Review Article

Ruling out acute myocardial infarction based on a single high-sensitivity troponin measurement in the emergency department: a clinical practice review

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Abstract: Emergency departments (EDs) around the world are under increasing pressure, with overcrowding increasing preventable errors, patient discomfort, violence and aggression, staff burnout, and patient morbidity and mortality. Chest pain is one of the most common reasons that patients present to the ED. Accelerated diagnostic pathways use clinical assessment, electrocardiograms and cardiac biomarkers to help emergency medicine providers to quickly and accurately identify patients who are at low risk of myocardial infarction, and who therefore can be safely discharged, whilst ensuring that high-risk patients receive prompt and appropriate care. Accelerated diagnostic pathways decrease ED length of stay, which may reduce overcrowding. The diagnosis of acute myocardial injury has previously required at least two cardiac troponin measurements to be taken at least 6–12 hours apart. More recently, the use of accelerated diagnostic pathways in conjunction with high sensitivity cardiac troponin assays, allow a single sample measuring very low troponin concentration to be used to exclude acute myocardial injury. This enables the early discharge of a significant number of patients presenting to EDs with possible acute coronary syndrome, therefore decreasing ED overcrowding and improving patient flow. This clinical practice review describes the clinical perspective of ED specialists which differs from that of cardiologists and clinical chemists. We summarise the development of decision-making pathways for the assessment of chest pain, and describe the current changes taking place in pathway use involving single test rule out of acute myocardial infarction in the ED. The purpose of this clinical practice review is to provide clinical biochemists with an understanding of how emergency clinicians use and approach cardiac troponin results within the ED.

Keywords: Troponin; acute coronary syndrome; myocardial infarction; diagnosis

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Introduction

Background

Emergency departments (EDs) around the world are increasingly overcrowded, with excess numbers of patients and long wait times, both associated with significant patient harm (1-3). Treatment delays increase morbidity and mortality for both low- and high-acuity patients (4,5). Additionally, rates of preventable error increase (6), additional patients who require urgent assessment and treatment leave without being seen by a doctor (7,8), and ambulances are diverted (9).

Access block has been defined as: '*the situation where patients are unable to gain access to appropriate hospital beds within a reasonable amount of time*, *no greater than 8 hours*' (10). It is a significant contributor to overcrowding, and leads to longer hospital stays and higher costs (11-13). ED overcrowding is also associated with increased violence and aggression towards staff, staff turnover, staff distraction leading to error (14,15), and contributes to high levels of burnout in emergency physicians (16). Patient experiences are also poor, with patients being cared for on trolleys in corridors or in the ED waiting room (17).

Public awareness campaigns around the world encourage patients with symptoms potentially associated with myocardial infarction to promptly seek medical attention. As a result, acute chest pain is one of the most common presentations to EDs, accounting for between 5–10% of ED attendances (18-20), and with hospital admission rates of 40–70% (21,22), although the numbers of patients with acute myocardial infarction (AMI) are relatively low (23-25). Mortality rates for all acute chest pain presentations are approximately 1–2%, however there is significant variation depending on the underlying cause and patient demographics (26,27).

Missed heart attack carries risk. There are many reasons for chest pain, some life-threatening, however only a minority will be eventually diagnosed with an acute coronary syndrome (ACS). This means that the assessment and safe decision making for the management of these patients is challenging and time-consuming. Patients presenting to ED with chest pain are assessed for AMI, and if this can confidently be ruled out they may be discharged from ED. Patients who are considered at high risk for underlying coronary artery disease (CAD) as a cause for their symptoms may require further investigation (19).

Although the development of protocolized chest pain pathways using serial troponin assays have decreased the time that patients with chest pain spend in ED, the absolute number of these presentations (28) means that the burden on the health system remains significant, and even small improvements in ED or hospital length of stay can reduce overcrowding and improve health care for all those presenting to EDs (29,30).

The diagnosis of acute myocardial infarction cannot be made on either cTn alone, or with a single result. Dynamic cTn concentration change is required in the clinical context of myocardial ischaemia, identified by symptoms suggestive of AMI, electrocardiogram (ECG) changes or imaging including coronary angiography (19,31). AMI may be further defined as Type 1, related to coronary artery plaque rupture and superimposed thrombosis or Type 2, characterised by an imbalance between myocardial oxygen supply and demand, such as in sepsis or pulmonary embolism (31), however this differentiation is not always clear during a short ED visit, and often requires further testing as an inpatient. Acute myocardial injury, with rising and/or falling concentrations of cTn, can also be differentiated from chronic myocardial injury with static concentrations about the 99th percentile (31). In this review with use the term 'acute myocardial infarction' or AMI to describe both type 1 and type 2 MI.

Rational and knowledge gap

Cardiac troponin (cTn) (I or T) is endorsed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the National Academy of Clinical Biochemistry (NACB) and expert societies worldwide as the preferred biomarker for the assessment of possible ACS (31-35), with clinical guidelines recommending a turn-around time (TAT) of less than 60 minutes for high sensitivity troponin assays (hs-cTn) (32,34,35). Although ED overcrowding is multifactorial, a delayed time between a sample being taken and the results being available for the clinician to act on the result can be considerably longer than the lab TAT (36). This has been cited as a contributing factor to ED overcrowding (37,38).

ED clinicians and clinical biochemists (39) may view cardiac troponin differently. Clinical biochemists focus on the analytical performance of a test, whereas emergency physicians focus on the clinical predictive performance use of the test, particularly in relation to accurate 'rule-out' of AMI. Cardiologists (40,41) focus on the accurate identification of patients with AMI secondary to coronary artery disease (as opposed to other causes of an increase in troponin) who may benefit from procedural or therapeutic

interventions.

When assessing patients with cardiac chest pain, the primary goal of the emergency physician is to rapidly identify those patients at low risk of AMI to expediate discharge, while ensuring that those at high risk receive prompt treatment and referral to cardiology or other inpatient teams. Single test rule out strategies involve decision making at very low troponin concentration thresholds, and therefore emergency physicians require assays with accuracy at low cTn concentrations.

Objective

The objective of this review is to summarise the development of decision-making pathways for the assessment of chest pain, and describe the current changes taking place in pathway use involving single test rule out of AMI in the ED. The purpose of this clinical practice review is to provide clinical biochemists with an understanding of how emergency clinicians use and approach cardiac troponin results within the ED.

How high-sensitivity troponin assays are used within the emergency department

Characteristics of high-sensitivity troponin assays

cTn assays are becoming increasingly sensitive, with the ability to precisely measure cTn at very low concentrations, allowing for the earlier rule-out of myocardial injury. Hs-cTn assays are characterised by the detection of cTn in 50% of healthy individuals below the 99th percentile, with a coefficient of variation (CV) of 10% or less at the 99th percentile (33,42). Compared to previous lower sensitivity (contemporary) assays, hs-cTn assays allow for earlier recognition of a rise and/or fall in concentration, and therefore the rapid rule-out of ACS through accelerated diagnostic chest pain algorithms (21,29,35,43). It is important to note that there is strong evidence that patients need to be tested at least 3 hours after onset of symptoms (19,34,44). High-sensitivity troponin assays also allow for the use of gender-specific upper reference limits (35,43,45).

Use of high-sensitivity troponin assays in clinical decision making

There is a rule-out threshold lower than the 99th centile that is specific to each hs-cTn assay. Application of these cTn thresholds in decision-making pathways used to rule out myocardial infarction will miss fewer cardiac events than those relying on the 99th centile (46). When deriving the hs-cTn threshold concentration for use in a chest pain decision pathway, both the (statistical) sensitivity and negative predictive value (NPV) of the assay at a threshold must be considered.

The prevalence of ACS in ED studies varies greatly from 1% to over 20% (23-25). A high NPV is easily achieved (for a pathway designed to rule-out ACS) in a population with a very low prevalence of disease. Data presented by Mahler *et al.* (23) using the History, ECG, Age, Risk factors, and initial Troponin (HEART) score to rule out ACS demonstrates that with a low prevalence of disease (1.1%), there is a very high NPV (99.4%), but an unsafe sensitivity (58.3%). Therefore, the assay characteristics must be considered in the context of the disease prevalence of the population within which the test is being used.

The sensitivity of a threshold is the most important consideration. A survey of over 1,000 emergency medicine physicians from Australasia, United States of America and Canada found that the most acceptable rate of error for a missed diagnosis of AMI was between ≤1 in 100 (1%) and ≤1 in 1,000 (0.1%) in patients discharged from ED. This suggests that a sensitivity of 99% or higher is required for a test comprising a low cTn threshold, a risk scoring system, and an electrocardiogram, which allows for the early discharge of chest pain patients from ED (47).

Development of accelerated diagnostic pathways (ADPs)

The traditional management of patients presenting to EDs with potential cardiac chest pain was to admit the majority of patients to hospital, allowing for serial biomarker testing. A delay of up to six to nine hours between samples was previously needed as contemporary sensitive troponin assays could not safely rule out AMI at presentation (48). With an assumed prevalence rate of ACS of approximately 20%, *Figure 1* demonstrates that up to 70% of patients would be unnecessarily admitted to hospital for prolonged observation and other investigations (such as exercise stress test or angiography) (see *Figure 1*, pre-ADPs).

With the advent of hs-cTn assays, and increasing knowledge around the risk stratification of patients with chest pain, ADPs have been developed with the aim of identifying patients at low and intermediate risk of ACS, who can have ACS ruled-out and therefore discharged from ED at earlier time points (see *Figure 1*, post-ADPs).

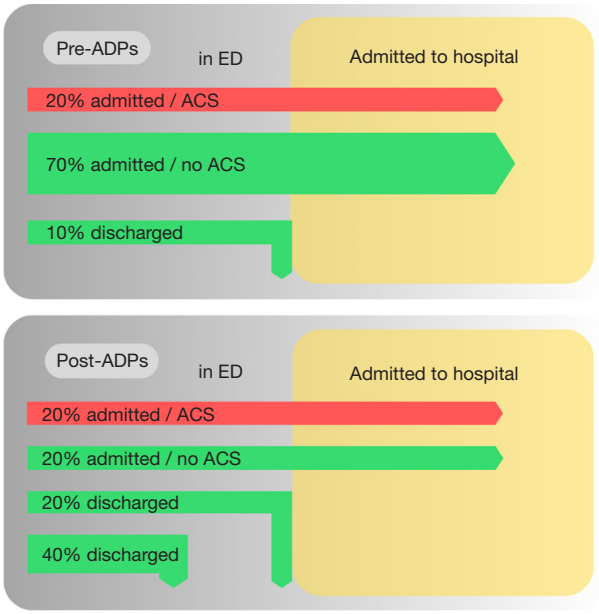

Figure 1 Patient flow pre- and post-adoption of ADPs. ADPs, accelerated diagnostic pathways; ED, emergency department; ACS, acute coronary syndrome.

ADPs are designed to enable clinicians to quickly and accurately identify patients who are at low risk of acute myocardial infarction, and who therefore can be safely discharged, whilst ensuring that high-risk patients receive prompt and appropriate care.

Five approaches have been taken to the development of ADPs.

(I) The use of clinician gestalt plus a risk stratification algorithm based on troponin alone. This was the approach of the 0/1 h and 0/2 h algorithms in the European Society of Cardiology guidelines (34).

(II) A score made-up by an expert(s) that incorporates troponin. This was the approach taken for the development of the HEART score (23,49), incorporated within a pathway including serial troponin (50).

(III) Modification of a pre-existing risk score, Thrombolysis In Myocardial Infarction (TIMI) (51), related to mortality outcomes following MI in conjunction with ECG and troponins, the ADAPT ADP (52).

(IV) Development of a risk score that predicts major adverse cardiac events (MACE) with signs, symptoms, demographics, and patient history on presentation to the ED, Emergency Department Assessment of Chest Pain Score (EDACS) used in conjunction with ECG and troponin (53).

(V) Development of a statistical/machine learning algorithm which predicts the likelihood of MI based on troponin and other variables gathered on presentation to ED, Troponin-only Manchester Acute Coronary Syndromes (T-MACS) (54), MI^3 (55), CoDE-ACS (25).

Until recently, a serial (double) test rule out within an ADP was standard of care, however the precision of hs-cTn assays have improved, and when an hs-cTn assay is used in conjunction with an appropriate ADP, it is now possible to rule-out AMI in a proportion of low-risk patients with hs-cTn concentrations close to or below the limit of detection (LoD).

Single test rule-out of acute myocardial infarction

The aim of a single test rule-out pathway is to identify patients at such low risk of having myocardial infarction that they don't require a second test, allowing early discharge from the ED. A number of studies have demonstrated that very low hs-cTn concentrations at presentation can be used to risk stratify patients (56-58), with concentrations well below the 99th percentile upper reference limit (URL) able to identify those at very-low risk of an AMI. A prospective study of 4,870 patients with possible ACS (of whom 16% had AMI) demonstrated that an hs-cTn concentration ≤5 ng/L at presentation had an NPV of 99.6% (95% CI: 99.3–99.8%) for AMI, or MI or death within 30 days (59). This threshold enabled the identification and discharge of two-thirds of the patients without an AMI after a single test. Caution is noted for those patients who present within 2 hours of onset of pain, where repeat testing is recommended as the NPV of a single test is lower, in this study in these patients 97.6% (95% CI: 95.8–99.2%).

The possibility of using a single blood draw with a low-concentration of cTn to rule-out AMI was raised with the advent of hs-cTn assays (56). Two large international meta-analyses of the performance of single test rule-out thresholds, one for the Roche hs-cTnT assay (44) and one for the Abbott hs-cTnI assay (60), provided the evidence on safety and performance needed for adoption of these thresholds into clinical practice. Across 11 cohorts and 9,241 participants a low-risk hs-cTnT test of <5 ng/L (i.e., at the LoD of the assay) and no-new ischaemia on ECG classified 30.6% as low-risk with an NPV of 99.3% (95% CI: 97.3–99.8%) and sensitivity of 98.7% (95% CI: 96.6–99.5%) for AMI. Across 19 cohorts and 22,457 participants a low-risk

hs-cTnI test of <5 ng/L (3 ng/L above the LoD) classified 49.0% low-risk with an NPV of 99.5% (95% CI: 99.3–99.6%) for 30-day AMI. Both of these studies observed that approximately 50% of the missed cases occurred in participants in whom the blood draw was within 3 hours of symptom onset.

For most other assays, a single-test rule-out threshold has been established simply by finding in a cohort the threshold that if applied clinically would have resulted in an NPV ≥99.5% or sensitivity ≥99.0%. The safety of these threshold are validated in other cohorts. Whilst sometimes called optimal thresholds, they are almost always based on small numbers of AMIs (sometimes <100) which means that they are dependent on the exact concentrations of just one or two patients (61). By analogy, this is similar to a process to determine a 99th centile with just 100 subjects. Despite the inherent imprecision in these threshold estimates, their safety record is strong and in most jurisdictions, where prevalence is not high, they enable rule-out of AMI in a substantial proportion of patients.

A single troponin test for rule-out of ACS should only be used within ADPs. There are several single-test rule-out pathways in use globally. Commonly used pathways include the:

(I) EDACS pathway (62) (see Figure S1).
EDACS pathways were developed in Australasia and are commonly used in this region (63). They combine a structured risk assessment (EDACS) with ECG findings, time from symptom onset, and the presence of unstable features such as crescendo angina or abnormal vital signs to determine which patients, and which troponin threshold, can be used for single-test and serial-test rule-out of AMI (64).

(II) European Society of Cardiology (ESC) pathway (see Figure S2).
The ESC-based pathways recommend the use of clinical judgement and ECG interpretation in combination with an algorithmic troponin threshold approach. The ESC guidance provides assay-specific threshold recommendations for single-test rule-out. The ESC pathway was developed in Switzerland and has a good European following. Both this and the EDACS pathway have some additional usage beyond their own regions.

(III) HEART score-based pathways (50) (see Figure S3).
Pathways based on the HEART score probably have the widest usage internationally, particularly in the USA. The HEART score was originally created in The Netherlands (49). Variants that use single-test for troponin test rule-out are often referred to as HEAR pathways (representing history, ECG, age and risk factors) which are then combined with troponin thresholds.

(IV) High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome (High-STEACS) (59) (see Figure S4).
The High-STEACS pathway was developed in Edinburgh and is widely used in the local region. The High-STEACS pathway developers have troponin-specific thresholds for single-test rule-out and the pathway does not incorporate clinical findings and examination findings as long as the patient is stable.

(V) T-MACS pathway (54).
The T-MACS pathway combines a mathematical algorithm of clinical findings with troponin results within a calculator to predict patient likelihood of AMI and provides guidance about probability (54).

All of these pathways have been validated in real-life patient care, are considered safe to use, and have been shown to be effective in facilitating earlier discharge of patients from the ED (34,50,54,59,62,63). Shah *et al.* (65) showed this to be the case in over 31,000 patients.

Some countries or regions, e.g., New Zealand and several Australian states, have developed a cross-system consistent approach to patient assessment. In New Zealand, for example, every hospital has a single-test rule out approach within its AMI assessment pathway. The most common approach in New Zealand is based upon the EDACS pathway however a small number of centres also use an ESC-based approach.

The place of point-of-care (POC)

POC troponin testing, performed by clinical staff at or near the site of the patient, are able to significantly reduce TAT by reducing specimen transport and handling time. POC testing allows for results to the treating clinician within 20 minutes or less (66-71), as well as testing in a range of healthcare environments, such as ambulances or rural clinics distant from laboratories. Rapid test results can allow rapid decision making to occur in conjunction with ADPs, which can reduce ED length of stay and therefore promote better outcomes for low-risk patients who only require a single troponin for rule-out of AMI.

The limiting factor in the use of POC troponin testing

in clinical practice until recently is that POC and central laboratory assays do not show equivalent analytical precision. New POC hs-Tn assays are now beginning to demonstrate comparable precision to laboratory-based assays (72,73). Using a validated very low concentration threshold in patents presenting at least 2–3 hours after the onset of symptoms these may allow the rule-out of AMI (34) after only one blood sample (66,67,74). Such high sensitivity POC cTn assays have only just begun to be used in EDs for clinical decision-making. They have the potential to significantly reduce TAT and ED length of stay and overcrowding.

Single test "rule-in"

A single test does not allow for a detection of a rise and/or fall in cardiac biomarkers; a requirement for the diagnosis of AMI. One hs-cTn result above the 99th percentile does not differentiate between acute and chronic myocardial injury, and does not allow for the determination of a Type 1 versus Type 2 AMI. Further testing such as angiography demonstrating critical coronary artery stenosis or imaging providing evidence of new regional wall motion abnormalities are often required to make a conclusive diagnosis of the cause for a cTn rise (and therefore determination of a Type 1 versus Type 2 AMI). Such testing is not usually available in EDs, and so a single test rule-in strategy is rarely feasible outside the context of an ST elevation AMI. Some risk-stratification algorithms, such as those recommended in the ESC guidelines, use an elevated (above the URL) troponin threshold and the term "rule-in" to risk stratify patients into a high-risk group where they may receive more immediate attention from cardiologists.

Strengths and limitations

The principle strength of this clinical practice review is that it has been written predominantly by emergency physicians, and so provides an ED perspective on the use of single test rule out for AMI. It focusses on the experience of assessing patients with chest pain in ED, rather than from a cardiology (40,41) or laboratory (39) viewpoint; consequently a limitation is that the views of these groups are not emphasised.

Conclusions

High sensitivity troponin assays have improved precision at measuring low concentrations of circulating troponin compared to contemporary assays. This allows the identification of patients at very low probability of having AMI that don't require repeat testing. When used within a structured decision making pathway, this facilitates safe early discharge from the ED.

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Footnote

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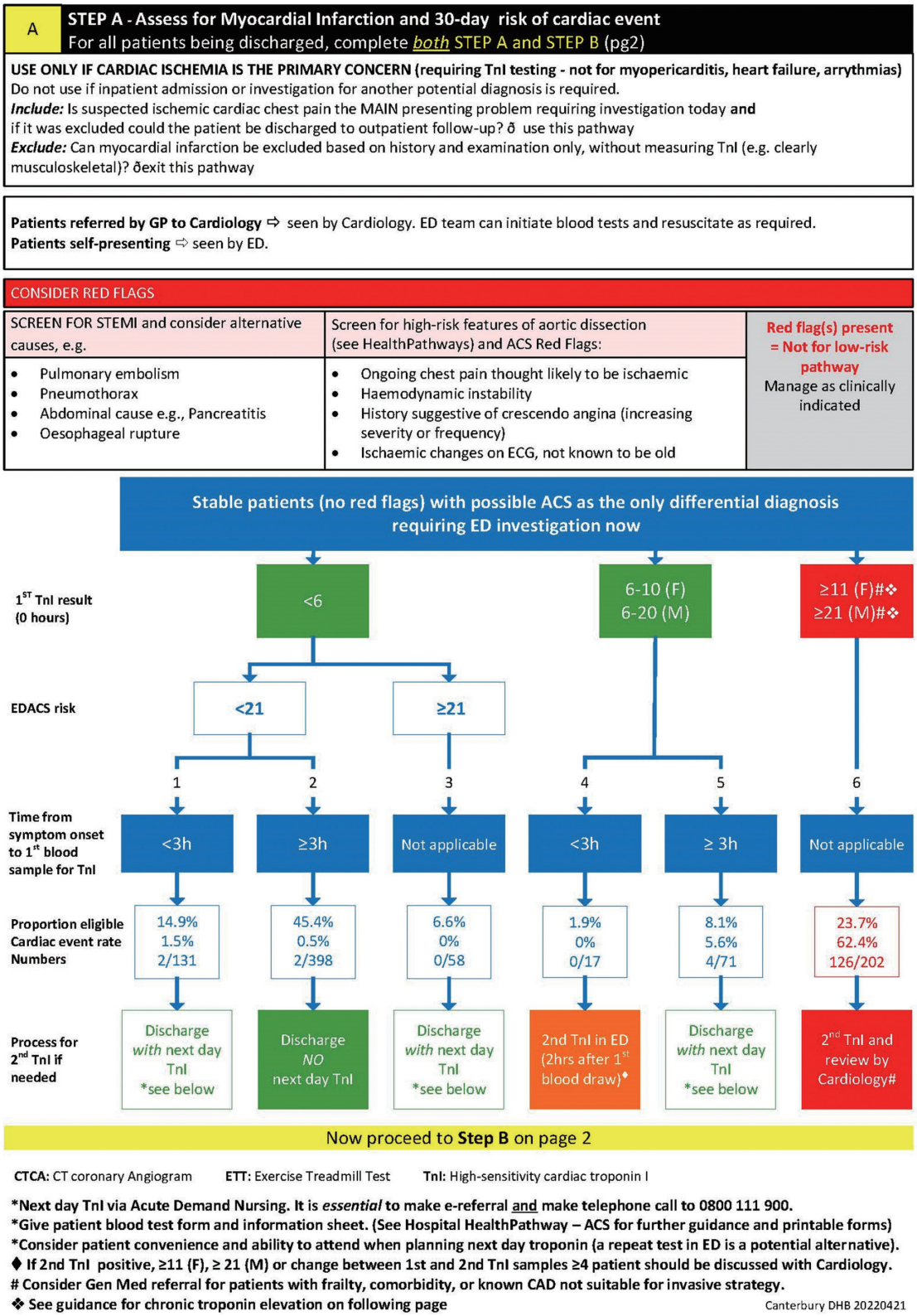

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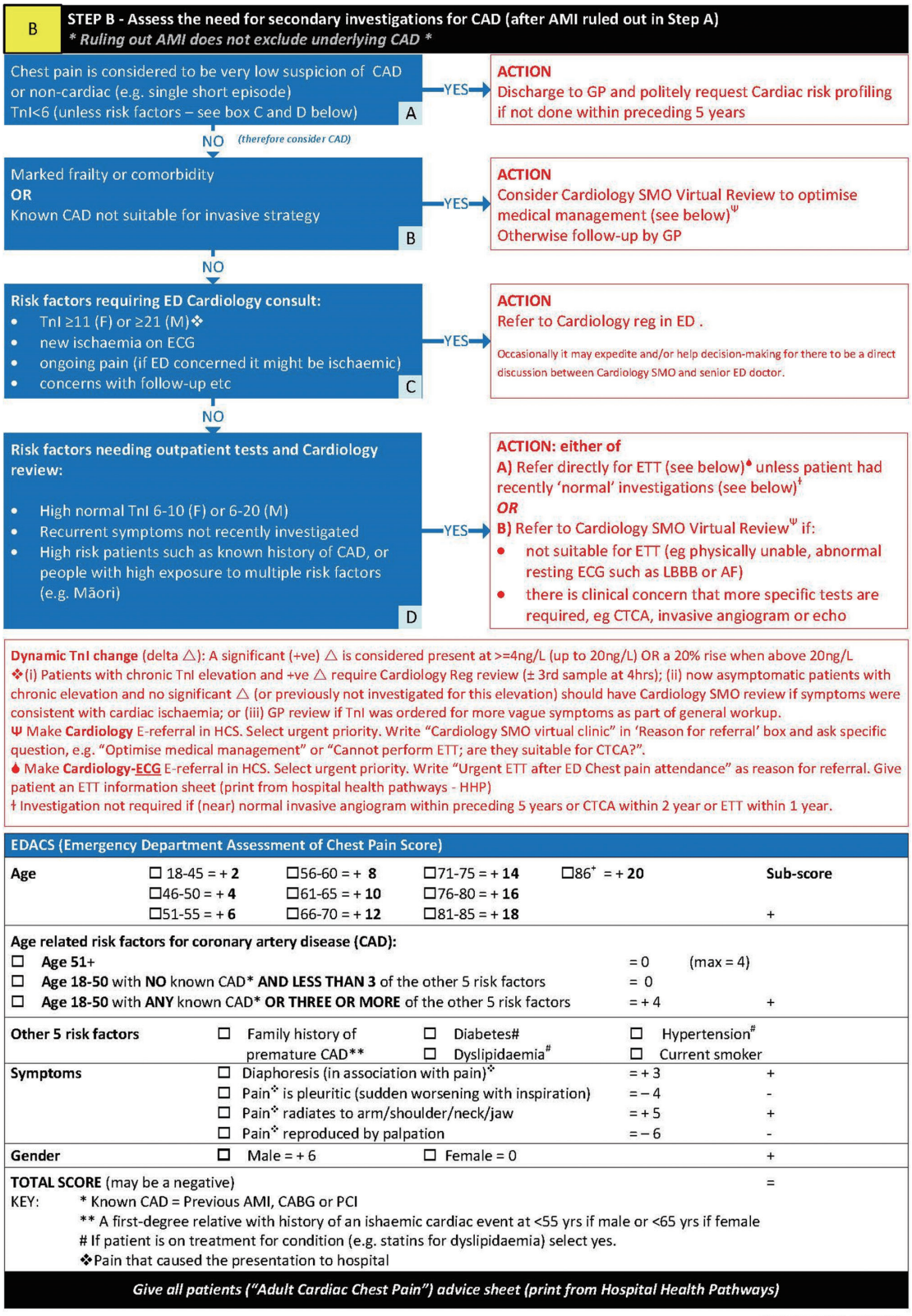

Figure S1 Application of Pathway utilising EDACS score (reproduced with permission of Dr. Martin Than, Christchurch Hospital).

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ACS Rule-in Rule-out Pathway (0-1h) Southland ED

For risk stratification of patients with undifferentiated non-traumatic chest pain that may represent ACS, whereby patients who are low risk (<1% 30 day MACE rate) may be safe for discharge.

NB: The term "chest pain" can include other potentially ischaemic symptoms (eg chest heaviness, arm/jaw pain, SOB, etc), at the discretion of the clinician

Inclusion
- Episode of continuous symptoms >5 mins
- Age >20 years

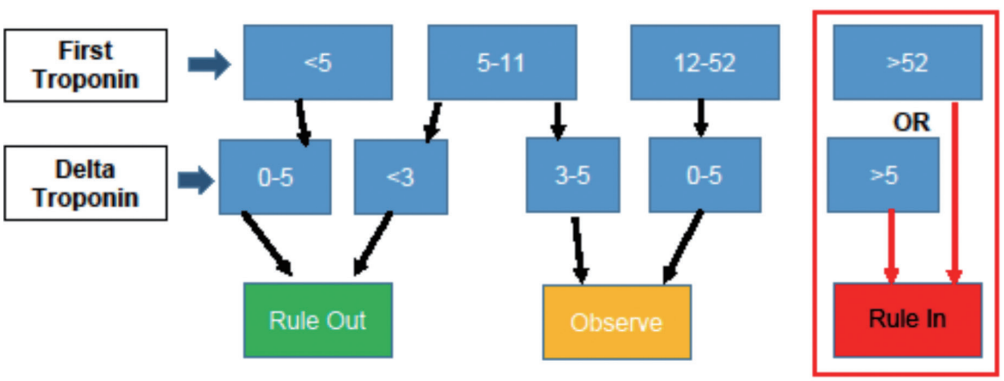
Exclusion
- STEMI
- Haemodynamic instability (arrhythmia, hypotension, APO)
- Suspected alternative diagnosis such as PE or dissection
- Acute ischaemic changes on ECG
- Crescendo angina, persistent or recurrent pain in ED
- Known cause of symptoms (eg pneumonia)

First TnT = blood draw on arrival is time zero. Second TnT is taken at 1 hour after first blood draw

Δ (delta) TnT = absolute difference between 0-1 hour results

Disposition is decided by a combination of the first Troponin and the Delta

NB: if first Tn is >52 OR the Δ is >5, patient is Rule IN



- **Rule Out** (0h <5 or 0h <12 + Δ<3)
  - (<1% prevalence of AMI, <1% 30 day MACE rate)
  - Confirm differential diagnoses considered
  - Chest Pain handout
  - Discharge home
  - GP review in 1-2 weeks to review CAD risk factors
- **Rule In** (0h >52 or Δ>5)
  - (60-70% prevalence of AMI)
  - Admit
  - Consider early ACS treatment
- **"Observe"** (Any other result)
  - (10-20% prevalence of AMI)
  - 3h troponin: if all three <15 = Rule Out. Otherwise discuss with ED Consultant

Figure S2 Application of ESC-based pathway (reproduced with permission of Dr. Chris Johnstone, Invercargill Hospital).

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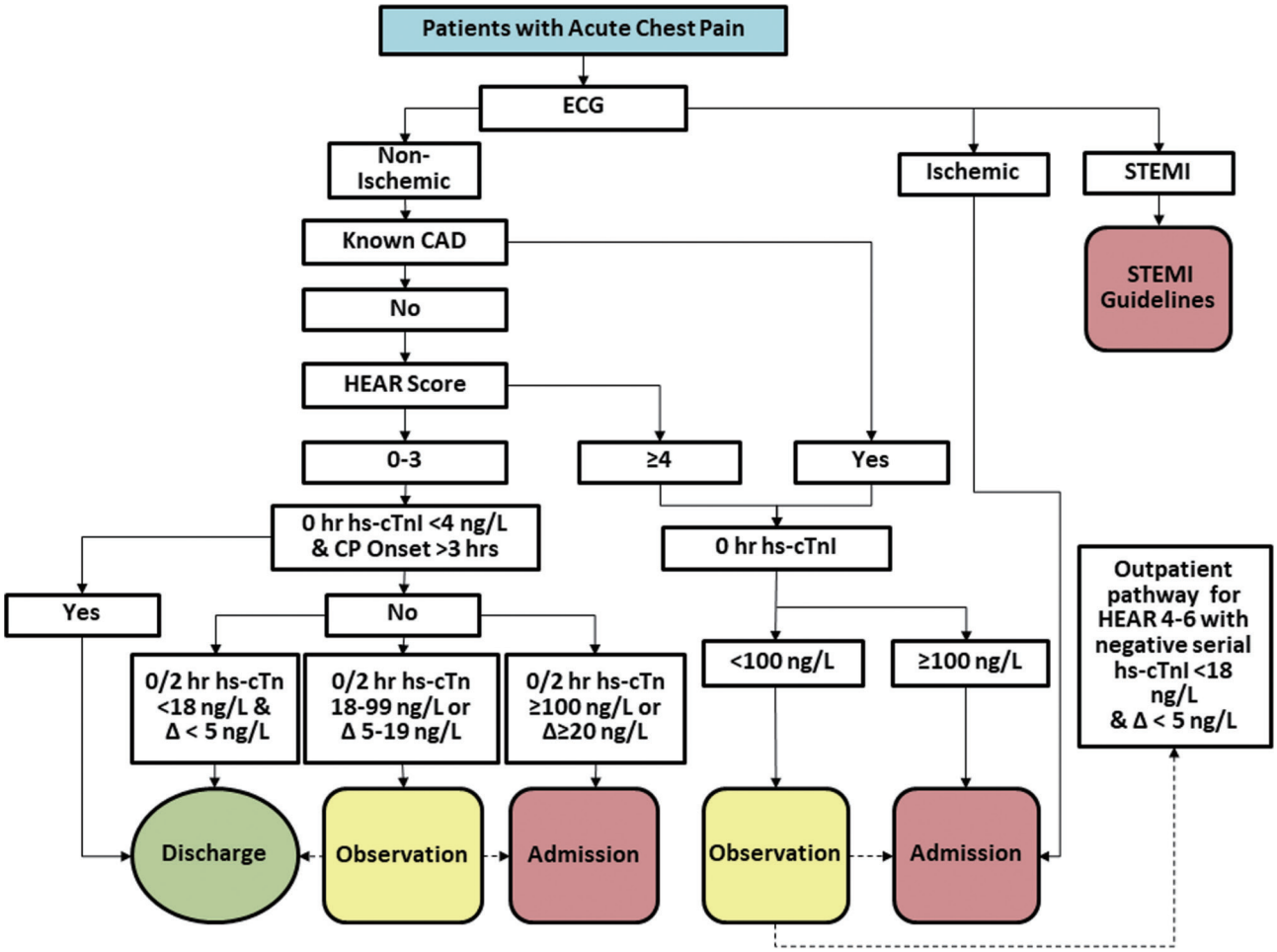

Figure S3 Application of HEART-based pathway (reproduced with permission of Dr. Simon Mahler, Wake Forest Baptist Health, Winston-Salem, USA).

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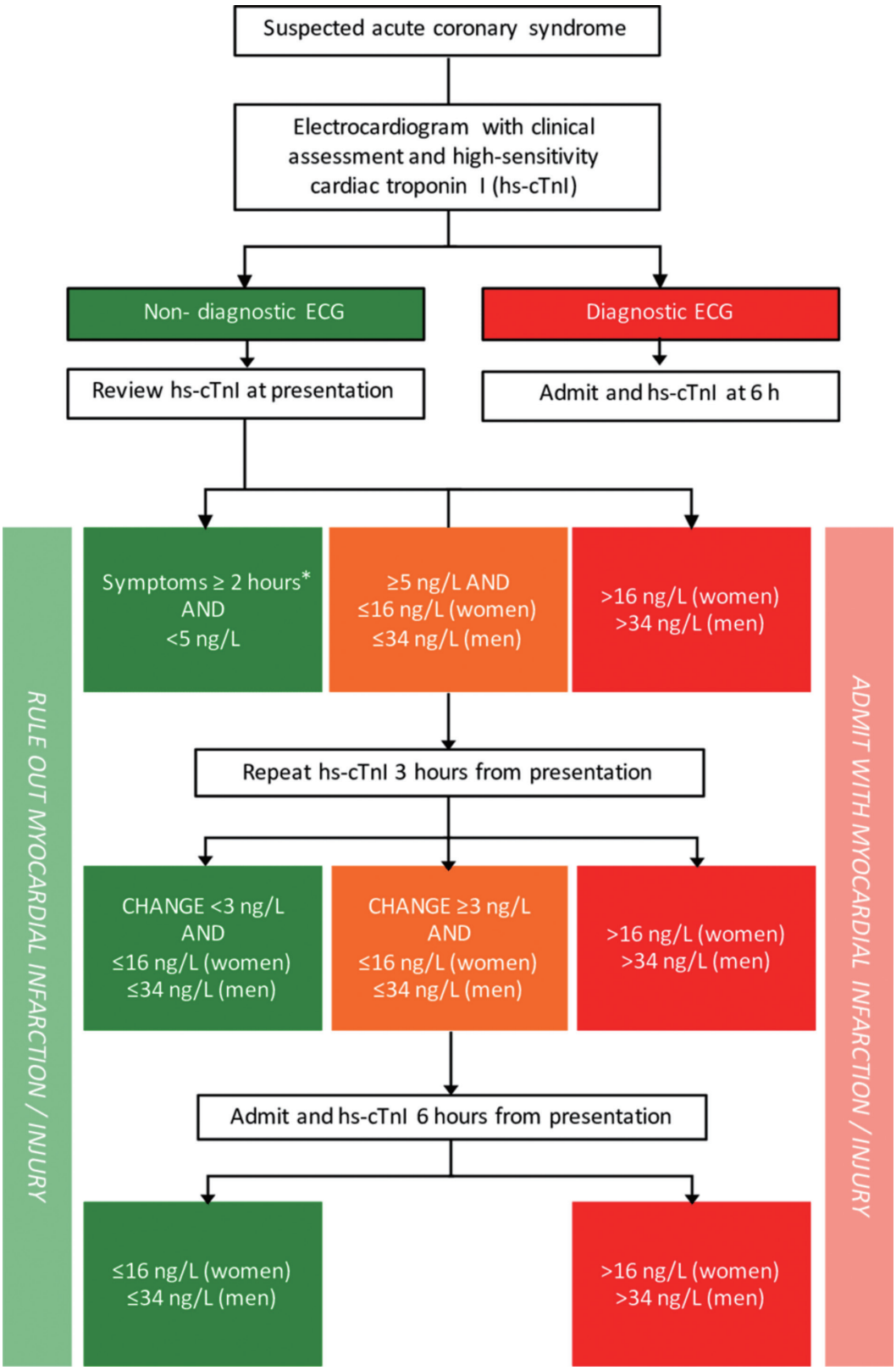

Figure S4 Application of High-STEACS-based pathway.

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