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The comparison of very early rule-out strategies for non-ST elevation myocardial infarction in emergency departments: protocol for a multicenter prospective cohort study

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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 (ED) 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 study is to validate and compare the diagnostic accuracy of clinical impression-based strategy, 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-, two secondary-level community hospitals, and one university hospital in Japan. The study has begun in July 2018, and recruitment period will be about one year. A board-certified emergency physician will complete standardized 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 NPV, sensitivity and effectiveness, defined as the proportion of patients categorized as low risk for NSTEMI. We will also evaluate inter-rater reliability of the clinical impression-based risk estimation.

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.

ARTICLE SUMMARY

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 NSTEMI in patients with symptoms suggestive of acute coronary syndrome in ED.
- We 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 three hours after presentation to ED and therefore, we may miss some MIs.

INTRODUCTION

Background

Because ruling-out non-ST elevation myocardial infarctions (NSTEMI) 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 to 12 h after symptom onset or admission to the emergency department (ED).(1, 2) 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 United Kingdom and the United States.(3, 4) However, in about 80 to 90% of patients presenting to EDs for a possible MI, the presenting symptoms are not cardiac in origin. 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 less than one to two percent to patients directly discharged from the ED. (5, 6)

Recently, several high-sensitive-troponins (hs-troponin) have decreased the recommended time for troponin monitoring for MI diagnosis to 3-6 h (2014 ACC/AHA guidelines (7)), and further to 0-3 h (2015 ESC guidelines (8)). 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.(9) 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.(10)

Although troponin is crucial for the acute management of MI, history, physical findings and electronic cardiogram (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 consisting of the clinical impression-based risk estimation of history and physical findings, ECG and troponin. 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, based on clinical impression, might vary greatly, depending on a physician's background.(11, 12)

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,(13) HEART,(14) EDACS,(15) and T-MACS(16) rules. Most of the newer prediction rules that have incorporated hs-troponin have achieved an NPV of >99% and have been validated.(17-20) Prediction rules, however, are not widely used, despite their excellent NPVs, partly because they have not been compared against clinical impression-based strategies.(21)

There are several hs-troponin-based strategies that use only hs-troponin, such as the 0 and 1h algorithm,(22) the 0 and 2h algorithm(23) and the High-STEACS pathway.(24) These strategies are simple, and they rely on a measurement of troponin only, with demonstrated NPVs of >99%. However, clinicians consider patient history and physical findings (including the ECG) as being essential components of the evaluation of a patient's status, with no clear pathway to include these in hs-troponin-based strategies. Moreover, 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,(25, 26) has not being considered. As such, hs-troponin-based strategies may be less efficient in highly aged populations, such as in Japan.

Rationale for the study

First, a direct comparison of the clinical impression-based strategies, prediction-rules and hs-troponin-based strategies to rule out NSTEMI has not yet been published and, therefore, there is a need for a well-designed study to compare their accuracy.

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.(10) 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 cutoff value.

Third, although many kinds of troponins are now available, the diagnostic accuracy and cutoff 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

1. Primary research objective

Our primary objective is to compare the NPV, sensitivity and effectiveness (defined as the proportion of patients categorized 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 h) only; 0 h and 1 h after; and 0 h and 2 h after, using the composite outcome of cardiac death or the occurrence of a type 1 MI within 30 days of the ED consultation.

2. Secondary research objectives

Our secondary research objectives are:

2.1. To validate and compare the NPV, sensitivity and effectiveness between clinical impression-based strategies, prediction rules and hs-troponin-based strategies.

2.2. 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

Inclusion criteria

1. Age ≥25 years
2. Have any one of the following symptoms suspected to be MI

   Chest pain

   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 six hours to focus on early presenters, the most difficult population to rule-out NSTEMI very early (27)
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 less than six months)
3. Need for resuscitation (physiological shock, continuous oxygen administration)
4. Indication of emergency catheterization 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 enrollment 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 centers. 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.

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 authorized 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 standardized 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; 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. (7, 8, 28)

Troponin

We will evaluate the following four types of troponin, three high-sensitive and one sensitive. The 99th percentile and the Limit of detection (LoD) values for the four types of troponin are summarized 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 h); and at one hour (1 h), two hours (2 h), and three hours (3 h) after the first blood draw. After centrifugation, serum samples will be stored at less than -20°C until measured in each manufacturer's laboratory in a blinded fashion.

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 I (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 indicates limit of detection

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. Each troponin will be adapted for each strategy, as needed. We will define the troponin cutoff 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 clinical impression-based strategies

1. The 0 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival is below the 99th percentile

2. The 0 h and 1 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival and at 1 h apart are both below the 99th percentile

3. The 0 h and 2 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival and at 2 h 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(29) and a systematic review.(30) We define the new ischemic 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 0.05mV or more at J point in two or more contiguous leads. A negative T wave is defined by T wave inversions of 0.1mV 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 h troponin(31)

   Components: age, coronary risk factors, use of aspirin, significant coronary stenosis, severe angina, ECG, and troponin (at 0 and 2 h)

   Cutoff: we will define the score of 0 as a low risk for MI

2. HEART(14)

   Components: history, ECG, age, risk factors, and troponin

   Cutoff: we will define the score of 0-3 and negative troponin as a low risk for MI

3. EDACS(15)

   Components: age, sex, coronary artery disease or risk factors, symptoms, ECG, and troponin (at 0 and 2 h)

   Cutoff: we will define low risk when all three conditions are satisfied, namely: a score < 16; no new ischemia on ECG; and negative troponin at 0 and 2 h

4. T-MACS(16)

   Components: (a) hs-troponin T (at 0 h), (b) ECG, (c) objective sweating, (d) vomiting, (e) systolic blood pressure <100 mmHg on arrival, (f) worsening angina, and (g) pain radiating to the right arm or shoulder

   $$\text{probability} = 1 / (1 + e^{-(0.068a + (0.17(b - 0.28) / 1.35) + 1.75c + 1.85d + 1.72e + 1.46f + 0.92g + 0.87h - 4.83)})$$

   Cutoff: we will define low risk if the probability is <0.02

5. TRUST(32)

   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 more than 60 min, pain occurring with increasing frequency, hypotension, acute shortness of breath, pain within 6 weeks of an MI or revascularization, ECG, hs-troponin (at 0 h)

Cutoff: we will define low risk when all three conditions are satisfied: the score of 0 or 1, non-ischemic ECG, and negative troponin

Hs-troponin-based strategies

Hs-troponin-based strategies are comprised of hs-troponin only, with cutoff 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 cutoff values of each strategy, we regard a patient as being at low risk for an MI.

1. The 0 h algorithm(33, 34)

   Roche hs-troponin T: 0 h <5 ng/L$^{(*1)}$

   Abbott hs-troponin I: 0 h <2 ng/L$^{(*2)}$

   Siemens hs-troponin I: 0 h <3 ng/L$^{(*3)}$

   Siemens sensitive-troponin I: 0 h <0.5 ng/L$^{(*4)}$

2. The 1 h algorithm(22, 34-36)

   Roche hs-troponin T: 0 h <12 ng/L AND Δ0-1 h <3 ng/L$^{(*5)}$

   Abbott hs-troponin I: 0 h <5 ng/L AND Δ0-1 h <2 ng/L$^{(*6)}$

   Siemens hs-troponin I: 0 h <6 ng/L AND Δ0-1 h <3 ng/L$^{(*7)}$

   Siemens sensitive-troponin I: 0 h <10 ng/L AND Δ0-1 h <4 ng/L$^{(*8)}$

3. The 2 h algorithm(23, 36, 37)

   Roche hs-troponin T: 0 and 2 h <14 ng/L AND Δ0-2 h <4 ng/L

   Abbott hs-troponin I: 0 and 2 h <6 ng/L AND Δ0-2 h <2 ng/L

   Siemens sensitive-troponin I: 0 and 2 h <10 ng/L

4. The 0 and 1h algorithm(8, 34)

   Roche hs-troponin T: *1 OR *5

   Abbott hs-troponin I: *2 OR *6

   Siemens hs-troponin I: *3 OR *7

   Siemens sensitive-troponin I: *4 OR *8

5. The High-STEACS pathway (only for Abbott hs-troponin I at the moment) (24)

   If hs-troponin I at 0 h <5 ng/L AND symptom onset ≥2 h, AMI is ruled out.

   If 5≤ hs-troponin I at 0 h ≤26.2 ng/L OR symptom onset <2 h, hs-troponin I at 2 h is required. If Δ0-2 h hs-troponin I <3ng/L AND hs-troponin I at 3 h ≤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 h); 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 h.

The diagnosis of MI will be made in accordance with the forth universal definition of myocardial infarction,(38) 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 use Radiometer AQT90 FLEX Troponin T and Abbott ARCHITECT hs-troponin I to adjudicate the final diagnosis in three facilities which using Radiometer AQT90 FLEX Troponin T as in-house troponin. Because Radiometer troponin T is less sensitive than Abbott ARCHITECT hs-troponin I and therefore, we generally prioritize the result of hs-troponin I if the results of the two types troponin are discordant.(27, 39) We also consider clinical judgement and all available clinical information to interpret the discordant cases. We will use Abbott ARCHITECT hs-troponin I to adjudicate the final diagnosis in two facilities which using Abbott ARCHITECT hs-troponin I as in-house troponin. The 99th percentile values for Abbott hs-troponin I has previously been defined. The 99th percentile values for Radiometer AQT90 FLEX Troponin T will be 17 ng/L. For Abbott hs-troponin I and Radiometer AQT90 FLEX Troponin T, we will define a significant rise and/or fall as 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 as relative increase of >20% of the initial value if the initial troponin values is greater than the 99th percentile value.(40) 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 (e.g. coronary artery spasm; tachyarrhythmia; respiratory failure; or anemia). 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. 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 revascularization 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. Whilst 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. We will conduct a sensitivity analysis to determine the effect of missing patients on our findings, using the worst case scenario.

Sample size calculation

Assuming that the event rate of the primary clinical outcome is 5 to 10%,(9, 10) with a sensitivity and specificity of the clinical impression-based strategies of 95% and 55%, respectively,(41) 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

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, area under the receiver operating characteristic curve (AUC), and decision curve analysis (DCA) for each strategy. Although we will compare the NPV, sensitivity, effectiveness and AUC among the three strategies, we will regard a strategy as being clinically useful if the point estimate for NPV is ≥99%. If the point estimate for NPV is ≥99%, we will regard a strategy with shorter observational period as superior.

Secondary research objective 1

We will describe the NPV, sensitivity, effectiveness, AUC and DCA for the clinical impression-based strategies, prediction rules, and hs-troponin-based strategies for each troponin. If the point estimate for NPV is ≥99%, we will regard a strategy with higher effectiveness and 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; past history of ischemic heart disease or revascularization; age; sex; and presence of chest pain considering its certainty. We will define the cutoff 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; 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 determine the effect of missing patients on our findings, using the worst case scenario.

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 results of the study through peer-reviewed journals and conference presentations.

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 cutoff 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 which is 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.

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Author contributions

MT, NW wrote the first draft. All other authors, HA, NY, KK, HN, SM, HI, TA, RO, TK, TK, HU, HT, HM, HI, KM, YS, HY, MA, YM, NI, SK, TI, HT, AC, NM, HH and TF contributed to the conception and design of the study. All the authors read and approved the final manuscript.

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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. ARC has received honoraria from Abbott Diagnostics and AstraZeneca. NLM has received honoraria and consultancy from Abbott Diagnostics, Roche Diagnostics and Singulex. TF 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. All other authors report no conflicts.

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TRIPOD Checklist: Prediction Model Validation

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5-7
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	7-8
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	1
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	3
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	3, 9-10
	5b	Describe eligibility criteria for participants.	8-9
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	16-18
	6b	Report any actions to blind assessment of the outcome to be predicted.	16
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	10-12
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	11
Sample size	8	Explain how the study size was arrived at.	18
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	18, 20
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	12-16
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	18-19
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	
Model performance	16	Report performance measures (with CIs) for the prediction model.	
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

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

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

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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 (ED) 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-, two secondary-level community hospitals, and one university hospital in Japan. The study has begun in July 2018, and recruitment period will be about one year. A board-certified emergency physician will complete standardized 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 NPV, sensitivity and effectiveness, defined as the proportion of patients categorized as low

risk for NSTEMI. We will also evaluate inter-rater reliability of the clinical impression-based risk estimation.

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.

ARTICLE SUMMARY

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 NSTEMI in patients with symptoms suggestive of acute coronary syndrome in 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 three hours after presentation to ED and we follow-up patients mainly by telephone interview, and therefore, we may miss some subsequent 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 generalizability 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.

INTRODUCTION

Background

Because ruling-out non-ST elevation myocardial infarctions (NSTEMI) 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 to 12 h after symptom onset or admission to the emergency department (ED).(1, 2) 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 United Kingdom and the United States.(3, 4) However, between 75% and 95% of patients presenting to the EDs with symptoms suggestive of MI did not have MI.(5, 6) 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 less than one to two percent to patients directly discharged from the ED. (7, 8)

Recently, several high-sensitive-troponins (hs-troponin) have decreased the recommended time for troponin monitoring for MI diagnosis to 3-6 h (2014 ACC/AHA guidelines (9)), and further to 0-3 h (2015 ESC guidelines (10)). 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.(6) 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.(11)

Although troponin is crucial for the accurate diagnosis of MI, the clinical history, physical findings and electrocardiogram (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.(12, 13)

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,(14) HEART,(15) EDACS,(16) and T-MACS(17) rules. Most of the newer prediction rules that have incorporated hs-troponin have achieved an NPV of >99% and have been validated.(18-21) Prediction rules, however, are not widely used, despite their excellent NPVs, partly because they have not been compared against clinical impression-based strategies.(22)

There are several hs-troponin-based strategies that use only hs-troponin, such as the 0 and 1h algorithm,(23) the 0 and 2h algorithm(24) and the High-STEACS pathway.(25) 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.(26) On the other hand, the clinical history, physical findings, and ECG readings are sometimes not reliable, and different physicians often have different interpretations.(13, 27) 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,(28, 29) 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.(11) 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 cutoff value.

Third, although many kinds of troponins are now available, the diagnostic accuracy and cutoff 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

1. Primary research objective

Our primary objective is to compare the NPV, sensitivity and effectiveness (defined as the proportion of patients categorized 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 h) only; 0 h and 1 h after; and 0 h and 2 h after, using the composite outcome of cardiac death or the occurrence of a type 1 MI within 30 days of the ED consultation.

2. Secondary research objectives

Our secondary research objectives are:

2.1. To validate and compare the NPV, sensitivity and effectiveness between clinical impression-based strategies, prediction rules and hs-troponin-based strategies.

2.2. 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. We will recruit further hospitals in other regions in Japan

Inclusion criteria

1. Age ≥25 years
2. Have any one of the following symptoms suspected to be MI
   Chest pain
   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 six hours to focus on early presenters, the most difficult population to rule-out NSTEMI very early (30)
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 less than six months)

3. Need for resuscitation (physiological shock, continuous oxygen administration)
4. Indication of emergency catheterization 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 enrollment 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 centers. 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.

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 authorized 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 standardized 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; 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. (9, 10, 31)

Troponin

We will evaluate the following four types of troponin, three high-sensitive and one sensitive. The 99th percentile and the limit of detection (LoD) values for the four types of troponin are summarized 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 h); and at one hour (1 h), two hours (2 h), and three hours (3 h) after the first blood draw. After centrifugation, serum samples will be stored at less than -20°C until measured in each manufacturer's laboratory in a blinded fashion.

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 indicates limit of detection

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 two hours apart from the first one. Because it generally takes about one hour to take the first blood sample, we will include strategies with troponin taken up to three 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 cutoff 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 clinical impression-based strategies

1. The 0 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival is below the 99th percentile

2. The 0 h and 1 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival and at 1 h apart are both below the 99th percentile

3. The 0 h and 2 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival and at 2 h 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(32) and a systematic review.(33) We define the new ischemic 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 0.05mV or more at J point in two or more contiguous leads. A negative T wave is defined by T wave inversions of 0.1mV 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. The details of each prediction rule are shown in the online supplementary appendix.

Prediction rules

1. TIMI + 2 h troponin(34)

Components: age, coronary risk factors, use of aspirin, significant coronary stenosis, severe angina, ECG, and troponin (at 0 and 2 h)

Cutoff: we will define the score of 0 as a low risk for MI

2. HEART(15)

Components: history, ECG, age, risk factors, and troponin

Cutoff: we will define the score of 0-3 and negative troponin as a low risk for MI

3. EDACS(16)

Components: age, sex, coronary artery disease or risk factors, symptoms, ECG, and troponin (at 0 and 2 h)

Cutoff: we will define low risk when all three conditions are satisfied, namely: a score < 16; no new ischemia on ECG; and negative troponin at 0 and 2 h

4. T-MACS(17)

Components: (E) ECG ischemia, (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)

Probability $=1 / (1 + e^{-(1.713E + 0.847A + 0.607R + 1.417V + 2.058S + 1.208H + 0.089T - 4.766)})$

Cutoff: we will define low risk if the probability is <0.02

5. TRUST(35)

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 more than 60 min, pain occurring with increasing frequency, hypotension, acute shortness of breath, pain within 6 weeks of an MI or revascularization, ECG, hs-troponin (at 0 h)

Cutoff: we will define low risk when all three conditions are satisfied: the score of 0 or 1, non-ischemic ECG, and negative troponin

6. GRACE(10)

Components: age, history of congestive heart failure, history of myocardial infarction,

resting heart rate, systolic blood pressure, ST-segment depression, initial serum creatinine, elevated cardiac enzymes, no in-hospital percutaneous coronary intervention

Cutoff: we will define the score less than 140 AND negative troponin at 0 and 2 h

Hs-troponin-based strategies

Hs-troponin-based strategies are comprised of hs-troponin only, with cutoff 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 cutoff 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 three hours from presentation to the ED.(25) Because there is often a delay of up to one hour for the first blood sample, the average time between the first and second troponin measurement is two hours, and therefore, we include the High-STEACS pathway without modification.

1. The 0 h algorithm(36, 37)

Roche hs-troponin T: 0 h <5 ng/L(*1)

Abbott hs-troponin I: 0 h <2 ng/L(*2)

Siemens hs-troponin I: 0 h <3 ng/L(*3)

Siemens sensitive-troponin I: 0 h <0.5 ng/L(*4)

2. The 1 h algorithm(23, 37-39)

Roche hs-troponin T: 0 h <12 ng/L AND Δ0-1 h <3 ng/L(*5)

Abbott hs-troponin I: 0 h <5 ng/L AND Δ0-1 h <2 ng/L(*6)

Siemens hs-troponin I: 0 h <6 ng/L AND Δ0-1 h <3 ng/L(*7)

Siemens sensitive-troponin I: 0 h <10 ng/L AND Δ0-1 h <4 ng/L(*8)

3. The 2 h algorithm(24, 39, 40)

Roche hs-troponin T: 0 and 2 h <14 ng/L AND Δ0-2 h <4 ng/L

Abbott hs-troponin I: 0 and 2 h <6 ng/L AND Δ0-2 h <2 ng/L

Siemens sensitive-troponin I: 0 and 2 h <10 ng/L

4. The 0 and 1h algorithm(10, 37)

Roche hs-troponin T: *1 OR *5

Abbott hs-troponin I: *2 OR *6

Siemens hs-troponin I: *3 OR *7

Siemens sensitive-troponin I: *4 OR *8

5. The High-STEACS pathway (only for Abbott hs-troponin I at the moment) (25)

If hs-troponin I at 0 h <5 ng/L AND symptom onset ≥2 h, AMI is ruled out.

If 5≤ hs-troponin I at 0 h ≤26.2 ng/L OR symptom onset <2 h, hs-troponin I at 2 h is required. If Δ0-2 h hs-troponin I <3ng/L AND hs-troponin I at 3 h ≤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 h); 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 h.

The diagnosis of MI will be made in accordance with the forth universal definition of myocardial infarction,(41) 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 three 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.(23, 26) 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 (e.g. coronary artery spasm; tachyarrhythmia; respiratory failure; or anemia). 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. 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 revascularization 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. Whilst 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 to 10%,(6, 11) with a sensitivity and specificity of the clinical impression-based strategies of 95% and 55%, respectively,(42) 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

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 generalized 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 ≥99%. If the point estimate for NPV is ≥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 ≥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; past history of ischemic heart disease or revascularization; age; sex; and presence of chest pain considering its certainty. We will

define the cutoff 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.

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

No patients were 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 cutoff 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.

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Author contributions

MT, NW wrote the first draft. All other authors, HA, NY, KK, HN, SM, HI, TA, RO, TK, TK, HU, HT, HM, HI, KM, YS, HY, MA, YM, NI, SK, TI, HT, AC, NM, HH and TF contributed to the conception and design of the study. All the authors read and approved the final manuscript.

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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. ARC has received honoraria from Abbott Diagnostics and AstraZeneca. NLM has received honoraria and consultancy from Abbott Diagnostics, Roche Diagnostics and Singulex. TF 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. All other authors report no conflicts.

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Supplementary appendix

The components of prediction rules

1. TIMI + 2 h troponin (34)

1) Troponin level at 0 and 2 h below 99th percentile value

2) No new ischemic changes on the initial ECG

3) TIMI score = 0 (all items below have to be negative)

a. Age ≥65 years

b. Three or more risk factors for coronary artery disease

(family history of coronary artery disease, hypertension, hypercholesterolaemia, diabetes, or being in a current smoker)

c. Use of aspirin in the past 7 days

d. Significant coronary stenosis (previous coronary stenosis ≥50%)

e. Severe angina (≥2 angina events in past 24 h or persistent discomfort)

f. ST-segment deviation of ≥0.05 mV on first ECG

g. Increased troponin

Low risk: all parameters, 1), 2), and 3) are satisfied

2. HEART (15)

		score
1) History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
2) ECG	Significant ST depression	2
	Nonspecific repolarization disturbance	1
	Normal	0
3) Age	≥65 year	2
	45-65 year	1
	<45 year	0
4) Risk factors	≥3 risk factors or history of atherosclerotic disease	2

	1 or 2 risk factors	1
	No risk factors known	0
5) Troponin	>2x normal limit	2
	1-2x normal limit	1
	≤ normal limit	0

Low risk: the score of ≤3 AND troponin <99th percentile value

3. EDACS (16)

1) Age	score
18 – 45	+2
46 – 50	+4
51 – 55	+6
56 – 60	+8
61 – 65	+10
66 – 70	+12
71 – 75	+14
76 – 80	+16
81 – 85	+18
86 ≤	+20
2) Male sex	+6
3) Aged 18 – 50 years and either:	
a. known coronary artery disease	+ 4
b. ≥3 risk factors	
4) Symptom and signs	
Diaphoresis	+3
Radiates to arm or shoulder	+5
Pain occurred or worsened with inspiration	-4
Pain is reproduced by palpation	-6

Low risk: EDACS <16, AND no new ischemia on ECG, AND both 0 and 2 h troponin <99th percentile

4. T-MACS (17)

E) ECG ischemia

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)

$$\text{Probability} = 1 / (1 + e^{-(1.713E + 0.847A + 0.607R + 1.417V + 2.058S + 1.208H + 0.089T - 4.766)})$$

Low risk: probability <0.02

5. TRUST (35)

1) Modified Goldman risk score ≤1

   a. Typical new-onset chest pain at rest

   b. Pain the same as previous myocardial infarction

   c. Pain not relieved by glyceryl trinitrate spray within 15 min

   d. Pain lasting more than 60 min

   e. Pain occurring with increasing frequency

   f. Hypotension (systolic blood pressure < 100 mm Hg)

   g. Acute shortness of breath

   h. Pain within 6 weeks of a myocardial infarction or revascularization

2) Non-ischemic ECG

3) High-sensitivity troponin T concentration at presentation <14 ng/L

Low risk: all parameters, 1), 2), and 3) are satisfied

6. GRACE (10)

1) Age	score
≤39	0
40 – 49	18

50 – 59	36
60 – 69	55
70 – 79	73
80 – 89	91
≥90	100
2) History of congestive heart failure	24
3) History of myocardial infarction	12
4) Resting heart rate (beats/min)	
≤49.9	0
50 – 69.9	3
70 – 89.9	9
90 – 109.9	14
110 – 149.9	23
150 – 199.9	35
≥200	43
5) Systolic blood pressure (mm Hg)	
≤79.9	24
80 – 99.9	22
100 – 119.9	18
120 – 139.9	14
140 – 159.9	10
160 – 199.9	4
≥200	0
6) ST-segment depression	11
7) Initial serum creatinine (mg/dl)	
≤0.39	1
0.4 – 0.79	3
0.8 – 1.19	5
1.2 – 1.59	7
1.6 – 1.99	9

2 – 3.99	15
≥4	20
8) Elevated cardiac enzymes	15
9) No in-hospital percutaneous coronary intervention	14

Low risk: the score of ≤140 AND both 0 and 2 h troponin <99th percentile

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

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

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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 (ED) 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-, two secondary-level community hospitals, and one university hospital in Japan. The study has begun in July 2018, and recruitment period will be about one year. A board-certified emergency physician will complete standardized 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 NPV, sensitivity and effectiveness, defined as the proportion of patients categorized as low

risk for NSTEMI. We will also evaluate inter-rater reliability of the clinical impression-based risk estimation.

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.

ARTICLE SUMMARY

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 NSTEMI in patients with symptoms suggestive of acute coronary syndrome in 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 three hours after presentation to ED and we follow-up patients mainly by telephone interview, and therefore, we may miss some subsequent 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 generalizability 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.

INTRODUCTION

Background

Because ruling-out non-ST elevation myocardial infarctions (NSTEMI) 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 to 12 h after symptom onset or admission to the emergency department (ED).(1, 2) 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 United Kingdom and the United States.(3, 4) However, between 75% and 95% of patients presenting to the EDs with symptoms suggestive of MI did not have MI.(5, 6) 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 less than one to two percent to patients directly discharged from the ED. (7, 8)

Recently, several high-sensitive-troponins (hs-troponin) have decreased the recommended time for troponin monitoring for MI diagnosis to 3-6 h (2014 ACC/AHA guidelines (9)), and further to 0-3 h (2015 ESC guidelines (10)). 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.(6) 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.(11)

Although troponin is crucial for the accurate diagnosis of MI, the clinical history, physical findings and electrocardiogram (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.(12, 13)

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,(14) HEART,(15) EDACS,(16) and T-MACS(17) rules. Most of the newer prediction rules that have incorporated hs-troponin have achieved an NPV of >99% and have been validated.(18-21) Prediction rules, however, are not widely used, despite their excellent NPVs, partly because they have not been compared against clinical impression-based strategies.(22)

There are several hs-troponin-based strategies that use only hs-troponin, such as the 0 and 1h algorithm,(23) the 0 and 2h algorithm(24) and the High-STEACS pathway.(25) 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.(26) On the other hand, the clinical history, physical findings, and ECG readings are sometimes not reliable, and different physicians often have different interpretations.(13, 27) 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,(28, 29) 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.(11) 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 cutoff value.

Third, although many kinds of troponins are now available, the diagnostic accuracy and cutoff 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

1. Primary research objective

Our primary objective is to compare the NPV, sensitivity and effectiveness (defined as the proportion of patients categorized 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 h) only; 0 h and 1 h after; and 0 h and 2 h after, using the composite outcome of cardiac death or the occurrence of a type 1 MI within 30 days of the ED consultation.

2. Secondary research objectives

Our secondary research objectives are:

2.1. To validate and compare the NPV, sensitivity and effectiveness between clinical impression-based strategies, prediction rules and hs-troponin-based strategies.

2.2. 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 ≥25 years
2. Have any one of the following symptoms suspected to be MI
   Chest pain
   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 six hours to focus on early presenters, the most difficult population to rule-out NSTEMI very early (30)
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 less than six months)
3. Need for resuscitation (physiological shock, continuous oxygen administration)
4. Indication of emergency catheterization 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 enrollment 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 centers. 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 emergency department 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 authorized 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 standardized 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; 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. (9, 10, 31) We will check all case report forms immediately after we receive them from hospitals. If there are some missing values, we will ask co-researchers 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 (LoD) values for the four types of troponin are summarized 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 h); and at one hour (1 h), two hours (2 h), and three hours (3 h) after the first blood draw. After centrifugation, serum samples will be stored at less than -20°C until measured in each manufacturer's laboratory in a blinded fashion.

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 indicates limit of detection

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 two hours apart from the first one. Because it generally takes about one hour to take the first blood sample, we will include strategies with troponin taken up to three 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 cutoff 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

1. The 0 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival is below the 99th percentile

2. The 0 h and 1 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival and at 1 h apart are both below the 99th percentile

3. The 0 h and 2 h model

1) Clinical impression-based risk estimation for history and physical findings is not high risk
2) No new ischemic findings on ECG
3) Troponin taken on arrival and at 2 h 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(32) and a systematic review.(33) We define the new ischemic 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 0.05mV or more at J point in two or more contiguous leads. A negative T wave is defined by T wave inversions of 0.1mV 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 h troponin(34)

   Components: age, coronary risk factors, use of aspirin, significant coronary stenosis, severe angina, ECG, and troponin (at 0 and 2 h)

   Cutoff: we will define the score of 0 as a low risk for MI

2. HEART(15)

   Components: history, ECG, age, risk factors, and troponin

   Cutoff: we will define the score of 0-3 and negative troponin as a low risk for MI

3. EDACS(16)

   Components: age, sex, coronary artery disease or risk factors, symptoms, ECG, and troponin (at 0 and 2 h)

   Cutoff: we will define low risk when all three conditions are satisfied, namely: a score < 16; no new ischemia on ECG; and negative troponin at 0 and 2 h

4. T-MACS(17)

Components: (E) ECG ischemia, (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)

Probability $=1 / (1 + e^{-(1.713E + 0.847A + 0.607R + 1.417V + 2.058S + 1.208H + 0.089T - 4.766)})$

Cutoff: we will define low risk if the probability is <0.02

5. TRUST(35)

   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 more than 60 min,

pain occurring with increasing frequency, hypotension, acute shortness of breath, pain within 6 weeks of an MI or revascularization, ECG, hs-troponin (at 0 h)

Cutoff: we will define low risk when all three conditions are satisfied: the score of 0 or 1, non-ischemic ECG, and negative troponin

6. GRACE(10)

Components: age, history of congestive heart failure, history of myocardial infarction, resting heart rate, systolic blood pressure, ST-segment depression, initial serum creatinine, elevated cardiac enzymes, no in-hospital percutaneous coronary intervention

Cutoff: we will define the score less than 140 AND negative troponin at 0 and 2 h

Hs-troponin-based strategies

Hs-troponin-based strategies are comprised of hs-troponin only, with cutoff 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 cutoff 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 three hours from presentation to the ED.(25) Because there is often a delay of up to one hour for the first blood sample, the average time between the first and second troponin measurement is two hours, and therefore, we include the High-STEACS pathway without modification.

1. The 0 h algorithm(36, 37)

Roche hs-troponin T: 0 h <5 ng/L(*1)

Abbott hs-troponin I: 0 h <2 ng/L(*2)

Siemens hs-troponin I: 0 h <3 ng/L(*3)

Siemens sensitive-troponin I: 0 h <0.5 ng/L(*4)

2. The 1 h algorithm(23, 37-39)

Roche hs-troponin T: 0 h <12 ng/L AND Δ0-1 h <3 ng/L(*5)

Abbott hs-troponin I: 0 h <5 ng/L AND Δ0-1 h <2 ng/L(*6)

Siemens hs-troponin I: 0 h <6 ng/L AND Δ0-1 h <3 ng/L(*7)

Siemens sensitive-troponin I: 0 h <10 ng/L AND Δ0-1 h <4 ng/L(*8)

3. The 2 h algorithm(24, 39, 40)

Roche hs-troponin T: 0 and 2 h <14 ng/L AND Δ0-2 h <4 ng/L

Abbott hs-troponin I: 0 and 2 h <6 ng/L AND Δ0-2 h <2 ng/L

Siemens sensitive-troponin I: 0 and 2 h <10 ng/L

4. The 0 and 1h algorithm(10, 37)

Roche hs-troponin T: *1 OR *5

Abbott hs-troponin I: *2 OR *6

Siemens hs-troponin I: *3 OR *7

Siemens sensitive-troponin I: *4 OR *8

5. The High-STEACS pathway (only for Abbott hs-troponin I at the moment) (25)

If hs-troponin I at 0 h <5 ng/L AND symptom onset ≥2 h, AMI is ruled out.

If 5≤ hs-troponin I at 0 h ≤26.2 ng/L OR symptom onset <2 h, hs-troponin I at 2 h is required. If Δ0-2 h hs-troponin I <3ng/L AND hs-troponin I at 3 h ≤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 h); 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 h.

The diagnosis of MI will be made in accordance with the forth universal definition of myocardial infarction,(41) 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 three 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.(23, 26) 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 (e.g. coronary artery spasm; tachyarrhythmia; respiratory failure; or anemia). 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 revascularization 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. Whilst 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 to 10%,(6, 11) with a sensitivity and specificity of the clinical impression-based strategies of 95% and 55%, respectively,(42) 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 generalized 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 ≥99%. If the point estimate for NPV is ≥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 ≥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; past history of ischemic heart disease or revascularization; age; sex; and presence of chest pain considering its certainty. We will define the cutoff 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

No patients were 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 cutoff 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.

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Author contributions

MT, NW wrote the first draft. All other authors, HA, NY, KK, HN, SM, HI, TA, RO, TK, TK, HU, HT, HM, HI, KM, YS, HY, MA, YM, NI, SK, TI, HT, AC, NM, HH and TF contributed to the conception and design of the study. All the authors read and approved the final manuscript.

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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. ARC has received honoraria from Abbott Diagnostics and AstraZeneca. NLM has received honoraria and consultancy from Abbott Diagnostics, Roche Diagnostics and Singulex. TF 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. All other authors report no conflicts.

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Supplementary appendix

The components of prediction rules

1. TIMI + 2 h troponin (34)

1) Troponin level at 0 and 2 h below 99th percentile value

2) No new ischemic changes on the initial ECG

3) TIMI score = 0 (all items below have to be negative)

a. Age ≥65 years

b. Three or more risk factors for coronary artery disease

(family history of coronary artery disease, hypertension, hypercholesterolaemia, diabetes, or being in a current smoker)

c. Use of aspirin in the past 7 days

d. Significant coronary stenosis (previous coronary stenosis ≥50%)

e. Severe angina (≥2 angina events in past 24 h or persistent discomfort)

f. ST-segment deviation of ≥0.05 mV on first ECG

g. Increased troponin

Low risk: all parameters, 1), 2), and 3) are satisfied

2. HEART (15)

		score
1) History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
2) ECG	Significant ST depression	2
	Nonspecific repolarization disturbance	1
	Normal	0
3) Age	≥65 year	2
	45-65 year	1
	<45 year	0
4) Risk factors	≥3 risk factors or history of atherosclerotic disease	2

	1 or 2 risk factors	1
	No risk factors known	0
5) Troponin	>2x normal limit	2
	1-2x normal limit	1
	≤ normal limit	0

Low risk: the score of ≤3 AND troponin <99th percentile value

3. EDACS (16)

1) Age	score
18 – 45	+2
46 – 50	+4
51 – 55	+6
56 – 60	+8
61 – 65	+10
66 – 70	+12
71 – 75	+14
76 – 80	+16
81 – 85	+18
86 ≤	+20
2) Male sex	+6
3) Aged 18 – 50 years and either:	
a. known coronary artery disease	+ 4
b. ≥3 risk factors	
4) Symptom and signs	
Diaphoresis	+3
Radiates to arm or shoulder	+5
Pain occurred or worsened with inspiration	-4
Pain is reproduced by palpation	-6

Low risk: EDACS <16, AND no new ischemia on ECG, AND both 0 and 2 h troponin <99th percentile

4. T-MACS (17)

E) ECG ischemia

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)

$$\text{Probability} = 1 / (1 + e^{-(1.713E + 0.847A + 0.607R + 1.417V + 2.058S + 1.208H + 0.089T - 4.766)})$$

Low risk: probability <0.02

5. TRUST (35)

1) Modified Goldman risk score ≤1

   a. Typical new-onset chest pain at rest

   b. Pain the same as previous myocardial infarction

   c. Pain not relieved by glyceryl trinitrate spray within 15 min

   d. Pain lasting more than 60 min

   e. Pain occurring with increasing frequency

   f. Hypotension (systolic blood pressure < 100 mm Hg)

   g. Acute shortness of breath

   h. Pain within 6 weeks of a myocardial infarction or revascularization

2) Non-ischemic ECG

3) High-sensitivity troponin T concentration at presentation <14 ng/L

Low risk: all parameters, 1), 2), and 3) are satisfied

6. GRACE (10)

1) Age	score
≤39	0
40 – 49	18

50 – 59	36
60 – 69	55
70 – 79	73
80 – 89	91
≥90	100
2) History of congestive heart failure	24
3) History of myocardial infarction	12
4) Resting heart rate (beats/min)	
≤49.9	0
50 – 69.9	3
70 – 89.9	9
90 – 109.9	14
110 – 149.9	23
150 – 199.9	35
≥200	43
5) Systolic blood pressure (mm Hg)	
≤79.9	24
80 – 99.9	22
100 – 119.9	18
120 – 139.9	14
140 – 159.9	10
160 – 199.9	4
≥200	0
6) ST-segment depression	11
7) Initial serum creatinine (mg/dl)	
≤0.39	1
0.4 – 0.79	3
0.8 – 1.19	5
1.2 – 1.59	7
1.6 – 1.99	9

2 – 3.99	15
≥4	20
8) Elevated cardiac enzymes	15
9) No in-hospital percutaneous coronary intervention	14

Low risk: the score of ≤140 AND both 0 and 2 h troponin <99th percentile

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3,4
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	5-7
	4	Study objectives and hypotheses	7-8
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	3
Participants	**6**	Eligibility criteria	9-10
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	10
	8	Where and when potentially eligible participants were identified (setting, location and dates)	9, 10
	9	Whether participants formed a consecutive, random or convenience series	3
Test methods	**10a**	Index test, in sufficient detail to allow replication	13-17, appendix
	10b	Reference standard, in sufficient detail to allow replication	18-19
	11	Rationale for choosing the reference standard (if alternatives exist)	19
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	13-17
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	18-19
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	18
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	18
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	20, 21
	15	How indeterminate index test or reference standard results were handled	18
	16	How missing data on the index test and reference standard were handled	19, 20
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	21
	18	Intended sample size and how it was determined	19, 20
RESULTS			
Participants	**19**	Flow of participants, using a diagram	
	20	Baseline demographic and clinical characteristics of participants	
	21a	Distribution of severity of disease in those with the target condition	
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	
	27	Implications for practice, including the intended use and clinical role of the index test	
OTHER INFORMATION			
	28	Registration number and name of registry	11
	29	Where the full study protocol can be accessed	NA
	30	Sources of funding and other support; role of funders	23

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.