

# BMJ Open A comprehensive validation of very early rule-out strategies for non-ST-segment elevation myocardial infarction in emergency departments: protocol for a multicentre prospective cohort study

Masafumi Tada,<sup>1</sup> Hiroyuki Azuma,<sup>2</sup> Naoki Yamada,<sup>3</sup> Ken-ichi Kano,<sup>2</sup> Hideya Nagai,<sup>2</sup> Shigenobu Maeda,<sup>2</sup> Hiroshi Ishida,<sup>2</sup> Takahiko Aoyama,<sup>4</sup> Ryota Okada,<sup>3</sup> Takahisa Kawano,<sup>3</sup> Taketsune Kobuchi,<sup>3</sup> Hiroyasu Uzui,<sup>5</sup> Hideyuki Matano,<sup>6</sup> Hose Iwasaki,<sup>6</sup> Koji Maeno,<sup>7</sup> Yoshimitsu Shimada,<sup>8</sup> Hiroyuki Yoshida,<sup>9</sup> Masaki Ando,<sup>10</sup> Yoshimasa Murakami,<sup>11</sup> Naotsugu Iwakami,<sup>12</sup> Sanae Kishimoto,<sup>1</sup> Taku Iwami,<sup>13</sup> Hiroshi Tada,<sup>5</sup> Andrew Chapman,<sup>14</sup> Nicholas Mills,<sup>14</sup> Hiroyuki Hayashi,<sup>3</sup> Toshi A Furukawa,<sup>1</sup> Norio Watanabe<sup>1</sup>

**To cite:** Tada M, Azuma H, Yamada N, *et al.* A comprehensive validation of very early rule-out strategies for non-ST-segment elevation myocardial infarction in emergency departments: protocol for a multicentre prospective cohort study. *BMJ Open* 2019;**9**:e026985. doi:10.1136/bmjopen-2018-026985

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-026985>).

Received 30 September 2018

Revised 06 June 2019

Accepted 11 July 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Masafumi Tada;  
tada.masafumi.76r@kyoto-u.jp

## ABSTRACT

**Introduction** Recent advances in troponin sensitivity enabled early and accurate judgement of ruling-out myocardial infarction, especially non-ST elevation myocardial infarction (NSTEMI) in emergency departments (EDs) with development of various prediction-rules and high-sensitive-troponin-based strategies (hs-troponin). Reliance on clinical impression, however, is still common, and it remains unknown which of these strategies is superior. Therefore, our objective in this prospective cohort study is to comprehensively validate the diagnostic accuracy of clinical impression-based strategies, prediction-rules and hs-troponin-based strategies for ruling-out NSTEMIs.

**Methods and analysis** In total, 1500 consecutive adult patients with symptoms suggestive of acute coronary syndrome will be prospectively recruited from five EDs in two tertiary-level, two secondary-level community hospitals and one university hospital in Japan. The study has begun in July 2018, and recruitment period will be about 1 year. A board-certified emergency physician will complete standardised case report forms, and independently perform a clinical impression-based risk estimation of NSTEMI. Index strategies to be compared will include the clinical impression-based strategy; prediction rules and hs-troponin-based strategies for the following types of troponin (Roche Elecsys hs-troponin T; Abbott ARCHITECT hs-troponin I; Siemens ADVIA Centaur hs-troponin I; Siemens ADVIA Centaur sensitive-troponin I). The reference standard will be the composite of type 1 MI and cardiac death within 30 days after admission to the ED. Outcome measures will be negative predictive value, sensitivity and effectiveness, defined as the proportion of patients categorised as low risk for NSTEMI. We will also evaluate inter-rater reliability of the clinical impression-based risk estimation.

## Strengths and limitations of this study

- This is the first prospective study to compare clinical impression-based strategies, prediction-rules and hs-troponin-based strategies for ruling-out non-ST elevation myocardial infarction in patients with symptoms suggestive of acute coronary syndrome in emergency department (ED).
- We will also evaluate the inter-rater reliability of the clinical impression-based risk estimation and discuss the usefulness of the strategies considering both the diagnostic accuracy and the inter-rater reliability.
- We will use three high-sensitive-troponin and one sensitive-troponin which are currently widely available in order to increase the applicability of the results of our study.
- A limitation of the study is that troponin will rarely be taken later than 3 hours after presentation to ED and we follow-up patients mainly by telephone interview, and therefore, we may miss some subsequent myocardial infarctions (MIs), although it is very unlikely that patients will have a MI and not reattend hospital.
- Because the study population is only from Japan, the generalisability of the results might be limited, although the prevalence of MI varies largely among previous studies and that of our study will be somewhere among them.

**Ethics and dissemination** The study is approved by the Ethics Committees of the Kyoto University Graduate School and Faculty of Medicine and of the five hospitals where we will recruit patients. We will disseminate the study results through conference presentations and peer-reviewed journals.

## INTRODUCTION

### Background

Because ruling-out non-ST elevation myocardial infarctions (NSTEMIs) is often challenging, the American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) 2007 guidelines mandate the serial troponin tests over a period of 6–12 hours after symptom onset or admission to the emergency department (ED).<sup>1 2</sup> This long period of observation is the principal reason for admitting patients with symptoms that might be related to an myocardial infarction (MI) and is, in fact, the most frequent reason for admission in ED in both the UK and the USA.<sup>3 4</sup> However, between 75% and 95% of patients presenting to the EDs with symptoms suggestive of MI did not have MI.<sup>5 6</sup> Therefore, earlier and safer strategies to rule-out an MI in EDs, which would allow patients to be discharged directly from the ED, have been in a great demand. It is generally accepted that the risk of MI and death within 30 days should be <1–2% to patients directly discharged from the ED.<sup>7 8</sup>

Recently, several high-sensitive-troponins (hs-troponin) have decreased the recommended time for troponin monitoring for MI diagnosis to 3–6 hours (2014 ACC/AHA guidelines<sup>9</sup>), and further to 0–3 hours (2015 ESC guidelines<sup>10</sup>). Furthermore, a large individual patient-level data meta-analysis reported that when the initial troponin value was much lower than the 99th percentile, the negative predictive value (NPV) was consistently >99% across the included cohorts.<sup>6</sup> Therefore, the time frame of serial troponin monitoring could be greatly shortened, or even made unnecessary, for certain populations. The population in East Asia may be appropriate for very early ‘ruling-out’ strategies of MI since the incidence of MI in East Asia, especially in Japan, is much lower than in Western countries.<sup>11</sup>

Although troponin is crucial for the accurate diagnosis of MI, the clinical history, physical findings and ECG are also essential. Several clinical decision-making models have been developed for MI, including the clinical impression-based strategy, prediction rules and the hs-troponin-based strategy. The clinical impression-based strategy is a traditional approach where clinical gestalt is used to estimate risk based on the history and physical findings, and review of the ECG and troponin. Although few reports are available, this approach remains common in practice, especially in Japan. However, the inter-rater reliability of the risk estimation for MI based on clinical impression has not been comprehensively evaluated, and previous studies suggested that risk estimation for MI varies greatly, depending on the physician’s experience and background.<sup>12 13</sup>

Prediction rules have been developed that consider clinical findings and troponin monitoring in a structured way to determine the risk of an MI. Several prediction rules to estimate the risk of an MI have been defined, including the TIMI,<sup>14</sup> HEART,<sup>15</sup>

EDACS<sup>16</sup> and T-MACS<sup>17</sup> rules. Most of the newer prediction rules that have incorporated hs-troponin have achieved an NPV of >99% and have been validated.<sup>18–21</sup> Prediction rules, however, are not widely used, despite their excellent NPVs, partly because they have not been compared against clinical impression-based strategies.<sup>22</sup>

There are several hs-troponin-based strategies that use only hs-troponin, such as the 0 and 1 hour algorithm,<sup>23</sup> the 0 and 2 hour algorithm<sup>24</sup> and the High-STEACS pathway.<sup>25</sup> These strategies are simple, and they rely on a measurement of hs-troponin only, with demonstrated NPVs of >99%. Hs-troponin assays have excellent precision at very low concentrations with very few analytical false positives.<sup>26</sup> On the other hand, the clinical history, physical findings and ECG readings are sometimes not reliable, and different physicians often have different interpretations.<sup>13 27</sup> Although they are essential components of a comprehensive clinical assessment, the first risk stratification might be better to be based on something that is highly reliable, with subsequent risk stratification performed using clinical judgement, especially in ED where physicians with differing backgrounds and experience work. However, the cutoffs of troponin levels in these hs-troponin strategies tend to be much lower than the 99th percentile and patient age, which has previously been associated with an increase in troponin level,<sup>28 29</sup> may affect the proportion of patients to be ruled-out. As such, hs-troponin-based strategies may be less efficient in highly aged populations, such as in Japan.

### Rationale for the study

First, although many strategies to rule-out MI have been proposed, a comprehensive prospective validation of the clinical impression-based strategies, prediction-rules and hs-troponin-based strategies to rule-out MI has not been performed.

Second, although the use of serial troponin and the cutoffs below the 99th percentile of troponin are recommended in Western countries, it has not yet been proven well in East Asia, where the incidence of MI is low and reliance on the clinical impression-based strategy is common.<sup>11</sup> Because serial troponin is not only time consuming, but requires additional resources and medical expenses, there is a need, particularly in East Asia, to evaluate the NPV of clinical impression-based strategies, combined with troponin levels obtained at different time points, using the 99th percentile cut-off value.

Third, although many kinds of troponins are now available, the diagnostic accuracy and cut-off are each troponin specific. Our proposed study will include the four types of troponin that are currently widely available: Roche hs-troponin T; Abbott hs-troponin I; Siemens hs-troponin I; Siemens sensitive-troponin I in order to increase the applicability of our results to as many facilities as possible.

## Study objectives

### Primary research objective

Our primary objective is to compare the NPV, sensitivity and effectiveness (defined as the proportion of patients categorised into low risk to all patients to whom a strategy was applied) of the three clinical impression-based strategies with three time frames of troponin monitoring: on arrival (0 hour) only; 0 and 1 hour after; and 0 and 2 hour after, using the composite outcome of cardiac death or the occurrence of a type 1 MI within 30 days of the ED consultation.

### Secondary research objectives

Our secondary research objectives are:

1. To validate and compare the NPV, sensitivity and effectiveness between clinical impression-based strategies, prediction rules and hs-troponin-based strategies.
2. To evaluate the inter-rater reliability of the clinical impression-based strategy, in estimating the risk estimation of an MI, when performed by board-certified emergency physicians and senior residents of emergency medicine, general internists, cardiologists, junior residents and nurses.

## METHODS AND ANALYSIS

### Setting

We will recruit patients from five EDs in two tertiary-level community hospitals (Fukui Prefectural Hospital, Nagoya East Medical Center), two secondary-level community hospitals (Fukui-ken Saiseikai Hospital, Japanese Red Cross Fukui Hospital) and one university hospital (Fukui University Hospital) in Japan. Because patient recruitment is slow, we are adding a number of hospitals. We have purposively selected hospitals which cover the majority of emergency cases in the rural as well as urban to suburban areas.

### Inclusion criteria

1. Age  $\geq 25$  years.
2. Have any one of the following symptoms suspected to be MI.
  - a. Chest pain.
  - b. Non-chest pain, including radiating pain, syncope, dyspnea, nausea/vomiting and fatigue, and other symptoms which emergency physicians judge to need to rule out an MI.
3. Presentation to the ED within 6 hours from symptom onset. We will set the threshold at 6 hours to focus on early presenters, the most difficult population to rule-out NSTEMI very early.<sup>30</sup>
4. No apparent ST elevation on arrival.
5. The use of both ECG and the troponin test, as deemed to be required by the ED physician.

### Exclusion criteria

1. Cardiopulmonary arrest on arrival.
2. Non-cardiac terminal illness (expected survival  $< 6$  months).

3. Need for resuscitation (physiological shock, continuous oxygen administration).
4. Indication of emergency catheterisation on arrival.
5. Inability of the patient to provide consent.
6. Previous inclusion in the study.
7. Unable to contact for follow-up after 30 days.
8. Unknown time of onset of symptoms.
9. Apparent need to admit for a diagnosis other than acute coronary syndrome on arrival.
10. Patients on maintenance dialysis.
11. Judged as ineligible by an emergency physician.

### Participants recruitment

When an MI is suspected, an ECG will be obtained first, as per usual practice. If there is no significant ST elevation, a board-certified emergency physician will assess the eligibility of the patient for enrolment into the study. Because board-certified emergency physicians are not regularly available at night or on weekends in three of the participating hospitals (Fukui-ken Saiseikai Hospital; Japanese Red Cross Fukui Hospital; and Nagoya East Medical Center), patients will only be recruited when board-certified emergency physicians are working in these centres. In the other two facilities (Fukui Prefectural Hospital and Fukui University Hospital), board-certified emergency physicians are available around the clock and, therefore, patients will be recruited as they present to the EDs. We will review the patient recruitment status regularly by checking clinical records of all patients who visit ED in all hospitals to ensure representativeness and minimise spectrum bias.

### Informed consent

We will obtain written informed consent from all patients. Because MI is more common in the elderly, it may be sometimes difficult to obtain informed consent from some patients due to dementia. Because excluding these patients will impair the validity of the study, we will seek to obtain consent from patient's authorised proxy in such cases. We will conduct this study in accordance with the Declaration of Helsinki and its amendments. This study is registered in the UMIN-CTR registry (UMIN 000029992).

### Clinical assessments

The following assessments will be performed at each site using standardised case report forms (CRF): history; physical examination; clinical impression-based risk estimation; ECG; standard blood tests; ultrasonography; and troponin levels (using both in-house and research troponin types). Clinical impression-based risk estimation for a NSTEMI will be classified as low, intermediate or high for analysis. The certainty of each item of the clinical history and ECG will be measured using a 4-point Likert scale. The inter-rater reliability will be evaluated between a board-certified emergency physician and one of the following medical staff: a board-certified emergency physician; an emergency medicine resident; a junior resident; a general practitioner;

**Table 1** The 99th percentile and LoD values for four types of troponin

Troponin	99th percentile (ng/L)	LoD (ng/L)
Roche Elecsys hs-troponin T (general)	14.0	3.0
Roche Elecsys hs-troponin T (male)	15.5	
Roche Elecsys hs-troponin T (female)	9.0	
Abbott ARCHITECT hs-troponin I (general)	26.2	1.9
Abbott ARCHITECT hs-troponin I (male)	34.2	
Abbott ARCHITECT hs-troponin I (female)	15.6	
Siemens ADVIA Centaur hs-troponin I (general)	46.5	2.2
Siemens ADVIA Centaur hs-troponin I (male)	58.1	
Siemens ADVIA Centaur hs-troponin I (female)	39.6	
Siemens ADVIA Centaur sensitive-troponin I	40.0	6.0

LoD, limit of detection.

a cardiologist; or a nurse for 300 consecutive patients enrolled into the study. The following variables will be included for inter-rater reliability: clinical impression-based risk estimation; each item of the clinical history; ECG; ultrasonography. Assessors will not be provided with results of the troponin levels, ultrasonography examination or the previous assessment performed by another emergency physician or cardiologist before completion of the CRF. Because it will occasionally be difficult to mask this information, we will report the masking status. Management of patients will be left to the discretion of treating emergency physicians and cardiologists, based on the results of in-house troponin measurements in each hospital. The indication of early invasive strategy will follow current guidelines.<sup>9 10 31</sup> We will check all CRF immediately after we receive them from hospitals. If there are some missing values, we will ask coresearchers and make efforts to retrieve them as much as possible.

### Troponin

We will evaluate the following four types of troponin, three high-sensitive and one sensitive. The 99th percentile and the limit of detection values for the four types of troponin are summarised in table 1. We will use sex-specific 99th percentile values for three types of hs-troponin in sensitivity analyses. We will collect blood samples in serum tubes for troponin levels on arrival (0 hour); and at 1, 2 and 3 hours after the first blood draw. After centrifugation, serum samples will be stored at less than  $-20^{\circ}\text{C}$  until measured in each manufacturer's laboratory in a blinded fashion.

### Index tests

We will evaluate the three types of decision-making models to rule-out MI: the clinical impression-based

strategies, prediction rules and hs-troponin-based strategies. An author (MT) searched PubMed (December 2017) for prediction rules and hs-based strategies to rule-out MI in ED. We also consulted reviews on this topic to identify suitable decision-making models. Among identified prediction-rules and hs-troponin-based strategies, we selected those which were validated and showed an NPV of  $>99\%$ , using any types of troponin. We will include strategies with troponin taken up to 2 hours apart from the first one. Because it generally takes about 1 hour to take the first blood sample, we will include strategies with troponin taken up to 3 hours from presentation. All the intervals of troponin sampling we showed below are the time from the first blood draw. Each troponin will be adapted for each strategy, as needed. We will define the troponin cut-off at the 99th percentile value, except for hs-troponin-based strategies, and the T-MACS. The troponin cutoffs for hs-troponin-based strategies are specific for each type of troponin, as detailed below. Troponin values will be incorporated as a continuous variable in the T-MACS. We will adopt cutoffs for each strategy in accordance with the original publication for each strategy. The details of each prediction rule are shown in the online supplementary appendix. All the index tests will be applied to a patient using prospectively collected clinical information after we complete patient recruitment.

### The clinical impression-based strategies

- The 0 hour model.
  - Clinical impression-based risk estimation for history and physical findings is not high risk.
  - No new ischaemic findings on ECG.
  - Troponin taken on arrival is below the 99th percentile.
- The 0 and 1 hour model.
  - Clinical impression-based risk estimation for history and physical findings is not high risk.
  - No new ischaemic findings on ECG.
  - Troponin taken on arrival and at 1 hour apart are both below the 99th percentile.
- The 0 and 2 hour model.
  - Clinical impression-based risk estimation for history and physical findings is not high risk.
  - No new ischaemic findings on ECG.
  - Troponin taken on arrival and at 2 hour apart are both below the 99th percentile.

We will evaluate the clinical impression-based risk estimation for history and physical findings based on the AHA/ACC guideline<sup>32</sup> and a systematic review.<sup>33</sup> We define the new ischaemic findings on ECG as an ST depression and negative T wave not known to be old. An ST depression is defined by a depression of 0.05 mV or more at J point in two or more contiguous leads. A negative T wave is defined by T wave inversions of 0.1 mV or more in two or more contiguous leads. If all three

components of each model are satisfied, we regard a patient as being at low risk for an MI.

### Prediction rules

1. TIMI+2 hour troponin.<sup>34</sup>
  - a. Components: age, coronary risk factors, use of aspirin, significant coronary stenosis, severe angina, ECG and troponin (at 0 and 2 hours).
  - b. Cut-off: we will define the score of 0 as a low risk for MI.
2. HEART.<sup>15</sup>
  - a. Components: history, ECG, age, risk factors and troponin.
  - b. Cut-off: we will define the score of 0–3 and negative troponin as a low risk for MI.
3. EDACS.<sup>16</sup>
  - a. Components: age, sex, coronary artery disease or risk factors, symptoms, ECG and troponin (at 0 and 2 hours).
  - b. Cut-off: we will define low risk when all three conditions are satisfied, namely: a score < 16; no new ischaemia on ECG; and negative troponin at 0 and 2 hours.
4. T-MACS.<sup>17</sup>
  - a. Components: (E) ECG ischaemia, (A) worsening or crescendo angina, (R) right arm or shoulder pain, (V) vomiting, (S) sweating observed, (H) hypotension (systolic blood pressure <100 mm Hg), (T) high-sensitivity troponin T concentration on arrival (ng/L).
  - b.  $\text{Probability} = 1 / (1 + e^{-(1.713E + 0.847A + 0.607R + 1.417V + 2.058S + 1.208H + 0.089T - 4.766)})$ .
  - c. Cutoff: we will define low risk if the probability is <0.02.
5. TRUST.<sup>35</sup>
  - a. Components: typical new-onset chest pain at rest, pain the same as previous MI, pain not relieved by glyceryl trinitrate within 15 min, pain lasting >60 min, pain occurring with increasing frequency, hypotension, acute shortness of breath, pain within 6 weeks of an MI or revascularisation, ECG, hs-troponin (at 0 hour).
  - b. Cutoff: we will define low risk when all three conditions are satisfied: the score of 0 or 1, non-ischaemic ECG and negative troponin.
6. GRACE.<sup>10</sup>
  - a. Components: age, history of congestive heart failure, history of MI, resting heart rate, systolic blood pressure, ST-segment depression, initial serum creatinine, elevated cardiac enzymes, no in-hospital percutaneous coronary intervention.
  - b. Cut-off: we will define the score <140 AND negative troponin at 0 and 2 hours.

### Hs-troponin-based strategies

Hs-troponin-based strategies are comprised of hs-troponin only, with cut-off values being troponin specific, as shown below for the five algorithms that will be used in

the study. If a troponin value is below the cut-off values of each strategy, we regard a patient as being at low risk for an MI. In the High-STEACS pathway, a second troponin measurement is obtained 3 hours from presentation to the ED.<sup>25</sup> Because there is often a delay of up to 1 hour for the first blood sample, the average time between the first and second troponin measurement is 2 hours, and therefore, we include the High-STEACS pathway without modification.

1. The 0 hour algorithm.<sup>36 37</sup>
  - a. Roche hs-troponin T: 0 hour <5 ng/L<sup>(\*1)</sup>.
  - b. Abbott hs-troponin I: 0 hour <2 ng/L<sup>(\*2)</sup>.
  - c. Siemens hs-troponin I: 0 hour <3 ng/L<sup>(\*3)</sup>.
  - d. Siemens sensitive-troponin I: 0 hour <0.5 ng/L<sup>(\*4)</sup>.
2. The 1 hour algorithm.<sup>23 37–39</sup>
  - a. Roche hs-troponin T: 0 hour <12 ng/L AND  $\Delta$ 0-1 hour <3 ng/L<sup>(\*5)</sup>
  - b. Abbott hs-troponin I: 0 hour <5 ng/L AND  $\Delta$ 0-1 hour <2 ng/L<sup>(\*6)</sup>
  - c. Siemens hs-troponin I: 0 hour <6 ng/L AND  $\Delta$ 0-1 hour <3 ng/L<sup>(\*7)</sup>
  - d. Siemens sensitive-troponin I: 0 hour <10 ng/L AND  $\Delta$ 0-1 hour <4 ng/L<sup>(\*8)</sup>
3. The 2 hour algorithm.<sup>24 39 40</sup>
  - a. Roche hs-troponin T: 0 and 2 hour <14 ng/L AND  $\Delta$ 0-2 hour <4 ng/L.
  - b. Abbott hs-troponin I: 0 and 2 hour <6 ng/L AND  $\Delta$ 0-2 hour <2 ng/L
  - c. Siemens sensitive-troponin I: 0 and 2 hour <10 ng/L.
4. The 0 and 1 hour algorithm.<sup>10 37</sup>
  - a. Roche hs-troponin T: \*1 OR \*5.
  - b. Abbott hs-troponin I: \*2 OR \*6.
  - c. Siemens hs-troponin I: \*3 OR \*7.
  - d. Siemens sensitive-troponin I: \*4 OR \*8.
5. The High-STEACS pathway (only for Abbott hs-troponin I at the moment).<sup>25</sup>
  - a. If hs-troponin I at 0 hour <5 ng/L AND symptom onset  $\geq$ 2 hours, AMI is ruled out.
  - b. If  $5 \leq$  hs-troponin I at 0 hour  $\leq$ 26.2 ng/L OR symptom onset <2 hours, hs-troponin I at 2 hours is required. If  $\Delta$ 0-2 hour hs-troponin I <3 ng/L AND hs-troponin I at 3 hours  $\leq$ 26.2 ng/L, AMI is ruled out.

### Reference standard

#### Final diagnosis adjudication

Two cardiologists of each facility will independently adjudicate the final diagnosis based on the results of the follow-up telephone interview and all available clinical information obtained 30 days or more after the admission to the ED: each item of the clinical history; physical examination; laboratory tests (both in-house troponin and hs-troponin T taken at 0 and 3 hours); ECG; ultrasonography; cardiac stress test; radiological test; and coronary angiography. Disagreements will be resolved through discussions between the two cardiologists. If they are unable to reach consensus, a third cardiologist

will be consulted. All cardiologists will be masked from the results of index tests and the research hs-troponin obtained at 1 and 2 hours.

The diagnosis of MI will be made in accordance with the fourth universal definition of MI,<sup>41</sup> and classified as type 1, type 2, type 4b and myocardial injury. Briefly, an MI will be diagnosed if there is a significant rise and/or fall of troponin, with at least one value above the 99th percentile, in a clinical setting consistent with acute myocardial ischemia. We will adjudicate final diagnosis with each of hs-troponin assays (Roche hs-troponin T, Abbott hs-troponin I and Siemens hs-troponin I). We will use the same hs-troponin to adjudicate the final diagnosis as that used for index tests to avoid unequal incorporation bias. We will define a significant rise and/or fall for 3 hours as 6 ng/L for Roche hs-troponin T; the relative increase of >50% of the respective 99th percentile value if the initial troponin value is equal or less than the 99th percentile value, and the relative increase of >20% of the initial value if the initial troponin values is greater than the 99th percentile value for Abbott hs-troponin I and Siemens hs-troponin I.<sup>23 26</sup> Type 1 MI is defined as myocardial necrosis with symptoms suggestive of MI or test results which prove myocardial ischemia. Type 2 MI is defined as myocardial necrosis, with a condition other than coronary artery disease, which contributes to an oxygen supply-demand imbalance (eg, coronary artery spasm; tachyarrhythmia; respiratory failure; or anaemia). Type 4b is an MI associated with stent thrombosis.

### Clinical outcomes

The primary clinical outcome will be the composite of type 1 MI and cardiac death within 30 days of the ED admission. We will add type 2 and 4b MI to the primary clinical outcome as a sensitivity analysis, because it will be occasionally difficult to differentiate type 1 MI and other types of MI. If patients consult an ED or cardiac service in the study facility again, emergency physicians or cardiologists will ask patients if they have had an MI or if they have undergone any cardiac tests or revascularisation in other hospitals. Because not all patients can be expected to consult a study facility again, research staffs will conduct structured telephone follow-up interview with all patients enrolled into the study, 30 days after the ED admission. At 30 days, if patients have either consulted a study facility again or if sufficient clinical information is available, we will include only type 1 MI as the primary clinical outcome. While for patients who do not consult a study facility again and, therefore, only information from the telephone follow-up is for clinical outcomes, it will be difficult to differentiate type 1 MI from other types of MI. In these cases, we will include all MI types (1, 2 and 4b) as the primary clinical outcome. Similarly, the adjudication of a cause of death might be difficult in some patients. In this case, we will include an unknown cause of death into our primary outcome. Patients who do not consult a study facility again and could not be reached for the

telephone follow-up interview will be excluded from the primary and secondary research objectives.

### Sample size calculation

Assuming that the event rate of the primary clinical outcome is 5%–10%,<sup>6 11</sup> with a sensitivity and specificity of the clinical impression-based strategies of 95% and 55%, respectively,<sup>42</sup> 1500 patients will need to be enrolled into the study if the lower limit of 95% CI of the NPV is to surpass 98%.

### Data analysis

#### Missing values

For missing values in clinical assessments, we will use the multiple imputation technique to minimise bias and preserve study power. We will also perform complete case analysis as a sensitivity analysis.

#### Primary research objective

We will describe the NPV, sensitivity and effectiveness of the three clinical impression-based strategies, using the 95% CI for each troponin. We will also calculate the specificity, positive predictive value and area under the receiver operating characteristic curve (AUC) for each strategy. We will derive a generalised score statistic to compare NPV, and use the McNemar test to compare sensitivity and effectiveness. We will regard a strategy as being clinically useful if the point estimate for NPV is  $\geq 99\%$ . If the point estimate for NPV is  $\geq 99\%$ , we will regard a strategy with shorter observational period as superior.

#### Secondary research objective 1

We will describe the NPV, sensitivity, effectiveness, AUC for the clinical impression-based strategies, prediction rules and hs-troponin-based strategies for each troponin. If the point estimate for NPV is  $\geq 99\%$ , we will regard a strategy with higher effectiveness and/or shorter observational period as superior.

#### Secondary research objective 2

Reliability will be evaluated for 300 consecutive patients. We will use Cohen's weighted Kappa-statistic and the boot-strap method, with 1000 replications, to determine the 95% CI boundaries of reliability.

### Sensitivity analysis

A sensitivity analysis will be performed including type 2 and 4b MI to the primary clinical outcome. We will compare the NPV, sensitivity and effectiveness of the index tests between subgroups stratified by: time from symptom onset to hospital arrival; the clinical impression-based risk estimation; previous history of ischaemic heart disease or revascularisation; age; sex; and presence of chest pain considering its certainty. We will define the cut-off of the clinical impression-based risk estimation as neither moderate nor high. We also perform analyses by changing the cutoffs of other strategies. We will combine the hs-troponin-based strategies with clinical impression-based risk estimation and/or ECG, and evaluate

the NPV, sensitivity and effectiveness. We will use each of Roche Elecsys hs-troponin T; Siemens ADVIA Centaur hs-troponin I; and Siemens ADVIA Centaur sensitive-troponin I for the adjudication of MI. We will use sex-specific 99th percentiles of three types of hs-troponin for the index tests. We will perform complete case analysis for primary and secondary research objectives.

### Ethics and dissemination

This study is approved by the Ethics Committees of the Kyoto University Graduate School and Faculty of Medicine (R1380, 27 February 2018) and the five hospitals where we will recruit patients. We will disseminate the results of the study through peer-reviewed journals and conference presentations. For the study participants, we will disseminate the brief summary of the results of the study to all the EDs of study hospitals.

### Patient and public involvement

Patients were not involved in the design of this study and asked for input in the creation of this article.

### Summary

Along with the advance in troponin monitoring, the early management of MI suspected patients is markedly changing. Though many troponins are available now, diagnostic accuracy and cut-off values are specific for each type of troponin. Although many prediction-rules and hs-troponin-based strategies have been published, it is still unknown if these algorithms are superior to clinical impression-based strategies. The study will be the first prospective study to compare clinical impression-based strategies, using four different types of troponin that are commonly used to estimate the risk of an MI with prediction-rules and hs-troponin-based strategies. We will also evaluate the inter-rater reliability of the clinical impression-based risk estimation, and discuss the usefulness of these strategies, considering both the diagnostic accuracy and the inter-rater reliability.

### Author affiliations

<sup>1</sup>Department of Human Behavior and Health Promotion, Kyoto University, Kyoto, Japan

<sup>2</sup>Department of Emergency Medicine, Fukui Prefectural Hospital, Fukui, Japan

<sup>3</sup>Department of Emergency Medicine, Fukui University Hospital, Fukui, Japan

<sup>4</sup>Cardiology, Vascular Center, Fukui Prefectural Hospital, Fukui, Japan

<sup>5</sup>Department of Cardiovascular Medicine, Fukui University Hospital, Fukui, Japan

<sup>6</sup>Department of Emergency Medicine, Fukui-ken Saiseikai Hospital, Fukui, Japan

<sup>7</sup>Department of Cardiology, Fukui-ken Saiseikai Hospital, Fukui, Japan

<sup>8</sup>Department of Emergency Medicine, Japanese Red Cross Fukui Hospital, Fukui, Japan

<sup>9</sup>Department of Cardiology, Japanese Red Cross Fukui Hospital, Fukui, Japan

<sup>10</sup>Department of Emergency Medicine, Nagoya City East Medical Center, Nagoya, Japan

<sup>11</sup>Department of Cardiovascular Medicine, Nagoya City East Medical Center, Nagoya, Japan

<sup>12</sup>Department of Research Promotion and Management, National Cerebral and Cardiovascular Center, Suita, Japan

<sup>13</sup>Department of Health Service, Kyoto University, Kyoto, Japan

<sup>14</sup>British Heart Foundation Center for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

**Correction notice** This article has been corrected since it was published.

**Acknowledgments** The authors sincerely thank the patients who are participating in the study. The authors warmly thank emergency physicians, S Tanizaki, M Sera, M Hayashi, T Nakanishi, H Watanabe and J Tanaka in Fukui prefectural hospital; T Kimura, H Morita, T Yamanaka, T Hamada, H Tsuji, Y Kuwabara and Y Kamikawa in Fukui university hospital; M Inagaki, T Miura and T Ohno in Nagoya city east medical center. The authors would like to thank cardiologists, S Fujino, M Yamaguchi, Y Noji, H Kato, R Yamamura, N Ukawa and Y Takahashi in Fukui prefectural hospital; S Miyazaki, K Ishida, K Kaseno, K Hasegawa, T Morishita, Y Fukuoka, H Ikeda, N Tama, Y Shiomi, J Yamaguchi, D Aoyama, T Aiki, E Ishikawa, M Mukai, A Matsui and K Miyahara in Fukui university hospital; H Takemori, K Ohkura, M Hirazawa, S Ohkura and H Tsuneyama in Fukui-ken Saiseikai hospital; T Akiyoshi, K Sarazawa, K Sakakibara, J Yamaguchi and T Kataoka in Japanese red cross Fukui hospital; T Saeki, N Tamai, S Yamashita, T Yoshida, T Sekimoto, K Hachiya, T Hasuo, T Hashimoto and T Noda in Nagoya city east medical center. The authors also thank general physicians, residents, nurses and clinical technologists of the five study hospitals for their voluntary co-operation. The authors acknowledge clinical laboratory technologists of the five study hospitals for blood sample handling; and the Roche and T Kikuchi, the Abbott and S Sugawa, and the Siemens and T Yokoyama for biomarker measurement including troponin. The authors also appreciate K Yamamoto and the Union Think for offering an optical character recognition programme to incorporate data of paper CRF into REDCap (version 8.1.17; Nashville, TN) electronic data capturing system.

**Author contributions** MT and NW wrote the first draft. All other authors, HA, NY, K-iK, HN, SM, HI, TA, RO, TKa, TKo, HU, HM, HI, KM, YS, HY, MA, YM, NI, SK, TI, HT, AC, NM, HH and TAF contributed to the conception and design of the study. All the authors read and approved the final manuscript.

**Funding** The study is supported by grants from Nakatani Foundation (Tokyo, Japan), and from Radiometer (Tokyo, Japan).

**Competing interests** MT received non-financial support from Roche, Abbott and Siemens during the conduct of the study; personal fees from Japan Medical Journal, outside the submitted work. AC has received honoraria from Abbott Diagnostics and AstraZeneca. NM has received honoraria and consultancy from Abbott Diagnostics, Roche Diagnostics and Singulex. TAF reports personal fees from Meiji Seika, grants and personal fees from MSD, personal fees from Pfizer, outside the submitted work. NW has received research funds from the Japanese Ministry of Health Labor and Welfare, the Japanese Ministry of Education, Science, and Technology and National Center of Neurology and Psychiatry, Intramural Research Grant for Neurological and Psychiatric Disorders. He has also received royalties from Sogensha and Akatsuki.

**Patient consent for publication** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

### REFERENCES

- Anderson JL, Adams CD, Antman EM, *et al.* ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American heart association Task force on practice guidelines (writing Committee to revise the 2002 guidelines for the management of patients with unstable Angina/Non ST-elevation myocardial infarction): developed in collaboration with the American College of emergency physicians, the Society for cardiovascular angiography and interventions, and the Society of thoracic surgeons: endorsed by the American association of cardiovascular and pulmonary rehabilitation and the Society for academic emergency medicine. *Circulation* 2007;116:e148–304.
- Bassand J-P, Hamm CW, Ardissino D, *et al.* Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;28:1598–660.
- Niska R, Bhuiya F, Xu J. National Hospital ambulatory medical care survey: 2007 emergency department summary. *Natl Health Stat Report* 2010;26:1–31.



4. The Health and Social Care Information Centre. Hospital episode statistics, admitted patient Care—England, 2013-14: primary diagnosis, 3 characters table. Available: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/hospital-episode-statistics-admitted-patient-care-england-2013-14#resources> [Accessed 30 Jan 2019].
5. Hollander JE, Than M, Mueller C. State-Of-The-Art evaluation of emergency department patients presenting with potential acute coronary syndromes. *Circulation* 2016;134:547–64.
6. Chapman AR, Lee KK, McAllister DA, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. *JAMA* 2017;318:1913–24.
7. Miller C. Evaluation of patients with chest pain at low or intermediate risk for acute coronary syndrome. Up to date. Available: [https://www.uptodate.com/contents/evaluation-of-patients-with-chest-pain-at-low-or-intermediate-risk-for-acute-coronary-syndrome?search=Evaluation%20of%20patients%20with%20chest%20pain%20at%20low%20or%20intermediate%20risk%20for%20acute%20coronary%20syndrome.&source=search\\_result&selectedTitle=1~150&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/evaluation-of-patients-with-chest-pain-at-low-or-intermediate-risk-for-acute-coronary-syndrome?search=Evaluation%20of%20patients%20with%20chest%20pain%20at%20low%20or%20intermediate%20risk%20for%20acute%20coronary%20syndrome.&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1) [Accessed 30 Jan 2019].
8. Mahler SA, Miller CD, Hollander JE, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. *Int J Cardiol* 2013;168:795–802.
9. 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;130:e344–426.
10. Roffi M, Patrono C, Collet J-P, et al. 2015 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). *Eur Heart J* 2016;37:267–315.
11. Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* 2008;118:2702–9.
12. Hess EP, Brison RJ, Perry JJ, et al. Development of a clinical prediction rule for 30-day cardiac events in emergency department patients with chest pain and possible acute coronary syndrome. *Ann Emerg Med* 2012;59:115–25.
13. Wu WK, Yiadom MYAB, Collins SP, et al. Documentation of heart score discordance between emergency physician and cardiologist evaluations of ED patients with chest pain. *Am J Emerg Med* 2017;35:132–5.
14. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–42.
15. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the heart score. *Nett Heart J* 2008;16:191–6.
16. Than M, Flaws D, Sanders S, et al. Development and validation of the emergency department assessment of chest pain score and 2 H accelerated diagnostic protocol. *Emerg Med Australas* 2014;26:34–44.
17. Body R, Carlton E, Sperrin M, et al. Troponin-only Manchester acute coronary syndromes (T-MACS) decision aid: single biomarker re-derivation and external validation in three cohorts. *Emerg Med J* 2017;34:349–56.
18. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol* 2013;62:1242–9.
19. Meller B, Cullen L, Parsonage WA, et al. Accelerated diagnostic protocol using high-sensitivity cardiac troponin T in acute chest pain patients. *Int J Cardiol* 2015;184:208–15.
20. McCord J, Cabrera R, Lindahl B, et al. Prognostic utility of a modified heart score in chest pain patients in the emergency department. *Circ Cardiovasc Qual Outcomes* 2017;10.
21. Carlton EW, Khattab A, Greaves K. Identifying patients suitable for discharge after a Single-Presentation high-sensitivity troponin result: a comparison of five established risk scores and two high-sensitivity assays. *Ann Emerg Med* 2015;66:635–45.
22. Adams ST, Leveson SH. Clinical prediction rules. *BMJ* 2012;344:d8312.
23. 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;172:1211–8.
24. Reichlin T, Cullen L, Parsonage WA, et al. Two-Hour algorithm for triage toward rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Am J Med* 2015;128:369–79.
25. Chapman AR, Anand A, Boeddinghaus J, et al. Comparison of the efficacy and safety of early Rule-Out pathways for acute myocardial infarction. *Circulation* 2017;135:1586–96.
26. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012;33:2252–7.
27. Body R, Carley S, Wibberley C, et al. The value of symptoms and signs in the emergent diagnosis of acute coronary syndromes. *Resuscitation* 2010;81:281–6.
28. Riedlinger D, Möckel M, Müller C, et al. High-Sensitivity cardiac troponin T for diagnosis of NSTEMI in the elderly emergency department patient: a clinical cohort study. *Biomarkers* 2018;23:551–7.
29. Welsh P, Preiss D, Shah ASV, et al. Comparison between high-sensitivity cardiac troponin T and cardiac troponin I in a large general population cohort. *Clin Chem* 2018;64:1607–16.
30. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;361:858–67.
31. Kimura T, Issiki T, Ohno T, et al. Guidelines for management of acute coronary syndrome without persistent ST segment elevation (JCS 2012). Available: [http://www.j-circ.or.jp/guideline/pdf/JCS2012\\_kimura\\_h.pdf](http://www.j-circ.or.jp/guideline/pdf/JCS2012_kimura_h.pdf) [Accessed 30 Jan 2019].
32. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American heart association Task force on practice guidelines (writing Committee to revise the 2002 guidelines for the management of patients with unstable Angina/Non-ST-Elevation myocardial infarction) developed in collaboration with the American College of emergency physicians, the Society for cardiovascular angiography and interventions, and the Society of thoracic surgeons endorsed by the American association of cardiovascular and pulmonary rehabilitation and the Society for academic emergency medicine. *J Am Coll Cardiol* 2007;50:e1–157.
33. Fanaroff AC, Rymer JA, Goldstein SA, et al. Does this patient with chest pain have acute coronary syndrome?: the rational clinical examination systematic review. *JAMA* 2015;314:1955–65.
34. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the adapt trial. *J Am Coll Cardiol* 2012;59:2091–8.
35. Carlton EW, Cullen L, Than M, et al. A novel diagnostic protocol to identify patients suitable for discharge after a single high-sensitivity troponin. *Heart* 2015;101:1041–6.
36. Rubini Giménez M, Hoeller R, Reichlin T, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. *Int J Cardiol* 2013;168:3896–901.
37. Boeddinghaus J, Twerenbold R, Nestelberger T, et al. Clinical validation of a novel high-sensitivity cardiac troponin I assay for early diagnosis of acute myocardial infarction. *Clin Chem* 2018;64:1347–60.
38. Rubini Gimenez 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;128:861–70.
39. Druey S, Wildi K, Twerenbold R, et al. Early rule-out and rule-in of myocardial infarction using sensitive cardiac troponin I. *Int J Cardiol* 2015;195:163–70.
40. Boeddinghaus J, Reichlin T, Cullen L, et al. Two-Hour algorithm for triage toward Rule-Out and Rule-In of acute myocardial infarction by use of high-sensitivity cardiac troponin I. *Clin Chem* 2016;62:494–504.
41. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237–69.
42. Body R, Cook G, Burrows G, et al. Can emergency physicians 'rule in' and 'rule out' acute myocardial infarction with clinical judgement? *Emerg Med J* 2014;31:872–6.