A Novel Accelerated Diagnostic Protocol to Identify Emergency Department Patients with Chest Pain who may be Suitable for Discharge after a Single High-Sensitivity Troponin

TRUST: **T**riage **R**ule-out **U**sing high-**S**ensitivity **T**roponin Chest Pain Study

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Dedication

For my wife Helen and my son Charlie (who arrived half-way through my PhD journey).

Abstract

Background

Chest pain makes up a quarter of medical admissions in the United Kingdom. A diagnostic strategy that prevents unnecessary hospital admission in a large proportion of this patient group would have significant benefits for healthcare services by reducing hospital admission rates, ED overcrowding, duplication of staff time and resource use. A clinically applicable protocol that allows the discharge of a significant proportion of patients after a single blood draw at presentation to the emergency department remains an attractive yet elusive goal.

Objective

To establish whether a novel accelerated diagnostic protocol (ADP) for suspected acute coronary syndrome (ACS) could successfully identify low-risk patients suitable for discharge after a single high-sensitivity troponin T (hs-cTnT) taken at presentation to the Emergency Department (ED). Comparison of the diagnostic accuracy of this ADP with strategies utilising initial undetectable hs-cTnT was made.

Methods

This prospective observational study evaluated the ability of the Triage Rule-out Using high-Sensitivity Troponin (TRUST) ADP to identify low-risk patients with suspected ACS. The ADP incorporated a single presentation hs-cTnT of <14ng/L, a non-ischaemic electrocardiogram and a modified Goldman risk score. Diagnostic performance of the

ADP was compared with the detection limit cut-offs of hs-cTnT (<5ng/L and <3ng/L). The primary endpoint was major adverse cardiac events (MACE) occurring within 30 days.

Results

960 participants were recruited, mean age 58.0 years, 97 (10.1%) had MACE. The TRUST ADP classified 382 (39.8%) as low-risk with a sensitivity for identifying MACE of 99.0% (95%CI 93.7-99.9). Hs-cTnT detection limits (<5ng/L and <3ng/L) had a sensitivity of 96.8% (90.6-99.2) and 98.9% (93.8-99.9) respectively. The TRUST ADP identified more patients suitable for early discharge at 39.8% vs 29.3% (<5ng/L) and 7.9% (<3ng/L) (P<0.001) with a lower false-positive rate for MACE detection; specificity 44.1% (95%CI 43.6-44.3) vs 32.3% (95%CI 31.6-32.6) and 8.7% (95%CI 8.1-8.8) respectively.

Conclusion

The TRUST ADP, which incorporates structured risk-assessment and a single presentation hs-cTnT blood draw, has potential to allow early discharge in 40% of patients with suspected ACS and has greater clinical utility than undetectable hs-cTnT strategies.

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Key Messages

What is already known about the subject? The use of undetectable high-sensitivity troponin levels and risk scores in combination with early biomarker testing have recently been put forward as diagnostic tools aiming to reduce door-to-discharge times in patients with suspected acute coronary syndromes. However, a clinically applicable protocol that allows the discharge of a significant proportion of patients after just a single high sensitivity troponin blood draw at presentation to the emergency department remains an attractive yet elusive goal.

What does this study add? Using a simple clinical risk score, together with the results of a single high-sensitivity troponin result, the Triage Rule-out Using high-Sensitivity Troponin Accelerated Diagnostic Protocol, may enable immediate discharge in up to 40% of patients. This strategy identifies more patients suitable for early discharge, with lower false-positive rates than undetectable troponin strategies.

How might this impact on clinical practice? Chest pain makes up a quarter of medical admissions in the United Kingdom. A diagnostic strategy that prevents unnecessary hospital admission in a large proportion of this patient group would have significant benefits for healthcare services by reducing hospital admission rates, ED overcrowding, duplication of staff time and resource use.

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Author's Declaration

I declare that the work in this dissertation was carried out in accordance with according to the Bournemouth University Code of Practice for Research Degrees and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, this work is my own work. Work done in collaboration with, or with the assistance of others, is indicated as such. I have identified all material in this dissertation which is not my own work through appropriate referencing and acknowledgement. Where I have quoted or otherwise incorporated material which is the work of others, I have included the source in the references. Any views expressed in the dissertation, other than the referenced material, are those of the author.

Chapter 1.

The Conceptual Development of the

TRUST Accelerated Diagnostic Pathway

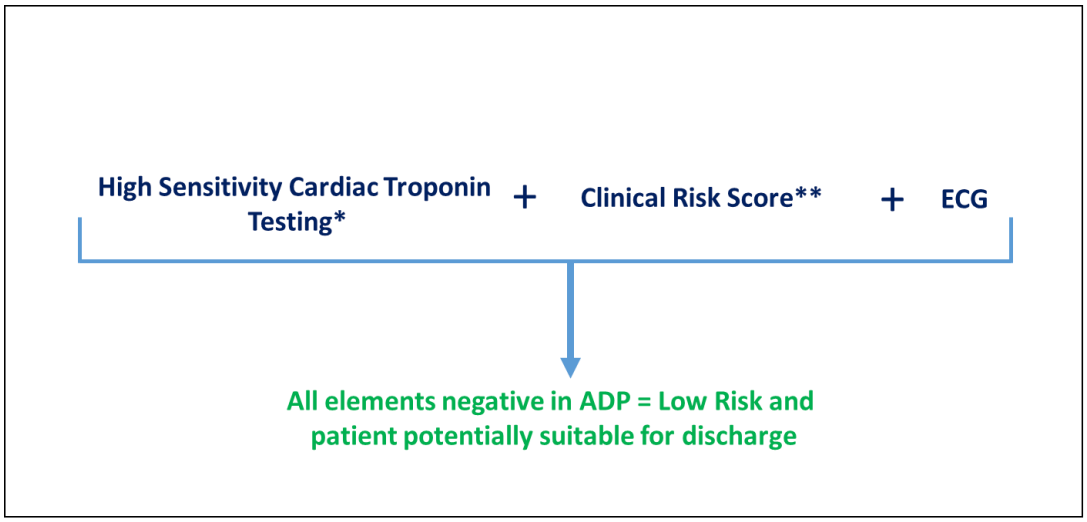
1.1 Background

Chest pain makes up a significant proportion of Emergency Department (ED) attendances. In fact, 6% of all presentations to UK EDs are due to chest pain which amounts to 700,000 patients per year UK-wide (Goodacre et al. 2005). Due to the potentially catastrophic consequences of missed Acute Myocardial Infarction (AMI) both medically and medico-legally, the majority of chest pain patients are admitted for further assessment. As a result, although 25% of all acute medical admissions to hospitals are due to chest pain, 85% are subsequently shown not to have a final diagnosis of a AMI (Pollack et al. 2006). Since each chest pain admission costs on average £2500 this has a huge impact on National Health Service resources (Oluboyede et al. 2008).

The author has developed a novel Accelerated Diagnostic Protocol (ADP) (Figure 1) for the assessment of patients with suspected cardiac chest pain that, if proven to be safe, will allow the early discharge of over 30% of patients after a single blood test at presentation. This pathway combines the use of an established risk-stratification tool and a sensitive biomarker of myocardial necrosis called high-sensitivity troponin (hs-cTn). The use of hs-cTn has been shown to be highly sensitive in the detection of AMI (Keller et al. 2009 and Reichlin et al. 2009) but whether it is also effective in rapid rule-out strategies that incorporate structured clinical assessment, has yet to be established. The TRUST study will investigate whether the ADP will enable early identification of low risk patients on the basis of a normal ECG, a low score on a questionnaire-based risk assessment tool (the modified Goldman Score) and a low hs-

cTn level taken within the first hour of arrival in the Emergency Department (ED). These patients are suitable for early discharge and do not need hospital admission. It is estimated that the TRUST ADP will demonstrate a safe reduction in the number of hospital admissions due to chest pain by 30%. This single-centre prospective observational cohort study has been designed to test the accuracy of the TRUST ADP in an acute hospital setting through analysis of AMI rates and 30 day major adverse cardiac events (MACE) in the study population.

Figure 1. The diagnostic elements of an Accelerated Diagnostic Protocol for the assessment of suspected cardiac chest pain.



**The TRUST Accelerated Diagnostic Protocol (ADP) uses a single high-sensitivity troponin result taken at presentation to the Emergency Department. Previous ADPs have used serial troponin testing over 2 hours (Cullen et al 2013)*
***The TRUST ADP uses the modified Goldman Risk Score (from Reilly et al. 2002)*
ECG: Electrocardiogram

The following discussion covers the evidence base behind each element of the TRUST ADP, cardiac troponin testing, clinical risk scores and ECG testing.

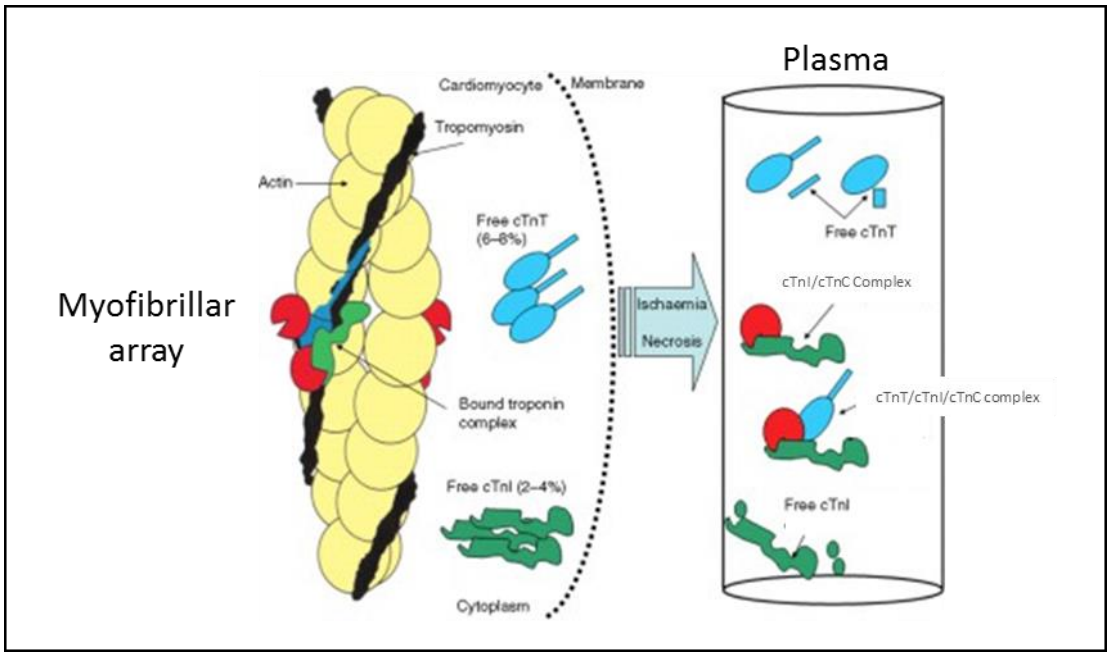
1.2 Cardiac Troponin Testing

1.2.1 Troponin: The Biomarker of Choice for the Detection of Myocardial Injury

Biomarkers that are released when myocardial necrosis occurs are needed to assist in the diagnosis of those AMIs that are not clinically obvious. Biomarkers in earlier use, such as creatinine kinase and myoglobin, are not specific to myocardial tissue, and this limits their clinical utility (Wu et al. 1999). Therefore cardiac troponin is currently the biomarker of choice for the detection of myocardial injury.

The troponin complex (cTnT, cTnI and cTnC), together with tropomysin, is located on the actin filament, and is essential for the calcium-mediated contraction of skeletal and cardiac muscle (Takeda et al. 2003). Because the cardiac isoform of troponin C is shared by slow-twitch skeletal muscles, troponin C does not have cardiac specificity and thus is not used in assays for the diagnosis of myocardial injury (Schreier et al. 1990). Cardiac troponins are largely bound into the myofibrillar array, although small amounts (<10%) are in a free cytosolic pool. Cardiomyocyte necrosis firstly releases the cytosolic pool, but as cardiomyocytes die further myofibrilar troponins are released (Apple and Collinson 2012) (Figure 2). As these assays specifically target cardiac troponins, they are extremely specific to necrosis of cardiac muscle (Korff et al. 2006).

Figure 2. The binding and subsequent release of cardiac troponin after ischaemic injury



cTnT/cTnI/cTnC: Cardiac troponin T/C/I complex

Image adapted from Gaze and Collinson 2008

The proportion of troponin that reaches the plasma after myocardial injury is greater for troponin than for earlier biomarkers, such as creatine kinase (Vatner et al. 1978). Katus et al. demonstrated (1991) that elevated troponin levels persist in the blood after myocardial injury. This prolonged window of troponin elevation leads increased detection of myocardial injury and enables use in a clinical environment.

1.2.2 Troponin and the Third Universal Definition of Myocardial Infarction

In 2000 AMI was redefined by an international consensus group as being a “rise and/or fall of cardiac biomarkers (preferably troponin)” with at least one value above the reference limit together with clinical evidence of myocardial ischaemia from symptoms, ECG, or cardiac imaging (Alpert et al. 2000). The reference limit is defined

as the 99th percentile of a sample of troponin levels from a normal population, i.e. the highest troponin levels normally detected.

The Third Universal Definition of Myocardial Infarction

Criteria for AMI:

BOTH of

- Rise and/or fall of troponin (or another cardiac biomarker)
    - One value must be above the 99th percentile reference limit
- Evidence of myocardial ischaemia from symptoms, ECG, or cardiac imaging.

After Thygesen et al. 2012a

The universal definition mandated the level of assay precision expected of troponin tests in terms of the degree of agreement between repeated tests at the reference limit (the coefficient of variation), but very few of the tests available at the time of the original definition were able to achieve this, which stimulated active development of improved tests (Jesse 2010). The limits of detection (see critical definitions below) of troponin assays have steadily improved during their development (Table 1). Early assays had a limit of detection of 500 nanograms per litre (then generally expressed as 0.5 micrograms per litre or nanograms per millilitre), and this threshold has fallen with successive generations of assays. The limit at which assays have an acceptable coefficient of variability has also fallen – so both assay threshold and accuracy have improved.

Critical definitions in the use of troponin assays:

99th Percentile Value:
Cut-off concentration used to discriminate myocardial necrosis. In laboratory medicine, the 99th percentile is typically determined from a normal, healthy population. This is usually the "positive/negative" cut-off used in clinical practice.

The Limit of Blank (LoB):
The highest apparent analyte concentration expected to be found when replicates of a blank sample containing no analyte are tested (Armbruster and Pry 2008).

The Limit of Detection (LoD):
The lowest analyte concentration likely to be reliably distinguished from the LoB at which detection is feasible (Armbruster and Pry 2008).

Coefficient of Variation (CV):
A measure of how consistently an assay is able to produce the same result on the same sample. A CV of 10% is the level of precision suggested for troponin assays.

Table 1. Classification of cardiac troponin assays

	Introduction into Clinical Practice	**Ability to measure cTn levels**	**Lower limit of detection (ng/L)**	**Detection in a normal reference population**	**Consensus Recommendations on Time to Testing**
1st Generation	Late 1980s	High abnormal only	500	<1%	12 hours
2nd Generation	Late 1990s	Abnormal only	100	<1%	12 hours
3rd Generation "Contemporary"	2000s	Abnormal to near-normal	50	1-2%	10-12 hours
4th Generation High-sensitivity	2010-2012	High-normal	1-3	>50%	3-6 hours
5th Generation Ultra-high sensitivity	In pre-clinical use	Normal levels	0.2	>95%	To be confirmed

After Jesse (2010) and Apple and Collinson (2012)

1.2.3 Characteristics of Troponin Assays

There is one cTnI isoform in myocardial tissue which has a significant dissimilarity in amino acid sequencing when compared to other isoforms. This dissimilarity has enabled the development of highly specific monoclonal antibodies to allow their detection in circulating plasma (Babuin and Jaffe 2005). Myocardial tissue contains four cTnT isoforms, but only one is characteristic of the normal adult human heart (Anderson et al. 1995). Highly specific antibodies have been made for this isoform. Patent restrictions mean that production of assays which detect the cTnT isoform are only available through one diagnostics company, (*Roche*, Switzerland) whereas numerous companies produce cTnI assays.

For all intents and purposes cTnI and cTnT provide comparable information with regards to myocardial injury (Babuin and Jaffe 2005). However, it must be recognized that there is huge variability in the sensitivity of the assays available, from various manufacturers, due to variation in epitope recognition by antibodies. Table 2a summarizes the analytical characteristics and target epitopes of troponin assays in common clinical and research use, declared by manufacturer. The 99th percentile cut-off value can be applied consistently across assays even if the assays change. For some assays there may be a need to alter the 99th centile value depending on race, age or sex (Apple and Murakami 2004 and Eggers et al. 2014)

Table 2a. Analytical characteristics of commonly used clinical and research troponin assays

Company/Platform/Assay	LoB (ng/L)	LoD (ng/L)	99th Percentile (ng/L)	10% CV (ng/L)	Epitopes recognized by assay antibodies
Abbott AxSYM ADV	20		40	160	C 87-91, 41-49; D 24-40
Abbott Architect	<10		28	32	C 87-91, 24-40; D: 41-49
Abbott Architect STAT hs-cTnI	0.7 – 1.3	1.1 – 1.9	26.2	4.7	C: 24-40; D: 41-49
Abbott i-STAT	20		80	100	C: 41-49, 88-91; D: 28-39, 62-78
Alere Triage Cardio 3	2	10	17	37	C: 27-39; D: 83-93, 190-196
Beckman Coulter Access Accu	10		40	60	C: 41-49; D: 24-40
bioMerieux Vidas Ultra	<10	<10	10	110	C: 41-49, 22-29; D: 87-91, 7B9
Mitsubishi PATHFAST cTnI-II	2	8	29	3.1	C: 41-49; D: 71-116, 163-209
Ortho VITROS Troponin I ES	7	12	34	34	C: 24-40, 41-49; D: 87-91
Radiometer AQT90 FLEX TnI		9.5	23	39	C: 41-49, 190-196; D: 137-149
Roche E 2010 /cobas e 411 / E 170 / cobas e 601 / 602 TnT (4th gen)	10			30	C: 125-131; D:136-147
Roche E 2010/cobas e 411 / E 170 / cobas e 601 / 602 hs-cTnT	3	5	14	13	C: 87-91, 190-196; D: 23-29, 27-43
Siemens ADVIA Centaur TnI-Ultra	6		40	30	C: 41-49, 87-91; D: 27-40
Singulex Erenna hs-cTnI*	0.09		10.1	0.88	C: 41-49; D: 27-41

**Research use only*

LoB: Level of Blank, LoD: Level of Detection, CV: Coefficient of Variation

Adapted from International Federation of Clinical Chemistry and Laboratory Medicine 2013

1.2.4 High-Sensitivity Troponin

The previously limited ability of troponin assay to detect low levels of troponin circulating in the blood resulted in the need to wait for the release of reliably detectable levels after chest pain onset. Accordingly it has not been possible to safely rule-out AMI until 10-12 hours after onset of the patient's worst pain (National Institute for Health and Care Excellence (NICE) 2010) and this has resulted in large resource expenditures in many hospitals as large numbers of patients occupy beds whilst they wait for troponin results (Hwang et al. 2010).

Time and performance pressures have stimulated development of a new generation of assays called high-sensitivity troponin (hs-cTn). Hs-cTn assays demonstrate normal levels of circulating troponin, such that they can detect troponin in over 50% of normal people (Giannitsis et al. 2010 and Thygesen et al. 2012b) and in even higher proportions of those with risk factors or chronic coronary disease (Reiter et al. 2011 and Saunders et al. 2011). The ability to detect much lower levels of troponin allows for testing at earlier time points and opens up a range of possibilities for use in early rule-out of AMI.

The one hs-cTnT assay which is available (Roche Elecsys Troponin T high-sensitivity) has a coefficient of variation of 9% at 14ng/L, which is below its 99th centile and thus it meets the Universal Definition of myocardial infarction criteria (Thygesen et al. 2012a). The upper limit of normal (99th centile) in a reference healthy population of blood donors, is 14ng/L (Giannitsis et al 2010).

While many manufacturers supply cTnI assays, in 2014 NICE determined that only the Abbott Architect STAT hs-cTnI assay fulfilled the definition of a high-sensitivity assay. The current high-sensitivity assays available and their performance characteristics are summarized in Table 2b.

A recent study has suggested that hs-cTnI may have a better ability to identify patients with higher cardiovascular risk than hs-cTnT (Omland et al. 2013). Both hs-cTnT and hs-cTnI have been tested in the acute clinical situation but their performance characteristics in this patient group remains poorly understood (Hoeller et al. 2013).

Table 2b. Analytical characteristics of commercially available (U.K. 2015) high-sensitivity troponin assays

Manufacturer	Name	Assay	99th percentile value	Coefficient of variation at 99th centile value	Laboratory turnaround time
Roche	Elecsys	hs-cTnT	14ng/L	<10%	18 minutes
Abbott	Architect	hs-cTnI	26.2ng/L	4%	16 minutes

Adapted from NICE 2014

1.2.5 High-Sensitivity Troponin: Ruling-in Acute Myocardial Infarction

While the focus of the TRUST study is on the early rule-out of AMI, an important area that must be discussed are the implications that high-sensitivity assays may have for the adjudication of major adverse cardiac events, and more specifically AMI, both within the context of a research study and in clinical practice.

Although cardiac troponin is by definition completely specific for myocardial injury it is not specific for the diagnosis of AMI. This leads to a problem for hs-cTn where specificity has been reported to be 80-85% in comparison to figures of 97% for earlier

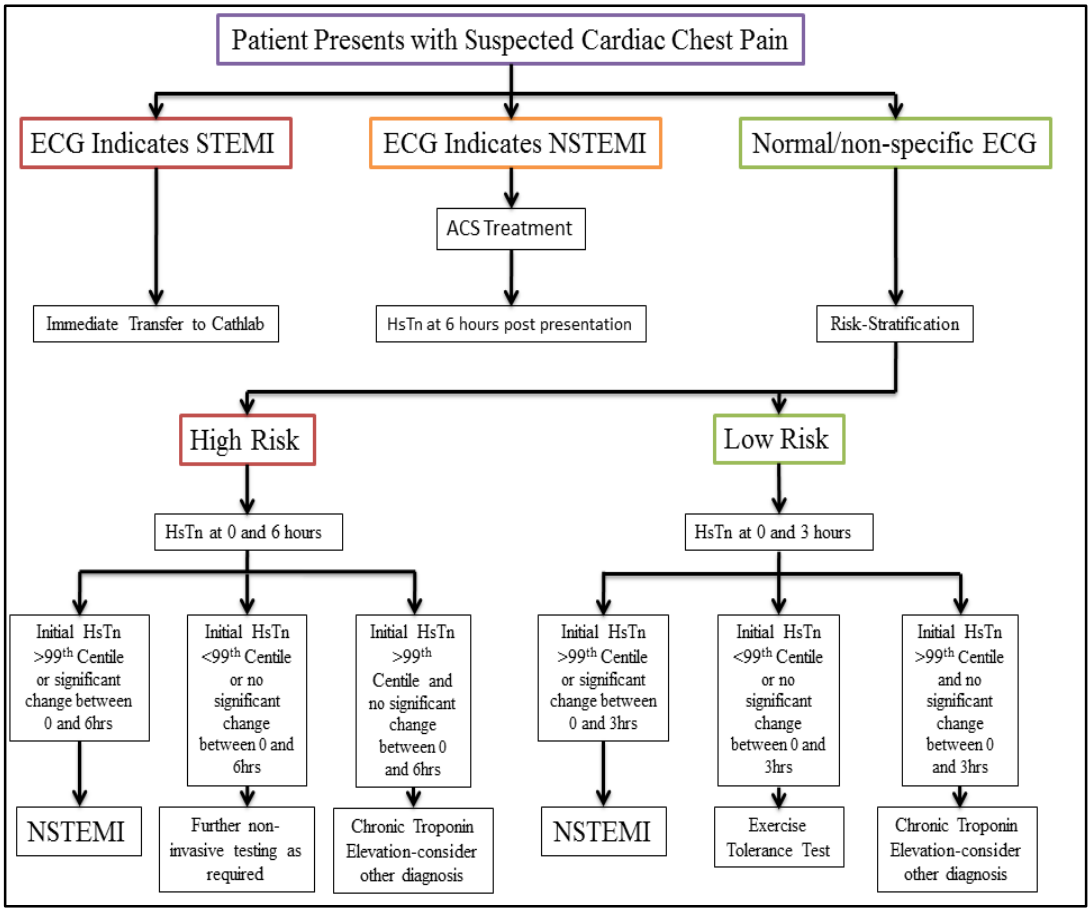
generation troponins (Reichlin et al. 2009). This may have considerable impact on the utility of hs-cTn testing, as higher false-positive rates may lead to unnecessary subsequent invasive investigations, such as angiography, and misdiagnosis. However these lower specificities are based upon hs-cTn testing at much earlier time points and under-estimate the specificity of hs-cTn. In fact Aldous et al. (2011a), demonstrated that if early hs-cTn testing is assessed against diagnoses made on the basis of serial hs-cTn testing, specificity is improved to 92%.

Also, the issue of lower diagnostic specificity may not be relevant in clinical practice and conversely the implementation of an hs-cTn assay has been demonstrated by Mills et al. (2011) to increase the proportion of patients diagnosed with AMI and identify patients at high risk of recurrent AMI or death, while lowering the diagnostic threshold of the plasma concentration of hs-cTn was associated with major reductions in morbidity and mortality.

Despite taking these points into account the lower specificity of hs-cTn testing remains a limitation in accurately diagnosing AMI. To improve this, serial sampling is required – which is in fact necessary to satisfy the agreed criteria for a diagnosis of AMI. The Universal Definition (Thygesen et al. 2012a) requires a *change* in troponin to be detected, although this has been frequently ignored in clinical practice, perhaps due to unwanted complexity or lack of general understanding of this concept. Sampling hs-cTn at admission and then a later time point allows calculation of the change between the two samples (known as the “delta” value). If this is small it is considered to be a product of analytical or biological variation, whereas larger changes represent continuing troponin leak from damaged cells and hence suggest an AMI.

The extent of change in troponin levels required to diagnose an AMI is recommended by the European Society of Cardiology (Thygesen et al. 2012b) guidance as over a 20% relative change (in those patients with an elevated initial hs-cTn). However this figure of 20% is based on research using older troponin assays, and although it is widely quoted in guidelines, there is evidence that in particular for hs-cTnT testing an absolute change of 9.2ng/L provides better discrimination (Mueller et al. 2012), but this remains experimental. Figure 3 is a suggested clinical pathway incorporating serial hs-cTn testing for the diagnosis of AMI.

Figure 3. Clinical use of high-sensitivity troponin testing – a suggested framework



Note that excluding AMI does not exclude unstable angina or ischaemic heart disease
ECG: Electrocardiogram, STEMI: ST-elevation Myocardial Infarction, NSTEMI: Non-ST segment elevation Myocardial Infarction, ACS: Acute Coronary Syndrome, HsTn: High-sensitivity troponin
After Collinson 2011

Many clinicians will agree that there is a problem in daily practice whereby any abnormal troponin result is automatically assumed to represent an AMI. This problem will potentially worsen as our ability to detect much lower levels of troponin increases. Hs-cTn is detectable in the majority of unwell patients, which reflects low-level myocardial injury rather than myocardial infarction (Rosjo et al. 2011). Elevated levels often represent myocardial injury induced by numerous acute non-cardiac disease, such as pulmonary embolism, subarachnoid haemorrhage or renal failure (Newby et al, 2012). In some cases, troponin release will be due to a mismatch between myocardial blood supply and demand, or injuries not related to ischaemia, resulting in a "Type 2 AMI" (Table 3). Table 4 summarises the expected degree of hs-cTn elevation for the Abbott and Roche hs-cTn assays according to possible diagnoses.

Table 3. Causes of elevations of cardiac troponin due to myocardial injury and Type 2 acute myocardial infarction

Type 1 Acute Myocardial Infarction: Injury related to primary myocardial ischaemia
Atherosclerotic plaque rupture Intraluminal coronary artery thrombus formation
Type 2 Acute Myocardial Infarction
Injury related to supply/demand imbalance of myocardial ischaemia
Tachy-/brady-arrhythmias Aortic dissection or severe aortic valve disease Hypertrophic cardiomyopathy Cardiogenic, hypovolaemic, or septic shock Severe respiratory failure Severe anaemia Hypertension with or without LVH Coronary spasm Coronary embolism or vasculitis Coronary endothelial dysfunction without significant coronary artery disease
Injury not related to myocardial ischaemia
Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks Rhabdomyolysis with cardiac involvement Myocarditis Cardiotoxic agents, e.g. anthracyclines, Herceptin
Multifactorial or indeterminate myocardial injury
Heart failure Stress (Takotsubo) cardiomyopathy Severe pulmonary embolism or pulmonary hypertension Sepsis and critically ill patients Renal failure Severe acute neurological diseases, e.g. stroke, subarachnoid haemorrhage Infiltrative diseases, e.g. amyloidosis, sarcoidosis Strenuous exercise

Adapted from Thygesen et al. 2012b

Table 4. The expected degree of elevation for the Abbott and Roche hs-cTn assays according to underlying diagnosis

Level	Abbott Architect Hs-cTnI ng/L	Roche Elecsys Hs-cTnT ng/L	Possible Diagnoses
	>1000	>10000	Large AMI/Severe Myocarditis
	500	1000	Medium AMI, PE, Takotsubo, Critical Illness
	100	100	Small AMI, myocarditis, sepsis, PE, subarachnoid, chronic renal failure
	50	14-30	Micro AMI, myocarditis, congestive cardiac failure, sepsis, PE, subarachnoid, chronic renal failure
99th Percentile Value	<26.2	<14	Stable Angina, LVH, subclinical heart disease, old age, comorbidities
Level of Detection	<1.9	<5	Healthy Patient

Hs-cTn: High-sensitivity cardiac troponin, AMI: Acute Myocardial Infarction, PE: Pulmonary Emebolism, LVH: Left Ventricular Hypertrophy

Adapted from Agewall et al. 2011

Even when hs-cTn elevation is not caused by AMI, it still provides important information. In every condition in which it has been assessed, elevated troponin levels correlate with an adverse prognosis. Examples would include heart failure (Nagarajan et al. 2012), atrial fibrillation (Van den Bos et al. 2011), pulmonary embolism (Lankeit et al, 2011) and chronic obstructive pulmonary disease (Hoiseth et al. 2011). These findings are not confined to acute illness but also apply to chronic stable disease. For example, in stable outpatients with risk factors for coronary disease, the level of hs-cTnT detected in stored blood samples correlated closely with prognosis, with the

highest risk group, who had hs-cTnT of over 14ng/L, having a four times higher risk of death over a mean follow up period of 9.4 years (Omland et al. 2013).

The use of hs-cTn assays has important implications in the diagnosis of acute myocardial infarction and both clinicians and researchers must be aware of the diagnostic criteria for AMI and the other possible cause of hs-cTn elevation.

1.2.6 High-Sensitivity Troponin: The Early Rule-Out of Acute Myocardial Infarction

The key concept in the TRUST study is the ability of a single presentation high-sensitivity troponin to allow safe discharge of patients presenting to the ED with chest pain. Time pressures, ED crowding and the high frequency with which patients present with suspected cardiac chest pain has led to the development and testing of numerous strategies that attempt to assist with the early rule-out of AMI. The advent of hs-cTn assays has allowed researchers to utilize the exquisitely sensitive properties of these assays to try to develop strategies that allow rule-out of AMI earlier in patient presentation safely, these are discussed below.

The 99th Percentile Value at Presentation

Multiple observational studies (Table 5) have demonstrated that a single hs-cTnT result of below the 99th percentile value at presentation has an inadequate sensitivity to rule-out AMI (Range 83.3%-95%). However, sensitivities improve over the hours following presentation to somewhere approaching 100% at 3 hours, enabling the strategy of testing at admission and at 3 hours after admission advocated by the European Society of Cardiology (Thygesen et al. 2012b).

Table 5. Published papers demonstrating the ability of hs-cTnT to rule-out AMI when tested at presentation using the 99th percentile value (14ng/L)

Author/year	Study Design	N	Admission Sensitivity (95% CI)	Admission Negative Predictive Value (95% CI)	End-point	Critique
Reichlin et al. 2009	Prospective Multi-center Observational	718	95% (90-98)	99% (97-100)	AMI	Blanket testing of all ED patients- including those with ECG abnormalities
Aldous et al. 2011	Prospective Single-center Observational	332	83.6% (77.4-88.6)	91.2% (87.8-93.9)	AMI	Only 23% of patients recruited who fulfilled inclusion criteria
Body et al. 2011	Prospective Single-Center Observational	703	85.4% (78.1-91)	96.1 (94.0-97.7)	AMI	Samples tested had been frozen for 2.5 years
Aldous et al. 2012b	Prospective Single-center Observational	939	88.3% (83.3-91.8)	96.2% (94.7-97.3)	1. Diagnosis of NSTEMI on admission 2. 1 year MACE	Convenience sampling resulted in high-risk population studied
Aldous et al. 2012a	Prospective Single-center Observational	385	90.7% (82.9-94.8)	97.0% (94.6-98.5)	AMI	Only 40% of patients recruited who fulfilled inclusion criteria
Hoeller et al.2014	Prospective Multi-center Observational	2072	89.6% (86.4-92.3)	96.5 (95.4-97.4)	AMI	AMI adjudicated using the research assay

AMI: Acute Myocardial Infarction, NSTEMI: Non-ST segment Elevation Myocardial Infarction, MACE: Major Adverse Cardiac Events, ED: Emergency Department, ECG: Electrocardiogram

Undetectable High-Sensitivity Troponin at Presentation to ED

Strategies that utilize a high-sensitivity troponin level of below the level of detection (LoD) taken at presentation to the ED have been explored and give promise as a discharge tool. Several studies have demonstrated that it may be possible to exclude AMI on arrival if patients have an ECG with no evidence of cardiac ischaemia and the initial hs-cTnT result is undetectable. Both the level of blank (LoB), and the level of detection (LoD), have been used as thresholds to define detectability.

In 2014, NICE produced a guidance statement regarding the clinical use of high sensitivity troponin assays. In the systematic review that informed the guidelines, 14 studies reported accuracy of hs-cTnT for the detection of acute MI on single samples taken at presentation. Five of these studies used diagnostic thresholds equivalent to the LoB and LoD (Body et al. 2011, Aldous et al. 2011a, Reiter et al. 2011, Aldous et al. 2012b and Hoeller et al. 2013). Two studies that described the LoD reported a summary estimate for using the LoD threshold of 5ng/L at 95% (95% CI 92% to 97%) sensitivity for AMI (Aldous et al. 2012b and Aldous et al. 2011a). The three studies reporting the LoB (3ng/L) had a 98% (95% CI 95% to 99%) sensitivity for AMI. These studies were published near the time of the release of a technical bulletin recommending recalibration of the hs-cTnT assay (Kuster et al. 2013). Unfortunately, only one (Hoeller et al. 2013) out of five hs-cTnT studies used in the NICE guidance address this issue directly. The results of at least some of the other studies were affected by this need for recalibration. Calibration issues also apply to the hs-cTnT assay batch being used at the time of the cohort studied by Bandstein et al. (2014) which may have contributed to the very high numbers of hs-cTnT results reported as below 5ng/l. It should also be noted that

variation between batches is a recognised phenomenon and that such variation may be especially important at low levels of detection at which there is decreased analytical reproducibility. This may limit the on-going reliability of this diagnostic strategy using future batches of hs-cTnT.

Through informal collaboration with worldwide researchers in the field, unpublished data from a worldwide validation of the LoD strategy in 6275 chest pain patients, has been obtained. In this cohort the index test strategy (no ischaemic changes on initial ECG and presentation hs-cTnT < 5ng/L) classified 11.4% to 73.5% as being at low-risk for AMI (Table 6). The negative predictive value for this strategy varied from 98.9% (95% confidence interval 97.7% to 99.5%) to 100% (98.3% to 100%). Peer review and publication of these results is eagerly anticipated.

Table 6. Unpublished data from an informal international collaborative examining the diagnostic utility of a presentation hs-cTnT of <5ng/L (LoD) and non-ischaemic ECG for AMI in 6275 ED chest pain patients

Reference	Study	Sensitivity	Specificity	NPV	PPV	Proportion defined as Low Risk	Prevalence of AMI
Collinson et al. 2012	RATPAC	89.6 %	79.0 %	98.9 %	27.1 %	73.5%	8.0%
Than et al. 2012a	ADAPT-Brisbane	98.5 %	35.2 %	99.6 %	11.7 %	32.5%	8.1%
Body et al. 2011	Manchester	100 %	40.5 %	100 %	27.6 %	33.0%	18.5%
Rubini Giminez et al. 2013	APACE	99.8 %	28.0 %	99.8 %	26.6 %	22.2%	20.8%
Than et al. 2012a	ADAPT-Christchurch	99.6 %	14.8 %	99.2 %	26.3 %	11.4%	23.4%

NPV: Negative Predictive Value, PPV: Positive Predictive Value, AMI: Acute Myocardial Infarction, RATPAC: Randomised Assessment of Treatment using Panel Assay of Cardiac markers, ADAPT: Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Troponin, APACE: Advantageous Predictors of Acute Coronary Syndromes Evaluation

Data kindly provided by Prof Martin Than, January 2015

While it is undeniable that undetectable hs-cTn troponin strategies hold promise, currently, as a result of batch variation and inaccuracy of measurement at low levels, expert consensus (Thygesen et al. 2012 and NICE 2014) suggests that levels below the LoD and LoB should not be reported or used in clinical practice.

Early Rule-Out Strategies Utilizing Troponin Change over Time

An algorithm developed by Reichlin et al. in 2012 used a presentation hs-cTnT level lower than 12ng/L and an absolute change within an hour of less than 3ng/L, and allowed AMI to be ruled-out with 100% sensitivity in 1 hour using only these two samples in 77% of patients. Carlton et al. (2012) identifies two fundamental flaws with the study methodology which may impact this algorithm's applicability. Firstly, a large cohort of high-risk patients were excluded prior to analysis and convenience sampling was undertaken, both of which may lead to selection bias. Secondly, due to laboratory turnaround times and staff availability it may be questionable whether a 1-hour sampling strategy is feasible outside of a research environment. Publication and external and multicenter validation of this strategy is anticipated.

The use of a single hs-cTn for the rule out of AMI at presentation to the ED would be cost-effective, as suggested by Thokala et al. (2012) but as yet evidence that it's use may be unsafe remains unequivocal (Shah et al. 2013). The TRUST Study explores a novel approach to using a single hs-cTn result at presentation to the ED.

1.3 Clinical Risk Assessment-The Chest Pain History

Chest pain history remains the cornerstone of clinical assessment in patients with suspected ACS, complemented by electrocardiogram (ECG) and the results of cardiac troponin testing (Panju et al. 1998 and Amsterdam et al. 2010). A proportion of patients will have a non-diagnostic ECG (Panju et al. 1998) and the results of troponin testing may not be immediately available, therefore ED physicians are reliant upon chest pain history to make rapid management decisions.

It is well recognized that typical features provide useful diagnostic and prognostic information in patients with stable coronary artery disease (Diamond and Forrester, 1979, Pryor et al. 1993 and Genders et al. 2011). Yet, in the acute population the widely held assertion that these typical features can be used to identify high-risk patients has come into question (Goodacre 2002, Henrikson et al. 2003, Chun and McGee 2004, Swap and Nagurney 2005, Goodacre et al. 2009b, Body et al. 2010, Greenslade et al. 2012 and Rubini-Gimenez et al. 2014). Despite this, both American Heart Association (AHA) (Jneid et al. 2012) and European Society of Cardiology (ESC) (Hamm et al. 2011) guidelines for patients presenting to the ED with suspected ACS advocate the use of typical features. For example, AHA guidelines suggest that "chest or left arm pain or discomfort as the chief symptom reproducing prior documented angina" is associated with a high likelihood of ACS. Whilst the European Society of Cardiology (ESC) guidelines state that "the typical clinical presentation of (non-ST elevation) ACS is retrosternal pressure or heaviness radiating to the left arm, neck or jaw" and that "symptoms occurring at rest have a worse prognosis." Conversely, chest pain features that do not fall into the typical category have been termed "atypical."

However authors and clinicians often disagree on the definition of atypical chest pain, making its use potentially confusing (Swap and Nagurney 2005).

While it is evident that certain features of chest pain history may change the probability that a patient may or may not have an AMI (Table 7), ruling out an acute cardiac cause in an individual presenting with chest pain from the history alone is almost impossible. Add to this the wide differential of possible causes of chest pain, which includes the pulmonary, musculoskeletal, gastrointestinal, dermatologic, psychiatric and cardiovascular systems (Spalding 2003) and the task for the diagnosing emergency physician becomes even harder. So what features of the chest pain history are useful to the ED physician who wishes to rule-out AMI?

Table 7. Value of specific components of the chest pain history for the diagnosis of acute myocardial infarction

Pain Descriptor	Reference	Number of Patients	Positive Likelihood Ratio* (95% CI)
Increased Likelihood of Acute Myocardial Infarction			
Radiation to the Right arm or Shoulder	Chun and McGee 2004	770	4.7 (1.9-12)
Radiation to both arms or shoulders	Goodacre 2002	893	4.1 (2.5-6.5)
Associated with Exertion	Goodacre 2002	893	2.4 (1.5-3.8)
Radiation to the Left arm	Panju 1998	278	2.3 (1.7-3.1)
Associated with sweating/diaphoresis	Panju 1998	8426	2.0 (1.9-2.2)
Associated with nausea and vomiting	Panju 1998	970	1.9 (1.7-2.3)
Worse than previous angina or similar to previous MI	Chun and McGee 2004	7734	1.8 (1.6-2.0)
Decreased Likelihood of Acute Myocardial Infarction			
Described as Pleuritic	Chun and McGee 2004	8822	0.2 (0.1-0.3)
Described as positional	Chun and McGee 2004	8330	0.3 (0.2-0.5)
Described as sharp	Chun and McGee 2004	1088	0.3 (0.2-0.5)
Reproducible with palpation	Chun and McGee 2004	8822	0.3 (0.2-0.4)
Not associated with exertion	Goodacre 2002	893	0.8 (0.6-0.9)

**The likelihood ratio (LR) estimates the diagnostic value of each piece of information. The higher the LR is above 1 the more useful the finding is for ruling in AMI. The lower the LR below 1 the more useful the finding is for ruling out AMI. 95% CI: 95% Confidence Interval.*

1.3.1 Pain Quality

Traditional teaching dictates that chest pain described as pressure or aching is indicative of chest pain of cardiac origin. However, meta-analysis by Panju et al. (1998), Chun and McGee (2004) and Swap and Nagurney (2005) consistently demonstrate that these typical features of pain are not independently useful in ruling-in an AMI.

What may be more useful is the presence of atypical qualities. Pain described as sharp or stabbing significantly decreases the likelihood of chest pain representing an AMI (Body et al. 2010) though may make other important diagnosis such as pulmonary embolism more likely (Kline and Stubblefield 2013). However, this finding may also be subject to cultural and ethnic differences (Greenslade et al. 2012).

Significantly, pain described as similar, or worse than a previous ischaemia has been consistently demonstrated to be a useful predictor for AMI (Goldman et al. 1988 and Chun and McGee 2004). This quality also shows excellent inter-observer variability with a kappa score of 0.92/absolute agreement of 97%, albeit in a study with only 38 independent ratings (Body et al. 2010).

1.3.2 Pain Location

Few studies have examined the location of chest pain as a predictor for AMI. Everts et al. (1997) concluded that the localisation of chest pain to the centre or left of the chest had limited use in predicting AMI in a Coronary Care population. However, more recently, Body et al. (2010) found in an undifferentiated ED population that patients with central chest pain were more likely to be having an AMI compared to those with left anterior chest pain.

1.3.3 Radiation

Radiation is the term that describes pain originating in the chest but moving to non-chest areas such as the arms, shoulder, jaw/throat and back. Radiation has consistently been found to be a useful positive predictor for AMI in multiple studies (Panju et al. 1998, Goodacre et al. 2002, Chun and McGee 2004 and Body et al. 2010). However, contrary to traditional teaching (Silverman 1987) and media campaigns (British Heart Foundation 2014) radiation of pain down solely the right arm may be a more useful predictor than the left in the undifferentiated ED population (Berger et al. 1990 and Body et al. 2010). A possible explanation for this may be the impact of public health campaigns (British Heart Foundation 2014) meaning that patients will attend with any pain in the left arm due to the concern for "heart attack", whereas they will only attend with right arm pain under exceptional circumstances (Goodacre et al. 2009b) .

Mackay et al. (2011) used percutaneous coronary intervention balloon inflation as a model of myocardial ischaemia and concluded that women were more likely to report radiation to the throat/jaw (OR 2.91; 95% CI 1.58-5.37). However gender-specific variations are not large enough to be of clinical use when tested in the undifferentiated ED population (Canto et al. 2007).

1.3.4 Severity

Mandated pain scales have been shown to improve the frequency of ED analgesic administration for a variety of conditions (Nelson et al. 2004) however, there appears to be no prognostic significance in the severity of chest pain in predicting the likelihood of AMI (Edwards et al. 2011).

1.3.5 Duration of Pain

UK National Institute for Health and Care Excellence (NICE 2010) Chest pain of recent onset guidance states that pain lasting longer than 15 minutes is suggestive of an acute coronary syndrome, however, there remains a paucity of data to support this. Goldman et al. (1996) reported that pain of longer duration than previous angina is predictive of adverse cardiac events however no lower or upper time limit is defined. Importantly however, Goodacre et al. (2009b) illustrated that patients with an ACS were more likely to have a longer duration of pain (Mean 53.6 minutes) compared to those without ACS (P=0.03). Body et al. (2010) found that pain of greater than 60 minutes duration had a sensitivity of 77% for AMI. Evidence remains limited with regards to the significance of prolonged pain and requires further exploration.

1.3.6 Associated Features

Symptoms such as nausea, vomiting and sweating (diaphoresis) have been shown to be predictive of AMI in two meta-analyses (Chun and McGee 2004 and Panju et al. 1998). Body at al. (2010) demonstrated that the most exquisite sign for the rule-in of AMI was if sweating was observed by the ED clinician, with a specificity of 94.3% and positive LR of 6.39, however this finding is yet to be validated.

1.3.7 Risk Factors for Chronic Coronary Disease

Since the Framingham Heart Study (Kannel et al. 1978) physicians have used risk factors for development of chronic cardiac disease to empirically establish cardiovascular risk in those patients presenting with acute chest pain. These markers include hypertension, hyperlipidaemia (Csastelli and Anderson 1986), tobacco smoking (Doyle et al. 1988), diabetes mellitus (Kannel and McGee 1979) and family history

(Myers et al. 1990). However their utility for predicting the presence of acute events in patients presenting to the ED may come into question.

Jayes et al. (1992) demonstrated in a large epidemiological cohort study, that in women, the presence of classical risk factors does not increase the risk of acute ischaemia. In men, only family history and diabetes were of any value (relative risks 2.1 and 2.4 respectively). This work was supported by that of Han et al. (2007) albeit through retrospective registry analysis, who concluded that cardiac risk factor burden had limited clinical value in diagnosing acute coronary syndromes in the ED.

Most recently Body et al. (2008) prospectively examined the risk factor burden of ED patients presenting with suspected cardiac chest pain compared to the final diagnosis of MI. Although limited by small study numbers, there was no trend towards increasing incidence of MI with increasing numbers of risk factors. The authors concluded that risk factor burden is not useful in the diagnosis or exclusion of AMI in ED patients.

The presence or absence of certain clinical features in the context of chest pain may be used to shift the pre-test probability of an acute coronary syndrome being present. No single clinical finding can be used to confirm or exclude AMI. However, when used in combination, or with other diagnostic tools, such as the ECG and biomarkers, clinical features may be used to direct further testing (Goldman et al. 1996) or identify those suitable for early discharge (Than et al. 2011, Than et al. 2012a and Cullen et al. 2013). By combining clinical features with ECG and cardiac biomarkers the concept of the clinical decision rule or accelerated diagnostic pathway (ADP) has been developed.

1.4 Clinical Risk Scores

Accelerated diagnostic protocols (ADPs) are tools designed to be used at the bedside to assist rapid physician decision making, they may also be described as clinical decision rules (McGinn et al. 2000). They are derived from original research and incorporate variables from the history, physical examination and basic laboratory tests (Stiell and Wells 1999). Since Pozen et al. (1980) researchers have been refining decision rules for use in the assessment of suspected cardiac chest pain, in order to improve service quality, ED efficiency and overcrowding (Steurer et al. 2010). These rules use a varying combination of history and examination findings, ECG and biomarker testing to identify those patients at low risk of major adverse cardiac events (MACE-serious outcomes that emergency physicians would wish to avoid after discharge), who may be suitable for early discharge or to identify those at higher risk who may benefit from early aggressive intervention.

Major Adverse Cardiac Events (MACE)

Serious outcomes that Emergency Physicians would wish to avoid following discharge from the Emergency Department.

MACE include: death, cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia or high-degree atrioventricular block needing intervention, and acute myocardial infarction (Cullen et al. 2010).

A persistent concern in the assessment of patients presenting with suspected cardiac chest pain is the diagnosis of unstable angina and it is these patients that may drive the development of ADPs. By definition, patients with unstable angina will not have a troponin rise and as such their rule-out is a clinical diagnosis (Keller et al. 2009 and Korley and Jaffe 2013). From a prognostic perspective at least some of these patients benefit from early intervention and are at a higher risk of adverse events (Hamm et al. 2011). It seems that the vital factor in assessing troponin results is tying this information closely to the clinical assessment of the patient. Yet, data is critically needed to establish the optimal methods of integrating clinical prediction rules and early troponin testing into emergency department clinical practice (Thygesen et al. 2012b).

1.4.1 Methodological Standards for the Development of Clinical Decision Rules

Laupacis et al. (1997) and Stiell and Wells (1999) summarized the methodological standards for the development and validation of clinical decision rules; these may be summarized as follows:

1) The outcome or diagnosis to be predicted should be clearly defined and the assessment of this outcome should be blinded.

2) The clinical findings to be used as predictors must be clearly defined and standardized and their assessment must be done without knowledge of the outcome.

3) The reliability or reproducibility of the clinical findings must be demonstrated.

4) The subjects should be selected without bias and should represent a wide spectrum

of clinical and demographic characteristics to increase generalizability of results.

5) The mathematical techniques for deriving the rule must be identified.

6) Clinical decision rules should be sensible.

7) The accuracy of the decision rule in classifying patients with (sensitivity) and without (specificity) the targeted outcome should be demonstrated.

8) Prospective validation on a new set of patients is an essential test of accuracy as misclassification is commonly higher when decision rules are tested on a population other than derivation set.

9) Implementation to demonstrate a true effect on patient care is the ultimate test of a clinical decision rule.

Both Hess et al. (2008) and Steurer et al. (2010) in systematic reviews of the available literature concluded that prediction rules for chest pain had substantial methodological flaws, had not been successfully implemented in a clinical setting and did not fulfil the safety requirements for physicians, limiting their role in the rapid rule-out of AMI. However risk prediction rules have been shown to aid clinicians in prioritising patients for investigations (Reilly et al. 2002) and identify those patients at higher risk who may benefit from invasive strategies (Goldman et al. 1996 and Pollack et al. 2006).

Although expert consensus (Thygesen et al. 2012b) and national guidelines (NICE 2010) suggest that formal risk stratification and risk scores aid in the assessment of suspected cardiac chest pain and should be implemented in clinical practice there is no consensus as to which risk score should be used in the ED.

1.4.2 Selecting a Risk Score for the TRUST Study

The Original Goldman Rule

In 1996 Goldman et al. described the derivation and validation of a straightforward clinical approach to assessing the risk of major adverse events at 72 hours in patients presenting to the emergency department with suspected cardiac chest pain. This group used recursive partitioning to assess the ability of 50 predictive variables from history, examination and ECG to discriminate between patients with adverse events and those without adverse events in a cohort of 10,682 North American patients.

Goldman identified older age, male sex, description of pain as the same as previous myocardial infarction or worse than prior angina, systolic blood pressure below 100 mmHg, rales above the bases on clinical examination of the chest and initial ECG changes suggestive of acute myocardial infarction as factors associated with MACE (Table 8).

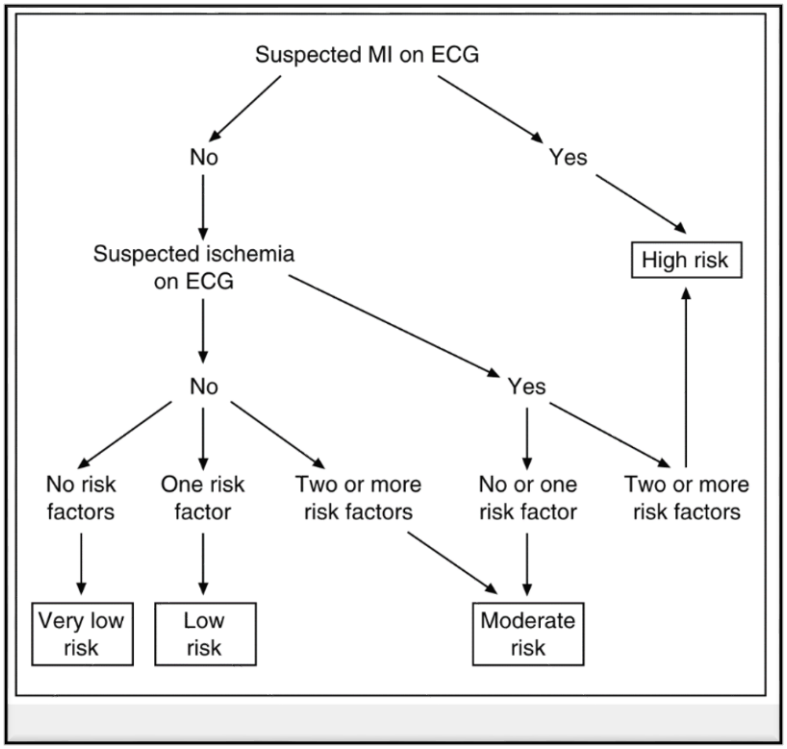
Table 8. Factors which act as positive predictors for major adverse cardiac events included in the Goldman rule

Factors at presentation	Derivation Set (N=10,682) Relative Risk (95%CI)	Validation Set (N=4656) Relative Risk (95%CI)
Age ≥60 years	1.9 (1.5-2.4)	2.2 (1.4-3.4)
Male Sex	1.7 (1.4-2.1)	1.6 (1.2-2.3)
Pain same as previous myocardial infarction or worsening angina	2.8 (2.3-3.4)	4.2 (3.1-5.7)
Systolic Blood Pressure <100	5.0 (3.6-7.1)	2.0 (1.0-3.9)
Rales above bases	4.5 (3.4-5.9)	3.3 (1.9-5.6)
ECG abnormalities (ST depression or T wave inversion not known to be old)	6.8 (5.4-8.6)	5.1 (3.6-7.3)

Adapted from Goldman et al. 1996

Through consideration of the factors present at presentation to the ED, Goldman was able to define 4 separate risk groups which accurately predicted MACE in an independent validation set of 4656 patients (Figure 4 and Table 9):

Figure 4. Goldman risk stratification on the basis of data available at time of presentation to the Emergency Department



Risk factors included systolic blood pressure < 100mmHg, rales heard above lung bases on physical examination, and known unstable ischaemic heart disease, defined as worsening of previously stable angina, new onset of post-infarction angina, or pain the same as previous myocardial infarction ***Reproduced from Goldman et al. 1996***

Table 9. Rate of major adverse cardiac events at 72 hours according to Goldman level of risk at presentation to the Emergency Department

	Percentage of Major Adverse Cardiac Events at 72 Hours	
Risk	**Derivation**	**Validation**
High	21.5	16.1
Moderate	8.1	7.8
Low	3.6	3.9
Very Low	0.8	0.6

Adapted from Goldman et al. 1996.

The exquisite derivation of four separate risk groups enabled Goldman et al. to conclude that this approach to risk-stratification would enable a rationalisation of the use of inpatient hospital facilities, however they did not explore its use in the early discharge of patients from the Emergency Department.

Further analysis into the use of the Goldman strategy and its impact on physician decision making was undertaken by Reilly et al. in 2002. At this time modifications were made to Goldman's original rule. Reilly explored the safety and efficiency of a modified Goldman (m-Goldman) rule by establishing firstly the proportion of patients with MACE admitted to inpatient cardiac care beds and secondly the proportion of patients without major complications who were triaged to an ED observation unit, in a prospective before-after impact analysis conducted at a large, urban US public hospital. The intervention group included over 1000 patients in whom the diagnosis of acute cardiac ischaemia remained possible after evaluation by the ED physician.

Reilly et al. demonstrated a reduction in inappropriate admission to intensive inpatient settings, using the m-Goldman criteria, of 15% (95% CI 8-21%, $p<0.001$) without a reduction in safety (difference 5%, 95% CI -11%-39%, $p=0.57$). However, sample numbers were not large enough to detect differences in events between pre-intervention and intervention groups. Importantly, rates of MACE at 72 hours were similar to those illustrated by Goldman et al. (1996). Table 10 compares the proportions of patients in each risk category according to Goldman et al. (1996) and Reilly et al. (2002).

Table 10. A comparison of the proportion of patients in each of the four Goldman risk categories together with rates of major adverse cardiac events

	Goldman et al. 1996		Reilly et al. 2002	
Risk	**Proportion**	**MACE 72hr**	**Proportion**	**MACE 72hr**
High	9.7%	21.5%	9%	11%
Moderate	18.2%	8.1%	25%	4%*
Low	14.1%	3.6%	17%	6%*
Very Low	57.9%	0.8%	48%	0.8%

**The difference between MACE events is not significant (P=0.06) and may explain the discrepancy between Low and Moderate Risk categories.*
MACE: Major Adverse Cardiac Events
Adapted from Goldman et al. 1996 and Reilly et al. 2002

In 2001 Limkakeng et al. became the first group to prospectively test the original Goldman rule in combination with troponin testing to attempt to identify a subgroup of patients suitable for early discharge from the ED. This observational study of 998 low-risk patients concluded that the combination of Goldman risk of ≤4% (i.e. very-low or low risk) and second generation cardiac Troponin I of ≤ 0.3ng/mL did not identify a subgroup with <1% likelihood of MACE at 30 days. Therefore this group concluded that these patients would not be suitable for immediate discharge.

The fact that the Limkakeng study used a second generation troponin assay with the ability to detect only highly abnormal levels (see Table 1) limits the interpretation of the results in the era of high-sensitivity troponin. Several other methodological issues may limit the interpretation and applicability of the Limkakeng results: Firstly, broad inclusion criteria (Age >24 and having an ECG for chest pain symptoms) will have resulted in recruitment of a large number of participants with clearly non-cardiac chest

pain, creating selection bias. Next, data for calculation of the Goldman criteria was taken from clinical notes by trained research assistants rather than calculated by physicians themselves, a potential source for misclassification. In not utilising the physicians own judgement specificity may have been reduced (Goldman et al. 1996). Finally, the most recent and best validated m-Goldman criteria were not utilised as suggested by Reilly et al. (2002), leaving the score with less discriminatory power. As a result of these methodological weaknesses, it may be concluded that the m-Goldman criteria require further evaluation as a discharge tool in the era of high-sensitivity troponin.

The Modified Goldman Rule

It is important to identify the modifications made to Goldman's original decision rule which were made for institutional pragmatic reasons by Reilly et al. in 2002. These may be summarised as follows:

a) The presence of Left bundle-branch block (not known to be old) was also considered as evidence of ischaemia on the ECG.

b) Two further subgroups of patients were also considered moderate-high risk in the absence of other Goldman risk factors: Firstly, if patients had ongoing angina despite maximal medical therapy in the ED and secondly if they had a high probability of significant coronary artery disease using the Diamond and Forrester criteria (1979). The addition of responsiveness to medical therapy, prolonged duration of pain and the presence of 'typical' anginal chest pain according to the Diamond and Forrester criteria (Table 11) became important clinical variables in the m-Goldman risk score.

Table 11. The Diamond and Forrester criteria for angina

Typical Angina: (1) Substernal chest discomfort with a characteristic quality and duration that is (2) provoked by exertion or emotional stress and (3) relieved by rest or nitro-glycerine
Atypical angina (probable): Meets 2 of the above characteristics
Non-cardiac chest pain: Meets ≤1 of the typical angina characteristics

Adapted from Diamond 1983

As a result of modifications by Reilly et al. (2002) and clinical use over time the current 8 point m-Goldman risk score (Table 12) has been introduced into everyday practice. It is this score that is incorporated into the TRUST ADP. Despite modifications, the m-Goldman criteria remains the most methodologically robust risk-stratification system developed and validated in a low risk ED population with factors easily available at presentation. There is currently no published data available on its performance as a risk stratification tool in allowing early discharge or rationalising existing resources in the era of high-sensitivity troponin.

Table 12. The modified Goldman risk score

Predictive variable	Reason for Inclusion
1. Typical new onset chest pain at rest	Introduced by Reilly et al. after incorporation of the Diamond and Forrester criteria
2. Pain same as previous Myocardial Infarction	From original derivation set
3. Pain not relieved by GTN within 15 minutes	
4. Pain lasting more than 60 minutes	Further clarification of worsening of previously stable angina: after Reilly
5. Pain occurring with increasing frequency	
6. Hypotension (Systolic Blood Pressure <100 mmHg)	From original derivation set
7. Acute Shortness of Breath	Adapted for clinical use from original derivation set as surrogate for "rales heard above bases"
8. Pain within 6 weeks of a Myocardial Infarction or Revascularisation	From original derivation set

1 Point given for each variable present. Patients defined as low risk if only 0 or 1 variable present.

GTN: Glyceryl Trinitrate

After Goldman et al. 1996 and Reilly et al. 2002

1.4.3 Other Risk Scores

The Thrombolysis in Myocardial Infarction Score

The most commonly used and best validated risk score is the Thrombolysis in Myocardial Infarction (TIMI) risk score (Hess et al. 2010). The TIMI Score (Table 13) was originally developed for use in high risk patients with acute coronary syndromes to predict myocardial infarction, revascularization or death and to guide therapeutic decision making (Antman et al. 2000). However since 2000 its use has become increasingly commonplace in assessing prognosis in ED patients with suspected cardiac chest pain.

Hess' meta-analysis of 2010 evaluated 10 prospective cohort studies validating the TIMI risk score in ED patients demonstrated a sensitivity of 97.2% (95%CI 96.4-97.8), specificity of 25.0% (95%CI 24.3-25.7) in patients with a score of 0 (Figure 5). Hess concluded that this sensitivity and specificity was insufficient to recommend the TIMI risk score as the sole means for determining patient disposition and that the risks may be more relevant to general cardiology practices rather than undifferentiated ED patients. This broad sample of 17265 patients supports the consistent performance of TIMI in the ED population however suffers from one major limitation: the fact that the reporting characteristics of biomarkers used, an integral part of the risk score (e.g. type, thresholds and sample times) were unreported. It is likely that 12-hour biomarker testing was used, in line with consensus guidance at the time of publication (NICE, 2010), meaning the applicability of these results may come into question in the era of hs-cTn.

Table 13. The Thrombolysis in Myocardial Infarction Score

Characteristic	*OR (95% CI) for prediction of Death/MI or Revascularisation at 14 days
1. Age ≥65 years	1.75 (1.35-2.25)
2. ≥ 3 risk factors for Coronary Artery Disease†	1.54 (1.16-2.06)
3. Significant coronary artery stenosis (Prior myocardial infarction/Stenosis >50%)	1.70 (1.30.2.21)
4. ST Deviation on ECG	1.51 (1.13-2.02)
5. Severe angina (≥2 episodes in prior 24hrs)	1.53 (1.20-1.96)
6. Use of aspirin in last 7 days	1.74 (1.17-2.59)
7. Elevated serum cardiac markers††	1.56 (1.21-1.99)

Each variable = 1 point

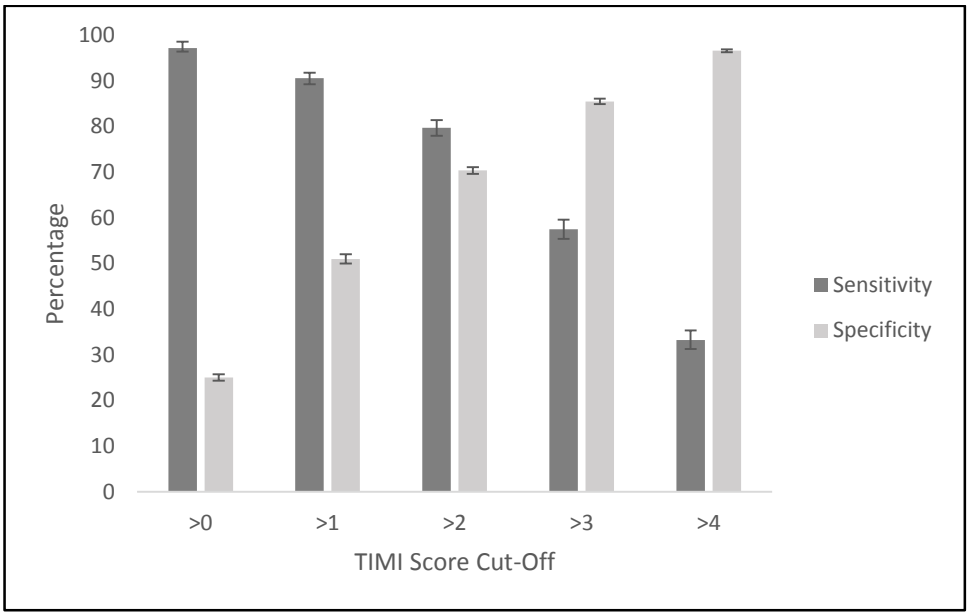
**OR: Odd's Ratio taken from the original derivation study in a high-risk ACS Cohort*

† Risk factors: family history of coronary disease (<65years), hypertension, hyperlipidaemia, diabetes mellitus, current smoker

†† As per standard guidance: Cardiac Troponin

Adapted from Antman et al. 2000

Figure 5. The diagnostic accuracy of the TIMI score for the detection of acute myocardial infarction in the Emergency Department population incorporating 2nd or 3rd generation troponin assays



Error bars: 95% Confidence Intervals
TIMI: Thrombolysis in Myocardial Infarction
Adapted from Hess et al. 2010

TIMI within an Accelerated Diagnostic Protocol

Since the Hess meta-analysis (2010) one group in particular, led by Professor Martin Than of Christchurch, New Zealand have continued to develop and use the TIMI score in combination with various biomarkers for the rapid rule-out of MACE. Results of sequential studies performed by this group are summarised in Table 14.

Table 14. Studies testing the TIMI Score within an accelerated diagnostic protocol

Study/Author Year	Study Type	N	Prevalence of MACE %	TIMI Score cut-off	Biomarker/ Testing Time	Sensitivity % (95%CI)	NPV % (95% CI)	Percentage Eligible for Rule-Out	Critique
ASPECT/Than et al. 2011	International Multi-centre Observational	3582	11.8	0	Point-of-care panel (troponin, CKMB, myoglobin)	99.3 (97.9-99.8)	99.1 (97.3-99.8)	9.8%	Large numbers, robust study design. Research nurses assessing risk. POC markers costly
ADAPT/Than et al. 2012a	Multi-centre Observational	1975	15.3	0	3rd Generation TnI at 0/2hours	99.7 (98.1-99.9)	99.7 (98.6-100)	20%	Robust study design. Research nurses assessing risk. 3rd Generation Troponin
ADAPT and APACE /Cullen et al. 2013	Multi-centre observational-2 cohort	1635/909	15.1/17.2	0/1	4th Generation high-sensitivity TnI 0/2hours	99.2 (97.1-99.8)/99.4 (96.5-100)	99.7 (98.9-99.9)/99.7 (98.4-100)	41.5%/38.6 %	Secondary analysis of existing cohort. Research nurses assess risk
Randomised Controlled Trial (Than et al. 2014a)	Single-Centre RCT	544	14.9	0	3rd Generation TnI at 0/2 hours	NR	98.9 (CI not reported)	19.3%	Robust. Not powered to test sensitivity. Demonstrates increased discharges before 6 hours

ASPECT: Asia-Pacific Evaluation of Chest pain trial, ADAPT: ADAPT: Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Troponin, APACE: Advantageous Predictors of Acute Coronary Syndromes Evaluation, RCT: Randomised Controlled Trial, TIMI: Thrombolysis in Myocardial Infarction Score, NPV: Negative Predictive Value, CKMB: Creatine Kinase, TnI: Troponin I

Within these papers, the Christchurch group have demonstrated that by using increasingly sensitive biomarkers (hs-cTn) and increasing the cut-off values of the TIMI score used (TIMI≤1) a strategy that allows discharge of 40% of patients can be achieved, albeit using serial biomarker testing over a 2-hour period (Cullen et al. 2013). The robust nature of the various strategies suggested by Than and colleagues are compelling. However, it is important to identify the methodological weaknesses of these studies in order to identify how they can be improved upon.

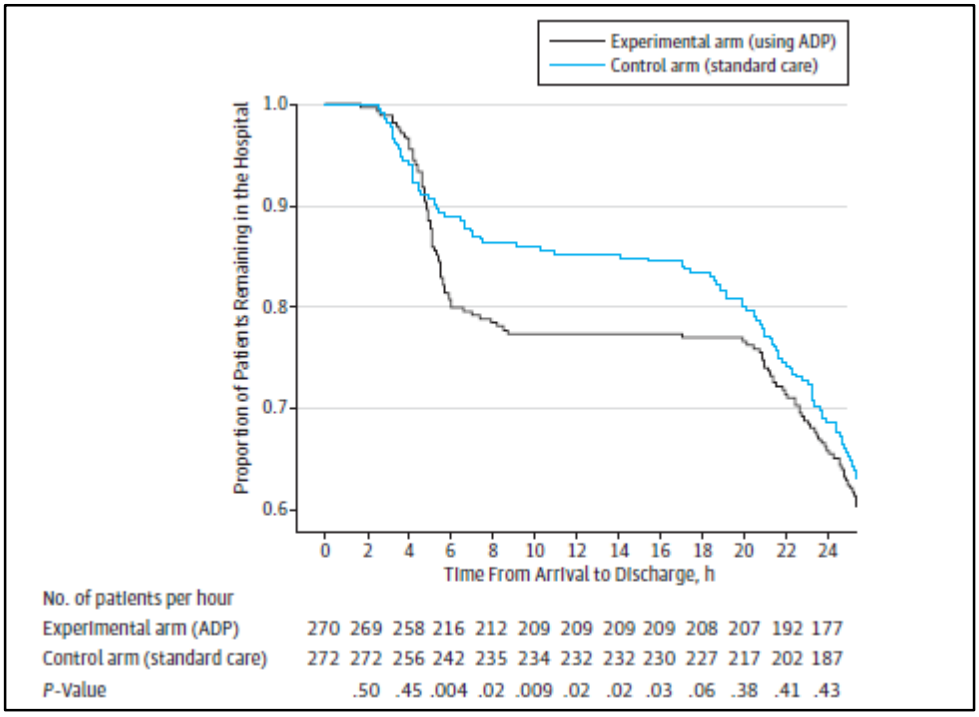
The ASPECT Study (Than et al. 2011), a large multicentre study, used point-of-care biomarkers (CKMB, Myoglobin) in addition to 3rd generation troponin, which have been shown to lack cost effectiveness (Fitzgerald et al. 2012) and add nothing to diagnostic accuracy when compared to 3rd generation troponin alone (Collinson et al. 2012) . This finding was confirmed in 2012 by Than et al. when, utilising the same cohort as the ASPECT study for the ADAPT trial. This analysis demonstrated that by using 3rd generation troponin as a single biomarker the proportion of patients suitable for early discharge could be doubled to 20% (Than et al. 2012a). This was further increased to 40% through the use of high-sensitivity troponin and by raising the TIMI score cut-off to 1 (Cullen et al. 2013). However, these cohorts of patients were recruited during working hours (selection bias), had risk scores calculated by research nurses (work-up bias) and the strict research protocols used for blood sampling at early time points may limit their applicability to the real-world.

In order to address these methodological flaws and assess pragmatic utility of the TIMI ADP, Than et al. (2014a) undertook a randomised controlled trial comparing the TIMI ADP (TIMI Score 0; ECG; and 0/2 hour 3rd generation troponin testing) to standard care (prolonged observation and troponin testing 6-12 hours after onset of pain), in which

clinicians performed risk scores. Discharge from hospital within 6 hours without MACE was chosen as the primary outcome measure and a statistically significant difference between experimental (19.3%) and standard care (11.0%) pathways was found, albeit with wide 95% confidence intervals (1.8%-14%). The authors of this analysis argue that by using old 3rd generation troponin assays, a larger proportion of patients were suitable for early discharge due to the potential for false positive results when using high-sensitivity assays. However, this argument may be counter-intuitive and therefore the impact on both the safety and efficiency of this pathway utilising high-sensitivity troponin assays early remains unknown.

A fundamental problem with recent studies incorporating TIMI into an ADP remains the requirement for two separate blood samples for troponin analysis at 0 and 2 hours. The RCT by Than et al. (2014a) demonstrates that in real terms, by requiring a troponin sample at 2 hours after patient arrival, there is no impact on discharge times until the patient has been in the ED for over 4 hours (Figure 6). Outside of a research environment, a 2 hour sampling time will be affected by the availability of staff to undertake blood draws, speed the sample reaches the central laboratory, laboratory processing time , which itself is affected by ED patient volume (Hwang et al. 2010) and the availability of ED physicians to acknowledge and interpret results (Thokala et al. 2012).

Figure 6. Illustrating the reduction in time to discharge when using the 2-hour TIMI ADP



Of note there is no improvement in time to discharge before 4 hours
ADP: Accelerated Discharge Protocol
Reproduced from Than et al. 2014a

Although the TIMI risk score remains popular in both the literature and clinical use (Dunham et al. 2010) for the assessment of patients with acute suspected cardiac chest pain it may be argued that this popularity may be counter-intuitive. Although validated in a low risk ED cohort, the score itself was developed in a high-risk ACS population. It also fails to incorporate any of the useful variables present in patient history and by doing so removes the utility of clinician judgement. Therefore, it may be hypothesised that by utilising a risk score developed specifically to identify those patients at low-risk of MACE, incorporating clinician judgement and patient history,

such as m-Goldman, it may be possible to use just a single high-sensitivity troponin result taken at presentation to identify patients suitable for early discharge.

Other Validated Risk Scores (HEART, GRACE, Vancouver, MACS)

As previously discussed, symptomatic history and the presence of chronic risk factors for coronary artery disease may not be as predictive of acute coronary syndromes in an ED setting as previously thought (Goodacre et al. 2002, Body et al. 2008, Goodacre et al. 2009b, Body et al. 2010 and Greenslade et al. 2012). Therefore, it may be argued that there remains a clear need for a well-developed and effective ED-based chest pain prediction rule. Even though recent focus has been on the TIMI risk score, other scoring systems may be better suited to the ED setting. In 2011, Challen and Goodacre identified 27 risk-stratification tools for use in ED patients with ACS or potential ACS and this list has since grown, with development and validation of the History, ECG, Age, Risk factors and Troponin (HEART) Score (Backus et al. 2013), Manchester Acute Coronary Syndromes (MACS) rule (Body et al. 2014a) and Emergency Department Assessment of Chest Pain Score (EDACS) (Than et al. 2014b). Such rules vary greatly in their popularity with regards to clinical use (Dunham et al. 2010) and many rules have been developed retrospectively or have methodological flaws limiting their applicability in practice (Steurer et al. 2010).

The Global Registry of Acute Cardiac Events (GRACE) (Brieger et al. 2009) score was developed in high-risk ACS cohorts and as such its use in a low-risk ED population remains counter-intuitive. In fact, despite guideline recommendations (NICE, 2010) to the contrary, evidence to support the GRACE score in this population is unfavourable, with some suggestion that it is little better than age alone as a predictor of MACE at 30

days (Goodacre et al. 2012).

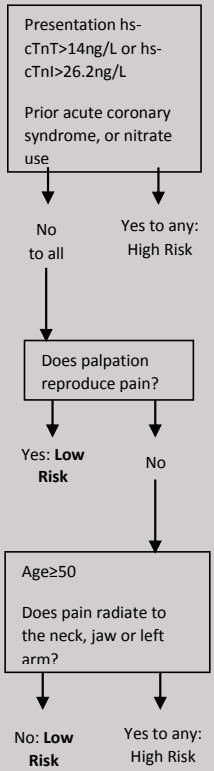
The HEART Score, has been shown to compare favourably with the TIMI score and has been validated in a multinational ED cohort where up to 28% are identified as low risk (Six et al. 2013). However, the score was developed through literature review and clinical experience rather than from a selection of candidate clinical variables and its negative predictive value with a single troponin (not high-sensitivity) at presentation was only 98.3% in the multinational validation cohort.

In an attempt to identify ED patients that may be successfully discharged, the Vancouver chest pain rule, using troponin as the only biomarker has been developed (Hess et al. 2012a). This rule has been validated externally with hs-cTn (Cullen et al. 2014a), to demonstrate that up to 20% of patients may be discharged with a sensitivity of 99.1% (95%CI 97.4-99.7). Despite this promise, the specificity of the rule, 16.1% (95%CI 14.2-18.2) may be too low to allow clinical application. Both this low specificity and relatively low number of patients suitable for discharge may be improved upon.

To date, most existing risk scores remain untested as rule-out tools in conjunction with a single hs-cTn taken at presentation to the ED and the resultant diagnostic accuracy has never been compared. A clinically applicable protocol that allows safe discharge of a significant proportion of patients with suspected ACS, after just a single hs-cTn result remains an attractive yet elusive goal.

Variables to calculate TIMI, GRACE, HEART, and Vancouver scores are summarised in Table 15. These variables will be obtained during data collection for the TRUST study. This will enable cross-comparison of all strategies for early discharge in combination with a single hs-cTn taken at presentation. This will provide novel comparative data that does not exist in the literature.

Table 15. Variables that make up the TIMI, GRACE, HEART scores and the Vancouver chest pain rule, incorporating a single hs-cTn result to identify low risk patients

Risk Score	TIMI	GRACE	HEART	Vancouver Chest Pain Rule
Clinical Variables	**Age≥65 yrs.** **≥3 Risk factors* for coronary artery disease** **Use of aspirin in last 7 days** **Significant coronary stenosis (>50%)** **Recent severe angina (≥angina events in preceding 24h)**	**Killip Class:** I: 0 points II: 20 III: 39 IV: 59 **Systolic BP (mmHg):** ≤80: 58 points 80-99: 53 100-119: 43 120-139: 34 140-159: 24 160-199: 10 ≥200: 0 **Heart Rate:** ≤50: 0 points 50-69: 3 70-89: 9 90-109: 15 110-149: 24 150-199: 38 ≥200: 46 **Age:** ≤30: 0 points 30-39: 8 40-49: 25 50-59: 41 60-69: 58 70-79: 75 **Creatinine Level (µmol/L):** ≤35: 1 point 36-70: 4 71-105: 7 106-140: 10 141-175: 13 176-350: 21 >350: 28 **hs-cTnT >14ng/L or hs-cTnI >26.2ng/L:** 15 points	**History:** Highly suspicious: 2 Moderately suspicious: 1 Slightly suspicious: 0 **ECG:** Significant ST depression: 2 Non-specific repolarisation disturbance: 1 Normal: 0 **Age:** ≥65 years: 2 45-65 years: 1 <45 years: 0 **Risk Factors:** ≥3 Risk factors† for coronary artery disease: 2 1 or 2 risk factors: 1 No risk factors: 0 **Troponin** **hs-cTnT:** ≥30ng/L†: 2 >14ng/L to <30ng/L†: 1 ≤14ng/L: 0 **OR hs-cTnI:** ≥78.6ng/L††: 2 >26.2ng/L to <78.6ng/L††: 1 ≤26.2ng/L: 0	
Score calculation	1 point for each factor present	Total score depending on categorical data	Total score dependent on presence of clinical variables	Binary rule-out decision tool
Definition of low-risk for both hs-cTn assays	hs-cTnT ≤14ng/L/hs-cTnI≤26.2ng/L, non-ischaemic ECG, TIMI Score 0 or 1	Non-ischaemic ECG and GRACE Score <60 OR <80 points (GRACE incorporates hs-cTn)	Heart Score 2 or 3 (HEART Incorporates ECG and hs-cTn)	Non-ischaemic ECG, and clinical features as described in decision tree

The Manchester Acute Coronary Syndromes (MACS) Decision Rule and the Incorporation of Heart-Type Fatty Acid Binding Protein

In 2014, Body et al. published a derivation and external validation of their MACS decision rule. This computer-based algorithm risk-stratifies patients with chest pain according to symptoms and signs present at presentation, together with hs-cTnT results and a novel biomarker assay, Heart-type fatty acid binding protein (H-FABP). H-FABP is a small cytoplasmic protein released from cardiac myocytes following an episode of ischaemia. In 2010, Bruins and colleagues demonstrated in a systematic review, encompassing 3709 patients, that H-FABP did not fulfil the requirements needed for safe and early diagnosis of AMI when used as a stand-alone test. Yet, Body et al. (2014) have demonstrated a potential additive role for H-FABP as part of a combination strategy with clinical findings and hs-cTnT.

The components of the MACS rule are detailed in Table 16. This rule achieved excellent discriminatory ability for the prediction of MACE; area under the curve (see Text Box below) of 0.95 (95% CI 0.93-0.97) and 0.92 (95% CI 0.89-0.95 during derivation (698 patients) and validation (463 patients) respectively. The authors concluded that the MACS decision rule could identify 25% of patients that could be immediately discharged as well as identify high-risk patients.

The MACS rule undeniably holds excellent promise and validation within a randomised controlled trial is currently underway (personal communication). However, the moderate numbers of patients in the validation study lead to wide confidence intervals for the sensitivity of the rule (93-99.8%) and the requirement for an additional blood test (H-FABP), which is not currently widely available, may limit the applicability of the study results. Though not included in the primary analysis, data from the TRUST Study,

to include H-FABP testing, has been used in the first external validation of the MACS rule (*Appendix 15*).

Area Under the Curve (AUC): The c-statistic or AUC is derived from receiver-operating characteristic curves (ROC) and is used to determine the discriminatory ability of a diagnostic test. AUC equals 0.5 when the diagnostic test corresponds to random chance (null hypothesis) and 1.0 indicates perfect diagnostic accuracy.

Table 16. Components of the MACS decision rule

Clinical Variable	Odds Ratio (95% Confidence Interval) for Prediction of MACE
High Sensitivity Troponin T	1.1 (1.0-1.1)
Heart-type fatty acid binding protein	1.2 (1.0-1.4)
ECG ischaemia	5.8 (3.1-10.8)
Sweating observed	6.3 (3.0-13.3)
Vomiting	5.6 (1.9-16.6)
Systolic blood pressure <100mmHg	4.3 (1.2-15.1)
Worsening angina	2.5 (1.2-5.2)
Pain radiating to the right arm	2.4 (1.0-5.6)

Adapted from Body et al. 2014a

1.5 The Electrocardiogram

American Heart Association guidelines define ECGs with new, or presumably new, transient ST-segment deviation (≥0.1 mm) or T-wave inversion in multiple precordial leads as diagnostic for ischaemia secondary to coronary artery disease (Table 17) (Amsterdam et al. 2010).

Table 17. ECG criteria representing an acute coronary syndrome secondary to coronary artery disease

	High Likelihood	Intermediate Likelihood	Low Likelihood
ECG Criteria	New, or presumably new, transient ST-segment deviation (≥0.1 mm) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.05 to 0.1 mm or T-wave inversion >0.1 mm	T-wave flattening or inversion 0.1 mm in leads with dominant R waves or normal ECG

ECG: Electrocardiogram

Adapted from Amsterdam et al. 2010

An important limitation to the majority of studies evaluating symptoms associated with ACS is that they have included patients with abnormal or diagnostic ECG's. The ECG is a quick and simple tool that allows the clinician to identify those patients with ST segment changes and who would benefit from early aggressive treatment and admission. The ECG is therefore a vital tool in the assessment of patients with suspected ACS (Panju et al. 1998). Clinical features that help to confirm a diagnosis of ACS in a patient with a diagnostic ECG will be of limited practical value to the clinician. Therefore by including those patients with diagnostic ECG's in any analysis of symptoms may not be relevant when identifying those suitable for early rule-out pathways and this requires further evaluation.

1.6 Additional Analysis Within the TRUST Study

1.6.1 The Role of Nursing Staff

ED nursing staff remain in a unique position to apply evidence based protocols during the initial assessment of patients shortly after arrival in the ED. Despite this, the potential for nurse-led protocols to improve quality of care remains unexplored in the ED setting.

Advanced nursing interventions during initial patient assessment have been proven to reduce time to treatment and diagnosis, improve patient flow through the ED and reduce length of stay across a wide variety of emergency presentations (Lee et al. 1996, Graff et al. 2000, Campbell et al. 2004, Cooper et al. 2008, Rowe et al. 2011, Stauber 2013). It is also evident that chest pain-specific risk scores, such as a modified TIMI score, can improve the accuracy of nursing assessments (Ho and Suen 2013). Yet, the ability of ED nursing staff to safely risk-stratify low-risk patients with suspected ACS who may be suitable for early rule-out biomarker testing and therefore early discharge has never been investigated. Consequently, ED nursing staff remain a potentially underused resource in the assessment of chest pain.

In the assessment of suspected cardiac chest pain, rapid identification of those patients suitable for early discharge protocols utilising high-sensitivity troponin by ED nursing staff may facilitate early physician decision-making and decrease treatment time or ED length of stay. However, the unintended consequences of such protocols and unnecessary diagnostic testing remain unexplored. Therefore the TRUST study will analyse the accuracy of nursing risk-stratification through inter-observer reliability assessments between untrained nursing assistants, ED nursing staff and physicians

which will give vital insights into this previously unexplored area of diagnostic literature.

1.6.2 Patient Satisfaction with Early Discharge Protocols

Patient satisfaction, patient involvement and care related to patient needs have been highlighted as key elements in the development of quality emergency care (Pham et al. 2011). Any new clinical intervention should provide some evidence of patient acceptability in addition to clinical effectiveness. The recent drive to implement rapid rule-out protocols to allow the early discharge of low-risk patients with suspected cardiac chest pain directly from the ED comes from physicians and healthcare providers. Previously, such patients would have been admitted to a hospital bed for delayed biomarker testing and a period of observation. However, to date, there has been little assessment of patient perspectives of such strategies, in what is known to be a high-anxiety presentation (Webster et al. 2012).

The two patient satisfaction studies of relevance compared protocolized management of patients admitted to chest pain units with standard inpatient care (Rydman et al. 1997 and Richards et al. 2002). While these studies concluded that rapid assessment of patients with chest pain was acceptable from a patient perspective, both suffered from the methodological and practical problems inherent in such studies. Such studies are at risk of bias from low response rates, when and by whom questionnaires are administered and the fact that patients are part of a clinical trial. The patients' evaluation will ultimately be subjective, which can be influenced by a number of factors including demographics and previously held opinions (Calnan 1988) , while it is

also known that patient satisfaction surveys tend to generate very high levels of satisfaction even if patients have been unhappy with certain aspects of care (Hall and Dornan 1998) .

A more recent study by Tekwani (2013) identified reduced satisfaction in patients discharged from an ED during times of high occupancy rate. While no conclusions can be drawn from this single-centre retrospective study, the themes discussed are consistent with the recurring themes of the ED quality improvement agenda. Therefore, the TRUST study will attempt to explore patient perspectives on whether early discharge after a rapid rule-out biomarker testing is acceptable in a low risk short-stay suspected ACS population.

1.7 Risk and Measures of Diagnostic Accuracy

Croskerry and colleagues (2009) define risk in medicine as "the probability of danger, loss or injury within the health system." This may be both risk to the patient or to the physician as a result as missed diagnosis. Both may apply in the context of patients who present with acute chest pain where missing the diagnosis of an acute myocardial infarction may have both medical (heart failure, sudden death) and medico-legal consequences. However the miss rate that clinicians are willing to accept in the context of AMI or MACE is poorly understood.

Only one study has sought to establish an acceptable standard of care with regards to diagnosis in chest pain (Than et al. 2012b). This survey of over 1000 emergency physicians suggest that a miss rate between 1/100 and 1/1000 with the majority accepting a miss rate of 0.5% or less. However, this subjective opinion may not represent a standard approach to diagnosis as this study may be subject to bias. The emergency physicians chosen to undertake the survey were mainly conference delegates (the conference theme is not mentioned) and had a survey response rate of 84%. Subjective opinion may be subject to bias also. Where this study is useful is highlighting that a small level of risk may be acceptable when discharging patients from the ED which is useful when developing a diagnostic strategy to rule-out MACE. In broad terms therefore a test sensitivity above 99% and ideally >99.5% may be acceptable to most ED physicians. In the absence of expert consensus guidance on the diagnostic accuracy thresholds needed for a rule-out protocol to be implemented in a clinical environment these cut-offs are a reasonable compromise.

A key concept in the evaluation of diagnostic strategies examining early rule-out of ACS

is the reporting and interpretation of diagnostic accuracy statistics, primarily sensitivity and negative predictive value (NPV). The NPV is directly related to the prevalence of the target disease in the specific population under consideration and represents the post-test probability of a negative test. When considering clinical implementation of a diagnostic strategy, it is important to establish the NPV for each hospital so that an attending clinician can best interpret a negative test, i.e. how does the test perform in a given clinical population. NPV should therefore not be used to recommend generalization of a test across populations with varying disease prevalence. Sensitivity, on the other hand, is not affected by the disease prevalence and represents the true positive rate. This is more useful to clinicians in establishing the validity of a diagnostic test on an individual patient level. The primary marker as to whether a rule-out strategy is ready for implementation in a clinical environment is safety, and this can only be truly gauged from the reporting of sensitivity. Therefore, the primary measure of diagnostic performance of the TRUST ADP, and other rule-out strategies tested within this thesis, is sensitivity.

Summary

Identifying a significant proportion of patients with suspected cardiac chest pain who may be suitable for early discharge remains a critical challenge to improving ED care. The recent development of high-sensitivity troponin assays has enabled a reduction in the time to biomarker testing, however no strategy so far tested has enabled the use of a single hs-cTn at presentation to safely rule-out AMI or medium-term (30 day) MACE. Clinical variables available from history and examination may alter the likelihood of a patient with chest pain having a final diagnosis of acute myocardial infarction and they have been used in the form of risk scores to improve clinician decision making and facilitate early discharge. Yet, there remains a clear need for a well-developed clinical decision rule that allows safe discharge of a large proportion of ED chest pain patients. The modified Goldman Score fulfils all the necessary methodological criteria and held early promise however it remains untested in the era of high-sensitivity troponin. The TRUST study aims to test a novel accelerated diagnostic protocol which incorporates a single hs-cTn test at presentation, together with electrocardiogram and m-Goldman Score results in a real world emergency department setting.

Key Points:

1. Chest pain makes up a quarter of medical admissions in the United Kingdom. A diagnostic strategy that prevents unnecessary hospital admission in a large proportion of this patient group would have significant benefits for healthcare services by reducing hospital admission rates, ED overcrowding, duplication of staff time and resource use.

2. High-sensitivity Troponin (hs-cTn) assays may allow earlier safe discharge of patients presenting to the Emergency Department with chest pain.

3. A clinically applicable protocol that allows the discharge of a significant proportion of patients after just a single hs-cTn blood draw at presentation remains an attractive yet elusive goal.

4. The adjunctive use of risk scores may rapidly identify low-risk patients suitable for early discharge when used in combination with hs-cTn assays, in a strategy called an accelerated diagnostic protocol (ADP). Currently, ADPs require serial troponin testing and remain untested with a single hs-cTn result.

5. The ability of ED nursing staff to safely risk-stratify low-risk patients with suspected ACS who may be suitable for early rule-out biomarker testing and therefore early discharge has never been investigated. ED nursing staff remain a potentially underused resource in the assessment of chest pain.

CHAPTER 2.

Study Development

2.1 Hypothesis

The TRUST accelerated diagnostic pathway (ADP) can identify up to 30% of patients who present to the Emergency Department with suspected acute coronary syndrome (ACS) who are at 0% risk of MACE at 30 days, and are therefore suitable for early discharge.

2.2 Study Aims

The primary aim of the TRUST study is:

To establish whether the TRUST ADP for suspected ACS patients consisting of hs-cTn, a non-ischaemic ECG and the m-Goldman score, could successfully identify low risk patients suitable for discharge after a single blood draw at presentation to the ED.

Secondary aims are:

1. To establish potential improvements in system efficiency using the TRUST ADP through time-and-motion analysis of hs-cTnT testing

2. To compare the diagnostic accuracy of the TRUST ADP with strategies utilising initial undetectable hs-cTnT levels

3. To compare the ability of five established risk scores, when used in conjunction with either high-sensitivity troponin T (Elecsys hs-cTnT) or I (Architect hs-cTnI), to

identify low risk patients with chest pain symptoms suggestive of ACS suitable for early discharge after a single blood draw at presentation to ED.

4. To establish the diagnostic accuracy of ED nursing staff risk assessment, using the TRUST ADP, with regard to prediction of future MACE in patients with suspected ACS, and evaluate the inter-observer reliability of nursing and physician assessments within a chest pain specific risk score.

5. To establish the discriminatory value of physician interpretation of typicality of chest pain, in patients with a non-diagnostic ECG, considered to have a potential ACS, and the impact of clinical experience upon diagnostic accuracy, for the prediction of acute myocardial infarction (AMI) and significant coronary artery disease (CAD) with and without high-sensitivity troponin (hs-cTn) elevation.

6. To investigate patient perspectives on whether early discharge after a rapid rule-out biomarker testing is acceptable in a low-risk short-stay suspected ACS population.

2.3 The TRUST Accelerated Diagnostic Protocol

The pre-designed TRUST ADP (Table 18) defines a patient as 'low risk' if the following conditions are satisfied at presentation to the ED:

1. **A modified Goldman score of ≤1** (Table 18)

2. **A normal or non-ischaemic ECG**

Defined as the absence of:

Either:

ST-segment elevation ≥1 mm or Q-waves of 0.04 s or more, in 2 or more consecutive leads.

Or:

ST-segment depression ≥1 mm or T-wave inversion consistent with the presence of ischemia.

Or:

Arrhythmias: new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias.

(Amsterdam et al. 2010)

3. **A single central laboratory hs-cTnT (Roche Diagnostics) of <14ng/L (99th centile value) taken at presentation to the ED.**

Table 18. The modified Goldman score and the TRUST ADP

MODIFIED GOLDMAN RISK SCORE	*1 point for each variable present*
Typical new onset chest pain at rest	
Pain the same as previous myocardial infarction	
Pain not relieved by Glyceryl Trinitrate (GTN) within 15 minutes	
Pain lasting more than 60 minutes	
Pain occurring with increasing frequency	
Hypotension (Systolic Blood Pressure <100mmHg)	
Acute shortness of breath	
Pain within 6 weeks of a myocardial infarction or revascularisation	
Modified Goldman Total:	
TRUST ACCELERATED DIAGNOSTIC PROTOCOL (TRUST ADP)	
Low risk* (Suitable for discharge)	1. Modified Goldman Score ≤1 2. Non-ischaemic ECG 3. Presentation high-sensitivity troponin T <14ng/L
Not Low Risk	1. Modified Goldman Score >1 2. Ischaemic ECG 3. Presentation high-sensitivity troponin T ≥14ng/L
***Safety Point:** Protocol not validated in age ≥80 years*	

ECG: Electrocardiogram

From Carlton et al. 2015a

2.4 Outcome Measures

2.4.1 Primary Outcome Measure:

30 Day Major Adverse Cardiac Events

MACE are defined according to standardised data definitions (Cullen et al. 2010) (these include events during initial hospital inpatient stay) and are identical to large scale studies investigating rapid discharge protocols (Than et al. 2011, Collinson et al. 2012, Cullen et al. 2013):

1. **Death secondary to ischaemic heart disease**

2. **Diagnosis of acute myocardial infarction (AMI) as per standard guidance** (see below) (Thygesen et al. 2012a)

3. **Emergency or urgent symptom induced revascularisation** (to include Emergency or Urgent Percutaneous Coronary Intervention or Coronary Artery Bypass Graft and/or procedure required during the same admission to minimize chance of further clinical deterioration)**.**

4. **Cardiogenic shock, ventricular arrhythmia, high-degree atrioventricular block needing intervention.**

2.4.2 Secondary Outcome Measures:

1. Acute Myocardial Infarction

The presence of AMI is defined according to the Third Universal Definition of MI which states that a rise and/or fall in troponin, with at least one value above the 99th centile value in the context of a patient with ischaemic symptoms or signs (ECG changes or imaging evidence) would satisfy the diagnosis (Thygesen et al. 2012a). Based on current consensus guidance for high-sensitivity troponin assays, a rise or fall of 20% (delta) is considered statistically significant and consistent with a diagnosis of AMI (Thygesen et al., 2012b).

2. Significant Coronary Artery Disease

In order to overcome the diagnostic adjudication challenges associated with high-sensitivity troponin assays and small elevations in troponin (Mills et al. 2011) the diagnostic outcome measure of significant CAD (available only in those patients subsequently referred for coronary angiography within 30 days) was included for some analysis. This is defined as ≥70% luminal diameter narrowing of at least one major coronary artery as reported on visual assessment by the angiographic operator (Pryor et al. 1993).

2.5 Justification of Research

The TRUST Study is novel and justified for the following reasons:

1. No pragmatic prospective study analysing the diagnostic accuracy of an ADP, which incorporates a clinical risk score, and a single high-sensitivity troponin test at presentation to the ED, to identify low-risk patients suitable for early discharge has been undertaken.

2. No study has compared the diagnostic accuracy of an ADP, which incorporates clinical assessment, with alternative discharge strategies which utilise initially undetectable hs-cTn results.

3. To date, existing risk scores remain untested as rule-out tools in conjunction with a single hs-cTn taken at presentation to the ED and the resultant diagnostic accuracy has never been compared.

4. No study has compared the accuracy of nursing with physician-based assessment of chest pain using a cardiac risk-assessment tool.

5. No study has investigated the diagnostic value of physician interpretation of typicality of chest pain, and the impact of clinical experience upon diagnostic accuracy.

6. No published data exists to allow us to understand whether patients with chest pain want more rapid diagnosis and discharge.

2.5.1 Benefits of Research

Should this study demonstrate that the TRUST ADP is capable of delivering a much earlier discharge in patients presenting to the ED with chest pain the main benefits would be:

1. **For Patients**: to allow a reduction in the anxiety, inconvenience and risks of hospital admission.

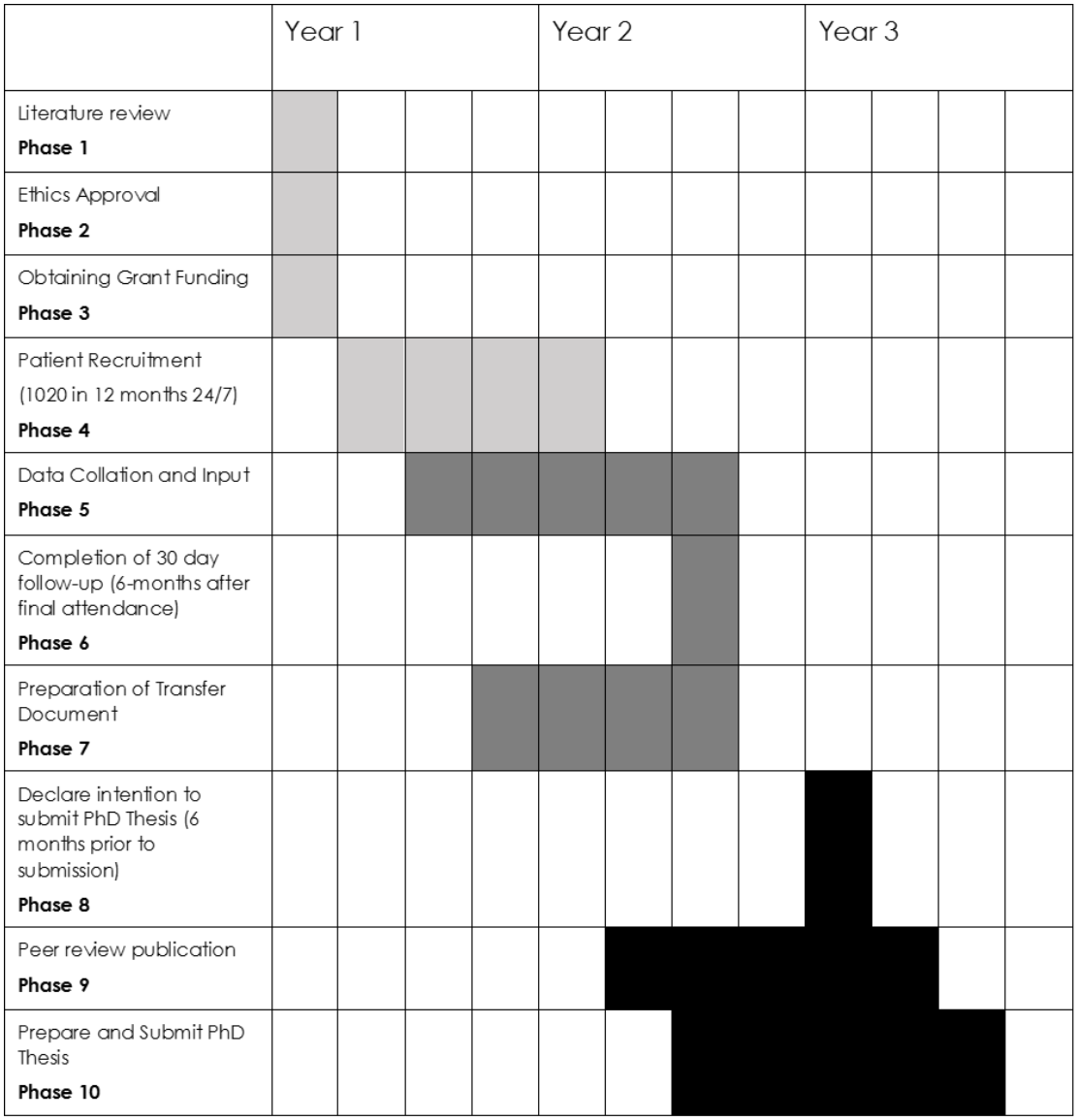
2. **For Acute Services**: by avoiding unnecessary admissions, duplication of staff activities and overcrowding.

3. **For Healthcare Services in general**: to allow potential cost-savings and to help achieve the Department of Health Quality Indicator Target for total time spent in ED (4-hours). The TRUST Study addresses an international health delivery issue.

2.6 Phases of the Study

This thesis summarises the work undertaken over a 4 year period from 2011-2015. Registration for post-graduate study (PhD Studentship Bournemouth University), occurred in September 2012. It should be noted that design and planning of the TRUST study began a year before commencement of the Studentship during a postgraduate Quality Improvement Fellowship funded by South Central Strategic Health Authority. Study design and planning was carried out by the student investigator with the support of Professor Kim Greaves. The overall timeline for the study is illustrated in Figure 7.

Figure 7. Phases of the TRUST Study over the period of the Studentship



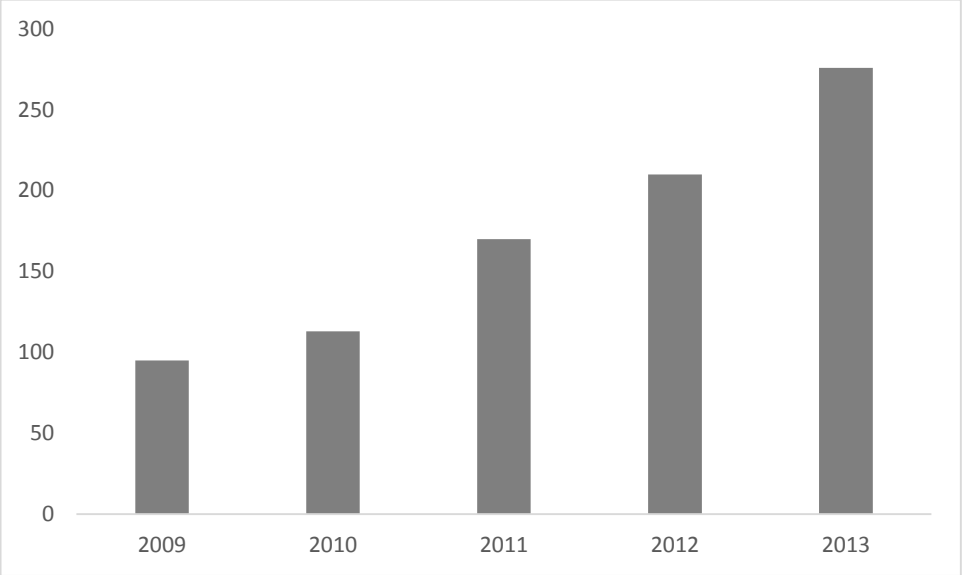
2.7 Literature Search

An initial literature search was conducted during the first phase of the study. However, it is acknowledged that due to the relatively new introduction of hs-cTn assays into clinical practice that this is a very active area in the literature, therefore new papers are being published almost weekly (Figure 8). The literature search phase has therefore been dynamic and ongoing throughout all phases of the study. All searches were conducted using EMBASE, MEDLINE AND CINAHL and Cochrane Databases searched through NHS Evidence. The student has also utilised contacts within the field of research and social media (Twitter™) to keep up to date with new publication releases.

The following were excluded as it was recognised that sufficient evidence would exist without analysis of:

- Conference Abstracts
- Case Report Series
- Foreign Language Journals

Figure 8. Publications per year including the search term "High-Sensitivity Troponin"



Data from Pubmed.gov (Accessed March, 2014)

2.8 Grant Funding

Grant funding was obtained through open international competition and peer review of study methodology. The TRUST Study won funding of £10,000 from the UK College of Emergency Medicine during the 2012 funding competition.

The TRUST Study has obtained industry funding from Abbott Laboratories, USA, for high-sensitivity Troponin I analysis and Randox Life Sciences, Ireland, for Heart Fatty Acid Binding Protein Analysis (as part of a collaborative study to validate the Manchester Acute Coronary Syndromes Rule (Body et al. 2014a)).

2.9 Ethical Considerations

Full Ethical Approval was granted by the Frenchay Research Ethics Committee (*Appendix 1*) 12/SW/0133 on 30/05/2012 for Study Protocol 3.0.

Major Amendments to the protocol have been approved as follows:

Version 3.1 09/06/2013: To allow change in Chief Investigator, alteration of final recruitment numbers and collection of data from those patients missed from the consent process.

Version 3.2 17/01/2014: To allow extension of follow-up from 30 days to 1 year and enable testing of Abbott high-sensitivity troponin I on frozen serum samples.

The following Ethical Issues were specifically taken into account during the application process:

i) An upper cut-off age of 79 was chosen as in the host institution patients aged 80 and above were admitted for assessment by an entirely separate clinical team who had not been consulted in the design of the study, and whose standard care of this group of patients may vary considerably from other inpatient teams.

ii) Participants will not be required to attend the department for any longer than the time required to perform the procedures that are done as part of routine care. All patients will have blood sampling from a vein in either arm as part of standard care within 1 hour of arrival, it is at this time we request

an extra 3.5mls (half a teaspoon) is given for high- sensitivity troponin testing and storage of serum. No patient will be subjected to an extra needle procedure for the sake of this study.

iii) On discharge participants will be asked to fill out a short questionnaire regarding their satisfaction with their admission. This will be fully anonymised and participants will be reassured that it will not affect their ongoing care. It will take approximately 5 minutes to complete. The questionnaire has been designed with direct patient involvement and is written in layman's English.

iv) For 30 day follow up, the data for adverse events will be taken from the hospital electronic patient record. Where data from this is insufficient we will contact the participants GP for further clarification. Participant involvement will not be required after discharge.

v) There may be no direct benefit to research participants. It is hoped that the results we obtain may provide evidence to support service improvement recommendations in care pathways for this group of patients in the future. Participants may benefit from the knowledge that their feedback regarding services may contribute directly to improving practice.

vi) All patients will receive a participant information sheet. Due to the pragmatic and emergency nature of the study participants will not be

informed at sampling that an extra 3.5mls of blood will be taken for research purposes. Written consent for use of this sample will be obtained after participants have read a patient information leaflet detailing the study, have had the opportunity to ask questions and have them answered satisfactorily and are comfortable and pain free. The consent form is attached (Appendix 3). Patients will be entitled to withdraw their consent at this time.

vii) Nursing staff will also be classed as research participants for the purpose of this study. A written participant information sheet will be provided for all members of the ED nursing team. Written consent to participate will be requested prior to study commencement but may be withdrawn at any time during the duration of the study.

viii) For reasons of practicality consent will not be obtained from potential participants who are unable to understand English fully. They will therefore not be recruited as study participants. Due to the short period of time that patients will have to consider taking part it will be impractical to find an independent translator in this time. It may sometimes take hours to find an independent registered translator. Our institution has very low numbers of non-English speaking patients.

ix) Access to medical records (electronic patient records) will be required by authorised members of the research governance department for the

purposes of monitoring and auditing the study to ensure it is conducted correctly.

x) Personal data will be kept in paper files within a locked and alarmed room on trust property. Patient data will only be kept electronically on secure hospital servers. Only anonymised data may be transferred to another NHS computer, this will be carried out using an encrypted memory stick. Consent will be obtained from participants to allow members of the Sponsor (Poole Hospital NHS Foundation Trust) to access personal data.

xi) No clinical decisions will be made upon review of research troponin results when reviewed at 30 days. All patients will have been through a standard treatment pathway and as such their treatment should not be altered on the basis of results from a research study.

xii) Risks to Patients- Patients enrolled in the study are covered by standard NHS Indemnity Arrangements for clinical negligence claims in the NHS. Risks to patients were determined to be negligible.

2.10 Study Preparation

During Phase 1-3 of the study specific documentation was prepared as follows:

a. Participant Information Sheet **(Patient):** *Appendix 2*

b. Participant Information Sheet **(Nursing Staff):** *Appendix 3*

c. Consent Form **(Patient):** *Appendix 4*

d. Consent Form **(Nursing):** *Appendix 5*

e. Nursing Risk Assessment Sheet: *Appendix 6*

f. Patient Questionnaire: *Appendix 7*

2.11 Sponsorship

The TRUST Study is a Bournemouth University/NHS collaboration. Poole Hospital NHS Foundation Trust agreed to act as Sponsor for the TRUST Study. The hospital Research Governance Department have undertaken regular audit of study procedures to ensure compliance with the sponsor's terms and conditions.

2.12 Trial Registration

The study is registered with the Controlled Trials Database ISRCTN No. 21109279.

Chapter 3.

Methods

3.1 Study Design

A single-centre prospective blinded diagnostic observational cohort study.

The protocol was designed to be truly pragmatic in order to enhance the widespread applicability of the study results (Tunis et al. 2003); with attending clinicians performing m-Goldman risk scores, rostered clinical (not research) staff undertaking blood sampling, real-time sample processing and 24/7 recruitment. The study was designed using the Standards for Reporting Diagnostic Accuracy (STARD) (Bossuyt et al. 2003).

3.2 Setting

The TRUST study was carried out in Poole Hospital NHS Foundation Trust Emergency Department. This Emergency Department (ED) is situated in a large acute general hospital, in Dorset, United Kingdom. The hospital provides a range of district hospital care for the 270,000 people living in Poole and East Dorset (NHS Choices 2013). The ED has an annual census of 62000 and an estimated 3600 presentations with atraumatic chest pain per annum (personal review of ED demographic data and retrospective sampling). This estimate is similar to that of prospective data which estimated that 6% of all ED attendances nationwide were due to chest pain and related complaints (Goodacre et al. 2005). All patients from the local catchment area with acute ECG findings ST-elevation myocardial infarction (STEMI) bypass the ED and were transferred directly to a nearby angioplasty centre.

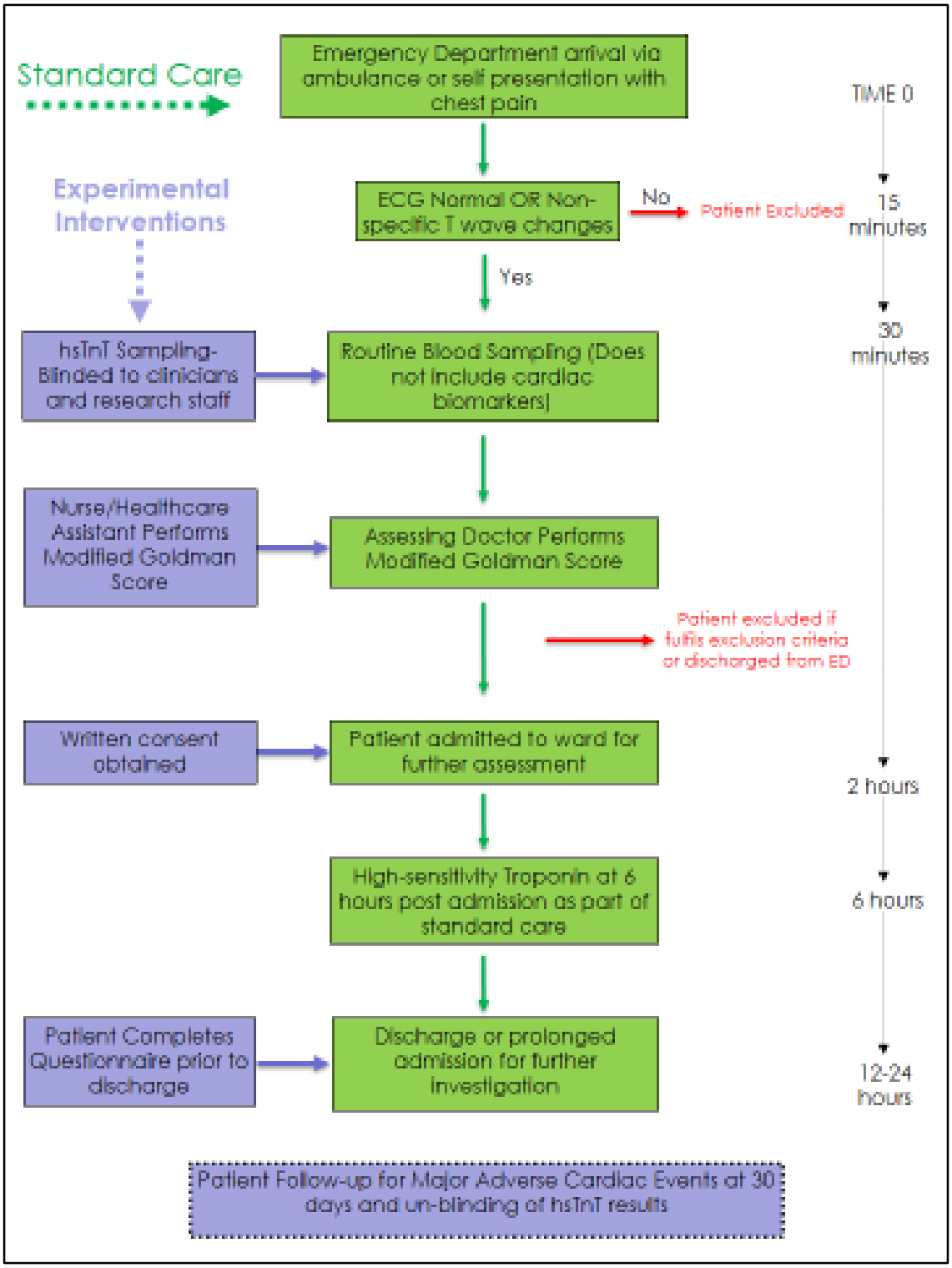
Key population demographics from census data highlight a higher proportion of age >65 (26.2% as opposed to 17.0% nationally) and predominantly white British population (98.99% as opposed to 90.92% nationally) (Dorset County Council 2011).

Patients with suspected ACS were managed according to the Poole hospital protocol, which involved risk assessment by ED physician staff using the m-Goldman risk score and blood drawn for hs-cTnT at 6 hours after presentation. As part of the study protocol, blood was also taken at presentation for hs-cTnT analysis. Historical clinical protocols, at the time of this study, did not include troponin measurement at presentation, in contravention of consensus guidance (Amsterdam et al. 2010 and NICE 2010). However, this had the methodological benefit of ensuring that treating physicians were blinded to the initial hs-cTnT result to avoid selection bias (Stiell and Wells 1999) and ensured the decision to admit or investigate further was made by the treating physician independently of any cardiac biomarker result. All patients who required a 6 hour troponin test were admitted to an inpatient assessment unit under the care of an acute general physician, the decision to admit being at the discretion of the assessing ED physician. Onward cardiology consultation, stress testing or discharge for outpatient follow-up was at the discretion of the acute physician.

3.3 Trial Schema

Figure 9, is a schema demonstrating TRUST Study interventions alongside clinical practice. During initial assessment in the ED clinical staff drew blood for routine admission samples (not including cardiac biomarkers) and an additional 3.5mls of whole blood in a pre-labelled study specific serum settling tube for hs-cTnT analysis. Treating physicians were blinded to the presentation hs-cTnT result. All serum samples were tested prior to freezing by laboratory staff blinded to patient outcomes.

Figure 9. Trial schema (standard care and illustration of experimental interventions)



Hs-cTnT: high-sensitivity cardiac troponin T, ECG: Electrocardiogram

3.4 Participant Selection

3.4.1 Inclusion Criteria

Potentially eligible patients were screened by ED and research staff who provided trial information and obtained written consent. Consecutive patients attending the ED with suspected ACS were prospectively screened from July 2012 to August 2013. Patients were included if they were at least 18 years of age and had at least 5 minutes of chest pain suggestive of ACS, and for whom the attending physician determined inpatient evaluation was required. Possible cardiac symptoms included acute chest, epigastric, neck, jaw or arm pain, or discomfort or pressure without an apparent non-cardiac source, in accordance with the American Heart Association case definitions (Luepker et al. 2003). Atypical symptoms (fatigue, nausea, vomiting, diaphoresis, faintness, and back pain) were not used as inclusion criteria in the absence of chest pain.

3.4.2 Exclusion Criteria

1. Age <18 or ≥80 years
2. STEMI or left bundle branch block not known to be old and ECG changes diagnostic of ischaemia (ST segment depression ≥1mm or T-wave inversion consistent with the presence of ischaemia) (Amsterdam et al. 2010)
3. Arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias)
4. hs-cTnT not suitable for analysis (e.g. haemolysis),
5. Atypical symptoms in the absence of chest pain or discomfort
6. An alternative cause of chest pain is suspected at presentation (e.g. pulmonary embolism, pneumonia, aortic dissection)
7. Refusal of patient consent
8. Renal failure requiring dialysis
9. Non-English speaking
10. Inability to be contacted after discharge
11. Trauma with suspicion of myocardial contusion
12. Another medical condition that necessitates hospital admission
13. Prisoners
14. Pregnancy

3.5 Sample Size

Estimated Study Size Prior to Study Commencement: 1200 Participants

On commencement of the study the aim was to recruit 1200 consenting participants with data and blood tests suitable for full analysis.

3.5.1 Justification of Sample Size

In evaluating the accuracy of a diagnostic strategy in medicine, the sample size plays an important role either for estimation or testing of diagnostic accuracy. A small sample size produces an imprecise estimate of accuracy with wide confidence intervals (Jones et al. 2003) which is non-informative for clinicians who may wish to implement the diagnostic pathway in a clinical environment. An unnecessarily large sample size is a waste of valuable research resources.

In estimating the diagnostic accuracy and to obtain a desired level of statistical power to detect an effect size for testing the TRUST ADP, calculation of the minimum sample size is therefore required. This calculation is reliant on 2 factors. Firstly, the proportion of patients who may be suitable for early discharge using the TRUST ADP. Secondly the diagnostic accuracy of the rule-out pathway (in this case the precision estimate of test sensitivity (as discussed on Page 77). It has been argued that when estimating sample size around test sensitivity the consideration of disease prevalence is not required (Jones et al. 2003).

To estimate the proportion of patients who may be suitable for early discharge, a retrospective analysis of 100 patients presenting to the Emergency Department with suspected cardiac chest pain was undertaken prior to study commencement. The m-Goldman Score was applied to each patient through adjudication from clinical notes by the student investigator. From this analysis it was estimated that approximately 30% would be classified as low-risk, and therefore potentially suitable for early discharge. This target of 30% also improves upon the best performing ADP currently in the literature (Cullen et al. 2013).

Three essential elements are required when estimating sample size according to test sensitivity (Hajian-Tilaki, 2013): 1) a pre-determined point estimate value of sensitivity, estimated from published research or clinical judgement, 2) the confidence interval (1-α) for statistical judgement, where α is the probability of a Type 1 (false positive) error and 3) the precision estimates of sensitivity.

Therefore to define the diagnostic accuracy of the TRUST ADP a point estimate target sensitivity for MACE was set at 99%; the cut-off at which the majority of emergency physicians may expect diagnostic strategies for the assessment of suspected ACS to achieve (Than et al. 2012b).

The sample size was then calculated according to the precision estimates of the sensitivity of the TRUST ADP. Assuming a 100% sensitivity of this ADP, for the identification of MACE, with a 95% confidence interval (α 0.05) that would extend no lower than 99%, 400 low-risk patients would be required to demonstrate statistical significance. With an estimated 30% of patients being eligible for discharge, a total sample size of 1200 patients was required.

3.5.2 Adjustment of Sample Size

An interim analysis following recruitment of the first 700 participants was undertaken. This showed that a higher proportion of patients (41.4%) were classified as low risk. This enabled a reduction in the total numbers recruited to **966**.

Sackett et al. (2011) estimate that 20% of study participants will not provide data to the final analysis. However, the observational nature of the TRUST study meant this number was far fewer. The interim analysis identified the following reasons for data loss:

a) Failure or loss of study blood sampling (0.28%)
b) Haemolysis of research blood samples rendering them uninterpretable (4.85%)
c) Loss to follow-up (2.6%)

Therefore 7.76% of participants recruited at the time of interim analysis had incomplete data. To take this into account the sample size was recalculated to **1040**.

3.6 Recruitment

In order to reduce the potential for selection bias (Laupacis et al. 1997 and Stiell and Wells 1999) recruitment to the TRUST study was undertaken 24 hours a day, 7 days a week. This is the first large scale study of its kind to do so and was facilitated by a retrospective consent process. Prior to study commencement it was estimated that 2.5 participants would be recruited per day, acknowledging that up to 10% of eligible patients would be missed from the consent process. Therefore approximately 400 days were required for recruitment.

The final recruitment period was: **18th July 2012 – 30th August 2013**

3.7 Study Data

3.7.1 Recording of the m-Goldman Score

Data were collected prospectively using a published data dictionary (Cullen et al. 2010) and is available in *Appendix 8*. ED physicians were also asked to complete the m-Goldman risk score following their own initial patient assessment. Treating ED physicians completed the m-Goldman risk score on a pre-designed clinical report form to enable accurate recording of demographic data. Where m-Goldman scores were not completed by treating physicians, adjudication of scores was carried out by study researchers blinded to patient outcomes and hs-cTnT results from ED records separate to hospital records.

ED nursing staff undertaking initial assessment were also asked to record the m-Goldman risk score on a case report form, at the time of patient presentation to the ED. They were provided with written explanatory notes on how to complete the risk score but no specific training in the clinical evaluation of patients with chest pain. The nursing risk score was kept separate from the clinical notes in a coloured envelope and removed by a member of the research team at the earliest opportunity. No adjudication of nursing staff risk scores was undertaken. Where possible, subjective elements of other risk scores were evaluated directly from data provided by the treating clinician.

3.7.2 Data for the Calculation of Other Risk Scores

Risk scores were selected a priori if they were known to be in common clinical use (Dunham et al. 2010) and had been prospectively validated in large ED cohort studies. Index tests were pre-determined definitions of low-risk applied to each risk score (Summarised in Table 15) established from existing validation studies designed with the specific intention of improving ED efficiency: TIMI (Cullen et al. 2013); GRACE (Goodacre et al. 2012); HEART (Backus et al. 2013) and Vancouver (Cullen et al. 2014a). Where biomarker results were not included as a variable in the original score, hs-cTnT and hs-cTnI were incorporated accordingly using the 99th percentile cut-off value as a baseline. As only patients with a non-ischemic ECG were recruited to the study, where ischemic ECG changes were included in the original risk scores, these variables were removed, as reflected in clinical practice where patients with ischemic ECG changes are immediately defined as high-risk (Amsterdam et al. 2010). Data points for each risk score were included within primary data collection. Where possible, ED clinician interpretation of individual elements of each risk score (such as typicality of chest pain) was used in order to incorporate subjective interpretation. A computer-based algorithm was designed to calculate each score automatically from the admission data, without interpretation by the study investigator.

3.7.3 Assessing Typicality of Chest Pain

Clinicians were requested to record, in a yes/no tick box, using their own clinical judgment and taking into account all factors from history and examination as to whether they thought the chest pain described was typical cardiac chest pain or atypical (question derived from the m-Goldman risk score). The level of experience for assessing physicians was recorded. Clinical experience was defined a priori as either "experienced" or "novice." Experienced ED physicians were either Consultants (Fellows of the UK College of Emergency Medicine) or Registrars with at least 2 years of ED experience. Novice ED physicians were Senior House Officers with less than one years' ED experience. During the study period there were 12 experienced physicians and 32 novice physicians undertaking clinical assessments.

Physician assessments were anonymized to protect staff identity (as requested by ethics board), therefore the number of assessments recorded by each individual could not be recorded. Clinical data was recorded during the initial patient assessment and therefore treating physicians were blinded to the patient outcome. As biochemical results were not available at the point of assessment, ED staff were also blinded to troponin results.

3.7.4 High-Sensitivity Troponin Measurement

The fourth generation Roche ELECSYS hs-cTnT assay (Roche, Basel, Switzerland), which has a Limit of Blank of 3ng/L, Limit of Detection of 5ng/L, 99th percentile of 14ng/L and 10% coefficient of variation of <10% at 9ng/L, was used for both research (presentation) and clinical (6-hour) samples. Clinical samples were reported to a lower

level of 14ng/L (where a sample was <14ng/L this was reported as such). Research samples were reported down to a level of 3.0ng/L and were recorded to the degree of a single decimal point. Research serum blood samples were spun down and tested for hs-cTnT upon receipt in the laboratory. Remaining spun serum was frozen immediately and stored at -80^{o}C.

In December 2014, industry funding was obtained to test remaining frozen samples for high-sensitivity troponin I. Stored presentation samples were tested for hs-cTnI using the Abbott ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Laboratories, USA), which has a 99th percentile value of 26.2ng/L with a corresponding coefficient of variation of <5% and a limit of detection of 1.9ng/L.

3.7.5 Patient Questionnaire

This quantitative questionnaire was designed with closed answer questions with responses standardized along a 5-point Likert scale (Likert 1932) (*Appendix 7*). In order to obtain the opinion of those patients who may have been eligible for immediate discharge, only those patients who were discharged within 36 hours, directly from the short stay ward, were asked to complete the questionnaire. Respondents were asked to complete the written survey upon discharge from the ward and hand it to a member of the ward team.

3.8 Statistical Analysis

Baseline characteristics of the study population were analysed with conventional group descriptive statistics. x^2 analyses were used to generate 2 x 2 tables for the calculation of sensitivity, specificity, negative predictive values (NPV) and positive predictive values (PPV), and negative (-LR) and positive (+LR) likelihood ratios. For the majority of analyses the ability of the test to perform as a rule-out tool (sensitivity) is the result of primary interest. Statistical significance was calculated using the Fisher's exact test for contingency tables and Mann-Whitney U test for non-parametric data; all reported p-values are two-tailed. Inter-observer reliability of variables between ED Physicians and Nurses were made using a Cohen's Kappa score. Binary logistic regression analysis was used to identify predictors of dissatisfaction with early discharge within the patient questionnaire. All statistical analysis was carried out using SPSS version 20.

The study database is available upon request and is in the form of an SPSS data file. All patient identifiable data is anonymised. All SPSS syntax files for calculation of endpoints are also available.

3.8.1 Receiver-Operating Characteristic Curves

Where applicable receiver-operating characteristic (ROC) curves were obtained by plotting sensitivity against 1-specificity. The ROC provides information in the case of quantitative diagnostic tests (such as high-sensitivity troponin, or the m-Goldman score) as to what extent test results differ between patients who do or do not have the diagnosis of interest. The area under the ROC curve (AUC) was chosen as the primary measure of discriminatory value, as it gives a global measure of test performance.

The AUC was tested against the null hypothesis that the true AUC was 0.50 with a significance of <0.05. AUC equals 0.5 when the diagnostic test corresponds to random chance (null hypothesis) and 1.0 indicates perfect diagnostic accuracy.

3.9 Follow-up

Follow-up was undertaken by independent review of hospital electronic patient records, summary of health records from the patient's General Practitioner (GP) obtained at least 6-months after attendance and a national clinical records search (which identifies death). GPs were therefore requested to provide all information regarding presentation to other institutions with chest pain, cardiology outpatient review and cardiac testing, including angiography with or without intervention. Where a participant had not attended hospital follow-up and/or a GP had failed to provide a health record/not GP-registered, the patient was regarded as lost to follow-up.

3.10 Dissemination and Publication of Results

This will be carried out according to the **Declaration of Helsinki. Principle 27**

"Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available."

Chapter 4.

Results

4.1 Study Participants

For the primary analysis, 964 consenting patients were recruited. Participants were predominantly white, older men who commonly had risk factors for coronary artery disease (Table 19). Patients presented to the ED at a median of 2.4 hours (IQR 0.4-4.29) after chest pain onset.

4.2 Loss to Follow-Up

Of the 964 patients recruited, 4 patients were lost to follow-up meaning that 99.6% were successfully monitored for 30 days. In those patients lost to follow-up health records pertaining to presence of outcome measures were unobtainable despite repeated requests to General Practitioners for information. These patients were not included in the final statistical analysis, however, no patient lost to follow-up died within 30 days of attendance.

4.3 Incidence of Major Adverse Cardiac Events

97/960 (10.1%) had a MACE within 30 days. Patients with MACE were significantly older, more likely to be male with hypertension, diabetes, dyslipidaemia and a prior history of coronary artery disease. Frequency of MACE during initial hospital attendance or 30 day follow-up are shown in Table 20. The 97 patients with MACE had a total of 139 events, the most common being fatal/non-fatal AMI (8.3% of total population).

Table 19. Patient demographics as per primary outcome (MACE)

	Total (N=960)	MACE Negative at 30 days (N=863)	MACE Positive at 30 days (N=97)	Significance of difference between MACE positive and negative groups (p value)
Age, yrs. (Mean±SD)	58.0 ± 13.3	57.4 ± 13.4	63.4 ± 10.6	**<0.0001**
Sex (% male)	565 (58.9)	498 (57.7)	67 (69.1)	**0.031**
Ethnicity (% British Caucasian)	914 (95.2)	825 (95.6)	89 (91.8)	0.093
Risk factors N (%)				
Hypertension	528 (55.0)	454 (52.6)	74 (76.3)	**<0.0001**
Diabetes	164 (17.1)	140 (16.2)	24 (24.7)	**0.035**
Dyslipidaemia	635 (66.1)	557 (64.5)	78 (80.4)	**0.002**
Smoking Current	231 (24.1)	209 (24.2)	22 (22.7)	0.737
Smoker Ex	343 (35.1)	307 (35.6)	36 (37.1)	0.764
Family History of Coronary Artery Disease	354 (36.9)	318 (36.8)	36 (37.1)	0.959
Medical History				
Angina	251 (26.1)	214 (24.8)	37 (38.1)	**0.005**
Myocardial Infarction	204 (21.3)	171 (19.8)	33 (34.0)	**0.001**
Percutaneous Coronary Intervention	183 (19.1)	154 (17.8)	29 (29.9)	**0.004**
Congestive Cardiac Failure	30 (3.1)	26 (3.0)	4 (4.1)	0.258
Atrial Arrhythmia	119 (12.4)	109 (12.6)	10 (10.3)	0.340
Stroke	63 (6.6)	57 (6.6)	6 (6.2)	0.875
Coronary Artery Bypass Graft	50 (5.2)	41 (4.8)	9 (9.3)	0.057
Baseline Medications				
Aspirin	361 (37.6)	311 (36.0)	50 (51.5)	**0.003**
Clopidogrel	112 (11.7)	102 (11.8)	10 (10.3)	0.661
Beta Blocker	281 (29.3)	249 (28.9)	32 (33.0)	0.396
ACE Inhibitor	272 (28.3)	236 (27.3)	36 (37.1)	**0.043**
Statin	369 (38.4)	322 (37.3)	47 (48.5)	**0.032**
Median Length of Hospital Stay (hrs.) (IQR)	18.8 (2.6-35.0)	17.4 (8.7-26.1)	109.5 (54.3-164.7)	**<0.0001**

MACE: Major Adverse Cardiac Events, SD: Standard Deviation, IQR: Interquartile Range

Table 20. Frequency of major adverse cardiac events during initial hospital attendance or 30 day follow-up

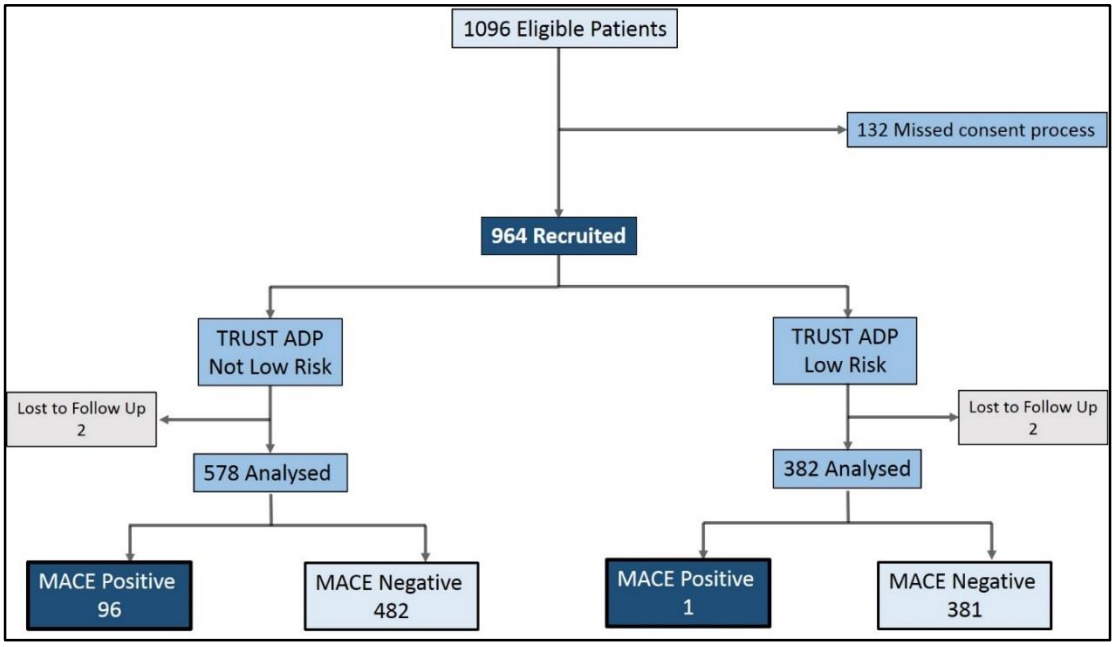
	Number of Events	Frequency of Event Type (%)
Acute Myocardial Infarction	**80**	**8.3**
Non-ST Elevation Myocardial Infarction	**77**	**8.0**
ST Elevation Myocardial Infarction	**3**	**0.03**
Emergency/Urgent Revascularization	**56**	**5.8**
Cardiovascular Death	**1**	**0.01**
Ventricular Arrhythmia	**1**	**0.01**
High atrioventricular block	**0**	**0**
Cardiac Arrest	**1**	**0.01**

4.4 The Diagnostic Accuracy of the TRUST ADP

> ***Primary Aim of the TRUST Study:*** *To establish whether the TRUST ADP for suspected ACS patients consisting of hs-cTn, a non-ischaemic ECG and the m-Goldman score, could successfully identify low-risk patients suitable for discharge after a single blood draw at presentation to the ED.*

For analysis of the diagnostic accuracy of the TRUST ADP, 964 consenting participants were recruited (Figure 10), 4 patients were lost to follow-up (health records pertaining to presence of outcome measures unobtainable) meaning that 99.6% were successfully monitored for 30 days. However, no patient lost to follow-up died within 30 days of attendance.

Figure 10. Participant recruitment flowchart (Primary Analysis)



The TRUST ADP classified 382 (39.8%) of patients as at low-risk of MACE, with a sensitivity of 99.0% (95% CI 93.7-99.9) and NPV of 99.7% (95% CI 98.4-100).

The TRUST ADP classified 382 (39.8%) of patients as at low-risk of MACE, with a sensitivity of 99.0% (95% CI 93.7-99.9) and NPV of 99.7% (95% CI 98.4-100) and had a similar diagnostic performance for the secondary outcome measure (AMI) (Table 21/22).

Figure 11 demonstrates that the combination of components that make up the ADP were more accurate at ruling-out patients for MACE (sensitivity) than the individual components themselves (m-Goldman score ≤ 1 and/or hs-cTnT <14 ng/L). The m-Goldman risk score, if used in isolation missed 28/457 (6.1%) of patients with MACE at day 30, whilst hs-cTnT missed 22/766 (2.9%). This improved diagnostic accuracy for the rule-out of MACE was at the expense of a lower specificity of 44.1% (95% CI 43.6-44.3) when compared to m-Goldman ≤ 1 (49.7%; 95% CI 48.6-50.6) and hs-cTnT <14 ng/L (86.2%; 95% CI 85.2-87.0) alone.

A single patient (0.3%) classified as low-risk by the TRUST ADP had a major adverse cardiac event. This patient was a 78-year-old female classified as low-risk on the m-Goldman score and had an hs-cTnT of 13ng/L at presentation. However, a minor hs-cTnT elevation to 20ng/L (delta change 27%) occurred on the second hs-cTnT test at 6 hours and was therefore diagnosed with an AMI. The patient was medically managed and had no further complications.

Table 21. Contingency tables demonstrating the occurrence of 30 day MACE and index AMI According to TRUST ADP and its component parts

Index Test	MACE	No MACE	Total
TRUST ADP			
Not Low Risk	96	482	578
Low Risk	1	381	382
m-Goldman Score			
>1	69	434	503
≤1	28	429	457
hs-cTnT			
≥14 ng/L	75	119	194
<14 ng/L	22	744	766
	AMI	**No AMI**	**Total**
TRUST ADP			
Not Low Risk	79	499	578
Low Risk	1	381	382
m-Goldman Score			
>1	54	449	503
≤1	26	431	457
hs-cTnT			
≥14 ng/L	67	127	194
<14 ng/L	13	753	766

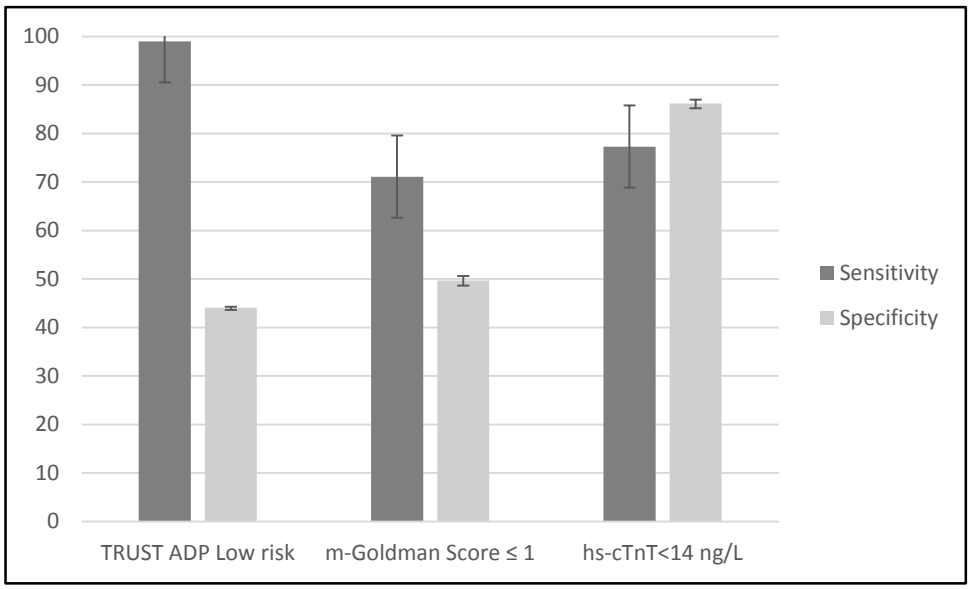
MACE: Major Adverse Cardiac Events at 30 days, AMI: Acute Myocardial Infarction (Fatal/non-fatal) occurring within 30 days

Table 22. Diagnostic accuracy of the TRUST ADP and its components for the prediction of MACE and AMI

	Number of Events/Number Low Risk (%)	Sensitivity (95% CI)	Negative Predictive Value (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	% eligible for early discharge
Primary Outcome MACE								
TRUST ADP Low risk	1/382 (0.3)	99.0 (93.7-99.9)	99.7 (98.4-100)	44.1 (43.6-44.3)	16.6 (15.7-16.8)	1.772 (1.659-1.793)	0.023 (0.001-0.145)	39.8
m-Goldman Score ≤ 1	28/457 (6.1)	71.1 (61.4-79.4)	93.9 (91.8-95.6)	49.7 (48.6-50.6)	13.7 (11.8-15.3)	1.414 (1.195-1.609)	0.581 (0.406-0.794)	47.6
hs-cTnT<14 ng/L	22/766 (2.9)	77.3 (68.3-84.6)	97.1 (96.0-98.0)	86.2 (85.2-87.0)	38.7 (34.2-42.3)	5.607 (4.617-6.522)	0.263 (0.177-0.372)	79.8
Secondary Outcome AMI								
TRUST ADP Low risk	1/382 (0.3)	98.8 (92.4-99.9)	99.7 98.4-100)	43.3 (42.7-43.4)	13.7 (12.8-13.8)	1.741 (1.613-1.766)	0.029 (0.002-0.178)	39.8
m-Goldman Score ≤ 1	26/457 (5.7)	67.5 (56.5-77.1)	94.3 (92.4-96.0)	49.0 (48.0-49.8)	10.7 (9.0-12.3)	1.323 (1.085-1.536)	0.664 (0.460-0.907)	47.6
hs-cTnT<14 ng/L	13/766 (1.7)	83.8 (74.1-90.6)	98.3 (97.3-99.0)	85.6 (84.7-86.2)	34.5 (30.6-37.4)	5.803 (4.842-6.558)	0.190 (0.109-0.306)	79.8

MACE: Major Adverse Cardiac Events at 30 days, AMI: Acute Myocardial Infarction (Fatal/non-fatal) occurring within 30 days

Figure 11. The sensitivity and specificity of the TRUST ADP and its component parts for MACE at 30 days



Error bars: 95% Confidence Intervals

Table 23 illustrates the demographic differences between TRUST ADP low-risk groups and those not classified as low risk, with all being statistically significant except current smoking and family history of coronary artery disease.

Table 23. Patient demographics as per TRUST ADP risk group

	TRUST ADP not Low Risk (N=578)	TRUST ADP Low Risk (N=382)	Significance of difference between TRUST ADP groups (p value)
Age, yrs. (Mean±SD)	60.4 ± 12.8	55.6 ± 19.4	**<0.0001**
Sex (% male)	360 (62.3)	205 (53.7)	**0.008**
Ethnicity (% British Caucasian)	549 (95.0)	365 (95.5)	0.687
Risk factors N (%)			
Hypertension	319 (55.2)	123 (34.8)	**<0.0001**
Diabetes	124 (21.4)	40 (10.5)	**<0.0001**
Dyslipidaemia	429 (74.2)	206 (53.9)	**<0.0001**
Smoking Current	129 (22.3)	102 (26.7)	0.120
Smoker Ex	229 (39.6)	114 (29.8)	**0.002**
Family History of Coronary Artery Disease	215 (37.2)	139 (36.4)	0.799
Medical History			
Angina	207 (35.8)	44 (11.5)	**<0.0001**
Myocardial Infarction	174 (30.1)	30 (7.9)	**<0.0001**
Percutaneous Coronary Intervention	146 (25.3)	37 (9.7)	**<0.0001**
Congestive Cardiac Failure	25 (4.3)	5 (1.3)	**0.009**
Atrial Arrhythmia	86 (14.9)	33 (8.6)	**0.004**
Stroke	45 (7.7)	18 (4.7)	0.060
Coronary Artery Bypass Graft	41 (7.1)	9 (2.4)	**0.001**
Baseline Medications			
Aspirin	276 (47.8)	85 (22.3)	**<0.0001**
Clopidogrel	84 (14.5)	28 (7.3)	**0.001**
Beta Blocker	210 (36.3)	71 (18.6)	**<0.0001**
ACE Inhibitor	195 (33.7)	77 (20.2)	**<0.0001**
Statin	276 (47.8)	93 (24.3)	**<0.0001**
Mean Length of Stay (Standard Deviation)	56.9 (17.7-96.1)	26.1 (7.1-45.1)	**<0.0001**
Median Length of Hospital Stay (hrs.) (Interquartile Range)	22.4 (-8.6-53.4)	14.1 (7.9-20.3)	**0.009**

SD: Standard Deviation

4.5 Improving Efficiency with the TRUST ADP

> ***Aim:*** *To establish potential improvements in system efficiency using the TRUST ADP through time-and-motion analysis of hs-cTnT testing.*

Patients identified as low risk by the TRUST ADP had a mean length of hospital stay of 26.1 hours (SD 7.1-45.1) and a median of 14.1 hours (IQR 7.9-20.3). Time and motion analysis (Figure 12) of real-time hs-cTnT laboratory testing identified that blood results would be available to the treating physician at a median of 2.06 hours (IQR 1.61-2.52) after arrival in the ED. In a 'doctor-on-demand' scenario (Thokala et al. 2012), in which medical staff are available 24 hours a day to make a discharge decision within 60 minutes of results being available, then discharge may be achieved within 2.66 hours (IQR 2.21-3.12) of attendance (Figure 13).

Figure 12. Time and motion analysis of hs-cTnT testing

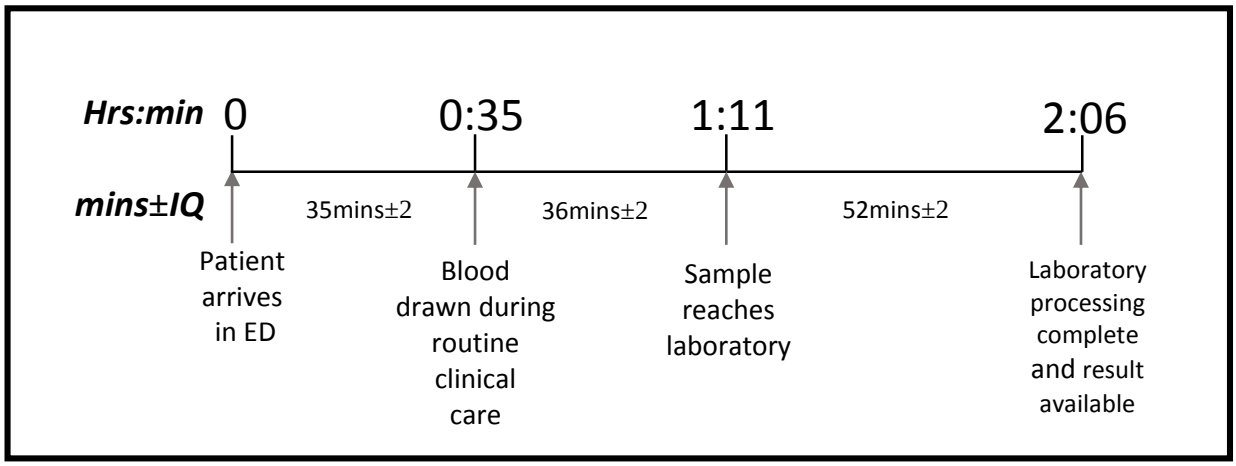
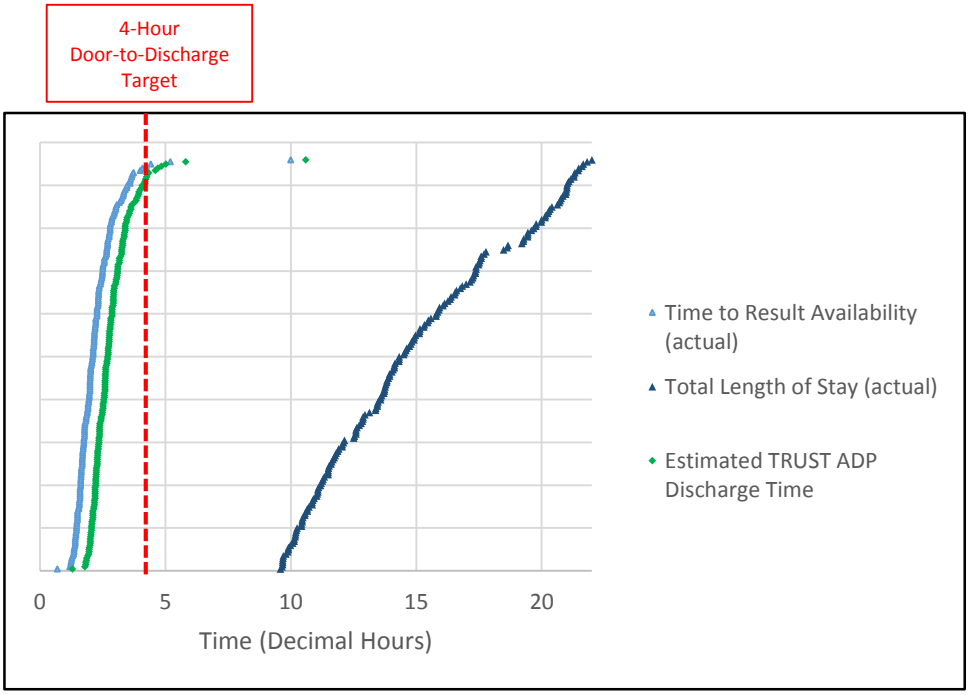


Figure 13. A group scatter plot demonstrating the difference between actual length of stay and estimated TRUST ADP discharge time



4.6 Undetectable hs-cTnT Discharge Strategies

Aim: *To compare the diagnostic accuracy of the TRUST ADP with strategies utilising initial undetectable hs-cTnT levels.*

The occurrence of MACE and AMI during the index hospital visit or at 30 days, according to hs-cTnT detection limits are shown in Table 24. The diagnostic performance of hs-cTnT limit of detection cut-off values in patients with a non-ischaemic ECG are shown in Table 25. By using the limit of detection cut-off value of 5ng/L for the primary outcome measure (MACE) the sensitivity was 96.8% (95%CI 90.6-99.2) and 29.3% of patients were eligible for early discharge. Three patients (1.1%) identified as suitable for discharge using this strategy required urgent revascularization (clinical characteristics summarized in Table 26), all had blood samples taken over 6 hours from chest pain onset. Using the limit of blank (<3ng/L) the sensitivity for MACE was improved to 98.6% (95%CI 91.9-99.9), but only 7.9% would have been eligible for early discharge. One patient (1.4%) with an hs-cTnT <3ng/L required urgent revascularization. Using the secondary outcome measure (AMI) both the limit of detection (<5ng/L) strategy and limit of blank (<3ng/L) strategy achieved 100% sensitivity.

Table 24. Occurrence of 30 day MACE and index AMI according to hs-cTnT detection limits

Index Test	MACE	No MACE	Total
Hs-cTnT<5ng/L*			
≥5ng/L	92	560	652
<5ng/L	3	267	270
Hs-cTnT<3ng/L*			
≥3ng/L	94	755	849
<3ng/L	1	72	73
	AMI	**No AMI**	**Total**
Hs-cTnT<5ng/L*			
≥5ng/L	78	570	648
<5ng/L	0	270	270
Hs-cTnT<3ng/L*			
≥3ng/L	78	771	849
<3ng/L	0	73	73

**922/960(96%) results are reported for the hs-cTnT detection limits. This was due to computer error whereby 38 results were only reported as <14ng/L.*
MACE: Major Adverse Cardiac Events at 30 days, AMI: Acute Myocardial Infarction (Fatal/non-fatal) occurring within 30 days

Table 25. Diagnostic accuracy of detection limit cut-offs of hs-cTnT for the prediction of MACE and AMI

	Number of Events/Number Low Risk (%)	Sensitivity (95% CI)	Negative Predictive Value (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	% eligible for early discharge
Primary Outcome MACE								
hs-cTnT <5ng/L	3/270 (1.1)	96.8 (90.6-99.2)	98.9 (96.7-99.7)	32.3 (31.6-32.6)	14.1 (13.2-14.5)	1.430 (1.323-1.470)	0.098 (0.025-0.299)	29.3
hs-cTnT <3ng/L	1/73 (1.4)	98.9 (93.8-99.9)	98.6 (91.9-99.9)	8.7 (8.1-8.8)	11.1 (10.5-11.2)	1.084 (1.020-1.096	0.121 (0.006-0.769)	7.9
Secondary Outcome AMI								
hs-cTnT <5ng/L	0/270 (0.0)	100 (94.3-100)	100 (98.3-100)	32.0 (31.5-32.1)	12.0 (9.7-12.0)	1.474 (1.378-1.474)	0.000 (0.000-0.182)	29.3
hs-cTnT <3ng/L	0/73 (0.0)	100 (94.4-100)	100 (94.0-100)	8.6 (8.1-8.6)	9.2 (8.7-9.2)	1.095 (1.028-1.095)	0.000 (0.000-0.685)	7.9

MACE: Major Adverse Cardiac Events at 30 days, AMI: Acute Myocardial Infarction (Fatal/non-fatal) occurring within 30 days

Table 26. Clinical characteristics of patients diagnosed with MACE at 30 Days with an initial hs-cTnT<5ng/L

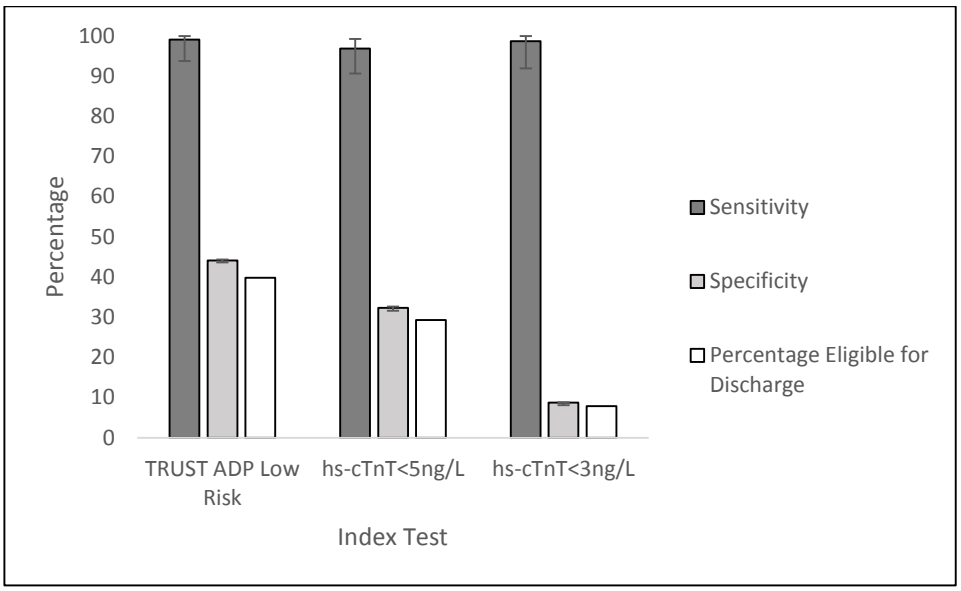
Age (Years)	Sex	Time Since Chest Pain Onset (hours)	Initial hs-cTnT (ng/L)	6 hour hs-cTnT (ng/L)	m-Goldman Score	Type of MACE	Angiographic Results
49	F	6.91	3.0	4.6	2	Urgent Revascularisation	>70% Stenosis (LAD)*
49	M	24.75	3.5	4.1	2	Urgent Revascularisation	>70% Stenosis (LAD)*
48	M	7.15	4.9	5.3	2	Urgent Revascularisation	>70% Stenosis (RCA)*

**LAD: Left Anterior Descending Coronary Artery, RCA: Right Coronary Artery*
Hs-cTnT: High-sensitivity cardiac troponin T, MACE: Major Adverse Cardiac Event at 30 days

4.6.1 Comparison of the TRUST ADP and Undetectable hs-cTnT Discharge Strategies

The TRUST ADP identified significantly more patients suitable for immediate discharge at 39.8% vs 29.3% (<5ng/L) and 7.9% (<3ng/L) (P<0.001) with a lower false-positive rate; specificity 44.1% (95%CI 43.6-44.3) vs 32.3% (95%CI 31.6-32.6) and 8.7% (95%CI 8.1-8.8) respectively, whilst maintaining a high diagnostic accuracy for the rule-out of MACE (Figure 14).

Figure 14. Comparison of the diagnostic utility of the TRUST ADP and undetectable hs-cTnT discharge strategies for the detection of MACE



Error bars: 95% Confidence Intervals

4.7 An Alternative High-Sensitivity Troponin Assay: Abbott hs-cTnI

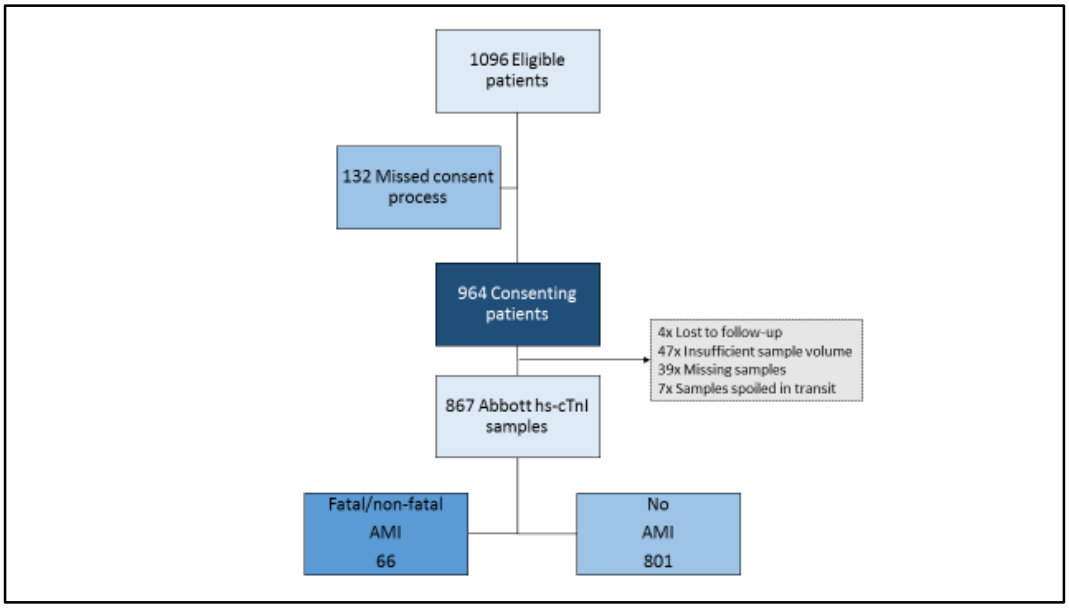
For all analysis incorporating Abbott hs-cTnI the outcome measure of fatal/non-fatal AMI has been used as a primary outcome measure, as opposed to MACE. This outcome measure does not include revascularisation. This is in an attempt to remove the bias associated with the use of Roche hs-cTnT in clinical practice where it would be used to guide referral for angiography and revascularisation decisions.

It is important to acknowledge that another commercially available high-sensitivity troponin assay (Abbott hs-cTnI) is available (NICE 2014), and this assay is in use in many clinical centres. Therefore in order to establish the general applicability of the TRUST ADP, it is necessary to assess the performance of this assay in the TRUST study cohort and evaluate hs-cTnI in comparison to hs-cTnT.

867 samples were suitable for Abbott hs-cTnI testing after transport to University College Dublin biochemistry laboratory (analysis performed in December 2014). This represents 89.9% of the consenting study population (Figure 15).

66/867 (7.6%) had the outcome event (AMI) within 30 days, including the initial hospital attendance.

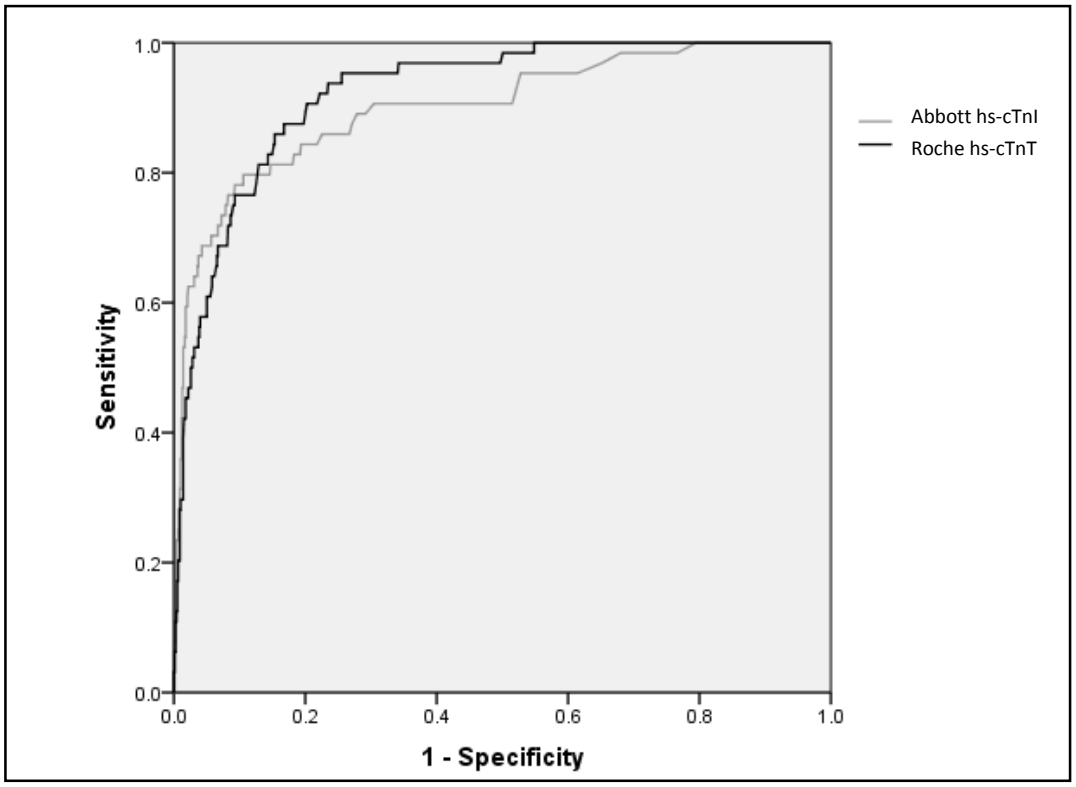
Figure 15. Participant recruitment flow chart for Abbott hs-cTnI analysis



4.7.1 Comparison of the Diagnostic Accuracy of hs-cTnT and hs-cTnI Assays at Presentation for the Detection of AMI

Receiver-operating characteristic (ROC) curves for discrimination of fatal/non-fatal AMI for hs-cTnT and hs-cTnI at presentation are shown in Figure 16. The area under the curve (AUC) for hs-cTnT and hs-cTnI at presentation were 0.925 (95%CI 0.899-0.950) and 0.903 (95%CI 0.860-0.947) respectively, and were not significantly different (p=0.575). However at the 99th percentile cut-off hs-cTnT identified significantly more AMIs at presentation compared to hs-cTnI; 66/79 (83.5%) vs. 41/66 (62.1%) (P=0.004) with a higher sensitivity; 83.5% (95%CI 73.8-90.5) vs. 62.1% (95% CI 51.9-70.8).

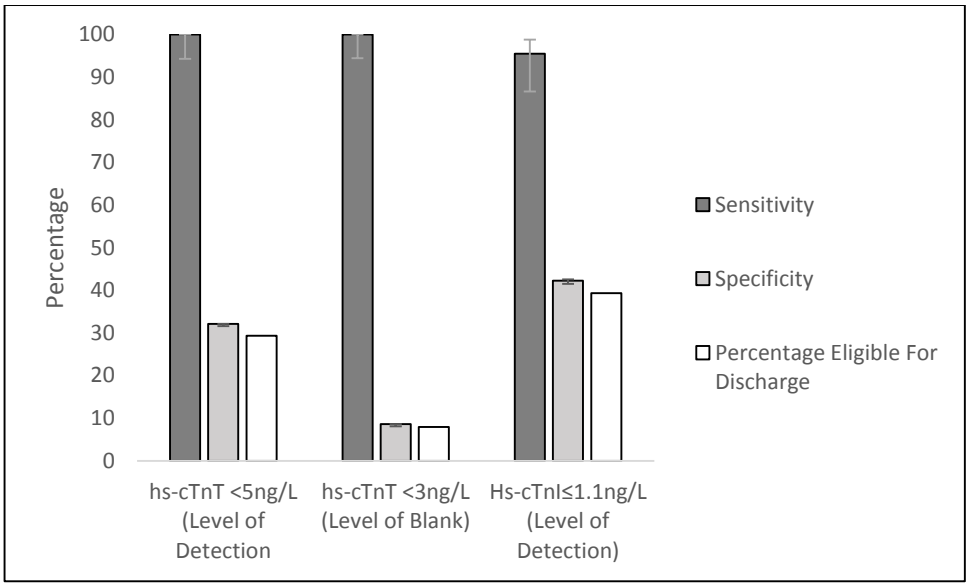
Figure 16. Receiver-operating characteristic curves for AMI using hs-cTnT and hs-cTnI results taken at presentation to the Emergency Department



4.7.2 Undetectable Troponin Rule-Out Strategies: Roche hs-cTnT vs. Abbott hs-cTnI

The diagnostic utility of the levels of detection (LoD) for hs-cTnT and hs-cTnI are summarised in Figure 17. It should be noted that the assay manufacturers, Abbott, do not provide a level of blank for their hs-cTnI assay. The hs-cTnI assay identified significantly more patients suitable for early discharge when compared to hs-cTnT at the LoD; 39.3% vs. 29.3% (P<0.0001). This improved efficiency was at the expense of a reduced sensitivity for the detection of AMI of 95.5%, compared to 100% for hs-cTnT, although it should be noted that the lower 95% confidence intervals for hs-cTnT include those of hs-cTnI, suggesting that performance of assays as a rule-out tool may be similar. The clinical characteristics of the 3 patients with a diagnosis of AMI not detected using the LoD of the hs-cTnI assay are summarised in Table 27.

Figure 17. Comparison of the diagnostic utility of undetectable hs-cTnT and hs-cTnI discharge strategies for the detection of AMI



Error Bars: 95% Confidence Intervals

Table 27. Clinical characteristics of patients with a diagnosis of AMI not detected using the level of detection of the Abbott hs-cTnI assay

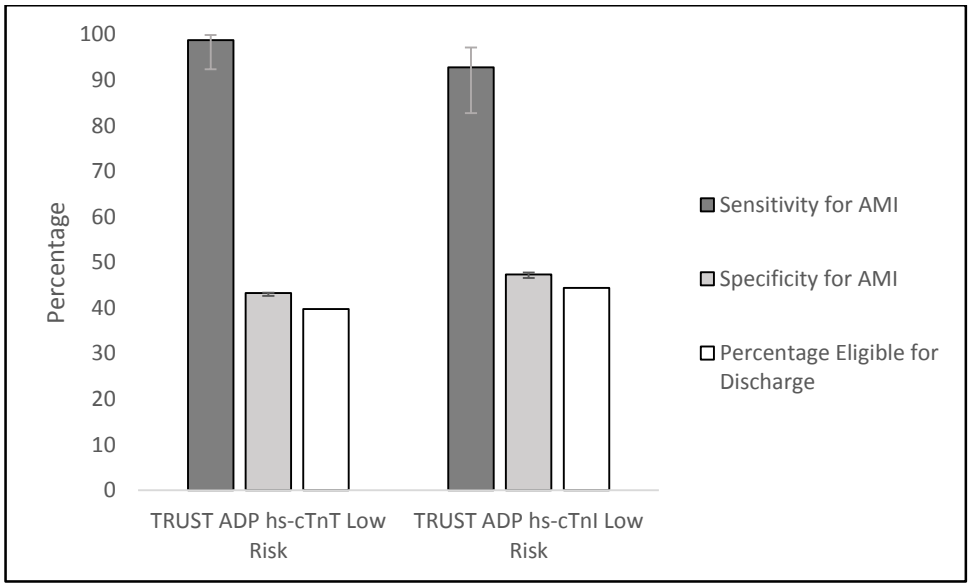
Age (Years)	Sex	Time Since Chest Pain Onset (hours)	Initial Abbott hs-cTnI (ng/L)	Initial Roche hs-cTnT (ng/L)	6 hour Roche hs-cTnT (ng/L)	Change in hs-cTnT (%)	Angiographic Results
68	M	48.6	1.0	22.9	17.5	24	N/A
60	M	1.85	0.9	29.0	53.0	83	Severe Stenosis LMS/LAD* with intervention
48	M	7.9	0.5	20.7	16.0	23	Mild Coronary Artery Disease

**LMS: Left Main Stem, LAD: Left Anterior Descending Coronary Artery*

4.7.3 The TRUST ADP: Comparing the use of Roche hs-cTnT and Abbott hs-cTnI

The diagnostic accuracy of the TRUST ADP when either hs-cTnT or hs-cTnI are used is presented in Figure 18. By integrating hs-cTnI at the 99th percentile cut-off value (26.2ng/L) for this assay the sensitivity of the TRUST ADP for the detection of AMI drops to 92.8% (95% CI 82.8-97.2) and 5 patients with AMI would have been missed. More patients were classified as low risk using hs-cTnI (44.4% vs 39.8%; P=0.046) with an improved specificity for the diagnosis of AMI (47.4% vs 43.3%).

Figure 18. Comparison of the diagnostic accuracy of the TRUST ADP integrating hs-cTnT and hs-cTnI at the 99th percentile cut-off value



Error Bars: 95% Confidence Intervals,
AMI: Acute Myocardial Infarction (fatal/non-fatal) within 30 days

4.8 A Diagnostic Comparison of Five Established Risk Scores and Two High-Sensitivity Assays

Aim: To compare the ability of five established risk scores, when used in conjunction with either high-sensitivity troponin T (Elecsys hs-cTnT) or I (Architect hs-cTnI), to identify low risk patients with chest pain symptoms suggestive of ACS suitable for early discharge after a single blood draw at presentation to ED.

For risk score summaries see Table 15, Page 70.

To define the clinical utility of each rule-out protocol a target miss-rate of fatal or non-fatal AMI for each risk score as 0.5% or less was set (NPV>99.5%), this is the cut-off at which the majority of emergency physicians may expect diagnostic strategies for the assessment of suspected ACS to achieve (Than et al. 2012b). Also, for a risk score to be of substantial benefit, significant numbers of patients need to be identified as low-risk, a target of >30% was set, in line with existing ADPs which incorporate hs-cTn testing (Cullen et al. 2013).

Test performance of each risk score (m-Goldman, TIMI, GRACE, HEART and Vancouver) and their pre-defined cut-offs for determination of low risk status in combination with presentation Roche hs-cTnT and Abbott hs-cTnI are shown in Tables 28 and 29 respectively.

Figure 19 presents sensitivity vs. 1-specificity for each risk score and both hs-cTn assays. When considering the upper bounds of the 95% confidence intervals for test sensitivity, only two risk scores (GRACE<80 and HEART≤3) did not have the potential to achieve the threshold of 98% sensitivity for the diagnosis of AMI, when used in

conjunction with hs-cTnT. For hs-cTnI, three risk scores (m-Goldman≤1, TIMI≤1 and GRACE<80) did not have the potential to achieve this sensitivity threshold. Within those tests that did have the potential to achieve a sensitivity threshold of 98% (Kline et al. 2005), there was a wide variation in test specificity. This ranged from 10.6% (95% CI 10.1-10.6) for GRACE<60 with hs-cTnT to 53.5% (95%CI 52.8-53.8) for TIMI<1 with hs-cTnT.

Table 28. Diagnostic accuracy for each risk score with pre-defined cut-offs for determination of low risk status in combination with presentation Roche hs-cTnT results for fatal/non-fatal AMI

	m-Goldman Score 0 and hs-cTnT ≤14ng/L	m-Goldman ≤1 and hs-cTnT≤14ng/L (TRUST ADP)	TIMI Score 0 and hs-cTnT ≤14ng/L	TIMI Score ≤1 and hs-cTnT ≤14ng/L	GRACE <60 (incorporates hs-cTnT)*	GRACE<80 (incorporates hs-cTnT)*	HEART Score ≤2 (incorporates hs-cTnT)	HEART Score ≤ 3 (incorporates hs-cTnT)	Vancouver Chest Pain Rule (incorporates hs-cTnT)
Number of AMI with number of patients defined as low-risk (%)	1/102 (1.0)	1/382 (0.3)	0/308 (0.0)	4/444 (0.9)	0/93 (0.0)	6/301 (2.0)	1/125 (0.8)	5/303 (1.7)	0/154 (0.0)
Sensitivity (95% CI)	98.7 (92.5-99.9)	98.8 (92.4-99.9)	100 (94.3-100)	94.9 (87.0-98.4)	100 (94.4-100)	92.3 (83.7-96.8)	98.7 (92.4-99.9)	93.7 (85.5-97.6)	100 (94.4-100)
Negative predictive value (95% CI)	99.0 (94.2-99.9)	99.7 (98.4-100)	100 (98.5-100)	99.1 (97.7-99.7)	100 (95.3-100)	98.0 (95.8-99.2)	99.2 (95.2-100)	98.3 (96.2-99.4)	100 (97.1-100)
Specificity (95% CI)	11.5 (10.9-11.6)	43.3 (42.7-43.4)	35.0 (34.5-35.0)	50.0 (49.3-50.3)	10.6 (10.1-10.6)	33.8 (33.0-34.2)	14.1 (13.5-14.2)	33.9 (33.1-34.2)	17.5 (17.0-17.5)
Positive predictive value (95% CI)	9.1 (8.5-9.2)	13.5 (12.6-13.7)	12.1 (11.4-12.1)	14.6 (13.4-15.1)	9.1 (8.6-9.1)	11.1 (10.0-11.6)	9.4 (8.8-9.5)	11.3 (10.3-11.8)	9.8 (6.4-9.8)
Positive likelihood ratio (95% CI)	1.115 (1.038-1.130)	1.741 (1.611-1.766)	1.538 (1.440-1.538)	1.899 (1.717-1.979)	1.119 (1.050-1.119)	1.393 (1.249-1.470)	1.149 (1.069-1.165)	1.416 (1.278-1.484)	1.212 (1.137-1.212)
Negative likelihood ratio (95% CI)	0.110 (0.006-0.691)	0.029 (0.002-0.180)	0.000 (0.000-0.165)	0.101 (0.033-0.263)	0.000 (0.000-0.555)	0.228 (0.093-0.495)	0.090 (0.005-0.561)	0.187 (0.069-0.439)	0.000 (0.000-0.331)
% defined as low-risk	10.6	39.8	32.1	46.2	9.7	31.6	13.0	31.6	16.0

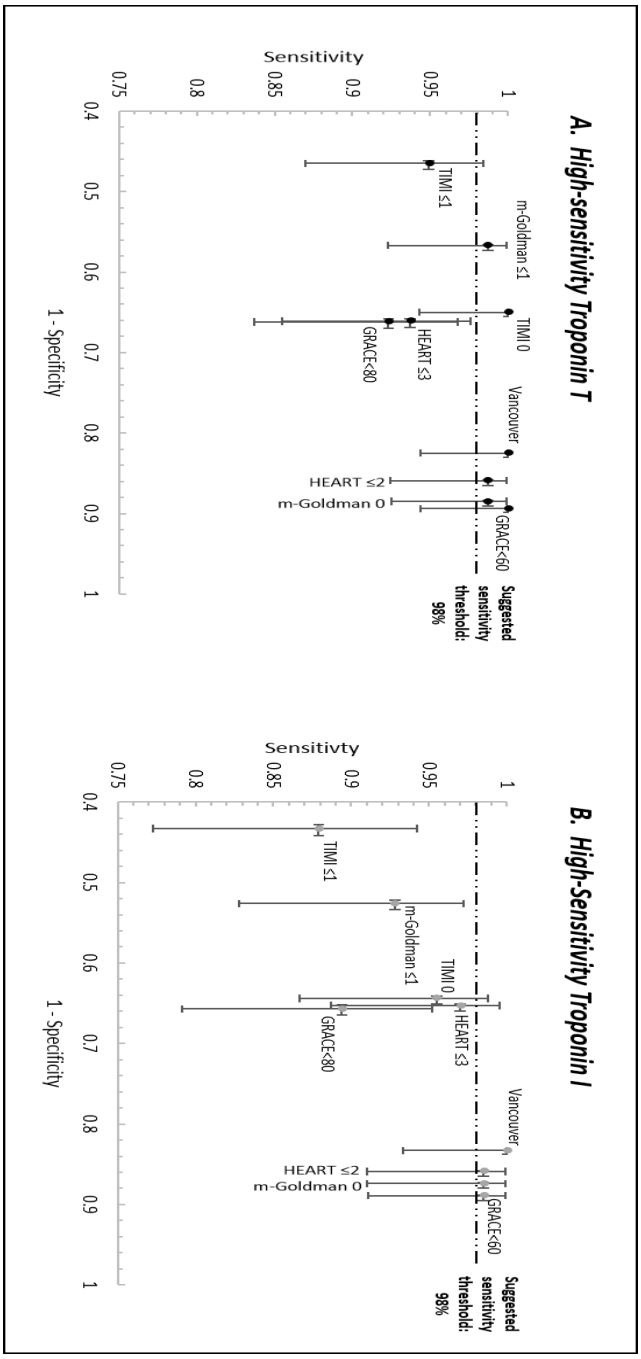
**Incomplete GRACE scores in 7 cases due to missing creatinine results*

Table 29. Diagnostic accuracy for each risk score with pre-defined cut-offs for determination of low risk status in combination with presentation Abbott hs-cTnI results for fatal/non-fatal AMI

	m-Goldman Score 0 and hs-cTnI ≤26.2ng/L	m-Goldman ≤1 and hs-cTnI ≤26.2ng/L (TRUST ADP)	TIMI Score 0 and hs-cTnI ≤26.2ng/L	TIMI Score ≤1 and hs-cTnI ≤26.2ng/L	GRACE <60 (incorporates hs-cTnI)*	GRACE<80 (incorporates hs-cTnI)*	HEART Score ≤2 (incorporates hs-cTnI)	HEART Score ≤3 (incorporates hs-cTnI)	Vancouver Chest Pain Rule (incorporates hs-cTnI)
Number of AMI with number of patients defined as low risk (%)	1/102 (1.0)	5/385 (1.3)	3/288 (1.0)	8/428 (1.9)	1/89 (1.1)	7/280 (2.5)	1/114 (0.9)	2/280 (0.7)	0/134 (0.0)
Sensitivity (95% CI)	98.5 (91.0-99.9)	92.8 (82.8-97.2)	95.5 (86.7-98.8)	87.9 (77.3-94.2)	98.5 (91.1-99.9)	89.4 (79.1-95.2)	98.5 (91.0-99.9)	97.0 (88.7-99.5)	100 (93.3-100)
Negative predictive value (95% CI)	99.0 (94.2-99.9)	98.7 (97.0-99.5)	99.0 (96.9-99.7)	98.1 (96.5-99.1)	98.9 (93.4-99.9)	97.5 (95.1-98.9)	99.1 (94.8-100)	99.3 (97.3-99.9)	100 (96.7-100)
Specificity (95% CI)	12.6 (12.0-12.7)	47.4 (46.6-47.8	35.6 (34.9-35.9)	52.4 (51.6-53.0)	11.1 (10.5-11.2)	34.3 (33.5-34.8)	14.1 (13.5-14.2)	34.7 (34.0-34.9)	16.7 (16.2-16.7)
Positive predictive value (95% CI)	8.5 (7.9-8.6)	12.7 (11.3-13.3)	10.9 (9.9-11.3)	13.2 (11.6-14.2)	8.4 (7.8-8.5)	10.2 (9.0-10.8)	8.6 (8.0-8.8)	10.9 (10.0-11.2)	9.0 (8.4-9.0)
Positive likelihood ratio (95% CI)	1.127 (1.035-1.145)	1.758 (1.551-1.863)	1.482 (1.330-1.541)	1.848 (1.596-2.003)	1.107 (1.017-1.125)	1.361 (1.190-1.461)	1.147 (1.052-1.165)	1.485 (1.345-1.528)	1.201 (1.114-1.201)
Negative likelihood ratio (95% CI)	0.120 (0.006-0.746)	0.160 (0.059-0.370)	0.128 (0.033-0.383)	0.231 (0.109-0.440)	0.137 (0.007-0.852)	0.309 (0.137-0.624)	0.107 (0.006-0.665)	0.087 (0.015-0.332)	0.000 (0.000-0.412)
% eligible for early discharge	11.8	44.4	33.2	49.4	10.3	32.5	13.1	32.2	15.4

**Incomplete GRACE scores in 6 cases due to missing creatinine results*

Figure 19. Test performance of each risk score in combination with presentation A. hs-cTnT and B. hs-cTnI results as illustrated by sensitivity against 1-specificity



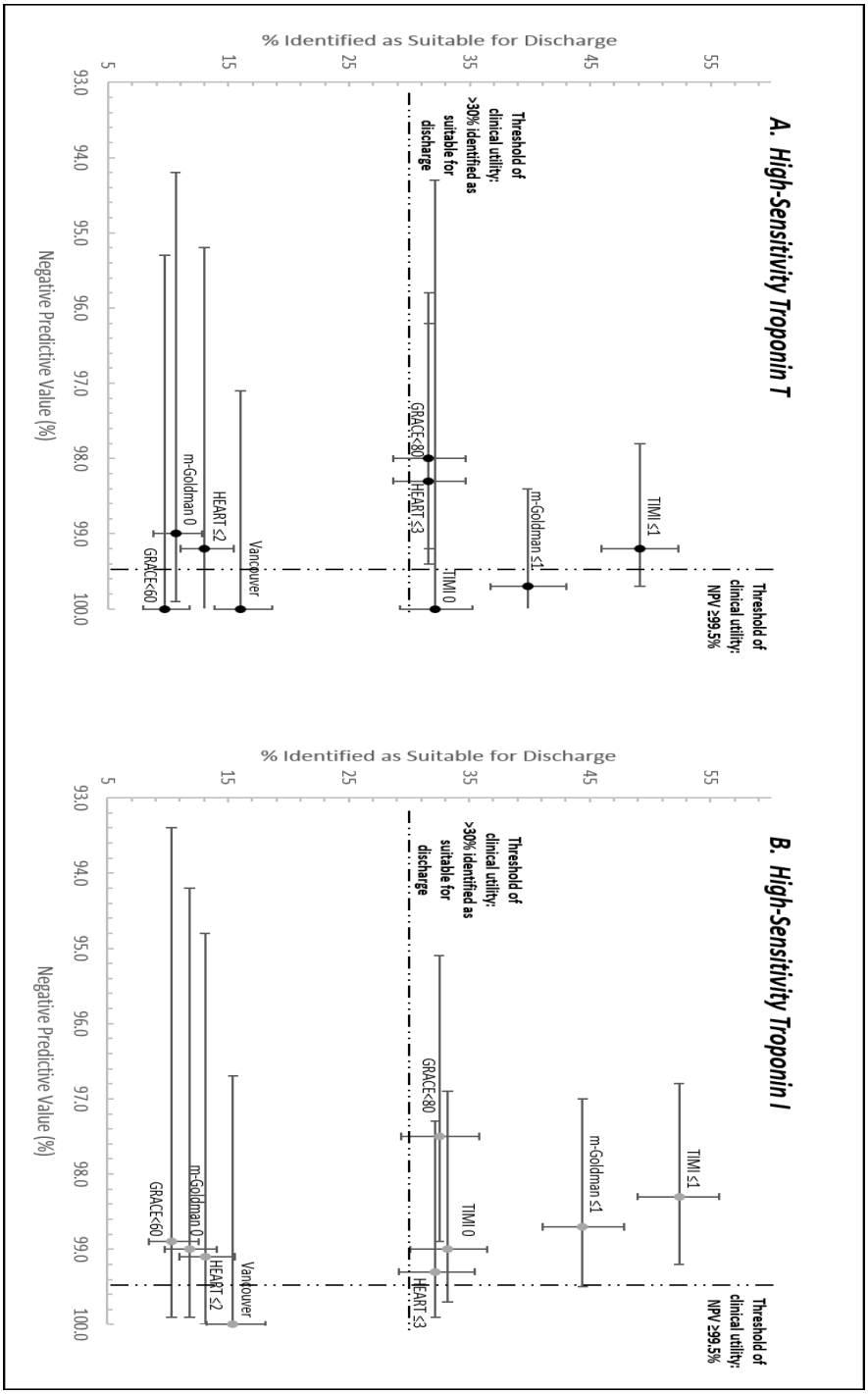
Sensitivity threshold of 98% suggested by Kline et al. 2005 as the threshold at which the risks of false-positive testing (beyond biomarker analysis) outweigh the risk of untreated disease.

Error Bars: 95% Confidence Intervals

4.8.1 Clinical Utility of Risk Scores and Presentation hs-cTn Testing

The potential clinical utility of each risk score is shown in Figure 20. This demonstrates the percentage defined as suitable for discharge against the NPV for the diagnosis of fatal or non-fatal AMI. When considering the upper bounds of the 95% confidence intervals for each test, TIMI 0 or ≤1 and m-Goldman≤1 with hs-cTnT, and TIMI 0 and HEART≤3, with hs-cTnI have the potential to achieve an NPV ≥99.5% while identifying >30% of patients as suitable for immediate discharge.

Figure 20. Clinical utility of risk scores in combination with presentation A. hs-cTnT and B. hs-cTnI results



Threshold of Clinical Utility: defined according to a miss-rate of fatal/non-fatal acute myocardial infarction of a negative predictive value ≥99.5% and >30% being eligible for discharge

Each risk score has been tested in combination with the 99th percentile value of hs-cTnT or hs-cTnI taken at presentation

Error Bars: 95% Confidence Intervals

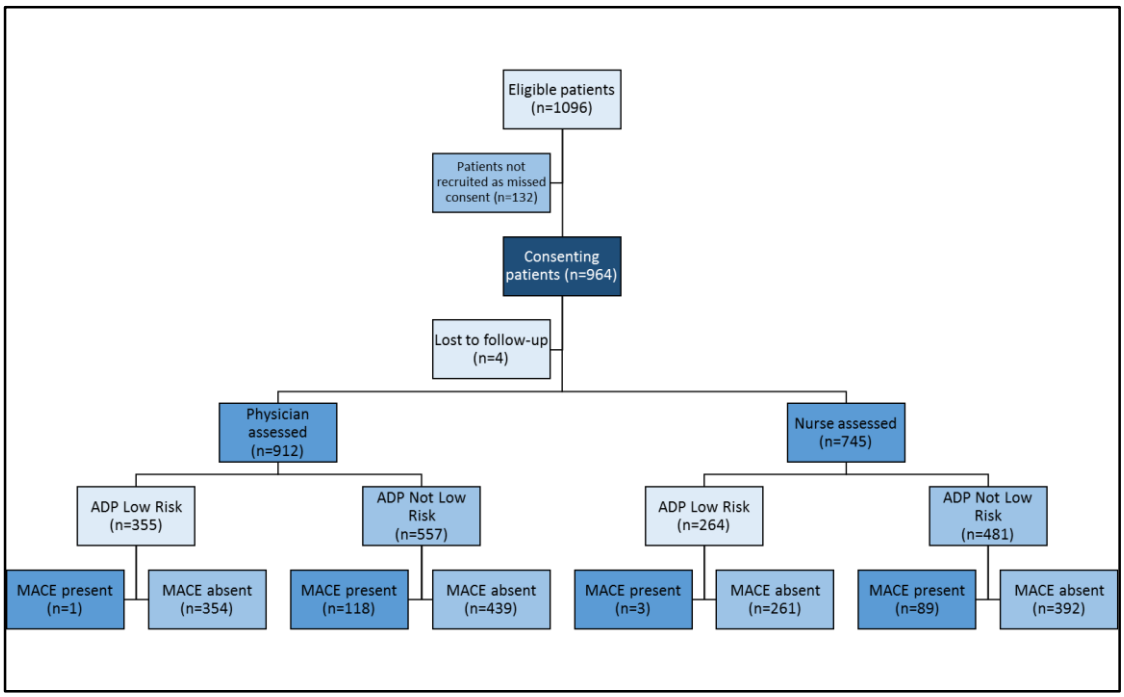
4.9 Evaluating the Diagnostic Accuracy of Emergency Department Nursing Staff Risk Assessment

> ***Aim:*** *To establish the diagnostic accuracy of ED nursing staff risk assessment, using the TRUST ADP, with regard to prediction of future MACE in patients with suspected ACS, and evaluate the inter-observer reliability of nursing and physician assessments within a chest pain specific risk score.*

Figure 21 depicts a participant recruitment flow chart according to physician and nursing assessments using the TRUST ADP. 912/960 (95.0%) had m-Goldman scores recorded by ED physicians and 745/960 (77.6%) by nursing staff.

There were no significant differences between physician and nursing patient-groups in age, gender, risk factors for coronary artery disease, prior cardiovascular history and hospital length of stay ($P>0.05$ for all).

Figure 21. Participant recruitment flow chart according to physician and nursing assessments using the TRUST ADP



ADP: The TRUST Accelerated Diagnostic Protocol, MACE: Major Adverse Cardiac Events occurring within 30 days

4.9.1 Diagnostic Accuracy of the TRUST ADP: Comparison of Physician and Nursing Assessments

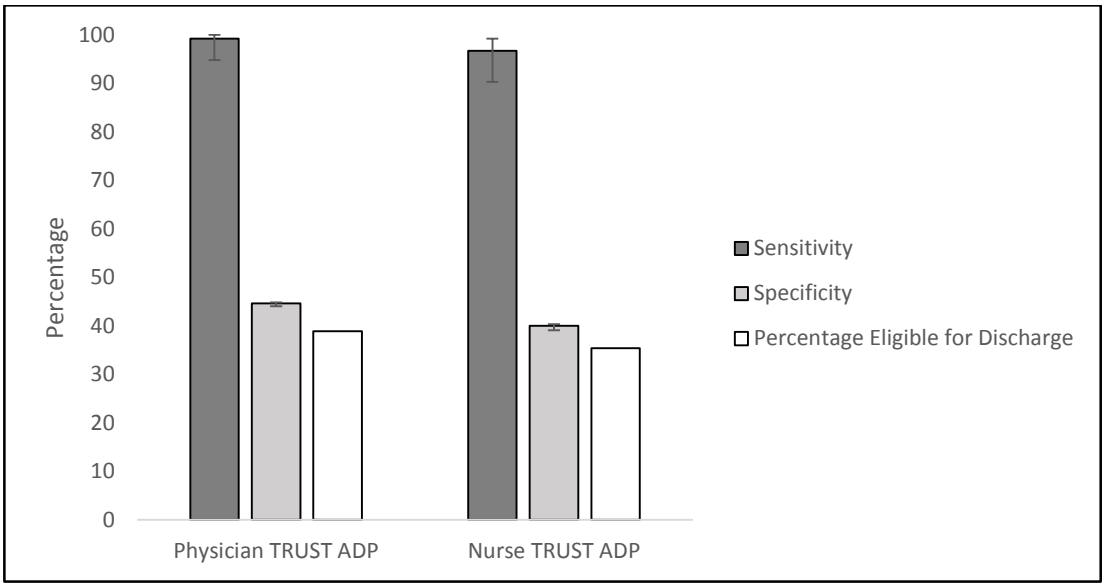
Table 30 presents the statistical analysis of the TRUST ADP and it's parameters for predicting MACE at 30 days according to assessor groups. One patient in the physician group (0.3%), and three patients (1.1%) in the nursing group were classified as low risk by the ADP yet had MACE at 30 days. There was a non-significant trend towards diagnostic accuracy being lower for nursing assessments with regard to sensitivity (99.2% vs. 96.7%) and specificity (44.6% vs. 40%), furthermore fewer patients were eligible for discharge (38.9% vs. 34.5%; P=0.144) when compared to physician assessments. These findings are summarised graphically in Figure 22.

As shown in Figure 23 the area under the curve (AUC) for the m-Goldman score (without incorporation of hs-cTnT) in predicting 30 day MACE was 0.647 (95% CI 0.594-0.700) for physicians and 0.572 (95% CI 0.510-0.634) for nursing staff assessments. This difference did not reach statistical significance (P=0.09).

Table 30. Diagnostic accuracy of the TRUST ADP and an m-Goldman Score of ≤1 for predicting MACE at 30 days according to assessor groups

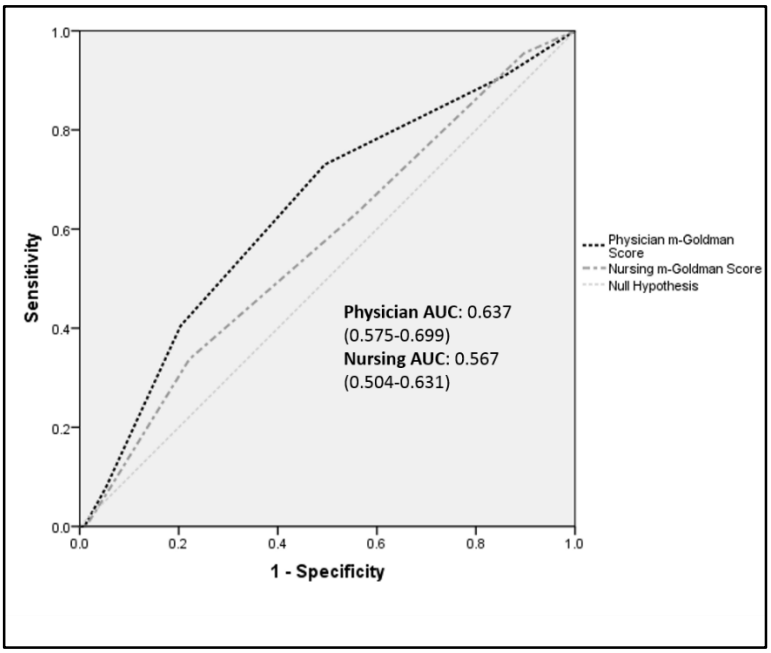
	Physician m-Goldman Score ≤1	Nurse m-Goldman Score ≤1	Physician TRUST ADP	Nurse TRUST ADP
Number of Patients Assessed	912	745	912	745
Number of low risk patients with 30-day MACE missed (%)	31/426 (7.3)	34/328 (10.4)	1/355 (0.3)	3/264 (1.1)
Sensitivity (95% CI)	73.9 (65.5-81.1)	63.0 (53.0-72.3)	99.2 (94.8-100)	96.7 (90.3-99.2)
Negative predictive value (95% CI)	92.7 (90.4-94.7)	89.6 (86.8-92.2)	99.7 (98.3-100)	98.9 (96.6-99.7)
Specificity (95% CI)	49.8 (48.5-50.9)	45.0 (43.6-46.3)	44.6 (44.0-44.8)	40.0 (39.1-40.3)
Positive predictive value (95% CI)	18.1 (16.0-19.9)	13.9 (11.7-15.9)	21.2 (20.3-21.4)	18.5 (17.3-19.0)
Negative Likelihood Ratio (95% CI)	0.52 (0.37-0.71)	0.82 (0.60-1.08)	0.02 (0.00-0.12)	0.08 (0.02-0.25)
Positive Likelihood Ratio (95% CI)	1.47 (1.27-1.65)	1.15 (0.94-1.35)	1.79 (1.69-1.81)	1.61 (1.48-1.66)

Figure 22. Diagnostic accuracy of the TRUST ADP for predicting MACE at 30 Days according to physician and nursing assessments



Error Bars: 95% Confidence Intervals

Figure 23. Receiver operating characteristic curves of the m-Goldman score (without incorporation of hs-cTnT analysis) according to assessor groups



AUC: Area Under the Curve

4.9.2 Inter-Observer Reliability between Physicians and Nursing Staff

Table 31 summarizes inter-observer reliability of individual components of the m-Goldman score and those patients identified as low-risk (m-Goldman ≤1). The degree of reliability varied with four components showing fair agreement, three showing moderate agreement and only one showing substantial agreement (though the finding of pain within 6 weeks of an AMI or revascularization was only present in 1.1% of the population). Using the m-Goldman score alone without incorporating hs-cTnT results, there was fair agreement (Landis and Koch 1977) in the identification of low risk patients between physicians and nursing staff (kappa 0.31, 95% CI 0.24-0.38).

Table 31. Inter-observer reliability of the m-Goldman score between physician and nursing assessments

Clinical Feature	Proportion of patients with finding n (%) (Physician n=912)	Proportion of patients with finding n (%) (Nursing n=745)	Significance of difference	Kappa	95% Confidence Interval	Level of agreement (after Landis and Koch 1977)
Typical new onset chest pain at rest	394 (43.2)	299 (40.1)	P=0.21	0.22	0.15-0.30	Fair
Pain the same as previous AMI	115 (12.6)	75 (10.1)	P=0.11	0.53	0.43-0.63	Moderate
Pain not relieved by Glyceryl Trinitrate Spray within 15 minutes	166 (18.2)	133 (18.0)	P=0.85	0.54	0.46-0.62	Moderate
Pain lasting more than 60 minutes	537 (58.9)	472 (63.4)	P=0.06	0.38	0.31-0.44	Fair
Pain occurring with increasing frequency	140 (15.4)	146 (19.6)	P=0.02	0.23	0.14-0.32	Fair
Hypotension (Systolic Blood Pressure <100mmHg)	23 (2.5)	16 (2.1)	P=0.62	0.43	0.22-0.64	Moderate
Acute shortness of breath	167 (18.3)	177 (23.8)	P=0.007	0.26	0.18-0.34	Fair
Pain within 6 weeks of AMI or revascularization	10 (1.1)	8 (1.1)	P=0.97	0.80	0.58-1.00	Substantial
Low risk patients (m-Goldman ≤1)	426 (46.7)	328 (44.0)	P=0.28	0.31	0.24-0.38	Fair

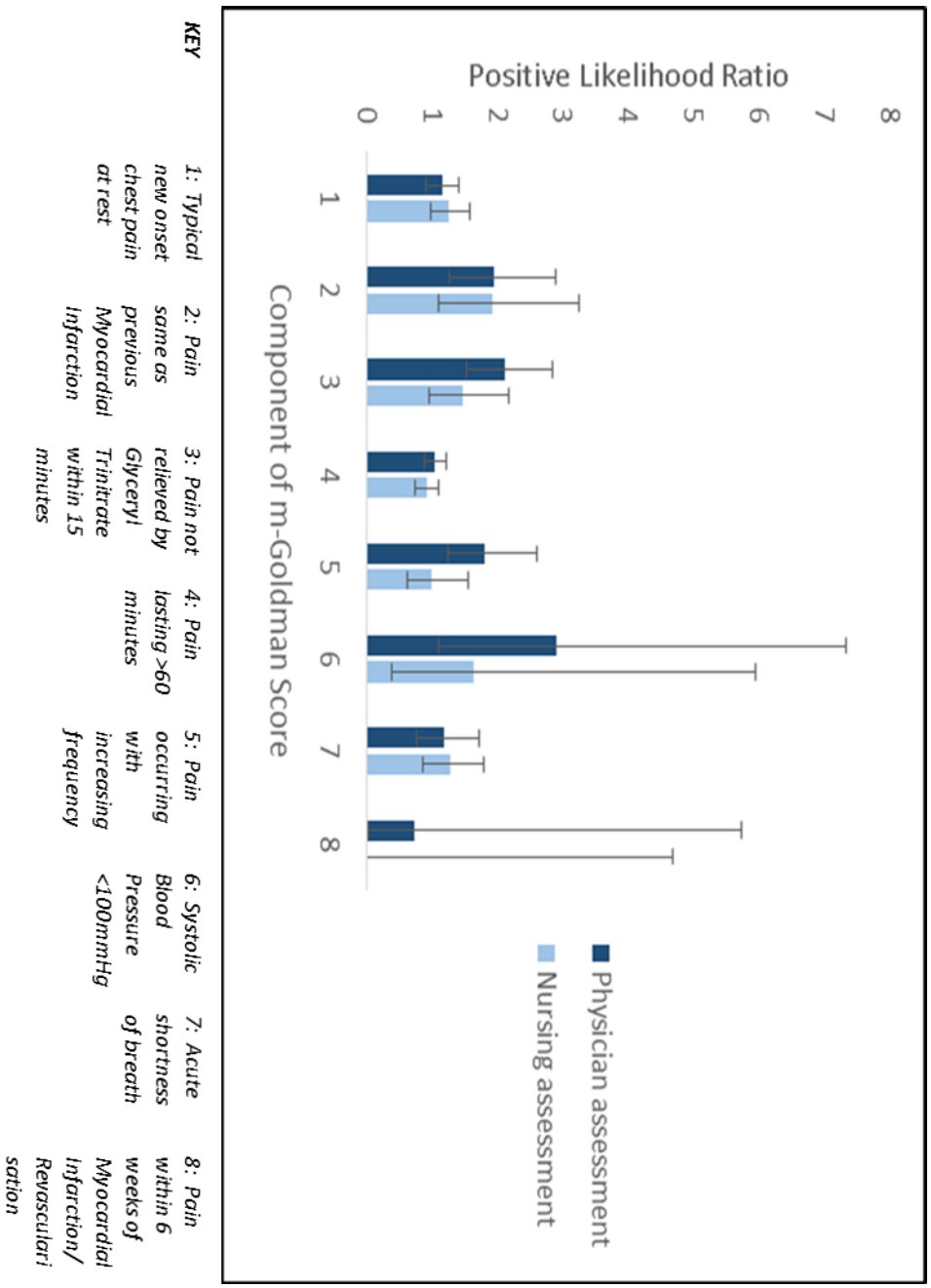
4.9.3 Breaking down the m-Goldman Score and its Components for the Prediction of MACE

The occurrence of 30 day MACE according to each component of the m-Goldman score are shown in Table 32. Through analysis of positive likelihood ratios to demonstrate the ability of each component to predict MACE, it is evident that some parts of the score have greater diagnostic value than others (Figure 24). Pain the same as previous MI, pain not relieved by GTN, pain occurring with increasing frequency and the presence of hypotension all achieve statistical significance as positive predictors (confidence of positive likelihood ratio does not include 1.0) when assessed by physicians. Whilst typical new onset chest pain at rest, pain lasting >60 minutes and acute shortness of breath do not achieve statistical significance. The prevalence of pain within 6 weeks of a myocardial infarction or revascularisation is so low, occurring in only 10/912 (1.1%) of the total physician assessed population that it is difficult to draw any conclusions with regards to its additive value.

Table 32. Occurrence of MACE at 30 Days according to each component of the m-Goldman score

	Physician Assessment		Nursing Assessment	
	MACE	No MACE	MACE	No MACE
Typical new onset chest pain at rest				
Factor present	58	336	45	254
Factor not present	61	457	47	399
Pain same as previous Myocardial Infarction				
Factor present	26	89	16	59
Factor not present	93	704	76	594
Pain not relieved by Glyceryl Trinitrate within 15 minutes				
Factor present	40	126	23	111
Factor not present	79	667	69	542
Pain lasting >60 minutes				
Factor present	73	465	54	418
Factor not present	46	328	38	235
Pain occurring with increasing frequency				
Factor present	30	110	18	128
Factor not present	89	683	74	525
Systolic Blood Pressure <100mmHg				
Factor present	7	16	3	13
Factor not present	112	777	89	640
Acute shortness of breath				
Factor present	25	142	27	130
Factor not present	94	651	65	503
Pain within 6 weeks of Myocardial Infarction/Revascularization				
Factor present	1	9	0	8
Factor not present	118	784	92	645

Figure 24. Ability of component parts of the m-Goldman score to act as positive predictors of MACE



4.10 The Discriminatory Value of Physician Interpretation of Typicality of Chest Pain and the Impact of Clinical Experience

Aim: *to establish the discriminatory value of physician interpretation of typicality of chest pain, in patients with a non-diagnostic ECG, considered to have a potential ACS, and the impact of clinical experience upon diagnostic accuracy, for the prediction of ACS.*

912 participants had typicality of chest pain assessed by treating physicians (Figure 25). Of these, 114/912 (12.5%) had an AMI and 157/912 (17.2%) had angiographic assessment, of whom 90/157 (57.3%) had hs-cTn elevation and 67/157 (42.7%) didn't. Of those patients without hs-cTn elevation assessed angiographically 31/67 (46.2%) had significant CAD, of whom 21 (67.7%) had percutaneous coronary intervention.

Specific to this analysis and in order to overcome the diagnostic adjudication challenges associated with high-sensitivity troponin assays and small elevations in troponin (Mills et al. 2011) and evaluate the discriminatory ability of chest pain typicality in those patients without an hs-cTnT elevation who may have had clinically relevant CAD (Reichlin et al. 2013), a secondary diagnostic outcome measure for those patients assessed angiographically was included. This was the presence of significant CAD, either with high sensitivity troponin elevation (hs-cTnT ≥ 14ng/L at either 0 or 6 hours) or without high-sensitivity troponin elevation (hs-cTnT<14ng/L at presentation to ED and 6 hours later). CAD was defined as ≥70% luminal diameter narrowing of at least one major coronary artery as reported on visual assessment by the operator.

Of typicality assessments, 227/912 (24.9%) were made by experienced ED physicians and 685/912 (75.1%) were made by novice ED physicians. Table 33 summarizes recruited patient demographics according to physician provider group, there were no significant differences in clinical characteristics or outcomes (P>0.05 for all). When assessed by experienced physicians a lower proportion of patients were identified as having typical chest pain when compared to novices (35.2% vs. 45.8%, p=0.005).

Contingency tables showing the occurrence of AMI and CAD with and without hs-cTn elevation according to the presence or absence of typical chest pain are shown in Table 34.

Experienced ED physicians: Consultants (Fellows of the UK College of Emergency Medicine) or Registrars with at least 2 years of ED experience.

Novice ED physicians: Senior House Officers with less than one years' ED experience.

During the study period there were 12 experienced physicians and 32 novice physicians undertaking clinical assessments.

Figure 25. Participant recruitment flowchart for the evaluation of chest pain typicality

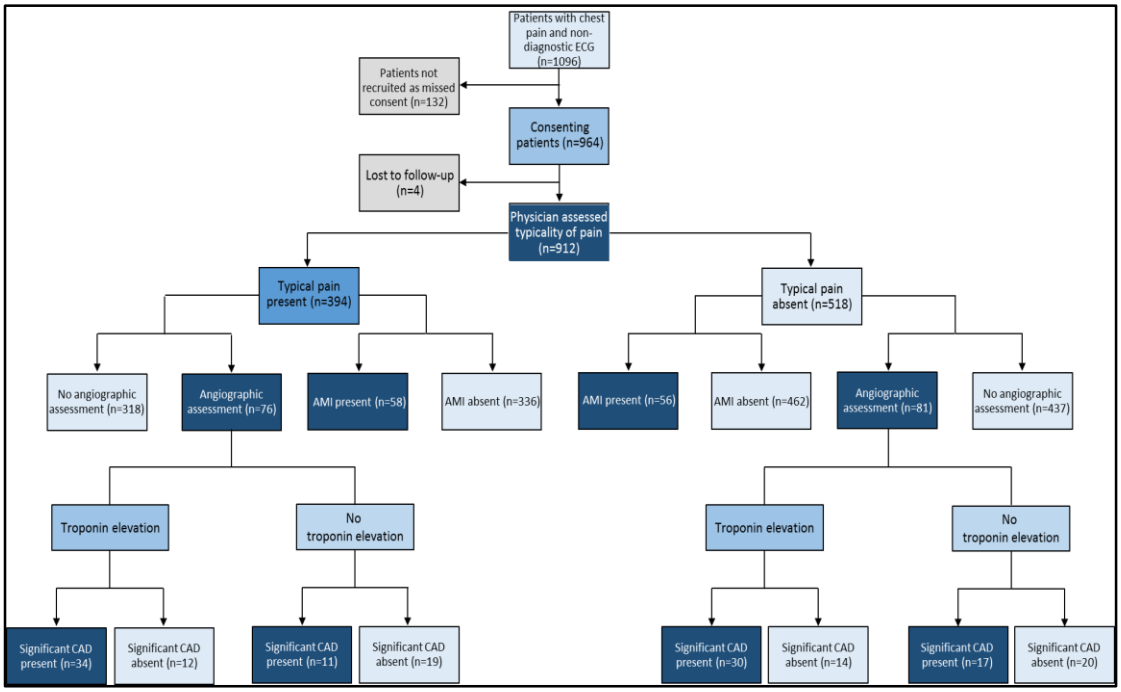


Table 33. Patient characteristics and outcome prevalence according to experienced and novice physician groups

	Total (N=912)	Experienced Physicians (N=227)	Novice Physicians (N=685)
Age, yrs. (Mean/Standard Deviation)	58.0/SD 13.3	58.5/SD 12.8	57.8/SD 13.4
Male Sex (%)	546 (59.9)	137 (60.4)	409 (59.7)
Ethnicity (% White British)	869 (95.3)	219 (96.5)	650 (94.9)
Risk factors N (%)			
Hypertension	505 (55.4)	126 (55.4)	379 (55.3)
Hyperlipidemia	601 (65.9)	154 (67.8)	447 (65.3)
Smoking Current	219 (24.0)	61 (26.9)	158 (23.1)
Diabetes	152 (16.7)	31 (13.7)	121 (17.7)
Family History of Coronary Artery Disease	340 (37.3)	78 (34.4)	262 (38.2)
Medical History			
Angina	238 (26.1)	51 (22.5)	187 (27.3)
Myocardial Infarction	194 (21.3)	42 (18.5)	152 (22.2)
Percutaneous Coronary Intervention	173 (19.0)	40 (17.6)	133 (19.4)
Atrial Arrhythmia	115 (12.6)	26 (11.5)	89 (13.0)
Stroke	62 (6.8)	14 (6.2)	48 (7.0)
Coronary Artery Bypass Graft	47 (5.2)	11 (4.8)	36 (5.3)
Typical Chest Pain Present	394 (43.2)	80 (35.2)	314 (45.8)
Outcomes			
Fatal/Non-fatal AMI	114 (12.5)	34 (14.9)	80 (11.6)
Significant CAD with Troponin Elevation	64 (7.0)	19 (8.3)	45 (6.5)
Significant CAD Without Troponin Elevation	28 (3.1)	10 (4.4)	18 (2.6)

AMI: Index Acute Myocardial Infarction, CAD: Coronary Artery Disease

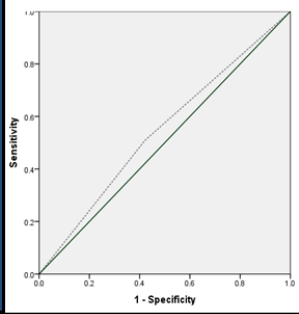
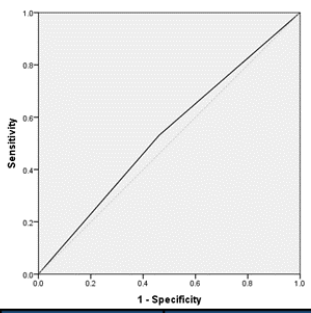
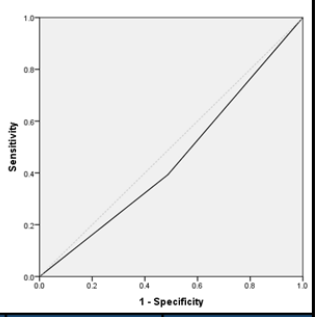
Table 34. Contingency tables showing the occurrence of AMI and significant CAD according to the presence of typical chest pain

	Acute Myocardial Infarction	No Acute Myocardial Infarction
All Physicians		
Typical Chest Pain Present	58	336
Typical Chest Pain Absent	56	462
Experienced Physicians		
Typical Chest Pain Present	14	66
Typical Chest Pain Absent	20	127
Novice Physicians		
Typical Chest Pain Present	44	270
Typical Chest Pain Absent	36	335
	Significant Coronary Artery Disease and hs-cTnT≥14ng/L	**No Significant Coronary Artery Disease and hs-cTnT≥14ng/L**
All Physicians		
Typical Chest Pain Present	34	12
Typical Chest Pain Absent	30	14
Experienced Physicians		
Typical Chest Pain Present	8	5
Typical Chest Pain Absent	11	6
Novice Physicians		
Typical Chest Pain Present	26	7
Typical Chest Pain Absent	19	8
	Significant Coronary Artery Disease and hs-cTnT<14ng/L	**No Significant Coronary Artery Disease and hs-cTnT<14ng/L**
All Physicians		
Typical Chest Pain Present	11	19
Typical Chest Pain Absent	17	20
Experienced Physicians		
Typical Chest Pain Present	2	3
Typical Chest Pain Absent	8	6
Novice Physicians		
Typical Chest Pain Present	9	16
Typical Chest Pain Absent	9	14

4.10.1 Discriminatory Value of Typicality of Chest Pain

Receiver-operating characteristic curves demonstrating the discriminatory ability of typicality of chest pain, assessed by all physicians in the ED, as a diagnostic tool for AMI and CAD without hs-cTn elevation are presented in Figure 26, together with the AUC's according to provider groups for all outcomes. When tested against the null hypothesis that the true AUC is 0.50, the P-value for all providers is >0.05, suggesting that typicality of chest pain has limited discriminatory ability in the diagnosis or exclusion of AMI, CAD with and without hs-cTn elevation in this cohort.

Figure 26. Discriminatory ability of typicality of pain for the diagnosis AMI and significant CAD with and without hs-cTnT elevation

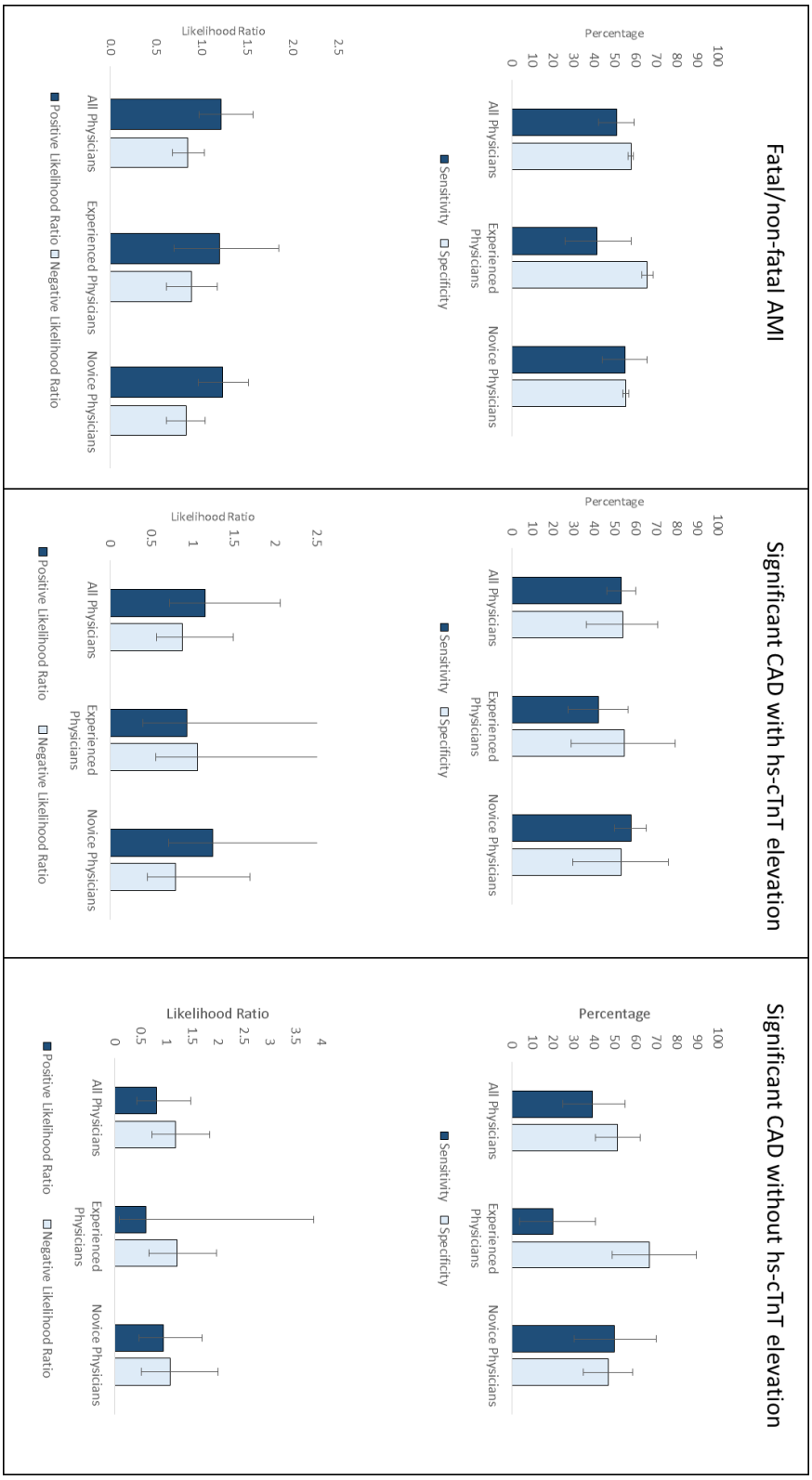
	Fatal/non-fatal AMI		Significant CAD with hs-cTnT elevation		Significant CAD without hs-cTnT elevation	
Receiver-Operating Characteristic Curves for Typicality of Pain, assessed by All Physicians.						
Provider	**Area Under the Curve**	**Significance against null hypothesis of AUC (0.5)**	**Area Under the Curve**	**Significance against null hypothesis of AUC (0.5)**	**Area Under the Curve**	**Significance against null hypothesis of AUC (0.5)**
All Physicians	0.54 (0.49-0.60)	P=0.129	0.54 (0.40-0.67)	P=0.606	0.45 (0.31-0.59)	P=0.513
Experienced Physicians	0.54 (0.43-0.64)	P=0.517	0.48 (0.27-0.70)	P=0.880	0.43 (0.17-0.70)	P=0.624
Novice Physicians	0.55 (0.49-0.62)	P=0.131	0.56 (0.39-0.73)	P=0.522	0.48 (0.31-0.65)	P=0.848

AMI: Acute Myocardial Infarction, CAD: Coronary Artery Disease, AUC: Area Under the Curve

4.10.2 Diagnostic Accuracy and Impact of Clinical Experience

Figure 27 presents the sensitivity, specificity, positive and negative likelihood ratios for typicality of chest pain as a diagnostic tool, when assessed by experienced and novice physicians. Specificity of the finding of typical chest pain for the diagnosis of AMI was significantly higher for experienced physicians at 65.8% (95%CI 63.1-68.7) compared to novices 55.4% (53.9-56.8). There was also a non-significant trend towards increasing test specificity when typicality was assessed by experienced physicians for CAD without hs-cTn elevation (66.7% vs. 46.7%). There was no significant difference in test sensitivity for any outcome measure. Confidence intervals for both positive and negative likelihood ratios across all provider groups and all outcomes include 1.0, suggesting that in this patient cohort, typicality of chest pain has little positive or negative value in the prediction of AMI, or CAD either with or without hs-cTn elevation.

Figure 27. Predictive value and likelihood ratios of typicality of chest pain for AMI and significant CAD with and without hs-cTnT elevation



Error Bars: 95% Confidence Intervals

4.11 Patient Perspectives on Early Discharge after Rapid Rule-Out Testing

Aim: *To investigate patient perspectives on whether early discharge after a rapid rule-out biomarker testing is acceptable in a low-risk short-stay suspected ACS population.*

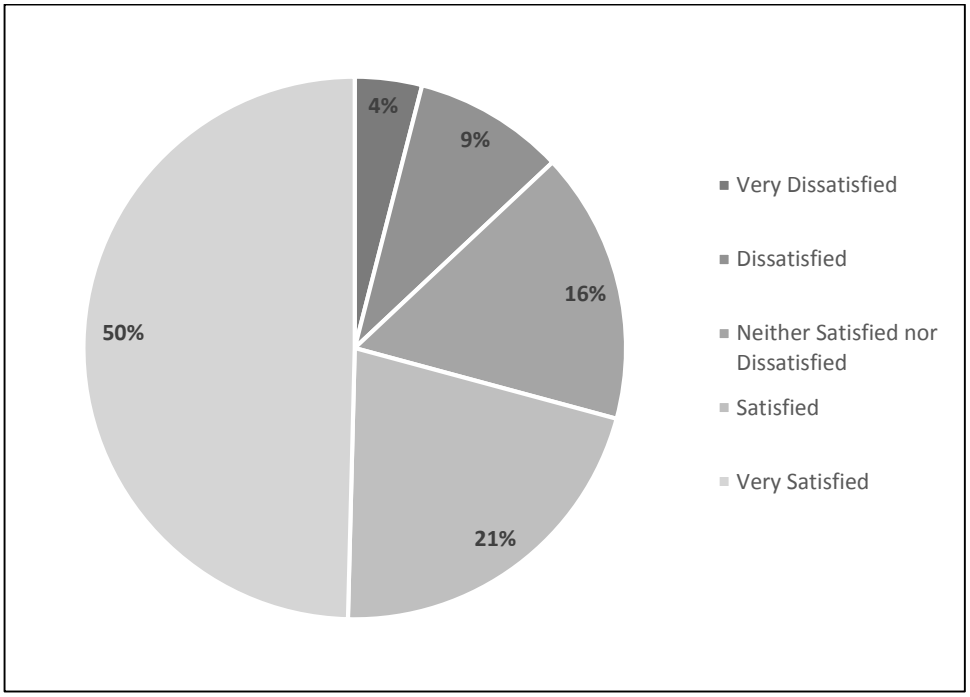
739 patients were requested to complete the survey, 278 (37.6%) responded. Mean age 56.6 years (SD 13.4), 263/278 (94.6%) White British, mean length of stay 15.5 hours (SD 6.6), 6/278 (2.2%) had MACE at 30 days. There was a greater proportion of female responders compared to non-responders (49.6% vs 37.5%, P=0.001), otherwise groups were matched in age, cardiac risk factors, length of stay and the presence of MACE (P>0.05 for all).

Table 35 summarises the overall questionnaire results, with satisfaction for the concept of safe early discharge represented in Figure 28. 197/278 (70.8%) would have been satisfied or very satisfied with early discharge directly from the ED, with 36/278 (13.0%) expressing dissatisfaction with a proposed rapid rule-out protocol. However, 249/277 (89.9%) of responders were reassured by admission to the ward and 112/273 (41.0%) felt they could not have spent any less time in hospital.

Table 35. Summary of written questionnaire results

	Strongly Disagree N (%)	Disagree N (%)	Neither Agree or Disagree N (%)	Agree N (%)	Strongly Agree N (%)
I could have spent less time in hospital	26 (9.5)	86 (31.5)	102 (37.4)	52 (19.0)	7 (2.6)
I felt reassured when I was admitted to the ward for a period of observation	4 (1.4)	3 (1.1)	21 (7.6)	128 (46.2)	121 (43.7)
	Very Dissatisfied N (%)	Dissatisfied N (%)	Neither Satisfied or Dissatisfied N (%)	Satisfied N (%)	Very Satisfied N (%)
If you could have been discharged earlier, directly from the Emergency Department, with the same degree of safety, how satisfied with your treatment would you have been?	11 (4.0)	25 (9.0)	45 (16.2)	59 (21.2)	138 (49.6)

Figure 28. Patient satisfaction with the concept of a proposed early discharge decision



Through binary logistic regression analysis (Table 36) potential predictors of dissatisfaction with early discharge were analysed, these were sex, age, severity and type of pain at presentation, previous ischaemic heart disease, family history; none were found to be significant (95% confidence interval for the odds ratio of all predictors includes 1.0).

Table 36. Binary logistic regression analysis of potential predictors of dissatisfaction with early discharge

Predictor Variable	Odds Ratio	95% Confidence Interval of Odds Ratio
Sex	1.03	0.48-2.17
Age	1.02	0.99-1.06
Pain Score at Presentation	1.03	0.86-1.22
Pain Score on Discharge from ED	1.01	0.82-1.24
Typical Ischaemic Chest Pain	0.81	0.31-2.12
Previous Ischaemic Heart Disease	0.59	0.18-1.92
Family History of Ischaemic Heart Disease	1.01	0.46-2.21
Heart Rate at Presentation	1.01	0.99-1.04

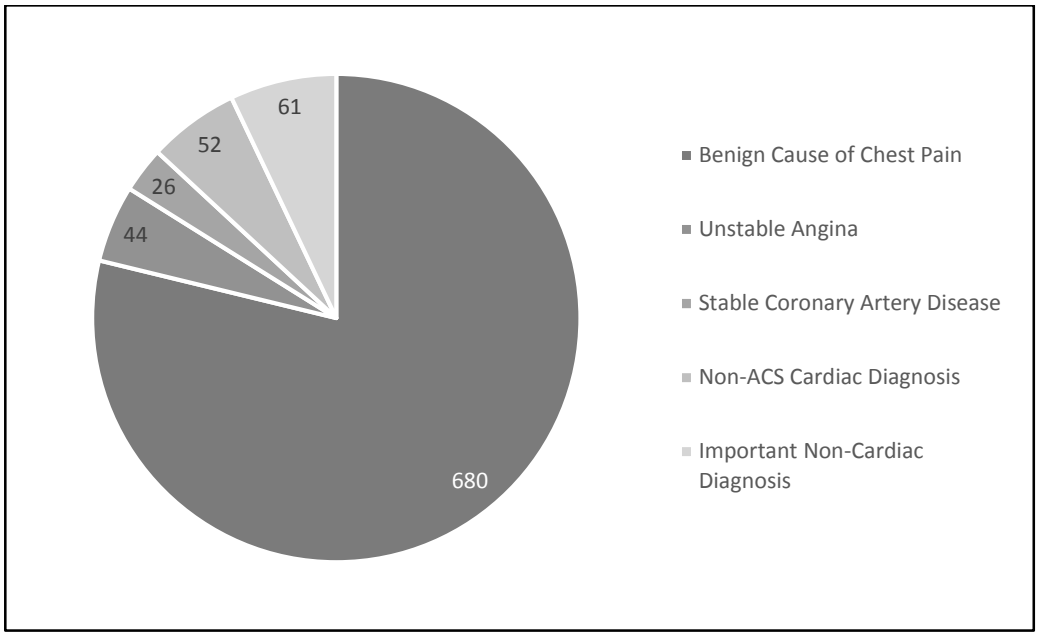
4.12 Study Population Outcomes and Follow-up Testing

4.12.1 Discharge Diagnoses in Patients without MACE

642/960 (66.9%) of patients received a discharge diagnosis of a benign cause of chest pain (Figure 30). Data with regards to specific benign causes of chest pain were not recorded, however, it was noted that patients classified as having benign chest pain were often described by treating physicians as “atypical,” “musculoskeletal,” “non-cardiac” and “gastro-oesophageal reflux.”

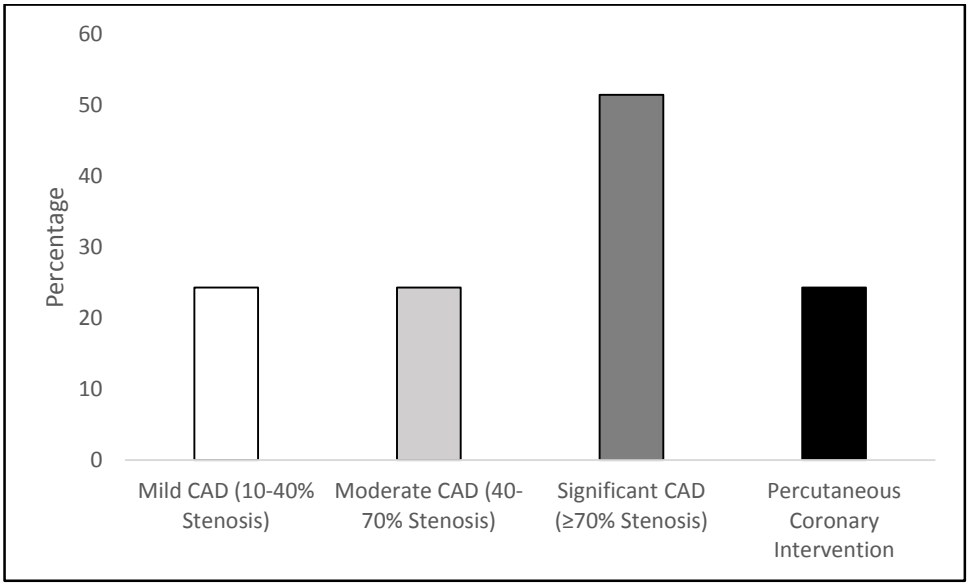
44/960 (4.5%) of patients had a diagnosis of unstable angina at discharge from hospital but did not fulfil the criteria for MACE, of these 37 had angiographic assessment (Figure 30) within 30 days and 9 required elective percutaneous coronary intervention. 26/960 (2.7%) had a prior history of angina or ischaemic heart disease but after evaluation this presentation was not thought to be due to unstable angina (stable coronary artery disease).

Figure 29. Discharge diagnosis of patients without MACE



***** *Important/Treatable non-ACS cardiac and non-cardiac diagnoses are summarized in Table 37 (below)*

Figure 30. Angiographic outcome of patients diagnosed with unstable angina at hospital discharge



CAD: Coronary Artery Disease

Of the total study population, 113/960 (11.8%) patients had an important treatable non-ACS cause for their chest pain presentation identified, these are summarized in Table 37.

Table 37. Frequency of Important/Treatable Non-Acute Coronary Syndrome Cardiac and Non-Cardiac Discharge Diagnoses Identified as Potential Cause of Chest Pain

Non-ACS Cardiac Diagnosis	Frequency	Non-Cardiac Diagnosis	Frequency
Atrial Tachyarrhythmia (Atrial Fibrillation/Supraventricular Tachycardia)	**2.6%**	Sepsis/hypovolaemia	**1.6%**
Bradyarrhythmia	**0.4%**	Pneumonia	**1.6%**
Hypertrophic Cardiomyopathy	**0.1%**	Respiratory Failure	**0.3%**
Takotsubo's Cardiomyopathy	**0.1%**	Biliary Pathology	**1.1%**
Severe Valvular Disease	**0.3%**	Stroke	**0.3%**
Myo/pericarditis	**2.2%**	Pulmonary Embolism	**0.4%**
Coronary Spasm	**0.2%**	Lung Cancer	**0.1%**
Total Frequency	**5.4%**	**Total Frequency**	**6.3%**

Non-ACS: Non-Acute Coronary Syndrome

4.12.2 Confirmatory Testing

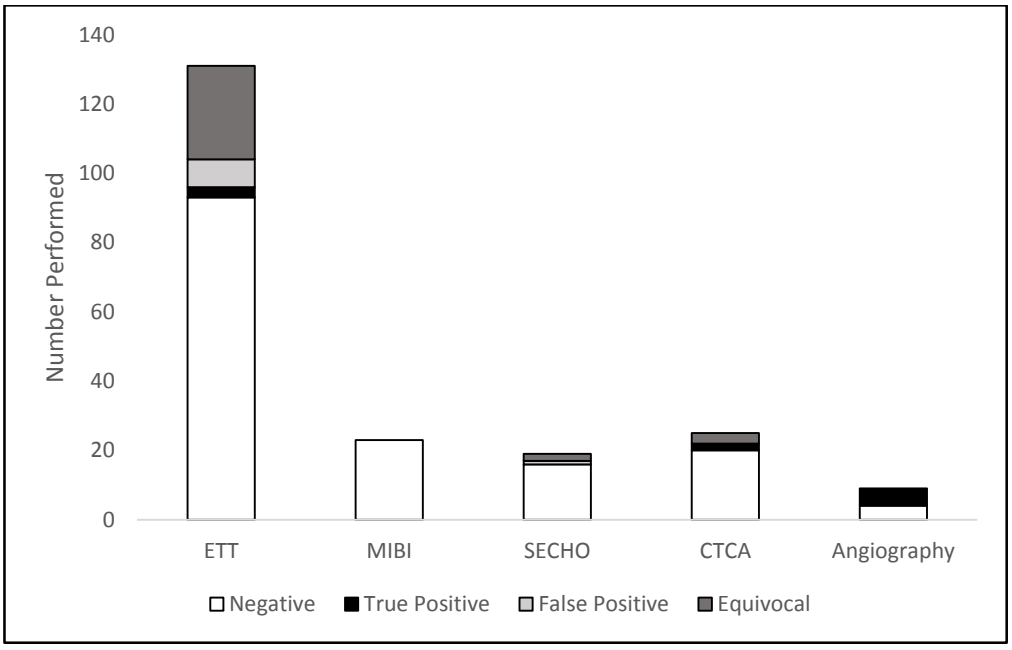
Due to the observational nature of the TRUST study it is important to recognise that many patients identified as low risk by the TRUST ADP had confirmatory cardiac testing from exercise tolerance testing to advanced imaging. This has important implications in applying the ADP in clinical practice and the need for follow-up. This section summarises to follow-up undertaken during the study period.

After inpatient admission for 6 hour troponin testing, current clinical practice dictates a proportion of patients will be referred for further confirmatory testing, in order to identify clinically relevant ischaemia in the absence of troponin elevations. For this analysis, significant coronary artery disease (CAD), defined as ≥70% luminal diameter narrowing of at least one major coronary artery as reported on visual assessment by the operator, and percutaneous coronary intervention were the outcomes of interest (true positive tests). During the study period, treating physicians had available exercise tolerance testing (ETT), stress nucleotide myocardial perfusion imaging (MIBI), stress echocardiography (SECHO), CT coronary angiography (CTCA) and invasive angiography as options for confirmatory testing.

Of patients identified as low risk by the TRUST ADP, 152/382 (39.8%) had confirmatory testing within 30 days of attendance with chest pain. No patient was referred directly for invasive angiography without first undergoing a non-invasive test. A total of 205 confirmatory tests were performed in 152 patients with no additional MACE detected, 5 additional patients were identified as having significant CAD, and 3 of these required

outpatient elective revascularization. Therefore, confirmatory testing had a 2% pick-up rate of significant CAD and 1.4% for percutaneous coronary intervention in the TRUST ADP low risk group. Given the prevalence of coronary heart disease in the UK population which, in 2006, was 6.5% across all age groups (Townsend et al. 2012), the utility of confirmatory testing in TRUST ADP low risk patients may be limited. Figure 31 summarises the outcome of confirmatory test results in the TRUST ADP low risk group.

Figure 31. The outcome of further testing in patients identified as low risk by the TRUST ADP



A test was described as "positive" if a positive test led to detection significant CAD at invasive angiography (reference test); ETT: Exercise Tolerance Test, MIBI: Stress Nucleotide Myocardial Perfusion Imaging, SECHO: Stress Echocardiography, CTCA: Computed Tomography Coronary Angiography

4.12.3 Non-Recruited Patients

Due to lack of research staff availability 132 patients who fulfilled eligibility criteria were discharged prior to providing written, informed consent. Simple demographic data and m-Goldman scores for these patients were obtained, with ethics board approval, and compared with recruited patients (chi-squared) to ensure no significant differences between consenting and non-consenting groups existed. Significance testing for this analysis is summarized in Table 38. There were no statistically significant differences in m-Goldman scores and demographics between recruited and non-recruited patients, except for dyslipidaemia which was slightly more prevalent in the recruited group (66.1% vs 56.3% p=0.03). This is likely to represent a spurious result of multiple significance testing (Bland and Altman, 1995) and is unlikely to have implications in the interpretation of study results.

Table 38. Comparison of demographics and m-Goldman scores between recruited and non-recruited patients

Demographic	Significance when tested against consenting patients (p value)
Age, yrs. (Mean±Standard Deviation)	0.332
Sex	0.127
Risk factors N (%)	
Hypertension	0.113
Diabetes	0.097
Dyslipidaemia	**0.030**
Smoking Current	0.368
Family History of Coronary Artery Disease	0.240
Medical History	
Angina	0.591
Myocardial Infarction	0.908
Percutaneous Coronary Intervention	0.399
Sum of m-Goldman Score	**0.182**

Chapter 5.

Discussion

5.1 The Diagnostic Accuracy of the TRUST ADP and Improving Efficiency

This study demonstrates that the TRUST ADP for suspected ACS may successfully identify 40% of patients as low-risk after just a single hs-cTnT taken at presentation to the ED, with a sensitivity of 99.0% (95% CI 93.7-99.9) (Table 22, Page 125).

These results suggest that the introduction of this ADP has the potential to reduce the length-of-stay for low risk patients (demonstrated as 14 hours in this study) after a single laboratory-based troponin and avoid the necessity for two separate blood draws. Uptake of this protocol may have significant benefits for healthcare services worldwide by reducing hospital admission rates, ED overcrowding, duplication of staff time and resource use. Furthermore, by using ED physicians to carry out risk-stratification and real-time troponin sampling with 24-hour recruitment it has been demonstrated that this ADP is truly applicable.

Prior studies investigating high-sensitivity troponin testing have relied on the use of frozen serum samples. As a result few studies have been able to illustrate the temporal impact a rapid discharge strategy incorporating central laboratory high-sensitivity troponin testing taken at presentation may have. As shown in Figure 12, Page 129, through real-time troponin testing the TRUST study demonstrates that even though laboratory processing times are quoted as 18 minutes (NICE 2014), in a real-world clinical environment, results will not be available until at least 2-hours after arrival. This may explain why strategies that rely on two blood samples taken 2-hours

apart may have little impact on patient length of stay until 6-hours after patient arrival (Figure 6, page 67) (Than et al. 2014a).

The TRUST ADP, which incorporates a structured risk-assessment and single presentation hs-cTnT blood draw, has the potential to allow early discharge in 40% of patients with suspected ACS.

5.2 High-Sensitivity Troponin Cut-off Values

The cut-off value for hs-cTnT used in the TRUST ADP of <14ng/L (99th percentile value) was chosen prior to study commencement due to international guideline bodies suggesting this cut-off value for clinical use despite limited evidence for this (Thygesen et al. 2012b). As shown in Table 22, Page 125, in common with previous studies, the 99th percentile cut-off value has limited value in isolation as a diagnostic tool at presentation, but has the potential to be an effective cut-off for use in combination with a clinical risk score (m-Goldman).

It must be noted that the 99th percentile value of 14ng/L was derived from healthy blood donors, while a population presenting to hospital with chest pain will almost certainly differ from this in both age and comorbidities. One study of patients aged greater than 70 who did not have a final diagnosis of AMI, 51% had hs-cTnT levels above the 99th percentile (Reiter et al. 2011), while 52% of patients admitted to hospital without a cardiac diagnosis may have hs-cTnT levels above the 99th percentile value (Iversen et al. 2013). The decreased specificity of hs-cTn assays remains a limitation to their use and further research is required to establish age, sex and potentially race-specific cut-off values.

As a confirmation that this is a very active area on the literature, in early 2015, Zhelev and colleagues published a meta-analysis of the diagnostic accuracy of a single baseline measurement of high-sensitivity troponin T (hs-cTnT) for the diagnosis of AMI in the ED. This work complemented the recent NICE guidance (NICE 2014) on the use of high-sensitivity assays and highlights the potential benefits of their introduction into clinical practice. However, the results of the TRUST study demonstrate that the

author's assertion that an initially undetectable hs-cTnT result may be used as a diagnostic strategy to reduce the number of patients undergoing further testing and therefore relieve pressure on EDs- should be treated with caution. The reasons for this are two-fold:

Firstly, the single outcome measure used in the Zhelev meta-analysis (AMI) and lack of incorporation of urgent revascularisation as an endpoint failed to realise and represent the full spectrum of ACS. As a result the clinical application of the undetectable hs-cTnT strategy may be limited. As demonstrated by the TRUST study, in the context of undetectable troponin levels clinicians may be encouraged to disregard important risk stratification factors gathered from clinical evaluation. Revascularisation as an endpoint is important as it has been demonstrated patients with unstable angina with a change in hs-cTnT of as little as 2ng/L in the first hour of presentation to the ED still have up to a 16% risk of AMI and death at 30 days (Reichlin et al. 2013), and this may explain why the sensitivity of undetectable hs-cTnT, when urgent revascularisation is included as an endpoint may be as low as 90%.

Secondly, the authors of this meta-analysis point out that reducing the cut-off value of high-sensitivity troponin T from 14ng/L to 5ng/L, may be of value helping physicians rule out AMI early in the triage process. However, the test specificity is reduced from 77.1% to 42.4%. While the authors acknowledge that this "threshold effect" is a trade-off, the cost-benefit implications of this cannot be ignored. Evidence now confirms that rule-out tests with poor specificity lead to increased downstream costs and increasing need for time-consuming additional confirmatory tests. For example, one study demonstrated that a rapid rule-out biomarker strategy for suspected ACS

achieved a 20% reduction in hospital admissions (Collinson et al. 2012). However, this was countered by an increase in coronary care bed use and outpatient clinic follow-ups - paradoxically increasing overall costs by approximately £200 per patient (Fitzgerald et al. 2011).

When comparing the TRUST ADP to strategies using undetectable hs-cTnT in Figure 14, Page 133, more patients are eligible for early discharge with lower false-positive rates, suggesting this approach has greater clinical utility. Furthermore, by incorporating clinical risk stratification, the TRUST ADP has improved accuracy in identifying those who require urgent revascularization. With the short-comings of an undetectable hs-cTnT rule-out strategy in mind, the TRUST ADP becomes an inviting alternative rule-out strategy by allowing the detection of patients with a requirement for revascularization and lowering the false positive rates and identifying a greater proportion of low risk patients.

The TRUST ADP has superior clinical utility when compared to undetectable hs-cTnT strategies. Future research should focus on methodologies that incorporate clinical assessment with high-sensitivity troponin testing rather than troponin testing alone.

5.3 Using an Alternative High-Sensitivity Troponin Assay

Whilst the primary aim of the TRUST study was to test the diagnostic performance of an ADP which incorporated the Roche hs-cTnT, it is important to acknowledge that another commercially available high-sensitivity troponin assay (Abbott hs-cTnI) is available (NICE 2014). Therefore in order to establish the general applicability of the TRUST ADP, it was necessary to assess the performance of this assay in the TRUST study cohort and evaluate hs-cTnI in comparison to hs-cTnT.

Although Figure 16, Page 136, shows that the area under the curve for each high-sensitivity troponin assay does not differ significantly between Roche hs-cTnT and Abbott hs-cTnI, this analysis highlights important differences in accuracy for the detection of AMI that may have important clinical implications. It must be stated that any comparison of hs-cTnT with hs-cTnI in this study is limited by the fact that outcome adjudication for AMI was made using the Roche hs-cTnT assay that was in clinical use at the time of the study. Despite this, the finding that sensitivity of hs-cTnI at presentation (including in those presenting early after symptom onset) for the diagnosis of AMI is lower than that of hs-cTnT at the 99th percentile value is consistent with the findings of Aldous and colleagues (2011b) who re-adjudicated AMI using each individual assay. However, the finding that hs-cTnI only achieves a sensitivity of 95.5% for AMI when the level of detection cut-off is used (Figure 17, Page 137) is in contrast to the only available comparative analysis, where this assay achieved 100% sensitivity at this cut-off (Rubini Giminez et al. 2013). The reasons for this may be twofold: Firstly, the cases of AMI missed by the hs-cTnI may have been false positive cases adjudicated using the hs-cTnT assay. This may apply to two of the three missed AMI cases, in whom there was no other evidence of myocardial infarction other than a mild

delta change in hs-cTnT. However, this is unlikely to be the case in the third, in which there was angiographic evidence of severe left main stem disease and is therefore likely to be a genuine false negative not detected with the hs-cTnI assay.

Secondly, given that the number of patients with undetectable levels of Abbott hs-cTnI in the TRUST cohort is much greater than those in the study by (Rubini Giminez et al. 2013) at nearly 40% vs 10%, the issue of batch variation cannot be ignored. Although one simple explanation for this may be differences in the demographics of the two study populations (e.g. Rubini Giminez recruited high risk patients with abnormal ECGs) batch variation may be especially important at low levels of detection at which there is decreased analytical reproducibility and may also lead to a greater proportion of patients with undetectable troponin levels.

A further consideration in the interpretation of hs-cTnI results within this analysis is the potential effect of long-term storage and freezing upon the stability of cardiac troponin I. Whilst hs-cTnT testing was carried out immediately after sampling, hs-cTnI analysis was carried out after serum samples had been frozen at -80 degrees centigrade for a period of 12 months. There is some data to suggest that prolonged freezing of >12 months may falsely lower troponin results using third generation assays (Basit el al. 2007). Although changes are likely to be very small and therefore have minimal clinical impact, this effect may be of great importance when using level of detection strategies. However, the consequences of prolonged storage of serum on high-sensitivity troponin testing remains unclear.

One of the strengths of the TRUST study is the outcome adjudication using a high-sensitivity assay in conjunction with available clinical data, to ensure even those patients with small AMIs could be identified. Therefore, this variation in performance

between assays is also likely to be population-specific and is of great importance to clinicians who may not be able to select, or may not be aware, which assay is used in their institution.

Variations in diagnostic accuracy exist between the two commercially available high-sensitivity troponin assays when taken at presentation to the ED. This has implications in the clinical use of rapid rule-out protocols.

5.4 Other Accelerated Diagnostic Protocols

No previous study has integrated presentation high-sensitivity troponin assay results with multiple established risk scores to provide a diagnostic comparison. This analysis has demonstrated that it may be possible to identify over 30% at low risk of AMI with a miss-rate of <0.5% (NPV >95.5%) after a single blood draw (Figure 20, Page 146). These findings support the use of formal risk stratification in combination high-sensitivity troponin testing, but also highlight important variation in the performance of existing risk scores, together with performance variation in hs-cTn assays which will have implications in the introduction of rapid rule-out protocols.

While the focus of such pathways should be on safety, and a number of pathways achieved 100% NPV (albeit with wide confidence intervals), in reality there will always be a small percentage of patients with ACS that are not identified during routine clinical assessment (Pope et al. 2000). Although evidence is limited regarding which miss-rate is acceptable, a miss-rate of 0.5% (equating to an NPV of >99.5%) was chosen, which appears to be acceptable to the majority of ED physicians (Than et al. 2012b). By using a clinically applicable miss-rate, together with the necessity to identify over 30% of patients as low-risk, this analysis has demonstrated that the TRUST ADP (with hs-cTnT) is the most clinically applicable single blood draw rule-out strategy in this cohort.

Risk scores such as TIMI and GRACE were originally developed as 'rule-in' tools in patients with confirmed ACS and as such their use in a low risk cohort may be counter-intuitive. Both fail to take into account patient history, are influenced heavily by age or the presence of risk factors for chronic coronary disease, which may not be as

predictive for ACS as previously thought (Body et al. 2008). In fact, despite guideline recommendations for its use (NICE 2010), previous evidence suggests that the GRACE score may be little better than age alone as a predictor of MACE at 30-days in a low-risk ED cohort (Goodacre et al. 2012). Results shown in Figure 19, Page 144, confirm that even at very low score cut-offs the diagnostic performance of GRACE as a rule-out tool in combination with high-sensitivity troponin is poor.

In comparison with the largest and most independent validation of the HEART score (Six et al. 2013), results from this cohort are similar, with a missed event rate of approximately 1.5% and 30% eligible for early discharge, using a cut-off of ≤3. The previous validation by Six et al. (2013) used 3rd generation rather than high-sensitivity troponin, therefore it does not appear that use of a high-sensitivity assay improves the diagnostic accuracy of the HEART score as a rule-out tool. In contrast with the conclusions of the authors of the previous validation of the HEART score (Six et al. 2013), who suggested clinical use of the score, given the low event rates in the low risk group, it may be argued that other scores perform better in this regard whilst maintaining a similar, if not improved diagnostic accuracy.

This analysis also confirms that the Vancouver Chest pain rule has excellent diagnostic accuracy for the rule-out of AMI, and it is the only risk score to achieve 100% NPV using the Abbott hs-cTnI assay (Figure 20, Page 146). This supports the findings of a similar external validation study (Cullen et al. 2014a). However, the low proportion of patients (approximately 15%) identified as suitable for early discharge may limit clinical applicability in comparison to other strategies tested here.

Ideally, the single hs-cTn rule-out strategies tested in this cohort should be directly compared in a diagnostic randomized controlled trial. The data presented here may be

useful in directing which head-to-head comparisons should be made. However, with ever-increasing pressure on emergency departments such controlled trials may be one step too far in the trail of evidence. At some point, pragmatic decisions about using these single hs-cTn rule-out strategies in practice must be made. This evidence suggests that when this does occur clinicians must take into account local population factors, assay availability and pathways must be subject to continuous audit and evaluation to ensure safety.

It may be possible to identify over 30% of low-risk patients with an NPV of >99.5% for the diagnosis of AMI using an hs-cTn result taken at presentation to the ED, in combination with established risk scores. There is important variation in the performance of risk scores and hs-cTn assays which has implications in the clinical use of rapid rule-out protocols.

5.5 Nursing Staff in Risk Assessment

This analysis (Table 30, Page 150) demonstrates that the diagnostic accuracy of ED nursing staff risk assessment, using the TRUST ADP to identify low-risk patients with suspected ACS, is slightly lower than that of ED physicians. However, with only a 1.1% miss-rate for MACE and fair inter-observer reliability of nursing and physician assessments in the identification of low-risk patients, the future role of nursing staff in rapid rule-out pathways holds promise.

This analysis breaks new ground in investigating the role of nursing staff in the assessment of suspected ACS and is the first to compare the use of an ADP between physician and nursing staff. The results suggest that in this setting, ED nursing staff with no specific training in the assessment of suspected cardiac chest pain are not yet able to have discharge decision making authority in this patient group. However, with tailored educational interventions it may be possible for the diagnostic accuracy of nursing staff to be improved. Studies investigating simple training interventions, such as workshops, in non-specialist ED nursing staff have consistently demonstrated improved correlation between physician and nurse ordering, as well as more accurate test interpretation (Seaberg and MacLeod 1998, Zhang and Hsu 2013 and Varvaroussis et al. 2014). As such, further research is required which incorporates formal training in chest pain assessment for nursing staff, and focuses on the identification of low risk patients who may be suitable for early discharge.

This analysis is also important in highlighting inter-observer reliability of chest pain assessment (Table 31, Page 153), which remains under-reported in the literature. The m-Goldman risk score uses elements of chest pain history to identify those patients

without unstable features, it therefore requires some clinical judgment and subjectivity in interpretation. Although nursing staff received no specific training in the use of the m-Goldman score, all nursing participants were experienced in the primary assessment of ED patients with chest pain. Therefore the only fair agreement between assessors may be seen as unexpected. This finding will not be limited to the TRUST ADP, as other commonly used risk scores also incorporate elements which require clinical judgment. Examples include the TIMI score (Antman et al. 2000), HEART Score (Backus et al. 2013) and Vancouver chest pain rule (Cullen et al. 2014a).

The diagnostic accuracy of ED nursing staff risk assessment, using the TRUST ADP to identify low-risk patients with suspected ACS, is lower than that of ED physicians. However, with only a 1.1% miss-rate for MACE and fair inter-observer reliability of nursing and physician assessments in the identification of low-risk patients, the future role of nursing staff in rapid rule-out pathways holds promise.

5.6 Typicality of Chest Pain

The terms “typical” and “atypical” chest pain are commonly used in the assessment of suspected ACS and stem from historical teachings. Physicians rely upon chest pain history to make management decisions in patients with ACS where the diagnosis is not immediately apparent through ECG and troponin testing. The results presented in Figure 26, Page 163, show that in emergency patients considered to have a potential ACS with a non-diagnostic ECG and without knowledge of troponin testing, typicality of chest pain is of limited discriminatory value when assessed subjectively by treating physicians. Diagnostic accuracy for the rule-in of AMI and significant CAD without troponin elevation may be improved with greater clinical experience but this finding is likely to have limited clinical applicability.

Chest pain history is embedded in medical teaching, with Heberden (Silverman, 1987) in 1768 providing the first description of ischemic chest pain: “a painful sensation in the breast accompanied by a strangling sensation, anxiety, and occasional radiation of pain to the left arm.” This description has barely evolved over three centuries of medical practice and contains the features commonly referred to as “typical” cardiac chest pain. Interpretation of whether chest pain is typical or atypical is subjective and influenced by cognitive biases, which in turn may influenced by clinical context and experience (Elstein and Schwartz, 2002).

It is increasingly evident that unstructured clinical assessment or ‘gestalt’ is important in the risk stratification of patient’s chest pain (Kline and Stubblefield 2013 and Body et al. 2014b). Interpretation of whether chest pain is typical or atypical is subjective and therefore influenced by cognitive biases, which in turn may influenced by clinical

context and clinical experience (Elstein and Schwartz, 2002). Studies investigating the diagnostic value of chest pain symptoms have, in the main, used data collected by research staff to analyze individual components of the chest pain history and have therefore failed to take into account this subjective assessment (Chun and McGee 2004, Swap and Nagurney 2005, Body et al. 2010, Greenslade et al. 2012 and Rubini Gimenez et al. 2014). This may have unseen influence on trial outcomes and affect the clinical applicability of results. Where studies have evaluated these subjective findings they are either in a context that cannot be applied to the acute situation e.g. outpatients; where the prevalence and perceived risk of disease may be lower (Pryor et al. 1993) or have failed to take into account clinical experience (Hess et al. 2012a). The failure of previous studies to take into account the cognitive and contextual influences on clinical assessment may have unseen influence on trial outcomes and affect the clinical applicability of results (Hajjaj et al. 2010).

Physicians are taught, as students, to take a meticulous history and perform a skilled examination to make a provisional diagnosis and initiate a management plan. In practice however, physicians may intuitively adopt a *Bayesian* approach to diagnosis, making an immediate diagnosis based on probabilities and then adjust the probabilities as more information becomes available (Sackett et al. 2011). Such an approach will be influenced by context and clinical experience (Elstein and Schwartz 2002). The importance of pre-test probability assessment becomes even greater in the era of high-sensitivity troponin assays. Until recently, contemporary cardiac troponin assays could be used reliably to identify those patients with a non-ischemic ECG who were at high risk for AMI and adverse events with low false positive rates (Panju et al. 1998). However, the development of high-sensitivity cardiac troponin assays, with

high precision at the 99th percentile clinical cut point and which can detect troponin in over 50% of apparently illness-free individuals (Korley and Jaffe 2013), has highlighted the problems around binary positive and negative interpretation of results. The potential for multiple acute conditions to cause elevations in hs-cTn (Newby et al. 2012), necessitates improved estimates of pre-test probability to allow improved management decisions based on elevated hs-cTn results. These results suggest that typicality of chest pain may be of limited use in this regard.

With the advent of high-sensitivity assays, there was hope that in clinical practice, their use may make the diagnosis of unstable angina obsolete (Twerenbold et al. 2012). By using hs-cTn to adjudicate the primary endpoint (AMI) and confirm the findings in a subset of patients who have undergone angiographic assessment two important findings have been demonstrated. Firstly, almost half of patients with acute chest pain have angiographically significant disease in the absence of troponin elevations, and a significant proportion of these require intervention. Secondly, in these patients, whom treating physicians most rely on the discriminatory value of the chest pain history, typicality of chest pain may be of limited use. Therefore the focus of clinical assessment must be on the application of risk scores, such as m-Goldman, which incorporate multiple variables from the history, ECG, observations and examination, to accurately risk stratify patients with suspected ACS, rather than using chest pain history alone.

It is important to recognize that this analysis included only patients with chest pain and a potential ACS with a non-diagnostic ECG who were admitted to a ward for delayed biomarker testing. As a result, the treating clinician had already used their clinical

judgment to identify patients with chest pain in whom there was a high index of suspicion for ACS and therefore required further inpatient evaluation. Those patients with diagnostic ECGs and those discharged directly from the ED with "non-concerning" histories were, as a result, intentionally excluded from analysis. Although this population may therefore be subject to significant selection bias, the analysis has intentionally focused on a cohort of patients that provide the greatest diagnostic challenge for acute physicians on a day-to-day basis. While it is likely that the discriminatory value of typicality of chest pain would be improved if those patients with clinically evident ACS had been recruited for analysis, by excluding those patients in whom there was no diagnostic uncertainty this has resulted in a novel insight into an everyday clinical problem.

Physician interpretation of 'typicality of chest pain' is of limited discriminatory value in patients being assessed for potential ACS, in the context of a non-diagnostic ECG. Greater clinical experience improves accuracy as a rule-in tool for AMI but this does not improve overall discriminatory ability.

5.7 Patient Perspectives on Early Discharge after Rapid Rule-Out Testing

It is evident from the results presented in Figure 28, Page 167, that approximately 10% of patients would be dissatisfied with early discharge after rapid rule-out testing, and in Table 36, Page 168, that no demographic or clinical factors can be used to predict dissatisfaction (although the study may have been underpowered to detect this). Strategies are needed that improve patient information and incorporate patient opinion with discharge decision-making. A recent study by Hess and colleagues (Hess et al. 2012b), demonstrated that when patients with acute chest pain are informed and involved in decisions, they are less likely to want to be admitted to hospital. Yet, patient decision aids that describe options and give personalised risk information are rarely, if ever, used in clinical practice. Barriers to adoption of decision aids into clinical practice include concerns about time taken to make decisions and lack of interest amongst patients (Gravel et al. 2006). However, with national health policy (Department of Health 2012) and cardiac specialty (Brindis and Spertus 2010) initiatives incentivising shared decision-making, these barriers must be overcome. With the advent of rapid rule-out chest pain protocols shared decision-making with patients is feasible (Hess et al. 2012b), however, this analysis demonstrates that there may be implications in matching resource use with some patients' preferences.

A small proportion of patients may be dissatisfied with rapid rule-out strategies. Within the development of rapid rule-out chest patient protocols, future research should incorporate the concept of shared patient-clinician decision-making.

5.8 The Need for Confirmatory Testing in TRUST ADP Low Risk Patients

Due to the observational nature of the TRUST study it is important to recognize that 40% of patients identified as low-risk by the TRUST ADP had confirmatory cardiac testing. This has important implications in applying the TRUST ADP in clinical practice and the rationalizing the need for outpatient follow-up.

The results presented in Figure 31, Page 173 demonstrate that the diagnostic yield from advanced testing in this cohort was extremely low, with no additional MACE detected and a 1.4% yield for CAD requiring intervention. This brings into question the need for confirmatory testing in TRUST ADP low-risk patients. American Heart Association guidelines (2010) state that "the role of confirmatory testing as part of an ADP [sic] is to further minimize the likelihood of ACS to a level so low that discharge is safe." Therefore questioning the need for confirmatory testing is provocative, however, results from our analysis are strikingly similar to those of Hermann et al. (2013) who demonstrated a diagnostic yield from confirmatory testing for obstructive coronary artery disease of <1% in low-risk ED patients with chest pain. There is also increasing recognition that biomarker testing alone may identify patients safe for discharge with very low adverse event rates (Scheuermeyer et al. 2012 and Redberg 2012), making further risk-stratification attempts redundant. Confirmatory testing is also not without risk, with potential harms including radiation exposure, false-positive tests (4.9% in this cohort), contrast-induced nephropathy and resource utilization (Pauker and Kassirer, 1980). It may therefore be time to question the need for confirmatory testing in this already low-risk patient group and the approach of

discharge without secondary testing should be done through a rigorously designed randomized controlled trial.

The role of confirmatory testing in TRUST ADP low-risk patients may be limited. This limited testing strategy requires evaluation as part of a rigorously designed randomised controlled trial.

Chapter 6.

Limitations

6.1 Diagnostic Accuracy

The 95% confidence interval is a range of values around an estimate that have a 95% probability of encompassing the ‘‘true’’ value of that estimate.

The fundamental barrier to implementation of the TRUST ADP into clinical practice is the lower limit of the 95% confidence intervals (CI) of the sensitivity for the diagnosis of MACE. This extends down to 93.7% (Table 22, Page 125), which has important prognostic implications for patients and medicolegal implications for clinicians. The 95% CI can be used to estimate the likelihood of a type II (false negative) statistical error, and is determined by the sample size. The relatively wide CIs therefore suggest that either the miss-rate for MACE may be higher than suggested or the study is not adequately powered due to deficiencies in the sample size. Whilst the number of patients recruited is approaching the required number from the initial sample size calculation, this calculation made the assumption that no adverse events would occur in the TRUST ADP low-risk group, which in retrospect was erroneous. The TRUST ADP must therefore be prospectively validated in large independent populations prior to clinical implementation.

6.2 Study Design

The TRUST study is a single centre diagnostic observational study which analysed the performance of an ADP/Clinical decision rule. Using the Oxford Centre for Evidenced-based medicine (2009) classification (Table 39) this is a Level 1b study.

Despite achieving Level 1b, it may be suggested, that a multicenter randomized diagnostic controlled trial (RCT) design would have offered a more appropriate evaluation of the TRUST ADP.

Publication of RCTs which evaluate diagnostic interventions is very rare (Rodger et al. 2012) and the reasons for this are likely to be due to the increased resources required-as is the case with the TRUST study; together with uncertainty surrounding the safety of new diagnostic tests-the principle of clinical equipoise (Freedman 1987). Despite this it has been suggested that diagnostic RCT's are critical in the evaluation of novel diagnostic techniques in the presence of standard care (Rodger et al. 2012). The reasons for this become evident when comparing the merits of observational diagnostic accuracy cohort studies and RCTs (Table 40).

Table 39. Levels of evidence for diagnostic studies

Level	Diagnostic Study
1a	Systematic Review of Level 1 diagnostic studies or multicenter validation of a clinical decision rule
1b	Validating cohort study with good reference standards; **or clinical decision rule tested within one centre**
1c	A diagnostic finding whose Sensitivity/specificity is so high that a Negative/positive result rules-out/in the diagnosis.
2a	Systematic Review of > Level 2 studies
2b	Exploratory cohort study with good reference standards; a clinical decision rule validated on split sample databases only
3a	Systematic review of 3b and better studies
3b	Non-consecutive study; or without consistently applied reference standards
4	Case-control study, poor reference standard
5	Expert opinion

Adapted from Oxford Centre for Evidence Based Medicine 2009

Table 40. Comparative advantages and disadvantages of observational and randomized diagnostic trials

Diagnostic observational cohort study	Diagnostic Randomized Controlled Trial
Advantages • Simple to run • Inexpensive • Accepted amongst medical community • Allow calculation of diagnostic accuracy • Tests safety of a novel test when clinical equipoise* may not justify a randomized design	**Advantages** • Remove threats to validity that occur with observational studies • Permit direct comparison of experimental and standard tests with clinically relevant outcomes • Can result in the experimental test being better than the reference standard • Can be conducted when there is no accepted reference standard • Can accurately determine cost effectiveness/efficiency improvements
Disadvantages • Simply compares experimental test to reference standard • Does not measure hard patient outcomes • Difficult to establish cost-effectiveness • No new diagnostic test can beat the reference standard	**Disadvantages** • Expensive • Resource heavy • Can only be performed if the diagnostic test is known to be safe (clinical equipoise*)

**Clinical equipoise means there is genuine uncertainty within the medical community as to whether the diagnostic test will be safe (Freedman 1987).*

Examples of where diagnostic RCTs can provide information that observational studies are unable, within the field of accelerated diagnostic protocols in chest pain, are provided by two large diagnostic studies. The first, the randomised assessment of treatment using panel assay of cardiac biomarkers (RATPAC) study (Fitzgerald et al. 2011) was able to robustly demonstrate a reduction in length of stay in patients assessed using a rapid biomarker rule-out strategy but a paradoxical increase in downstream testing was revealed. The second, by Than et al. (2014a) demonstrated that a 2-hour accelerated diagnostic protocol only achieved reduction in length of stay after 6 hours (Figure 6, Page 67). Neither of these effects would have been robustly demonstrated through an observational design.

The TRUST study's observational design also may have resulted in threats to both internal and external validity as summarized in Table 41. Diagnostic RCTs may eliminate or reduce the likelihood for many of the potential biases that threaten internal validity of diagnostic accuracy cohort studies (Rodger et al. 2012).

Table 41. Threats to validity of the TRUST Study

Threat	Definition	In context of TRUST Study
Internal Validity (bias)		
Context bias	Experimental test more likely to be reported as abnormal in populations with high disease prevalence	False-positive high-sensitivity troponin elevations
Clinical review bias	Experimental test or reference standard interpreted with knowledge of participant clinical characteristics	6 hour troponin result interpreted after notes review
Test review bias	Experimental test interpreted with knowledge of the reference standard test results	Un-blinding of presentation troponin results to assess change over time
Diagnostic review bias	Reference standard test interpreted with knowledge of the experimental test results	Clinicians blinded to experimental (presentation troponin) test results
External validity (generalisability)		
Spectrum of participants	Disease severity, participant demographics or participant co-morbidity influence experimental test accuracy	Limited due to single centre, predominantly white Caucasian population Age>80 excluded
Confounding	Potential study participants with confounders known to influence experimental test accuracy excluded from study	Patients with abnormal ECG excluded Age>80 excluded

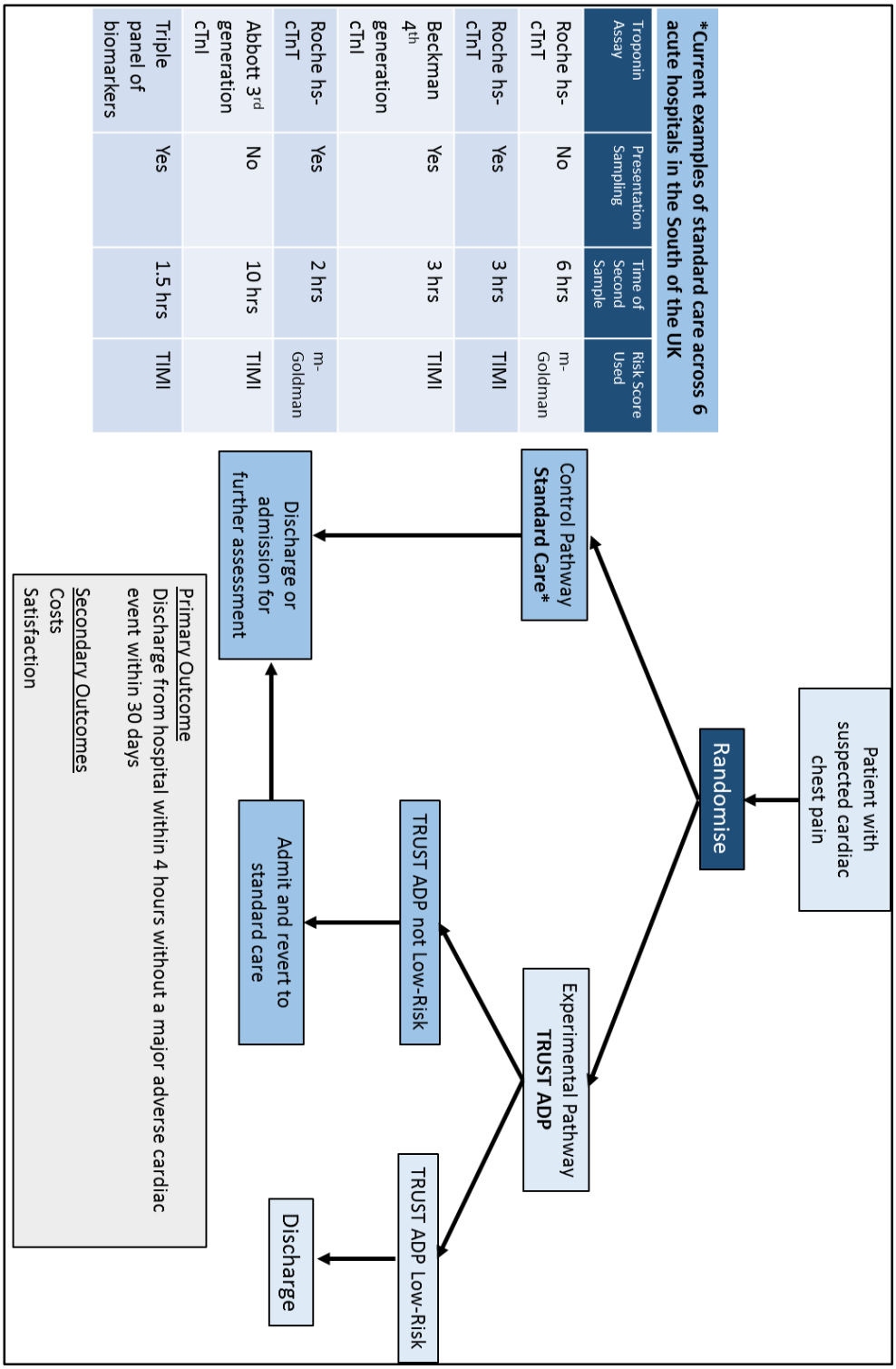
Adapted from Rodger et al. 2012

It is therefore important to recognise that the TRUST ADP ideally requires validation as part of a multicentre randomised controlled trial. However, it may be argued that without first analysing the safety of this diagnostic strategy through an observational

cohort design, the principle of clinical equipoise may not have justified a randomised study design (Freedman 1987).

A suggested design to test the TRUST ADP within an RCT is included in Figure 35. The aim of this RCT would be to compare the effectiveness of two investigative pathways for the assessment of patients with suspected cardiac chest pain. Effectiveness would be established through measurement of the primary outcome measure: discharge within 4 hours of attendance without MACE at 30 days. As demonstrated in Figure 32, the TRUST ADP could be compared with multiple standard care processes by incorporating multiple centres. In order to achieve maximal clinical applicability this trial design follows the CONSORT extension statement for pragmatic trials (Zwarenstein et al. 2008), and therefore clinical management would not strictly be controlled. Although pathways for the intervention and control arms would be provided, the final management decision, based on either subjective or structured clinical assessment, as well as test results, would be at the discretion of the treating physician.

Figure 32. Suggested trial schema to test the TRUST ADP within a diagnostic randomized control trial against standard care



6.3 Study Population

In the evaluation of a diagnostic strategy, such as the TRUST ADP, the study population should be representative of the population who would receive the test in routine practice (Goodacre 2009). If the population is highly selected then this will bias estimates of sensitivity and specificity. By recruiting consecutive patients with appropriate inclusion and exclusion criteria the generalizability of the TRUST study results has been maximized. However, the generalizability of the TRUST ADP may still be limited by the characteristics of the population selected.

Participants were only recruited if treating physicians planned to investigate as an inpatient, therefore patients discharged directly from the ED at the discretion of the ED doctor were not included. It should be noted that this direct discharge group may in fact have a miss-rate for acute coronary syndromes of up to 5% (Christenson et al. 2004) which in itself is not insignificant.

6.3.1 Demographics

An integral part of the TRUST ADP and the analysis of typicality of pain are patient reported symptoms. It is known that symptoms reported by patients are varied and are influenced by factors such as age, sex and medical history. Women with AMI may be more likely to report atypical rather than typical symptoms (Rubini Gimenez et al. 2014). While older patients and those with various chronic diseases may make cardiac symptoms more difficult to recognise (Horne et al. 2000). These factors may therefore limit the TRUST study's applicability.

The inclusion of predominantly British Caucasian patients may also limit the applicability to international settings. The high proportion (>95%) British Caucasian

patients is reflective of the local population demographic and is greater than that of the majority of the UK (Dorset County Council 2011) this has important implications in applying the study findings to more diverse populations. For example, (Greenslade et al. 2012) identified cross-cultural differences in symptoms reported by patients with suspected ACS. Furthermore reference values for high-sensitivity troponin assays have been determined in Western populations and limited data is available regarding expected values in Asian populations (Gaggin et al. 2014).

6.3.2 Exclusion of Patients over 80 years

As a result of the exclusion of patients > 80 years, a "Safety Point" has been added to the published TRUST ADP. This ensures clinicians are aware the ADP is not validated in the elderly.

The upper age cut-off of ≥80 years was chosen for pragmatic reasons. In our institution, patients above this age are admitted to a separate and dedicated assessment area. The TRUST Study is therefore guilty of not recruiting the fastest growing sector of the population, and furthermore physiologically the elderly cannot be classed as equivalent to those decades younger (Watts 2012). This consideration is of great importance with regard to high-sensitivity troponin assays, where it is known a high proportion of patients have elevations in troponin due to sub-clinical disease (deFilippi et al. 2010). Therefore it is recognized that this may affect the applicability of the findings in those >80 years of age and any clinical uptake of the protocols described should therefore not be applied to those over the age of 80 years.

As a counterpoint to this, it may also be argued that older people must not be discharged overnight due to welfare concerns (Banerjee et al. 2013), and given that

over 40% of the TRUST cohort presented outside 0800-1800 hours, an ADP in this age-group may have minimal impact on length of hospital stay. If the TRUST study were to be repeated however, careful consideration of the positive inclusion of elderly patients, in order to address these issues, would be appropriate.

6.3.3 Exclusion of Patients with an Ischaemic Electrocardiogram

Patients were only recruited if they had a non-ischaemic ECG at presentation - thereby reducing the prevalence of MACE in the study population. This may be described as a significant limitation of the TRUST study. However, expansion of the inclusion criteria to include those patients with ECG changes consistent with ACS would have added little practical value because this group are not suitable for early discharge anyway. Patients with a clear diagnosis of ACS, were intentionally excluded, to focus on a particular group that remain a major diagnostic challenge.

In fact, it has been argued that recruiting patients with an ECG that is diagnostic for ischaemia is a limitation of prior papers that have evaluated the clinical features of acute chest pain (Goodacre et al. 2009). This is because clinical features that simply help to confirm the diagnosis of ACS in a patient with a diagnostic ECG are likely to be of limited practical value.

6.4 Outcome Selection and Adjudication Challenges

6.4.1 Major Adverse Cardiac Events

On commencement of the study the primary outcome chosen for analysis of the TRUST ADP was the presence of MACE at 30 days, including the initial hospital visit. This was defined according to prior large-scale studies investigating rapid rule-out protocols (Than et al. 2011, Collinson et al. 2012 and Cullen et al. 2013). This definition may be open to criticism, specifically for the use of urgent revascularization-which may be argued is subjective and may be influenced by adjudication bias. Subjective ischemic endpoints such as revascularization are likely to be driven by local practices, and in the case of this study, the hs-cTnT assay in clinical use. As a result of this, for the paper summarizing the diagnostic accuracy of the TRUST ADP published in BMJ Heart (Carlton et al. 2015) the primary outcome was switched to fatal/non-fatal AMI.

It may be argued, however, that the inclusion of revascularization is important, as patients with a requirement for revascularization are known to be a short term risk of death and AMI, even in the absence of elevations in high-sensitivity troponin (Reichlin et al. 2013). Therefore, when assessing suitability for discharge from the ED revascularization should still be included as an outcome measure.

Subtle variations in the use of MACE within published literature have also been identified and should be accounted for by the reader. For example, in a recent validation of the Manchester Acute Coronary Syndromes (MACS) rule (Body et al. 2014a), MACE included patients with >50% coronary stenosis in the absence of revascularization. There is an evident requirement for a Universal Definition of MACE.

6.4.2 Acute Myocardial Infarction

The initial intention was to undertake blinded adjudication of AMI according to only those high-sensitivity troponin results taken at 6 hours after attendance. Whilst this blinded approach would have been methodologically correct (Stiell and Wells 1999), it was adjudged significant flaw in the study design. The 3rd Universal Definition of AMI requires a rise or fall in troponin to be detected over time (Thygesen et al. 2012a), therefore AMI adjudication using just one 6 hour sample would not be guideline driven. It was therefore decided to un-blind the adjudication process.

This lead to a further problem in selecting an appropriate "significant" change over time for the hs-cTnT assay used for outcome adjudication. Current consensus guidance (Thygesen et al. 2012b) suggest the use of a delta change of 20% over a period of 3-6 hours and this approach was selected. However, it should be acknowledged that evidence for this comes from third generation assays and is not specific to the hs-cTnT assay used in the TRUST study. Another approach considered was the use absolute change of 9ng/L, over time which may lead to improve specificity, however this approach is experimental and requires validation (Mueller et al. 2012).

6.4.3 Significant Coronary Artery Disease

Significant CAD was used as an outcome measure in the analysis of typicality of chest, in order to provide an anatomical outcome measure and overcome the adjudication challenges associated with high-sensitivity troponin assays (Mills et al. 2011). For this outcome measure, those patients selected for coronary angiography were done so according to the results of biomarker testing, stress testing or the clinical suspicion of

treating cardiologists. Therefore this outcome may have been subject to 'referral' or 'verification' bias. Furthermore, interpretation of degree of stenosis was made according to visual assessment. Heterogenicity due to differences between providers in angiography referral criteria and interpretation of degree of stenosis may have therefore influenced these results. However the proportion identified as having significant coronary artery disease at angiography (58.2%) is in line with a recent study in a stable chest pain population which analysed typicality of chest pain (Genders et al. 2011).

6.5 Follow-up

It may be suggested that patient follow-up, which did not involve direct patient contact, may lead to potential missed outcome events. The ethics committee did not grant permission for direct patient contact as they felt that comprehensive follow-up data relating to adverse events could be obtained accurately through GP records. This is because in the U.K., GPs hold comprehensive records for individuals relating to primary, secondary and tertiary care. GP records have been demonstrated to be more accurate at reporting hospital admissions, including those for cardiac related events, than patients (Taylor et al. 2003).

6.6 Evaluation of Other Risk Scores

Although data for each risk score was collected prospectively from data derived from that recorded by the treating physician at initial assessment, only the m-Goldman score was performed by the physician themselves. The approach of deriving risk scores from large prospective datasets is commonplace in the literature (Goodacre et al. 2012, Six et al. 2013 and Cullen et al. 2014a). Accepting that subjective interpretation may be important in risk-stratifying patients with chest pain (Kline and Stubblefield 2013 and Body et al. 2014b), this methodological approach may be flawed, and only resolved through direct comparison of each pathway through pragmatic randomized controlled trials.

6.7 Evaluation of Chest Pain Typicality

It may be argued that the use of a binary yes/no answer to evaluate chest pain typicality severely limits the interpretation of these results. As a result of this potential methodological flaw, the focus of discussion moved towards the potential impact of context and cognitive biases. This resulted in the expansion of the analysis to incorporate clinician experience and therefore a greater utility in the conclusions. However, it should be recognised that the assessment of unstructured clinician judgement may have been better assessed using a 5-point Likert scale, as performed by (Body et al. 2014b), in their analysis of clinician *gestalt* and if this analysis were to be repeated alterations of the methods to include this would be appropriate.

6.8 Patient Survey

Given the low response rate of this survey, non-response bias should be considered when interpreting the data. Despite the written nature of the survey, no screening was undertaken to account for illiteracy or those whose first language was not English.

The quantitative nature of the questionnaire will also provide a limited interpretation of patient perspectives which may be improved with qualitative methodology. In any study of this kind, there will be factors leading to further potential limitations, these will include the patient socio-demographic factors, patient experiences during admission, institutional reputation, ED crowding, staff attitudes and the fact that all respondents were recruited to a clinical trial.

Conclusions

The TRUST ADP, which incorporates a structured risk-assessment and single presentation hs-cTnT blood draw, has the potential to allow early discharge in 40% of patients with suspected acute coronary syndromes. Uptake of this protocol may have significant benefits for healthcare services worldwide by reducing hospital admission rates, ED overcrowding, duplication of staff time and resource use. Furthermore, by using ED physicians to carry out risk-stratification and real-time troponin sampling with 24-hour recruitment it has been demonstrated that this ADP is truly applicable. The TRUST ADP has superior clinical utility when compared to undetectable hs-cTnT strategies and other existing risk scores in this cohort. Future research should focus on methodologies that incorporate clinical assessment with high-sensitivity troponin testing rather than troponin testing alone, and the comparison of early rule-out strategies using diagnostic randomised controlled trials.

Chapter 7.

Publication and Future Directions

7.1 Presentation at International Scientific Conferences

Presentation of results from the TRUST Study has taken place at the American College of Cardiology Scientific Sessions 2014 (poster: *Appendix 9*), World Congress of Cardiology 2014 (poster: *Appendix 10*) and the International Conference on Emergency Medicine 2014 (oral presentation).

7.2 Publication in Print

Clinical and translational work such as the TRUST Study may quickly become outdated. Therefore there must be a focus on progressing to publication in high-impact peer reviewed medical journals. The following papers have been published or are in print:

7.2.1 A Novel Diagnostic Protocol to Identify Patients Suitable for Discharge after a Single **High-Sensitivity Troponin**

Carlton EW, Cullen L, Than M, Gamble J, Khattab A, Greaves K.

Heart. 2015 Feb 17. pii: heartjnl-2014-307288.

Abstract:

Objective

To establish whether a novel accelerated diagnostic protocol (ADP) for suspected acute coronary syndrome (ACS) could successfully identify low-risk patients suitable for discharge after a single high-sensitivity troponin T (hs-cTnT) taken at presentation to the Emergency Department (ED). We also compared the diagnostic accuracy of this ADP with strategies utilising initial undetectable hs-cTnT.

Methods

This prospective observational study evaluated the ability of the Triage Rule-out Using high-Sensitivity Troponin (TRUST) ADP to identify low-risk patients with suspected ACS. The ADP incorporated a single presentation hs-cTnT of <14ng/L, a non-ischaemic electrocardiogram and a modified Goldman risk score. Diagnostic performance of the ADP was compared with the detection limit cut-offs of hs-cTnT (<5ng/L and <3ng/L). The primary endpoint was fatal/non-fatal acute myocardial infarction (AMI) within 30 days.

Results

960 participants were recruited, mean age 58.0 years, 80 (8.3%) had an AMI. The TRUST ADP classified 382 (39.8%) as low-risk with a sensitivity for identifying AMI of 98.8% (95%CI 92.5-99.9). hs-cTnT detection limits (<5ng/L and <3ng/L) had a sensitivity of 100% (94.3-99.9) and 100% (94.4-100) respectively. The TRUST ADP identified more patients suitable for early discharge at 39.8% vs 29.3% (<5ng/L) and 7.9% (<3ng/L) (P<0.001) with a lower false-positive rate for AMI detection; specificity 43.3% (95%CI 42.7-43.4) vs 32.1% (95%CI 31.6-32.1) and 8.6% (95%CI 8.1-8.6) respectively.

Conclusion

The TRUST ADP, which incorporates structured risk-assessment and a single presentation hs-cTnT blood draw, has potential to allow early discharge in 40% of patients with suspected ACS and has greater clinical utility than undetectable hs-cTnT strategies.

(**Full Manuscript:** *Appendix 11*)

7.2.2 'Chest Pain Typicality' in Suspected Acute Coronary Syndromes and the Impact of Clinical Experience

Carlton EW, Than M, Cullen L, Khattab A, Greaves K.

American Journal of Medicine 2015. doi: 10.1016/j.amjmed.2015.04.012.

Abstract:

Background

Physicians rely upon chest pain history to make management decisions in patients with suspected acute coronary syndromes, particularly where the diagnosis is not immediately apparent through ECG and troponin testing.

Objective

To establish the discriminatory value of 'typicality of chest pain' and the effect of clinician experience, for the prediction of acute myocardial infarction and presence of significant coronary artery disease.

Methods

Prospective single-center observational study undertaken in a U.K. General Hospital emergency department. We recruited consecutive adults with chest pain and a non-diagnostic ECG, for whom the treating physician determined delayed troponin testing was necessary. Using their own clinical judgment, physicians recorded whether the chest pain described was typical or atypical for acute coronary syndrome. Physicians were defined as "experienced" or "novice" according to postgraduate experience. Acute myocardial infarction was adjudicated using a high-sensitivity troponin (hs-cTn) assay, while coronary artery disease was adjudicated angiographically.

Results

Overall, 912 patients had typicality of chest pain assessed, of whom 114/912 (12.5%) had an acute myocardial infarction and 157/912 (17.2%) underwent angiography. In patients

undergoing angiography, 90/157 (57.3%) had hs-cTn elevation, of whom 60 (66.7%) had significant coronary artery disease. 67/157 (42.7%) patients had angiography without hs-cTn elevation, of these 31 (46.2%) had significant coronary artery disease. For the diagnosis of acute myocardial infarction, chest pain typicality had an area under the curve (AUC) of 0.54 (95%CI 0.49-0.60). For the prediction of significant coronary artery disease with hs-cTn elevation AUC: 0.54 (0.40-0.67), and without hs-cTn elevation AUC: 0.45 (0.31-0.59). When assessed by experienced physicians, specificity for the diagnosis of acute myocardial infarction was higher at 65.8% (63.1%-68.7%) vs. 55.4% (53.9%-56.8%) for novices.

Conclusions

Subjective interpretation of 'typicality of chest pain' is of limited discriminatory value in the assessment of suspected acute coronary syndromes, in the context of a non-diagnostic ECG. Greater clinical experience improves accuracy as a rule-in tool but does not improve overall discriminatory ability.

(**Full Manuscript**: *Appendix 12*)

7.2.3 Beyond Triage: The Diagnostic Accuracy of Emergency Department Nursing Staff Risk Assessment in Patients with Suspected Acute Coronary Syndromes

Carlton EW, Khattab A, Greaves, K.

Accepted Manuscript In Print: Emergency Medicine Journal

Abstract:

Objectives

To establish the accuracy of emergency department (ED) nursing staff risk-assessment, using an established chest pain risk score alone and when incorporated with presentation high-sensitivity troponin testing as part of an accelerated diagnostic protocol (ADP).

Design

Prospective observational study comparing nursing and physician risk-assessment using the modified Goldman (m-Goldman) score and a pre-defined ADP, incorporating presentation high-sensitivity troponin.

Setting

A U.K. District ED.

Patients

Consecutive patients, aged ≥18, with suspected cardiac chest pain and non-ischaemic ECG, for whom the treating physician determined serial troponin testing was required.

Outcome Measures

30 day major adverse cardiac events (MACE).

Results

960 participants were recruited. 912/960 (95.0%) had m-Goldman scores recorded by physicians and 745/960 (77.6%) by nursing staff. The AUC of the m-Goldman score in predicting 30 day MACE was 0.647 (95% CI 0.594-0.700) for physicians and 0.572 (95% CI 0.510-0.634) for nursing staff (P=0.09). When incorporated into an ADP, sensitivity for the rule-out of MACE was 99.2% (95% CI 94.8-100) and 96.7% (90.3-99.2) for physicians and nurses respectively. One patient in the physician group (0.3%), and three patients (1.1%) in the nursing group were classified as low-risk yet had MACE.. There was fair agreement in the identification of low-risk patients (kappa 0.31, 95% CI 0.24-0.38).

Conclusion

The diagnostic accuracy of ED nursing staff risk-assessment is similar to that of ED physicians and inter-observer reliability between assessor groups is fair. When incorporating high-sensitivity troponin testing, a nurse-led ADP has a miss-rate of 1.1% for MACE at 30 days.

(**Full Manuscript:** Appendix 13)

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

Carlton EW, Khattab A, Greaves K.

In Press: Annals of Emergency Medicine

Abstract:

Objective

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

Methods

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

Results

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

and TIMI 0 and HEART≤3, with hs-cTnI have the potential to achieve an NPV ≥99.5% while identifying >30% for discharge.

Conclusion

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

(**Full Manuscript:** Appendix 14)

7.2.5 External Validation of the Manchester Acute Coronary Syndromes Rule

Carlton E, Body R, Greaves K.

Accepted Manuscript In Print: Academic Emergency Medicine

Abstract:

Objectives

The Manchester Acute Coronary Syndromes (MACS) decision rule has been shown to be a powerful diagnostic tool in emergency department (ED) patients with suspected acute coronary syndromes (ACS). It has the potential to improve system efficiency by identifying patients suitable for discharge after a single blood draw, for high-sensitivity troponin and heart-type fatty acid binding protein analysis, at presentation to the ED. We aimed to externally validate the MACS decision rule and establish its diagnostic accuracy as a discharge tool in a new set of prospectively recruited ED patients.

Methods

In this post-hoc analysis of a prospectively recruited single-centre cohort we included consecutive ED patients ≥18 years with suspected ACS. Testing for heart-type fatty acid binding protein and high-sensitivity troponin T was undertaken on serum drawn on arrival and clinical features required to calculate the MACS rule recorded. The primary outcome was major adverse cardiac events (MACE) within 30 days (acute myocardial infarction (AMI), death or revascularisation). The secondary outcome was AMI alone, adjudicated using 6 h troponin results.

Results

Of the 782 participants included, 78 (10.0%) developed MACE and 61 (7.8%) had an AMI. Of participants, 133 (17.0%) were identified as 'very low risk' and therefore suitable for immediate discharge with a 0% incidence of MACE or AMI. The sensitivity was 100% (95% CI 95.4-100) for MACE at 30 days and 100% (95% CI 94.1-100) for AMI. Of the 'high risk' group, 53.3% had a MACE within 30 days. The area under the ROC curve was 0.87 (95% CI 0.83 – 0.91) for the MACS rule in the prediction of MACE.

Conclusion

In this prospectively recruited cohort, the MACS decision rule identifies a significant proportion of patients who are suitable for immediate discharge after a single blood draw at presentation, with a 0% risk of MACE. The rapid assessment and discharge of these patients is likely to reduce healthcare resource burden and costs.

(**Full Manuscript:** Appendix 15)

7.3 Collaborative Research Work

The TRUST Study has stimulated world-wide interest. Active collaboration is underway with the following researchers in the field for the following projects:

7.3.1 The Investigation of the Incremental Benefit of the use of Sex-Specific Versus Overall Cut Points for High-Sensitivity Troponin I Assays in Predicting Short and Long-Term Events in Emergency Department Patients

This prospective analysis combines data from the TRUST Study with large cohorts in Australia and New Zealand to investigate the benefits of se-specific cut-offs. Follow-up from the TRUST Study has been extended to include 12 month outcomes for this analysis. This analysis is funded by Abbott Technologies who supplied the Troponin I assay for the TRUST Study.

Manuscript accepted for publication: *BMJ Heart*

Collaborator: Associate Professor **Louise Cullen**, Emergency Department, Royal Brisbane and Women's Hospital, Brisbane, Australia.

7.3.2 Rapid rule-out of AMI in chest-pain patients using single undetectable high-sensitivity troponin T concentrations: external validation in multiple centres

An informal collaborative which aims to externally validate, in six countries, a strategy for the rapid rule-out of acute myocardial infarction utilizing an undetectable initial high-sensitivity troponin T result and non-ischemic ECG in patients presenting to emergency departments with chest pain. Data from the TRUST Study has been incorporated into this analysis and publication of the results is imminent.

Collaborator: Professor **Martin Than**, Emergency Department, Christchurch Hospital, New Zealand.

7.4 Proposed Future Research

The student investigator is developing an NIHR grant application to run the following study:

The Level of Detection of Troponin in the Emergency Department (*LoD-ED)* Assessment of Chest Pain Randomised Controlled Trial

Rationale for Research

Current data suggest that the diagnostic accuracy of the cut-off of hs-cTnT (Roche Elecsys assay) in common clinical use (the 99th centile value: 14ng/L), when used in isolation is too low to allow immediate discharge of patients presenting to ED after a single blood draw on arrival (Reichlin et al. 2009 and Keller et al. 2009). However, the hs-cTnT assay has enabled more reliable detection of very low concentrations of troponin T and multiple observational studies have tested the Level of Detection (LoD: lowest analyte concentration likely to be reliably distinguished at which detection is feasible) of 5ng/L. In a meta-analysis published in 2015 (Zhelev et al. 2015) gave a pooled sensitivity for the rule-out of acute myocardial infarction (AMI) of 97.4% using the LoD. However, diagnostic accuracy may be further improved by incorporating the finding of an electrocardiogram (ECG) on arrival with no evidence of cardiac ischemia. This strategy was tested in a recent retrospective analysis (Bandstein et al. 2014) of 14,636 chest pain patients who presented to EDs in Sweden. Sixty one percent (8,907) of patients had an initial hs-cTnT level of <5 ng/l (LoD) and no ST-segment changes indicating myocardial ischemia on their ECG. Subsequent analysis of hospital records and registry data showed a minimal occurrence of AMI (0.2%) or death (0%) in these patients within 30 days of arrival at the ED. Our group has validated this approach through analysis of pooled results from a series of international prospectively collected data in 5 geographically diverse cohorts. In an as yet un-published analysis incorporating 6275 participants, the index test of no new ischaemia on an initial ECG and hs-cTnT <5ng/L achieved a negative predictive value for major

adverse cardiac events (MACE) of between 98.3-99.7% with between 11.4% and 73.5% of patients being suitable for early discharge.

Whilst these results are promising, the effectiveness of the level of detection diagnostic strategy requires testing in a pragmatic randomised controlled trial (RCT). This will enable us to establish whether such a strategy works under real-life conditions. A key feature in this study design is that, although pathways for the intervention and control arms are provided, management will not be strictly controlled. The final management decision, after test results, will be at the discretion of the treating clinician. Clinicians do not predictably follow protocols or act on test results as expected (Than et al. 2014a). Therefore the critical question this trial will answer is whether the new pathway works in practice, with clinicians actually discharging patients early, without subsequent harm or increased downstream resource use, in significant numbers. Results from this RCT are more likely to promote knowledge translation than an observational trial.

Aims

To compare the effectiveness, when applied to clinical practice, of a Level of Detection of high-sensitivity troponin T rapid rule-out strategy against the existing diagnostic process used in three centres – specific objectives are:

1. Compare the rate of successful discharge at 4 hours after ED attendance.

2. Measure hospital bed usage, length of stay, resource use, cost effectiveness and rate of major adverse cardiac events at 30 days.

Research Design and Methods

Participants: Consenting adults presenting to the ED with chest discomfort suggestive of acute coronary syndrome (Luepker et al. 2003) in whom the attending clinician(s) (after initial

assessment) intends to perform serial troponins, as part of the existing chest pain investigation pathway for possible acute myocardial infarction.

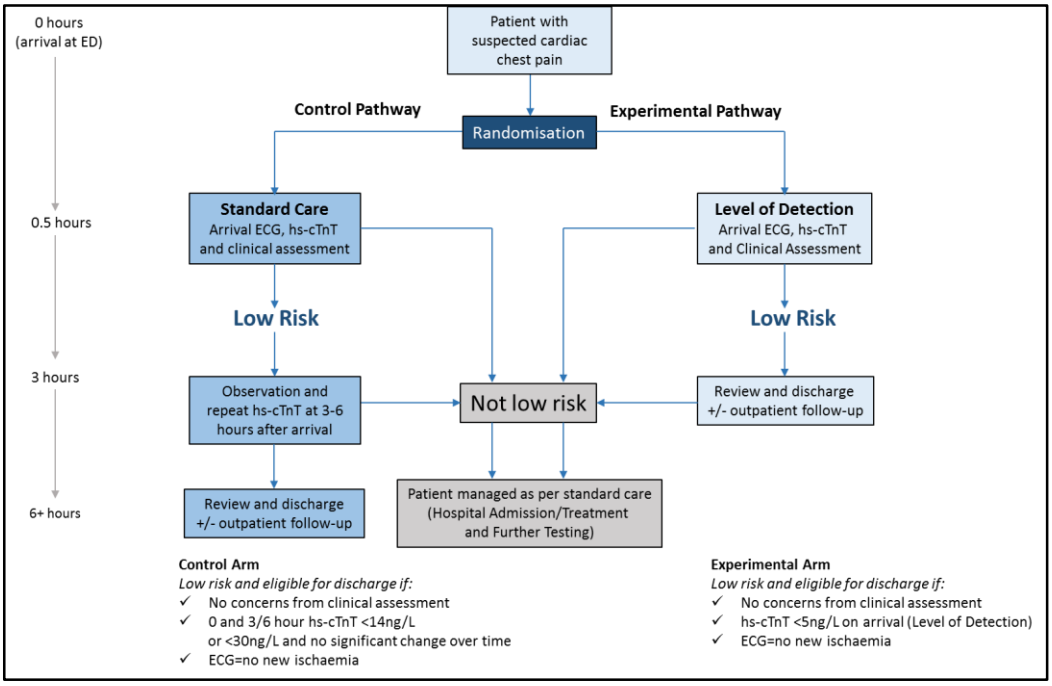
Exclusion criteria: ST Segment Elevation Myocardial Infarction (STEMI); persisting pain and patients requiring admission regardless of a negative ECG/Troponin, due to other medical or social reasons; arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias); refusal or inability to provide informed consent; inability to be contacted after discharge.

Interventions: Participants will be randomised to have a diagnostic assessment using either: a) Level of Detection strategy (experimental pathway) or b) existing chest pain investigation pathway (control pathway). In order to achieve maximal clinical applicability this trial design follows the CONSORT extension statement for pragmatic trials (Zwarenstein et al. 2008), therefore clinicians will not have to follow trial pathways if they believe they are not best for the patient. (Intention to diagnose analysis will be used).

1. **Control Pathway:** These are existing diagnostic pathways in use in recruiting centres, these may have subtle variations between centres and will not be altered for research use. These pathways include ECG assessment on arrival, followed by clinical assessment and serial hs-cTnT testing at presentation and after 3-6 hours of observation, as per consensus guidelines to identify patients who are low-risk and then suitable for discharge/outpatient investigations. The cut-off of hs-cTnT used to definitively rule out acute myocardial infarction in usual care is the 99th centile value (<14ng/L).

2. **Experimental Pathway:** Patients in the experimental arm are defined as low-risk following a single blood draw at presentation to the ED if they have (i) no new ischaemic ECG changes and (ii) an hs-cTnT below the Level of Detection (<5ng/L) and (iii) the treating clinician thinks discharge is safe. Low-risk patients will be eligible for early discharge/outpatient

investigations. Patients who do not fulfil low-risk criteria in the experimental arm will require further hs-cTnT testing after 3-6 hours of observation as per standard care.



Primary Outcome: The proportion of patients successfully discharged home within 4 hours of arrival with no MACE during the following 30 days.

Secondary Outcomes: (i) MACE (death, acute myocardial infarction, ventricular arrhythmia, emergency revascularisation), (ii) non-trauma hospital re-attendance within 30 days, (iii) length of stay in hospital, (iv) use of advanced cardiac testing (stress testing, CT coronary angiography and invasive angiography) and (v) cost-effectiveness.

Patients who suffer MACE after discharge will not be classified as "successful" discharge home because it is possible that they may have benefitted from hospital admission.

Assessment of Outcomes

Research nurses will record baseline data, the results of initial assessment (and tests), and admission/discharge from the ED. Electronic patient records will be used to record

management decisions at initial attendance, and identify subsequent attendances/admissions. Patient status at 30 days will be confirmed using national clinical records, hospital information systems, telephone follow-up and GP records. Structured adjudication of all final diagnoses including AMI, and other adverse events will be performed by two blinded reviewers.

Sample Size

Current research gives estimates of the proportion suitable for discharge in the experimental arm of the RCT from between 10% and 40% (Zhelev et al. 2015). Even if the experimental arm were to only achieve early discharge in 10% of patients then this would be an important difference. This study will be powered to detect a 10% difference between the early discharge rates with a β=0.10 (90% power) and a 2-tailed α=0.05. This will require 286 patients in each arm and 572 patients in total. Based on recruitment in our previous study and with recruitment 0900-1700 Monday to Friday this will take 3 centres (e.g. Southmead Hospital, Bristol Royal Infirmary and Royal United Hospital, Bath) 10 months to complete.

Anticipated Outcomes

Implementation of positive study findings will decrease admissions and processing times for patients with chest pain. This will positively impact upon the Department of Health ED 4-hour target and also upon hospital and ED overcrowding. There is an urgent need for improvement in this area. In addition to scientific publications wider dissemination of positive study findings will be achieved in the UK through the medical royal colleges and the National Institute for Health and Care Excellence.

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Abbreviations

ACS	Acute Coronary Syndrome
ADP	Accelerated Diagnostic Protocol
AMI	Acute Myocardial Infarction
ANI	Advanced Nursing Interventions
AV	Atrio-Ventricular
BP	Blood Pressure
COPD	Chronic Obstructive Pulmonary Disease
ECG	Electrocardiogram
ECHO	Echocardiogram
ED	Emergency Department
GP	General Practitioner
GRACE (Risk Score)	Global Registry of Acute Coronary Events
HEART (Risk Score)	History/ECG/Age/Risk Factors/Troponin
Hs-cTn	High-sensitivity Troponin
LoB	Level of Blank
LoD	Level of Detection
MACE	Major Adverse Cardiac Events
MG (Risk Score)	Modified Goldman
NICE	National Institute of Health and Clinical Excellence
N-STEMI	Non-ST Elevation Myocardial Infarction
STEMI	ST-Elevation Myocardial Infarction
TIMI (Risk Score)	Thrombolysis in Myocardial Infarction
Tn	Troponin
UA	Unstable Angina

APPENDICES

Appendix 1: Ethics Approval Letter

NHS
Health Research Authority

NRES Committee South West - Frenchay
Bristol Research Ethics Centre
Level 3, Block B
Whitefriars
Lewins Mead,
Bristol
BS1 2NT

Telephone: 0117 342 1334
Facsimile: 0117 342 0445

30 May 2012

Dr Edward W Carlton
Cardiorespiratory Department
Poole Hospital
Longfleet Road,
Poole
BH15 2JB

Dear Dr Carlton

Study title:	**An Accelerated Diagnostic Pathway incorporating the Modified Goldman Criteria and 1-hour high-sensitivity troponin testing to identify low-risk Emergency Department patients with chest pain who may be suitable for immediate discharge.**
REC reference:	**12/SW/0133**
Protocol number:	**2**

Thank you for your letter of 24 May 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		10 April 2012
Covering Letter		24 May 2012
Investigator CV		23 February 2012
Letter from Statistician		25 November 2011
Other: Unfavourable opinion letter - Berkshire REC		30 March 2012
Other: Nursing risk assessment sheet	2	04 April 2012
Other: Sample blood request sticker	1	23 February 2012
Other: Data collection sheet	1	05 April 2012
Other: Data protection and Caldicott assessment	2	09 April 2012
Participant Consent Form: Patient	2.1	24 May 2012
Participant Information Sheet: Patient	2.1	24 May 2012
Participant Information Sheet: Nursing	1.1	24 May 2012
Protocol	2.1	24 May 2012
Questionnaire: Patient chest pain questionnaire	2.1	24 May 2012
REC application		05 April 2012
Referees or other scientific critique report		10 January 2011
Response to Request for Further Information		24 May 2012
Summary/Synopsis	1	23 February 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/SW/0133	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Robert Beetham
Vice-Chair

Email: ubh-tr.SouthWest5@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mary Burrows, Poole Hospital NHS Foundation Trust*
Professor Kim Greaves, Poole Hospital NHS Foundation Trust

Appendix 2. Participant Information Sheet (Patient)

Poole Hospital NHS
NHS Foundation Trust

STUDY TITLE: An Accelerated Diagnostic Pathway incorporating the Modified Goldman Criteria and 1-hour high-sensitivity troponin testing to identify low-risk Emergency Department patients with chest pain who may be suitable for immediate discharge.

TRUST: Triage Rule-Out Using Sensitive Troponin Chest Pain Study

Investigators: Dr Edward Carlton, Dr Nick Jenkins, Dr Martin Than, Dr Joe Begley, Dr Richard Body, Dr Simon Bell and Professor Kim Greaves

PARTICIPANT INFORMATION SHEET: CHEST PAIN WITH A NORMAL ECG

Invitation to take part:

You have been invited to take part in a research study. This will look at patients attending the emergency department with chest pain that may be caused by heart problems.

What is the purpose of the study?

One of the tests we do to rule-out heart problems is a blood test taken 6 hours after you arrive in the Emergency Department. We are trying to see whether this can be done safely within 1 hour of arrival. This is a novel way of managing patients with chest pain.

Why have I been chosen?

You have been chosen because it is unlikely that the chest pain you are having is related to your heart and because your heart tracing (ECG) is normal. However, the doctors looking after you may want you to be admitted to the ward for a period of observation and further tests (including a blood test) to safely rule-out heart problems.

Do I have to take part?

Your taking part in the study is entirely voluntary. If you do choose to take part we will ask you to give us written permission. When you are comfortable and settled a member of the research team will ask you to sign a consent form.

What will happen if I take part?

YOUR TREATMENT WILL NOT CHANGE IN ANY WAY

You will be assessed as normal in the Emergency Department/Medical Admissions Unit. We do appreciate that an emergency ward can be busy, stressful and loud. You will be given time during your admission to ask any questions you might have.

While you were having blood tests on your arrival in the Emergency Department, we took an extra half a spoonful for use in the study. We would like your permission to use this blood sample in our research.

Your additional blood sample will be sent to the hospital laboratory where it will be analysed for heart muscle proteins. The doctors and nurses looking after you will not know the results of this blood test. This blood test will not alter the treatment you receive.

We would also like to store the blood test in the laboratory. No blood cells will be stored. This may enable us in future, to develop new tests to improve patient care.

The study investigators will then look through your notes for this hospital attendance and see whether you could have been discharged safely after the research blood test on arrival.

In some circumstances we may also need access to your GP records.

You may be given a questionnaire on discharge where you can rate our services. This will be fully confidential and will not affect your future care. It will help us to develop ways in which we can improve our services.

Who will supervise this study?

The Chief Investigator, Dr Edward Carlton will supervise the study. Prof Greaves, a Consultant Cardiologist (Heart Specialist) will be in overall control of the study.

What if I withdraw?

You are free to withdraw at any time. This will NOT affect your future care at Poole Hospital or anywhere in the NHS.

What are the benefits of taking part?

Chest pain is a very common problem. Most people who come to the Emergency Department with chest pain will not have any problem with their heart. Doctors do not want to miss those people who do have heart problems and as a result most patients will require admission to a ward for further blood tests. We hope to find a

way of safely preventing people being admitted for further testing. You are being invited to take part to help us to do this.

This may pave the way for new methods to improve patient care, reduce hospital overcrowding and reduce costs to the NHS.

Will my details be kept confidential?

Yes. We will follow ethical and legal practice and all details about you will be handled in confidence. Your name will be replaced with a code number that will be used on all documents for the study. No personal details will be used.

What if there is a problem?

If you have any concern about this study, you can speak to the chief investigator (details below). If you are still unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

What happens once the study is over?

Once the study is over the results will be sent to a medical journal and presented at conferences to teach other doctors. Your personal details will NOT appear anywhere in these publications or presentations.

If you would like to be sent a summary of the study results, once it is over, please let us know when you sign the consent form. (You will not receive any unsolicited mail from the TRUST Study investigators and we will not pass on your details to any third parties).

Who has reviewed this study?

All research in the NHS is assessed by an independent group, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the Frenchay Research Ethics Committee.

How much time can I have to decide about taking part?

Once you are comfortable and settled on the ward, a member of the research team will come and discuss the study with you and answer any questions you may have. When you feel ready you will be asked to sign a consent form at some point during your admission. Even if you sign the consent form you can still withdraw from the study at any time if you change your mind.

We would like to thank you for considering taking part in this study. If you have any questions please feel free to discuss them with the chief investigator.

Chief Investigator:

Dr Edward Carlton (Emergency Department Registrar) MBChB, MCEM

Telephone:
01202 442037 (Office) 07595040112 (Mobile)

Email:

edward.carlton@poole.nhs.uk

Thank you for taking the time to read this information sheet.

Appendix 3. Participant Information Sheet (Nursing)

Poole Hospital NHS
NHS Foundation Trust

STUDY TITLE: An Accelerated Diagnostic Pathway incorporating the Modified Goldman Criteria and 1-hour high-sensitivity troponin testing to identify low-risk Emergency Department patients with chest pain who may be suitable for immediate discharge.

TRUST: Triage Rule-Out Using Sensitive Troponin Chest Pain Study

Investigators: Dr Edward Carlton, Dr Nick Jenkins, Dr Martin Than, Dr Joe Begley, Dr Richard Body, Dr Simon Bell and Professor Kim Greaves

NURSING PARTICIPANT INFORMATION SHEET

Invitation to take part:

You are invited to take part in the TRUST Research Study. As part of this study we are aiming to see how accurate Nursing Staff are when performing a risk-stratification score during initial assessment of patients with chest pain and a normal ECG.

What is the Purpose of the Study?

We are aiming to identify a group of patients that will be suitable for early discharge in the future. As you are aware the majority of patients presenting with chest pain are admitted for troponin testing at 6 hours. We hope that by combining a low score on the tick box risk assessment score together with a low troponin result taken on routine admission bloods that these patients will be safe for discharge.

As part of the study we will be trying to establish whether nurses can accurately complete the tick box risk assessment that is already in use by doctors. If nurses are proved to be accurate this may improve the overall efficiency of the ED in future.

Who is involved?

We will be asking all ED Nursing staff (including HCA's) to give their consent to take part.

Do I have to take part?

Your taking part in the study is entirely voluntary. If you do chose to take part we will ask you to sign a written consent form prior to the study starting.

You can withdraw your consent for participating in the study at any time. This decision will not affect your work and will be kept confidential.

What will I have to do if you do take part?

THERE IS NO RIGHT OR WRONG ANSWER: We are just asking you to record what you think on the Assessment Form. The Information you record is for research only and will not be used in patient care.

1. For all patients who you think have chest pain that may be cardiac and have a normal ECG we request that you complete the TRUST Study Risk Assessment Form - this should take no longer than a minute and you will get the answers from questions you should be asking in your initial assessment.

2. Copy the Unique Study Number that is on the top of the Risk Assessment Sheet into your nursing documentation booklet.

3. After completing the assessment place in the TRUST Study Folder at the Nurses Station.

4. If you are taking routine admission bloods from a TRUST Patient please take an extra **yellow top** bottle and send to the lab on a TRUST Study request form. Ensure the Study Number is the same on the request form and the pre-prepared sticker for the bottle. There is no need to inform the patient that you are taking the extra blood sample at this stage, as written consent will be obtained later by the research team.

Who will supervise this study?

The Chief Investigator, Edd Carlton will supervise the study. Nick Jenkins is the Emergency Department Lead. Prof Greaves, a Consultant Cardiologist will be in overall control of the study.

CH Andy Fraser and SN Georgina Gemmell are your mentors should you have any queries.

Will my details be kept confidential?

Yes, other than asking you to complete your nursing band on the risk assessment form we will not know any other details about you. Any information we obtain will be anonymous.

What if there is a problem?

If you have any concern about this study, you can speak to Andy Fraser, Georgina Gemmell, Edd Carlton or Nick Jenkins. If you are still unhappy and wish to complain please speak to your line manager.

Who has reviewed this study?

All research in the NHS is assessed by an independent group, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the Frenchay Research Ethics Committee.

How much time can I have to decide about taking part?

We are aiming to start the study in June. Edd Carlton will talk with all of you before this time and ask for your consent to take part.

The study is scheduled to run for 12 months

Thank you for considering taking part in this study and with your help we hope it will run smoothly. If you have any questions please do not hesitate to contact me.

Principle Investigator

Edd Carlton (ED SPR)

Office: Ext 2037
Mobile: 07595040112

Email: edward.carlton@poole.nhs.uk

Appendix 4. Patient Consent Form

Version 2.1 24/5/2012

Poole Hospital NHS
NHS Foundation Trust

PATIENT CONSENT FORM

Unique Study Number_____

TITLE: An Accelerated Diagnostic Pathway incorporating the Modified Goldman Criteria and 1-hour high-sensitivity troponin testing to identify low-risk Emergency Department patients with chest pain who may be suitable for immediate discharge.

TRUST: Triage Rule-Out Using Sensitive Troponin Chest Pain Study

Investigators: Dr Edward Carlton, Dr Nick Jenkins, Dr Martin Than, Dr Joe Begley, Dr Richard Body, Dr Simon Bell and Professor Kim Greaves

Contact: Dr Edward Carlton, Cardiorespiratory Department, Poole Hospital, Longfleet Road, Poole. Extension: 2037

Please initial each point

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason. ☐
3. I agree to take part in the study. ☐
4. I understand that my medical records may be looked at by authorised individuals from the Sponsor for the study, the UK Regulatory Authority or the Independent Ethics Committee in order to check the study is being carried out correctly. ☐
5. I consent for members of the research team to take follow up details from my medical notes and GP records. ☐
6. I consent to the storage including electronic, of personal information for the purpose of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. ☐
7. I consent for my blood sample to be processed in the laboratory and stored as serum (all cells removed) for future analysis. ☐
8. I consent to take part in a written questionnaire on discharge. ☐

Please tick if you would like to receive a summary of results once the study has finished ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 5. Nursing Consent Form

Version 1 4/4/2012

Poole Hospital NHS
NHS Foundation Trust

NURSING CONSENT FORM

TITLE: An Accelerated Diagnostic Pathway incorporating the Modified Goldman Criteria and 1-hour high-sensitivity troponin testing to identify low-risk Emergency Department patients with chest pain who may be suitable for immediate discharge.

TRUST: Triage Rule-Out Using Sensitive Troponin Chest Pain Study

Investigators: Dr Edward Carlton, Dr Nick Jenkins, Dr Martin Than, Dr Joe Begley, Dr Richard Body, Dr Simon Bell and Professor Kim Greaves

Contact: Dr Edd Carlton, Cardiorespiratory Department, Poole Hospital, Longfleet Road, Poole. Extension: 2037

Please initial each point

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason. ☐

3. I agree to take part in the study. ☐

4. I understand that my risk assessment of patients using the tick-box Goldman score and Nursing Band will be recorded for research purposes only. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 6. Nursing Risk Assessment and Completion Guidance Notes

Poole Hospital NHS
NHS Foundation Trust

TRUST STUDY – Nursing Risk Assessment Sheet

If your patient has Chest Pain which may be cardiac *AND* a Normal ECG
Please complete this:

Unique Study Number……

Time of risk assessment:_____

Nursing Band:_____

Please complete the following risk assessment:
(This should be your assessment only, it will be filed away anonymously in the TRUST study file and will not be used in patient care)

***Explanatory Notes can be found on the reverse of this sheet**

□ **Typical* new onset chest pain at rest

**Constricting discomfort in the front of the chest, with radiation to the neck, jaw, shoulders or arms*

☐ Pain the same as previous MI
☐ Pain not relieved by own GTN within 15 minutes
☐ Pain lasting more than 60 minutes
☐ Pain occurring with increasing frequency
☐ Hypotension (SBP <100mmHg)
☐ Acute shortness of breath
☐ Pain within 6 weeks of AMI or revascularisation

Very Low risk: No to all
Low risk: Yes to 1
Intermediate risk: Yes to 2 or more

Many Thanks,

Now Please Return to TRUST Study File

Nursing Risk Assessment Version 2.1 24/5/2012

Explanatory Notes for Completing Risk Score

1. Tick each box that applies to your patient

2. ***Typical* new onset chest pain at rest**:

   Typical chest pain must be "textbook": - For example: "I had central chest pain, like an elephant sitting on my chest and an ache down my left arm." **DO NOT** Tick this box unless this applies.

3. **Pain the same as previous MI**:

   Ask if the patient has had a previous heart attack and if so if the pain is the same.

4. **Pain not relieved by own GTN within 15 minutes**:

   Ask if the patient has their own GTN Spray, then ask if they used it but it didn't work. **DO NOT** tick if the GTN was given by an ambulance crew or by us on arrival.

5. **Pain lasting more than 60 minutes**:

   Ask if the pain lasted longer than an hour

6. **Pain occurring with increasing frequency:**

   Ask if the pain has been occurring more often in the last few days

7. **Hypotension (SBP <100mmHg):**

   SBP<100mmHg = Systolic Blood Pressure less than 100.

8. **Acute shortness of breath:**

   Ask "Are you short of breath?"

9. **Pain within 6 weeks of AMI or revascularisation:**

   Has your patient been diagnosed with a heart attack in the last 6 weeks? Have they had an angiogram where they unblocked an artery in the last 6 weeks? Have they had a bypass in the last 6 weeks?
   If YES to any of these tick the box.

For <u>any</u> questions about this please do not hesitate to ask Dr Edd Carlton (ED SPR)/SN Georgina Gemmell or CN Andy Fraser

Nursing Risk Assessment Version 2.1 24/5/2012

Appendix 7. Patient Chest Pain Questionnaire

Poole Hospital NHS
NHS Foundation Trust

Patient Chest Pain Questionnaire

Unique Study Number_____

At Poole Hospital we are constantly looking to improve our services. Your feedback is a vital tool in enabling us to do this effectively.

This survey should take under 5 minutes of your time

The Information you give will be anonymous and WILL NOT effect the care you are given. It will not be seen by any of the doctors or nurses caring for you.

The results of this survey may be published in medical journals to improve health services worldwide

Part 1.
Sex: Male ☐ / Female ☐ (please tick)
Age:

18-30 ☐
31-40 ☐
41-50 ☐
51-60 ☐
61-70 ☐
71-80 ☐

What was your pain score on arrival in the Emergency Department?

1 2 3 4 5 6 7 8 9 10
No Pain Worst possible pain

What was your pain score on discharge from the Emergency Department?

1 2 3 4 5 6 7 8 9 10
No Pain Worst possible pain

Part 2.

Please indicate your degree of agreement with the following statements by putting a tick in the appropriate box. *There is no right or wrong answer- we are simply interested in your views.*

Poole Hospital NHS
NHS Foundation Trust

A. I feel I could have spent less time in hospital

Strongly agree	Agree	Neither Agree or disagree	Disagree	Strongly Disagree
1	2	3	4	5

B. I felt reassured when I was admitted to the ward for a period of observation

Strongly agree	Agree	Neither Agree or disagree	Disagree	Strongly Disagree
1	2	3	4	5

C. I am pleased with the decision to be discharged from hospital at this stage

Strongly agree	Agree	Neither Agree or disagree	Disagree	Strongly Disagree
1	2	3	4	5

D. I would have preferred to stay in hospital longer

Strongly agree	Agree	Neither Agree or disagree	Disagree	Strongly Disagree
1	2	3	4	5

Taking your answers to the questions above into account:

Your current management involved being admitted to a ward following treatment in the Emergency Department to ensure that you could be discharged safely. If you could have been discharged earlier, directly from the Emergency Department with the same degree of safety, how satisfied with your treatment would you have been?

Very Dissatisfied				Very Satisfied
1	2	3	4	5

Many thanks for your time

The TRUST Study Research Team

Appendix 8. Data Collection

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

Subject Details		
Unique Study Number		
Date of Birth (DD/MM/YYYY)		
Ethnicity	1. White British	
	2. White Irish	
	3. White Traveller	
	4. Any other white	
	5. Asian/Asian Brit	
	6. Black Afr	
	7. Black Carib	
	8. Any other Black	
	9. Chinese	
	10. Any other ethnic group	

m-Goldman Scores	Dr Assessment (Include Grade)	Nurse Assessment
1. Typical New Onset Chest Pain at rest		
2. Pain Same as Previous MI		
3. Pain not relieved by GTN		
4. >60 mins		
5. Increased frequency		
6. Hypotension		
7. Acute SOB		
8. Pain 6 weeks post AMI/Revasc		

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

Presentation Dates		
ACS Symptom Onset: Date (DD/MM/YYYY) / Time (24hr)		
Date of ED presentation: Date / Time		
Symptoms at Presentation		
Chest Pain (If Patient complained of chest pain that was present on presentation- if resolved prior to arrival report 'no')		
Repeat Presentation with possible ischaemia (Yes/No) and define time period		
Pain Location	Left Chest	
	Right Chest	
	Sternal/parasternal	
	Throat/Jaw	
	Back	
	Epigastrium	
	Left arm	
	Right arm	
	Both arms	
Character	Dull	
	Sharp	
	Burning	
	Heavy	
	Indigestion	
	Crushing	
	Stabbing	
	Other	
	Tightness	

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

Exacerbating Factors	Inspiration	
	Exertion	
	Palpation	
	Movement	
	Positional	
Radiation	L Chest	
	R Chest	
	Sternal/parasternal	
	Left arm	
	Right Arm	
	Both Arms	
	Throat/Jaw	
	Back	
	Epigastric	
Associated factors	Nausea	
	Vomiting	
	Sweating Reported	
	Sweating Observed	
	Syncope/blackout/LOC	
	SOB/Breathlessness	

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

Adjudicated Cardiovascular History		
Previous MI (date)		
Prior Angina		
Prior Ventricular Arrhythmia		
Prior PCI (Date)		
Prior Atrial Arrhythmia		
Prior Congestive Cardiac Failure		
History of Stroke/TIA		
Peripheral Arterial Disease		
Previous CABG (Date)		
Rheumatoid Arthritis		
Pulmonary Embolism		
Known stenosis >50%		
Risk Factors for Chronic Coronary Disease		
Hypertension	History of hypertension	
	Blood pressure >140/90mmHg 2 occasions	
	Current use of antihypertensive medications	
Diabetes	Diet	
	Oral	
	Insulin	
Dyslipidaemia		
Family History of CAD (MI/Angina/Cardiac Death Age <65)		
Smoking	Current (within 1 month of this admission)	
	Recent (between 1 month and 1 year)	
	Former (greater than 1 year)	

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

MEDICATIONS	
Nitrates (e.g. GTN/Isosorbide mononitrate)	
Aspirin	
Clopidogrel	
Other antiplatelet (e.g.dipyridamole/prasugrel)	
Warfarin	
Oral Beta-blockers (e.g.atenolol/bisoprolol/propranolol)	
Calcium Channel Blockers (e.g.amlodipine, verapamil, diltiazem)	
ACE inhibitors (e.g. lisinopril/ramipril)	
Diuretics (e.g.furosemide/spironolactone/bumetanide)	
Other Antihypertensive agent	
Statin (e.g. atorvastatin, simvastatin, pravastatin)	
Other Lipid Lowering Drugs (e.g. fibrates-ezetimibe)	
Other	

PHYSICAL MEASURES		
Temeperature		
Heart Rate		
Blood Pressure (First recorded in ED - *NOT* Ambulance)		
Respiration Rate		
Lung Auscultation	Absence of rales	
	Rales over 50% or less of lung fields	
	Ralesover more than 50% of lung field	
	Not done	

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

TREATMENT IN HOSPITAL	
Aspirin (single dose, <24h, >24h)	
Low Molecular Weight Heparin (Clexane)- single dose, <24h, >24h	
Factor XA Inhibitor (Fondaparinux)- single dose, <24h, >24h	
Clopidogrel (single dose, <24h, >24h)	
Other antiplatelet (prasugrel)	

ELECTROCARDIOGRAM (First ECG)	
Date (DD/MM/YYYY), Time 24h	
Normal	
Non-specific ST-T wave changes (e.g. inverted T-wave III/V1)	
Abnormal but not diagnostic of ischaemia (Prolonged PR, QRS, QTc, bundle branch blocks, LVH with strain)	
Ischaemia or Previous Infarction known to be old	
Paced	
Atrial Fibrillation	

Core Laboratory Blood Tests		
Haemoglobin		
Serum Creatinine		
Roche High-Sensitivity Troponin T	Research (Time: Collected/Received/Reported)	
	6 hour (Time: Collected/Received/Reported)	
Abbott High-Sensitivity Troponin I	Research Only	

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

NON-INVASIVE INVESTIGATIONS		
Exercise Tolerance Test (ETT) *DD/MM/YYYY*	Positive	
	Negative	
	Equivocal	
Stress Radionuclide Imaging (MIBI) *DD/MM/YYYY*	Positive	
	Negative	
	Non-diagnostic	
Stress Echocardiogram (SECHO) *DD/MM/YYYY*	Positive	
	Negative	
	Indeterminate	
Echocardiography (non-stress) *DD/MM/YYYY*	Ejection Fraction >55%	
	% EF if less than 55%	%
	Regional Wall motion Abnormaility Present	
CT Coronary Angiography		
	Calcium Score	
	Normal coronaries	
	Mild 10-40%	
	Moderate 40-70%	
	Severe >70%	
	Uninterpretable	
	Culprit Artery	Left Main Stem
		Left Anterior Decending
		Circumflex
		Right Coronary
		Other

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

Cardiac Catheterisation/Angiography		
	DD/MM/YYYY	
	Normal coronaries	
	Mild 10-40%	
	Moderate 40-70%	
	Severe >70%	
	Occluded	
	Culprit Artery	Left Main Stem
		Left Anterior Decending
		Circumflex
		Right Coronary
		Other
	Percutaneous Intervention	Left Main Stem
		Left Anterior Decending
		Circumflex
		Right Coronary
		Other
DISCHARGE INFORMATION		
Date of ED Discharge		
Time of ED Discharge		
Date of Hospital Discharge		
Time of Hospital Discharge		
Destination	Home	
	Self-discharge	
	Discharge to another facility	

TRUST STUDY Data Collection- Adapted from Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments (Australasia)

OUTCOMES	INDEX ADMISSION/30 DAYS	
Death	Cardivascular	
	Cardiac	
	Non-cardiac	
	Non-cardiovascular	
	Death of uncertain cause	
Cardiac Arrest		
Cardiogenic shock		
STEMI		
NSTEMI (acccording to thrid universal definition and 20% delta)		
Ventricular arrhythmias		
High degree AV block (3rd or 2nd degree requiring pacing or pharmacological intervention)		
Emergency Revascularisation		
Urgent revascularisation procedure (required as inpatient)		
Elective revascularisation		
Unstable Angina		
Patient refused to comply with medical advice/treatment		
Stable Coronary Artery Disease		
Other Cardiovascular Problem		
Non-cardiovascular Problem		
Reattend with Chest Pain (DD/MM/YYYY)		
Non-cardiac chest pain/atypical/GORD		
Chronic Troponin Rise		
Lost to Follow Up		

Appendix 9. Poster Presented at the American College of Cardiology Scientific Sessions 2014

Poole Hospital NHS
NHS Foundation Trust

Bournemouth University

The College of Emergency Medicine

American College of Cardiology Scientific Session 2014

A Modified Goldman Risk Score in Combination with a One-Hour High-Sensitivity Troponin T Proves Superior to TIMI in the Evaluation of Suspected Acute Cardiac Chest Pain

Carlton. E (1), Khattab A (2), Cullen. L (3), Than. M (4), Greaves. K (5)

Background:

- A single high-sensitivity Troponin (hsTn) result below the 99th centile value taken at presentation in Emergency Department (ED) patients with suspected cardiac chest pain has a sensitivity for MI between 88-95% (1,2).
- Some patients will require revascularisation despite negative biomarkers (3).
- The combination of clinical risk scoring and early hsTn testing has been shown to identify a group suitable for early discharge (3).
- Recent literature focuses on the TIMI score, which was originally developed as a 'rule-in' for high-risk ACS cohorts (8).
- Accelerated Diagnostic Protocols (ADPs) using TIMI require hsTn sampling at 0 AND 2 hours (3-6)

Hypothesis: ***A Modified Goldman (MG) score, designed to identify those without unstable clinical features and validated in a low-risk ED cohort would be superior to the TIMI score in identifying a higher proportion of patients at low risk of Major Adverse Cardiac Events (MACE) and therefore suitable for early discharge after a single hsTn at presentation.***

THE MODIFIED GOLDMAN RISK SCORE (7)
Typical new onset chest pain at rest
Pain the same as previous myocardial infarction
Pain not relieved by Glyceryl Trinitrate Spray within 15 minutes
Pain lasting more than 60 minutes
Pain occurring with increasing frequency
Hypotension (Systolic BP <100mmHg)
Acute shortness of breath
Pain within 6 weeks of an myocardial infarction or revascularisation

Vs.

THE TIMI SCORE (8)
Age ≥65
≥ 3 risk factors for CAD
Significant coronary artery stenosis (Prior MI/Stenosis >50%)
ECG ST Deviation* *(Patients with ST deviation were immediately classified as high risk and therefore not recruited)*
Severe angina (≥2 episodes in prior 24hrs)
Use of aspirin in last 7 days

Methods:

- Prospective observational study carried out from July 2012 to August 2013 in a UK District ED.
- Recruitment was undertaken 24/7 and included patients aged 18-79 years who presented with suspected cardiac chest pain and a non-ischemic ECG.
- Performance of the MG and TIMI scores in combination with a single hsTnT of <14ng/L (Roche Elecsys 99th Centile value) taken at presentation was compared. Follow-up for MACE at 30 days was undertaken from electronic, patient, or General Practitioner records.

Results:

N= 964

- Median age: 58.9
- Male: 58.8%
- Median Length of Stay: 18.36hrs
- Prevalence of MACE: 13.1%
- **An MG Score of ≤1 identified a significantly higher proportion of patients suitable for early discharge when compared to a TIMI score of ≤1: 39.5% compared to 34.4% (P=0.01) in combination with a one-hour hsTnT**
- **Sensitivity using the MG score was 99.2% compared to 96.8% using TIMI**

	TIMI Score 0 and Troponin <14ng/L	TIMI Score 0/1 and Troponin <14ng/L	MG Score 0 and Troponin <14ng/L	MG Score 0/1 and Troponin <14ng/L
Number of MACE in early discharge cohort (N/%)	1/60 (1.6)	4/344 (1.19)	0/101 (0)	1/381 (0.26)
Sensitivity (95% Confidence Interval)	99.2 (94.9-99.9)	96.8 (91.4-99)	100 (96.3-100)	99.2 (94.9-100)
Negative Predictive Value (95% CI)	98.4 (90.0-99.9)	98.8 (96.8-99.6)	100 (95.5-100)	99.7 (98.3-100)
Specificity (95% CI)	7.1 (5.5-9.2)	39.5 (36.2-42.9)	12.1 (10-14.6)	45.2 (41.8-48.7)
Positive Predictive Value (95%CI)	13.6 (11.5-16.1)	19.1 (16.2-22.5)	14.4 (12.1-16.9)	60.4 (57.3-63.6)
Negative Likelihood Ratio (95%CI)	0.11 (0.02-0.82)	0.08 (0.03-0.21)	0	0.02 (0.002-0.13)
Positive Likelihood Ratio (95%CI)	1.07 (1.04-1.09)	1.6 (1.5-1.7)	1.14 (1.12-1.17)	1.81 (1.69-1.93)
% Eligible for Early Discharge	6.3	34.4	10.6	39.5

Conclusion: A modified Goldman risk score in combination with a single hsTnT result at presentation safely identifies significantly more patients at very low risk of MACE at 30 days who may be suitable for early discharge when compared to the TIMI score.

Authors Declarations
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(2) Professor Ahmed Khattab: Bournemouth University, UK
(3) Associate Professor Louise Cullen: Emergency Department Royal Brisbane and Women's Hospital, Australia (Funding: Abbott Diagnostics, Roche, Alere, Siemens, Radiometer Pacific for clinical trials)
(4) Professor Martin Than: Emergency Department Christchurch Hospital, New Zealand (Funding: Alere, Abbott, Beckman and Roche for clinical trials)
(5) Professor Kim Greaves: Department of Cardiology, Nambour Hospital, Australia (Funding: AstraZenica for clinical trials)

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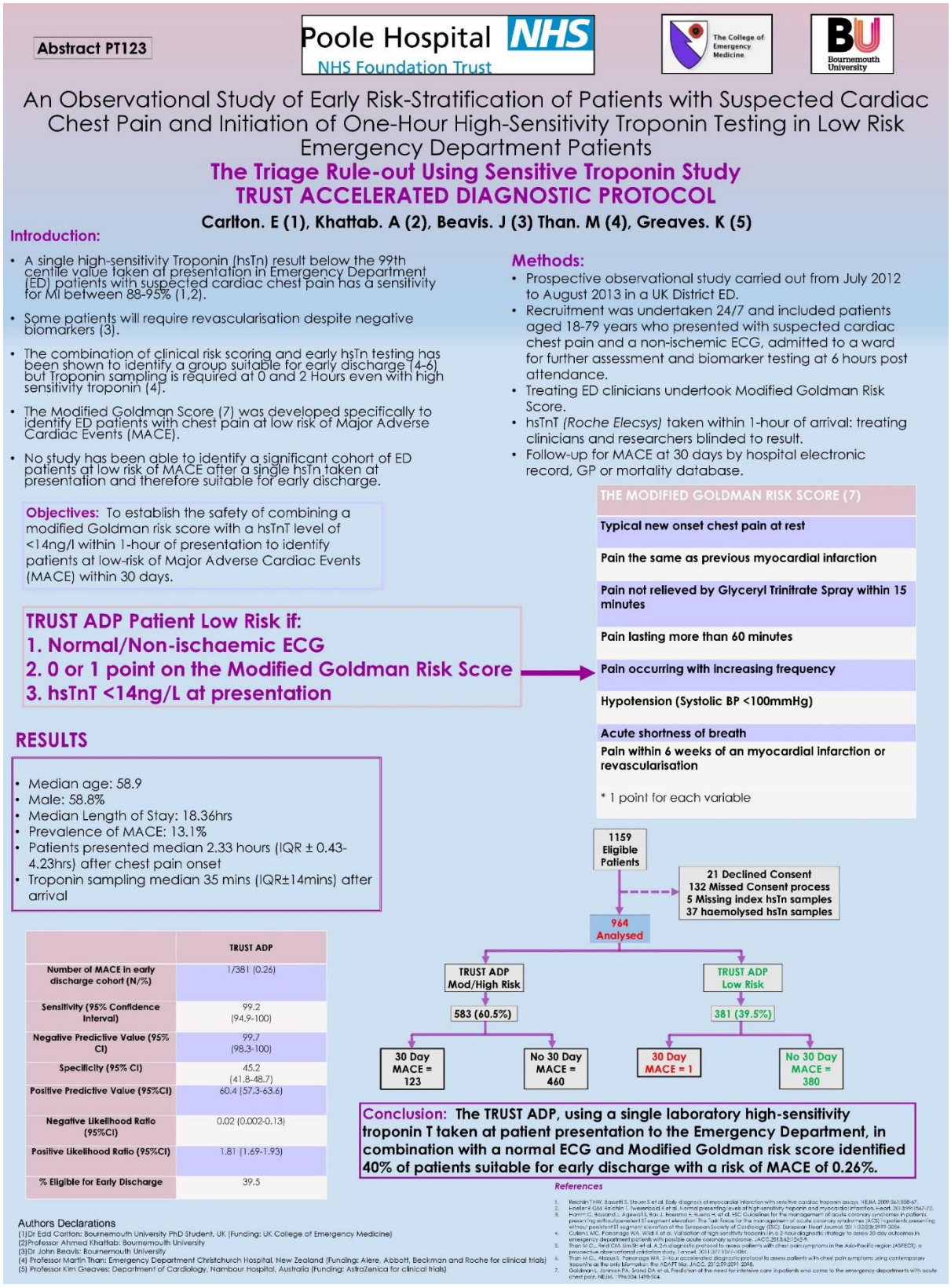
Appendix 10. Poster presented at the World Congress of Cardiology 2014



Abstract PT123

Poole Hospital NHS
NHS Foundation Trust

The College of Emergency Medicine

Bournemouth University

An Observational Study of Early Risk-Stratification of Patients with Suspected Cardiac Chest Pain and Initiation of One-Hour High-Sensitivity Troponin Testing in Low Risk Emergency Department Patients

The Triage Rule-out Using Sensitive Troponin Study
TRUST ACCELERATED DIAGNOSTIC PROTOCOL

Carlton. E (1), Khattab. A (2), Beavis. J (3) Than. M (4), Greaves. K (5)

Introduction:

- A single high-sensitivity Troponin (hsTn) result below the 99th centile value taken at presentation in Emergency Department (ED) patients with suspected cardiac chest pain has a sensitivity for MI between 88-95% (1,2).
- Some patients will require revascularisation despite negative biomarkers (3).
- The combination of clinical risk scoring and early hsTn testing has been shown to identify a group suitable for early discharge (4-6) but Troponin sampling is required at 0 and 2 Hours even with high sensitivity troponin (4).
- The Modified Goldman Score (7) was developed specifically to identify ED patients with chest pain at low risk of Major Adverse Cardiac Events (MACE).
- No study has been able to identify a significant cohort of ED patients at low risk of MACE after a single hsTn taken at presentation and therefore suitable for early discharge.

Objectives: To establish the safety of combining a modified Goldman risk score with a hsTnT level of <14ng/l within 1-hour of presentation to identify patients at low-risk of Major Adverse Cardiac Events (MACE) within 30 days.

Methods:

- Prospective observational study carried out from July 2012 to August 2013 in a UK District ED.
- Recruitment was undertaken 24/7 and included patients aged 18-79 years who presented with suspected cardiac chest pain and a non-ischemic ECG, admitted to a ward for further assessment and biomarker testing at 6 hours post attendance.
- Treating ED clinicians undertook Modified Goldman Risk Score.
- hsTnT *(Roche Elecsys)* taken within 1-hour of arrival: treating clinicians and researchers blinded to result.
- Follow-up for MACE at 30 days by hospital electronic record, GP or mortality database.

THE MODIFIED GOLDMAN RISK SCORE (7)

Typical new onset chest pain at rest
Pain the same as previous myocardial infarction
Pain not relieved by Glyceryl Trinitrate Spray within 15 minutes
Pain lasting more than 60 minutes
Pain occurring with increasing frequency
Hypotension (Systolic BP <100mmHg)
Acute shortness of breath
Pain within 6 weeks of an myocardial infarction or revascularisation

* 1 point for each variable

TRUST ADP Patient Low Risk if:
1. Normal/Non-ischaemic ECG
2. 0 or 1 point on the Modified Goldman Risk Score
3. hsTnT <14ng/L at presentation

RESULTS

- Median age: 58.9
- Male: 58.8%
- Median Length of Stay: 18.36hrs
- Prevalence of MACE: 13.1%
- Patients presented median 2.33 hours (IQR ± 0.43-4.23hrs) after chest pain onset
- Troponin sampling median 35 mins (IQR±14mins) after arrival

	TRUST ADP
Number of MACE in early discharge cohort (N/%)	1/381 (0.26)
Sensitivity (95% Confidence Interval)	99.2 (94.9-100)
Negative Predictive Value (95% CI)	99.7 (98.3-100)
Specificity (95% CI)	45.2 (41.8-48.7)
Positive Predictive Value (95%CI)	60.4 (57.3-63.6)
Negative Likelihood Ratio (95%CI)	0.02 (0.002-0.13)
Positive Likelihood Ratio (95%CI)	1.81 (1.69-1.93)
% Eligible for Early Discharge	39.5

Conclusion: **The TRUST ADP, using a single laboratory high-sensitivity troponin T taken at patient presentation to the Emergency Department, in combination with a normal ECG and Modified Goldman risk score identified 40% of patients suitable for early discharge with a risk of MACE of 0.26%.**

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Appendix 11. A Novel Diagnostic Protocol to Identify Patients Suitable for Discharge after a Single High-Sensitivity Troponin

Paper Published in BMJ Heart 2015

Heart Online First, published on February 17, 2015 as 10.1136/heartjnl-2014-307288
Coronary artery disease

OPEN ACCESS

ORIGINAL ARTICLE

A novel diagnostic protocol to identify patients suitable for discharge after a single high-sensitivity troponin

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2014-307288).

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ABSTRACT

Objective To establish whether a novel accelerated diagnostic protocol (ADP) for suspected acute coronary syndrome (ACS) could successfully identify low-risk patients suitable for discharge after a single high-sensitivity troponin T (hs-cTnT) taken at presentation to the emergency department. We also compared the diagnostic accuracy of this ADP with strategies using initial undetectable hs-cTnT.

Methods This prospective observational study evaluated the ability of the Triage Rule-out Using high-Sensitivity Troponin (TRUST) ADP to identify low-risk patients with suspected ACS. The ADP incorporated a single presentation hs-cTnT of <14 ng/L, a non-ischaemic ECG and a modified Goldman risk score. Diagnostic performance of the ADP was compared with the detection limit cut-offs of hs-cTnT (<5 ng/L and <3 ng/L). The primary end point was fatal/non-fatal acute myocardial infarction (AMI) within 30 days.

Results 960 participants were recruited, mean age 58.0 years, 80 (8.3%) had an AMI. The TRUST ADP classified 382 (39.8%) as low-risk with a sensitivity for identifying AMI of 98.8% (95% CI 92.5% to 99.9%). hs-cTnT detection limits (<5 ng/L and <3 ng/L) had a sensitivity of 100% (94.3 to 100) and 100% (94.4 to 100), respectively. The TRUST ADP identified more patients suitable for early discharge at 39.8% vs 29.3% (<5 ng/L) and 7.9% (<3 ng/L) (p<0.001) with a lower false-positive rate for AMI detection; specificity 43.3% (95% CI 42.7% to 43.4%) vs 32.0% (95% CI 31.5% to 32.0%) and 8.6% (95% CI 8.1% to 8.6%), respectively.

Conclusions The TRUST ADP, which incorporates structured risk-assessment and a single presentation hs-cTnT blood draw, has potential to allow early discharge in 40% of patients with suspected ACS and has greater clinical utility than undetectable hs-cTnT strategies.

Trial registration number ISRCTN No. 21109279.

INTRODUCTION

Patients with suspected acute coronary syndrome (ACS) make up to 10% of all emergency department (ED) attendances and 25% of acute hospital admissions.[1] Current guidelines recommend two serial measurements of non-high-sensitivity troponin between 6 h and 12 h after patient presentation to the ED.[2] As a result, the majority of patients require prolonged assessment prior to safe discharge despite the fact that only 15–25% of these patients have a final diagnosis of ACS.[1]

Consensus reports suggest that high-sensitvity troponin (hs-cTn) assays may be used to reduce door-to-discharge times by using serial testing over 3–6 h.[3] Investigators have reduced blood draw times further by incorporating structured clinical risk assessment protocols with hs-cTn,[4] or analysing δ change over time.[5] Despite successfully identifying between 40% and 60% of low-risk patients, these algorithms still require serial testing of hs-cTn which will delay discharge from the ED. This delay may be associated with significant healthcare costs,[6] and contribute to ED overcrowding.

To address these issues, several studies have investigated the effectiveness of a single undetectable hs-cTn value taken at presentation to the ED in identifying those at very low risk of acute myocardial infarction (AMI).[7–9] Despite demonstrating promising results as a rule-out strategy for AMI, this protocol has not been recommended by expert guidelines due to concerns over assay analytical interference and poor test specificity.[3] Therefore, a clinically applicable protocol that allows the discharge of a significant proportion of patients after just a single hs-cTn blood draw at presentation remains an attractive yet elusive goal.

Using binary hs-cTn results alone to guide discharge decisions fails to use a wealth of clinical information available to treating physicians. The Goldman risk score[10] uses simple variables that are immediately available to the ED physician and are derived from the history, examination and ECG findings. Since its inception, the score has been modified to improve physician decision making in the identification of low-risk patients. This has led to improved use of hospital resources.[11] Despite achieving the highest level of evidentiary support for use in ED patients with chest pain the modified Goldman (m-Goldman) risk score remains untested as a discharge tool in combination with a single presentation hs-cTn.

The Triage Rule-out Using high-Sensitivity Troponin (TRUST) study's primary aim was to establish whether a novel accelerated diagnostic protocol (ADP) for patients with suspected ACS consisting of hs-cTn, a non-ischaemic ECG and the m-Goldman score, could successfully identify low-risk patients suitable for discharge after a single blood draw at presentation to the ED. Secondary aims were to compare the diagnostic accuracy of the ADP with strategies using initial undetectable hs-cTnT levels.

To cite: Carlton EW, Cullen L, Than M, *et al*. *Heart* Published Online First: [*please include* Day Month Year] doi:10.1136/heartjnl-2014-307288

METHODS

This prospective observational clinical trial was designed to assess the predefined TRUST ADP. The protocol was designed to be truly pragmatic in order to enhance the widespread applicability of the study results[12]; with attending clinicians performing m-Goldman risk scores, rostered clinical (not research) staff undertaking blood sampling, real-time sample processing and 24/7 recruitment. The study was designed using the Standards for Reporting Diagnostic Accuracy.[13] and approved by the UK National Research Ethics Service. All participants provided written informed consent. The TRUST study was registered with the Controlled Trials Database (ISRCTN No. 21109279) and complies with the *Declaration of Helsinki*.

Study setting, recruitment and data collection

Poole NHS Foundation Trust is a UK District General Hospital, its ED has approximately 62 000 new patient attendances per year. Patients with suspected ACS are managed according to the local hospital protocol, which involves risk assessment by ED physician staff using the m-Goldman risk score and blood drawn for hs-cTnT at 6 h after presentation. As part of the study protocol, blood was also taken at presentation for hs-cTnT analysis. While historical clinical protocols, at the time of this study, did not include troponin measurement at presentation, this had the benefit of ensuring that treating physicians were blinded to the initial hs-cTnT result to avoid selection bias.[14]

The fifth generation Roche ELECSYS hs-cTnT assay (Roche, Switzerland), which has a limit of detection (lowest analyte concentration likely to be reliably distinguished from the limit of blank at which detection is feasible) of 5 ng/L, limit of blank (highest apparent analyte concentration expected to be found when replicates of a blank sample containing no analyte are tested) of 3 ng/L, 99th centile of 14 ng/L and 10% coefficient of variation of <10% at 9 ng/L, was used for research (presentation) and reference (6-h) samples. During initial assessment clinical staff drew blood for routine admission samples and an additional 3.5 mL of whole blood in a prelabelled study-specific serum settling tube for hs-cTnT analysis. All serum samples were tested in real time.

Consecutive patients attending the ED with suspected ACS were prospectively screened from July 2012 to August 2013. Patients were included if they were at least 18 years of age and had at least 5 min of chest pain suggestive of ACS, and for whom the attending physician determined inpatient evaluation was required. Possible cardiac symptoms included acute chest, epigastric, neck, jaw or arm pain, or discomfort or pressure without an apparent non-cardiac source, in accordance with the American Heart Association case definitions.[15] Patients were excluded if any of the following were present: ST-segment elevation myocardial infarction or left bundle branch block not known to be old, ECG changes diagnostic of ischaemia (ST segment depression ≥1 mm or T-wave inversion consistent with the presence of ischaemia),[2] arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias), hs-cTnT not suitable for analysis (eg, haemolysis), age ≥80 years, atypical symptoms in the absence of chest discomfort, a clear non-ACS cause for chest pain was found at presentation (eg, pulmonary embolism, pneumonia, aortic dissection), another medical condition requiring hospital admission, refusal or inability to give informed consent, non-English speaking, pregnancy, renal failure requiring dialysis or inability to be contacted after discharge.

Data were collected prospectively using a published data dictionary.[16] Attending ED clinicians completed the m-Goldman risk score on a predesigned clinical report form. Follow-up was undertaken by independent review of hospital electronic patient records, summary of health records from the patient's general practitioner (GP) obtained at least 6 months after attendance and a national clinical records search (which identifies death). The ethics committee did not grant permission for direct patient contact as they felt that comprehensive follow-up data relating to adverse events could be obtained accurately through GP records. This is because in the UK, GPs hold comprehensive records for individuals relating to primary, secondary and tertiary care. GP records have been demonstrated to be more accurate at reporting hospital admissions, including those for cardiac related events, than patients.[17] GPs were therefore requested to provide all information regarding presentation to other institutions with chest pain, cardiology outpatient review and cardiac testing, including angiography with or without intervention. Where a participant had not attended hospital follow-up and/or a GP had failed to provide a health record/not GP-registered, the patient was regarded as lost to follow-up.

Index tests

The primary index test was the TRUST ADP (table 1), this defined a patient as 'low-risk' if all of the following conditions were satisfied at presentation: a m-Goldman Score of 0 or 1, a non-ischaemic ECG and a single central laboratory hs-cTnT of <14 ng/L at presentation.

Secondary index tests were the detection limits for hs-cTnT (5 ng/L and 3 ng/L) and non-ischaemic ECG at presentation.

Outcome measures

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

The presence of AMI was defined according to the Third Universal Definition of MI which states that a rise and/or fall in

Table 1 The Modified Goldman Score and the TRUST accelerated diagnostic protocol (ADP)

Modified Goldman risk score	*1 point for each variable present*
Typical new-onset chest pain at rest	
Pain the same as previous myocardial infarction	
Pain not relieved by glyceryl trinitrate (GTN) spray within 15 min	
Pain lasting more than 60 min	
Pain occurring with increasing frequency	
Hypotension (systolic blood pressure <100 mm Hg)	
Acute shortness of breath	
Pain within 6 weeks of a myocardial infarction or revascularisation	
Modified Goldman total	
Trust ADP	
Low risk* (Suitable for discharge)	1. Modified Goldman score ≤1 2. Non-ischaemic ECG 3. Presentation high-sensitivity troponin T <14 ng/L
Not low risk	1. Modified Goldman score >1 2. Ischaemic ECG 3. Presentation high-sensitivity troponin T ≥14 ng/L

*Safety point: protocol not validated in age ≥80 years.
TRUST, Triage Rule-out Using high-Sensitivity Troponin.

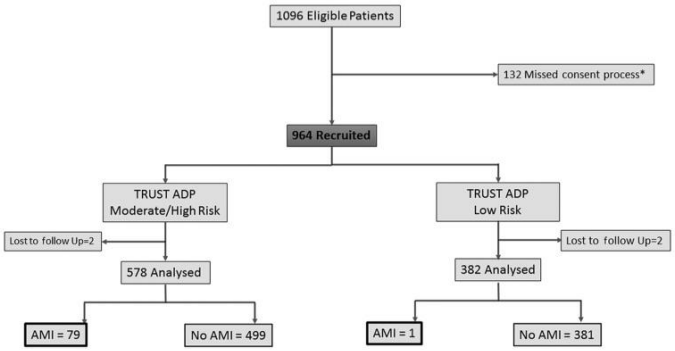

Figure 1 Participant recruitment flow chart. The 132 patients who missed the consent process were similar in age, gender, risk factors and m-Goldman scores (p>0.05 for all). ADP, accelerated diagnostic protocol; AMI, acute myocardial infarction; TRUST, Triage Rule-out Using high-Sensitivity Troponin.

troponin, with at least one value above the 99th centile value in the context of a patient with ischaemic symptoms or signs (ECG changes or imaging evidence) would satisfy the diagnosis.[18] Based on current consensus guidance for hs-cTn assays, a rise or fall of 20% (δ) was considered statistically significant and consistent with a diagnosis of AMI.[3] Adjudication of the primary end point was carried out by two local cardiologists blinded to the m-Goldman score but who had access to the clinical record, ECG and serial hs-cTnT results. If a troponin result was above the 99th centile value and a non-ischaemic cause of troponin elevation was identified this was considered by the adjudicating cardiologist in accordance with expert consensus.[19]

The presence of major adverse cardiac events (MACEs) occurring within 30 days of hospital attendance (including the index visit) was a secondary outcome measure. MACE included: death due to ischaemic heart disease, cardiac arrest, urgent revascularisation, cardiogenic shock, ventricular arrhythmia, high-degree atrioventricular block needing intervention and AMI. MACE was defined according to previous large scale studies assessing the safety of rapid discharge protocols.[4 20 21]

Table 2 Patient characteristics

	Total (N=960)	Fatal/non-fatal AMI positive at 30 days (N=80)	TRUST ADP intermediate/high risk (N=578)	TRUST ADP low risk (N=382)
Age, years (Mean±SD)	58.0±13.3	63.3±10.6	60.4±12.8	55.6±19.4
Sex (% male)	565 (58.9)	53 (66.3)	360 (62.3)	205 (53.7)
Ethnicity (% British Caucasian)	914 (95.2)	72 (90.0)	549 (95.0)	365 (95.5)
Risk factors N (%)				
Hypertension	452 (47.1)	59 (73.8)	319 (55.2)	123 (34.8)
Diabetes	164 (17.1)	20 (25.0)	124 (21.4)	40 (10.5)
Dyslipidaemia	635 (66.1)	63 (78.6)	429 (74.2)	206 (53.9)
Smoking current	231 (24.1)	19 (23.8)	129 (22.3)	102 (26.7)
Smoker ex	343 (35.1)	30 (37.5)	229 (39.6)	114 (29.8)
Family history of coronary artery disease	354 (36.9)	29 (36.3)	215 (37.2)	139 (36.4)
Medical history				
Angina	251 (26.1)	29 (36.3)	207 (35.8)	44 (11.5)
Myocardial infarction	204 (21.3)	26 (32.5)	174 (30.1)	30 (7.9)
Percutaneous coronary intervention	183 (19.1)	22 (27.5)	146 (25.3)	37 (9.7)
Congestive cardiac failure	30 (3.1)	4 (5.0)	25 (4.3)	5 (1.3)
Atrial arrhythmia	119 (12.4)	8 (10.0)	86 (14.9)	33 (8.6)
Stroke	63 (6.6)	5 (6.3)	45 (7.7)	18 (4.7)
Coronary artery bypass graft	50 (5.2)	7 (8.8)	41 (7.1)	9 (2.4)
Baseline medications				
Aspirin	361 (37.6)	40 (50.0)	276 (47.8)	85 (22.3)
Clopidogrel	112 (11.7)	8 (10.0)	84 (14.5)	28 (7.3)
β blocker	281 (29.3)	25 (31.3)	210 (36.3)	71 (18.6)
ACE inhibitor	272 (28.3)	29 (36.3)	195 (33.7)	77 (20.2)
Statin	369 (38.4)	37 (46.3)	276 (47.8)	93 (24.3)
Median length of hospital stay (h)±IQR	18.8±32.4	107.5±110.3	22.4±62.0	14.0±11.9

ADP, accelerated diagnostic protocol; AMI, acute myocardial infarction; TRUST, Triage Rule-out Using high-Sensitivity Troponin.

Statistical analysis

Baseline characteristics of the study population were analysed with conventional group descriptive statistics. Diagnostic protocol results and outcome status were cross-tabulated to permit calculation of sensitivity, specificity, negative predictive value (NPV), positive predictive value, positive likelihood ratio and negative likelihood ratio. Statistical significance was evaluated using McNemar's test. All statistical analysis was carried out using SPSS V.20.

RESULTS

Nine hundred and sixty-four consenting patients were recruited (figure 1), Four patients were lost to follow-up (health records pertaining to presence of outcome measures unobtainable) meaning that 99.6% were successfully monitored for 30 days. However, no patient lost to follow-up died within 30 days of attendance. Participants were predominantly white, older men who commonly had risk factors for coronary artery disease (table 2). Of the patients 80/960 (8.3%) had a primary outcome event (fatal or non-fatal AMI) and 97/960 (10.1%) had a MACE within 30 days, and 30/960 (3.1%) patients had a non-ischaemic cause of hs-cTnT elevation above the 99th centile identified (diagnoses summarised in the online supplementary appendix). Patients presented to the ED at a median of 2 h 20 min (IQR±228 min) after chest pain onset. Blood was taken for hs-cTnT at a median of 35 min (IQR±14 min) after patient arrival.

Diagnostic accuracy of the TRUST ADP

The TRUST ADP classified 382/960 (39.8%) of patients as at low risk of fatal or non-fatal AMI (table 3), with a sensitivity for identifying AMI of 98.8% (95% CI 92.4% to 99.9%) and NPV of 99.7% (95% CI 98.4% to 100%) and had a similar diagnostic performance for the secondary outcome measure (MACE) (table 4).

A single patient (0.3%) classified as low-risk by the TRUST ADP had an AMI during the initial hospital attendance and follow-up. This patient was a 78-year-old woman classified as low-risk on the m-Goldman score and had a hs-cTnT of 13 ng/L at presentation. However, a minor hs-cTnT elevation to 20 ng/L (δ change 27%) occurred on the second hs-cTnT test at 6 h and was therefore diagnosed with an AMI. The patient was medically managed and had no further complications.

Undetectable troponin strategies

The diagnostic performance of hs-cTnT limit of detection cut-off values in patients with a non-ischaemic ECG are shown in table 4. By using the limit of detection cut-off value of 5 ng/L for the primary outcome measure (AMI) the sensitivity was 100% (95% CI 94.3% to 100%) and 270/922 (29.3%) of patients were eligible for early discharge (table 3). However, using the secondary outcome measure (MACE), three patients (1.1%) identified as suitable for discharge using this strategy required urgent revascularisation (all three were aged in their 40s, two had severe left anterior descending artery disease and one severe right coronary artery disease). Using the limit of blank (<3 ng/L) the sensitivity for fatal/non-fatal AMI was 100% (95% CI 94.4% to 100%) and only 7.9% would have been eligible for early discharge. One patient (1.4%) with a hs-cTnT <3 ng/L required urgent revascularisation.

Table 3 Occurrence of fatal/non-fatal AMI and MACE during the index hospital visit or at 30 days according to index test

	AMI	No AMI	Total
TRUST ADP			
Not low risk	79	499	578
Low risk	1	381	382
Hs-cTnT<5 ng/L*			
≥5 ng/L	78	574	652
<5 ng/L	0	270	270
Hs-cTnT<3 ng/L*			
≥3 ng/L	78	771	849
<3 ng/L	0	73	73
	MACE	No MACE	Total
TRUST ADP			
Not low risk	96	482	578
Low risk	1	381	382
Hs-cTnT<5 ng/L*			
≥5 ng/L	92	560	652
<5 ng/L	3	267	270
Hs-cTnT<3 ng/L*			
≥3 ng/L	94	755	841
<3 ng/L	1	72	73

*922/960 (96%) results are reported for the hs-cTnT detection limits. This was due to computer error whereby 38 results were only reported as <14 ng/L.
ADP, accelerated diagnostic protocol; AMI, acute myocardial infarction; hs-cTnT, high-sensitivity troponin T; MACE, major adverse cardiac event; TRUST, Triage Rule-out Using high-Sensitivity Troponin.

Comparison of strategies

The TRUST ADP identified significantly more patients suitable for immediate discharge at 39.8% vs 29.3% (<5 ng/L) and 7.9% (<3 ng/L) (p<0.001) with a lower false-positive rate for AMI detection; specificity 43.3% (95% CI 42.7% to 43.4%) vs 32.0% (95% CI 31.5% to 32.0%) and 8.6% (95% CI 8.1% to 8.6%) respectively, while maintaining a high diagnostic accuracy for the rule-out of AMI.

DISCUSSION

This study demonstrates that the TRUST ADP for suspected ACS can successfully identify 40% of patients as low-risk after just a single hs-cTnT taken at presentation to the ED, with a NPV of >99.5%. When compared with strategies using undetectable hs-cTnT, more patients are eligible for early discharge with lower false-positive rates, suggesting this approach has greater clinical utility. Furthermore, by incorporating clinical risk stratification, the TRUST ADP has improved accuracy in identifying those who require urgent revascularisation.

Our results suggest that the introduction of this ADP has the potential to reduce the length of stay for low-risk patients (currently 14 h in our institution) after a single laboratory-based troponin and avoid the necessity for two separate blood draws. Uptake of this protocol may have significant benefits for healthcare services worldwide by reducing hospital admission rates, ED overcrowding, duplication of staff time and resource use. Furthermore, by using ED physicians to carry out risk-stratification and real-time troponin sampling with 24-h recruitment we have demonstrated that this ADP is truly applicable.

This analysis confirms the results of recent large-scale exploratory research that showed undetectable hs-cTnT held promise as a tool for rule-out of AMI or death.[9] However, we demonstrate that by using MACE (which also includes urgent revascularisation) missed-event rates of the undetectable troponin strategies

Table 4 Diagnostic accuracy of TRUST ADP and detection limit cut-offs of hs-cTnT for the prediction of fatal/non-fatal AMI and MACE in patients with a non-ischaemic ECG

	Number of events (%)	Sensitivity (95% CI)	NPV (95% CI)	Specificity (95% CI)	PPV (95% CI)	+LR (95% CI)	−LR (95% CI)	Percentage of eligible for early discharge
Primary outcome fatal/non-fatal AMI								
TRUST ADP Low risk	1/382 (0.3)	98.8 (92.4 to 99.9)	99.7 (98.4 to 100)	43.3 (42.7 to 43.4)	13.7 (12.8 to 13.8)	1.741 (1.613 to 1.766)	0.029 (0.002 to 0.178)	39.8
hs-cTnT <5 ng/L	0/270 (0.0)	100 (94.3 to 100)	100 (98.3 to 100)	32.0 (31.5 to 32.0)	12.0 (11.3 to 12.0)	1.470 (1.375 to 1.470)	0.000 (0.000 to 0.183)	29.3
hs-cTnT <3 ng/L	0/73 (0.0)	100 (94.4 to 100)	100 (94.0 to 100)	8.6 (8.1 to 8.6)	9.2 (8.7 to 9.2)	1.095 (1.028 to 1.095)	0.000 (0.000 to 0.685)	7.9
Secondary outcome MACE								
TRUST ADP Low risk	1/382 (0.3)	99.0 (93.7 to 99.9)	99.7 (98.4 to 100)	44.1 (43.6 to 44.3)	16.6 (15.7 to 16.8)	1.772 (1.659 to 1.793)	0.023 (0.001 to 0.145)	39.8
hs-cTnT <5 ng/L	3/270 (1.1)	96.8 (90.6 to 99.2)	98.9 (96.7 to 99.7)	32.3 (31.6 to 32.6)	14.1 (13.2 to 14.5)	1.430 (1.323 to 1.470)	0.098 (0.025 to 0.299)	29.3
hs-cTnT <3 ng/L	1/73 (1.4)	98.9 (93.8 to 99.9)	98.6 (91.9 to 99.9)	8.7 (8.1 to 8.8)	11.1 (10.5 to 11.2)	1.084 (1.020 to 1.096)	0.121 (0.006 to 0.769)	7.9

ADP, accelerated diagnostic protocol; AMI, acute myocardial infarction; hs-cTnT, high-sensitivity troponin T; +LR, positive likelihood ratio; −LR, negative likelihood ratio; MACE, major adverse cardiac event; NPV, negative predictive value; PPV, positive predictive value; TRUST, Triage Rule-out Using high-Sensitivity Troponin.

rise above 1%, this may be unacceptable to the majority of ED clinicians.[22] Therefore, consistent with consensus guidelines,[3] we cannot recommend uptake of undetectable hs-cTnT rule-out strategies in this setting.

Our data suggest that focus move away from strategies that use a stand-alone single initial undetectable hs-cTn result to guide discharge decisions, and towards protocols that also incorporate structured clinical risk assessment. A number of reports combining these two strategies have been reported recently and show early promise. For example, the History, ECG, Age, Risk Factors and Troponin (HEART) score,[23] may enable safe early discharge after a single troponin at presentation but requires validation with hs-cTn, and the Manchester Acute Coronary Syndromes (MACS) decision rule,[24] has demonstrated excellent discriminatory power but requires the use of heart-type fatty acid binding protein in addition to hs-cTn. Prospective comparison of these strategies is required.

There are some limitations to this study. The inclusion of predominantly British Caucasian patients may limit the applicability to international settings. The upper age cut-off of ≥80 years was chosen for pragmatic reasons. In our institution, patients above this age are admitted to a separate and dedicated assessment area. Therefore we recognise that this may affect the applicability of TRUST ADP in those >80 years of age.

Patients were only recruited if they had a non-ischaemic ECG at presentation—thereby reducing the prevalence of MACE in the study population. Expansion of the inclusion criteria to include those patients with ECG changes consistent with ACS would have added little practical value because this group is not suitable for early discharge anyway. We therefore intentionally excluded patients with a clear diagnosis of ACS to focus on a particular group that remains a major diagnostic challenge.

Key messages

What is already known on this subject?
The use of undetectable high-sensitivity troponin levels and risk scores in combination with early biomarker testing have recently been put forward as diagnostic tools aiming to reduce door-to-discharge times in patients with suspected acute coronary syndromes. However, a clinically applicable protocol that allows the discharge of a significant proportion of patients after just a single high sensitivity troponin blood draw at presentation to the emergency department remains an attractive yet elusive goal.

What might this study add?
Using a simple clinical risk score, together with the results of a single high-sensitivity troponin result, the Triage Rule-out Using high-Sensitivity Troponin accelerated diagnostic protocol, may enable immediate discharge in up to 40% of patients. This strategy identifies more patients suitable for early discharge, with lower false-positive rates than undetectable troponin strategies.

How might this impact on clinical practice?
Chest pain makes up a quarter of medical admissions in the UK. A diagnostic strategy that prevents unnecessary hospital admission in a large proportion of this patient group would have significant benefits for healthcare services by reducing hospital admission rates, emergency department overcrowding, duplication of staff time and resource use.

We recognise that the TRUST ADP now requires validation as part of a multicentre randomised controlled trial. However, without first analysing the safety of this diagnostic strategy through an observational cohort design, the principle of clinical equipoise may not have justified a randomised study design.[25]

CONCLUSION

The TRUST ADP, which incorporates a structured risk-assessment and single presentation hs-cTnT blood draw, has the potential to allow early discharge in 40% of patients with suspected ACS. This ADP has superior clinical utility when compared with undetectable hs-cTnT strategies. Future research should focus on methodologies that incorporate clinical assessment with hs-cTn testing rather than troponin testing alone.

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Contributors Each author has contributed to the analysis and interpretation of the data, and drafting and approval of the final manuscript. All authors have also contributed to the conception/design of the study reported in this manuscript.

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Appendix 12. 'Chest Pain Typicality' in Suspected Acute Coronary Syndromes and the Impact of Clinical Experience

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CLINICAL RESEARCH STUDY

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'Chest Pain Typicality' in Suspected Acute Coronary Syndromes and the Impact of Clinical Experience

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ABSTRACT

BACKGROUND: Physicians rely upon chest pain history to make management decisions in patients with suspected acute coronary syndromes, particularly where the diagnosis is not immediately apparent through electrocardiography and troponin testing. The objective of this study was to establish the discriminatory value of "typicality of chest pain" and the effect of clinician experience, for the prediction of acute myocardial infarction and presence of significant coronary artery disease.

METHODS: This prospective single-center observational study was undertaken in a UK General Hospital emergency department. We recruited consecutive adults with chest pain and a nondiagnostic electrocardiogram, for whom the treating physician determined that delayed troponin testing was necessary. Using their own clinical judgment, physicians recorded whether the chest pain described was typical or atypical for acute coronary syndrome. Physicians were defined as "experienced" or "novice" according to postgraduate experience. Acute myocardial infarction was adjudicated using a high-sensitivity troponin (hs-cTn) assay, whereas coronary artery disease was adjudicated angiographically.

RESULTS: Overall, 912 patients had typicality of chest pain assessed, of whom 114/912 (12.5%) had an acute myocardial infarction and 157/912 (17.2%) underwent angiography. In patients undergoing angiography, 90/157 (57.3%) had hs-cTn elevation, of whom 60 (66.7%) had significant coronary artery disease. Sixty-seven of 157 (42.7%) patients had angiography without hs-cTn elevation; of these, 31 (46.2%) had significant coronary artery disease. For the diagnosis of acute myocardial infarction, chest pain typicality had an area under the curve (AUC) of 0.54 (95% confidence interval [CI], 0.49-0.60). For the prediction of significant coronary artery disease with hs-cTn elevation AUC: 0.54 (95% CI, 0.40-0.67), and without hs-cTn elevation AUC: 0.45 (95% CI, 0.31-0.59). When assessed by experienced physicians, specificity for the diagnosis of acute myocardial infarction was higher at 65.8% (95% CI, 63.1%-68.7%) vs 55.4% (95% CI, 53.9%−56.8%) for novices.

CONCLUSIONS: Subjective interpretation of "typicality of chest pain" is of limited discriminatory value in the assessment of suspected acute coronary syndromes, in the context of a nondiagnostic electrocardiogram. Greater clinical experience improves accuracy as a rule-in tool but does not improve overall discriminatory ability.

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KEYWORDS: Acute coronary syndrome; Chest pain; Clinical experience; Coronary artery disease; Emergency department; High-sensitivity troponin; Myocardial infarction

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Patients with chest pain symptoms suggestive of acute coronary syndromes account for 10% of all emergency department attendances.[1] Yet, only 15%-20% have a final diagnosis of acute coronary syndrome.[2] In the remainder, distinguishing whether a patient presenting with chest pain has an acute coronary syndrome or a non cardiac problem is difficult.[3] While some alternative diagnoses become apparent using history alone, the ongoing diagnostic uncertainty in the remainder of patients has been shown to lead to emergency department overcrowding, higher levels of resource use, and increased health care costs.[4-6]

In patients with chest pain and potential acute coronary syndrome, clinical assessment includes electrocardiography and the results of cardiac troponin testing.[7] However, over half of patients will have a nondiagnostic electrocardiogram (ECG),[2] and at least 10% with unstable angina will not have troponin elevations, even in the era of high-sensitivity assays.[8] This sizeable group of patients represents a significant diagnostic and resource challenge. In these situations, physicians often use the perceived discriminatory value of the chest pain history. This will assist in deciding whether a patient is more or less likely to have cardiac chest pain, and the subsequent need for further observation and investigation.[9]

Published data demonstrate that typical symptoms provide useful diagnostic information in patients with stable coronary artery disease.[10-12] In contrast, evidence examining the value of typical symptoms in patients presenting with chest pain in the acute setting have demonstrated a poor correlation with the final diagnosis of acute coronary syndrome.[3,13-19] However, these studies have tended to either include patients with diagnostic ECG changes, focus on specific chest pain characteristics rather than overall typicality, or use research nurses to extract this information. Although it is evident that unstructured clinical judgment, or gestalt, has an important role to play in the overall risk assessment of acute chest pain patients,[20] the subjective interpretation of typicality of chest pain and the impact that clinical experience may have upon its diagnostic accuracy remain poorly understood.

This study therefore aimed to establish, in patients presenting with chest pain and potential acute coronary syndrome with a nondiagnostic ECG, the discriminatory value of "typicality of chest pain" and the effect of clinical experience, for the prediction of acute myocardial infarction and presence of significant coronary artery disease.

CLINICAL SIGNIFICANCE

- In emergency patients being assessed for potential acute coronary syndromes with a nondiagnostic electrocardiogram, where troponin results are not yet available, typicality of chest pain is of limited discriminatory value in the prediction of acute myocardial infarction or the presence of significant coronary artery disease.
- The diagnostic accuracy of chest pain typicality for the rule-in of acute myocardial infarction appears to be greater with a higher level of clinical experience, but this effect is small.

METHODS

Study Design and Setting

This was a planned substudy of a single-center prospective diagnostic cohort study undertaken from July 2012 to August 2013. This study was designed to assess physician risk assessment of emergency department patients with chest pain using an accelerated diagnostic pathway, the results of which have been published previously.[21] It was approved by the UK National Research Ethics Service, registered with the Controlled Trials Database (ISRCTN No. 21109279), and designed using the Standards for Reporting Diagnostic Accuracy.[22] All patient participants provided written informed consent. The study institution's Emergency Department was situated within a UK District General Hospital and has approximately 62,000 new patient attendances per year.

Selection of Participants

We recruited consecutive adults of at least 18 years of age, who had a primary complaint of chest pain, and for whom the treating physician in the Emergency Department determined that delayed (6 hours post attendance) troponin testing was required for the assessment of an acute coronary syndrome. Clinical protocols at the time of the study did not include troponin testing at presentation, unless >12 hours had elapsed since peak symptoms, therefore, assessing physicians were blinded to initial troponin results. In order to focus upon the patient group that provides the greatest diagnostic challenge to physicians, patients were recruited only if they had a nondiagnostic ECG. Patients who were discharged directly from the emergency department at the discretion of the treating physician without delayed troponin testing were not recruited. All patients who required 6-hour troponin testing were admitted to an inpatient assessment unit under the care of an acute general internist; the decision to admit was at the discretion of the assessing physician in the emergency department. Onward cardiology consultation, stress testing, or discharge for outpatient follow-up was at the discretion of the acute internist. Referral for invasive angiography was at the discretion of cardiologists. Recruitment was undertaken 24 hours a day, 7 days a week. Patients were screened by a dedicated researcher and assessed for eligibility and consented in collaboration with the treating physician. Patients were excluded if any of the following were present: ST-segment elevation myocardial infarction or left bundle branch block not known to be old, ECG changes diagnostic of ischemia (ST-segment

depression ≥1 mm or T-wave inversion consistent with the presence of ischemia), arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias), troponin not suitable for analysis (eg, hemolysis), age ≥80 years, a clear nonacute coronary syndrome cause for chest pain was found at presentation (eg, pulmonary embolism, pneumonia, aortic dissection), another medical condition requiring hospital admission, refusal or inability to give informed consent, non-English-speaking, pregnancy, renal failure requiring dialysis, or inability to be contacted after discharge.

Methods and Measurements

On-duty Board Certified Attendings, Senior Emergency Medicine Residents, and Junior Residents all undertook assessments of pain typicality during the study period and completed standardized data collection forms after genuine clinical consultations and before obtaining results of diagnostic tests (other than the initial ECG). To standardize recruitment, ECG evaluation was undertaken by members of the research team. A trained researcher reviewed the hospital record to collect data on the level of clinical experience of the assessing physician, cardiovascular history, cardiac risk factors, and all investigations related to the visit according to standardized data definitions.[23]

We instructed clinicians to record whether they thought the chest pain described was typical cardiac chest pain in a "*yes*" or "*no*" tick box, using their own clinical judgment and taking into account all factors from history and examination. The level of experience for assessing physicians was recorded. Clinical experience was defined a priori as either "experienced" or "novice." Experienced physicians were either Board Certified Attendings (Fellows of the UK College of Emergency Medicine) or Senior Residents with at least 2 years of emergency department experience. Novice physicians were Junior Residents with <1 years' emergency department experience. During the study period there were 12 experienced physicians and 32 novice physicians undertaking clinical assessments.

Each participating patient had pain typicality assessed by only one treating physician. As such, if a patient had a primary consultation with a novice physician, followed by a review by an experienced physician, only the interpretation of the primary assessing physician was recorded.

The fifth-generation Roche ELECSYS high-sensitivity troponin-T assay (Roche, Basel, Switzerland), which has a 99th percentile reference limit of 14 ng/L and 10% coefficient of variation of <10% at 9 ng/L, was used for both presentation and 6-hour samples. All serum samples were tested in real time.

In order to provide a quantitative measure of pretest probability and ensure provider groups were similar in this regard, researchers calculated the Thrombolysis in Myocardial Infarction (TIMI) Score[24] for each patient. This was assessed from data available at presentation and without knowledge of either the treating physicians' interpretation of chest pain typicality or troponin results.

Outcomes

The primary endpoint was the diagnosis of fatal or nonfatal acute myocardial infarction occurring during the index visit. The presence of acute myocardial infarction was defined according to the Third Universal Definition, which states that an increase or decrease in troponin with at least one value above the 99th centile value in the context of a patient with ischemic symptoms or signs (ECG changes or imaging evidence) would satisfy the diagnosis.[25] Based on current consensus guidance for high-sensitivity troponin assays, an increase or decrease of 20% (delta) was considered statistically significant and consistent with a diagnosis of acute myocardial infarction.[26] Adjudication of this endpoint was carried out by 2 local cardiologists blinded to the physician interpretation of typical pain, but whom had access to the in-hospital clinical record, General Practitioner records, ECG, troponin, and angiography results.

In order to overcome the diagnostic adjudication challenges associated with high-sensitivity troponin assays, such as small elevations in troponin,[27] and evaluate those patients without troponin elevation that have clinically relevant coronary artery disease, we also included a secondary diagnostic outcome measure for those patients assessed angiographically. This was categorized into the presence of significant coronary artery disease with or without high-sensitivity troponin-T elevation (hs-cTnT ≥14 ng/L at either presentation or 6 hours later vs hs-cTnT <14 ng/L at presentation and 6 hours later). Significant coronary artery disease was defined as ≥70% luminal diameter narrowing of at least one major coronary artery as reported on visual assessment by the operator.

Analysis

As this was a planned substudy, no formal power calculation was undertaken, however, previous observational studies reporting the diagnostic utility of chest pain characteristics have typically recruited upwards of 400 participants.[13,14,16-19] Chi-squared analyses were used to generate 2 × 2 tables for the calculation of sensitivity and specificity; 95% confidence intervals (CI) are reported. Receiver-operating characteristic curves were obtained by plotting sensitivity against 1-specificity. The area under the receiver-operating characteristic curve (AUC) was chosen as the primary measure of discriminatory value, as it gives a global measure of diagnostic test performance. The AUC was tested against the null hypothesis that typicality of chest pain has no discriminatory ability in determining the presence or absence of acute myocardial infarction or significant coronary artery disease, and therefore the true AUC was 0.50, with a significance of <.05. AUC equals 0.5 when the diagnostic test corresponds to random chance (null hypothesis) and 1.0 indicates perfect diagnostic accuracy. For

analysis of the effect of clinical experience, sensitivity (ability of the test to rule out a condition) and specificity (ability of the test to rule in) were compared. All reported *P*-values are 2-tailed. Statistical analysis was carried out using SPSS version 20 (IBM, Armonk, NY).

RESULTS

Characteristics of Study Subjects

Overall, 912 patients had typicality of chest pain assessed, of whom 394 (43%) were recorded as having had typical chest pain (Figure 1). Acute myocardial infarction occurred in 114/912 (12.5%), and 157/912 (17.2%) underwent angiographic assessment. In those undergoing angiography, 90 (57.3%) had hs-cTnT elevation, of whom 64 (71.1%) had significant coronary artery disease. In the 67 (42%) patients who had angiography without hs-cTnT elevation, 28 (41.7%) had significant coronary artery disease, of whom 21 (67.7%) required percutaneous coronary intervention.

Of the assessments for typicality of chest pain, 227 (24.9%) were made by experienced emergency department physicians and 685 (75.1%) were made by novices. Table 1 summarizes recruited patient demographics according to physician experience; there were no significant differences in clinical characteristics or outcomes ($P > .05$ for all). When assessed by experienced physicians, a lower proportion of patients were identified as having typical chest pain when compared with novices (35.2% vs 45.8%, $P = .005$).

Table 2 demonstrates that there was no significant difference in quantitative pretest probability between provider groups when assessed using the TIMI score (in the absence of troponin results).

Contingency tables showing the occurrence of acute myocardial infarction and significant coronary artery disease, with and without hs-cTn elevation according to the presence or absence of typical chest pain, are shown in the Appendix (available online).

Discriminatory Value of Typicality of Chest Pain

The receiver-operating characteristic curves demonstrating the discriminatory ability of typicality of chest pain as assessed by all physicians in the emergency department, either as a diagnostic tool for acute myocardial infarction, or significant coronary artery disease both with and without hs-cTn elevation, are presented in Figure 2. Below this are also listed the values for AUCs according to specific provider groups. When tested against the null hypothesis that the true AUC is 0.50, the *P*-value for all providers is >.05, suggesting that typicality of chest pain has limited discriminatory ability in the diagnosis or exclusion of acute myocardial infarction and significant coronary artery disease with or without hs-cTn elevation in this cohort across all providers.

Diagnostic Accuracy and Impact of Clinical Experience

Figure 3 presents the sensitivity and specificity of typicality of chest pain for the diagnosis of acute myocardial infarction and significant coronary artery disease both with and without hs-cTn elevation, according to provider groups. As a rule-in tool,

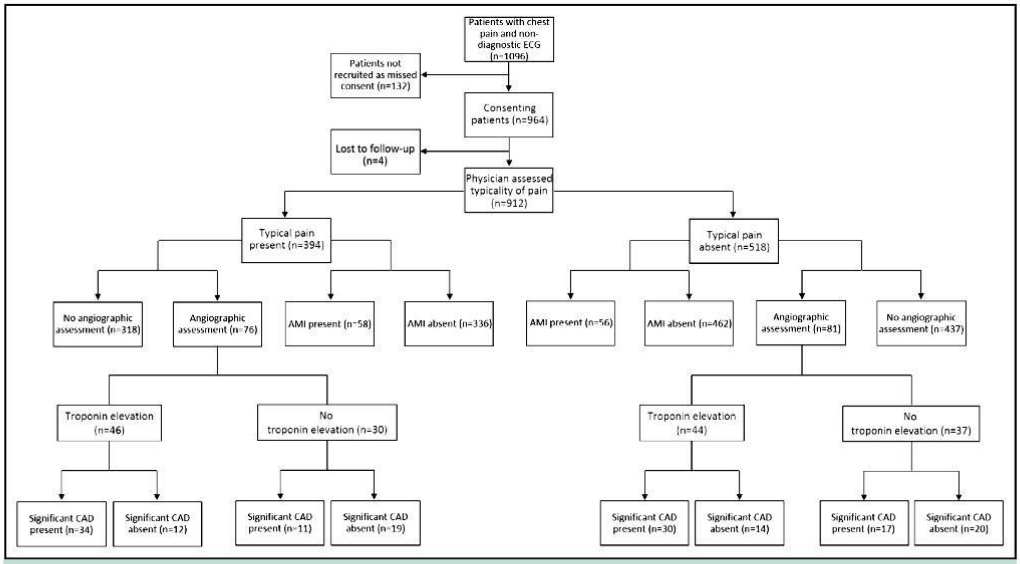


Figure 1 Participant recruitment flow chart. AMI = acute myocardial infarction; CAD = coronary artery disease; ECG = electrocardiogram.

Table 1 Patient Characteristics According to Provider Groups

	Total (N = 912)	Experienced Physicians (n = 227)	Novice Physicians (n = 685)
Age, y (Mean/SD)	58.0/13.3	58.5/12.8	57.8/13.4
Male sex (%)	546 (59.9)	137 (60.4)	409 (59.7)
Ethnicity (% White British)	869 (95.3)	219 (96.5)	650 (94.9)
Risk factors, n (%)			
Hypertension	505 (55.4)	126 (55.4)	379 (55.3)
Hyperlipidemia	601 (65.9)	154 (67.8)	447 (65.3)
Smoking Current	219 (24.0)	61 (26.9)	158 (23.1)
Diabetes	152 (16.7)	31 (13.7)	121 (17.7)
Family History of CAD	340 (37.3)	78 (34.4)	262 (38.2)
Medical history			
Angina	238 (26.1)	51 (22.5)	187 (27.3)
Myocardial infarction	194 (21.3)	42 (18.5)	152 (22.2)
Percutaneous coronary intervention	173 (19.0)	40 (17.6)	133 (19.4)
Atrial arrhythmia	115 (12.6)	26 (11.5)	89 (13.0)
Stroke/TIA	62 (6.8)	14 (6.2)	48 (7.0)
Coronary artery bypass graft	47 (5.2)	11 (4.8)	36 (5.3)
Typical chest pain present	394 (43.2)	80 (35.2)	314 (45.8)
Outcomes			
Fatal/nonfatal AMI	114 (12.5)	34 (14.9)	80 (11.6)
Significant CAD with troponin elevation	64 (7.0)	19 (8.3)	45 (6.5)
Significant CAD without troponin elevation	28 (3.1)	10 (4.4)	18 (2.6)

No significant difference seen between physician groups; $P > .05$ for all variables.
AMI = acute myocardial infarction; CAD = coronary artery disease; TIA = transient ischemic attack.

specificity of typical chest pain for all outcomes, when adjudicated by physicians as a whole, ranged from 51.3%-57.9% (95% CI, 40.8%-70.8%). However, when assessing the ability of typicality of chest pain as a rule-in tool according to physician experience, the specificity for the diagnosis of acute myocardial infarction was higher for experienced physicians, at 65.8% (95% CI, 63.1%-68.7%), compared with novices at 55.4% (95% CI, 53.9%-56.8%). Similarly, in patients with significant coronary artery disease without hs-cTnT elevation, there was a trend toward higher specificity when assessed by experienced physicians: 66.7% (95% CI, 48.8%-89.5%) vs 46.7% (95% CI, 34.8%-58.6%). It is important here to note that this finding was not statistically significant due to wide and overlapping 95% confidence intervals. In patients with significant coronary artery disease and hs-cTnT elevation, there was no difference in test specificity between physician groups: 54.5% (95% CI, 28.8-79.4) vs 53.3% (95% CI, 29.6-75.9).

As a rule-out tool for all outcomes, sensitivity of typicality of chest pain ranged from 39.3%-53.1% (95% CI, 24.7%-60.6%). There was no significant difference in the ability of typicality of chest pain to act as a rule-out tool for any outcome measure when comparing experienced and novice physicians.

DISCUSSION

Physicians rely upon chest pain history to make management decisions in patients with suspected acute coronary syndromes,

Table 2 Quantitative Estimates of Pretest Probability Using the TIMI Risk Score,[24] in the Absence of High-sensitivity Troponin Results, According to Provider Groups

TIMI Score* Total N (%)	Total (n = 912)	Experienced Physicians (n = 227)	Novice Physicians (n = 685)	Significance of Difference Between Experienced and Novice Physicians (*P*-value)
0	210 (23)	50 (22)	160 (23.4)	.680
1	285 (31.3)	80 (35.2)	205 (29.9)	.134
2	157 (17.2)	33 (14.5)	124 (18.1)	.218
3	175 (19.2)	42 (18.5)	133 (19.4)	.762
4	77 (8.4)	20 (8.8)	57 (8.3)	.818
5	8 (0.9)	2 (0.9)	6 (0.9)	.990

*The Thrombolysis in Myocardial Infarction (TIMI) Score[24] was calculated from the following 5 parameters from data available at presentation and without the knowledge of troponin results: 1) Age 65 years or older; 2) Three or more risk factors for coronary artery disease (family history, hypertension, hyperlipidemia, diabetes or being a current smoker); 3) Use of aspirin in the past 7 days; 4) Significant coronary artery stenosis; 5) Severe angina (2 or more angina events in the past 24 hours). One point was assigned for each variable present.

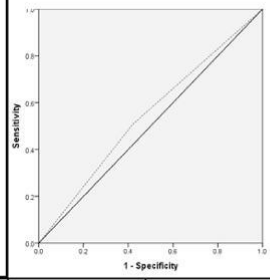
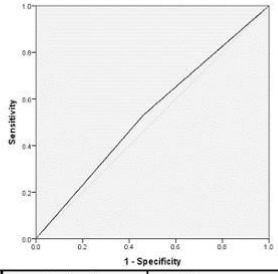
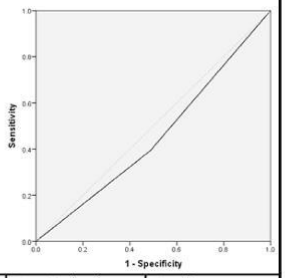
	Acute Myocardial Infarction		Significant coronary artery disease with troponin elevation		Significant coronary artery disease without troponin elevation	
Receiver-Operating Characteristic Curves for Typicality of Pain, assessed by All Physicians.						
Provider	**Area Under the Curve**	**Significance against null hypothesis of AUC (0.5)**	**Area Under the Curve**	**Significance against null hypothesis of AUC (0.5)**	**Area Under the Curve**	**Significance against null hypothesis of AUC (0.5)**
All Physicians	0.54 (0.49-0.60)	P=0.129	0.54 (0.40-0.67)	P=0.606	0.45 (0.31-0.59)	P=0.513
Experienced Physicians	0.54 (0.43-0.64)	P=0.517	0.48 (0.27-0.70)	P=0.880	0.43 (0.17-0.70)	P=0.624
Novice Physicians	0.55 (0.49-0.62)	P=0.131	0.56 (0.39-0.73)	P=0.522	0.48 (0.31-0.65)	P=0.848

Figure 2 Discriminatory ability of the typicality of chest pain for either acute myocardial infarction, or significant coronary artery disease with and without high-sensitivity troponin-T elevation.

where the diagnosis is not immediately apparent through ECG and troponin testing. Our results show that in emergency patients being assessed for a potential acute coronary syndrome with a nondiagnostic ECG, where troponin results are not yet available, typicality of chest pain is of limited discriminatory value in the prediction of acute myocardial infarction or the presence of significant coronary artery disease. With regard to clinician experience, the diagnostic accuracy for the rule-in of acute myocardial infarction appears to be greater with more experience, but this difference is small and therefore likely to have limited clinical applicability.

Our report has several important implications. Physicians intuitively adopt a *Bayesian* approach to diagnosis, making an initial diagnosis based on probabilities, then adjusting these probabilities as more information becomes available.[28] This diagnostic approach is applied readily in the risk assessment of patients with acute chest pain. In the absence of diagnostic ECG changes, physicians weigh up all the information gathered from the history and physical assessment to establish pretest probability before the results of troponin testing. Chest pain typicality has been traditionally central to this assessment, yet our results bring its value into question.

Until recently, contemporary cardiac troponin assays could be used reliably to identify those patients with a non-ischemic ECG who were at high risk for acute myocardial infarction and adverse events with low false-positive rates.[7] However, the development of high-sensitivity cardiac troponin assays, which can detect troponin in over 50% of apparently illness-free individuals,[26] has raised concerns around binary positive and negative interpretation of results. The potential for multiple acute conditions to cause elevations in hs-cTn[29] has necessitated better estimates of pretest probability to allow improved management decisions based on elevated hs-cTn results. Our results suggest that chest pain typicality may also be of limited use in this regard.

With the advent of high-sensitivity assays, there was the potential that in clinical practice, their use may make the diagnosis of unstable angina obsolete.[30] By using hs-cTn to adjudicate our primary endpoint and confirm the findings in a subset of patients who have undergone angiographic assessment, we have demonstrated an important finding. In our cohort, over 40% of

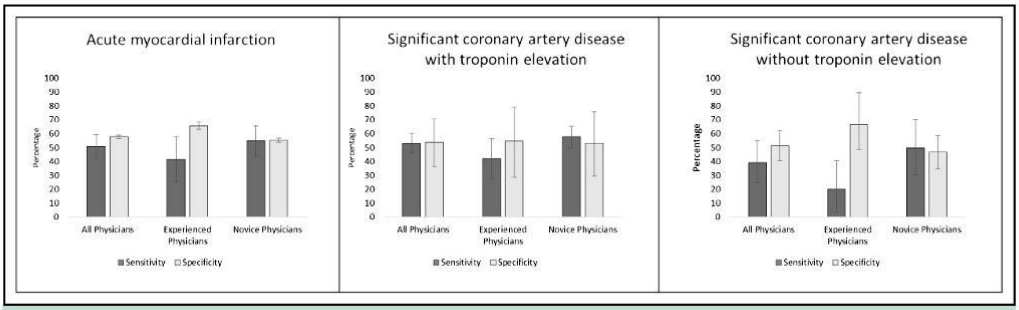


Figure 3 Sensitivities and specificities of typicality of chest pain for the diagnosis of acute myocardial infarction and significant coronary artery disease with and without high-sensitivity troponin elevation.

patients assessed angiographically had significant coronary artery disease, in the absence of high-sensitivity troponin elevations, and two-thirds of these required intervention. It is these patients in whom treating physicians most rely on the discriminatory value of the chest pain history, yet we demonstrate that typicality may again be of limited use.

We therefore suggest that there should be a focus on the clinical application of accelerated diagnostic protocols, which combine risk scores with high-sensitivity troponin testing[21,31-34] rather than unstructured subjective clinical assessment or gestalt.[20]

Importantly, this study included only patients with chest pain and a potential acute coronary syndrome with a nondiagnostic ECG who were admitted to a ward for delayed biomarker testing. As a result, the treating clinician had already used clinical judgment to identify patients with chest pain in whom there was a high level of suspicion for acute coronary syndrome and therefore required further inpatient evaluation. Those patients with diagnostic ECGs and those discharged directly from the emergency department with "non-concerning" histories were, as a result, intentionally excluded from analysis. Although our population therefore may be subject to significant selection bias, we have focused intentionally on a cohort of patients that provide the greatest diagnostic challenge for acute physicians on a day-to-day basis. It is possible that the discriminatory value of typicality of chest pain would have improved if patients with clinically evident acute coronary syndromes also had been recruited for analysis. However, the exclusion of those patients in whom there was no diagnostic uncertainty has allowed us to provide novel insight into an everyday and highly relevant clinical problem.

There are some limitations to this study. The applicability of the results may be limited by the characteristics of the population selected. The inclusion of predominantly white patients may limit the applicability to international settings, especially as cross-cultural differences in symptom reporting exist.[18] The upper age cut-off of $\geq$80 years was chosen for pragmatic institutional reasons, as patients were cared for by different inpatient teams. This may limit further the general applicability of the findings, as firstly, older individuals are more likely to report atypical symptoms[35] and secondly, older cohorts are known to have high proportions of patients with elevated hs-cTn assay results, often due to subclinical disease.[36]

CONCLUSION

Physician interpretation of "typicality of chest pain" is of limited discriminatory value in patients being assessed for potential acute coronary syndromes, in the context of a nondiagnostic ECG. Greater clinical experience improves accuracy as a rule-in tool for acute myocardial infarction, but this does not improve overall discriminatory ability.

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Conflict of Interest: EC has received funding from Abbott in support for related research. MT has received funding from Alere, Abbott, Beckman, and Roche for speaking and support for other research. LC has received funding from Abbott, Roche, Alere, Siemens, and Radiometer Pacific for clinical trials, and from Alere, Boehringer Ingelheim, Pfizer, Astra Zeneca, Abbott, Novartis, and Radiometer Pacific for speaking and education. AK has no conflicts of interest. KG has received funding from AstraZeneca and Takeda UK for related research.

Authorship: Each author has contributed to the analysis and interpretation of the data, drafting and approval of the final manuscript. All authors have also contributed to the conception/design of the study reported in this manuscript.

SUPPLEMENTARY DATA

Supplementary tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.04.012.

APPENDIX

Contingency tables showing the occurrence of acute myocardial infarction (**Supplementary Table 1**) and significant coronary artery disease with and without troponin elevation (**Supplementary Table 2**) according to the presence or absence of typical chest pain.

Supplementary Table 1 The occurrence of acute myocardial infarction according to the presence or absence of typical chest pain

	Acute Myocardial Infarction	No Acute Myocardial Infarction	Total
All physicians			
Typical chest pain present	58	336	394
Typical chest pain absent	56	462	518
Total	114	798	912
Experienced physicians			
Typical chest pain present	14	66	80
Typical chest pain absent	20	127	147
Total	34	193	227
Novice physicians			
Typical chest pain present	44	270	314
Typical chest pain absent	36	335	371
Total	80	605	685

Supplementary Table 2 The occurrence of significant coronary artery disease with and without troponin elevation according to the presence or absence of typical chest pain

	Significant Coronary Artery Disease and hs-cTnT ≥14 ng/L	No Significant Coronary Artery Disease and hs-cTnT ≥14 ng/L	Total
All physicians			
Typical chest pain present	34	12	46
Typical chest pain absent	30	14	44
Total	64	26	90
Experienced physicians			
Typical chest pain present	8	5	13
Typical chest pain absent	11	6	17
Total	19	11	30
Novice physicians			
Typical chest pain present	26	7	33
Typical chest pain absent	19	8	27
Total	45	15	60
	Significant Coronary Artery Disease and hs-cTnT <14 ng/L	**No Significant Coronary Artery Disease and hs-cTnT <14 ng/L**	**Total**
All physicians			
Typical chest pain present	11	19	30
Typical chest pain absent	17	20	37
Total	28	39	67
Experienced physicians			
Typical chest pain present	2	3	5
Typical chest pain absent	8	6	14
Total	10	9	19
Novice physicians			
Typical chest pain present	9	16	25
Typical chest pain absent	9	14	23
Total	18	30	48

Hs-cTnT = high-sensitivity troponin-T elevation.

Appendix 13. Beyond Triage: The Diagnostic Accuracy of Emergency Department Nursing Staff Risk Assessment in Patients with Suspected Acute Coronary Syndromes

Paper in print Emergency Medicine Journal

Appendix 14. Identifying Patients Suitable for Discharge after a Single High-Sensitivity Troponin Result: A Comparison of Five Established Risk Scores and Two High-Sensitivity Assays

In press The Annals of Emergency Medicine

Appendix 15. External validation of the Manchester Acute Coronary Syndromes (MACS) decision rule

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