Early Exclusion of Major Adverse Cardiac Events in Emergency Department
Chest Pain Patients: a prospective observational study

ABSTRACT

Background The current evaluation of chest pain patients presenting to an Emergency Department (ED) with suspected acute coronary syndrome (ACS) is a lengthy process involving serial measurements of troponin.

Objectives We aimed to validate the diagnostic accuracy of a Thrombolysis in Myocardial Infarction (TIMI) score with single high-sensitive cardiac troponin T (hs-cTnT) for early rule out of 30-day major adverse cardiac events (MACE), and to compare the TIMI score with combinations of heart-type fatty acid binding protein (H-FABP) and a modified HEART score.

Methods We recruited 602 consecutive adult patients with chest pain and suspected ACS in ED. Each patient had TIMI and HEART scores, and a point-of-care H-FABP test.

Results MACE occurred in 42 (7.0%) patients within 30 days. A low risk for 30-day MACE was identified by a modified TIMI score of 0 in 65 (11%) patients, and by a HEART score ≤2 in 96 (16%) patients. No MACE occurred in these groups giving both scores a sensitivity of 100% (95%CI 91.6-100%), and a specificity of 11.6% (95%CI 9.2-14.5%) and 17.1% (95%CI 14.2-20.5%) respectively. Use of combined TIMI and HEART scores improved the specificity further to 22.0% (95%CI 18.7-25.6%) without lowering sensitivity. Early H-FABP measurement >7µg/L had a
sensitivity of 41.5% (95%CI 27.8-56.6%) and a specificity of 91.1% (95%CI 88.4-93.2%) for predicting 30-day MACE.

**Conclusion** A modified TIMI score of 0 or a HEART score of ≤2, incorporating a single hs-cTnT level, will identify patients with low risk of 30-day MACE for early discharge within 2 hours of ED arrival.

**Key words:** acute coronary syndrome; chest pain; diagnosis; major adverse cardiac event
INTRODUCTION

Chest pain is one of the most common complaints in patients presenting to emergency departments (ED) globally,[1,2] representing 2.5% of all ED presentations in Hong Kong.[3] Acute coronary syndrome (ACS) cannot be immediately excluded in the majority of patients presenting with chest pain, and is confirmed in about 15-25% cases. The current evaluation of patients in most EDs is a lengthy process that involves serial electrocardiographs (ECGs) and troponin tests taken 3-6 hours apart.[4] However, challenges over ED crowding and the need for acceptable risk stratification have prompted the search for safe, cheap, but effective accelerated chest pain pathways.[4-7]

Risk stratification tools which predict a very low risk of major adverse cardiac events (MACE) may be more clinically relevant to the ED specialist than precise diagnostic labels. In the Asia-Pacific region a 2-hour diagnostic protocol involving serial point-of-care biomarkers, such as troponin I, creatine kinase MB, and myoglobin, combined with ECG changes and a Thrombolysis in Myocardial Infarction (TIMI) score has been shown to safely exclude 30-day MACE in low risk patients with chest pain.[4,5,8,9] High-sensitivity troponin T (hs-cTnT) and troponin I (hs-cTnI) tests perform well in the early diagnosis of acute myocardial infarction (AMI), non-ST elevation myocardial infarction (NSTEMI) and in the prediction of two year mortality.[10-12]

Despite evidence favoring early rule out pathways, there is still a need for further validation and refinement of such tools using different diagnostic pathways, in other clinical settings, evaluating other potential markers such as heart-type fatty acid binding protein (H-FABP), and with other clinical tools such as HEART score.[13-17]
H-FABP is thought to be superior to creatine kinase-MB or cardiac troponins in early
detection of ischemic myocardial necrosis.[18]

In this study we aimed firstly to validate an early TIMI score with hs-cTnT to rule out
30-day MACE, and secondly to compare this with H-FABP, a modified HEART
score and their combined use. Applying this protocol in clinical practice has the
potential to reduce ED waiting times, ED crowding and hospital admission rates for
chest pain patients. This is a sub-study of a prospective observational study of adult
patients with potentially cardiac chest pain who underwent computer tomography (CT)
scan to evaluate the usefulness of coronary calcium score in risk-stratifying chest pain
patients.

2 METHODS

2.1 Study design

We conducted a prospective study between 4 March 2013 and 31 March 2014 in the
ED of a tertiary referral university hospital in Hong Kong. The study is registered
with ClinicalTrials.gov (no. NCT02364271). Ethical approval was obtained from the
joint Institutional Review Board of the Chinese University of Hong Kong and Prince
of Wales Hospital. Written informed consent was taken from all participants, and the
study complied fully with the Declaration of Helsinki and Good Clinical Practice
Guidelines.[19,20] The ED has approximately 150,000 new patient registrations
every year, with an admission rate of 34%, and average waiting times to see a doctor
in the ED of over 4 hours during the busiest winter surges. Hospital bed occupancy
frequently exceeds 100%.

2.2 Participants
The study included consecutive eligible patients presenting to the ED from 9am to 4pm from Monday to Friday. We included patients who had chest or epigastric pain within 24 hours prior to ED presentation, and symptoms suggestive of cardiac chest pain, and for whom hs-cTnT measurement was requested by the assessing emergency physician. Patients were excluded if STEMI or ACS was confirmed immediately on ED arrival, or if there was hemodynamic instability, pregnancy, under the age of 18, or unable to obtain informed consent. Data collection commenced at triage. The funding for this study involved ED assessments for the role of CT calcium scoring to rule in ACS and MACE so we excluded patients if they had a pacemaker or any metal device implantation, or if there was previous coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). With this exclusion criteria and the recruitment in less than 8 hours a day and in working days only, the number of subjects included is not very high. Only one patient was lost in the 30 day telephone follow-up and was excluded from the analysis.

2.3 Measurements

Data collected by research staff included patient characteristics, medical history, conventional risk factors and current medication. An ECG and serial hs-cTnT (Elecsys® Troponin T hs, Roche Diagnostics, Germany, upper reference limit (99th percentile) 14ng/L) are part of the chest pain protocol in our hospital and all results were obtained from the hospital laboratory within about an hour of sampling. The H-FABP point-of-care (POCT) test (Shenzhen Kang Sheng Bao Bio-technology Co., Ltd; upper reference limit (99th percentile) 7μg/L) was performed at the same time as blood was withdrawn for hs-cTnT. The research staff obtained the hs-cTnT results from hospital central laboratory, performed the H-FABP measurement and scored the TIMI and HEART charts for all patients. We recorded a negative response if the
patient was unsure of an answer to a question (e.g. family history of cardiac disease).

Serial hs-cTnT measurements were performed when assessing physician decided it was necessary to confirm the diagnosis. Assessing physicians adjudicated the final diagnosis independently without reference to the scoring charts and the diagnosis was reviewed, also without reference to the charts, by the study investigator to ensure compliance with the Third Universal Definition of Myocardial Infarction. [22] We retrieved follow-up data, including subsequent visits to ED, hospital readmission for evaluation of chest pain and all cardiac procedures, from the hospital authority’s computerized medical system (CMS) and verified them via telephone follow-up at 30 days after initial presentation. We also obtained information about death, myocardial infarction, readmission for ACS, and all cardiac testing and coronary revascularization procedures, whether in our hospital or other hospitals from the CMS and the telephone follow ups. Research staffs collecting this data were not blinded from the ED data.

2.4 Definitions

MACEs include the condition at initial hospital presentation and subsequent events within 30 days, and encompass both safety and effectiveness elements. Safety outcomes consist of all-cause mortality (including cardiac death), cardiac arrest, myocardial infarction and cardiogenic shock. Effectiveness outcomes consist of revascularization (e.g. coronary artery bypass grafting or percutaneous coronary intervention), ventricular arrhythmia needing intervention and high-degree atrioventricular block needing intervention.[21] Myocardial infarction was defined according to global taskforce recommendations requiring evidence of myocardial necrosis and ischemia.[22-Error! Reference source not found.] Evidence of myocardial ischemia includes chest pain, or ECG
changes or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality. Necrosis was diagnosed on the basis of either a >100% change in the concentration of cardiac troponin in subsequent serial laboratory tests or an increase to >14ng/L in a subsequent serial troponin test while the concentration of the first test is <14ng/L and the patient has a glomerular filtration rate of ≥60ml/min with no history of cardiac failure. If no clear alternative cause of the troponin rise is apparent, and if the clinical presentation was suggestive of acute coronary syndromes, an adjudicated diagnosis of MI was made. MI consists of NSTEMI and ST elevation MI (STEMI).[22-Error! Reference source not found.]

2.5 TIMI and modified HEART Scores

We considered a TIMI score of 0 as low risk for 30-day MACE. We defined a negative initial hs-cTnT result as a concentration of ≤14ng/L. We considered a modified HEART score ≤2 as low risk for 30-day MACE. Modified from the original HEART score, only the presence of ST-deviation of >0.05mV was considered in the initial ECG result which scored one point. We used initial measurement of hs-cTnT as the biomarker in the score.

2.6 Primary Outcome

The primary outcome was the number of patients with one or more MACE within 30 days of initial ED presentation, including the diagnosis of initial ED presentation.

2.7 Statistical analysis

We showed baseline characteristics of the study population as conventional descriptive statistics. Median and interquartile range are reported (IQR). We used appropriate Chi-square, Fisher’s exact, and Cochrane-Armitate test for trend for comparison of characteristics with MACE. We set statistical significance at P<0.05.

We calculated sensitivity, specificity, and positive and negative predictive values
from two-by-two tables using SPSS (version 20.0.0, New York, United States) and WINPEPI (version 11.43). [Error! Reference source not found.] We did not perform an a priori sample size calculation.

3 RESULTS

We enrolled 604 consenting eligible patients, of whom 602 had complete test scores and 30-day follow-up. Figure 1 shows the patient recruitment, derived level of risk, and the relationships between risk, admission and 30-day MACE. Of the 123 (20.4%, 95%CI:17.3-23.8%) patients identified as having low risk of a MACE occurring within 30 days by either TIMI=0 or mHEART≤2, none had an event during the 30 day follow-up period.

Table 1 shows the baseline characteristics of all patients with and without 30-day MACE. A MACE occurred in 42 (7.0%, 95%CI: 5.1% to 9.2%) patients. 16 (2.7% 95%CI:1.6-4.2%) patients had NSTEMI and 11 (1.8% 95%CI:1.0-3.2%) had STEMI. 26 (4.3% 95%CI:2.8-6.3%) patients had emergency revascularization. 5 (0.8% 95%CI:0.3-1.9%) deaths were recorded.

Table 2 shows the predictive accuracy of the TIMI and HEART scores, initial hs-cTnT test and initial ECG, and H-FABP for the prediction of MACE within 30 days. A negative ECG result alone gave 23 false negative results. This reduced to 3 with the addition of hs-cTnT, and further reduced to zero false negatives when TIMI or the modified HEART scores were used. Initial H-FABP concentration ≤7μg/L alone resulted in 24 false negative cases when used as a rule-out tool. In data not shown, addition of H-FABP to TIMI or HEART score did not improve the performance of the scores.
Combining TIMI>0 and mHEART>2 identified 479 (80%, 95% CI 76-83%) patients to be high risk and suggested longer observation while 498 (83%, 95%CI 79-86%) patients in the current setting had a second hs-cTnT measurement.

4 DISCUSSION

The purpose of our study was to evaluate various combinations of risk-assessment tools for the early and safe discharge of patients. There is no recommended sensitivity level which has universal acceptance for acceptable safety in this context, although it is appreciated that no test or protocol can achieve absolute safety. We have set a point sensitivity of >99% as an essential parameter for selecting an appropriate rule-out tool. Once this level is achieved then we have aimed for optimal specificity thus allowing a maximum number of patients for safe early discharge.

Having set these criteria, we evaluated eight different combinations (see Table 2). Of these combinations, only TIMI, HEART and combined TIMI/HEART achieved a sensitivity >99%. The combined tool would allow the safe early discharge of 35 patients who were admitted under the current chest pain protocol of our hospital, 6.3% of the 560 patients with no evidence of 30-day MACE, a relative increase of 75% compared with TIMI alone, and a 46% increase compared with using HEART alone. Specificity of the combined tool increased as compared with TIMI or mHEART scores alone and the improvement was more prominent for TIMI score with no overlap in 95% confidence interval. We also examined the c-statistics of various combination of TIMI and HEART score and their components and found that TIMI and HEART scores together achieved higher c-statistics than the individual tests alone. [26] Whether this potential benefit is worthwhile is debatable as the staff time saved by early discharge of these patients must be weighed up against the fact that all patients will require a system for accurate TIMI and/or HEART assessment at triage.
This study shows that both a TIMI and modified HEART score, incorporating the initial result of hs-cTnT and ECG, identifies patients with chest pain for safe discharge within 2 hours of arrival. If both TIMI=0 and HEART≤2 are used to classify patients as low-risk, there is a further increase in specificity and with no loss in sensitivity compared with using either score alone. A 1st hs-cTnT alone, 1st ECG alone, combined 1st hs-cTnT/ECG, and 1st H-FABP yielded high specificity, and may be useful to rule in 30-day MACE, but their sensitivity was less than 95%, and so not suitable to identify patients for early discharge.

The findings in our study are similar to those in ASPECT but with important differences. The TIMI score incorporated a single hs-cTnT result, and with a cut off of 0, yielded a sensitivity of 100% for 30-day MACE and a specificity of 12%, which was similar to other studies. Carlton et al. had two studies on rapid rule-out protocols for patients with a low risk of 30-day acute myocardial infarction. One involved the use of hs-cTnT≤14 ng/L, non-ischaemic ECG and the modified Goldman Score≤1, has a potential to allow early discharge of 40% of patients with suspected ACS with a sensitivity for identifying AMI of 98.8%. The modified Goldman Score≤1 allows for a higher percentage of early discharge than our protocol, but it includes more presenting symptoms relating to the perception of pain than TIMI or HEART score and the mean age of patients in our study is 8 years older than their patient group, it may worth further study for the performance of these scores in elderly patient groups whose interpretation of pain may be less accurate. The other study also showed that, with single hs-cTnT result incorporated, TIMI score equals 0 and HEART score≤2 achieved a sensitivity of 100% and 98.7%, and a specificity of 35.0% and 14.1% respectively. A study by Santi et al. found that a HEART score ≤3 had 100% sensitivity and 43.7% specificity when used to rule-out patients for 30-
The sensitivities achieved are similar to our study while the higher specificities may again be due to younger patient groups in their studies. Different from these three studies, our study included all-cause mortality, suggesting that the combination of TIMI equals 0 and HEART score $\leq 2$ is not only safe for discharge without MACE within 30 days. Adding H-FABP POCT did not improve specificity compared with hs-cTnT.

4.1 Limitations

This study has a number of limitations. Firstly, modifications were made to both TIMI and HEART scores based on cut off criteria for hs-cTnT applied within our institution. However, this is to be expected as newer markers emerge. Secondly, this is a single centre study and patients who had stents or metal device implanted, or underwent coronary artery bypass grafting were excluded, giving a low MACE rate and wide confidence intervals in the accuracy measures. Nevertheless, these sensitivity results of TIMI=0 and HEART $\leq 2$ are very similar to the findings by Carlton et al.[28] Thirdly, the exact reason for admission is not always clear. Of the 286 patients admitted to hospital who had no MACE at 30 days, the combined scores tool could have prevented 35 (12.2%, 95%CI 8.8-16.4%) admissions, and an aggregate of 143.5 bed days. This assumes that patients were not admitted for other reasons than minimizing the risk of MACE but the fact that they were in a chest pain protocol suggests that ACS was the primary concern to the emergency physician. Fourthly, it is notable that POCT hs-cTnT is not available in our setting which delays the process and contributes to ED crowding.

CONCLUSIONS
In conclusion, we have found that TIMI and a modified HEART score alone and in combination, incorporating a single initial result of hs-cTnT and ECG, may be used to safely identify patients with low risk of 30-day MACE for early discharge. The strategy yielding the largest number of patients for safe discharge is a combined modified TIMI/HEART assessment including hs-cTnT. H-FABP provided no additional prognostic value to the scores as a rule-out tool.
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The authors declare no conflicts of interest.

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30.
**Article Summary**

**Why is this topic important?**
Chest pain is the second commonest presenting complaint in adults attending emergency departments (ED) globally, and the current evaluation of patients in most EDs is a lengthy process that involves serial ECGs and troponin tests taken 3-6 hours apart. There has been on-going research worldwide for protocols to speed up the process and to identifying patients at low risk of acute coronary syndrome and major adverse cardiac events for early discharge.

**What does this study attempt to show?**
We aimed firstly to validate an early TIMI score with hs-cTnT to rule out 30-day MACE, and secondly to compare this with H-FABP, a modified HEART score and their combined use.

**What are the key findings?**
We have found that TIMI and a modified HEART score alone and in combination, incorporating a single initial result of hs-cTnT and ECG, may be used to safely identify patients with low risk of 30-day MACE for early discharge. The strategy yielding the largest number of patients for safe discharge is a combined modified TIMI/HEART assessment including hs-cTnT. H- FABP provided no additional prognostic value to the scores as a rule-out tool.

**How is patient care impacted?**
More patients presenting with chest pain to EDs may be safely evaluated and discharged earlier thus reducing ED overcrowding.
Figure legend

Figure 1: Profile of participant recruitment and outcomes according to TIMI and mHEART score classifications.

TIMI=Thrombolysis in Myocardial Infarction score. MACE=major adverse cardiac event. mHEART=modified HEART score. ‘TIMI/mHEART’ means either TIMI or mHEART or both.

*The family history of cardiac disease in 36 patients was unclear and so were taken as ‘no family history of cardiac disease’.