictive value of post-PCI RFR and FFR with regard to SSR in CTO patients.
Secondary objectives:
To assess:
- The predictive value with regard to SSR of the RFR and FFR gradient across the stented segment.
- The correlation between post-PCI physiology (RFR, FFR, CFR, IMR) and SSR with anginal complaints (SAQ score), cardiovascular events and clinical (CCS and NYHA) classification
- The impact on physician-decision making based on OCT and physiology findings.

Study design: Prospective, multicentre, non-randomised investigator-initiated trial with a non-inferiority design

Study population: All patients of 18 years and older who are accepted for and successfully treated by PCI CTO in whom physiology measurements and OCT recordings are possible.
Main study endpoint: The AUC of post-PCI RFR compared to the AUC of post-PCI FFR with regard to SSR.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The anticipated benefit is improvement of our knowledge on how to optimize stent results in CTO PCI. Because the pressure wires and OCT camera that are used for the study-related measurements are commonly used interventional tools, this poses no study-related additional risk for participating patients. International guidelines recommend the use of intravascular imaging for PCI guidance, especially in complex cases leading to lower myocardial infarction, TVR and cardiac mortality. Pressure wires are clinically indicated to identify hemodynamic significant (remaining) lesions that needs to be revascularized. Due to study-related measurements the procedures will be moderately prolonged, most likely by approximately 15 minutes.
With minimal effort and risk, subjects included in this trial are able to contribute to research to that may improve the treatment of CTOs, which may have large impact on clinical practice and guidelines.

3. INTRODUCTION AND RATIONALE

Post-PCI intra-coronary physiology emerges as a useful tool to assess acute stent results. Several previous studies suggested a relationship between low post-PCI FFR and future adverse cardiac events [1, 2], although an optimal cutoff value has not been reported. Non-hyperemic pressure ratio (NHPR) is a new category of resting indices, such as resting full-cycle ratio (RFR), among others, that is calculated by measuring a resting pressure gradient across a coronary lesion under resting conditions (i.e., without pharmacologic hyperemia) to assess the hemodynamic significance of a stenosis [3]. The use of RFR instead of hyperemic physiology omits the use of a vasodilator, allowing the physician to perform multiple physiology assessments in less time and improving patient experience. In addition, RFR is potentially useful in the assessment of tandem lesions with minimal interaction between individual coronary stenoses. Currently, no data are available regarding post-PCI RFR or other non-hyperemic pressure ratios with regard to clinical outcome and stent result.

In the FFR-Search registry [4], 50% of all patients had a suboptimal FFR (≤ 0.90) after PCI with good angiographic result. Complex lesion characteristics, use of multiple stents and smaller reference vessel diameter were associated with a suboptimal FFR. This may explain an even higher rate of suboptimal FFR in chronic total occlusion (CTO) patients despite satisfactory angiographic results (65%) in the FFR-Search registry, but CTO lesions were present in only 5% of the total patient cohort. Karamasis et al. [5] also showed that post-PCI FFR ≤0.90 was present in 69% and ≤0.80 in one-third of patient after successful CTO PCI (n=26). The high incidence of low post-intervention FFR might be present in this particular group of patients because of longer stented segments and suboptimal stent results, including stent underexpansion, strut malapposition, stent edge dissection/hematoma, in-stent tissue protrusion [6, 7], or acutely smaller diameters of the newly reperfused CTO vessel.

Of note, studies including patients with an increased complexity (i.e., CTO or lesion length >28 mm) demonstrated a consistent benefit of intravascular ultrasound (IVUS)-guided PCI as compared with angiography only, mainly driven by a reduction of repeat revascularization for restenosis (MACE at 1 year: CTO-IVUS, 2.6% vs. 7.1%, P=0.035; IVUS-XPL, 2.9% vs. 5.8%, P=0.007) [8, 9]. Optical coherence tomography (OCT) guidance has been shown to be equivalent to IVUS guidance, but OCT might be more suitable to assess stent edge dissections and stent malapposition [10]. Thus, OCT may play an important role in the CTO treatment algorithm, determining the need for adjunctive therapies as well as adequate stent sizing and optimizing stent placement.

This suggests that intra-coronary physiology and intra-coronary imaging might be very useful to guide post-procedure decision-making and optimization of CTO PCI. Karamasis et al. [5] showed a significant 4 month recovery of post-PCI FFR in CTO (mean increase of 0.07 from 0.82 to 0.89). Previously, Werner et al. used a Doppler wire to measure coronary flow reserve immediately after CTO PCI and at 5 months follow-up. Their study showed an increase of coronary flow reserve (2.01±0.58 to 2.50±0.79) because of a decrease in the baseline (resting) average peak velocity [11]. Although the investigators interpreted these findings as the result of the resolution of the microvascular dysfunction caused by the CTO, they did not confirm this with specific parameters that address microvascular resistance, such the index of microcirculatory resistance (IMR). Distal luminal enlargement of the recanalized CTO vessels might be the most important explanation for increasing FFR at follow-up, due to restoration of flow, shear stress, and vasomotor properties of the distal vessel after the CTO recanalization.

These combined findings question the reliability of FFR in the acute stage and suggest that FFR may not be the optimal physiologic tool to assess PCI-result in the acute stage. Also, further effort is warranted to understand the pathophysiological substrate of low post-PCI FFR in CTO patients. Coronary physiology measurements, including RFR, FFR, IMR and coronary flow reserve (CFR) and the addition of OCT, will lead to a better understanding of the functional and anatomical aspects of CTO PCI to guide further optimization of procedural results.
Although non-hyperemic pressure ratio, such as RFR, is theoretically less subject to the factors influencing FFR, the usefulness of post-PCI RFR remains to be elucidated.
The ULTRA-CTO study will primarily evaluate both the value of post-PCI RFR and post-PCI FFR for detecting suboptimal stent result (SSR) in the acute phase, and the stability of these measurements over time in a subset of patients with a staged procedure and repeated physiologic assessment.

4. OBJECTIVES

4.1 Primary objective

To assess the predictive value of post-PCI RFR and FFR with regard to SSR in CTO patients.

4.2 Secondary objectives

- To assess the predictive value with regard to SSR of the RFR and FFR gradient across the stented segment
- To evaluate the correlation between positive RFR (≤0.89) and positive FFR (≤0.80) with regard to SSR following angiographically satisfactory CTO PCI.
- To evaluate the correlation between post-PCI physiology (RFR, FFR, CFR, IMR) and SSR with anginal complaints (measured using the Seattle Angina Questionnaire [SAQ] [12]), cardiovascular events and other clinical classifications (CCS and NYHA)
- To assess the impact on physician-decision making based on OCT and physiology findings.

4.3 Exploratory objectives

- To assess the change in RFR, FFR and other physiologic parameters over time (subset of patients)

5. STUDY DESIGN

ULTRA-CTO is a prospective multicentre non-randomised investigator-initiated trial designed to enrol 200 subjects with an indication for PCI CTO.

After angiographically successful CTO PCI, intra-coronary physiologic assessment (RFR, FFR, CFR and IMR) and subsequent OCT of the CTO vessel will be performed. OCT may also be performed during a staged procedure when indicated (i.e. high contrast use, procedural duration, major dissection or other safety reasons according to the operator)..

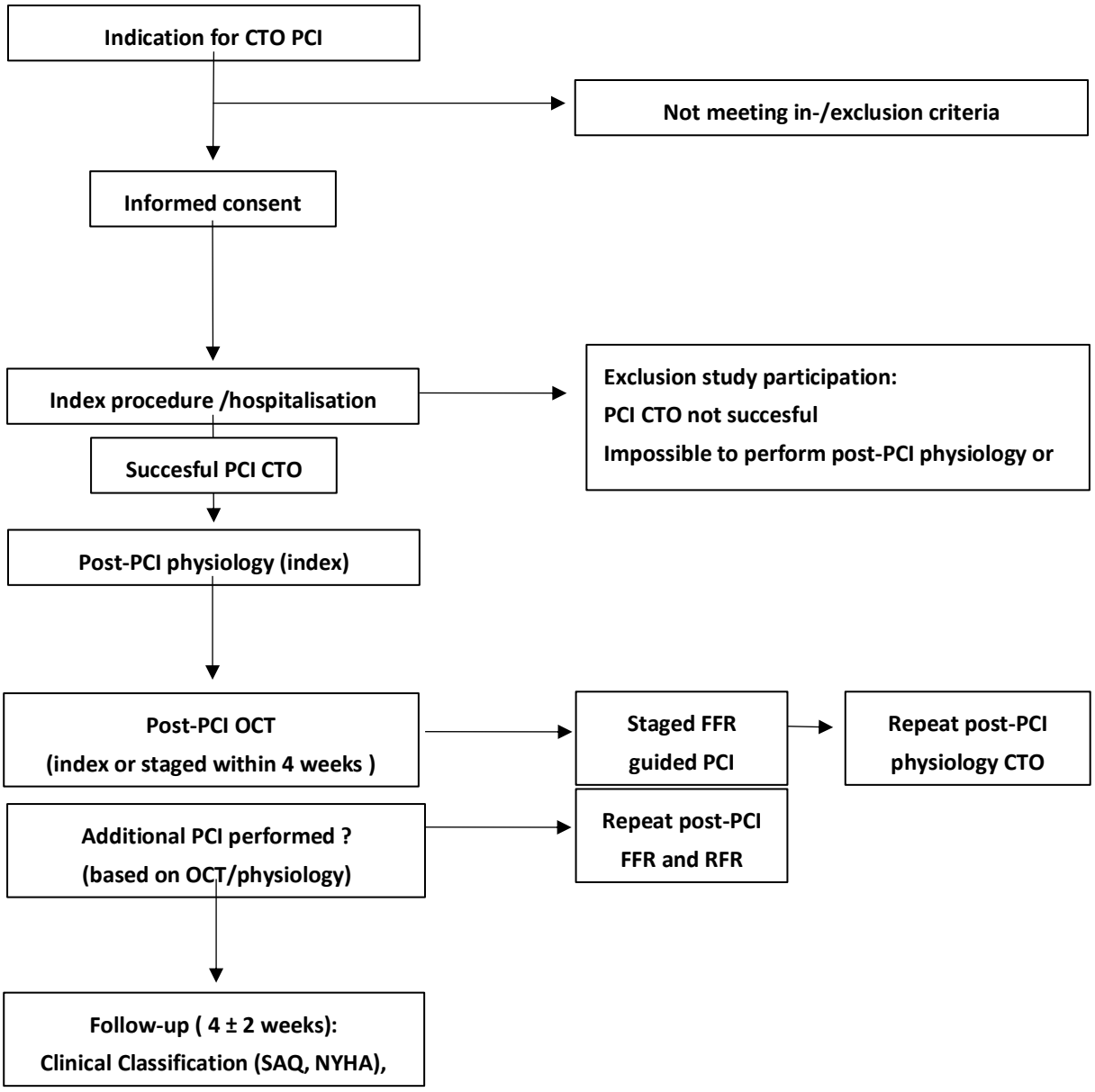
When intra-coronary physiologic assessment or OCT is not possible at all, the patients will not be included in the study (6.1).

When the operator decides to optimize the stent result (post-dilation or additional stenting), based on the OCT and/or physiology, post-PCI RFR and FFR should be repeated.

For patients with a remaining intermediate stenosis (angiographically 30-90%) in a non-CTO vessel or major side branch of the CTO vessel with diameter ≥ 2mm, clinically indicated FFR guided PCI will be planned within 4 ± 2 weeks. During this staged procedure, intra-coronary physiologic assessment (RFR, FFR, CFR and IMR) will be repeated in the CTO vessel for exploratory objectives (before additional PCI).

At 4 ± 2 weeks follow-up, the occurrence of cardiovascular events and clinical classification will be assessed for secondary objectives. See figure 2 for the study flow chart. A description of the primary and secondary endpoint(s) is included in paragraph 8.1.

Figure 2. Flowchart ULTRA-CTO



6. STUDY POPULATION

6.1 Inclusion criteria

In order to be eligible to participate in this trial, a subject must meet all of the following criteria:

1) Age 18 years and older.
2) Angiographically successful PCI CTO, which is considered acceptable and final by the operator, without any remaining lesion ≥ 30% proximal to the stented segment.
3) Possibility to perform physiologic measurements and OCT of sufficient quality.
4) Patients willing and capable to provide written informed consent.

6.2 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this trial:

1) Contra-indication for adenosine.

6.3 Screen failures

Subjects will be screened in hospital based on the information available. Subjects fulfilling the eligibility criteria and who have provided informed consent (IC) will be enrolled in the trial. Subjects who do not meet these criteria will be considered screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects and will be captured on trial electronic case report forms (eCRFs). No further clinical follow-up will be performed on these subjects.

6.4 Sample size calculation

This study is aimed at assessing a difference in the AUCs of paired data where each subject (with and without SSR) is subjected to FFR and RFR measurement post-PCI. This procedure compares two ROC curves for the paired sample case where in each subject has a known condition value (SSR) and test values from two diagnostic tests (RFR and FFR). The test values are paired because they are measured on the same subject.

Researchers wish to show that a new classification method works at least as well as the current method. The trial is powered for non-inferiority.

Based on previous studies the area under the curve of FFR in relation to SSR is assumed to be 0.90 and the incidence of SSR is assumed to be 40% [6, 7, 13].

Assuming an AUC of 0.90 for FFR, with a significance level α of 5%, and a non-inferiority limit margin 0.10 and an estimated prevalence of SSR of 40%, a total of 190 patients are needed to obtain a power of 80%. To account for a drop out of 5%, the sample size will be increased to 200 patients.

7. TREATMENT OF SUBJECTS

7.1 Overall treatment

Patients will be medically treated according to the international guidelines. Screening of eligible patients will be performed by the researchers. Eligible patients meeting the inclusion criteria will be asked for informed consent by one of the researchers. The PCI procedure, intra-coronary physiologic assessment and OCT will be performed according to local guidelines and common practice. The study-related measurements at index - and staged procedure are described below and more detailed in a designated Standard Operating Procedure (SOP).

7.1.1 Index procedure

1. After angiographically successful PCI of the CTO target vessel (no remaining lesion proximal or in-stent ≥ 30%, confirmed in two orthogonal projections with an angle ≥25 degrees apart), physiologic measurements must be performed in this vessel before additional OCT.

2. Physiologic assessment

   - Physiologic measurements must be performed using the Coroflow system (Coroventis) in combination with the PressureWire X (Abbott).
   - Physiologic measurements must be performed using intravenous adenosine and in the following order:

   1) Ensure adequate guide catheter position and adequate proximal venous access
   2) Administration of intracoronary nitrate (100 or 200 mcg)
   3) **RFR** 10 mm *proximal* to proximal stent edge.
   4) **Pd/Pa** (proximal arterial pressure/proximal aortic pressure without adenosine)
   5) **RFR** 10 mm *distal* to distal stent edge (without adenosine)
   6) **Pd/Pa** (distal arterial pressure/proximal aortic pressure without adenosine)
   7) Go to **CFR/IMR** mode: follow the steps and potential troubleshooting steps as indicated by the Coroventis software

   - Obtain the required hyperemia by infusion of intravenous adenosine with a dosage of 140 mcg/kg/min
     - **CFR** and **IMR** are calculated automatically.
   - Maintain hyperemia by continuing the infusion of adenosine

   8) Go to **FFR mode:**

- 10 mm *distal* to distal stent edge: FFR measurement after 20 heart beats during stable maximal hyperemia
- 10 mm *proximal* to proximal stent edge: FFR measurement after 20 heart beats during stable maximal hyperemia
- Stop infusion of adenosine
- **Check drift**: if drift >0.03 repeat physiologic measurements (description "drift")
- Additional OCT will be performed during the index procedure or staged when indicated..

3. OCT

- OCT imaging of the stented segment in the CTO target vessel; starting and visualizing 10 mm distal from the stent edge and ending/visualizing 10 mm proximal of the stent edge.
- Based on the OCT findings and/or physiologic assessment, stent optimization (postdilation or additional stent placement) to eliminate treatable components of SSR (as defined in appendix I) is left to the operator's discretion.
- Distal RFR and distal FFR should be repeated after stent optimization
- It must be noted on the designated form which component(s) of SSR were seen and treated by the operator.
- In case the operator decides to perform one or more additional interventions or decides to refrain from additional interventions, it will be noted on the designated form what motivated the operator to do so
- End of procedure.

7.1.2 Staged procedure (within 4 ± 2 weeks)

1) 1) OCT may be performed during a staged procedure when indicated (i.e. high contrast use, procedural duration, major dissection or other safety reasons according to the operator). See details for OCT at 7.1.1, section 3.
2) For patients with a remaining intermediate stenosis (angiographically 30-90%) in a non-CTO vessel or major side branch of the CTO vessel with diameter ≥ 2mm, clinically indicated FFR guided PCI will be planned within 4 ± 2 weeks. During this staged procedure, intra-coronary physiologic assessment (RFR, FFR, CFR and IMR) will be repeated in the CTO vessel for exploratory objectives (before additional PCI).
3) When the operator decides to optimize the CTO stent result (post-dilation or additional stenting), post-PCI RFR and FFR should be repeated.

7.2 Data transfer and analysis

All physiologic measurements and OCT recordings at index – and staged procedure for exploratory purposes (see paragraph 7.1.1 and 7.1.2) must be stored and the anonymized raw data must be send to Radboudumc Technology Center. Physiologic data will be checked and analysed by the researchers. The specific OCT analyses will be performed by the researchers.

8. METHODS

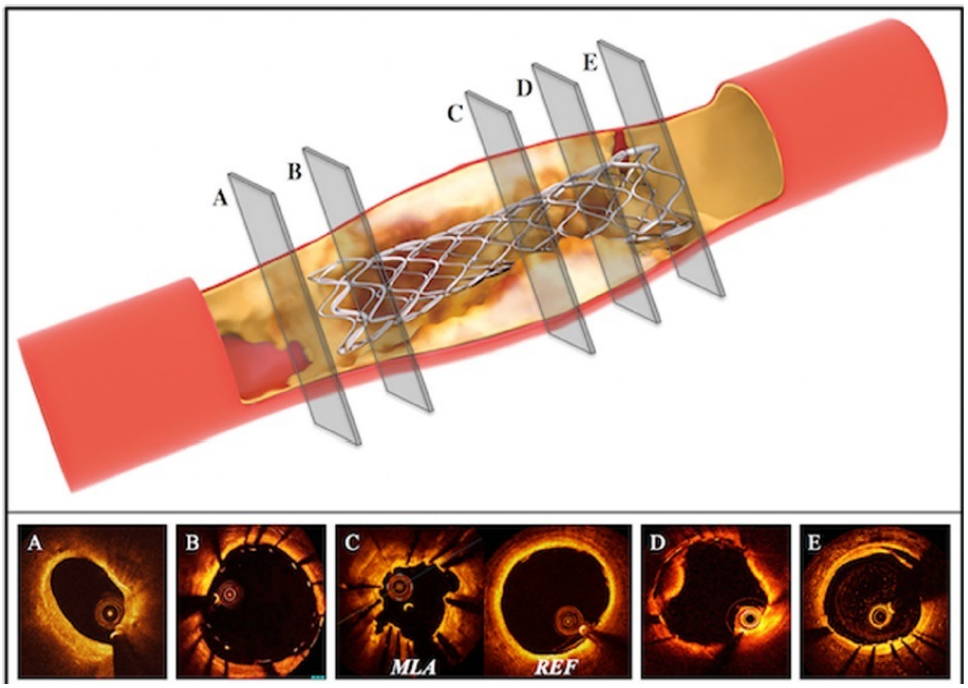
8.1 Study endpoints

8.1.1 Primary study endpoint

Primary endpoint is defined as:

The AUC of post-PCI RFR compared to the AUC of post-PCI FFR with regard to SSR.

Components of combined endpoint of SSR: Geographical miss (A), stent mal-apposition (B), stent mal-expansion (C) and intra-stent plaque protrusion/thrombus (D), edge dissection (E), as depicted in Figure 1. Definitions are described in appendix I.



8.1.2 Secondary study endpoints (definitions in appendix I)

Secondary endpoints are defined as :

- The predictive value of the RFR and FFR gradient across the stented segment with regard to SSR in CTO patients.
- The correlation between positive RFR (≤0.89) and positive FFR (≤0.80) with regard to SSR following angiographically satisfactory CTO PCI.
- The correlation between post-PCI physiology (RFR, FFR, CFR, IMR) and SSR with anginal complaints (SAQ score), NYHA and CCS classification and MACE at follow-up.

- The correlation between OCT and/or physiology findings and physician-decision making (perform or refrain from additional PCI)

8.1.3 Exploratory study endpoints

Exploratory endpoints are defined as:

- The change in RFR, FFR, Pd/Pa, IMR and CFR over time after CTO PCI in a subset of patients undergoing repeated physiologic assessment during a staged procedure

8.2 Randomisation, blinding and treatment allocation

There will be no randomisation and thus no blinding of the randomisation assignment.

8.3 Study procedures

The following study phases and procedures can be distinguished. See figure 3 for a schematic overview of all study procedures.

8.3.1 Baseline (pre procedure)

Screening of eligible patients will be performed by the researchers. Eligible patients meeting the inclusion criteria will be asked for informed consent by one of the researchers. The operator will be informed about participation in the trial.

Accordingly the following baseline characteristics will be obtained before start of the procedure: patient characteristics, medical history, risk factors, blood sampling (creatinine clearance), the indication for the CTO PCI and specific characteristics of the CTO.

8.3.2 Index Procedure

Several variables regarding procedure-related technical characteristics and the study-related measurements will be collected during the index procedure.

8.3.3 Discharge

Occurrence of (S)AEs including MACE and other complications will be registered at discharge.

8.3.1 Staged procedure

At 4 weeks, prior to the staged procedure, clinical classification, occurrence of (S)AEs including MACE and other events will be registered.

Similar to the index procedure, several variables regarding procedure-related technical characteristics and the study-related physiologic measurements will be collected during the staged procedure.

Study procedure	**Baseline (pre procedure)**	**Index procedure / hospitalization**	**Staged procedure (subset of patients)**	**Follow-up** 4 ± 2 weeks
Patient eligibility: Inclusion/exclusion	X[1]			
Patient informed consent	X[2]			
Baseline characteristics:				
- Patient characteristics	X			
- Blood sample (creatinine clearance)	X[3]			
- Use of medication	X			
- Medical history	X			
- Risk factors	X			
- Indication for CTO PCI	X			
- CTO characteristics	X			
PCI procedure variables				
- Technical characteristics		X	(X)	
- Physiology parameters		X	(X)	
- OCT		X	(X)	
Clinical classification[4]	X			X
Adverse events and complications		X	(X)	X

Figure 3. Study procedures

1. This study will be conducted in subjects fulfilling all inclusion criteria and none of the exclusion criteria (see paragraph 6.1 and 6.2).
2. Written informed consent will be obtained before enrollment in the trial.
3. Blood sampling (creatinine clearance) will be performed according to standard care. No more than 20 ml of blood will be obtained during each sample.
4. CCS classification, NYHA classification and at staged procedure also SAQ score, TLR, ST, MACE, TVF.

8.4 Withdrawal of individual subjects

Subjects can leave the trial at any time for any reason if they wish to do so without any consequences. The sponsor can decide to withdraw a subject from the trial for urgent medical reasons.

8.5 Replacement of individual subjects after withdrawal

Subjects will not be replaced after withdrawal from the trial unless a subject withdraw his or her consent before the start of procedure.

8.6 Premature termination of the study

A possible reason to prematurely end the study could be based on a decision of the sponsor. In that case a written statement will be prepared for the Medical Ethics Committee (MEC).

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the Medical Research involving Human Subjects Act (WMO), the sponsor will suspend the trial if there is sufficient ground that continuation of the trial will jeopardise subject health or safety. The sponsor will notify the accredited MEC without undue delay of a temporary halt including the reason for such an action. The trial will be suspended pending a further positive decision by the accredited MEC. The investigator will take care that all subjects are kept informed.

9.2 AEs and SAEs

9.2.1 Adverse events (AEs)

Adverse events (AEs) are defined as any undesirable experience occurring to a subject during the trial, whether or not considered related to coronary procedures. All AEs reported spontaneously by the subject or observed by the investigator or his staff will be recorded starting from enrolment onwards until follow-up or the staged procedure in a subset at 4 ± 2 weeks. Unchanged chronic conditions are not AEs and should not be recorded on the AE sheet.

9.2.2 Serious adverse events (SAEs)

A serious adverse event (SAE) is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization*;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

*<u>Hospitalization</u>:

Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, unless the admission is:

• planned before subject's inclusion in the trial (i.e. elective or scheduled surgery) or

• ambulant (shorter than 12 hours) or

• part of the normal treatment or monitoring of the studied disease (i.e. not due to a worsening of the disease)

9.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. AEs will not be followed up on once patients finish the study after 4 weeks.

SAEs will be collected and monitored throughout the entire course of the trial.

9.4 Adverse event reporting

Each AE or complication meeting the definition for SAE will be reported by site upon discovery to the Clinical Research Organization (CRO)/sponsor, within 24 hours of the site investigator's knowledge of the event. The accredited MEC will receive an overview of all SAEs annually.

10. STATISTICAL ANALYSIS

The principal features of the statistical analysis of the data are described in this chapter. A more technical and detailed elaboration will be written in a separate statistical analysis plan (SAP).

10.1 General methods

In general, statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, 25^{th} and 75^{th} percentile. Binary variables will be described with frequencies, percentages.

10.2 Analysis primary outcome

Primary objective of the study is to evaluate non-inferiority of with a pre-specified non-inferiority margin of 0.10 and AUC of 0.90. The hypothesis for testing non-inferiority is

$$H0: AUC_{RFR} - AUC_{FFR} \leq -0.10$$
$$H1: AUC_{RFR} - AUC_{FFR} > -0.10$$

Non-inferiority is established if the lower limit of a (1–2α) × 100% confidence interval of the difference between AUC_{RFR} and AUC_{FFR} is above -0.10 rather than the usual (1 − α) × 100% confidence interval. We will construct a 90% 2-sided confidence interval and use the lower bound to determine non-inferiority. If the lower boundary of the 90%CI of the difference is above -0.10 than RFR is non-inferior to FFR. If the lower boundary of the 90%CI of the difference is below -0.10 than RFR is inconclusive or inferior to FFR.

10.3 Analysis of secondary outcomes

Pearson *r* correlation and Spearman correlation coefficient rho (*r*) will be used to evaluate the degree of relationship between variables. For normally distributed variables, we will use the Pearson *r* correlation, while in case of skewed, ordinal data, the degree of association between variables will be quantified using Spearman correlation coefficient rho (*r*).

For repeated measurements (RFR, FFR, and other physiological parameters) we will use the paired t test for normally distributed variables and the Wilcoxon signed-rank test for skewed continuous data.

10.4 Safety analysis

The number, nature, frequency, severity and treatments will be described.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The trial will be conducted in compliance with the protocol, principles of the Declaration of Helsinki (2013), WMO, ICH-Good Clinical Practice, as well as local regulations and applicable regulatory requirements.

11.2 Recruitment and consent

Eligible patients meeting the inclusion criteria will be asked for IC by one of the cardiologists. Written IC will be obtained before the index PCI procedure. The information is intended to give each participant a thorough understanding of the purpose and the nature of the trial, the cooperation required, anticipated benefits, and potential hazards of the trial. The cardiologist also explains that the patient is completely free to refuse or to withdraw from the trial and that if he does so he receives standard treatment with the same degree of care.

11.3 Benefits and risks assessment and group relatedness

The anticipated benefit is improvement of our knowledge on how to optimize stent results in CTO PCI.

Because the pressure wires and OCT camera that are used for the study-related measurements are commonly used interventional tools, this poses no study-related additional risk for participating patients. International guidelines recommend the use of intravascular imaging for PCI guidance, especially in complex cases leading to lower myocardial infarction, TVR and cardiac mortality. Pressure wires are clinically indicated to identify hemodynamic significant (remaining) lesions that needs to be revascularized. Due to study-related measurements the procedures will be moderately prolonged, most likely by approximately 15 minutes. With minimal effort and risk, subjects included in this trial are able to contribute to research to that may improve the treatment of CTOs, which may have large impact on clinical practice and guidelines.

11.4 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor will arrange an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the trial.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Electronic Case Report Forms (eCRFs) have been developed to capture the trial information outlined in this protocol. Data from these eCRFs will be used in the analysis of trial results. Modification of the eCRFs will only be made if deemed necessary by the sponsor.

Data entered in to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries and other hospital or physician office/clinic documents. If no standard hospital or office document exists to capture some of the information that may be unique to this trial, a worksheet may be developed to record this information and be used as a source document. This worksheet needs to be signed by the person responsible for the registered data on the worksheet at the given site. These source documents will serve as the basis for monitoring the eCRFs. Electronic patient records will be considered as source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records will have to be printed and added to the paper patient file. A print-out of the eCRF cannot be used as source documentation.

The investigator will maintain all records pertaining to this trial for fifteen years following trial completion, or as otherwise instructed by the CRO, or per local requirements whichever is longer. Published data will not be traceable to the individual patient.

12.2 Monitoring and Quality Assurance

CRO and/or designee will monitor the trial over its duration according to the pre-specified monitoring plan. This will be done by means of personal visits to the site's facilities, telephone contacts to the investigator or designee, and/or remotely through the internet-based database with verification of the source data. The trial monitor may inspect all documents and required documents that are maintained by the investigator/site, including medical records (office, clinic or hospital) for the subjects in this trial. The investigator/site will permit access to such records.

Source documentation must be available to substantiate proper IC procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse event and accuracy of data collected on case report forms. A monitoring visit log will be maintained at the site. The investigator and/or research coordinator will be available for monitoring visits. It is expected that the investigator will provide the trial monitor with a suitable working environment for review of trial-related document.

A comprehensive, integrated data management plan, including on-line queries and (remote) data cleaning will be implemented to ensure the integrity of the data. All changes to the database will be tracked by an audit trail.

All site personnel will be trained on the protocol and internet-based database prior to the initiation of the trial at each respective site. Only trained (site) personnel will receive access to the internet-based database by means of a personalized username and password.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited MEC has been given. All amendments will be notified to the MEC that gave a favorable opinion.

12.4 Annual progress report

A summary of the progress of the trial will be submitted to the accredited MEC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited MEC of the end of the trial within a period of 8 weeks. The end of the trial is defined as the last patient's last visit.

The sponsor will notify the MEC immediately of a temporary halt of the trial, including the reason of such an action.
In case the trial is ended prematurely, the sponsor will notify the accredited MEC within 15 days, including the reasons for the premature termination.

Within one year after the end of the trial, the sponsor will submit a final trial report with the results of the trial, including any publications/abstracts of the trial, to the accredited MEC.

12.6 Publication policy

This trial will be registered at www.clinicaltrials.gov. The results of this prospective, multicentre, non-randomised investigator-initiated trial with a non-inferiority design are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses. The publication rights in regard to the main results of the trial, i.e., regarding the primary and secondary objectives, belong to the sponsor. No individual investigator may publish on the results of this trial, or their own patients, without prior approval from the sponsor. A minimum number of subjects per site needs to be included in the trial by the investigator in order to be considered as co-author for publication. This is further defined in a separate clinical trial agreement with each participating site.

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14. APPENDIX I: RELEVANT DEFINITIONS

Angiographic success	Successful PCI of the target lesion with a residual stenosis of less than 30% angiographically.
CCS	Canadian Cardiovascular Society.
Clinical classification	CCS classification, NYHA classification and at staged procedure also SAQ score, TLR, ST, MACE, TVF.
CTO	Lesion exhibiting TIMI 0-1 flow in a native coronary artery with an occlusion duration > 3 months[14].
Geographical miss	Incomplete stent coverage of plaques within 10 mm distal or proximal to the stent edges with residual stenosis on OCT of ≥ 50% cross-sectional area (CSA) as compared to the reference lumen area.
Intrastent plaque-protrusion	Distance between strut surface and the greatest extent of protrusion >100 µm[15].
Intrastent thrombus-protrusion	Irregular mass protruding into lumen >250 µm at the thickest point; thrombus may not be connected to the vessel wall[15].
MACE	Composite endpoint of all-cause mortality, myocardial infarction and any coronary revascularization.
Microvascular dysfunction	IMR > 25.
Myocardial infarction	Defined according to the expert consensus document[16].
NYHA	New York Heart Association.
Pd/Pa	Pressure-distal / pressure-aorta = ratio of mean resting distal coronary pressure to aortic pressure
Reference lumen area	The average of the two largest lumen areas proximal and distal to a stenosis but within the same segment (usually within 10 mm)[17].

Repeat revascularization	PCI or CABG (with specification of target vessel revascularization).
SAQ	Seattle Angina Questionnaire[12].
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
Stent edge dissection (clinically relevant)	Dissection width ≥ 200 µm, and/or dissection angle ≥ 60°, and/or dissection length > 0.67 mm[15]. Stent edge dissections meeting these criteria are considered components of SSR.
Stent edge dissection (other)	Stent edge dissections not meeting the criteria of clinically relevant stent edge dissections.
Stent malapposition	Distance from the center of the stent blooming artifact to the vessel wall of ≥ 200 µm[15] and present in at least 5 consecutive OCT frames[6].
Stent thrombosis	Presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent[18].
Stent underexpansion	In-stent minimal lumen area less than 90% of the average reference lumen area[15].
TLR	Re-intervention of the treated segment within 5 mm proximal or distal to the stent[18].
TVF	Composite endpoint of cardiac death, target-vessel myocardial infarction and clinically driven target-vessel revascularization.