

Rapid use of high-sensitive cardiac troponin I for ruling-in and ruling-out of acute myocardial infarction - the RACING-MI study

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Introduction

Chest pain is a key symptom of acute myocardial infarction (MI), but can also represent other cardiac and non-cardiac disease.^{1, 2} Rapid identification of MI in terms of ‘rule-in’ or ‘rule-out’ is essential in order to minimize treatment delay or time to discharge. In the absence of ST-segment elevation myocardial infarction (STEMI) at initial MI evaluation, the European Society of Cardiology (ESC) guidelines recommend repeated measurements of high-sensitive cardiac troponin (hs-cTn) at presentation (0h) and 3 hours (3h) after presentation to rule-in and rule-out MI.²

An accelerated algorithm for ruling-in and ruling-out MI after 1 hour (0h/1h algorithm) has been suggested by the ESC as a valid alternative to the standard approach.² The novel 0h/1h algorithm has only been validated for certain hs-cTn assays.³⁻⁷ The algorithm assigns patients to three groups: rule-in, observational zone and rule-out of MI based on absolute troponin values and troponin dynamics below the 99th percentile. However, routine use of the 0h/1h algorithm is still not widely recommended, as further data are warranted.^{2, 8}

A study of patients undergoing transcatheter ablation of septal hypertrophy, a clinical model of MI, shows that troponin concentrations measured by a hs-cTn assay significantly increase already after 15 min.⁹ This suggests that troponin dynamics may be evaluated even sooner than the 0h/1h algorithm.

So far, the 0h/1h algorithm has only been tested in a few patient cohorts.^{3-7, 10} Moreover, it has never been investigated whether rule-in and rule-out of MI can be done safely using a diagnostic algorithm after 30 minutes (0h/30m algorithm).

This study aims to derive and validate two accelerated diagnostic algorithms using a high-sensitive cardiac troponin I (hs-cTnI) Assay: a 0h/1h algorithm and a 0h/30m algorithm.

Methods

Study methodology

This is a prospective, observational study of 1000 patients undergoing MI evaluation using hs-cTnI measurements at 0h, 30m, 1h and 3h in patients presenting with chest pain.

Eligibility and exclusion criteria

Upon admission, the admitting physician decides whether to observe for myocardial infarction or not based on a mandatory evaluation of all patients, including electrocardiogram as well as vital

sign parameters (blood pressure, heart rate, peripheral oxygen saturation, respiratory rate and temperature). The admitting health care staff will assess the patient for study eligibility.

Patients with chest pain suggestive of MI are eligible for inclusion. Exclusion criteria are: STEMI at admission, <18 years of age, pregnancy or kidney failure requiring dialysis. Patients with incomplete blood sampling will be excluded from the primary analysis.

The study site is Regional Hospital Randers, Randers, Denmark. The hospital is a regional hospital without invasive capability. The hospital has a catchment area of approximately 230,000 patients, 220 beds, 164,000 outpatient visits and 37,564 patients being admitted each year.

Table 1: HEART risk score

History	Highly suspicious	2
	Moderately suspicious	1
	Slightly or non-suspicious	0
Electrocardiogram	Significant ST depression	2
	Nonspecific repolarization disturbance	1
	Normal	0
Age	65 years old or more	2
	46-64 years old	1
	45 years old or less	0
Risk Factors	3 or more risk factors <i>or</i> history of significant atherosclerosis	2
	1-2 risk factors	1
	No risk factors known	0
Troponin	More than or at 3x normal limit	2
	1-<3x normal limit	1
	Lower than or at normal limit	0

Patients

Patients will be stratified according to pre-test probability of MI using HEART risk score (Table 1), as this score is easily applicable to clinical practice.¹¹ The HEART score divides patients into low- (0-3 points), intermediate- (4-6) or high-risk groups (7-10), with mean risks of an event of 0.9%, 12% and 65%, respectively.¹¹ An event is defined as MI, Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG) or death within 6 weeks after presentation.

Oral and written consent will be obtained. The information will be given in a quiet setting, and the patient can ask questions. The patient will be given time to consider study participation. It will be possible for the patient to have a companion present (e.g. a family member). Patients will be asked for informed consent to have information passed on from the electronic patient journal regarding gender, age, medicine, previous myocardial infarction and co-morbidity for use in this study only. Patients declining to participate will receive standard treatment.

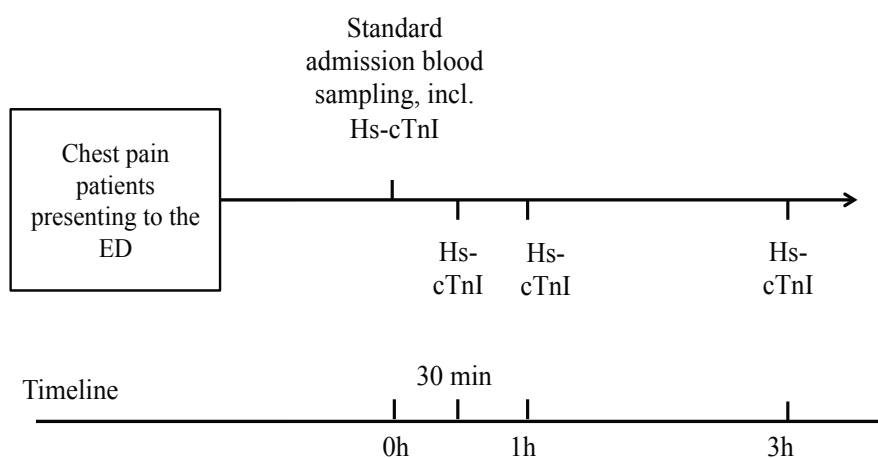
Patient handling

Time of first admission contact will be recorded for each patient in accordance with registrations in the electronic patient journal. All patients will receive routine clinical cardiac assessment at admission. The admitting nurse will request blood samples, which will be drawn at the following time points: 0h, 30m, 1h and 3h (Fig. 1). Standardized admission blood samples will include the first hs-cTnI (0h).

The medical laboratory technician will set the timer when collecting the 0h blood sample. The timer will notify the admitting physician or a research assistant of when to obtain the blood samples at 30m and 1h, respectively. Time of each blood draw will be registered.

Hs-cTnI will be measured in the central laboratory for each of the four time-points (0h, 30m, 1h and 3h). An additional 10 mL lithium heparin and 4 mL serum will be stored in a research biobank. The treating physician will be blinded to test results at 30m and 1h, with the final therapeutic decision relying on hs-cTnI measurements at 0h and 3h only.

Figure 1: study design



Chest pain data and baseline characteristics

A questionnaire will be distributed to all patients after admission and includes questions on: 1) time of chest pain onset and peak, 2) chest pain characteristics (localization, radiation, sensation), 3) additional symptoms at presentation (such as nausea, abdominal pain, syncope, dyspnea, palpitations), 4) height and weight, smoking status and family history of MI and 5) whether the patient believes that his or her symptoms are caused by MI (yes/no). If no, the patient will be asked to state what the patient believes to be the cause of hospital admittance.

Baseline characteristics will be recorded for all patients: age, gender, vital parameters, admission blood samples, Hs-cTnI results, electrocardiogram description, medication, previous MI and co-morbidity passed on from the electronic patient journal.

Final diagnosis

Two physicians will adjudicate the final diagnosis based on data from the electronic patient journal (including physical examination, patient history, laboratory results, electrocardiogram, and other examinations). In cases of disagreement between the two physicians a consensus decision will be reached after a case review. All available data from each patient will be linked to the final diagnosis, including baseline characteristics, chest pain characteristics, blood samples and HEART risk score.

Electrocardiogram

ST-segment elevation is defined according to ESC guidelines.¹² Ischemic electrocardiogram changes are defined by ST depression of ≥ 0.5 mm or T-wave inversion of ≥ 1 mm.²

Biochemical analysis

Troponin analyses will be performed in accordance with routine laboratory methodology on ADVIA Centaur using the high-sensitivity cardiac Troponin I (TNIH) assay (Siemens Healthcare GmbH, Erlangen, Germany) in an accredited clinical biochemical laboratory (DANAK ISO 15189 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.

Outcomes

Data from the first 500 patients will be used to derive two algorithms: a 0h/30m and a 0h/1h algorithm. Both algorithms will subsequently be validated in the last 500 patients. For the 0h/1h algorithm, data from the total patient cohort will also be used to further validate already existing 0h/1h algorithm cut-off values.

The primary outcomes will be the negative predictive value of the 0h/30m algorithm when ruling-out MI at 30m and the negative predictive value of the 0h/1h algorithm when ruling-out MI at 1h. Secondary outcomes will be positive predictive value, sensitivity and specificity at 30m and 1h. Results will be compared with the standard 0h/3h algorithm.

Statistics

The study is designed to enroll 1000 patients with complete blood samples. We expected the prevalence of MI in our population to be low due to pre-hospital risk-stratification conducted in the ambulance. Risk stratification is based on point-of-care troponin and electrocardiogram evaluation. Accordingly, patients with a very high risk of MI will not be admitted to the study site, as they will be directly transferred to a tertiary care centers with cardiac catheterization facilities.

In order to estimate the prevalence of MI in our study cohort, a pilot study calculation was performed, leading to an estimated MI prevalence of 7.4%. Assuming a negative predictive value of 99.7% in the rule-out group, and a distribution with 7% patients in the rule-in group and 20% in the observational zone, enrolment of at least 500 patients in each patient cohort, the derivation and the validation cohorts, will provide an acceptable lower boundary of 98.2% of the two-sided 95% confidence interval. We plan to include approximately 1400 patients. This allows for missing blood samples, loss of follow-up and patients who withdraw themselves from the study.

The diagnostic algorithms for the study will be developed using CART-tree analysis and receiver operating characteristic curves using baseline and absolute 30m or 1h changes in hs-cTnI values, respectively. The algorithms will be used to distinguish between the following diagnoses: MI and non-MI (such as unstable angina, non-coronary cardiac chest pain, non-cardiac chest pain and discharge with no diagnosis).

Data will be analyzed for normality using QQ-plots and histograms. Normally distributed continuous variables will be presented as mean (Standard Deviation (SD)). Non-normally distributed data will be presented as median (Interquartile Range (IQR)). 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-value <0.05 considered to be statistically significant. Statistical analyses will be performed using R statistical software, version 3.4.0.

Ethics

Permissions from the Danish Research Ethics Committee (1-10-72-213-16) and the Danish Data Protection Agency (1-16-02-530-16) have been obtained. The project will be carried out according to the Danish Health Act.

All patients will be asked specifically for informed consent to establish the research biobank.

Risk, side effects and other disadvantages

Blood samples will be obtained according to standard venous blood sampling using a venepuncture. When venepuncture is unsuccessful, or when a suitable cubital peripheral venous catheter is present, this may be used. In such cases, the first 10 mL blood obtained will be discarded at 2nd and 3rd blood draw to avoid haemolysis in the blood samples. This leads to a total of 84mL additional blood drawn from each patient compared to standard procedure, when adding discarded blood, blood for biobank establishment and hs-cTnI analysis at 30m and 1h. We believe that the extra volume of blood drawn will not lead to any significant adverse effects, such as fatigue or dizziness. Any patient discomfort during the study is small and outweighed by the information the study contributes. As the treating physician acts solely on the 0h/3h hs-cTnI results, the therapeutic decision will not be affected by the study.

Feasibility

The research group behind the project has carried out a retrospective audit of chest pain patients admitted to the emergency department at Randers Regional Hospital to ensure the feasibility of the project. On average, 5 eligible patients presented with chest pain per day in the emergency department (according to our in- and exclusion criteria). We found that approximately 7.4% of these patients were diagnosed with MI. To ensure study completion a 23-month data collection period is planned.

The group behind the project is established within the field of cardiovascular research, has previously completed a randomized clinical trial at Randers Regional Hospital and has the necessary expertise to ensure the completion of the study.

The project will be performed in close collaboration with the Emergency Department, Department of Internal Medicine and Department of Clinical Biochemistry at Randers Regional Hospital. The departments are involved to ensure that the project fits into a clinical setting and can be implemented properly throughout all units. Registration of patients, blood sampling etc. will be performed by the clinical staff in collaboration with the research group.

Financial statement

The project is investigator initiated. Application for study support will be send to appropriate funding agencies. Grant support for one of the lead investigators is provided by Randers Regional Hospital.

Investigators and publication

Camilla Bang, MD, and Camilla Hansen, MD, are the lead investigators of the outlined study. Professor Bo Løfgren, MD, PhD, FESC (PI) has committed himself as main supervisor and scientific mentor. Kasper Glerup Lauridsen, MD, PhD student, Christian Alcaraz Frederiksen MD, PhD, Morten Schmidt, MD, PhD, consultant Tage Jensen, MD and associate professor, consultant Nete Hornung, MD, PhD, have committed themselves as co-supervisors.

The results, whether positive, negative or inconclusive, will be submitted to an international peer-reviewed journal.

Perspectives

This study challenges existing time limits for MI evaluation by investigating the diagnostic value of hs-cTnI measurements at 30m. If our study shows that rule-in and rule-out of MI can be performed safely at 30m, MI evaluation can potentially be accelerated even further.

The study results can change clinical practice for patients presenting with chest pain in the future. Implementation of the algorithm can lead to improved patient outcomes, as a decrease in time to clinical decision-making favours early initiation of treatment. In addition, bed availability may rise in emergency departments to the benefit of patient safety.

References

1. Cohn JK, Cohn PF. Cardiology Patient Page – Chest Pain. *Circulation*. 2002;106:530-531
2. Roffi M, Patrono C, Collet JP, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2016;37:267-315.
3. Giménez M, Twerenbold R, Jaeger C. et al. One-hour Rule-in and Rule-out of Acute Myocardial Infarction Using High-sensitivity Cardiac Troponin I. *Am J Med*. 2015; 128; 861-870.
4. Reichlin T, Schindler C, Drexler B, et al. One-Hour Rule-out and Rule-in of Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T. *Arch Intern Med*. 2012; 172.
5. Reichlin T, Twerenbold R, Wren K, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. *CMAJ*. 2015;187.
6. Mueller C, Giannitsis E, Christ. Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T. *Ann Emerg Med*. 2015;:-1-12.
7. Jaeger C, Wikli K, Twerenbold R, Reichlin T, Gimenez MR, Mueller C. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. *Am Heart J* 2016;171:92-102.e5.
8. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 64:2645-87.
9. Liebetrau C, Möllmann H, Nef H, et. al. Release Kinetics of Cardiac Biomarkers in Patients Undergoing Transcatheter Ablation of Septal Hypertrophy. *Clin Chem*. 2012;58:1049-1054.
10. Shiozaki M, Inoue K, Suwa S, et al. Utility of the 0-hour/1-hour high-sensitivity cardiac troponin T algorithm in Asian patients with suspected non-ST elevation myocardial infarction. *Int J Cardiol*. 2017;249:32-35.

11. Backus BE, Six AJ, Kelder JC, et. al. Chest Pain in the Emergency Room: A Multicenter Validation of the HEART Score. *Crit Pathways in Cardiol.* 2010;9:164-169.
12. Steg G, et al. 2012 ESC Guidelines for the management of acute coronary infarction in patients presenting with persistent ST-segment elevation. *European Heart Journal.*