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Coronary CT angiography for improved assessment of patients with acute chest pain and low-range positive high-sensitivity troponins: study protocol for a prospective, observational, multicentre study (COURSE trial)

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ABSTRACT

Introduction Current evaluation of patients suspected of a non-ST-elevation acute coronary syndrome (NSTE-ACS) involves the use of algorithms that incorporate clinical information, electrocardiogram (ECG) and high-sensitivity cardiac troponins (hs-troponins). While primarily designed to rule out NSTE-ACS safely, these algorithms can also be used for rule in of NSTE-ACS in some patients. Still, in a substantial number of patients, these algorithms do not provide a conclusive work-up. These patients often present with an atypical clinical profile and low-range positive hs-troponin values without a characteristic rise or fall pattern. They represent a heterogeneous group of patients with various underlying conditions; only a fraction (30%–40%) will eventually be diagnosed with a myocardial infarction. Uncertainty exists about the optimal diagnostic strategy and their management depends on the clinical perspective of the treating physician ranging from direct discharge to admission for invasive coronary angiography. Coronary CT angiography (CCTA) is a non-invasive test that has been shown to be safe, fast and reliable in the evaluation of coronary artery disease. In this study, we will determine the usefulness of CCTA in patients with acute chest pain and low-range positive hs-troponin values.

Methods and analysis A prospective, double-blind, observational, multicentre study conducted in the Netherlands. Patients aged 30–80 years presenting to the emergency department with acute chest pain and a suspicion of NSTE-ACS, a normal or non-diagnostic ECG and low-range positive hs-troponins will be scheduled to undergo CCTA. The primary outcome is the diagnostic accuracy of CCTA for the diagnosis of NSTE-ACS at discharge, in terms of sensitivity and negative predictive value.

Ethics and dissemination This study was approved by the Medical Research Ethics Committee of Erasmus Medical Center in Rotterdam, the Netherlands (registration number MEC-2017-506). Written informed consent to participate will be obtained from all participants. This study's findings will be published in a peer-reviewed journal.

Strengths and limitations of this study

- The double-blind nature of this study will enable the assessment of potential policy change(s) that would arise from the use of coronary CT angiography (CCTA) in the emergency department.
- Final diagnosis of non-ST-elevation acute coronary syndrome will be adjudicated by independent cardiologists who are blinded to the results of the CCTA, thereby avoiding the occurrence of incorporation bias.
- This study excludes patients with a history of acute myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft, which has to be taken into account when generalising the results of this study.

Trial registration number ClinicalTrials.gov (NCT03129659).

INTRODUCTION

Chest pain is the principal symptom of a non-ST-elevation acute coronary syndrome (NSTE-ACS), a broad clinical spectrum ranging from unstable angina pectoris to myocardial infarction (MI). Every year, an estimated 15–20 million patients in Europe and the USA present to the emergency department (ED) with chest pain possibly due to an NSTE-ACS and missing this diagnosis can have grave consequences as these patients have higher mortality and morbidity rates if not treated properly.[1 2] At present, evaluation involves a clinical examination, ECG and sampling of biomarkers, in the majority of cases of cardiac-specific troponins. Recent years have seen the introduction of new high-sensitivity assays for cardiac troponins, with the capability of detecting smaller amounts of

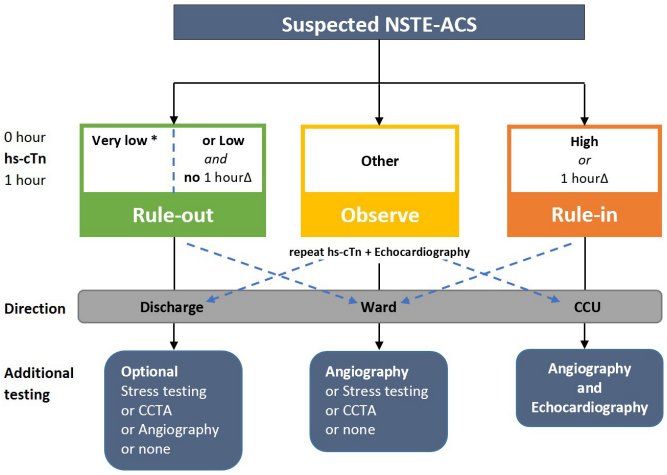

Figure 1 Adopted from the European Society of Cardiology 2020 guidelines. Proposed 0-hour/1-hour algorithm for the diagnostic work-up of suspected non-ST-elevation acute coronary syndrome (NSTE-ACS). *Only applicable if chest pain onset >3 hours; Δ, delta. CCTA, coronary CT angiography; CCU, coronary care unit; hs-cTn, high-sensitivity cardiac troponin.

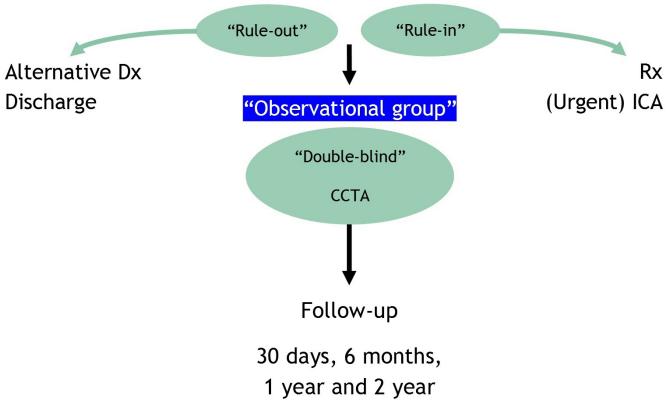

Figure 2 Study design. Observational group refers to patients who do not meet the criteria for either 'rule-out' or 'rule-in'. CCTA, coronary CT angiography; Dx, diagnosis; ICA, invasive coronary angiography; Rx, medication.

myocardial injury. International guidelines recommend specific clinical algorithms for the evaluation of NSTE-ACS incorporating high-sensitivity troponin (hs-troponin) values (figure 1).[3]

However, the current approach does not lead to a conclusive work-up in a substantial number of patients, which fall into the 'indeterminate' category.[3 4] These patients present with low-range positive hs-troponins, without a rise or fall pattern that is characteristic for MI.[5] They represent a heterogeneous group of patients with various underlying conditions; only a fraction (30%–40%) will eventually be diagnosed with an MI. Knowledge of the coronary status is preferred, because missing an MI has grave consequence. However, performing invasive coronary angiography (ICA) routinely is inefficient and burdensome because of its potential complications. At this moment, it is unclear what the optimal strategy is in these patients. Some will face a prolonged observational period in the hospital and will be exposed to potential risks of medical therapy and invasive testing, other might wrongfully be discharged with a missed NSTE-ACS.

Coronary CT angiography (CCTA) is a non-invasive alternative that accurately detects coronary artery disease and can serve as a gatekeeper for coronary angiography.[6–8] The aim of this study is to investigate whether CCTA can improve the diagnostic work-up of indeterminate hs-troponin patients suspected of NSTE-ACS.

METHODS AND ANALYSIS

The Coronary CT Angiography for Improved Assessment of Patients with Acute Chest Pain and Low-Range Positive High-Sensitivity troponins (COURSE) Study will be conducted according to the principles of the Declaration of Helsinki (10th version, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study is approved by the local institutional review board.

Study design

This study is a prospective, double-blind, observational, multicentre study. The study began in February 2018 and is currently ongoing. Patients will be recruited at secondary and tertiary care hospitals in the Netherlands. Patients with acute chest pain, a normal or non-diagnostic ECG and low-range positive hs-troponins will be scheduled to undergo CCTA (either at the ED or at the outpatient clinic). The usefulness and potential impact of CCTA on patient management will be evaluated. Patients will be recruited from the emergency ward. Follow-up contacts will take place at 30 days, 6 months, 1 year and 2 years (figure 2).

Inclusion and exclusion criteria

Patients aged 30–80 years presenting to the ED with acute chest pain and a suspicion of NSTE-ACS will be eligible. Patients eligible for inclusion are those with low-range positive hs-troponins who do not fulfil criteria for either 'rule-in' or 'rule-out' of NSTE-ACS (figure 3). Exclusion criteria are summarised in box 1.

Recruitment and consent

Eligible patients presenting to the ED will be informed about the study and asked for informed consent. An independent physician will be available for consultation. Patients willing to participate will provide informed consent in writing.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

CT study protocol

Coronary calcium scan

An ECG-triggered CT scan without contrast medium to assess the presence and quantity of calcified coronary plaque. Using the Agatston method, the total amount

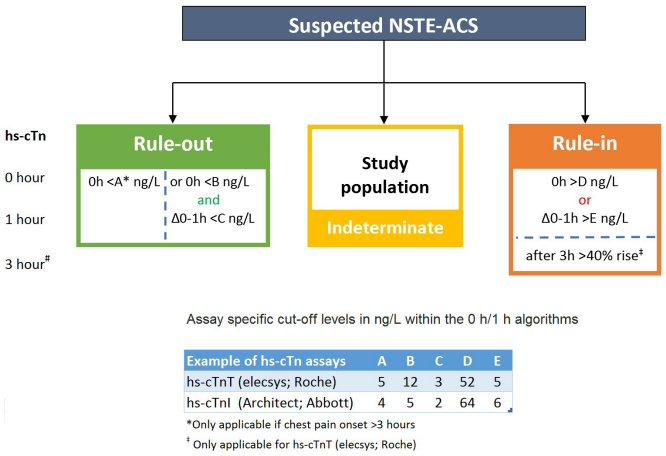

Figure 3 Rule-out and rule-in algorithm, adopted from the European Society of Cardiology 2020 guidelines for the diagnostic work-up of non-ST-elevation acute coronary syndrome (NSTE-ACS). '0 hour/1 hour' rule-out and rule-in algorithms using high-sensitivity cardiac troponin (hs-cTn) assays. #='0-hour/3-hour' algorithm is only used as a substitute in cases where the standard '0-hour/1-hour' algorithm is not feasible. 0 hour, 1 hour and 3 hour refer to the time (in hours) from first blood draw. hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; Δ, delta.

of calcium will be determined using semiautomated software.[9]

Coronary CT angiography

An ECG-triggered, contrast-enhanced CT scan to image the coronary artery lumen and detect the presence of obstructive coronary disease will be performed. The default scan protocol will be a prospectively ECG-triggered axial CT scan protocol. Retrospective gating may be used with prospectively ECG-triggered tube modulation in patients with an irregular or very fast heart rate. Oral or intravenous metoprolol will be given shortly before the scan for patients with high heart rates, depending on local expertise and CT scanner type, and repeated if necessary. Nitroglycerin sublingual will be given in all patients for vasodilation a few minutes before the scan, in the absence of contraindications.

After the scan is performed, the supervising CT reader, at the local hospital, will form a preliminary report. The treating clinician and patient are blinded to the CT results, except in the case of important findings. The results can be classified into the following groups:

1. CCTA reveals findings that do not mandate unblinding of the results.
2. CCTA reveals coronary findings that are shown to have important prognostic implications (significant left main artery disease, significant proximal left anterior descending artery disease, significant three vessel disease). These specific findings will be revealed to the treating physician and patient.
3. CCTA reveals other cardiac (non-coronary) findings that have important prognostic implications, which will be revealed to the treating physician and patient.
4. CCTA reveals significant non-cardiac findings warranting further management or follow-up. Findings will be revealed to the treating physician and patient.

All CT scans which are still blinded to the treating physician at the ED will be systematically read by two experienced CT readers at the initiating site at a later stage for final reading.

Questionnaires

Patients will be asked to fill in a questionnaire after 6 months, 1 year and 2 years (or interviewed by telephone when preferred). This is a non-standardised questionnaire to help determine the occurrence of any late major cardiovascular events, medical consumption and current medical therapy. If necessary, patients will be contacted by telephone to clarify their responses at follow-up. With written permission from the participants, information concerning possible medical events will be requested from other healthcare providers if needed.

Outcome measurements

Primary outcome

Diagnostic accuracy of ≥50% stenosis on CCTA to identify patients with NSTE-ACS associated with coronary plaque disruption, in terms of sensitivity and negative predictive value.

The diagnosis of NSTE-ACS is established by consensus of two independent cardiologists using all available clinical information including initial clinical presentation, ECG changes, serial laboratory results, (non)-invasive testing and information from the 30-day follow-up. This is considered an acceptable approach considering previous studies with conventional troponins with similar design.[10 11] All medical testing will be performed as indicated by treating physician and is not dependent on study participation. Because of ethical considerations, patients will not undergo standard invasive testing to determine final diagnosis when clinically not indicated. Results of CCTA will not be disclosed to the two independent cardiologists who establish the definitive clinical diagnosis.

Box 1 Exclusion criteria

- Inability or unwillingness to provide informed consent.
- History of proven CAD, defined as documented prior myocardial infarction, PCI or CABG surgery.
- Previous examination with either invasive angiography or CCTA in the last 3 years.
- Clinical instability: clinical heart failure, haemodynamic instability, severe chest pain.
- CCTA-specific contraindications: allergy to iodine contrast media; pregnancy; impaired renal function: eGFR <45 mL/min; severe arrhythmia likely to affect image interpretation; BMI >40 kg/m^2; inability to cooperate during the examination.

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCTA, coronary CT angiography; eGFR, estimated glomerular filtering rate; PCI, percutaneous coronary intervention.

Secondary outcome(s)

- Diagnostic accuracy of ≥70% stenosis for all coronary segments, except left main (≥50% stenosis), on CCTA to identify patients with NSTE-ACS, in terms of sensitivity and negative predictive value.
- The prevalence of atherosclerosis, extent and type, by qualitative analysis.
- Predictive value of CCTA for major adverse cardiac events: death, non-fatal MI and coronary revascularisation at 6 months, 1 year and 2 years.
- Diagnostic accuracy of coronary artery calcium scoring in comparison with CCTA.
- Potential improvement of diagnostic accuracy with fractional flow reserve-computed tomography (FFR-CT) in the diagnosis of NSTE-ACS. FFR-CT results will be acquired at a later stage and will not be used for clinical decision-making.
- Subgroup analyses: age, sex, ethnicity and risk scores.

Sample size calculation

Previous studies show that approximately 40% of all patients with an inconclusive diagnostic work-up eventually turn out to have NSTE-ACS.[5] Based on these observations, we assume that the pretest probability of NSTE-ACS will be 40% in this population. A total of 240 patients are required to demonstrate a negative predictive value of 97% with a lower margin of 90%, considering an α=0.05 and β=0.8 and a drop-out rate of 10%.

Adverse events

Adverse events occurring during the CCTA examination include allergic reactions and renal dysfunction. Clinical guidelines apply to avoid complications, and trained personnel are available to handle urgent situations. Although we do not expect the CCTA approach to be associated with an increase in adverse events, we will ask patients to inform us should any unexpected cardiovascular events occur. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Statistical analysis

Results will be reported as mean with SD or median with IQRs as appropriate. Data will be presented as categorical or continuous variables, as appropriate. Differences between independent data will be compared using the Student's t-test or the Pearson X^2 test, while the paired t-test or the McNemar X^2 test will be used for dependent data. Receiver operating characteristic curves with their corresponding areas under the curve (ie, c-statistic) will be constructed to assess the performance of CT. In addition, sensitivity, specificity, negative predictive value and positive predictive value will be calculated with their corresponding 95% CIs to assess the performance of CT. Variables with <5% missing data will be described unchanged, those with 5%–10% using imputation methods. In the case of considerable missing data, this variable will not be analysed.

DISCUSSION

The COURSE trial is a prospective, double-blind, multicentre, observational study to investigate whether CCTA can improve the diagnostic work-up of patients with suspected NSTE-ACS with indeterminate hs-troponins.

The definition of MI has gradually changed with the advent of high-sensitivity cardiac troponin assays. These assays are able to detect very small amounts of myocardial injury or necrosis, with a turnaround time that is much shorter than conventional troponin assays.[3] In patients with normal and serial low levels of hs-troponins, MI can be ruled out with a negative predictive value that is close to 100%. On one hand, this enables early discharge from the ED of patients with suspected ACS; on the other hand, it allows for expedite detection and treatment of alternative life-threatening causes of acute chest pain. Therapy for an ongoing MI is initiated more swiftly in the case of highly elevated hs-troponins and/or a typical rise or fall pattern during serial sampling,[12]

However, it is estimated that 20%–30% of the patients who present with chest pain suggestive of a cardiac origin do not fulfil the criteria of contemporary algorithms for either rule-in or rule-out of NSTE-ACS.[4] These patients typically present with a normal or inconclusive ECG and low-range positive hs-troponin values without a typical rise or fall pattern during serial sampling. Elevated hs-troponins indicate myocardial injury, however they do not differentiate the underlying aetiology, which includes atherosclerotic plaque disruption (type 1 MI), oxygen supply and demand imbalance (type 2 MI), and non-ischaemic myocardial injury.[13] Differentiating between these conditions may be challenging, but is crucial as they require a different therapeutic approach. Considering that ICA is a costly procedure which carries risks and that eventually less than half of these patients will turn out to have NSTE-ACS, it is sensible to look for more efficient and non-invasive alternatives.[5]

Non-invasive evaluation of coronary artery disease with CCTA

CCTA is a well-established diagnostic modality that detects and quantitates coronary artery disease very accurately in a matter of minutes.[6–8] Currently, it is being employed worldwide as an anatomical alternative to functional testing.[14–16] Previously, CCTA has successfully been tested in the ED in the assessment of patients suspected of NSTE-ACS.[17–19] Litt *et al* showed that a CCTA-based strategy in low-risk patients with acute chest pain allowed for a safe and expedited discharge as compared with standard clinical evaluation.[18] The Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography II trial reinforced these results by showing that early CCTA in low-risk patients with suspected ACS shortened the length of stay in the hospital, while maintaining patient safety. However, this strategy was associated with an increase in downstream testing and did not lead to decrease in cost of care.[17] It is important to note that these studies were performed in the era of conventional cardiac troponin assays. Since then, hs-troponins have been adopted as the preferred cardiac biomarker and clinical care has changed

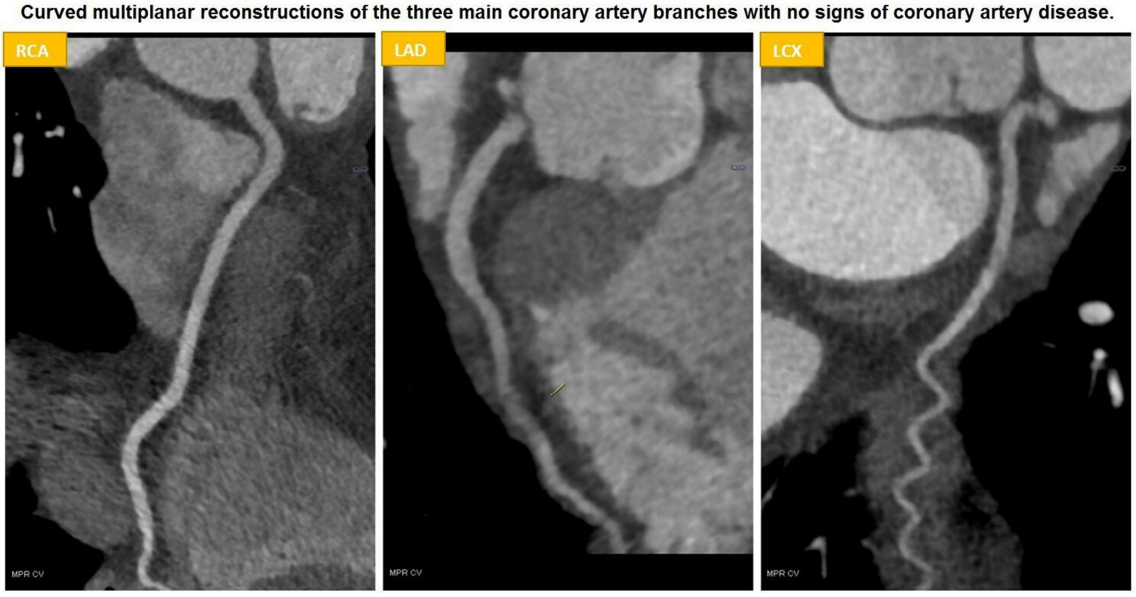

Figure 4 Exemplary case showcasing the use of CCTA as a gatekeeper for patients with low-range positive high-sensitivity troponin levels in the emergency department (ED). CAD, coronary artery disease; CCTA, coronary CT angiography; ESC, European Society of Cardiology; hs-TnT, high-sensitivity troponin T; ICA, invasive coronary angiography; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

substantially. Previously, in the Better Evaluation of Acute Chest Pain with Computed Tomography Angiography trial, we assessed the value of CCTA in the era of hs-troponins for the first time.[20] Mainly focused on patients with hs-troponins levels beneath the upper reference limit, we found that early CCTA was feasible and resulted in less outpatient testing and lowered direct medical costs. However, it became evident that patients with hs-troponins beneath the upper reference limit are at very low risk of cardiovascular events and might not even require any testing at all. It has been suggested that CCTA might be more beneficial in patients with higher risk.[21] In patients with low-range positive hs-troponin levels, CCTA might provide a more effective diagnostic work-up. With its excellent negative predictive value, CCTA is an ideal gatekeeper for invasive coronary angiography and might detect other conditions that cause acute chest pain and low-range positive hs-troponin levels (figure 4). Although its diagnostic accuracy slightly declines in patients of older age, CCTA remains a very reliable diagnostic modality.[22] As an anatomical modality, CCTA does not rely on the provocation of ischaemia, which is unattractive in the case of elevated hs-troponins. Detection of non-obstructive atherosclerotic plaque, considered to be a prerogative for future cardiovascular events and undetected by other diagnostic modalities, provides an opportunity for better prevention measures.[23] Recently, the Very Early vs Deferred Invasive Evaluation Using Computerized Tomography in Patients With Acute Coronary Syndromes trial, a randomised controlled trial in patients with confirmed NSTE-ACS, showed that CCTA has a high diagnostic accuracy to rule out clinically significant coronary artery disease. In contrast, our observational study will examine whether CCTA can improve the diagnostic work-up of patients presenting with low-range positive hs-troponins, without a rise or fall pattern that is characteristic for MI.

Ethics and dissemination

This study was reviewed and approved by the Medical Research Ethics Committee of Erasmus Medical Center in Rotterdam, the Netherlands (registration number MEC-2017-506). This study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). Written informed consent to participate will be obtained from all participants. The experimental data will be entered into an electronic case report form. Confidentiality of all participants will be protected by deleting participant identification and privacy information from all study documents. After data storage, only researchers directly involved in the data analysis will be permitted access to the final trial dataset. During the study, local independent data monitoring committees for the various participating centres will be responsible for monitoring the safety, progress, study integrity and design aspects of the trial. This study's findings will be published in scientific peer-reviewed journals and presented at scientific meetings.

Trial status

Protocol number: version 4-18.07.2019. Recruitment began in February 2018 and is currently ongoing. Expected study completion date: June 2021.

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Contributors AD and EAD conceived and designed the study. EAD obtained funding for the study. MA, AD and EAD drafted the manuscript. MA will coordinate the study and data collection. MA, BVG, and YJMVC are in charge of data acquisition. JS, PD, SB, MA, BVG, RPJB, YJMVC, JH, EAD and AD contributed to the writing and review of the manuscript protocol.

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Disclaimer The funding body has no role in the study design, data collection, data analysis, data interpretation, writing the report or decision to submit the report for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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