

openheart Rapid use of high-sensitive cardiac troponin I for ruling-in and ruling-out of acute myocardial infarction (RACING-MI): study protocol

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ABSTRACT

Introduction The European Society of Cardiology has suggested an accelerated algorithm for ruling-in and ruling-out myocardial infarction (MI) with high-sensitive cardiac troponin (hs-cTn) measured at admission (0 hour) and after 1 hour (1 hour) as an alternative to standard measurements at 0 hour and 3 hours. However, the 0 hour/1 hour algorithm has only been tested in a limited amount of patient cohorts and not for all hs-cTn assays. Moreover, it is unknown if MI can be ruled-out faster than 1 hour. In this single-centre, clinical trial, we will investigate whether MI safely can be ruled-in or ruled-out after 30 min and 1 hour.

Methods and analysis Patients with chest pain suggestive of MI admitted to the emergency department will be subjected to hs-cTn measurements at the following time points: 0 hour, 30 min, 1 hour and 3 hours. Chest pain characteristics will be recorded. In total, 1000 patients with all four blood samples will be included. The diagnostic algorithms will be derived based on the first 500 patients and validated in the subsequent 500 patients. The primary endpoint is the negative predictive value of the 0 hour/30 min and the 0 hour/1 hour algorithms. Secondary endpoints include positive predictive value, sensitivity and specificity. Results will be compared with the standard 0 hour/3 hour algorithm.

Ethics and dissemination Oral and written informed consent will be obtained from all patients. The trial is approved by The Regional Committee on Health Research Ethics and the Danish Data Protection Agency. Data will be disseminated and submitted to peer-reviewed scientific journals and meetings irrespective of study outcome.

Trial registration number NCT03634384

INTRODUCTION

Chest pain is a key symptom of myocardial infarction (MI) and accounts for 5%–20% of all non-surgery emergency department (ED) contacts.^{1–3} Nonetheless, only 1 in 10 patients admitted to the ED with chest pain are diagnosed with MI.^{1–3} Rapid ‘rule-in’ and ‘rule-out’ of MI are essential to minimise unnecessary bed allocation and time to

Key questions

What is already known about this subject?

- Recently, European Society of Cardiology introduced an assay-specific 0 hour/1 hour algorithm measuring troponin at admission and 1 hour later for accelerated rule-in and rule-out of acute myocardial infarction.
- Several countries have not yet implemented the algorithm because it has only been validated in few patient cohorts and for certain high-sensitive cardiac troponin assays. Moreover, it is unknown if myocardial infarction can be ruled out earlier than at 1 hour.

What does this study add?

- This trial will provide data on the performance of the 0 hour/1 hour algorithm in a patient cohort that differs from already existing studies.
- To reflect clinical practice, this trial will use ad hoc in addition to batch analysis of blood samples. Furthermore, this is the first large-scale trial to investigate measurements of high-sensitive cardiac troponin already 30 min after admission blood samples. This will allow investigation of a novel 0 hour/30 min algorithm, which has never been done before.

How might this impact on clinical practice?

- This trial will contribute with important knowledge on the performance of accelerated rule-in and rule-out algorithms and offers insights into early troponin kinetics. If the results of this trial support the use of the 0 hour/1 hour algorithm, this will add to the overall external validity of accelerated rule-in and rule-out algorithms and potentially favour a wide clinical implementation. In addition, we will be able to evaluate the performance of a novel 0 hour/30 min algorithm allowing for even faster rule-out of acute myocardial infarction.

discharge for patients without MI and ensure prompt treatment for patients with MI.⁴

In the absence of ST-segment elevation myocardial infarction (STEMI) on the

ECG, the European Society of Cardiology (ESC) recommend repeated measurements of high-sensitive cardiac troponin (hs-cTn) at presentation (0 hour) and 3 hours after presentation to rule-in or -out MI (the 0 hour/3 hour algorithm).^{5 6} An accelerated algorithm after 1 hour (1 hour) has been suggested,⁷⁻¹⁴ but remains largely to be implemented in clinical practice as it has mainly been investigated in patient cohorts originating from the APACE trial.¹⁵ Moreover, data on patients undergoing transcatheter septal ablation of septal hypertrophy have demonstrated an increase in troponin concentrations measured by a hs-cTn assay only 15 min after induction of myocardial injury.¹⁶ This finding indicates that it may be possible to evaluate troponin dynamics earlier than the 0 hour/1 hour algorithm.

We will investigate if high-sensitive cardiac troponin I (hs-cTnI) measurements at 30 min or 1 hour after initial hs-cTn measurements can safely rule-in or rule-out MI.

METHODS

Study design

We will conduct a single-centre, clinical trial of patients with chest pain suggestive of MI admitted to the ED. There will be no randomisation. Patients will be treated according to standard Danish practice, which follows the guidelines from ESC.⁶ To avoid any ethical concerns on whether or not to act on hs-cTnI results from the 30 min or 1 hour blood samples, the treating physician will be blinded to the 30 min and 1 hour results until the 3 hour results become available. As a consequence, the treating physician can act only on hs-cTnI at 0 hour and 3 hours, according to current clinical practice.

Study setting

In Denmark, patients are examined in the prehospital setting for symptoms and clinical findings suggestive of MI and subsequently admitted to a public hospital.¹⁷ Patients with STEMI or elevated point-of-care cardiac troponin measured in the ambulance will be admitted directly to an invasive heart centre. In the absence of STEMI or elevated point-of-care cardiac troponin, patients are referred to a regional hospital for observation and diagnostic workup. Currently, patients admitted to Danish hospitals under suspicion of MI are evaluated in accordance with the 0 hour/3 hour troponin algorithm.

RACING-MI will be carried out in the ED at Randers Regional Hospital, Denmark. As a consequence, the expected incidence of MI in our population will be relatively low due to the prehospital referral of patients with positive point-of-care measurements to the nearest university hospital. Inclusion was started on 21 November 2016 and will continue until fulfilment of the sample size. The trial is registered at <http://www.clinicaltrials.gov> (trial registration number: NCT03634384).

Eligibility and exclusion criteria

All patients with chest pain suggestive of MI will be eligible for inclusion. Exclusion criteria are defined as STEMI at

Table 1 Trial components and timeline for data collection of the RACING-MI study

Trial components	At admission (0 hour)	At 30 min	At 1 hour	At 3 hours	30 days after discharge
Patient screening	X				
Informed consent	X				
ECG	X				
Vital parameters	X				
Trial blood samples	X	X	X	X	
Routine blood samples	X			X	
Questionnaire	X				
Medication*	X				
Follow-up					X

*Registered as medication use at the time of admission.

admission, age <18 years, pregnancy and kidney failure requiring dialysis. As part of standard procedure, the admitting physician evaluates all patients, including ECG, on admission and decides whether to continue observation for MI or not. The admitting healthcare staff will hereafter assess the patient for trial eligibility.

Admission data

Time of first admission contact as registered in the electronic health record will be registered for each patient. The time of admission blood samples defines 0 hour. **Table 1** presents an overview of trial components and data collection time points. All patients will receive routine clinical cardiac assessment at admission (ECG and vital parameters such as blood pressure, pulse oximetry, respiratory frequency and temperature).

Blood tests

The admitting nurse will request the trial blood samples. Each patient will undergo serial blood sampling at 0 hour, 30 min, 1 hour and 3 hours (**table 1**). The admission hs-cTnI sample (0 hour) will be included in the standardised admission blood samples. Blood samples will be obtained by standard venous blood sampling. If a suitable peripheral venous catheter is available and venipuncture is unsuccessful or considered harmful by the patient, the venous catheter may be used for blood sampling. In such cases, the first 10 mL blood obtained will be discarded at the 30 min and 1 hour blood draw to avoid haemolysis in the blood samples.

A timer will be set by the medical laboratory technician at the 0 hour blood sampling to notify the admitting physician or a research assistant of when to obtain the 30 min and 1 hour blood samples. The exact time of each blood draw will be registered on a data sheet and on the blood requisition forms. The 30 min and 1 hour trial blood samples will be placed in a container and collected by a medical laboratory technician at the 3 hour blood sampling. Hs-cTnI will be measured in the central

laboratory for each blood sampling (0 hour, 30 min, 1 hour and 3 hours). An additional 10 mL lithium heparin and 4 mL serum for all four time-points will be stored in a research biobank.

Questionnaire

Patients will be asked to complete a 19-item questionnaire on their chest pain characteristics and cardiovascular risk profile (online supplementary table 1). The questionnaire covers (1) time of chest pain onset and peak, (2) chest pain characteristics (localisation, radiation, sensation), (3) additional symptoms at presentation (nausea, abdominal pain, syncope, dyspnoea and palpitations), (4) life style factors such as physical activity, smoking status, height and weight, (5) family history of MI and (6) whether the patient believes that his or her symptoms are caused by MI (yes/no). If no, the patient will be asked to elaborate on expected final diagnosis.

Data entry

A research assistant will record baseline characteristics for all patients from the electronic patient record. Data will include time of admission, age, sex, vital parameters on admission, admission blood test results, the four hs-cTnI results, ECG description by the physician, medication use on admission, previous MI and comorbidity (online supplementary table 2). The investigator will stratify patients according to HEART risk score¹⁸ when all data on admission are available, including initial hs-cTnI values, and record the preliminary final diagnosis.

Adjudication

After patient inclusion, two physicians will independently adjudicate the final diagnosis for each patient. In case of discrepancy, a third physician will be consulted, and the final diagnosis will be determined by consensus. All available clinical information (eg, patient history, physical examination, laboratory testing, radiology imaging, ECG, echocardiography and results from coronary angiography) pertaining to the patient from admission at the ED to 30 days after discharge, will be used as part of the adjudication. Follow-up will include major adverse cardiac events defined in accordance with previous studies on the HEART score, that is, MI, percutaneous coronary intervention, coronary artery bypass grafting and all-cause mortality.^{18–20} Non-fatal outcomes will be identified from hospital discharge diagnoses.¹⁷ Mortality will be identified from the Danish Civil Registration System.²¹ Patients will be classified with a final diagnosis of MI based on the fourth universal definition of MI.²² The final diagnosis of MI will be based on a rise and/or fall of troponin values with at least one value above the 99th percentile combined with evidence of myocardial ischaemia. In cases with elevated troponin with no troponin dynamics or no signs of myocardial ischaemia,

the case will be discussed and a consensus decision will be made in accordance with guidelines.²²

Clinical biochemistry

All trial blood samples will be centrifuged at 1500g for 10 min. Hs-cTnI is measured instantly from the 4 mL lithium heparin tube. Plasma from the 10 mL heparin and 4 mL serum tubes will be kept frozen at -80°C for later analysis.

Troponin analyses will be performed in accordance with routine laboratory methodology on ADVIA Centaur using the high-sensitivity troponin I (TNIH) assay (Siemens Healthcare GmbH, Erlangen, Germany). The method is accredited according to the DS/EN ISO 15189:2013 accreditation standard. The limit of detection for the TNIH assay is 2.21 ng/L, the 99th percentile cut-off point is 47.34 ng/L and the coefficient of variation is less than 10% at 4.46 ng/L.

Endpoints

Data from the first 500 patients will be used to derive diagnostic 0 hour/30 min and 0 hour/1 hour algorithms, which subsequently will be validated in the last 500 patients. For the 0 hour/1 hour algorithm, data from the total cohort will also be used to test and further validate already existing 0 hour/1 hour algorithm cut-off values.²³

The primary endpoint will be the negative predictive value of the 0 hour/30 min and the 0 hour/1 hour algorithms. Secondary endpoints will include positive predictive value and sensitivity and specificity at 30 min and 1 hour. Results will be compared with the standard 0 hour/3 hour algorithm.

Derivation of the algorithms

The 1 hour algorithm for rapid rule-in and rule-out of acute MI has previously been described.^{7 10 11 24 25} A 30 min algorithm has not previously been described. In brief, we will derive the two algorithms by incorporating both baseline and absolute changes in hs-cTn levels within the first 30 min (0 hour/30 min algorithm) and 1 hour (0 hour/1 hour algorithm). Rule-out will be defined as hs-cTn level changes within the first 30 min or 1 hour *less* than the trial derived hs-cTn cut-off values and rule-in as hs-cTn changes *greater* than the trial derived hs-cTn cut-off values. Patients fulfilling neither of the above criteria for rule-in or rule-out will be stratified to an 'observational zone' requiring further diagnostic work-up.

Sample size

The trial is designed to enrol 1000 patients with complete blood samples at 0 hour, 30 min, 1 hour and 3 hours. Pilot study calculations estimate an expected cumulative incidence of MI in our trial cohort of only 7%. Assuming a negative predictive value of 99.7% in the rule-out group, a distribution with 7% patients in the rule-in group and 20% assigned to the observational zone (patients not stratified to either the rule-out or rule-in group), enrolment of 500 patients (with complete data) in both the derivation

and validation cohorts will provide an acceptable lower boundary of 98.2% of the two-sided 95% CI.^{8 10 25}

Statistical analysis

Data will be analysed for normality using QQ-plots and histograms. Normally distributed continuous variables will be presented as mean±SD and non-normal as median (quartile 1; quartile 3). Categorical data will be presented as numbers and proportions. Statistical differences will be measured using appropriate parametric and non-parametric tests.

All hypothesis testing will be 2-tailed with a $p < 0.05$ considered to be statistically significant. Statistical analysis will be performed using R statistical software, V.3.4.0.

Strengths

This will be the first large-scale trial to measure hs-cTn already 30 min after admission blood sampling and the first trial to introduce a 0 hour/30 min diagnostic algorithm. Only one small trial including 71 patients with high risk of MI has investigated 30 min blood sampling using a single cut-off with no standard 3 hour hs-cTn reference.²⁶

In addition, this trial will provide data on the performance of the 0 hour/1 hour algorithm from a patient cohort that differs from already existing studies.¹⁵ As a result, this may add to the external validity of faster rule-in/rule-out algorithms of MI. This trial will use ad hoc in addition to batch analysis of blood samples. It will then be possible to investigate the difference between the analytical precisions of ad hoc and batch analysis.²⁷ In addition, a research biobank will be established with additional blood samples for each patient at all time points. The biobank will provide the opportunity to validate different troponin assays and further investigate the patient cohort.

Limitations

Potential limitations of the present trial should be considered. Currently, it is unknown if repeated blood sampling after 30 min is feasible in clinical practice. However, possibilities exist, for example, (1) implementation of automatic electronic notification as for the standard 3 hour blood sample and (2) prehospital blood draw in the ambulance, which is handed over for analysis on arrival.

This trial is not a randomised controlled trial. However, the patients will be used as their own control group and will not affect the measures of endpoints. In addition, it allows us to safely investigate the novel 0 hour/30 min algorithm.

Ethics and dissemination

Oral and written informed consent will be obtained from all patients in accordance with the Danish Health Act and the Declaration of Helsinki. The trial is approved by The Regional Committee on Health Research Ethics (no. 1-10-72-213-16) and the Danish Data Protection Agency (no. 1-16-02-530-16). The admitting healthcare staff will obtain the informed consent prior to the blood sampling.

The findings of this trial will be disseminated by peer reviewed publications, presentation at national

and international meetings as well as in other relevant channels.

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Data sharing statement For permission to use data from the RACING-MI study contact principal investigator, Professor Bo Løfgren, MD, PhD, FESC, FAHA on mail bl@clin.au.dk.

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