

## A direct comparison of decision rules for early discharge of suspected acute coronary syndromes in the era of high sensitive troponin

\*Pei Gee Chew<sup>1</sup>MBChB, \*Fredrick Frost<sup>1</sup>MBChB, Liam Mullen<sup>1</sup>MBBS, Michael Fisher<sup>2,3</sup> PhD, Heidar Zadeh<sup>2</sup>MBChB, Ruth Grainger<sup>4</sup>MSC, Khaled Albouaini<sup>2</sup>MD, James Dodd<sup>5</sup>MSc, Bilal Patel<sup>6</sup>PhD, Periaswamy Velavan<sup>3</sup>MD, Babu Kunadian<sup>3,7</sup>MD, Anju Rawat<sup>1</sup>BSc, Toba Obafemi<sup>1</sup>MBChB, Sarah Tong<sup>1</sup>MBChB, Julia Jones<sup>1</sup>MBChB, Aleem Khand<sup>\*1,3,8</sup>MD

\* authors contributed equally to this manuscript

1. Aintree University Hospital NHS trust
2. Royal Liverpool University Hospital NHS trust
3. Institute for cardiovascular medicine and Science, Liverpool Heart and Chest Hospital NHS trust
4. Northwest coast strategic clinical networks
5. Liverpool Cancer and clinical Trial Units, University of Liverpool
6. Blackpool Teaching Hospitals NHS Foundation Trust
7. Countess of Chester NHS trust
8. Institute of aging and chronic diseases, University of Liverpool

**Total word count: 4886 (inclusive of references)**

**Author contributions:** AK and JJ conceived the idea of the project, developed conversations with accident and emergency clinicians, designed the database and the chest pain proforma. PG, FF, LM, AR, TO, ST, JJ, AK entered data and computed risk scores from definition tables and relevant charts/proforma. AK, MF, HZ, KA, BP, BK, VV were consultant adjudicators for type 1 and type 2 myocardial infarction. RG undertook analysis and derived FU data from national linked database for hospital admissions per defined ICD 10 codes. AK, FF, PC, MF wrote the manuscript. AK is the guarantor of the data.

Corresponding author:

Dr Aleem Khand

Department of cardiology, University hospital Aintree NHS foundation Trust,  
Longmoor Lane, Liverpool L97AL

Email: [akhand31@aol.com](mailto:akhand31@aol.com), Tel No: 00441515292720, fax 00441515298720

## Abstract

**Background:** We tested the hypothesis that a single high sensitive troponin at limits of detection [LOD](HSTnT)( $<5\text{ng/l}$ ) combined with a presentation non-ischaemic ECG is superior to low risk GRACE( $<75$ ), TIMI( $\leq 1$ ) and HEART score( $\leq 3$ ) as an aid to early, safe discharge for suspected ACS (acute coronary syndrome)

**Methods:** In a prospective cohort study, risk scores were computed in consecutive patients with suspected ACS presenting to emergency room (ER) of a large English hospital. Adjudication of MI, as per 3<sup>rd</sup> universal definition, involved 2 physician blinded, independent review of all biomarker positive chest pain re-presentations to any national hospital. The primary and secondary outcome was a composite of type 1 MI, unplanned coronary revascularisation and all cause death [MACE] at 6 weeks and 1 year.

**Results:** Of 3054 consecutive presentations with chest pain 1642 had suspected ACS (52% male, median age 59, 14% diabetic, 20% previous MI). Median time from chest pain to presentation was 9.7 hours. Re-presentations occurred in 8 hospitals with 100% follow-up achieved. 211 (12.9%) and 279 (17%) were adjudicated to suffer MACE at 6 weeks and 1 year respectively. Only HEART  $\leq 3$  (negative predictive value [NPV] MACE 99.4%, sensitivity 97.6%, % discharge 53.4) and LOD HsTnT strategy (NPV MACE 99.8%, sensitivity 99.5%, % discharge 36.9) achieved pre-specified NPV of  $>99\%$  for MACE at 6 weeks. For type 1 MI alone the NPV at 6 weeks and 1 year was identical, for both HEART  $\leq 3$  and LOD HsTnT at 99.8% and 99.5% respectively.

**Conclusion:** HEART  $\leq 3$  or LOD HSTnT strategy rules out short and medium term MI with  $\geq 99.5\%$  certainty, and short-term MACE with  $> 99\%$  certainty allowing for early discharge of 53.4% and 36.9% respectively of suspected ACS. Adoption of either strategy has the potential to greatly reduce ER pressures and minimise follow-up investigations. *Very early presenters ( $<3$  hours), due to limited numbers, are excluded from these conclusions.*

Key words: high sensitivity troponin, acute coronary syndromes.

**Funding:** Aintree innovation award, Northwest Educational Cardiac Group

**Registration:** clinical trials.gov NCT02581540

**Abbreviations:**

HSTnT= high sensitivity troponin T, MI= Myocardial Infarction, MACE: major adverse cardiac event (composite of type 1 MI, unplanned coronary revascularisation[surgical or PCI) and all cause death, ER= emergency room, CP= chest pain, NPV= negative predictive value. PCI= percutaneous coronary intervention, LOD= limits of detection, ACS= acute coronary syndrome

## Introduction

Acute CP is one of the commonest presentations to ER in the Western world, the vast majority of which are not due to acute MI.<sup>1,2,3,4</sup> However early differentiation of type 1 MI from non-cardiac causes of troponin elevation remains a challenge despite the emergence of high sensitive troponins.<sup>5</sup> Early, safe discharge for a substantial proportion of chest pain presentations continues to be the single most important challenge, particularly for health care providers. Discharge at presentation with troponin<sup>6,7</sup> at the limits of detection [LOD] or early after a 1-hour high sensitivity troponin strategy remains an attractive proposition,<sup>8,9</sup> though there remains concerns about the sensitivity for rule-out of MI in the 1 hour algorithm particularly for early presenters.<sup>9,10</sup> It is not certain if these high sensitive troponin values, when combined with clinical assessment, ECG findings and risk factors improve early rule out. A number of risk scores which incorporate some or all of these factors have been in existence or been developed<sup>11</sup> to address this need but to date a high sensitive troponin strategy either alone or combined with risk scores as a tool for early discharge has not been tested prospectively in an **unselected, consecutive** chest pain population in whom there is suspicion of an underlying ischaemic cause.

We compared rule-out strategies; namely a single HSTnT (at limits of detection and at 99<sup>th</sup> percentile) combined with non-ischaemic ECG versus low score HEART ( $\leq 3$ ), TIMI ( $\leq 1$ ) and GRACE ( $< 75$ ) in an **unselected consecutive chest pain** patient population with suspected ACS. Our goal was to define the optimum rule-out strategy for suspected ACS using a single high sensitivity troponin T and presentation electrocardiogram.

## Methods

This study was conducted in concordance with STARD criteria for diagnostic studies (score sheet included in appendix). From June 2011 to November 2011 all patients presenting to university hospital Aintree emergency department with a predominant symptom of chest pain, who had both an

electrocardiogram and at least one blood sample for HSTnT check (suspected ACS population), were prospectively 'recruited' into this study. Aintree university hospital is a large hospital providing secondary care cardiology with annual attendances of 80,000 per annum to accident and emergency. Prior to the start of the study there was a 3-month 'roll-in' phase with conversations between accident and emergency clinicians and the development of a chest pain proforma (acute chest pain assessment sheet) that highlights important aspects of history taking in chest pain as well as allowing capture of relevant information important in computation of the risk scores noted. Use of this proforma was not mandatory but was incorporated with casualty sheets as an aide memoire for clinicians for assessment of chest pain. Research personnel prospectively and contemporaneously entered demographic, epidemiological data and results of blood tests together with timing of ECGs and troponins in a dedicated database. All ECGs were stored in an electronic register for subsequent analysis by the research team. Each ECG was read by an experienced clinician/ researcher, with a second reading if there was troponin elevation to adjudicate if type 1 MI definition had been met. The presence and absence of specific criteria were noted electronically in a standardised fashion. The definition of a non-ischaemic ECG was the following: sinus rhythm or atrial fibrillation or atrial flutter with ventricular rate <110 together and **absence** of the following: LBBB, paced rhythm, ST segment elevation, ST segment depression, T wave inversion or T wave flattening or biphasic T waves in 2 contiguous leads. For both HSTn T LOD and non-ischaemic ECG strategy and the 3 risk scores the first(presentation) ECG alone was used as the ECG input variable. Subsequent ECGs were extracted for adjudication of MI and to determine possibilities of MI in those with a single sampled HSTn T.

TIMI and GRACE scores were determined from online calculators by research staff with the use of the CP proforma, casualty sheets and ambulance proforma alone. To score positively for ST segment depression in GRACE and TIMI planar depression of at least 0.5mm after the J-point consistent with the Minnesota criteria.<sup>12</sup>

There was no specific troponin testing protocol for clinicians during recruitment. Guidelines recommended repeat troponin sampling for patients who presented <6 hours from chest pain particularly if presentation HSTnT was <99<sup>th</sup> percentile (<15ng/l). Discharge at <6 hours from chest pain with 'negative' troponin (HSTnT<15ng/l) was discouraged.

**Calculation of HEART score, follow-up, definition and adjudication of MACE events (and nonischaemic diagnoses)- see appendix**

### **High sensitivity cardiac troponin T assay**

The assay used was the high sensitivity troponin T (Roche Elecsys). This has been previously evaluated extensively and found to fulfil the definition of high sensitivity with 10% coefficient variation at the 99<sup>th</sup> percentile.<sup>16</sup> Performance of this assay across a number of centres has previously been evaluated.<sup>16</sup> Analysis was undertaken in-house of COBAS e601 analysers using a standard 18-minute assay. Quality control of assay (in-house) at Liverpool Clinical laboratories revealed a coefficient of variation of 11% at low value troponins (<10ng/l). External quality assurance provided by the independent United Kingdom National External quality assurance scheme (NEQA) revealed inter-hospital coefficient of variation of 10% (standard deviation 0.5) low level Troponin values. Assay performance (NEQA) was undertaken monthly throughout the duration of the study.

During recruitment of the study there was a downward shift in the ROCHE elecsys HSTn T that was a result of calibration of specific LOTS.<sup>17</sup> We recomputed HSTnT values by adjusting for the shift by reference to local laboratory calibration and that determined by a number of groups including the manufacturer.<sup>17,18</sup> The adjusted or recomputed values that were used in the analysis.

### **End-points**

The primary endpoint was type 1 MI, unplanned coronary revascularisation and all cause death (MACE)at 42 days (see appendix for definitions and adjudication). Unplanned coronary revascularisation

was defined as **admission for unstable angina or MI necessitating same day or same admission coronary revascularisation by percutaneous or surgical means**. Secondary endpoint included MACE at 1 year

## **Ethics**

This manuscript conforms to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals,

This was an all-comers chest pain study with national(English) hospital involvement for any representation with possible MI. The project was registered with the hospital research department and the regional ethics board which granted full consent to undertake this study. (north-west England regional ethics board) To allow for complete follow-up special permission was granted, in the absence of individual consent, via a confidential advisory group(UK government home office appointed) for the recruitment of consecutive CP population and collection of data from any hospital nationwide to facilitate the retrieval of clinical records and blood results for patients with possible acute coronary syndrome. (15/CAG/0171) [<http://www.hra.nhs.uk/>]

## **Statistics**

All analyses were performed in Stata v14.

Summary statistics were presented as n(%) if categorical and as median(IQR) if continuous. For categorical variables, a Pearson  $\chi^2$  test was used to determined p-value, except for cases where there were number of MACE events in any category was  $\leq 5$ , when Fisher's Exact test was used. For continuous variables, a t-test was performed to determine p.

Confidence intervals for PPV and NPV were calculated using exact binomial proportions.

To evaluate differences in NPV in patients who had their first HSTnT at  $\leq 3$ hrs and  $\leq 6$ hrs compared to those  $> 3$ hrs and  $> 6$ hrs, P-values were computed using a 2-sided Fisher's Exact Test.

ROC curves were plotted, and area under curve (AUC) computed, using the `rocreg` function in Stata to bootstrap and obtain standard errors and confidence intervals. The p-value for differences in the AUC was obtained using a Wald test.

It was not possible to compute an exact sample size at the time of recruitment as we had no information on events rates for HSTnT LOD at the time of starting the study or indeed good evidence of event rates for risk scores with high sensitivity troponins.

## Results

Figure 1 charts the global chest pain population and those with suspected ACS (defined as sampling of HSTnT together with presentation electrocardiogram). Missing data (loss of casualty cards and incomplete/ illegible CP proforma) was  $< 1.2\%$  of the global population. Follow-up was 100% with tracking of repeat presentations to ER/ admissions to 8 national hospitals (table 3 appendix). Retrieval of all necessary reports, blood results, ECGs, relevant imaging reports, for all patients that had biomarker positive presentations was achieved for the purposes of adjudication of MI.

Table 1 describes the characteristics of all patients (both those admitted and directly discharged from accident and emergency department). It further subdivides the population into those adjudicated to have suffered type 1 MI and MACE at 6 weeks. 444 patients (27%) were discharged directly from accident and emergency at a median of 363 minutes (IQR range 271, 468 minutes). Four of these patients suffered MACE by 6 weeks (0.9%) (3 were adjudicated to fulfil definition of type 1 MI at index admission [ie wrongly discharged]). The decision to admit or discharge was at the discretion of clinicians (at the time no specific protocol or risk score was in place to guide clinicians). Those adjudicated to have suffered a MACE events (type 1 MI, all cause death, unplanned coronary revascularisation) were older with greater



risk factors. Risk scores were consistently higher for all patients with type 1 MI or MACE at 6 weeks. There were 10.7% of patients adjudicated to have suffered a type 1 MI at index admission with another 0.3% between admission and 6 weeks at a median of 11 days following admission. The percentage of patients undergoing unplanned PCI and unplanned CABG up to 6 weeks were 2.7% and 0.8% respectively at a median of 7 and 18 days following admission. The number of patients undergoing emergency primary percutaneous coronary intervention for ST elevation myocardial infarction up to 1 year who were discharged with a diagnosis other than ACS was 4(0.2%) at a median of 80 days following discharge. The number of deaths at 6 weeks and 1 year were 25(1.5%) and 104(6.3%) respectively occurring at a median of 15 and 112 days respectively. Of the total deaths at 1-year 11% were in-hospital and 89% out of hospital. The overall type 1 MI and MACE event rate at 6 weeks was 11.2% and 12.9% respectively. For 1 year, the equivalent figures for type 1 MI and MACE were 11.6% and 17%. For the entire population diagnoses other than type 1 MI were the following: type 2 MI 1.2%, unstable angina 8.5%, atypical chest pain 8.5%, cardiac noncoronary chest pain 7.9%, non-cardiac symptoms 57.2%, CP unknown origin 2.8%. (see appendix for prespecified criteria)

Table 2 demonstrates performance of the rule out protocols at 6 weeks and 1 year for MACE and type 1 MI. Only HEART  $\leq 3$  and LOD HSTn T(with non-ischaemic ECG) achieved the prespecified NPV of  $>99\%$  at 6 weeks for MACE (NPV with prespecified 99% performance target represented graphically in figure 1 appendix). The discharge potential for these strategies were 53.4% and 36.9% for HEART  $\leq 3$  and LOD HSTn T(with non-ischaemic ECG) respectively. They achieved sensitivities for MACE of 97.6% and 99.5% for HEART  $\leq 3$  and LOD HSTn T(with nonischaemic ECG) respectively. For Type 1 MI alone as an endpoint the respective figures for sensitivity were 98.9% (HEART  $\leq 3$ ) and 99.4%(LOD HSTn T and nonischaemic ECG). The respective NPV at 6 weeks for type 1 MI for LOD HSTn T and HEART  $\leq 3$  was identical at 99.8%. At 1 year point estimates of NPV (99.5%) for type 1 MI was again identical for HEART  $\leq 3$  and HSTnT LOD. In terms of overlap between LOD HSTn T with nonischaemic ECG and

HEART $\leq$ 3, 521/606 (86.0%) of patients fulfilling discharge rules with LOD HSTn T + nonischaemic ECG also had a HEART score of  $\leq$ 3. The equivalent percentage for the reverse was 59.4% ie 59.4% with HEART score  $\leq$ 3 had a LOD HSTnT.

In terms of NPV for MACE events LOD HSTn T and non-ischaemic ECG was clearly differentiated from HSTn T  $\leq$ 14ng/l (99<sup>th</sup> percentile value)(with nonischaemic ECG) and TIMI  $\leq$ 1 but not GRACE <75 or HEART  $\leq$ 3. GRACE <75, in terms of discharge potential, could deliver only 28.6% discharges (similar to actual direct discharge of 27% in this cohort)

Table 1 (appendix) details patients with HEART  $\leq$ 3 and LOD HSTnT and non-ischaemic ECG with MACE events (the false negative population or those fulfilling rules for discharge but who had an adjudicated MACE). All 3 deaths  $\leq$  6weeks from index event, that represented 3 of the 5 false negative events for patients with HEART  $\leq$ 3, were clear noncardiac deaths. The performance of HEART $\leq$ 3 was considerably improved by not counting non-cardiac deaths as events. Sensitivity improved to 99% with NPV to 99.8% for MACE at 6 weeks. For patients with a first HSTnT LOD (<5ng/L) there were 2 patients with a 2<sup>nd</sup> troponin >14ng/l, both of which were adjudicated as suffering type 1 MI(only one of which had a non-ischaemic presentation ECG).

Figure 2 describes ROC(receiver operator characteristic) curves for continuous values of risk scores and with HSTnT being analysed without ECG interpretation as a continuous variable. Compared to HSTnT(ROC area 0.918) there was no significant difference in performance with HEART(ROC area 0.910, p<0.382) but there was significant separation of curves with TIMI(ROC area 0.855, p<0.001) and GRACE(ROC area 0.791,p<0.001). Figure 2 (appendix) describes time of chest pain to first HSTnT samples.

57% of patients had 1 HSTnT sampled. 51.9% of patients had >1 ECG (median time to first and 2<sup>nd</sup> ECG 10mins, [IQR 5,15mins] and 181 mins, [IQR 69,414 mins]). To determine the possibility of missed MI

due to single HSTnT<14ng/l we re-evaluated paired ECGs to determine if there were dynamic ECG changes(a significant change such as new t wave inversion, ST segment shift, development of LBBB). in those with a single HSTN T Only 3 patients with a single HSTnT had a dynamic change in ECG but in only one was a type 1 MI adjudicated (2<sup>nd</sup> ECG demonstrated STEMI). His initial ECG though was not normal thus excluding a false negative result for HEART  $\leq 3$  and HSTn T LOD (presentation HSTnT<5ng/l).

### **Sensitivity Analysis**

A sensitivity analysis was undertaken with GRACE values of <60 and <90 and TIMI score 0 and  $\leq 2$  for MACE at 42 days.

GRACE score <60 did achieve NPV of 99.6% with a sensitivity of 99.5% but percentage discharge dropped to 14.3%. GRACE score <90 did not achieve prespecified thresholds of NPV (NPV 97.2%) with a sensitivity of 90.5%. TIMI score 0 did achieve threshold NPV of 99.7% with a sensitivity of 99.1% and allowed discharge of 39.1% patients. TIMI score  $\leq 2$  allowed discharge of 74.1% but at a considerable loss of sensitivity and NPV of 73% and 95.3% respectively.

### **Inter-observer variability of determination or Risk scores**

Absolute agreement for risk scores was were good for HEART and TIMI and excellent (100%) per risk category ( $K=1$ ). No patients were categorised as high or intermediate risk that were initially deemed low risk (and vice versa) for HEART and TIMI scores. GRACE scores in terms of absolute agreement performed less well but still very good for risk category agreement ( $K=0.82$ ). (table 4 appendix)

## Discussion

We confirm the impressive rule-out strategy of HSTnT using limits of detection (or limit of blank alone  $<3\text{ng/l}$ )<sup>6,7,19</sup> combined with a non-ischaemic ECG. We have prospectively validated the 2 cornerstones in acute CP assessment, (namely troponins and ECG) as a simple and effective strategy for decision making with very low risk of adverse outcome. Rubini-Gimenez et al identified the potential of rule-out value of undetectable HSTn T and I.<sup>6</sup> Mokhtari et al further demonstrated incremental value of the combination of HSTn T LOD, nonischaemic ECG and low risk history but in a non-consecutive patient series.<sup>20</sup> As far as we are aware this is the only study that has **prospectively** assessed HSTn T at LOD and non-ischaemic EC) in an **unselected, consecutive** chest patient population. Our point estimate of NPV are similar to that of Bandstein et al<sup>7</sup> and Body et al<sup>19</sup> even though a lower limit of blank ( $<3\text{ng/l}$ ) was used in the latter study. Sandoval et al define the concept of LOD and LOB as rule out strategies.<sup>21</sup> The LOD provide higher NPV and sensitivities than that of Rubini-Gimenez et al.<sup>6</sup> Incorporation of a non-ischaemic ECG to the limits of detection of HSTnT could explain this; LOD HSTnT together with nonischaemic ECG increased sensitivity from 98.1% to 99.5% for MACE and 98.9% to 99.4% for type 1 MI at 6 weeks (table 2).

This study is the first to demonstrate that HEART score  $\leq 3$  in the era of high sensitive troponins (using conventional cut-offs of HSTnT) also, to a large extent, meets criteria for a rule-out strategy. HEART  $\leq 3$  was as effective as LOD HSTn T with a non-ischaemic ECG) for rule-out of type 1 MI at 6 weeks with NPV of 99.8% with a sensitivity of 98.9% allowing a discharge of 53.4% of patients (as opposed to 36.9% of patients with LOD HSTnT strategy). The performance of HEART  $\leq 3$  for type 1 MI is indicative of an acceptable risk for a discharge/ rule out for type 1 MI.<sup>22</sup> In terms of MACE sensitivity was  $<98\%$  but improved to 99% (at 6 weeks if only cardiac deaths were counted)

In addition this study have demonstrated that both rule-out strategies (HEART  $\leq 3$  and LOD HSTnT) have low event rates to 1 year for type 1 MI(99.5% at 1 year) indicating patients can be safely discharged and reassured without the need for early diagnostic testing in the absence of ongoing symptoms. This study suggests cardiac imaging for LOD HSTNT or low risk HEART score cannot seek to refine risk further and argues for a reduction to these requests in low risk patients.

TIMI score $\leq 1$  and GRACE score $< 75$  did not reach prespecified thresholds for rule-out. Although neither of these risk scores had been originally validated for suspected ACS, they have been evaluated with encouraging results in combination with high sensitive troponins in a number of different protocols in chest pain populations.<sup>232425</sup> Sensitivity analysis revealed that TIMI score of 0 had acceptable performance but discharged considerably less than HEART $\leq 3$ . (39.5% vs 53.4%)

A consecutive, unselected series of suspected ACS presentation, in a sample size this large, is important in terms of generalisability and therefore potential influence to change practise (as opposed to a selected population, a natural consequence of consent and limited or absent recruitment nocturnally or at weekends). There was 100% follow-up tracked nationally and there was adjudication of any index CP or representation with HSTn T that was above the 99<sup>th</sup> percentile. This allowed us not only to validate those coded for type 1 MI but to evaluate all patients with elevated troponins including those who were deemed to have noncardiac pathologies (a distinction from other noted studies).<sup>7</sup> Secondly we used all-cause death as an outcome rather than cardiac death as incorporated in some studies.<sup>3</sup> This is not to say that high sensitivity troponin can predict noncardiac death but to accept the uncertainty of cause of death, particularly for out of hospital deaths and the probability of misdiagnosis and therefore miscoding of cause of death.<sup>26</sup> Using all-cause death grants a safer estimate of rule-out protocols.

Recently Carlton et al directly compared risk scores using HSTn T and I in a select patient population of patients  $\leq 80$  years of age.<sup>27</sup> In a post-hoc analysis HEART  $\leq 3$  did not achieve pre-specified targets of  $> 99.5\%$  NPV and/or sensitivity of  $> 98\%$  with either HSTn T or HSTn I. Differences in study population

could explain this; Carlton et al had a population with much shorter time of CP to presentation which is likely to have reduced both NPV and sensitivity for HEART $\leq$ 3.

The largest study to date in a population of all-comers similar to ours was that by Shah et al.<sup>3</sup> The impressive NPV of 99.6% (high sensitive troponin I- Abbot) with both a derivation and validation cohort fulfilled criteria for safety and clinical utility (almost 2/3<sup>rd</sup> could be discharged). However, there was no reported sensitivity as far as our group could discern. NPV is affected by disease prevalence rates thus highlighting the attractiveness of risk scores such as HEART which to some extent incorporate this aspect allowing potential widespread applicability of rule-out strategies for suspected ACS. Multicentre validation studies, preferably with studies enriched with early presenters, and with competitor high sensitivity troponin assays incorporated in HEART are important to confirm (or refute) the potential of the HEART score as a tool for rule-out of ACS.

In a previous study by Backus et al investigating the same risk scores in 2338 suspected ACS in a multicentre observational study revealed superiority of HEART compared to TIMI and GRACE across all risk categories but there was a 1.7% MACE event at 6 weeks with HEART $\leq$ 3 with 4<sup>th</sup> generation (non-high sensitivity) troponins. This event rate would not be acceptable strategy as a rule-out in most health care systems.<sup>3</sup> High sensitivity troponins are likely to have improved sensitivity or rule-out value at the expense of reduced specificity.

### **Limitations**

Figure 2 (appendix) demonstrates time from chest pain to first HsTn T check. Only 4.4% of patients had a HsTn T check <3 hours (very early presenters) from chest pain. The equivalent number for  $\leq$ 6 hours was 240 (14.6%). There was no significant difference in NPV between those with  $\leq$ 6 hours and the global population when incorporated in a troponin and ECG strategy or as low risk scores. (table 5 appendix). However these results should be treated with caution due to the low number of events occurring in

patients presenting early. Most CP presentations to ER are late, and the study does represent comparable numbers of patients with very early ( $\leq 3$  hours)<sup>3</sup> and early presentations ( $\leq 6$  hours)<sup>7</sup> to similar 'all-comer' studies. This study does not validate discharge for very early presenters, based on a single HSTnT.

43% patients underwent serial troponins. As a rise or fall in troponins or biomarkers of myocyte necrosis is part of the universal definition of MI we cannot be certain that MIs were not missed although most presentations are late (median time from CP to presentation 9.6 hours) thus reducing the possibility of a later rise of HSTn T beyond 99<sup>th</sup> percentile. Furthermore analysis of paired ECGs, in those with a single HSTnT sampled, for sequential ECG changes only revealed one definite MI (evolving ECG changes from t wave inversion to STEV).

There was a downward shift seen with this ROCHE assay between 2010 and 2012.<sup>28</sup> The actual difference computed between affected lots and correct (re-assayed) values was 1.2ng/l in a similar population of suspected acute coronary syndrome.<sup>18</sup> Wildi et al suggested a small miss rate with LOD HSTnT in affected lots compared to corrected values with serial samples and re-adjudication for MI. However 2 other analyses suggest similar prevalence rates of MI and no 'missed' MI with LOD initial samples when ECG ischaemia was taken into account.<sup>29</sup> Body et al using LOD revealed 2 missed MIs using paired samples in 463 patients with affected lots with retesting, but both patients had ischaemic ECGs maintaining NPV at 100%. In addition ROCHE internally assessed the effect of affected lots with readjustment mathematically in 1033 patients presenting to ER.<sup>28</sup> The identical number of MIs were defined.

Finally HEART score was not determined by attending physicians but researchers following presentation raising concerns about scoring chest pain section of HEART. However due both to engagement and the production of a tick box chest pain proforma that emphasises character and duration of CP it was always possible to score chest pain with reasonable reflection of clinician suspicion.

## **Conclusion**

Heart  $\leq 3$  and LOD HSTnT (combined with a non-ischaemic ECG) are optimum rule-out strategies for MACE at 6 weeks, for a suspected ACS population. Further multicentre studies should test HEART  $\leq 3$  as a tool for early, safe discharge of patients with chest pain and suspected ACS particularly in early presenters. A randomised trial of LOD HSTnT versus a 1 hour HS troponin protocol decision rule to assess duration of stay and safety endpoints is urgently needed.

**Role of the funder:** The funder played no role in the design, execution nor had they any part in the writing up of the study. Aintree innovation awards (Dragons den) undertakes to award via competitive bids innovative works that have the potential to improve health care delivery. The trust board and executive do not oversee research or innovative work.

**Disclosures:** Dr Aleem Khand has the following potential conflicts of interest: free of charge material from ROCHE for research. Submissions pending for research funds from ROCHE and Abbott. Funding for national conferences from Daiichi Sankyo, Bayer. Funding for research from Bayer pharmaceuticals. Speaker and expert consultation fees from Astra Zeneca, Menarini, Bayer. No other authors report potential conflict of interest.



## References

1. Reichlin T, Schindler C, Drexler B et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med* 2012;**172**:1211–1218.
2. Giannitsis E, Becker M, Kurz K et al. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. *Clin Chem* 2010;**56**:642–650.
3. Shah AS V, Anand A, Sandoval Y et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet (London, England)* 2015;**386**:2481–2488.
4. Mueller M, Biener M, Vafaie M et al. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. *Clin Chem* 2012;**58**:209–218.
5. Thygesen K, Mair J, Giannitsis E, Mueller C et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012;**33**:21–24.
6. Rubini Giménez M, Hoeller R, Reichlin T et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. *Int J Cardiol* 2013;**168**:3896–3901.
7. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol Elsevier Ltd*; 2014;**63**:2569–2578.
8. Mueller C, Giannitsis E, Christ M et al. Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T. *Ann Emerg Med* 2015;**68**.
9. Pickering JW, Greenslade JH, Cullen L et al. Assessment of the European Society of Cardiology 0-

- Hour/1-Hour Algorithm to Rule-Out and Rule-In Acute Myocardial Infarction. *Circulation* 2016;**134**:1532–1541.
10. Jaffe AS TRAPID or Trapped? *Ann Emerg Med* Elsevier; 2016;**68**:88–91.
  11. Backus BE, Six a J, Kelder JC et al. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol* 2013;**168**:2153–2158.
  12. BLACKBURN H, KEYS A, SIMONSON E, RAUTAHARJU P et al. The Electrocardiogram in Population Studies: A Classification System. *Circulation* 1960;**21**:1160–1175.
  13. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–2567.
  14. Mueller-Hennessen M, Lindahl B, Giannitsis E et al. Diagnostic and prognostic implications using age- and gender-specific cut-offs for high-sensitivity cardiac troponin T - Sub-analysis from the TRAPID-AMI study. *Int J Cardiol* 2016;**209**:26–33.
  15. Skinner JS, Smeeth L, Kendall JM, et al. NICE guidance. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. *Heart* 2010;**96**:974–978.
  16. Saenger AK, Beyrau R, Braun S et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chim Acta* 2011;**412**:748–754.
  17. Hallermayer K, Jarausch J, Menassanch-Volker S et al. Clinical implications of a recent adjustment of the high sensitive troponin T assay: letter. *Clin Chem* 2012;**59**:573–574.
  18. Wildi K, Twerenbold R, Jaeger C et al. Clinical impact of the 2010-2012 low-end shift of high-sensitivity cardiac troponin T. *Eur Hear J Acute Cardiovasc Care* 2016;**131**:2041–2050.
  19. Body R, Carley S, McDowell G et al. Rapid exclusion of acute myocardial infarction in patients

- with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol* 2011;**58**:1332–1339.
20. Mokhtari A, Lindahl B, Smith JG et al. Diagnostic Accuracy of High-Sensitivity Cardiac Troponin T at Presentation Combined With History and ECG for Ruling Out Major Adverse Cardiac Events. *Ann Emerg Med* American College of Emergency Physicians; 2016;
  21. Sandoval Y, Smith SW, Apple FS. Present and Future of Cardiac Troponin in Clinical Practice: A Paradigm Shift to High-Sensitivity Assays. *Am. J. Med.* 2016. p. 354–365.
  22. Than M, Herbert M, Flaws D et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *Int J Cardiol* Elsevier; 2013;**166**:752–754.
  23. Aldous SJ, Florkowski CM, Crozier IG et al. Comparison of high sensitivity and contemporary troponin assays for the early detection of acute myocardial infarction in the emergency department. *Ann Clin Biochem* 2011;**48**:241–248.
  24. Bajaj RR, Goodman SG, Yan RT et al. Treatment and Outcomes of Patients With Suspected Acute Coronary Syndromes in Relation to Initial Diagnostic Impressions (Insights from the Canadian Global Registry of Acute Coronary Events [GRACE] and Canadian Registry of Acute Coronary Events [CANRACE]). *Am J Cardiol* 2013;**111**:202–207.
  25. Cullen L, Mueller C, Parsonage WA et al. Validation of High-Sensitivity Troponin I in a 2-Hour Diagnostic Strategy to Assess 30-Day Outcomes in Emergency Department Patients With Possible Acute Coronary Syndrome. *J Am Coll Cardiol* 2013;**62**:1242–1249.
  26. Roulson J, Benbow EW, Hasleton PS. Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology; a meta-analysis and review. *Histopathology*. 2005. p. 551–559.
  27. Carlton EW, Khattab A, Greaves K. Identifying patients suitable for discharge after a single-presentation high-sensitivity troponin result: A comparison of five established risk scores and two

high-sensitivity assays. *Ann Emerg Med* American College of Emergency Physicians; 2015;**66**:635–645e1.

28. Kuster N, Dupuy AM, Monnier K et al. Implications of adjustment of high-sensitivity cardiac troponin t assay. *Clin Chem* 2013;**59**:570–572.

29. Body R, Burrows G, Carley S et al. High-sensitivity cardiac troponin T concentrations below the limit of detection to exclude acute myocardial infarction: A prospective evaluation. *Clin Chem* 2015;**61**:983–989.

## Figure Legends

Figure 1: Flowchart of final population

Figures 2: ROC (receiver operator characteristics) curve for primary outcome (MACE) at 6 weeks

### Appendix figures

Figure 1: Negative and Positive predictive values for MACE (type 1 myocardial infarction, unplanned coronary revascularisation and all cause death) at 42 days according to rule-out protocols

Figure 2: Time of chest pain to first High sensitivity troponin check

**Table 1 Population characteristics**

|   |                  | All             | Type 1 MI (6 weeks) | MACE (6 weeks)  | P value |
|---|------------------|-----------------|---------------------|-----------------|---------|
| <b>Totals</b>   |                  | 1642            | 180                 | 211             |         |
| Age (median[IQR])   |                  | 59(47,72)       | 74(62,82)           | 74(62,82)       | <0.001  |
|   |                  | <b>N</b>        | <b>N</b>            | <b>N</b>        |         |
| Sex: (Male)   |                  | 858(52%)        | 109 (61%)           | 127(60%)        | 0.015   |
| Risk Scores   | TIMI (MEAN, sd)  | 1.50 (1.58)     | 3.47 (1.36)         | 3.38 (1.38)     | NA      |
|   | HEART (mean, sd) | 3.50 (2.30)     | 6.93 (1.61)         | 6.72 (1.71)     |         |
|   | GRACE (mean, sd) | 101.5 (39.6)    | 136.4 (32.1)        | 136.7 (35.7)    |         |
| Hypertension  |                  | 695(42%)        | 121 (67%)           | 140 (66%)       | <0.001  |
| Smoking*  | Current          | 457(28%)        | 42 (23%)            | 50 (24%)        | 0.005   |
|   | Previous         | 463(28%)        | 68 (38%)            | 82 (39%)        |         |
|   | Never            | 589(36%)        | 59 (33%)            | 66 (31%)        |         |
| Diabetes mellitus   |                  | 237(14%)        | 44 (24%)            | 55 (26%)        | <0.001  |
| Dyslipidaemia   |                  | 432(26%)        | 75 (42%)            | 82 (39%)        | <0.001  |
| Family History of premature CAD <sup>^</sup>              |                  | 337(21%)        | 34 (19%)            | 37 (18%)        | 0.302   |
| Previous MI   |                  | 322(20%)        | 65 (36%)            | 72(34%)         | <0.001  |
| Previous PCI  |                  | 170 (10%)       | 32 (18%)            | 36 (17%)        | 0.001   |
| Previous CABG   |                  | 91 (6%)         | 21 (12%)            | 22 (10%)        | 0.001   |
| Previous stroke   |                  | 118(7%)         | 22 (12%)            | 29 (14%)        | <0.001  |
| History of AF   |                  | 164(10%)        | 29 (17%)            | 36 (17%)        | <0.001  |
| Hb (median(IQR)) g/dl                                     |                  | 13.7(12.5,14.8) | 13.0(11.7,14.4)     | 12.9(11.7,14.3) | 0.023   |
| MCV (median (IQR)) femtolitres                            |                  | 88.7(85.6,92.0) | 89.6(86.1,92.7)     | 89.3(85.5,92.5) | 0.780   |
| Creatinine [median, IQR] mmol/l                           |                  | 91(79,105)      | 98(86,116)          | 97(84,118)      | <0.001  |
| C- reactive protein (median, IQR) mg/dl                   |                  | 4(4,9)          | 4(4,10)             | 4(4,13)         | 0.03    |
| Systolic BP (median(IQR)) mmHg                            |                  | 131(118,146)    | 139(122,152)        | 136(121,151)    | 0.001   |
| Heart Rate (median, IQR) {beats/min}                      |                  | 78(67,90)       | 77(66,88)           | 77(66,90)       | 0.89    |
| CP onset/peak to presentation (median, IQR) hours         |                  | 9.7(2.4,48.0)   | 4.2(1.6,15.7)       | 4.6(1.7,18.6)   | <0.001  |
| Time of chest pain <sup>+</sup> to presentation           |                  |                 |                     |                 | <0.001  |
|   | <6hrs            | 682(42%)        | 98 (56%)            | 111 (55%)       |         |
|   | ≥6hrs            | 946(58%)        | 73 (42%)            | 90 (43%)        |         |
| CP onset/peak to first troponin check (median, IQR) hours |                  | 14.0(6.8,49.0)  | 8.6(6.2,18.7)       | 9.2(6.2,21.0)   | <0.001  |
| Time of peak CP to first troponin                         |                  |                 |                     |                 | 0.001   |
|   | ≤6hrs            | 240(15%)        | 40 (22%)            | 47 (22%)        |         |
|   | >6hrs            | 1389(85%)       | 136 (75%)           | 159 (75%)       |         |
| ECG Ischaemic <sup>∞</sup>                                |                  | 463(28%)        | 107 (59%)           | 123 (58%)       | <0.001  |
| ST depression ≥0.5mms                                     |                  | 90(5%)          | 33 (20%)            | 37 (18%)        | <0.001  |
| T wave pathology  |                  |                 |                     |                 | <0.001  |
|   | Nil              | 1262(77%)       | 93 (52%)            | 113 (54%)       |         |
|   | Flat             | 73(4%)          | 12 (7%)             | 13 (6%)         |         |
|   | Biphasic         | 31(2%)          | 11 (6%)             | 14 (7%)         |         |
|   | Inverted         | 274(17%)        | 64 (36%)            | 71 (34%)        |         |
| Current aspirin use                                       |                  | 491(30%)        | 86 (48%)            | 99 (47%)        | <0.001  |

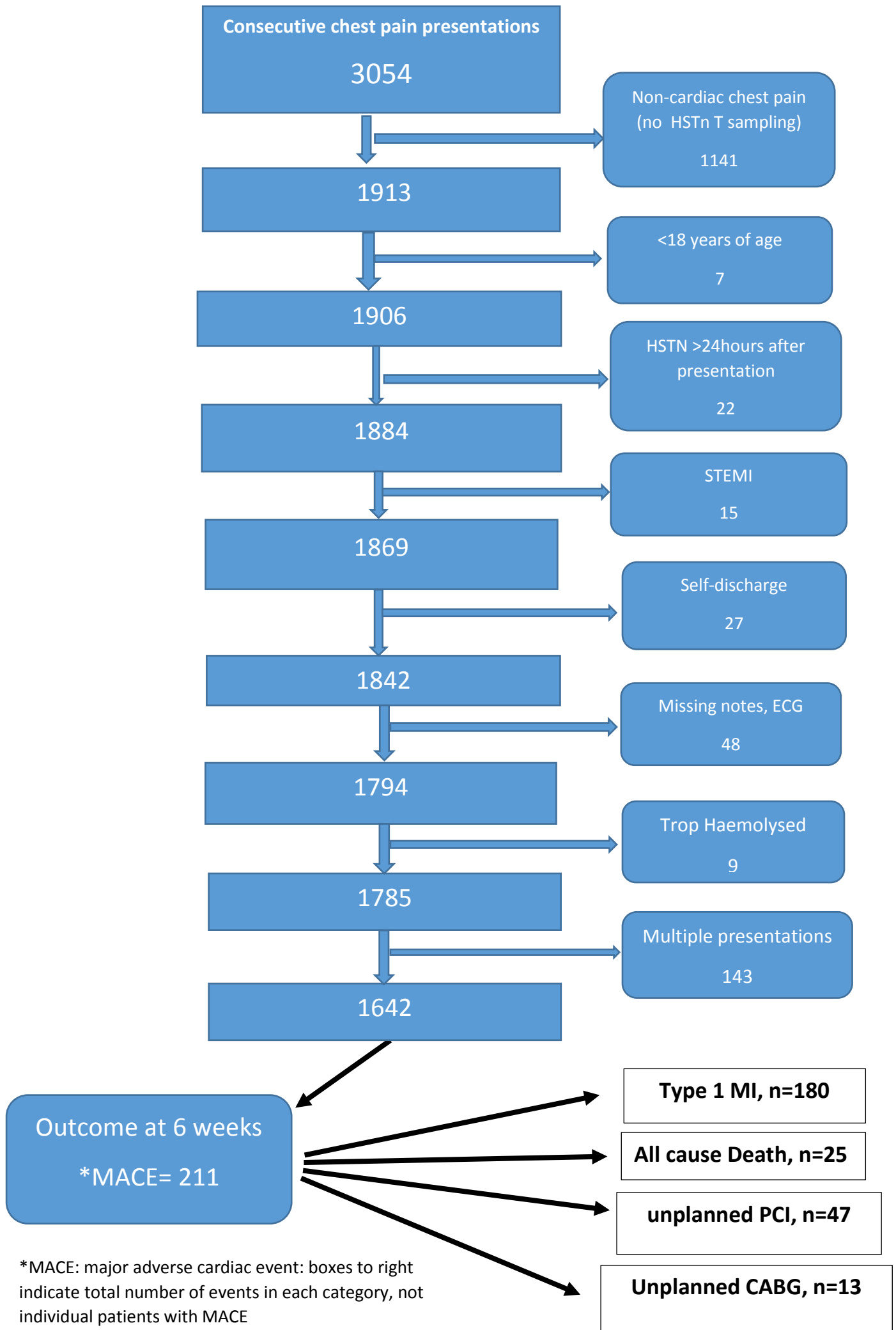
\*Ie not known smoking status in 8%, ^ not known in 32%, + timing of chest pain uncertain in 1%, ∞ ischaemic ECG was defined as the following: rhythm other than sinus rhythm or AF/flutter with heart rate >110bpm, LBBB, paced rhythm, ST segment elevation, ST segment depression, T wave inversion or T wave flattening or biphasic T waves in 2 contiguous leads

**Table 2: Performance of rule-out protocols for type 1 myocardial infarction and MACE at 6 weeks and 1 year**

| <b>MACE (type 1 Myocardial Infarction, unplanned coronary revascularisation and all cause death)</b> |                               |                         |                         |                            |                             |                         |                         |                            |                             |
|--|-------------------------------|-------------------------|-------------------------|----------------------------|-----------------------------|-------------------------|-------------------------|----------------------------|-----------------------------|
| <b>Rule-out protocol</b>   | <b>Discharge potential(%)</b> | <b>6 weeks</b>          |                         |                            |                             | <b>1 year</b>           |                         |                            |                             |
|  |                               | <b>PPV (95% CI)</b>     | <b>NPV (95% CI)</b>     | <b>Sensitivity (95%CI)</b> | <b>Specificity (95% CI)</b> | <b>PPV (95% CI)</b>     | <b>NPV (95% CI)</b>     | <b>Sensitivity (95%CI)</b> | <b>Specificity (95% CI)</b> |
| <b>TIMI ≤ 1</b>  | 56.7                          | 0.270<br>(0.238, 0.304) | 0.980<br>(0.968, 0.988) | 0.910<br>(0.863,0.945)     | 0.637<br>(0.612,0.662)      | 0.339<br>(0.304,0.375)  | 0.959<br>(0.944,0.971)  | 0.864<br>(0.818,0.902)     | 0.655<br>(0.629,0.680)      |
| <b>GRACE &lt;75</b>  | 28.6                          | 0.172<br>(0.151, 0.195) | 0.981<br>(0.964, 0.991) | 0.957(0.921,<br>0.980)     | 0.322<br>(0.298,0.347)      | 0.229<br>(0.205,0.254)  | 0.977<br>(0.958,0.988)  | 0.961<br>(0.931,0.980)     | 0.336<br>(0.311,0.362)      |
| <b>HEART ≤ 3</b>   | 53.4                          | 0.269<br>(0.238, 0.302) | 0.994<br>(0.987, 0.998) | 0.976<br>(0.946,0.992)     | 0.609<br>(0.584,0.635)      | 0.331<br>(0.297,0.365)  | 0.970<br>(0.957,0.981)  | 0.907<br>(0.866,0.938)     | 0.624<br>(0.598,0.650)      |
| <b>HSTnT&lt;5ng/l, ECG non-ischaemic</b>   | 36.9                          | 0.203<br>(0.179, 0.228) | 0.998<br>(0.991, 1.000) | 0.995<br>(0.974,1.000)     | 0.423<br>(0.397,0.449)      | 0.259<br>(0.232,0.286)  | 0.982<br>(0.968,0.991)  | 0.961<br>(0.931,0.980)     | 0.437<br>(0.410,0.463)      |
| <b>HSTnT&lt;15ng/l, ECG non-ischaemic</b>  | 59.4                          | 0.291<br>(0.257, 0.327) | 0.983<br>(0.972, 0.990) | 0.919<br>(0.874,0.952)     | 0.669<br>(0.644,0.694)      | 0.360<br>(0.323,0.398)  | 0.960<br>(0.946,0.971)  | 0.860<br>(0.814,0.899)     | 0.687<br>(0.661,0.711)      |
| <b>HSTnT&lt;5 ng/l alone</b>   | 43.3                          | 0.222<br>(0.196, 0.250) | 0.994<br>(0.986, 0.998) | 0.981<br>(0.952,0.995)     | 0.494<br>(0.468,0.520)      | 0.282 (0.254,<br>0.313) | 0.977 (0.964,<br>0.987) | 0.943<br>(0.909,0.967)     | 0.510<br>(0.483,0.537)      |
| <b>Type 1 Myocardial infarction</b>  |                               |                         |                         |                            |                             |                         |                         |                            |                             |
| <b>Rule-out protocol</b>   | <b>Discharge potential(%)</b> | <b>6 weeks</b>          |                         |                            |                             | <b>1 year</b>           |                         |                            |                             |
|  |                               | <b>PPV (95% CI)</b>     | <b>NPV (95% CI)</b>     | <b>Sensitivity(95%CI)</b>  | <b>Specificity (95% CI)</b> | <b>PPV (95% CI)</b>     | <b>NPV (95% CI)</b>     | <b>Sensitivity (95%CI)</b> | <b>Specificity (95% CI)</b> |
| <b>TIMI ≤ 1</b>  | 56.7                          | 0.232<br>(0.201, 0.265) | 0.984<br>(0.974, 0.991) | 0.917<br>(0.866,0.953)     | 0.627<br>(0.601,0.651)      | 0.245<br>(0.214, 0.278) | 0.982<br>(0.971, 0.989) | 0.911<br>(0.861,0.947)     | 0.630<br>(0.604,0.655)      |
| <b>GRACE &lt;75</b>  | 28.6                          | 0.149<br>(0.129, 0.171) | 0.989<br>(0.975, 0.997) | 0.972<br>(0.936,0.991)     | 0.318<br>(0.294,0.342)      | 0.158<br>(0.137, 0.180) | 0.987<br>(0.972, 0.995) | 0.969<br>(0.933,0.988)     | 0.319<br>(0.295,0.344)      |
| <b>HEART ≤ 3</b>   | 53.4                          | 0.233<br>(0.203, 0.264) | 0.998<br>(0.992, 1.000) | 0.989<br>(0.960,0.999)     | 0.598<br>(0.573,0.624)      | 0.244<br>(0.214, 0.277) | 0.995<br>(0.988, 0.999) | 0.979<br>(0.947,0.994)     | 0.602<br>(0.576,0.627)      |
| <b>HSTnT&lt;5ng/l, ECG non-ischaemic</b>   | 36.9                          | 0.173<br>(0.150, 0.197) | 0.998<br>(0.991, 1.000) | 0.994<br>(0.969,1.000)     | 0.414<br>(0.388,0.440)      | 0.181<br>(0.158,0.206)  | 0.995<br>(0.986, 0.999) | 0.984<br>(0.955,0.997)     | 0.416<br>(0.390,0.441)      |
| <b>HSTnT&lt;15ng/l, ECG non-ischaemic</b>  | 59.4                          | 0.250<br>(0.218, 0.285) | 0.987<br>(0.977, 0.993) | 0.928<br>(0.880,0.961)     | 0.658<br>(0.633,0.682)      | 0.261<br>(0.228, 0.296) | 0.983<br>(0.972, 0.990) | 0.911<br>(0.861,0.947)     | 0.660<br>(0.635,0.685)      |
| <b>HSTnT&lt;5ng/l alone</b>  | 43.3                          | 0.191<br>(0.166, 0.218) | 0.997<br>(0.990, 1.000) | 0.989<br>(0.960,0.999)     | 0.485<br>(0.459,0.511)      | 0.201<br>(0.176, 0.228) | 0.994<br>(0.986, 0.998) | 0.979<br>(0.947,0.994)     | 0.487<br>(0.461,0.513)      |

Abbreviations: MACE= major adverse cardiac event, NPV= negative predictive value, PPV= positive predictive value. HSTnT= high sensitivity troponin T

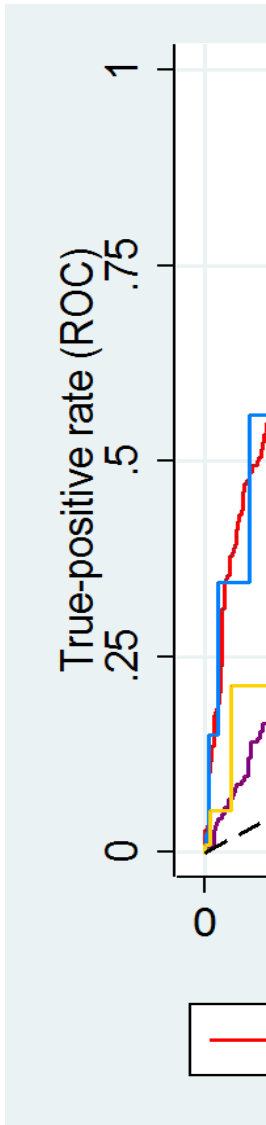
**Figure 1: Flowchart of final population**





**Figure 2: ROC (receiver operator characteristics) curve for primary outcome (MACE) at 6 weeks**

*ROC curves for risk scores (continuous) and high sensitive troponin T (HsTn T is a continuous variable without ECG criteria)*



Area under curve: HSTnT 0.918, HEART 0.910, TIMI 0.855 [p<0.001 cf to HSTnT], GRACE 0.791[p<0.001 cf to HSTnT]

# **A direct comparison of decision rules for early discharge of suspected acute coronary syndromes in the era of high sensitive troponin**

**Chew P, Khand A et al**

## **Calculation of the HEART score**

The character of CP was scored exclusively on the narrative in the admission documentation and/or chest pain proforma. A score of 2 was ascribed when chest pain had documented features suggestive of cardiac chest pain and an absence of non-specific features. A score of 1 was given if there was combination of suspicious and non-specific symptoms and a score of 0 was given if there were only non-specific features. Researchers were prompted to grant high suspicion (a score of 2) if there was central chest pain with at least one additional feature such as radiation to the arm/ neck/jaw or sweating or relief with GTN or provocation of chest pain with exertion or emotion/stress. Admission ECGs were reviewed and ascribed a score of 2 in the presence of ST depression  $\geq 0.5$ mm and 1 in the presence of bifid or inverted T waves or flat T waves in at least 2 contiguous leads of a 12 lead ECG. LBBB and paced rhythm were given a score of 1. Age categories were as per the HEART score. Risk factors considered were hypertension, smoking (current or ex-smoker <1 year), diabetes mellitus, hypercholesterolemia, positive family history and previous history of confirmed atherosclerotic coronary (this latter group included previous MI, CABG, percutaneous coronary intervention, cerebrovascular disease and stroke). We did not have consistent information on body weight and therefore were unable to score BMI >30 as a risk factor in HEART. The presence of  $\geq 3$ , 1-2 and 0 risk factors for coronary artery disease scored 2, 1 and 0 respectively (Confirmed atherosclerotic disease was attributed a score of 2 even in the absence of other risk factors).. A score of 0 was ascribed with HSTnT values of <15ng/l, values between 15 and 41ng/l a score of 1 was given and 2 for values >42. This is consistent

with HEART with scores dependant on 99<sup>th</sup> percentile of troponins in the reference population ( $0 \leq 99^{\text{th}}$  percentile, 1 for  $99^{\text{th}}$  percentile to  $3 \times 99^{\text{th}}$  percentile and a score of 2 for  $> 3 \times 99^{\text{th}}$  percentile).<sup>11</sup>

To ascertain inter-observer variability of risk score determination 2 researchers (AK and FF) undertook blinded assessment and repeat computation of risk scores of a random selection of 18 presentations with suspected ACS.

### **Follow-up**

All clinicians were blinded to outcome of patients (except for inpatient death or death during subsequent admission). However, they could be aware of presentation troponins.

Patients were tracked by a linked national database by their NHS number (these are 16 digit codes and act as unique identifiers to any hospital in England). Codes for readmission were for any chest pain code or any code for ischaemic heart disease or for any coronary revascularisation (PCI or CABG) – see appendix (table 2 for list of codes). Deaths were tracked via the national mortality database. There were 30 patients without NHS numbers. For these patients to ascertain outcome we systematically contacted their general practitioners and the records department of 5 hospitals in the Cheshire and Mersey region (comprising a catchment population of 2.1million). All analyses for outcomes were independently undertaken by the statistician with outcomes spreadsheet and index presentation/ risk scores linked by a unique patient identifier only.

### ***Adjudication of type 1 myocardial infarction/ MACE***

For all index presentations 2 research clinicians independently reviewed all cases where at least one HSTn T was above 99<sup>th</sup> percentile (ie 14ng/l). All investigations including serial

ECGS, echocardiograms, other imaging investigations and angiograms up to 6 weeks from index admission were scrutinised to determine if a definition of type 1 or 2 MI was met. For index admission 2<sup>nd</sup> adjudicator was not blinded to the adjudication/ diagnosis of the first (unblinded). Disagreements were resolved by adjudication by a consultant cardiologist experienced in endpoint definition in clinical studies. For all possible re-infarctions (patients who had a further episode of chest pain with repeat HSTnT sampling outwith the initial sampling period) following presentation and representations with chest pain to any English hospital (appendix table 3 appendix) up to 1 year from discharge were selected (table 2 for ICD 10 codes used). The presence or absence of biomarker elevation (according to local laboratory reference range) was determined. In case of biomarker elevation independent and blinded (to index event and risk scores) adjudication was undertaken by 2 experienced clinicians (with a 3<sup>rd</sup> involved for divergences in adjudication). The criteria for defining MI, for both index admission events and readmissions, was based on the 3<sup>rd</sup> universal definition for MI.<sup>13</sup> Adjudicators were recommended that 50% rise or fall in a 2<sup>nd</sup> troponin was confirmatory of MI but 20-50% rise or fall was suggestive particularly in the context of convincing ischaemic symptoms or other corroborating evidence.

Type 2 MI was defined as evidence of myocardial ischaemia with myocyte necrosis but associated with an imbalance in supply and demand such as tachydysrhythmia, profound anaemia, hypotension. Agreement between clinicians for the presence or absence of myocardial infarction (repeat presentation with biomarker elevation) was 85%, K=0.58.

For patients who had multiple repeat presentations with chest pain the first presentation was assessed for biomarker elevation and/ or adjudication for type 1 MI. If type 1 MI was confirmed, then subsequent admissions/ presentations were censored. If the first readmission was negative for type 1 MI or biomarker evaluation, then subsequent presentations with biomarker positive chest pain was adjudicated until a MACE (Major Adverse cardiac event)

was defined or presentations were exhausted. It is important to note that nationally not all hospitals utilised high sensitivity troponins. (table 3 appendix details all hospital with troponins used [for adjudication] with representation with a possible MI).

We did not apply sex specific cut-offs to HSTnT. This was not the practise in our institute and recent evidence suggests limited value and consequence to this approach using this HSTnT assay.<sup>14</sup>

For all coronary revascularisations (surgical or percutaneous) a single consultant cardiologist adjudicated (by reference to discharge letters, review of coronary angiograms, biochemistry, biomarkers status) if an attempt at revascularisation (coronary artery bypass surgery or percutaneous coronary artery intervention) did occur and if so whether it fulfilled criteria for unplanned coronary revascularisation. (defined as hospital admission with unstable angina/ acute coronary syndrome, deemed to require inpatient revascularisation inclusive of primary percutaneous coronary interventions). As a case ascertainment exercise all national codes for coronary revascularisation were compared to in-house linkage for any revascularisation at the local tertiary centre for revascularisation. An additional 2 cases of urgent/ emergency revascularisation were identified by this exercise (that had been miscoded as non-coronary surgical intervention). Contentious outcomes based on coronary revascularisation underwent adjudication by an endpoint committee. (AK, PC, LM, FF)

### **Non-MI adjudication in index admission**

Researchers were asked separately to diagnose non-MI diagnoses using all available information at index admission. The criteria for agreed and prespecified (drop-down) field settings.

**Unstable Angina:** Patients with normal cardiac troponin levels and typical angina at rest, a deterioration of a previously stable angina and in cases of positive cardiac exercise testing or cardiac catheterization with coronary arteries found to have a stenosis of 70% or greater.

**Atypical Chest Pain:** 2/3 features fulfilled for NICE criteria of ischaemic chest pain <sup>15</sup>

**Cardiac Non-Coronary Chest pain:** Convincing cardiac pathology with evidence for non-coronary disease; eg pericarditis, myocarditis, arrhythmia related

**Non-cardiac Chest Pain:** musculoskeletal pain, gastroesophageal disorder, pulmonary embolism or other causes of noncardiac chest pain

**Chest pain of unknown origin:** If diagnosis remained uncertain or insufficient diagnostic procedures/tests were performed

**Appendix: supplementary tables and figures**

**Table 1: Patients with False negative HEART  $\leq 3$  and HSTnT limit of Detection at 6 weeks – details of presentation and major adverse cardiac events**

| Age   | Gender | HEART score | Heart score criteria                                    | Presentation ECG                             | HstnT 1 | HStnT 2 | Timing of HSTN T: CP to HS tn T | Cause of death  | Additional descriptor  | ICD code                     | MACE Event               |
|---|--------|-------------|---|--|---------|---------|---------------------------------|---|--|------------------------------|--------------------------|
| <b>False Negative HEART score <math>\leq 3</math></b>                         |        |             |   |  |         |         |                                 |   |  |                              |                          |
| 61  | male   | 3           | Age (1), RF: smoking (1), moderately suspicious CP (1)  | SR, non-ischaemic                            | 6       |         | 40hr 25 mins                    | N/A   | Readmission with MI (Hstn T 87, 117) 16 days following discharge | R073 (pain in chest wall)    | <b>Subsequent MI</b>     |
| 93  | female | 3           | Age (2), hstn T (1)                                     | SR, 1 <sup>st</sup> degree HB, non-ischaemic | 19      | 33      | 5hr 8 mins                      | N/A   | Index MI (3 <sup>rd</sup> adjudicator involved)                  | R073                         | <b>Index MI</b>          |
| 51  | male   | 3           | Pvd (2), age (1)  | Sinus rhythm, non-ischaemia                  | 8       |         | 16hrs 30 mins                   | 1. Gastrointestinal bleed secondary alcohol excess 2. Acute liver failure | Clear non-cardiac cause - index admission death                  | K720 (acute hepatic failure) | <b>Non-cardiac Death</b> |
| 55  | female | 2           | Age (1), hypertension (1)                               | SR, non-ischaemic                            | 9       | 2       | 1hr 18 mins                     | Lung adenocarcinoma with bony metastases                                  | Clear non-cardiac cause, index admission death                   | C349,M8250 /3                | <b>Non-cardiac Death</b> |
| 69  | male   | 3           | Age (2), RFs: smoking, hypertension (1)                 | SR, non-ischaemic                            | 10      |         | 50hr 45 minutes                 | Small cell carcinoma of lung  | Died at home 3 days after discharge                              | C349 M8041/3                 | <b>Non-cardiac Death</b> |
| <b>False negative high sensitivity troponin T (LOD) and non-ischaemic ECG</b> |        |             |   |  |         |         |                                 |   |  |                              |                          |
| 65  | male   | 4           | Age (2), risk factors (1), moderately suspicious CP (1) | SR, non-ischaemic                            | 3       | 18      | 314minutes                      | N/A   | Index MI   | R072 (central chest pain)    | <b>Index MI</b>          |

Abbreviations: SR= sinus rhythm, Hstn T= high sensitivity troponin T, ECG= electrocardiogram, MI= myocardial Infarction, PVD= peripheral vascular disease, ICD = international classification of disease, CP= Chest pain, N/A = not applicable, LOD= limit of detection

**Table 2a: ICD 10 Revascularisation codes used**

| CLINICAL_CODE | CODE_SET_ID | VERSION | SHORT_DESC                       | LONG_DESC   | OPCS_VERSION |
|---------------|-------------|---------|----------------------------------|---|--------------|
| K40           | OPCS        | 4       | SAPHENOUS VEIN GRAFT REPLACEMENT | SAPHENOUS VEIN GRAFT REPLACEMENT OF CORONARY ARTERY         | 4.2          |
| K401          | OPCS        | 4       | Saphenous vein graft replaceme   | Saphenous vein graft replacement of one coronary artery     | 4.2          |
| K4010         | OPCS        | 4       | Coronary Artery Bypass Grafts    | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B10      | OPCS        | 4       | CORONARY ARTERY BYPASS GRAFTS    | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B11      | OPCS        | 4       | Coronary Artery Bypass Grafts    | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B14      | OPCS        | 4       | CORONARY BYPASS GRAFTS - ENDO    | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B16      | OPCS        | 4       | REPAIR ASC. AORTA & COR. BYPAS   | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B17      | OPCS        | 4       | REPAIR AORTIC ANEURYSM & BYPAS   | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B18      | OPCS        | 4       | CABG & OTHER MAJOR CARDIAC (EG   | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B1A      | OPCS        | 4       | TMR & CABG                       | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B1B      | OPCS        | 4       | CABG & CAROTID ENDARTERECTOMY    | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B1C      | OPCS        | 4       | CABG & ABDOMINAL AORTIC ANEURY   | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B21      | OPCS        | 4       | REPLACEMENT/REPAIR OF VALVE(S)   | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B22      | OPCS        | 4       | Coronary Artery Bypass Grafts    | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K4010B23      | OPCS        | 4       | COMPOSITE REPL AORTA, VALVE + C  | SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY     | 4.2          |
| K402          | OPCS        | 4       | Saphenous vein graft replaceme   | Saphenous vein graft replacement of two coronary arteries   | 4.2          |
| K4020         | OPCS        | 4       | Coronary Artery Bypass Grafts    | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B10      | OPCS        | 4       | CORONARY ARTERY BYPASS GRAFTS    | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B11      | OPCS        | 4       | Coronary Artery Bypass Grafts    | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B14      | OPCS        | 4       | CORONARY BYPASS GRAFTS - ENDO    | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B16      | OPCS        | 4       | REPAIR ASC. AORTA & COR. BYPAS   | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B17      | OPCS        | 4       | REPAIR AORTIC ANEURYSM & BYPAS   | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B18      | OPCS        | 4       | CABG & OTHER MAJOR CARDIAC (EG   | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B1A      | OPCS        | 4       | TMR & CABG                       | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B1B      | OPCS        | 4       | CABG & CAROTID ENDARTERECTOMY    | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B1C      | OPCS        | 4       | CABG & ABDOMINAL AORTIC ANEURY   | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B21      | OPCS        | 4       | REPLACEMENT/REPAIR OF VALVE(S)   | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B22      | OPCS        | 4       | CABG + AVR + Carotid Endartere   | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B23      | OPCS        | 4       | COMPOSITE REPL AORTA, VALVE + C  | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K4020B32      | OPCS        | 4       | Coronary Artery Bypass Grafts    | SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES   | 4.2          |
| K403          | OPCS        | 4       | Saphenous vein graft replaceme   | Saphenous vein graft replacement of three coronary arteries | 4.2          |
| K4030         | OPCS        | 4       | Coronary Artery Bypass Grafts    | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B10      | OPCS        | 4       | CORONARY ARTERY BYPASS GRAFTS    | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B11      | OPCS        | 4       | Coronary Artery Bypass Grafts    | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B14      | OPCS        | 4       | CORONARY BYPASS GRAFTS - ENDO    | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B16      | OPCS        | 4       | REPAIR ASC. AORTA & COR. BYPAS   | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B18      | OPCS        | 4       | CABG & OTHER MAJOR CARDIAC (EG   | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B1A      | OPCS        | 4       | TMR & CABG                       | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B1B      | OPCS        | 4       | CABG & CAROTID ENDARTERECTOMY    | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B1C      | OPCS        | 4       | CABG & ABDOMINAL AORTIC ANEURY   | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B21      | OPCS        | 4       | REPLACEMENT/REPAIR OF VALVE(S)   | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |
| K4030B22      | OPCS        | 4       | CABG + AVR + Carotid Endartere   | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES | 4.2          |



|          |      |   |                                 |  |     |
|----------|------|---|---------------------------------|--|-----|
| K4030B23 | OPCS | 4 | COMPOSITE REPL AORTA, VALVE + C | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES  | 4.2 |
| K4030B42 | OPCS | 4 | Coronary Artery Bypass Grafts   | SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES  | 4.2 |
| K404     | OPCS | 4 | Saphenous vein graft replaceme  | Saphenous vein graft replacement of four or more coronary ar | 4.2 |
| K4040    | OPCS | 4 | Coronary Artery Bypass Grafts   | SAPHENOUS VEIN GRAFT REPLACEMENT OF FOUR OR MORE CORONARY AR | 4.2 |
| K4040B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS   | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B11 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS   | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B14 | OPCS | 4 | CORONARY BYPASS GRAFTS - ENDO   | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B16 | OPCS | 4 | REPAIR ASC. AORTA & COR. BYPAS  | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B18 | OPCS | 4 | CABG & OTHER MAJOR CARDIAC (EG  | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B1A | OPCS | 4 | TMR & CABG                      | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B1B | OPCS | 4 | CABG & CAROTID ENDARTERECTOMY   | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B21 | OPCS | 4 | REPLACEMENT/REPAIR OF VALVE(S)  | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B22 | OPCS | 4 | CABG + AVR + CAROTID ENDARTERE  | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B23 | OPCS | 4 | COMPOSITE REPL AORTA, VALVE + C | SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES  | 4.2 |
| K4040B52 | OPCS | 4 | Coronary Artery Bypass Grafts   | SAPHENOUS VEIN GRAFT REPLACEMENT OF FOUR OR MORE CORONARY AR | 4.2 |
| K408     | OPCS | 4 | Other specified saphenous vein  | Other specified saphenous vein graft replacement of coronary | 4.2 |
| K409     | OPCS | 4 | Unspecified saphenous vein gra  | Unspecified saphenous vein graft replacement of coronary art | 4.2 |
| K41      | OPCS | 4 | OTHER AUTOGRAFT REPLACEMENT OF  | OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY               | 4.2 |
| K411     | OPCS | 4 | Autograft replacement of one c  | Autograft replacement of one coronary artery NEC             | 4.2 |
| K4110    | OPCS | 4 | CABG + AVR + Carotid Endertere  | AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC             | 4.2 |
| K4110B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS   | AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC             | 4.2 |
| K4110B11 | OPCS | 4 | Coronary Artery Bypass Grafts   | AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC             | 4.2 |
| K4110B1A | OPCS | 4 | TMR & CABG                      | AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC             | 4.2 |
| K4110B21 | OPCS | 4 | AUTO REPLACE ONE CON ART        | AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC             | 4.2 |
| K4110B22 | OPCS | 4 | CABG + AVR + Carotid Endertere  | AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC             | 4.2 |
| K412     | OPCS | 4 | Autograft replacement of two c  | Autograft replacement of two coronary arteries NEC           | 4.2 |
| K4120    | OPCS | 4 | CABG + AVR + Carotid Endertere  | AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC           | 4.2 |
| K4120B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS   | AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC           | 4.2 |
| K4120B11 | OPCS | 4 | Coronary Artery Bypass Grafts   | AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC           | 4.2 |
| K4120B1A | OPCS | 4 | TMR & CABG                      | AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC           | 4.2 |
| K4120B21 | OPCS | 4 | AUTO REPLACE TWO CON ART        | AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC           | 4.2 |
| K4120B22 | OPCS | 4 | CABG + AVR + Carotid Endertere  | AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC           | 4.2 |
| K413     | OPCS | 4 | Autograft replacement of three  | Autograft replacement of three coronary arteries NEC         | 4.2 |
| K4130    | OPCS | 4 | CABG + AVR + Carotid Endertere  | AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC         | 4.2 |
| K4130B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS   | AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC         | 4.2 |
| K4130B11 | OPCS | 4 | Coronary Artery Bypass Grafts   | AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC         | 4.2 |
| K4130B1A | OPCS | 4 | TMR & CABG                      | AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC         | 4.2 |
| K4130B21 | OPCS | 4 | AUTO REPLACE THREE CON ART      | AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC         | 4.2 |
| K4130B22 | OPCS | 4 | CABG + AVR + Carotid Endertere  | AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC         | 4.2 |
| K414     | OPCS | 4 | Autograft replacement of four   | Autograft replacement of four or more coronary arteries NEC  | 4.2 |
| K4140    | OPCS | 4 | CABG + AVR + Carotid Endertere  | AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC  | 4.2 |
| K4140B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS   | AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC  | 4.2 |
| K4140B11 | OPCS | 4 | Coronary Artery Bypass Grafts   | AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC  | 4.2 |
| K4140B1A | OPCS | 4 | TMR & CABG                      | AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC  | 4.2 |
| K4140B21 | OPCS | 4 | AUTO REPLACE FOUR > CON ART     | AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC  | 4.2 |

|          |      |   |                                |  |     |
|----------|------|---|--------------------------------|--|-----|
| K4140B22 | OPCS | 4 | CABG + AVR + Carotid Endertere | AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC  | 4.2 |
| K418     | OPCS | 4 | Other specified other autograf | Other specified other autograft replacement of coronary arte | 4.2 |
| K4180    | OPCS | 4 | TMR & CABG                     | OTHER SPECIFIED  | 4.2 |
| K4180B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS  | OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY OS            | 4.2 |
| K4180B11 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS  | OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY OS            | 4.2 |
| K4180B1A | OPCS | 4 | TMR & CABG                     | OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY OS            | 4.2 |
| K419     | OPCS | 4 | Unspecified other autograft re | Unspecified other autograft replacement of coronary artery   | 4.2 |
| K4190    | OPCS | 4 | TMR & CABG                     | UNSPECIFIED  | 4.2 |
| K4190B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS  | OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY UNSPECIFIED   | 4.2 |
| K4190B11 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS  | OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY UNSPECIFIED   | 4.2 |
| K4190B1A | OPCS | 4 | TMR & CABG                     | OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY UNSPECIFIED   | 4.2 |
| K42      | OPCS | 4 | ALLOGRAFT REPLACEMENT OF CORON | ALLOGRAFT REPLACEMENT OF CORONARY ARTERY                     | 4.2 |
| K421     | OPCS | 4 | Allograft replacement of one c | Allograft replacement of one coronary artery                 | 4.2 |
| K422     | OPCS | 4 | Allograft replacement of two c | Allograft replacement of two coronary arteries               | 4.2 |
| K423     | OPCS | 4 | Allograft replacement of three | Allograft replacement of three coronary arteries             | 4.2 |
| K424     | OPCS | 4 | Allograft replacement of four  | Allograft replacement of four or more coronary arteries      | 4.2 |
| K428     | OPCS | 4 | Other specified allograft repl | Other specified allograft replacement of coronary artery     | 4.2 |
| K429     | OPCS | 4 | Unspecified allograft replacem | Unspecified allograft replacement of coronary artery         | 4.2 |
| K43      | OPCS | 4 | PROSTHETIC REPLACEMENT OF CORO | PROSTHETIC REPLACEMENT OF CORONARY ARTERY                    | 4.2 |
| K431     | OPCS | 4 | Prosthetic replacement of one  | Prosthetic replacement of one coronary artery                | 4.2 |
| K432     | OPCS | 4 | Prosthetic replacement of two  | Prosthetic replacement of two coronary arteries              | 4.2 |
| K433     | OPCS | 4 | Prosthetic replacement of thre | Prosthetic replacement of three coronary arteries            | 4.2 |
| K434     | OPCS | 4 | Prosthetic replacement of four | Prosthetic replacement of four or more coronary arteries     | 4.2 |
| K438     | OPCS | 4 | Other specified prosthetic rep | Other specified prosthetic replacement of coronary artery    | 4.2 |
| K439     | OPCS | 4 | Unspecified prosthetic replace | Unspecified prosthetic replacement of coronary artery        | 4.2 |
| K44      | OPCS | 4 | OTHER REPLACEMENT OF CORONARY  | OTHER REPLACEMENT OF CORONARY ARTERY                         | 4.2 |
| K441     | OPCS | 4 | Replacement of coronary arteri | Replacement of coronary arteries using multiple methods      | 4.2 |
| K442     | OPCS | 4 | Revision of replacement of cor | Revision of replacement of coronary artery                   | 4.2 |
| K4420    | OPCS | 4 | POST OP ATTENTION TO GRAFTS -  | REVISION OF REPLACEMENT OF CORONARY ARTERY                   | 4.2 |
| K4420B15 | OPCS | 4 | POST OP ATTENTION TO GRAFTS -  | REVISION OF REPLACEMENT OF CORONARY ARTERY                   | 4.2 |
| K448     | OPCS | 4 | Other specified other replacem | Other specified other replacement of coronary artery         | 4.2 |
| K449     | OPCS | 4 | Unspecified other replacement  | Unspecified other replacement of coronary artery             | 4.2 |
| K451     | OPCS | 4 | Double anastomosis of mammary  | Double anastomosis of mammary arteries to coronary arteries  | 4.2 |
| K4510B10 | OPCS | 4 | DOUBLE ANASTOMOSIS OF MAMMARY  | DOUBLE ANASTOMOSIS OF MAMMARY ARTERIES TO CORONARY ARTERIES  | 4.2 |
| K4510B11 | OPCS | 4 | DOUBLE ANASTOMOSIS OF MAMMARY  | DOUBLE ANASTOMOSIS OF MAMMARY ARTERIES TO CORONARY ARTERIES  | 4.2 |
| K4510B21 | OPCS | 4 | CABG WITH VALVE REPAIR         | DOUBLE ANASTOMOSIS OF MAMMARY ARTERIES TO CORONARY ARTERIES  | 4.2 |
| K452     | OPCS | 4 | Double anastomosis of thoracic | Double anastomosis of thoracic arteries to coronary arteries | 4.2 |
| K453     | OPCS | 4 | Anastomosis of mammary artery  | Anastomosis of mammary artery to left anterior descending co | 4.2 |
| K4530    | OPCS | 4 | Coronary Artery Bypass Grafts  | ANASTOMOSIS OF MAMMARY ARTERY TO LEFT ANTERIOR DESCENDING CO | 4.2 |
| K4530B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS  | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B11 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS  | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B13 | OPCS | 4 | MIDCAB-MIN INVASIVE BYPASS GRA | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B14 | OPCS | 4 | CORONARY BYPASS GRAFTS - ENDO  | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B16 | OPCS | 4 | REPAIR ASC. AORTA & COR. BYPAS | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B18 | OPCS | 4 | CABG & OTHER MAJOR CARDIAC (EG | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |

|          |      |   |                                 |  |     |
|----------|------|---|---------------------------------|--|-----|
| K4530B1A | OPCS | 4 | TMR & CABG                      | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B1B | OPCS | 4 | CABG & CAROTID ENDARTERECTOMY   | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B21 | OPCS | 4 | REPLACEMENT/REPAIR OF VALVE(S)  | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B22 | OPCS | 4 | CABG + AVR + CAROTID ENDARTERE  | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B23 | OPCS | 4 | COMPOSITE REPL AORTA, VALVE + C | ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY  | 4.2 |
| K4530B62 | OPCS | 4 | Coronary Artery Bypass Grafts   | ANASTOMOSIS OF MAMMARY ARTERY TO LEFT ANTERIOR DESCENDING CO | 4.2 |
| K454     | OPCS | 4 | Anastomosis of mammary artery   | Anastomosis of mammary artery to coronary artery NEC         | 4.2 |
| K4540    | OPCS | 4 | Coronary Artery Bypass Grafts   | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B10 | OPCS | 4 | CORONARY ARTERY BYPASS GRAFTS   | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B11 | OPCS | 4 | Coronary Artery Bypass Grafts   | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B12 | OPCS | 4 | Coronary Artery Bypass Grafts   | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B14 | OPCS | 4 | CORONARY BYPASS GRAFTS - ENDO   | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B16 | OPCS | 4 | REPAIR ASC. AORTA & COR. BYPAS  | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B18 | OPCS | 4 | CABG & OTHER MAJOR CARDIAC (EG  | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B1A | OPCS | 4 | TMR & CABG                      | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B1B | OPCS | 4 | CABG & CAROTID ENDARTERECTOMY   | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B21 | OPCS | 4 | REPLACE/REPAIR VALVE(S) & CABG  | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B22 | OPCS | 4 | CABG + AVR + Carotid Endertere  | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K4540B23 | OPCS | 4 | COMPOSITE REPL AORTA, VALVE + C | ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC         | 4.2 |
| K455     | OPCS | 4 | Anastomosis of thoracic artery  | Anastomosis of thoracic artery to coronary artery NEC        | 4.2 |
| K456     | OPCS | 4 | Revision of connection of thor  | Revision of connection of thoracic artery to coronary artery | 4.2 |
| K458     | OPCS | 4 | Other specified connection of   | Other specified connection of thoracic artery to coronary ar | 4.2 |
| K459     | OPCS | 4 | Unspecified connection of thor  | Unspecified connection of thoracic artery to coronary artery | 4.2 |
| K46      | OPCS | 4 | OTHER BYPASS OF CORONARY ARTER  | OTHER BYPASS OF CORONARY ARTERY                              | 4.2 |
| K463     | OPCS | 4 | Implantation of mammary artery  | Implantation of mammary artery into heart NEC                | 4.2 |
| K468     | OPCS | 4 | Other specified other bypass o  | Other specified other bypass of coronary artery              | 4.2 |
| K469     | OPCS | 4 | Unspecified other bypass of co  | Unspecified other bypass of coronary artery                  | 4.2 |
| K49      | OPCS | 4 | TRANSLUMINAL BALLOON ANGIOPLAS  | TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY          | 4.2 |
| K491     | OPCS | 4 | Percutaneous transluminal ball  | Percutaneous transluminal balloon angioplasty of one coronar | 4.2 |
| K4910    | OPCS | 4 | LASER ANGIOPLASTY - ONE BALLOO  | PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY OF ONE CORONAR | 4.2 |
| K4910D11 | OPCS | 4 | ABANDONED PTCA                  | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D12 | OPCS | 4 | SIMPLE PTCA - ONE OR TWO BALLO  | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D21 | OPCS | 4 | SIMPLE PTCA-MORE THAN 2 BALLOO  | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D34 | OPCS | 4 | PTCA - ONE STENT & ONE BALLOON  | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D35 | OPCS | 4 | PTCA - 1 STENT, NO BALLOON      | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D37 | OPCS | 4 | LASER ANGIOPLASTY - ONE BALLOO  | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D41 | OPCS | 4 | PTCA - 2 OR MORE STENTS         | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D42 | OPCS | 4 | PTCA - 2 OR MORE STENTS, NO BA  | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D44 | OPCS | 4 | PTCA WITH STENT & ROTABLATOR    | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D45 | OPCS | 4 | PTCA WITH STENT - 2+ BALLOONS   | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D49 | OPCS | 4 | PTCA WITH 2+STENTS (2+ BALLOON  | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D4B | OPCS | 4 | LASER ANGIOPLASTY, MORE THAN O  | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K4910D4C | OPCS | 4 | LASER ANGIOPLASTY WITH STENT(S) | PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY  | 4.2 |
| K492     | OPCS | 4 | Percutaneous transluminal ball  | Percutaneous transluminal balloon angioplasty of multiple co | 4.2 |
| K4920    | OPCS | 4 | PTCA with Stent & Rotablator    | PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY OF MULTIPLE CO | 4.2 |

|          |      |   |                                |  |     |
|----------|------|---|--------------------------------|--|-----|
| K4920D11 | OPCS | 4 | ABANDONED PTCA                 | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D12 | OPCS | 4 | SIMPLE PTCA - ONE OR TWO BALLO | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D21 | OPCS | 4 | SIMPLE PTCA-MORE THAN 2 BALLOO | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D34 | OPCS | 4 | PTCA - ONE STENT & ONE BALLOON | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D35 | OPCS | 4 | PTCA - 1 STENT, NO BALLOON     | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D37 | OPCS | 4 | LASER ANGIOPLASTY - 1 BALLOON  | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D41 | OPCS | 4 | PTCA - 2 OR MORE STENTS        | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D42 | OPCS | 4 | PTCA - 2 STENTS, NO BALLOON    | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D44 | OPCS | 4 | PTCA WITH STENT & ROTABLATOR   | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D45 | OPCS | 4 | PTCA WITH STENT - 2+ BALLOONS  | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D49 | OPCS | 4 | PTCA WITH 2+STENTS (2+ BALLOON | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D4B | OPCS | 4 | LASER ANGIOPLASTY - 1 BALLOON  | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K4920D4C | OPCS | 4 | LASER ANGIOPLASTY WITH STENT(S | PERCUT TRANSLUM BALLOON ANGIOPLASTY MULTIPLE CORON ARTERIES  | 4.2 |
| K493     | OPCS | 4 | Percutaneous transluminal ball | Percutaneous transluminal balloon angioplasty of bypass graf | 4.2 |
| K4930    | OPCS | 4 | PTCA with Stent & Rotablator   | PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY OF BYPASS GRAF | 4.2 |
| K4930D12 | OPCS | 4 | SIMPLE PTCA - ONE OR TWO BALLO | PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART   | 4.2 |
| K4930D21 | OPCS | 4 | SIMPLE PTCA-MORE THAN 2 BALLOO | PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART   | 4.2 |
| K4930D34 | OPCS | 4 | PTCA - ONE STENT & ONE BALLOON | PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART   | 4.2 |
| K4930D35 | OPCS | 4 | PTCA - 1 STENT, NO BALLOON     | PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART   | 4.2 |
| K4930D41 | OPCS | 4 | PTCA - 2 OR MORE STENTS        | PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART   | 4.2 |
| K4930D44 | OPCS | 4 | PTCA WITH STENT & ROTABLATOR   | PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART   | 4.2 |
| K4930D45 | OPCS | 4 | PTCA WITH STENT - 2+ BALLOONS  | PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART   | 4.2 |
| K4930D49 | OPCS | 4 | PTCA WITH 2+STENTS (2+ BALLOON | PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART   | 4.2 |
| K494     | OPCS | 4 | Percutaneous transluminal cutt | Percutaneous transluminal cutting balloon angioplasty of cor | 4.2 |
| K498     | OPCS | 4 | Other specified transluminal b | Other specified transluminal balloon angioplasty of coronary | 4.2 |
| K4980    | OPCS | 4 | PTCA with Stent & Rotablator   | OTHER SPECIFIED  | 4.2 |
| K4980D34 | OPCS | 4 | PTCA - ONE STENT & ONE BALLOON | TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS       | 4.2 |
| K4980D41 | OPCS | 4 | PTCA - 2 OR MORE STENTS        | TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS       | 4.2 |
| K4980D44 | OPCS | 4 | PTCA WITH STENT & ROTABLATOR   | TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS       | 4.2 |
| K4980D45 | OPCS | 4 | PTCA WITH STENT - 2+ BALLOONS  | TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS       | 4.2 |
| K4980D49 | OPCS | 4 | PTCA WITH 2+STENTS (2+ BALLOON | TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS       | 4.2 |
| K499     | OPCS | 4 | Unspecified transluminal ballo | Unspecified transluminal balloon angioplasty of coronary art | 4.2 |
| K50      | OPCS | 4 | OTHER THERAPEUTIC TRANSLUMINAL | OTHER THERAPEUTIC TRANSLUMINAL OPERATIONS ON CORONARY ARTERY | 4.2 |
| K501     | OPCS | 4 | Percutaneous transluminal lase | Percutaneous transluminal laser coronary angioplasty         | 4.2 |
| K5010    | OPCS | 4 | LASER ANGIOPLASTY - NO BALLOON | PERCUTANEOUS TRANSLUMINAL LASER CORONARY ANGIOPLASTY         | 4.2 |
| K5010D36 | OPCS | 4 | LASER ANGIOPLASTY - NO BALLOON | PERCUTANEOUS TRANSLUMINAL LASER CORONARY ANGIOPLASTY         | 4.2 |
| K502     | OPCS | 4 | Percutaneous transluminal coro | Percutaneous transluminal coronary thrombolysis using strept | 4.2 |
| K503     | OPCS | 4 | Percutaneous transluminal inje | Percutaneous transluminal injection of therapeutic substance | 4.2 |
| K504     | OPCS | 4 | Percutaneous transluminal athe | Percutaneous transluminal atherectomy of coronary artery     | 4.2 |
| K508     | OPCS | 4 | Other specified other therapeu | Other specified other therapeutic transluminal operations on | 4.2 |
| K5080    | OPCS | 4 | PTCA with Rota -1 balloon,1 or | PTDA   | 4.2 |
| K5080D31 | OPCS | 4 | PTCA WITH ROTA -1 BALLOON,1 OR | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS   | 4.2 |
| K5080D32 | OPCS | 4 | CORONARY TEC - ONE BALLOON     | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS   | 4.2 |
| K5080D33 | OPCS | 4 | DCA - ONE BALLOON              | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS   | 4.2 |
| K5080D43 | OPCS | 4 | PTCA-2 OR MORE ROTABLATORS     | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS   | 4.2 |

|          |      |   |                                |  |     |
|----------|------|---|--------------------------------|--|-----|
| K5080D44 | OPCS | 4 | PTCA WITH STENT & ROTABLATOR   | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS               | 4.2 |
| K5080D46 | OPCS | 4 | PTCA WITH ROTABLATOR - 2+ BALL | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS               | 4.2 |
| K5080D47 | OPCS | 4 | CORONARY TEC - 2+ BALLOONS     | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS               | 4.2 |
| K5080D48 | OPCS | 4 | DCA - 2+BALLOONS               | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS               | 4.2 |
| K5080D4A | OPCS | 4 | CORONARY TEC WITH STENT(S) INC | OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS               | 4.2 |
| K509     | OPCS | 4 | Unspecified other therapeutic  | Unspecified other therapeutic transluminal operations on coronary artery | 4.2 |
| K75      | OPCS | 4 | PERCUTANEOUS TRANSLUMINAL BALL | PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY AND STENTING O             | 4.2 |
| K751     | OPCS | 4 | Percutaneous transluminal ball | Percutaneous transluminal balloon angioplasty and insertion              | 4.2 |
| K752     | OPCS | 4 | Percutaneous transluminal ball | Percutaneous transluminal balloon angioplasty and insertion              | 4.2 |
| K753     | OPCS | 4 | Percutaneous transluminal ball | Percutaneous transluminal balloon angioplasty and insertion              | 4.2 |
| K754     | OPCS | 4 | Percutaneous transluminal ball | Percutaneous transluminal balloon angioplasty and insertion              | 4.2 |
| K758     | OPCS | 4 | Other specified percutaneous t | Other specified percutaneous transluminal balloon angioplasty            | 4.2 |
| K759     | OPCS | 4 | Unspecified percutaneous trans | Unspecified percutaneous transluminal balloon angioplasty an             | 4.2 |

**Table 2b: ICD 10 codes used to identify type 1 myocardial infarctions**

| CLINICAL_CODE | CODE_SET_ID | VERSION | SHORT_DESC                          | LONG_DESC  |
|---------------|-------------|---------|-------------------------------------|--|
| I20           | ICD         | 10      | Angina pectoris                     | Angina pectoris  |
| I200          | ICD         | 10      |                                     | UNSTABLE ANGINA  |
| I201          | ICD         | 10      |                                     | ANGINA PECTORIS WITH DOCUMENTED SPASM                      |
| I208          | ICD         | 10      |                                     | OTHER FORMS OF ANGINA PECTORIS                             |
| I209          | ICD         | 10      |                                     | ANGINA PECTORIS, UNSPECIFIED                               |
| I21           | ICD         | 10      | Acute myocardial infarction         | Acute myocardial infarction                                |
| I210          | ICD         | 10      |                                     | ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF ANTERIOR WALL    |
| I211          | ICD         | 10      |                                     | ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF INFERIOR WALL    |
| I212          | ICD         | 10      |                                     | ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF OTHER SITES      |
| I213          | ICD         | 10      |                                     | ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF UNSPECIFIED SITE |
| I214          | ICD         | 10      |                                     | ACUTE SUBENDOCARDIAL MYOCARDIAL INFARCTION                 |
| I219          | ICD         | 10      |                                     | ACUTE MYOCARDIAL INFARCTION, UNSPECIFIED                   |
| I22           | ICD         | 10      | Subsequent myocardial infarction    | Subsequent myocardial infarction                           |
| I220          | ICD         | 10      |                                     | SUBSEQUENT MYOCARDIAL INFARCTION OF ANTERIOR WALL          |
| I221          | ICD         | 10      |                                     | SUBSEQUENT MYOCARDIAL INFARCTION OF INFERIOR WALL          |
| I228          | ICD         | 10      |                                     | SUBSEQUENT MYOCARDIAL INFARCTION OF OTHER SITES            |
| I229          | ICD         | 10      |                                     | SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE       |
| I24           | ICD         | 10      | Other acute ischaemic heart disease | Other acute ischaemic heart disease                        |
| I240          | ICD         | 10      |                                     | CORONARY THROMBOSIS NOT RESULTING IN MYOCARDIAL INFARCTION |
| I241          | ICD         | 10      |                                     | DRESSLER'S SYNDROME  |
| I248          | ICD         | 10      |                                     | OTHER FORMS OF ACUTE ISCHAEMIC HEART DISEASE               |
| I249          | ICD         | 10      |                                     | ACUTE ISCHAEMIC HEART DISEASE, UNSPECIFIED                 |
| I25           | ICD         | 10      | Chronic ischaemic heart disease     | Chronic ischaemic heart disease                            |
| I250          | ICD         | 10      |                                     | ATHEROSCLEROTIC CARDIOVASCULAR DISEASE, SO DESCRIBED       |
| I251          | ICD         | 10      |                                     | ATHEROSCLEROTIC HEART DISEASE                              |
| I253          | ICD         | 10      |                                     | ANEURYSM OF HEART  |
| I254          | ICD         | 10      |                                     | CORONARY ARTERY ANEURYSM                                   |
| I255          | ICD         | 10      |                                     | ISCHAEMIC CARDIOMYOPATHY                                   |

|      |     |    |                                |  |
|------|-----|----|--------------------------------|--|
| I256 | ICD | 10 |                                | SILENT MYOCARDIAL ISCHAEMIA                                  |
| I46  | ICD | 10 | Cardiac arrest                 | Cardiac arrest   |
| I460 | ICD | 10 |                                | CARDIAC ARREST WITH SUCCESSFUL RESUSCITATION                 |
| I461 | ICD | 10 |                                | SUDDEN CARDIAC DEATH, SO DESCRIBED                           |
| I469 | ICD | 10 |                                | CARDIAC ARREST, UNSPECIFIED                                  |
| R071 | ICD | 10 |                                | CHEST PAIN ON BREATHING                                      |
| R072 | ICD | 10 |                                | PRECORDIAL PAIN  |
| R073 | ICD | 10 |                                | OTHER CHEST PAIN   |
| R074 | ICD | 10 |                                | CHEST PAIN, UNSPECIFIED                                      |
| R96  | ICD | 10 | Other sudden death, cause unkn | Other sudden death, cause unkn                               |
| R960 | ICD | 10 |                                | INSTANTANEOUS DEATH  |
| R961 | ICD | 10 |                                | DEATH OCCURRING LESS THAN 24 HOURS FROM ONSET OF SYMPTOMS, N |
| R98X | ICD | 10 |                                | UNATTENDED DEATH   |
| R99X | ICD | 10 |                                | OTHER ILL-DEFINED AND UNSPECIFIED CAUSES OF MORTALITY        |

**Table 3 Re-presentation (up to 1 year following index discharge) to English hospitals with any ischaemic heart disease or coronary revascularisation code: troponin assays in use and reference ranges**

| Hospital  | Assay      | Manufacturer | High sensitive assay | Reference range            | Units        |
|---|------------|--------------|----------------------|----------------------------|--------------|
| St Helens and Knowsley NHS trust                        | Troponin I | Siemens      | No                   | ≤0.05                      | micrograms/l |
| East Cheshire Hospital NHS trust                        | TroponinI  | Beckman      | Yes                  | <34                        | nanograms/l  |
| Southport hospital NHS Trust                            | Troponin T | Roche        | yes                  | <15                        | nanograms/l  |
| Warrington Hospital NHS Trust                           | Troponin I | Siemens      | no                   | <0.03                      | Micrograms/l |
| University hospital Aintree NHS Foundation Trust        | Troponin T | Roche        | yes                  | <15                        | nanograms/l  |
| Royal Liverpool Hospitals                               | Troponin T | Roche        | yes                  | <15                        | nanograms/l  |
| Liverpool Heart and Chest hospital NHS foundation trust | Troponin T | Roche        | yes                  | <15                        | nanograms/l  |
| Pilgrim Hospital  | Troponin T | Roche        | Yes                  | <15 (female)<br><10 (male) | nanograms/l  |

**Table 4 Inter-observer variability in risk score determination**

| Risk SCORE   | Inter-observer variability in determination of risk scores |                |      |
|--------------|--|----------------|------|
|              | Absolute   | Risk category* |      |
|              | Agreement  | Agreement      | κ    |
| <b>HEART</b> | 16/18 (89%)  | 18/18 (100%)   | 1.0  |
| <b>TIMI</b>  | 13/18 (72%)  | 18/18 (100%)   | 1.0  |
| <b>GRACE</b> | 11/18 (61%)  | 17/18 (94%)    | 0.82 |

\*agreement of risk category determination (low, intermediate, high risk score determination of each risk score)

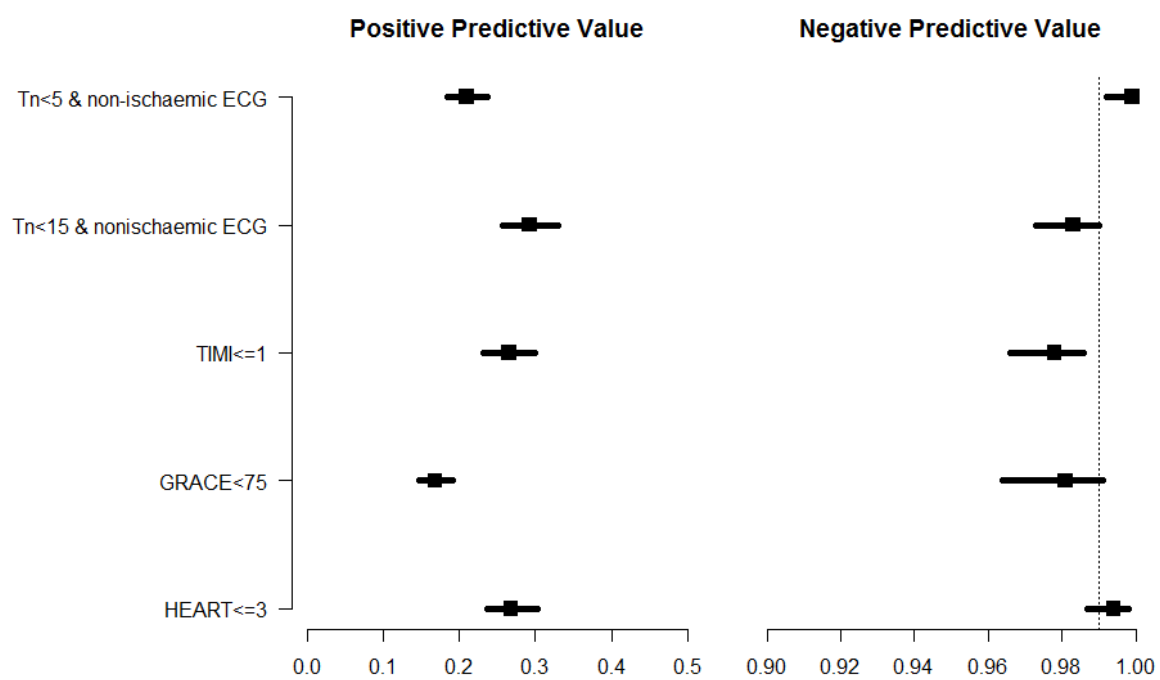


**Table 5 Interaction of timing of high sensitivity troponin T check relative to CP onset and outcome (MACE)**

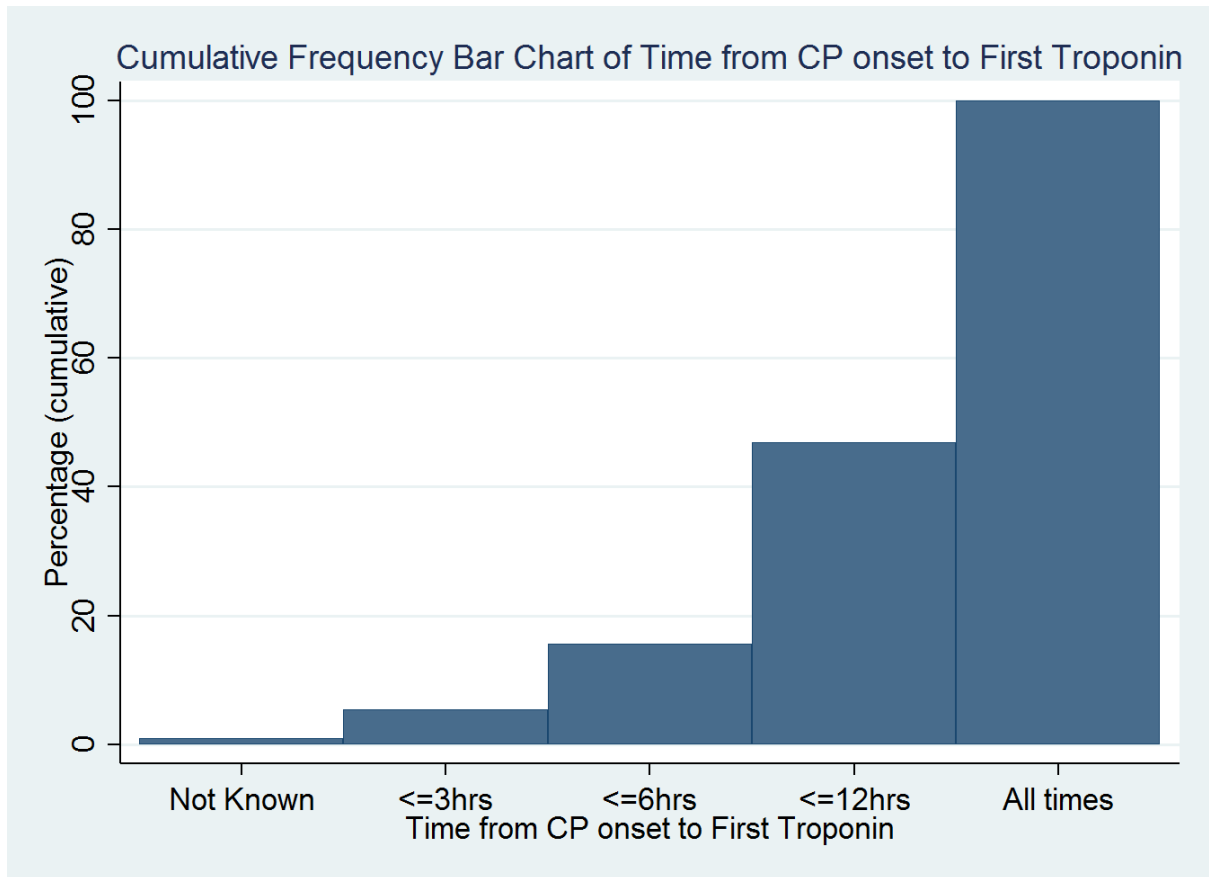
| Rule-Out Protocol                        | Chest pain (peak) to first troponin Check (hours) (n-discharged, npv with confidence intervals at 42 days) |                             |         |                           |                           |         |
|--|--|-----------------------------|---------|---------------------------|---------------------------|---------|
|  | <3   | ≥3                          | P value | <6                        | ≥6                        | P value |
| <b>HStnT &lt;15 and nonischaemic ECG</b> | 40 (0.976 (0.871 – 0.999))   | 913 (0.983 (0.972-0.990))   | 0.563   | 128 (0.985 (0.946-0.998)) | 825 (0.982 (0.971-0.990)) | 1.000   |
| <b>HsTnt &lt;5 and nonischaemic ECG</b>  | 23 (1.000 (0.852 – 1.000))   | 579 (0.998 (0.990 – 1.000)) | 1.000   | 71 (1.000 (0.949-1.000))  | 531 (0.998 (0.990-1.000)) | 1.000   |
| <b>HEART ≤3</b>                          | 36 (1.000 (0.903-1.000))   | 831 (0.994 (0.986-0.998))   | 1.000   | 101 (0.990 (0.947-1.000)) | 766 (0.995 (0.987-0.999)) | 0.464   |
| <b>TIMI≤1</b>                            | 40 (0.976 (0.871-0.999))   | 867 (0.980 (0.968-0.988))   | 0.581   | 116 (0.959 (0.906-0.986)) | 791 (0.983 (0.971-0.990)) | 0.090   |
| <b>GRACE ≤75</b>                         | 25 (0.962 (0.804 – 0.999))   | 433 (0.982 (0.965-0.992))   | 0.406   | 65 (0.970 (0.896-0.996))  | 393 (0.983 (0.964-0.993)) | 0.623   |

Abbreviations: NPV= negative predictive value

**Figure 1: Negative and Positive predictive values for MACE (type 1 myocardial infarction, unplanned coronary revascularisation and all cause death) at 6 weeks according to rule-out strategies (dashed lines represents 99% NPV)**



**Figure 2: Time of chest pain to first High sensitivity troponin T sampling**



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

# 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>.

