Team-based Interventional Triage in Acute Coronary Syndrome Based on Non-Invasive Computed Tomography Coronary Angiography Versus Invasive Coronary Angiography – a Randomized, Non-Inferiority Trial

PROTOCOL

Version 5.1

November 1, 2024

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Registration

Clinicaltrials.gov: NCT06101862

Ethics committee: H-23024848

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Protocol amendments

Date	Version	Amendments
November, **2022**	1.0	• Major revisions.
May 30, 2023	2.0	• Added description of recruitment and trial logistics.
June 25, 2023	3.0*	• Minor changes.
December 4, 2023	4.0	• Added inclusion criteria (ECG changes or troponin elevation) • Added exclusion criteria (recent prior CT or ICA) • Added definition of 'hospitalization with refractory angina' and 'hospitalization with heart failure' • Added possibility to use electronic signature for consent • Added summary section • Added amendments section • Revised study group section to include information on individual members of steering committee and participating centers • Reordered secondary outcomes • Changed title to include information on comparator group and non-inferior nature of trial • Added general criteria that should be used to determine indication for revascularization • Adjusted and simplified description of CT-guided PCI • Other minor changes
January 8, 2024	4.1	• Minor changes to financial aspects.
October 2, 2024	5.0	• Minor changes to summary • Added definition of valid ischemic ECG changes • Added exclusion criteria (probable type 2 myocardial infarction, severe valve disease, history of SCAD) • Added statistician to study group and updated steering committee • Revised Statistics in accordance with the statistical analysis plan. • Revised prioritization of secondary outcomes and added section "other endpoints" • Added secondary outcomes (unplanned coronary revascularization, time to revascularization or to decision not to perform revascularization) • Added subgroup analyses • Added definition of outcomes (non-fatal myocardial infarction, cardiovascular death, unplanned revascularization, total radiation dosage) • Added the 'Learning feedback' section • Added section (failure to conduct the allocated examination) • Changed sponsor to Rigshospitalet due to organizational changes.
November 1, 2024	5.1	• Added section 5.5 with scientific and ethical considerations regarding protocol amendments.

*Ethical approval and randomization of first patient.

Summary

Background

Coronary computed tomography angiography (CCTA) is a widely accepted diagnostic test for patients suspected of chronic coronary syndromes. So far, no large-scale randomized trial has examined the performance of CCTA as the alternative to invasive coronary angiography (ICA) in hospitalized patients with non-ST-segment elevation acute coronary syndrome (NSTEACS).

Hypothesis

We hypothesize that CCTA is non-inferior to ICA in terms of major adverse cardiac events at one year.

Methods

The TRACTION trial is an investigator-initiated, 1:1 randomized, assessor-blinded, non-inferiority trial. Patients (n = 2,300) admitted with NSTEACS and an indication for ICA will be randomized to CCTA and team-based interventional triage (intervention group) versus standard-of-care with conventional ICA (control group). Team-based interventional triage is performed with conference between an interventional cardiologist and a CCTA cardiologist. Enrollment is planned for 3 years.

Endpoints

The primary endpoint is major adverse cardiac events consisting of all-cause mortality, non-fatal myocardial infarction, hospitalization with refractory angina, or hospitalization with heart failure at 1 year. Other endpoints include cardiovascular death, revascularization, symptom score and quality of life, radiation exposure, adverse events, other clinical endpoints, and resource utilization.

Support

The trial is supported by The Danish Heart Association (2023-12398-22211).

1 Background

Ischemic heart disease is the most frequent cause of death world-wide and accounts for 12-14% of all deaths in the European Union.[1] Hospitalization for acute myocardial infarction, the most severe presentation of ischemic heart disease, occurs in more than 600.000 persons annually in the European Union.[1] The yearly health care costs in the European Union for treatment of ischemic heart disease total 18.9 billion €, of which 10.4 billion € are for in-patient care.[1] Expenses for hospital admission for acute myocardial infarction are high, estimated at 17.000 € per admission[2], and are primarily related to the number of days spent in hospital and the use of invasive examinations.

In the majority of patients admitted with an acute myocardial infarction (non-ST-elevation myocardial infarction) or unstable angina pectoris, collectively referred to as non-ST-elevation acute coronary syndrome (NSTEACS), it is recommended to perform invasive coronary angiography (ICA) while the patient is still hospitalized.[3] The ICA determines the invasive treatment strategy, i.e., identifies patients who require revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to reduce the risk of arrythmias, heart failure, and death.

Since only selected hospitals perform ICA, patients with NSTEACS often require interhospital transfers and prolonged hospital stays. Additionally, ICA carries a risk of invasive complications such as bleeding, vascular damage, arrythmia, or death. It would be beneficial to introduce a safe, broadly available, non-invasive, and affordable alternative to ICA to determine the invasive treatment strategy in patients with NSTEACS. CCTA would be especially valuable for the considerate proportion of patients with NSTEACS who do not require revascularization.[4]

An alternative to ICA is coronary computed tomography angiography (CCTA), which is a non-invasive procedure that can be conducted quickly and is widely available. CCTA is the only non-invasive examination that visualizes the coronary arteries in sufficient detail to evaluate the severity of ischemic heart disease. While CCTA is a well-established first-line examination for patients suspected of chronic coronary syndromes, there is only limited evidence supporting its use in the acute setting.

In patients with non-ST-elevation myocardial infarction, studies suggest that CCTA can reduce the need for ICA, that CCTA and ICA have similar prognostic strength[5,6], and that CCTA can support invasive cardiologists in guiding the revascularization technique.[7] In an observational study, CCTA was performed in 1,023 patients with non-ST-elevation myocardial infarction.[8] A high agreement between CCTA and ICA was found (sensitivity 96.5% and specificity 72.4%), and the prognostic strength of CCTA was comparable to that of ICA after 4.2 years of follow-up.[6] In a randomized trial of 1,748 patients suspected of NSTEACS, patients were randomized to either standard-of-care or CCTA.[5] This trial found a 20% reduction in the need of ICA in the CCTA-group and no difference in rates of revascularizations and myocardial infarctions at 1 year of follow-up. Only 60% of patients in the standard-of-care group were examined with ICA, signifying a low-risk population where a proportion of the patients turned out not to have NSTEACS. Only one small randomized trial of patients with verified non-ST-elevation myocardial infarction has been conducted.[9] In this trial, 207 patients were randomized to either ICA, CCTA or cardiac MRI. No differences in clinical outcomes or complications were found between the groups.

Thus, there are no large-scale randomized trial examining the performance of CCTA as an alternative to ICA in hospitalized patients with NSTEACS. If CCTA could replace ICA as the routine diagnostic procedure in patients with NSTEACS, it would reduce the risk of complications related to ICA, improve patient comfort, and speed-up the decision-making process. Furthermore, healthcare costs would be reduced due to a reduction in admission time, fewer interhospital transfers, and less use of personnel and equipment for invasive examinations.

1.1 Aim and hypothesis

We aim to compare the use of CCTA versus conventional ICA as the initial diagnostic examination in patients hospitalized with NSTEACS and a clinical indication for inpatient ICA. CCTA or ICA will be used to decide the invasive treatment strategy. For patients randomized to CCTA, the treatment strategy will be decided by a team of invasive and non-invasive cardiologists (coronary CT-team).

We hypothesize that CCTA is non-inferior to ICA in terms of the risks of major adverse cardiac events within one year.

2 Methods

2.1 Trial design

The TRACTION trial is an investigator-initiated, 1:1 randomized, assessor-blinded, non-inferiority trial. Patients hospitalized with NSTEACS with an indication for inpatient ICA will be offered inclusion and randomized to:

1. CCTA and team-based interventional triage (intervention group): Participants will be examined as early as possible during admission. The CCTA will be discussed at a coronary CT-team conference to determine the treatment strategy and guide the interventional procedure.
2. Standard-of-care with conventional ICA (control group): Participants will be examined with ICA as early as possible during admission.

Regardless of the allocation, the treatment decision after the ICA (in control group) or after the coronary CT-team conference (in intervention group) will be either medical treatment, PCI, or CABG. For patients where CABG is the preferred strategy, final decision of treatment strategy will be taken by the multidisciplinary Heart Team conference involving cardiac surgeons, as is routine. All participants will receive medical treatment according to guidelines and referred to cardiac rehabilitation after discharge.

2.2 Eligibility criteria

2.2.1 Inclusion criteria

- Hospitalized with NSTEACS and an indication for inpatient ICA
- Elevated troponin according to local hospital standards or ischemic ECG changes defined as transient ST-segment elevation, persistent or transient ST-segment depression, T wave

abnormalities including hyperacute T waves, T wave inversion, biphasic T waves, flat T waves, or pseudonormalization of T waves.[3]

- Written informed consent

2.2.2 Exclusion criteria

- Very high risk criteria or clinical instability requiring immediate ICA (including persistent chest pain, severe arrhythmias, or hemodynamic instability)[3]
- History of PCI or CABG
- eGFR < 30 mL/min/1.73m^2
- Probable type 2 acute myocardial infarction
- Severe valvular heart disease as primary diagnosis or potential need for valve intervention
- History of spontaneous coronary artery dissection
- Expected poor quality of the CCTA according to local standard
- Prior CCTA or ICA during index admission or within 1 week before admission
- Known allergy to beta-blockers or contrast agent
- Pregnant or nursing
- Previously randomized in this trial

2.3 Endpoints

2.3.1 Primary endpoint

- A combined endpoint of major adverse cardiac events (MACE) at 1 year, consisting of:
    - All-cause mortality
    - Non-fatal myocardial infarction
    - Hospitalization with refractory angina
    - Hospitalization with heart failure

2.3.2 Key secondary endpoints

- Composites of the primary endpoint at 1 year
- Cardiovascular death at 1 year
- Unplanned coronary revascularization after index hospitalization at 1 year
- Quality-of-life measured by EQ-5D-5L[10] at 1 year
- Angina symptom burden measured by Seattle Angina Questionnaire[11] at 1 year
- Total radiation dosage during index admission
- Length of index admission

2.3.3 Other endpoints

- Stroke at 1 year
- Any coronary revascularization at 1 year
- Serious adverse events associated with the diagnostic coronary examination (ICA or CCTA) before 1st hospital discharge
- Procedure-related complications associated with ICA, CCTA, PCI or CABG before 1st hospital discharge
- BARC 3 or 5 bleedings before 1st hospital discharge
- Hospitalization for any cardiac reason or related to cardiovascular treatment at 1 year
- Time to revascularization or to decision not to perform revascularization
- Contrast dose during index admission
- Invasive or non-invasive examinations for ischemic heart disease at 1 year (CCTA, ICA, cardiac MRI, Rb-PET, SPECT)
- Time from randomization to examination (initial diagnostic testing, ICA or CCTA)
- Time from index admission to examination (initial diagnostic testing, ICA or CCTA)
- Total cost of index hospitalization, all cardiovascular visits, hospitalizations, and procedures at 1 year.
- Total radiation dosage of all cardiac diagnostic examinations and interventions at 1 year

- Days alive out of hospital at 28 days following index admission

Supplemental analyses will be conducted evaluating outcomes stratified by gender. The population will be followed for up to 10 years by merging the dataset with data from the national registries to identify clinical endpoints and to further describe the population.

2.3.4 Subgroup analyses

The following subgroup analyses are planned

- Male versus female sex
- Age ≥ 64 years versus age < 64 years
- Elevated troponin versus troponin not elevated (elevated above upper reference level as defined by the local assay)
- GRACE[12] score ≤ 140 versus GRACE score > 140
- History of atherosclerotic cardiovascular disease (ASCVD) versus no history of ASCVD (defined as coronary artery disease, ischemic stroke, peripheral artery disease, or aortic disease)
- History of heart failure versus no history of heart failure
- Diabetes mellitus versus no diabetes mellitus
- Current or former smoker versus never-smoker
- Randomized at invasive center versus randomized at non-invasive center
- First 50% of patients versus last 50% of patients

2.3.5 Qualitative evaluation

To explore how patients experience the different treatment strategies, 15 patients from each randomization group will be interviewed using qualitative methods. A semi-structured interview guide will be developed and used and the data will be analyzed using content analysis.

2.3.6 Definition of selected endpoints

All-cause death:

Death from any cause.

Non-fatal myocardial infarction:

Non-fatal myocardial infarction is defined according to the fourth universal definition of myocardial infarction which require detection of a rise and/or fall of troponin values with at least 1 value above the 99th percentile URL and what at least one of the following:[13]

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves
- Imaging evidence of a new loss of myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

Non-fatal myocardial infarction includes peri-procedural myocardial infarction, defined as: A rise in high-sensitive cardiac troponin levels to ≥ 35 times the upper reference limit within 48 hours after PCI or CABG and at least one of the following: ECG with new significant Q-waves or equivalent, flow-limiting angiographic complications, or new loss of myocardial contractility on imaging.[14] This definition is applicable in both patients with normal or elevated (stable or falling) baseline cardiac troponin levels.

Hospitalization with refractory angina: Acute hospitalization due to chest pain not associated with myocardial infarction and a clinical suspicion of myocardial ischemia resulting in invasive coronary angiography.

Hospitalization for heart failure: Presentation to an acute care facility requiring at least 6 hours hospitalization with an exacerbation of heart failure requiring treatment – meeting the following criteria (at least one from each group of criteria):

a. Symptoms of heart failure: Worsening of dyspnea, worsening of orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue/worsening exercise tolerance
b. Signs of heart failure: rapid weight gain, pulmonary edema or rales, elevated jugular venous pressure, radiologic/clinical signs of heart failure, peripheral oedema, increasing abdominal distension or ascites, 3 gallop, hepatojugular reflux, elevated BNP or N-terminal pro-BNP
c. Treatment: Intravenous diuretics, initiation, or intensification (doubling) of maintenance diuretics, intravenous vasodilators, intravenous inotropes, dialysis or ultrafiltration, intra-aortic balloon pump.

Cardiovascular death: Cardiovascular death is defined as death resulting from cardiovascular causes according to ARC-2 criteria[15]:

- Death caused by acute myocardial infarction.
- Death caused by sudden cardiac, including unwitnessed, death.
- Death resulting from heart failure.
- Death caused by stroke.
- Death caused by cardiovascular procedures.
- Death resulting from cardiovascular hemorrhage.
- Death resulting from other cardiovascular cause.

Unplanned coronary revascularization: Any elective or non-elective CABG or PCI of any coronary artery that was not planned to be conducted after index admission.

Total radiation dosage: Estimated cumulative effective radiation dosage measured in mSv of all cardiac diagnostic or interventional procedures involving ionizing radiation, i.e., ICA, PCI, or CCTA, and PET or SPECT scans. We will convert all recorded exposures to estimated effective dose (measured in mSv) and calculate the sum. The conversion factor used for dose-area-product recorded during ICA or

PCI will be 0.207 mSv/(Gy·cm2) [16] and the conversion factor used for dose-length-product recorded during CCTA will be 0.014 mSv/(mGy·cm). [17] The effective dose from nuclear cardiac scans will be calculated using the conversion factors from The Society of Nuclear Medicine and Molecular Imaging guidelines. [18]

Serious adverse events (SAE): The definition of a serious adverse event is modified from the 'International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice' (ICH-GCP) [19], which is any untoward medical occurrence that either:

- Resulted in death,
- Was life-threatening,
- Required inpatient hospitalization,
- Prolonged existing hospitalization more than 24 hours,
- Resulted in persistent or significant disability, or
- Jeopardized the participant

Likely events are death, cardiac arrest, other serious arrythmia, bleeding (BARC type >2), stroke, or new non-fatal acute myocardial infarction.

Procedure-related complications: Serious and non-serious adverse events related to a diagnostic or interventional cardiac procedure as adjudicated by the Clinical Events Adjudication Board.

Time to revascularization or to decision not to perform revascularization: Time from randomization to 1) revascularization (when revascularization has been performed for all treated lesions during index admission) for patients treated with PCI or CABG, or 2) decision not to perform revascularization for patients not treated with PCI or CABG (at time of ICA with decision not to revascularize or at time of coronary conference after CCTA with decision not to perform ICA or PCI).

2.4 Recruitment of participants

The trial is conducted at several invasive centers in with participation from selected referring non-invasive hospitals.

After the diagnosis of NSTEACS has been established, patients may be recruited to the study in 3 ways:

1) If the patient has been directly admitted to an invasive center, the allocated examination will be performed at the invasive center.
2) If the admitting hospital is a non-invasive hospital with local inpatient CCTA availability, the CCTA (if randomized to CCTA) will be performed locally at the admitting hospital.
3) If the admitting hospital is a non-invasive hospital without inpatient CCTA availability, the patient is transferred to an invasive center for examination as is routine.

At first study-related contact with eligible patients, potential participants will receive oral information about the study and offered the needed period for reflection and further conversation about the study until informed consent is obtained. Potential participants will be made aware that it is possible to bring a person to assist in the conversation. The person who provides the oral information will be authorized and will have the professional prerequisites for communicating the content and be directly associated with the study. If the patient is interested in participating in the trial, written information about the study is provided and written informed consent is obtained.

Written consent will either be obtained traditionally (pen and paper) or electronically (singing an exact replica of the consent form using a finger or a mouse on a screen to produce a signature) in the secure, web-based electronic case report form (REDCap) hosted by the Capital Region of Denmark. Traditionally signed consent forms will be stored in a locked box in a locked secure room and electronically signed consent forms will be stored on the secure server in REDCap.

Information used to assess the eligibility of potential participants will be passed from the treating physicians to study personnel tasked with informing patients and obtaining consent. Hospital records of potential patients will only be accessed by study personal after obtaining consent.

A patient can be withdrawn from the study at any time if it is the wish of the patient or if it is clinically indicated. In any circumstance every effort should be made to document patient outcome, if possible.

Participation in the study may be discontinued by study personnel if the patient's general condition contraindicates continuing in the study, as judged by the investigator.

2.5 Randomization

Online randomization is performed to decide allocation. Computer generated central randomization will be performed with the use of a Web-based system (REDCap). Block randomization will be used with randomly permuted block of sizes of 2, 4, and 6, without stratification.

2.6 Study procedures

2.6.1 CCTA and team-based interventional triage (interventional group)

State-of-the-art CCTA is performed as quickly as possible after randomization. Logistics of CCTA, conference, and potential patient transfer will be arranged to ensure that PCI (if indicated) can be performed within 48 hours from admission. An electrocardiography-gated calcium score and contrast enhanced CCTA will be performed in all cases, according to best practice. Staff will be instructed to reduce radiation exposure and heart rate, and to use sublingual nitro glycerin and beta-blockers if needed. Patients will be monitored for adverse events for 30 minutes.

CCTAs will be reported according to the Society of Cardiovascular CT guidelines and the American Heart Association coronary artery segment model. Severity of atherosclerotic disease will be characterized as no (cross sectional stenosis <10%), mild (10-49%), moderate (50-70%), or obstructive coronary artery disease (>70% or >50% in the left main stem).

Analysis will be performed by a cardiologist specialized in CCTA shortly after the scan has been completed. Study-specific training will be completed by all cardiologists performing CT-readings for the trial.

An on-call group of invasive and CCTA-specialized cardiologists will be established at each invasive center. This group will conduct ad hoc conferences or teleconferences with the treating physicians at

the admitting hospital (treating physician and CCTA cardiologist from the admitting hospital, and CCTA cardiologist and invasive cardiologist at the invasive center, together called the coronary CT-team), to decide the treatment strategy for participants in the intervention group. Core responsibilities of the team will be to refine and maintain the ability to perform visitation of patients based on the CCTA and to strengthen the collaboration between invasive and non-invasive cardiologists. A consistently high quality will be ensured by conducting joint training sessions and frequently reviewing complex or illustrative cases.

The team conference will have access to all relevant patient information, including any prior CCTAs or ICAs, and the option to do additional 3D reconstructive analyses on the CCTA data. The conference decision for management will be either medical treatment, PCI, or CABG.

A decision to proceed with revascularization will be made in cases with obstructive coronary disease in one or more significant vessels, if reasonable, considering technical suitability, clinical, and paraclinical findings. In general, vessels of ≥2.5 mm in diameter will be considered significant. If CABG is assessed to be potentially the best strategy, a diagnostic ICA will be performed before Heart Team conference with cardiac surgeons, as is routine. In cases where the CCTA is non-diagnostic, an ICA will be performed to determine treatment strategy.

A decision of medical treatment will thus be made in cases with no coronary artery disease, non-obstructive coronary artery disease, or obstructive coronary artery disease where revascularization is either not indicated or not feasible.

If PCI or ICA is indicated in a patient examined with CCTA at a non-invasive hospital, the patient will be transferred to an invasive center without unnecessary delay.

If PCI has been decided, the CCTA images will be used by the interventional cardiologist to plan and guide the procedure. Lesion location and length, plaque distribution, extent and localization of calcified plaques, as well as bifurcations and vessel tortuosity will be assayed. CCTA might also be used to optimize viewing angulations and deciding guiding catheter. Angiography of arteries without disease on CCTA can be deferred.

2.6.1.1 Learning feedback

To achieve and sustain a high technical level of CCTA-imaging and consistent clinical quality in CT-conference decisions and patient management, recurring case-based review sessions will be conducted among participating clinicians and both ad hoc and systematic feedback will be provided to participating sites.

Quantitative information on technical CCTA quality and patient management will be provided to participating sites for the first 25 patients randomized to CCTA at each site, after this only qualitative case-based feedback will be provided.

2.6.2 Invasive coronary angiography (control group)

Patients not already admitted to an invasive center are transferred to the invasive center (Roskilde or Rigshospitalet), where ICA is performed according to routine. The procedure is performed in local anesthesia. Radial artery access is preferred, using 5 or 6 French sheaths, but femoral access is allowed. Patients are anticoagulated with 70 IE/kg Heparin and treated with anxiolytics on an as-needed basis. Angiograms are performed of the right and left coronary arteries with all segments visible in at least two projections. Care is taken to obtain the lowest reasonable radiation dose, using low-intensity radiation if possible, using the lowest reasonable frame rate, avoiding zoom, and using appropriate image collimation.

After ICA has been performed, preferred management strategy will be determined based on the images and the clinical information by the treating invasive cardiologist, as is routine. The management will be either medical treatment, PCI, or CABG. The decision to proceed with revascularization will be made based on the same criteria as for patients examined with CCTA. In case PCI is chosen, ad hoc PCI will in most cases be performed in direct continuation of the ICA, or in some cases with a staged invasive procedure during the same admission. If CABG is the preferred management strategy, a heart-team conference with cardiac surgeons will be performed to confirm final strategy.

Hemostasis will be obtained with compression wrist bands in the case of radial access, and arterial closure devices in the case of femoral access. Patients will be closely monitored for complications for at least 4 hours after the procedure.

2.6.3 Failure to conduct the allocated examination

The reason for failing to conduct any examination (whether no examination was performed or if the patient underwent a different examination than allocated) will be documented.

2.6.4 Echocardiography

A standardized transthoracic echocardiography according to guidelines from the Danish Society of Cardiology will be performed during index admission [20] prior to examination as is routine.

2.6.5 Antithrombotic treatment

According to national guidelines, patients with NSTEACS will initially be treated with acetylsalicylic acid (ASA) 300 mg orally, followed by 75 mg daily and fondaparinux 2.5 mg subcutaneous daily, until the invasive treatment strategy has been decided. The antithrombotic treatment strategy at index examination will be the same regardless of randomization:

- Patients without coronary artery disease will be examined for alternative etiologies and the antithrombotic treatment strategy will be decided on an individual basis.
- Patients with coronary artery disease (obstructive or non-obstructive) who do not require revascularization, will typically be treated with ASA 75 mg daily life-long and ticagrelor 90 mg twice daily for one year.
- Patients undergoing PCI, will typically be treated with ASA 75 mg daily life-long and ticagrelor 90 mg twice daily or prasugrel 10 mg daily for one year.

- Patients undergoing CABG, will typically be treated with ASA 75 mg daily life-long and an adenosine diphosphate receptor inhibitor (clopidogrel, ticagrelor or prasugrel) according to the heart team decision.
- Patients with an indication for anticoagulant therapy, will be treated with an anticoagulant life-long and clopidogrel 75 mg daily for one year, and ASA for a shorter period in accordance with guidelines and an individual assessment.

The strategy as described above can be modified on an individual basis by the treating physicians.

2.6.6 Spontaneous coronary artery dissection (SCAD)

Patients with previous SCAD are excluded from the trial as their invasive management differ from other patients with NSTEACS. On the other hand, patients that are suspected of SCAD based only on their clinical characteristics are still eligible to be included in the trial. If randomized to CCTA, the management of patients with suspected SCAD will differ from standard management in some regards depending on the CCTA findings.

If significant atherosclerotic coronary disease is detected, patients are handled as a normal NSTEACS.

If CCTA-findings are highly suggestive of SCAD (e.g., distal, tapered, long stenosis in otherwise normal vessels or obvious dissections), patients will be managed according to national SCAD guidelines, including conservative management unless signs of major-vessel occlusions and recommending prolonged hospital stay.

If CCTA is without atherosclerosis and without findings suggestive of SCAD, patients will be managed conservatively as NSTEACS. Considering the expected lower negative predictive value of CCTA compared with ICA for SCAD, SCAD will not be considered fully excluded, and these patients will be kept admitted for a prolonged hospital stay to at least 2 days without chest pain. The possibility of SCAD will be strongly considered in case of repeat admission with chest pain.

2.7 One-year follow-up

Outcomes will be obtained by telephone contact and by reviewing electronic records by dedicated study personnel. Additionally, all participants will be sent an electronic questionnaire to e-Boks to enhance the evaluation of the clinical outcomes and to gather data on quality of life and angina burden.

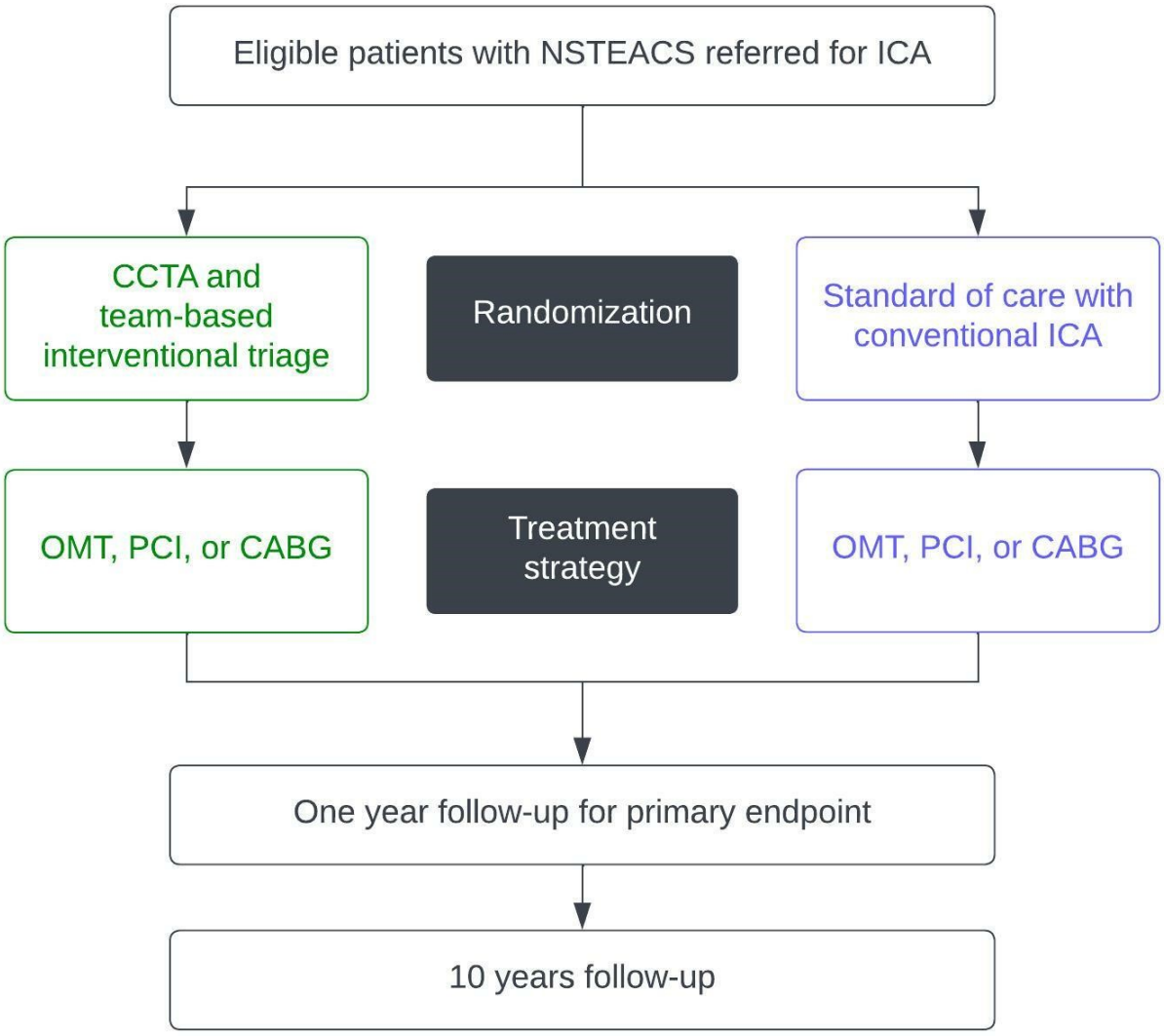
2.8 Clinical Endpoint Adjudication Board

An independent Clinical Endpoint Adjudication Board will perform blinded adjudication of the clinical endpoints that are associated with an element of expert evaluation. The adjudication board will evaluate all possible serious adverse events and complications that could be components of the primary or secondary endpoints. Dedicated study personnel will collect information on all potentially serious adverse events, and the board will be presented with these. The board will decide whether the event should be classified as serious, procedure-related, or both, based on this information.

2.9 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will be presented with an interim report when 25% and when 50% of planned patients have been randomized. The Data and Safety Monitoring Board will provide recommendations regarding the continuation of the study, taking into consideration the safety of the trial subjects and the continued scientific merit of the trial.

2.10 Trial flowchart



2.11 Patient and public involvement

This study will use public involvement with inspiration from the UK national standards of public involvement.[21] Public involvement can make a difference in research studies and involving the public can improve the quality of research and ease implementation afterwards. From existing patient-involvement panels at the participating centers, five persons will be invited to a user involvement group for this study. They will take part in activities such as review of patient information material,

discussion of recruitment strategy, and they will be invited to meetings where the results will be presented and discussed. Two patients will be invited to join the steering committee of the study.

3 Statistics

Please see the statistical analysis plan. The primary clinical question of interest is “is the risk of MACE within one year from admission not more than 5% higher when using CCTA instead of ICA for the initial diagnostic testing, among hospitalized patients with NSTEACS and an indication for ICA, regardless of any post-diagnostic management?”. Non-inferiority will be concluded if analyses based on both the intention-to-treat and per-protocol estimands are significant (the upper bound of the two-sided 95% confidence interval excludes a non-inferiority margin of 5 percentage points). Test for superiority of the primary endpoint will be performed if non-inferiority is met.

For secondary and other outcomes, effect estimates and 95% confidence intervals will be emphasized rather than individual p-values.

3.1 Non-inferiority margin and sample size

Please see the statistical analysis plan for further justification of non-inferiority margin.

We expect a frequency of the composite primary endpoint in the ICA group of 15%. This is based on data from the earlier trials testing an invasive versus conservative strategy in patients with acute coronary syndrome and on contemporary data from the Danish VERDICT trial.[4] In the VERDICT trial, 15% of patients died, had nonfatal recurrent myocardial infarction, or hospital admission for refractory myocardial ischemia or heart failure within 1 year.

With an expected frequency of the primary endpoint after 1 year of 15% in both groups, 2,146 patients, 1,073 patients in each group, are needed obtain 90% power. To account for the risk of lost-to-follow-up and drop-outs, it is planned to enroll 2,300 patients (1,150 patients in each group). With

this number of participants, the size of the 95% confidence interval for the point estimate of the difference between the groups regarding the primary endpoint will be ±3.0%.

4 Time schedule

Approximately 3,000 patients with NSTEACS are examined with ICA due to a diagnosis of NSTEACS at the three invasive centers in East Denmark each year. About 20% of these will be admitted during the weekends and will not be enrolled due to logistic reasons, and we expect 45% to be eligible according to the in- and exclusion criteria. With an expectation that 10% will decline participation in the trial, it should be possible to include 1,000 patients a year. It is therefore expected that the inclusion will be completed within 3 years.

5 Ethical considerations

5.1 Risks, adverse events, and short- and long-term side effects

CCTA carries a lower risk of complications compared to ICA. The most common complication associated with CCTA is allergic reactions to the contrast agent. Allergic reactions that require treatment occurs in approximately 0.04% of all patients undergoing CCTA. However, the same type of contrast is used during ICA. Thus, we do not expect the risk of allergic reactions to differ between the groups.

The primary risk for participants in the intervention group is failure to diagnose a coronary artery stenosis that requires revascularization. However, this risk is considered small since previous studies have found a high negative predictive value of CCTA in comparable population (sensitivity 96.5%).[8] Furthermore, stenoses overlooked will most likely be on small branches of the coronary arteries of low prognostic implication.

Patients will be examined with regular ICA should they choose not to participate in the trial.

5.2 Medication

Patients randomized to CCTA will be administered a short-acting beta-blocker (Metocar, metoprolol tartrate) prior to CCTA. Blood pressure and heart rate will be carefully monitored before and during CCTA. Side effects such as tiredness, low blood pressure, dizziness, headache, and low heart rate can occur. Arrythmias can occur in 0.1-1%. Furthermore, nitroglycerine will be administered as a sublingual spray. This medication can have side effects, but it is also administered routinely during ICA, why these side effects are applicable to both groups.

5.3 Ionizing radiation

Ionizing radiation is used both for CCTA and ICA. The total radiation dosage differs slightly between the two examinations. Current data show that the average radiation dosage is about 3.5 mSv from ICA and 3 mSv from CCTA. Participants randomized to CCTA who subsequently need revascularization will on average be exposed to 3 mSv more than if they had ICA performed as the primary examination. If the risk of inducing an uncurable cancer is increased by 5% when exposed to 1 Sv, the theoretically increased risk of cancer is of a magnitude of 0.003 x 5% = 0.015% for patients in the intervention group, thereby increasing the participants life-time risk from 25% to 25.015%. This is only applicable to participants in the intervention group, who require a subsequent ICA. Participants in the interventional group who can be discharged on basis of the CCTA, will receive a similar total radiation dosage as compared to patients in the control group.

According to guidelines from the National Scientific Ethics Committee the trial should be classified as IIb (according to appendix 2 “Retninglinjer om anvendelse af ioniserende stråling i sundhedvidenskablige forsøg”, from the National scientific ethics committee).

Overall, we believe that being randomized to the interventional group carries a lower risk of severe complications compared to the control group. Participants randomized to the control group will be examined as is the current standard of care. Therefore, participants in this group are not exposed to

any further risk by participating in the trial. A Data Safety Monitoring Board will be established to analyze interim reports.

5.4 Trial implications

In Denmark about 6,300 patients are examined with ICA due to NSTEACS each year. Most of these patients are admitted to their local hospital and transferred to an invasive hospital during admission.

If patients with NSTEACS can be examined with CCTA instead of ICA, future patients will be able to receive this examination at their local hospital. This will reduce wait times, decrease the length of hospital stay, and many patients will only need to be examined at their local hospital, which would decrease the need for interhospital transfers. All these factors may lead to significant reduction in health care expenses.

5.5 Protocol amendments

The first patient was included based on version 3.0 of the current protocol. Since then, after consultations with the steering committee and the trial statistician, minor adjustments have been made to inclusion and exclusion criteria, to the list of secondary outcomes, and definitions of several outcomes have been added. Inclusion criteria were changed with version 4.0 to include ischemic ECG-changes in patients without elevated biomarkers, to better define a true NSTEACS population and avoid patients with a low suspicion of coronary disease. Exclusion criteria were expanded to clarify special groups of patients that are outside the scope of the trial (with version 4.0: patients with very recent angiographic evaluation, with version 5.0: patients with probable type 2 myocardial infarction, patients with signficant valve disease, and patients with earlier SCAD). The population studied remains essentially the same – patients hospitalized with NSTEACS and a routine indication for ICA, and the changes does not impact comparability of participants recruited over time. The primary outcome has not been changed. The changes in secondary outcomes reflect a prioritization of non-primary outcomes in key secondary and other outcomes.

6 Biobank

No biological material will be stored.

7 Information from patient records

The following information from the patient records will be obtained: Sex, age, body mass index, smoking status, blood pressure, cholesterol levels, family history of cardiac diseases, kidney function, comorbidity status, roentgenological examinations, and medical status. Furthermore, information regarding admissions, examinations, and treatments, along with subsequent contacts to the health care system. The following information will be obtained by merging data from the Danish national registers: highest education level, civil status (married, window, etc.), income, use of medications, long-term outcomes, and cause of death. This information is necessary for the adequate characterization of participating subjects to interpret the results, and for determination of the clinical endpoints.

The consent provides the investigators, representatives of the responsible institution, and relevant authorities direct access to retrieve information from the participant's patient records, including electronic health records. Only Information which is necessary to be able to conduct the trial, and to monitor the trial in line with the obligations of investigators, institution, and authorities, will be retrieved.

8 Handling of personal data in the trial

All information regarding the participants will be saved in a REDCap database and stored in accordance with General Data Protection Regulation and the Danish Data Protection Act. Furthermore, permission from the Knowledge Center for Data reviews at the Capital Region will be

obtained. After database lock, the database will be anonymized and transferred to Statistics Denmark to obtain information from the nationwide registers.

None of participants personal information will be send abroad.

Data will be acquired and handled according to Danish and EU regulations and laws on data protection. Personal information will be treated confidentially.

9 Financial aspects

The Department of Cardiology at Rigshospitalet is the sponsor of this trial, which has been initiated by cardiologists at the Department. The trial has been supported by a grant of DKK 3.720.000 from The Danish Heart Association (grant number 2023-12398-22211). Funding will be sought from other external foundations for study personnel wages, with assignments to conduct follow-up on participants in the trial, along with other potential trial related assignments. Funding parties will not have any influence on how the trial is conducted, nor the interpretation of results or whether results are published. All funding will be managed through accounts administered by one or more participating hospitals.

10 Honorarium and/or other goods for trial participants

Participants will not receive honorarium or other goods as compensation for participation.

11 Publication

The results of the trial will be published in international peer-reviewed journals, regardless of the results. Interim results regarding immediate procedural results may be published before the main

result. Decisions regarding authorship and author sequence are taken by the steering committee based on individual contributions to the study. All authors must meet the ICMJE criteria.

12 Information regarding patient compensation

Study participants are covered by the Danish Patient Compensation Association from damage occurring because of their participation in the study.

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