Identifying Patients Suitable for Discharge After a Single Presentation High-Sensitivity Troponin Result- A Comparison of Five Established Risk Scores and Two High-Sensitivity Assays

Abstract

Objective

To compare the ability of five established risk scores to identify patients with suspected acute coronary syndromes (ACS) suitable for discharge after a single presentation high-sensitivity troponin (hs-cTn) result.

Methods

Prospective observational study conducted in a U.K. District General Hospital Emergency Department. Consecutive adults recruited with suspected ACS whom attending physicians determined evaluation with serial troponin testing was required. Index tests were definitions of low risk applied to Goldman, TIMI, GRACE, HEART and Vancouver risk scores, incorporating either hs-cTnT or hs-cTnI results. The endpoint was acute myocardial infarction (AMI) within 30 days. A test sensitivity threshold for AMI of 98% was chosen. Clinical utility was defined as a negative predictive value (NPV) ≥99.5% and identification of >30% suitable for discharge.

Results

959 patients underwent hs-cTnT and 867 hs-cTnI analysis. In the hs-cTnT group, 79/959 (8.2%) had an AMI and 66/867 (7.6%) in the hs-cTnI group. Two risk scores (GRACE<80, HEART≤3) did not have the potential to achieve a sensitivity of 98% with hs-cTnT and three
scores (Goldman≤1, TIMI≤1, GRACE<80) with hs-cTnI. TIMI 0 or ≤1 and m-Goldman≤1 with
hs-cTnT, and TIMI 0 and HEART≤3, with hs-cTnl have the potential to achieve an NPV ≥99.5%
while identifying >30% for discharge.

Conclusion

Using established risk scores, it may be possible to identify >30% of patients suitable for
discharge with an NPV ≥99.5% for the diagnosis of AMI using a single hs-cTn result taken at
presentation. There is variation in hs-cTn assays which may have implications in introducing
rapid rule-out protocols.
Introduction

Background and Importance

Patients with suspected cardiac chest pain account for over 6 million emergency department (ED) attendances annually across the United States (1). Current guidelines recommend serial measurements of (non-high sensitivity) cardiac troponin between 6 and 12 hours after patient presentation to the ED (2). As a result, the majority of patients require prolonged assessment prior to safe discharge despite the fact that only 15-25% of these patients have a final diagnosis of acute coronary syndrome (ACS) (1). This prolonged assessment leads to increased healthcare costs (3) and ED overcrowding, which has been shown to lead to increased adverse events in both ACS and non-ACS related chest pain patients (4). The efficient identification of low risk patients who can be safely discharged after rapid assessment in the ED remains an important issue.

Consensus reports have suggested that high-sensitivity troponin (hs-cTn) assays may be used to reduce door-to-discharge times by using serial testing over 3 hours (5). An hs-cTn assay is defined as an assay which has a coefficient of variation of <10% at the 99th percentile value (the upper limit of the reference population), and which is able to detect cardiac troponin in >50% of the reference population (5). Current data suggest that the diagnostic performance of high-sensitivity assays when used in isolation is too low to allow immediate discharge of patients presenting to ED after a single blood draw on arrival (6,7). Therefore, to reduce door-to-discharge times further, it has been suggested that the adjunctive use of clinical chest pain risk scores (which give an estimate of pre-test probability), in combination with hs-cTn testing will improve the diagnostic performance (8,9). Although these combination strategies are gaining acceptance, the optimum choice of
rapid rule-out protocol remains undetermined. This is because the majority of existing clinical risk scores remain untested in conjunction with a single hs-cTn taken at presentation to the ED and their resultant diagnostic performance has rarely been compared.

**Goals of This Investigation**

The aim of this study was to compare the ability of five established risk scores, when used in conjunction with either high-sensitivity troponin T (Roche Elecsys hs-cTnT) or I (Abbott Architect hs-cTnI), to identify patients with chest pain symptoms suggestive of acute coronary syndromes (ACS) suitable for early discharge after a single blood draw at presentation to ED.

**Methods**

**Study Design and Setting**

This was a planned post-hoc analysis of the Triage Rule-out Using high-Sensitivity Troponin (TRUST) Study (Controlled Trials Database ISRCTN No. 21109279), a single centre prospective diagnostic cohort study designed to establish the diagnostic performance of the modified Goldman (m-Goldman) risk score (10) in combination with a single laboratory hs-cTnT taken at presentation to the ED. The results of primary analysis have been published previously (9). The study protocol was designed using the Standards for Reporting Diagnostic Accuracy (STARD) (11) and approved by the U.K. National Research Ethics Service. All participants provided written informed consent.
The study was undertaken at Poole NHS Foundation Trust, a U.K. District General hospital, between July 2012 and August 2013. The ED has approximately 62 000 new patient attendances per year. Patients with suspected ACS were managed according to the local hospital protocol, which involved risk assessment by ED physician staff using the m-Goldman risk score and blood drawn for hs-cTnT at 6 hours after presentation. Whilst historical clinical protocols, at the time of this study, did not include troponin measurement at presentation, this had the benefit of ensuring that treating physicians were blinded to the initial hs-cTnT result to avoid work-up bias (12).

**Selection of Participants**

Consecutive patients were screened and recruited 24 hours a day, 7 days a week during the study period. Patients were included if they were at least 18 years of age and had at least 5 minutes of chest pain suggestive of ACS, and for whom the attending physician determined evaluation with serial troponin testing was required. Possible cardiac symptoms included acute chest, epigastric, neck, jaw or arm pain, or discomfort or pressure without an apparent non-cardiac source, in accordance with the American Heart Association case definitions (13). Patients were excluded if any of the following were present: ST-segment elevation myocardial infarction or left bundle branch block not known to be old, ECG changes diagnostic of ischemia (ST segment depression ≥1mm or T-wave inversion), arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias), age ≥80 years, atypical symptoms in the absence of chest discomfort, a clear non-ACS cause for chest pain was found at presentation (e.g. pulmonary embolism, pneumonia, aortic dissection), another medical condition requiring hospital admission,
refusal or inability to give informed consent, non-English speaking, pregnancy, renal failure requiring dialysis or inability to be contacted after discharge. For this analysis patients were also excluded if either Roche hs-cTnT or Abbott hs-cTnl levels at presentation were not available for their respective analysis.

**Methods and Measurements**

During initial assessment clinical staff drew blood for routine admission samples and an additional 3.5mls of whole blood in a pre-labelled study specific serum settling tube for hs-cTn analysis. Roche hs-cTnT was tested in real time by the central hospital laboratory. After centrifugation, samples were frozen at -80°C until transport on dry ice to a remote laboratory, where samples were thawed, then assayed for Abbott hs-cTnl in a blinded fashion.

The fourth generation Roche ELECSYS hs-cTnT assay (Roche, Switzerland), which has 99th percentile value of 14ng/L and 10% coefficient of variation of <10% at 9ng/L, was used for research (presentation) and reference (6-hour) samples. Stored presentation samples were also tested for hs-cTnl using the Abbott ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Laboratories, USA), which has a 99th percentile value of 26.2ng/L with a corresponding coefficient of variation of <5% and a limit of detection of 1.9ng/L.

All data were collected prospectively by trained research nursing staff using a published data dictionary (14) from data collected at admission only. Attending ED clinicians completed a standardised clinical report form designed to enable accurate recording of demographic data and variables required to calculate risk scores.
Risk scores were selected a priori if they had been prospectively externally validated in large ED cohort studies, designed with the intention of improving ED efficiency. Index tests were definitions of low risk applied to the modified Goldman, TIMI, GRACE and HEART scores and the Vancouver chest pain rule, incorporating either hs-cTnT or hs-cTnl results. Table 1 presents a summary of the clinical variables which make up each risk score and definitions of suitability for discharge according to each risk score, applied after evaluation of respective validation studies: m-Goldman (15); Thrombolysis in Myocardial Infarction (TIMI) (8); Global Registry of Acute Cardiac Events (GRACE) (16); History, ECG, Age, Risk Factors, Troponin (HEART) (17) scores and the Vancouver Chest Pain Rule (18). Where biomarker results were not included as a variable in the original score, hs-cTnT and hs-cTnl were incorporated accordingly using the 99th percentile cut-off value as a baseline. As only patients with a non-ischemic ECG were recruited to the study, where ischemic ECG changes were included in the original risk scores these variables were removed, as reflected in clinical practice where patients with ECG changes diagnostic of ischemia are immediately defined as high risk and therefore not suitable for discharge (19). A computer-based algorithm was designed to calculate each score automatically from the admission data, without interpretation by the study investigators.
Outcomes

The primary endpoint was the presence of fatal or non-fatal AMI occurring within 30 days of hospital attendance (including the index visit).

The presence of AMI was defined according to the Third Universal Definition of MI which states that a rise and/or fall in troponin, with at least one value above the 99th centile value in the context of a patient with ischemic symptoms or signs (ECG changes or imaging evidence) would satisfy the diagnosis (20). The final diagnosis of AMI was adjudicated according to presentation and 6 hour Roche hs-cTnT results, as this was in clinical use during the study period. Clinical blood samples taken 6 hours after patient presentation were not stored as part of the study protocol, therefore it was not possible to evaluate outcome separately using the Abbott hs-cTnI assay. Based on current consensus guidance for high-sensitivity troponin assays, a rise or fall of 20% (delta) was considered statistically significant and consistent with a diagnosis of AMI (5). Adjudication of the endpoint was carried out by two local cardiologists blinded to all risk scores but whom had access to the clinical record, ECG and serial hs-cTnT results.

Follow-up was undertaken by independent review of hospital electronic patient records, summary of health records from the patient’s General Practitioner (GP) obtained at least 6-months after attendance and a national clinical records search (which identifies death). Where a participant had not attended hospital follow-up and/or a GP had failed to provide a health record/not GP-registered, the patient was regarded as lost to follow-up.
Analysis

We estimated the sample size for the primary analysis according to the precision of the sensitivity of the m-Goldman accelerated diagnostic pathway (9). Assuming a 100% sensitivity of this decision rule with a 95% confidence interval that would extend no lower than 99%, with 40% of patients being eligible for discharge, a sample size of 966 patients was required.

Chi-squared analyses were used to generate 2 x 2 tables for the calculation of sensitivity, specificity, and positive and negative likelihood ratios. All statistical analysis was carried out using IBM SPSS version 20.

To illustrate the generalizability of each pathway as a rule-out tool, a sensitivity threshold of 98% was chosen, the threshold at which it has been suggested that the risks of false-positive testing (beyond biomarker analysis) outweigh the risk of untreated disease (21). Sensitivity for the diagnosis of AMI was plotted against 1-specificity to give a graphical representation of test performance. To define the optimum clinical utility of each rule-out protocol, according to the outcome prevalence within the study cohort, a target negative predictive value (NPV) for the diagnosis of fatal or non-fatal AMI of $\geq 99.5\%$, together with a proportion of patients identified as being suitable for discharge of $>30\%$ was set. An NPV $\geq 99.5\%$ was chosen in the absence of consensus agreement, but this has been shown to be the miss-rate which the majority of emergency physicians deem acceptable for diagnostic strategies in the assessment of suspected ACS (22). Also, for a risk score to be of substantial benefit, significant numbers of patients need to be identified as suitable for discharge, therefore a target of $>30\%$ was chosen, which is similar to existing rapid rule-out protocols which incorporate hs-cTn testing (8,9).
Results

Characteristics of Study Subjects

Overall, 963 consenting patients were recruited (Figure 1) and 4 patients were lost to follow-up. The remaining 959 patients underwent Roche hs-cTnT and 867 Abbott hs-cTnI analysis. An additional 132 patients were eligible but not recruited due to missing the consent process. Sufficient data was available to calculate all risk scores, with the exception of GRACE, where 7 cases were excluded from analysis, due to missing creatinine results.

The main outcome event (AMI within 30 days) occurred in 79/959 (8.2%) and 66/867 (7.6%) of the hs-cTnT and hs-cTnI groups, respectively. Patient characteristics for both hs-cTnT and hs-cTnI groups are shown in Table 2.

Main Results

Test Performance of Risk Scores in Combination with Presentation High-Sensitivity

Troponin

Test performance of each risk score and their pre-defined cut-offs for determination of low risk status in combination with presentation Roche hs-cTnT and Abbott hs-cTnI are shown in Tables 3 and 4 respectively.

Figures 2a and b present sensitivity vs. specificity for each risk score and both hs-cTn assays.

When considering the upper bounds of the 95% confidence intervals for test sensitivity, only two risk scores (GRACE<80 and HEART≤3) did not have the potential to achieve the threshold of 98% sensitivity for the diagnosis of AMI, when used in conjunction with hs-cTnT. For hs-cTnI, three risk scores (m-Goldman≤1, TIMI≤1 and GRACE<80) did not have the potential to achieve this sensitivity threshold. Within those tests that did have the potential
to achieve a sensitivity threshold of 98%, there was a wide variation in test specificity. This ranged from 10.6% (95% CI 10.1-10.6) for GRACE<60 with hs-cTnT to 53.5% (95%CI 52.8-53.8) for TIMI<1 with hs-cTnT.

**Clinical Utility of Risk Scores and Presentation High-Sensitivity Troponin Results.**

The potential clinical utility of each risk score is shown in Figures 3a and b. This demonstrates the percentage defined as suitable for discharge against the NPV for the diagnosis of fatal or non-fatal AMI. When considering the upper bounds of the 95% confidence intervals for each test, TIMI 0 or ≤1 and m-Goldman≤1 with hs-cTnT, and TIMI 0 and HEART≤3, with hs-cTnI have the potential to achieve an NPV ≥99.5% while identifying >30% of patients as suitable for immediate discharge.

**Comparison of Presentation High-Sensitivity Troponin Assay Results.**

Of 959 recruited patients, 92 (9.6%) had no presentation sample suitable for hs-cTnl analysis. The 99th percentile value had a sensitivity for the diagnosis of AMI of 83.5% (95% CI 73.8-90.5) using hs-cTnT, and 62.1% (95% CI 51.9-70.8) using hs-cTnI. The clinical characteristics of those patients diagnosed with an AMI, with a high-sensitivity troponin I less than the 99th percentile value (26.2ng/L) at presentation but a high-sensitivity troponin T greater than the 99th percentile (14ng/L) are available in the Web Appendix.
**Limitations**

There are some limitations to this study. We chose the endpoint of fatal and non-fatal AMI as a means of identifying those patients who may be suitable for early discharge from the ED. This has several implications. Firstly, the prevalence of the endpoint is low (8%) because patients with ischemic ECG changes were excluded and this will raise the negative predictive values of all index tests. Secondly, this risks introducing incorporation bias since the outcome is based upon the hs-cTnT results under evaluation. Thirdly, this endpoint excludes those patients with other ischemic end-points, such as unstable angina, who may require intervention. However, subjective ischemic endpoints such as revascularization are likely to be driven by local practices, and in the case of this study, the hs-cTnT assay in clinical use. Some of the scores assessed were designed through regression analysis to deliberately to identify those with unstable clinical features (m-Goldman and Vancouver) and it may be the case that the choice of endpoint will dramatically change the performance of each risk score. Lastly, although fatal or non-fatal AMI, may be useful in identifying those who may be suitable for early discharge, directly from the ED, these patients may still require non-urgent outpatient investigation and follow-up.

Although data for each risk score was derived for analysis at a later date from that recorded by the treating physician at the initial assessment, only the m-Goldman score was performed by the treating physician themselves at the time of presentation. This may be an explanation for the superior diagnostic performance of the m-Goldman score. The approach of deriving risk scores from large prospective datasets is commonplace in the literature (8, 16, 17, 18). However, this methodological approach may be have unseen limitations, and may only be resolved through direct comparison of each pathway through
randomized controlled trials. Furthermore, by using individual clinical measures to calculate risk scores our analysis has failed to take into account unstructured clinical judgement or ‘gestalt.’ Recently, Body et al. demonstrated that by combining clinician gestalt with the admission ECG and troponin level, 100% sensitivity for the diagnosis of AMI could be achieved (23). Accepting that subjective interpretation may be important in risk-stratifying patients with chest pain (23,24), we acknowledge that the performance of each pathway may be enhanced by taking into account clinician gestalt.

The upper age cut-off of ≥80 years was chosen for pragmatic reasons. In our institution, patients above this age are admitted to a separate and dedicated assessment area. Therefore we recognize that this may affect the applicability of the findings in those >80 years of age and any clinical uptake of the protocols described should therefore not be applied to this age group.

**Discussion**

This single-centre study prospectively evaluated the ability of a single hs-cTn (Roche hs-cTnT and Abbott hs-cTnI) result, taken at presentation to the ED, in conjunction with five established risk scores to identify patients with symptoms suggestive of ACS suitable for early discharge. We demonstrate that several diagnostic algorithms do not have the potential to achieve the diagnostic test sensitivity threshold of >98%, as suggested by Kline et al. (21). Whilst this analysis does demonstrate that it may be possible to identify over 30% of patients suitable for early discharge with an NPV of >99.5%, the results are indeterminate with respect to the diagnostic contraints applied and the hs-cTn assay used. For example, although TIMI≤1 and m-Goldmans≤1 reach the >30% potential discharge
constraint using either assay, both fail to meet the NPV threshold of >99.5% using hs-cTnI. These findings may support the use of a clinical risk score in combination with a single presentation hs-cTn result, to identify low risk patients suitable for early discharge. However, the marked variations in the performance of risk scores and individual hs-cTn assays has important implications when considering the introduction of rapid rule-out protocols.

Our data suggest that the introduction of adjunctive risk-scoring in combination with a single presentation hs-cTn result has the potential to reduce the length of stay for low risk patients and allow discharge after a single blood draw taken on arrival in the ED. Uptake of such protocols could have significant benefits for healthcare services worldwide by reducing hospital admission rates, ED overcrowding, duplication of staff time, the need for serial blood-testing and resource use.

By comparing the performance of multiple risk scores in combination with two commercially available hs-cTn assays, we have highlighted relevant assay-dependent variations in diagnostic performance. Although this variation between assays may represent misclassification bias due to hs-cTnT being the assay used for outcome adjudication, it may also be population-specific and is of great importance to clinicians who may not be able to select, or may not be aware, which assay is used in their institution. The introduction of rapid rule-out pathways such as those tested here must therefore take into account local population factors, assay availability and be subject to continuous audit and evaluation to ensure safety.

It may be possible to identify over 30% of patients with suspected ACS who are suitable for early discharge, with an NPV of >99.5% for the diagnosis of AMI using a single hs-cTn result
taken at presentation to the ED, in combination with established risk scores. However, there is important variation in the performance of individual risk scores, together with variation in hs-cTn assays which will have implications in the introduction of rapid rule-out protocols.

References


Figure Legends:

Figure 1. Recruitment flow chart

Figures 2a and b. Test performance of each risk score in combination with presentation with hs-cTnT (a) and hs-cTnI (b) results as illustrated by sensitivity against specificity

Error Bars: 95% Confidence Intervals

Figures 3a and b. Clinical utility of risk scores in combination with presentation hs-cTnT (a) and hs-cTnI (b) results

Error Bars: 95% Confidence Intervals