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Human Development and Health

The role of high sensitivity troponin outside the context of acute coronary syndromes

by

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Abstract

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Ischaemic heart disease remains the leading cause of mortality worldwide and, whilst there has been progress in reducing this, mainly due to smoking cessation, there are concerns that the obesity epidemic may negate this progress. Chest pain is a key presenting complaint for patients with ischaemic heart disease but it is also seen in a range of other conditions. Given that chest pain accounts for around 6% of emergency department presentations, healthcare systems need an efficient algorithm for managing these patients quickly. The use of biomarkers has become a central component in the diagnosis of myocardial infarction as defined by international guidelines. High sensitivity cardiac troponin (hs-cTn) is now considered the biomarker of choice and, as such, is widely used across a range of different healthcare systems.

Cardiac troponin (cTn) is a key component of the calcium-mediated contractile apparatus found within cardiac myocytes and is released upon injury to the myocardium. There are three isoforms of cTn, two of which have been found to be specific to the myocardium and, as such, these assays became embedded in routine practice. There was, however, one important limitation in their use; in order to reach adequate levels of sensitivity, a sample was needed at 10-12 hours after the onset of chest pain. This had significant resource implications for healthcare systems, and this became a driver for the development of high sensitivity cTn (hs-cTn) assays which now have

excellent performance within three hours of chest pain. Whilst this has proven highly beneficial to many aspects of clinical care, especially the ability to rule out a heart attack very early, the increased sensitivity of the assays, combined with increased usage, has resulted in concentrations above the manufacturer's upper limit of normal (ULN) being frequently detected across a range of presentations not traditionally associated with acute myocardial infarction (AMI). The result has been uncertainty, and some inaccuracy, about the interpretation of these results in clinical practice. Excitingly, however, there are emerging data to suggest that the hs-cTn concentration, outside the context of myocardial infarction, may act as a biomarker of prognosis.

In view of this, the aim of my thesis was to assess whether there was an association between hs-cTn concentration and mortality outside the context of AMI in several patient populations. The first two chapters of this thesis follow on from the original CHARIOT study (which was performed by my predecessor, Dr Mark Mariathas). In the first chapter I demonstrate that elevated hs-cTnI concentrations are frequently seen on presentation to the emergency department and, whilst these are associated with the severity of illness, they are also independent predictors of short term mortality. In the second chapter, I demonstrate that hs-cTnI concentrations are independently associated with one year mortality (both cardiovascular and non-cardiovascular) across a complete, consecutive hospital cohort of 20,000 patients (inpatients, outpatients and those in the emergency department) regardless of whether there was a clinical indication for the test. Finally, in a population of patients in critical care I show that the hs-cTnI concentration is associated with illness severity but is also independently associated with critical care mortality. Furthermore, that hs-cTnI concentration on admission to critical care performs as well as previously validated prognostic scores in discriminating critical care mortality.

In summary, this thesis demonstrates that hs-cTnI concentration is associated with both short and medium term outcomes across a range of populations. Further research is now required to assess whether any medical intervention can alter the risk in those patients identified by hs-cTn as having adverse prognosis. The potential clinical value of the concept that hs-cTn is a general biomarker for prognosis is far reaching: it would represent a novel application for the assay outside the context of its use to rule out AMI.

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Research Thesis: Declaration of Authorship

Print name: Jonathan Hinton

Title of thesis: The role of high sensitivity troponin outside the context of acute coronary syndromes

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as:

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   Hinton J, Mariathas M, Gabara L, Nicholas Z, Allan R, Ramamoorthy S, *et al*. Distribution of contemporary sensitivity troponin in the emergency department and relationship to 30-day mortality: The CHARIOT-ED substudy. Clin Med (Lond). 2020;20(6):528-34.

   Hinton J, Augustine M, Mariathas M et al. Distribution of high sensitivity troponin taken without conventional clinical indications in critical care patients and its association with mortality. Critical Care Medicine 2021 49 (9) 1451-1459

   Hinton J, Mariathas M, Gabara L et al. Relation of High-sensitivity Troponin to One Year Mortality in 20,000 Consecutive Hospital Patients Undergoing a Blood Test for Any Reason. American Journal of Cardiology 2021. 158 (1) 124-131

Signature: Date:

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Definitions and Abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
AHA	American Heart Association
AMI	Acute myocardial infarction
APACHE II	Acute Physiology and Chronic Health Evaluation II
AST	Asparate aminotransferase
AUC	Area under the receiver operator curve
BARI 2D	Bypass Angioplasty Revascularisation Investigation 2 Diabetes
BD	Twice per day
BMI	Body mass index
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAG	Confidentiality Advisory Group
CASABLANCA	Catheter Sampled Blood Archive in Cardiovascular Diseases
CC	Critical care
CCCU	Cardiothoracic critical care unit
CDU	Clinical decisions unit
CHADS2	Stroke risk score for patients with atrial fibrillation
CHADSVASc	Stroke risk score for patients with atrial fibrillation

Definitions and Abbreviations

CHARIOT	Is the Current Threshold for Diagnosis of 'Abnormality', including Non ST Elevation Myocardial Infarction, Using Raised Highly Sensitive Troponin Appropriate for a Hospital Population?
CHD	Congential heart disease
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
CK-MB	Creatine kinase subunit M and B
COMPASS MI	Calculation of Myocardial Infarction Risk Probabilities to Manage Patients with Suspicion of Myocardial Infarction
COPD	Chronic obstructive pulmonary disease
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
COVID-19	Coronavirus-19
CRP	C-reactive protein
cTn	Cardiac troponin
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CV	Coefficient of variation
DCCV	Direct current cardioversion
DCM	Dilated cardiomyopathy
DOAC	Direct oral anticoagulant
EC	Eye casualty
ECG	Electrocardiogram
ED	Emergency department
eGFR	estimated glomerular filtration rate

ESC	European Society of Cardiology
ESRF	End stage renal failure
EXAMINE	Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care
EXCEL	Evaluation of Xience versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation
FiO2	Fraction of inspired oxygen
GCCU	General critical care unit
GRACE	Global Registry of Acute Coronary Events
HCM	Hypertrophic cardiomyopathy
HES	Health Episode Statistics
HF	Heart failure
HIGH-STEACS	High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome
HR	Hazard ratio
HRA	Health Research Authority
Hs-cTn	High sensitivity troponin
Hs-cTnI	High sensitivity troponin I
Hs-cTnT	High sensitivity troponin T
ICOS-ONE	International CardiOncology Society-one
IHD	Ischaemic heart disease
IPD	Inpatient
IQR	Interquartile range
IRAS	Integrated Research Application System
JUPITER	Justification for the Use of Statins in Prevention: an International Trial Evaluating Rosuvastatin

Definitions and Abbreviations

LDH	Lactate dehydrogenase
LoB	Limit of blank
LoD	Limit of detection
LoQ	Limit of quantification
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MANAGE	Management of Myocardial Injury After Noncardiac Surgery
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NCCU	Neurosciences critical care unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
NPV	Negative predictive value
NSTEMI	Non-ST elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
ONS	Office of National Statistics
OPD	Outpatient
OR	Odds ratio
PaO2	Partial pressure of oxygen
PCI	Percutaneous coronary intervention
PEITHO	Pulmonary Embolism International Thrombolysis Study
PPV	Positive predictive value

PREVEND	Prevention of Renal and Vascular End-stage Disease
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
REC	Research Ethics Committee
ROC	Receiver operator curve
SAH	Subarachnoid haemorrhage
SCAI	Society for Cardiovascular Angiography and Interventions
ScTn	Standard cardiac troponin
SOFA	Sequential Organ Failure Assessment
T1MI	Type 1 myocardial infarction
T2aMI	Type 2a myocardial infarction
T2bMI	Type 2b myocardial infarction
T2MI	Type 2 myocardial infarction
T3MI	Type 3 myocardial infarction
T4aMI	Type 4a myocardial infarction
T4MI	Type 4 myocardial infarction
T5MI	Type 5 myocardial infarction
TAVI	Transcatheter aortic valve implantation
TIA	Transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
ULN	Upper limit of normal
VIF	Variance inflation factor
VISION	Vascular Events in Noncardiac Surgery Patients Cohort Evaluation
VT	Ventricular tachycardia
WBC	White blood cell count

WHF	World Heart Federation
WHO	World Health Organisation
WOSCOPS	West of Scotland Coronary Prevention Study

Chapter 1 Introduction

1.1 Prologue

Ischaemic heart disease (IHD) is the leading cause of mortality worldwide, with a crude death rate of 126 per 100,000 population in 2016 (1). The incidence of IHD increases with age and IHD will affect at least a third of males over the age of 75 years(2). In the developed world, there has, however, been a steady decline in IHD-related mortality, which can be mainly attributed to lifestyle changes, most importantly smoking cessation (2-5). In addition, the development of medical and interventional therapies for IHD has played an important role in this improvement by reducing the mortality after myocardial infarction (MI) (2-5). This reduction in mortality in developed countries is, however, accompanied by an increase in the deaths as a result of IHD in developing countries (1, 5).

Whilst smoking cessation has been a success story in the fight to reduce cardiovascular mortality, the progressive increase in obesity across developed countries and its associated metabolic consequences raise concern that this will lead to a new epidemic (5). The aging of the population, particularly in developed countries, also points to the likely increase in IHD.

Chest pain accounts for around 6% of emergency department presentations and around 1% of presentations to general practice (6, 7). Given the likely increase in the incidence of IHD, it is probable that presentations with chest pain will continue to form a significant proportion of presentations to medical services. The importance of having a test that can rapidly and accurately guide clinicians as to whether chest pain is related to AMI is therefore clear.

Cardiac injury biomarkers have become central to diagnosis of AMI, and their evolution has resulted in the current array of high sensitivity troponin (hs-cTn) assays. These assays demonstrate excellent diagnostic performance early in the patient pathway: specifically a negative test is capable of ruling out AMI very early after the onset of symptoms. However, this increased sensitivity has raised another issue: hs-cTn is frequently being detected in a range of conditions not traditionally associated with AMI (8-14). This is explained by two factors: firstly, the clinically applied upper limit of normal (ULN) for hs-cTn is based upon the 99^{th} centile of a distribution in a young, healthy population, which does not necessarily reflect the population in whom the test is being used (9, 15); secondly, hs-cTn elevation outside the context of MI is frequently associated with states of illness resulting in a myocardial oxygen supply and demand mismatch and other disparate causes of myocardial injury (8, 16). It is therefore unsurprising that elevated hs-cTn levels are commonly found in critically ill patients, for example (8, 17).

There has also been some evidence to suggest that patients with an elevated hs-cTn level outside the context of AMI have a higher future cardiovascular risk (13, 18-21). The work in this thesis was designed to address two key questions arising from this background.

1. Does the manufacturer's 99th centile, used in clinical practice as the ULN, apply to critical care populations?
2. Is hs-cTn associated with clinical outcome, particularly mortality, outside the context of AMI?

1.2 The evolution of cardiac biomarkers

Coronary artery disease (CAD) is not solely a disease entity related to modern lifestyles, and, in fact, has been found in four preindustrial populations including pre-agricultural hunter-gatherers dating back over 4000 years (22). The role of CAD in the pathogenesis of MI was first postulated in 1879 by the pathologist Luvig Hektoen who observed that MI was caused by coronary thrombosis, but, until the beginning of the 20th century it was assumed that this process was always fatal (23). The realisation that MI was not always fatal paved the way for the observation the chest pain was an indicator of MI and this remains central to making the diagnosis today (16). Around the same time, the first three lead electrocardiogram (ECG) was being built by William Einthoven, but it wasn't until 1954, after multiple revisions, that the 12-lead ECG, another cornerstone of the diagnosis of AMI, was introduced (16, 24). However, the ECG only has a sensitivity of between 55-75% for detection of AMI when evaluated against findings at autopsy (25). The need, and potential value, of a complementary biomarker to indicate MI was therefore obvious. As a result, testing for serum glutamic-oxaloacetic transaminase, now called asparate aminotransferase (AST), was introduced, marking the start of an evolution that has resulted in the development of the hs-cTn assays in use today (16, 26, 27). Each step in this evolution was driven initially by a lack of specificity and, subsequently, by the need for assays with higher sensitivity to allow rapid diagnosis of MI, crucial in today's finance- and time-scarce health care services. Figure 1 demonstrates this evolution (adapted from (27)).

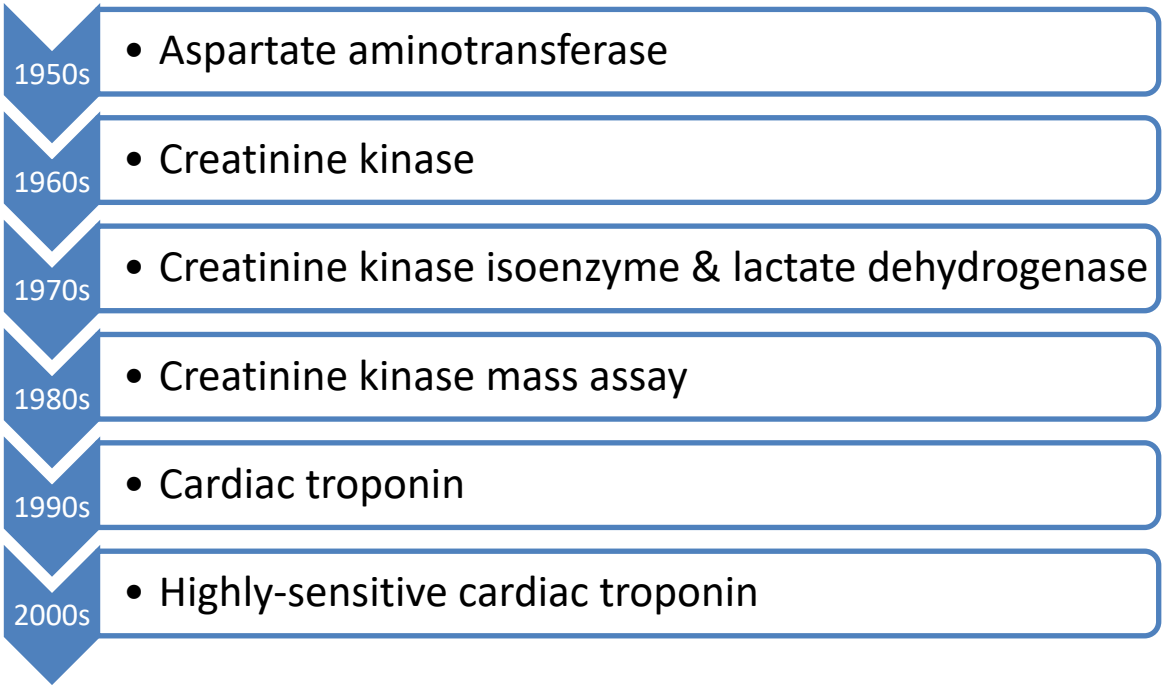

Figure 1: Evolution of diagnostic assays using cardiac enzymes

1.2.1 Aspartate aminotransferase

The observation that AST was widely distributed in animal tissues, but most concentrated in the myocardium, led to the analysis of its variation in MI (28). A key study, published in 1954, demonstrated that serum AST rose between 2-23 times the normal range within 24 hours in all sixteen patients with MI (28). Importantly, this study also highlighted that the AST levels in all of these patients normalised within 3 to 6 days (28). AST was therefore widely used in the 1960s and was included in the World Health Organisation's (WHO) contemporaneous definition of MI (29). However, it became apparent that a limitation for AST in this role was that it is not specific to the myocardium, given that it is also found in the liver, skeletal muscle, red blood cells and other tissues (30, 31). Further adding to the lack of diagnostic clarity was the observation that levels frequently rise as the result of liver congestion secondary to heart failure (31). In addition, the test also had an unacceptably high false negative rate of 8.8% (32). Furthermore, the assay processing at the time of discovery was prolonged (33). Thus, whilst AST did not prove to be the ideal biomarker of an MI, the evolution of the cardiac biomarkers had begun.

AST has, however, subsequently become established as a "liver enzyme" and, recently, studies have looked to assess whether liver serum markers (including AST) have a predictive value for future cardiovascular disease. A comprehensive meta-analysis demonstrated that the aminotransferases (including AST) do not predict cardiovascular risk in general populations but that other liver enzymes may do (34). A single study demonstrated that the aminotransferases were associated with the degree of luminal narrowing found at coronary angiography for MI (35). However, this retrospective study had a number of important flaws in its design. A further, retrospective study demonstrated that aminotransferases (including AST) are associated with poor short and long term outcomes in patients presenting with an MI (36). It is likely that this observation results from the liver congestion associated with heart failure following a large MI.

1.2.2 Creatine kinase

Creatine kinase (CK) is an enzyme which is present in skeletal muscle, brain, myocardium and also in small amounts in other visceral tissues (37-39). It acts by catalysing the reversible phosphorylation of creatine by adenosine triphosphate (37-40). Cell injury releases CK into the circulation, thereby providing a marker for injury to these tissues (38). CK was first utilised as a diagnostic aid in patients with muscular disorders, particularly in Duchenne's muscular dystrophy (39). It was, however, quickly noted that CK had diagnostic value in a range of other conditions, including MI (39). Levels of CK peak within 24-48 hours after MI and resolve to normal within four

to seven days (39). The introduction of CK for AMI diagnosis provided a clear advantage over AST because it was not affected by cardiac failure or liver injury (27, 39). Despite this, CK elevation, whilst sensitive for MI, lacks specificity given its presence in a variety of other tissues (38).

CK has also been assessed for its potential prognostic value outside the context of acute MI. It was noted that between 5% and 20% of patients after a percutaneous coronary intervention (PCI) had elevated CK levels (41). In a study of 253 patients undergoing elective PCI that were found to have CK elevation, there was an independent association between peak CK levels (high >3 times normal and intermediate 1.5-3 times normal) and late cardiac mortality (41). However, this has turned out to be contentious, and other studies using CK do not support this conclusion (42, 43). Whilst this observation highlights the potential prognostic value of cardiac enzymes, the lack of consistency combined with the development in the available cardiac enzymes means that CK does not form part of current clinical practice.

CK is composed of two sub-units, M and B, which combine to create three isoenzymes. This observation would turn out to have an important role in the future given that the CK-MB isoenzyme is almost exclusively found in the myocardium (38).

1.2.3 Lactate dehydrogenase

Lactate dehydrogenase (LDH) is an enzyme that converts lactate to pyruvate in order to facilitate energy production. Given its key role in energy production, LDH is found in all cells of the body with the highest concentrations in the heart, liver, muscle, kidneys, lungs and red blood cells (44). Early studies demonstrated that LDH elevation invariably occurred during the first 14 days following MI (33, 45). Unfortunately, due to the wide distribution of LDH within tissues it became apparent that this test lacked specificity (46). Like CK, there are isoenzymes of LDH, with improved specificity for MI achieved using isoenzyme-1 and the ratio between isoenzyme 1 and 2 (47). Further development of the immunochemical technique allowed improved, but still variable, sensitivity and specificity for MI (47, 48). LDH does have the advantage that elevated concentrations can be seen for a more prolonged period of time than CK and, as a result, has been used to give a retrospective diagnosis of MI in late presenting patients (46). LDH also became part of the first WHO definition of MI but, due to its lack of specificity, it no longer has a front line clinical role in the diagnosis of MI (29-31).

1.2.4 Creatine kinase MB

The observation that cardiac muscle has much higher levels of CK-MB (25-30%) compared with skeletal muscle (1%) and the development of electrophoresis methods resulted in marked improvements in cardiac specificity compared with CK (29, 30, 40). As a result, CK-MB rapidly became the standard biomarker for the detection of MI and played a key role in the revolution of care for MI in the 1970s and 1980s (30, 49). Initially, however, the measurements were relatively insensitive with a limit of detection that was later shown to be above the upper limit of the normal range (30, 49). The development of the mass assay for CK-MB resulted in improved sensitivity and specificity (49). The added value of measuring this isoenzyme increased the sensitivity for the diagnosis of an MI from around 70% with CK to close to 100% with CK-MB (25, 40).

Despite this advance, CK-MB was associated with up to 30% false positive rate in patients with renal failure, possibly due to skeletal muscle injury (50, 51). CK-MB elevation has also been demonstrated in athletes undergoing vigorous exercise (52). CK-MB was also not totally cardiospecific and was seen in a range of other conditions including surgery, trauma, asthma, pulmonary embolism, hypothyroidism and muscle disease (30, 49). Furthermore, in clinical practice CK-MB was associated with a small (2%) but important rate of patients with an MI being inappropriately discharged from the emergency department (53, 54). These issues, combined with some analytical challenges, lead to doubt about the validity of the test in clinical practice (49). Furthermore, there was no difference in myocardial infarction or death between patients admitted to hospital with acute ischaemic chest pain with and without CK-MB rises over a mean of nearly 28 months follow up (55). The size of the CK-MB rise has been demonstrated to be closely related to the infarct size (56). Thus, the stage was set for the development of a more specific diagnostic test with even greater levels of sensitivity…

The advent of more sensitive biomarkers and concerns around the effect of reperfusion on the kinetics and magnitude of CK-MB release have meant that there is no current clinical role for CK-MB and these assays have therefore been withdrawn from clinical use (49).

1.2.5 Troponin

The ongoing need for cardiac specificity resulted in extensive research into candidate biomarkers for AMI, which yielded cardiac troponin (cTn), a cardiac specific protein. (30). It took a further ten years before the diagnostic potential of cTn was demonstrated and validated (30, 57).

Troponin is a protein that regulates the contraction of striated muscle (which includes both skeletal and cardiac muscle) and is composed of three sub-units; I, T and C (58-61). The force generated by

striated muscle results from the interaction between actin (the thin filament) and myosin (the thick filament) (60). The troponin complex is bound to tropomysin by troponin T which attaches it to actin (58-60). Troponin I acts by binding and inhibiting interactions between actin and myosin (58). Troponin C has a binding site for ionised calcium which leads to a change in the conformation of the troponin protein resulting in disruption of the troponin I sub-unit (58-60). This causes the removal of tropomysin from actin and hence allows binding between actin and myosin, resulting in muscle contraction (58-60). Despite troponin being a key component of striated muscle, including skeletal muscle, troponin T and troponin I are encoded by different genes and, as a result, are expressed in different forms in various muscle types: in particular, there are isoforms specific to the myocardium (58, 61). Troponin C has two isoforms but neither are cardiospecific and, as such, no assays have been developed for this (58, 62). Isoforms of cTnI have never been detected in normal or diseased skeletal muscle (61). By contrast, isoforms of cTnT have been found in patients with muscle disease (for example polymyositis and Duchene muscular dystrophy) (61, 63). Importantly, the second generation assays did not detect the isoforms of cTnT expressed in diseased skeletal muscle (64).

Whilst the introduction of the original cTn assays was a major advance, these had an important limitation: the sensitivity to exclude MI within the first few hours was poor, which meant that further samples were needed at 10-12 hours to reach adequate diagnostic levels of sensitivity and specificity (11, 12, 65). This limitation not only resulted in potential delays in making the correct diagnosis but also had significant time and resource implications for hospital admission services.

These studies and the development of less time consuming assays resulted in a rapid, cardiospecific test of MI and led to the incorporation of cTn into the diagnostic algorithm for MI recommended by the European Society of Cardiology (ESC) and the American Heart Association (AHA) (59). Furthermore, the development of high sensitivity assays, which are able to detect cTn at much lower levels, has further refined the diagnostic pathway and, hence, has been incorporated into the latest versions of both the ESC and AHA guidelines (11, 12, 16, 66-68).

1.2.5.1 What is a high sensitivity assay?

The 'high sensitivity' label does not refer to a different form of cTn but reflects each assay's individual performance characteristics. There were initially no clearly defined criteria to classify whether a cTn assay was high sensitivity (66, 69). It has been suggested that in order to be classed as high sensitivity two criteria should be met: firstly, that the coefficient of variation (CV) at the 99th percentile should be less than 10%; secondly, that the assay should be able to detect

concentrations above the assay's limit of detection in at least 50% (ideally >95%) of healthy individuals (66). The initial validation study for hs-cTnT demonstrated that in 80% of healthy individuals the hs-cTnT level was above the limit of detection (70). However, further larger studies demonstrated that hs-cTnT was only detectable in around a quarter of healthy individuals (71). This observation highlights the challenges in classifying an assay as "high sensitivity" because the ability to detect low concentrations will depend on the population being studied. Furthermore, despite initially being classed as "high sensitivity" assays, the early iterations would fail to fulfil both of the above criteria (66). Modern assays are now able to detect hs-cTn levels in over half of the general population, with some able to detect levels in all of the general population (69). These assays now show excellent diagnostic performance, in terms of exclusion of an MI within a few hours of admission, with reported areas under the receiver-operator curve (AUC) of greater than 0.9 and up to 0.96 (10-12). Thus, early exclusion of AMI is a robust and well validated strength of the use of this assay. Much more contentious is its use to rule in AMI: a topic frequently misunderstood in frontline clinical practice.

1.2.5.2 Analytical definitions relating to hs-cTn

Table 1 explains some of the important analytical definitions relating to hs-cTn assays. The key feature in the interpretation of hs-cTn results is the upper limit of normal (ULN). This is based upon the 99th percentile for a reference population and, given its importance, will be discussed in more detail later. The CV is a measure of the imprecision of an assay (72): specifically, it is a measure of the assay variability for a certain concentration and is defined as the standard deviation divided by the mean (73). It is also of key importance when considering the merits of an assay. The terms limit of blank (LoB), limit of detection (LoD) and limit of quantification (LoQ) are used to describe the lowest levels that an assay can detect, Table 1 summarises these (74).

Function	Definition
Upper limit of normal (ULN)	This is the highest value that would be expected to be found in healthy individuals and is defined as the 99th percentile for the reference population
Coefficient of variation (CV)	A measure of imprecision which is defined by the standard deviation divided by the mean
Limit of Blank (LoB)	Highest value that could be expected upon analysis of the calibrator (which contains no sample i.e. hs-cTn)
Limit of Detection (LoD)	The lowest concentration that is reliably distinguished from the limit of blank
Limit of Quantification (LoQ)	This is the lowest concentration for which the CV is ≤20%

Table 1: Analytical definitions relating to cTn assays

1.2.5.3 What is the upper limit of normal?

Given that a rise in hs-cTn above the ULN is integral to the Fourth Universal Definition of MI, it is important to ascertain the appropriate ULN for the test (16). The level taken to be the ULN informs the clinical management of patients according to whether they are labelled as having AMI, but is also a key factor for studies using a diagnosis of MI as an outcome (75). This ULN is usually derived from the 99th percentile seen in an apparently healthy group of individuals enrolled into studies by the manufacturer of the assay (75). Despite the importance of the ULN, the selection of a "healthy" reference population has varied, with some studies using simple health questionnaires whilst others have used clinical examination, serum chemistry and echocardiography to define a group as healthy (75).

1.2.5.3.1 Sex differences in the 99th percentile

The introduction of the high sensitivity assays has highlighted that men have a higher 99th percentile than women (76-78). This raises the question: Is it therefore appropriate to have different ULN levels for men and women and does this observation have clinical relevance? Importantly there are frequent data demonstrating that women who present with AMI are (a) less likely to be given an accurate diagnosis and receive guideline-recommended therapies and (b) have worse in-hospital outcomes despite having less high-risk lesions on coronary angiography (79-83). This observation is

likely to have a multifactorial explanation, but it has been suggested that part of this may relate to the observation that women are less likely to have increased cardiac biomarkers than men (81, 84).

There has therefore been interest in whether using a gender specific ULN can improve this disparity. Shah *et al* demonstrated that by using a gender specific ULN the number of women diagnosed with an MI increased by 39% whilst there was a reduction of 8% in men (83). Interestingly, the group of women that were only identified with the gender specific hs-cTn limit were found to have similar risk of death or recurrent MI when compared to those women with hs-cTn concentrations above the generic ULN (83). Furthermore, Cullen *et al*, in a study of 2841 patients, also demonstrated that the use of a gender specific ULN reclassified a small number of females (25 patients) as having MI and a similar number of males (29 patients) as not having MI (85). Importantly, this reclassification improved the identification of women at risk for one year adverse events, but not amongst men (85). These studies highlight the potential benefit for female patients of a gender specific ULN. However, and by contrast, Gimenez *et al* demonstrated that the use of a gender specific ULN only resulted in a small number (3 patients from a cohort of 2734) of patients being reclassified and, whilst there was an increase in sensitivity for women (from 91.3% to 98.5%) there was a slight decrease in sensitivity for men (from 90.7% to 88.4%) (86). However, the use of gender specific thresholds resulted in a markedly reduced specificity in women (from 79.2% to 62.0%) (86). In addition, there was minimal added prognostic value from the reclassification (86). Moehring *et al* also showed that the use of a gender specific ULN would reclassify only two women as having had MI in a cohort of 2286 patients (87). In light of these data, the Fourth Universal Definition of an MI does not recommend the use of a gender specific ULN for hs-cTn (16).

1.2.5.3.2 Age differences in the 99th percentile

In both men and women, age has been shown to be associated with increasing hs-cTn levels (77, 88). In a community based study of 5461 patients between 66 and 96 years of age, 42.5% had an hs-cTn above the ULN, with age being most closely correlated with concentrations above the ULN (89). Furthermore, in 593 healthy subjects in the community, Olivieri *et al* found a marked difference in the 99th percentile for those over the age of 75 years compared with those younger than this (99th percentile <75 years = 16ng/L, 99th percentile ≥75 = 71ng/L) (90). This study highlights that there is a potentially large population of apparently healthy older patients in whom baseline hs-cTn concentrations are above the ULN, which has important implications for clinicians when interpreting hs-cTn results in hospital patients. It should be noted, however, that whilst this study included patients in the community, it is unclear as to whether these patients had coexisting cardiovascular disease and whether it was stable.

1.2.5.3.3 Effect of comorbidity on the 99th percentile

In a sub-study of the CORONA trial of elderly patients with stable heart failure, just under half (49.4%) had a hs-cTn level above the ULN (91). Interestingly, despite these patients having heart failure as well as being elderly the reported rate of hs-cTn levels above the 99th percentile is similar to those discussed above in the elderly without heart failure. It is, however, difficult to compare these groups due to differences in the assays used and potential differences in the selection criteria.

Given that the majority of cTn is excreted by the kidney, it is perhaps unsurprising that in both patients admitted to hospital and healthy populations there is a clear association between hs-cTn level and the creatinine clearance, although this finding is not universal (88, 92-95). Furthermore, in apparently healthy patients, a more detailed assessment of a number of clinical factors (including history, clinical criteria, examination, echocardiography and laboratory results) has been shown to be associated with an individual's hs-cTn level (88, 94, 95). Data presented by Koerbin *et al* highlight the impact that taking into consideration patient demographics and clinical criteria can have on the 99th percentile: in this study patients were excluded from the healthy cohort if here was evidence of cardiovascular disease on clinical assessment, echocardiography and biochemical analysis (including NT-proBNP) (88). This resulted in over 50% of patients being excluded from the previously labelled "healthy" population and, as a result, the 99th percentile for males under the age of 75 years fell from 22.9ng/L to 10.3ng/L (88). Furthermore, the value of the 99th percentile was seen to decrease in all age groups and, whilst these decreases were small, they are potentially clinically relevant (88).

These data raise the issue of how to define the 99th percentile given that this clearly varies according to age and comorbidity status. This poses challenges for the manufacturers when considering who to include in their studies to define the 99th percentile and how thorough the assessment needs to be in order to define the "healthy" population as being truly healthy. Of critical importance is how the manufacturer's provided 99th centile should be applied to the hospital population, and, in particular, how this should/can be used to diagnose AMI.

1.3 Types of myocardial infarction

The first collaboration to produce a definition of MI was led by the WHO in the 1950s, but this was mainly intended for epidemiological purposes (16, 96). The development of biomarkers lead the

ESC and American College of Cardiology (ACC) to develop a clinical definition of MI (16). Further iterations of this definition included more contributors including the AHA and the World Heart Federation (WHF) with support from the WHO (16). The Fourth Universal definition of MI, published in 2018, further defines five types of MI (see Table 2) and myocardial injury.

MI is defined as myocardial cell death due to prolonged ischaemia, with the first microscopic signs occurring within 10 minutes of the start of ischaemia (16). With ongoing ischaemia, a timely intervention to reverse this using a reperfusion therapy, whether that be percutaneous coronary intervention (PCI) or thrombolysis, can reduce the injury to the myocardium (97, 98).

Type of MI	**Description**
Type 1: Spontaneous	Spontaneous MI as a result of intraluminal thrombus as a complicating consequence of either atherosclerotic disease or dissection
Type 2: Secondary to ischaemic imbalance	An imbalance between myocardial oxygen supply and demand that is not precipitated by atherosclerotic coronary artery disease (but can occur in the presence of stable coronary artery disease)
Type 3: Resulting in death before biomarker values	Death occurring before biomarkers can be taken where the clinical presentation and ECG changes support a diagnosis of MI
Type 4a: Related to percutaneous coronary intervention	A rise of cTn greater than five times the upper limit of normal within 48 hours of PCI in association with any of: symptoms of myocardial ischaemia; new ECG changes; angiographic loss of a coronary artery or persistent slow/no-flow; new regional wall motion abnormality demonstrated on imaging.
Type 4b: Related to stent thrombosis	Stent thrombosis detected at either angiography or autopsy in patients presenting with signs or symptoms of myocardial ischaemia
Type 4c: Restenosis following angioplasty	MI that occurs as a result of either in-stent restenosis or restenosis following balloon angioplasty
Type 5: Related to coronary artery bypass grafting (CABG)	Within 48 hours of CABG, a biomarker rise ten time the upper limit of normal in association with any of: new pathological Q waves or LBBB; new graft or coronary artery occlusion; new regional wall motion abnormality demonstrated on imaging.

Table 2: Classification of myocardial infarction

1.3.1 Type 1 myocardial infarction

Type 1 MI (T1MI) is a spontaneous event, either as a result of atherosclerotic disease which results in a thrombotic vessel obstruction and subsequent myocardial necrosis (16). This is the classical type of acute MI labelled as ST- or non-ST-elevation MI. The search for T1MI is the commonest reason that a hs-cTn is requested in hospital practice. The detection of a rise or fall of cTn with at least one level above the 99th percentile is central to the diagnosis of a T1MI (16). In addition to this, (a point that is sometimes forgotten/misunderstood) at least one of the following criteria must also be met: symptoms of acute myocardial ischaemia, new ischaemic ECG changes, development of new pathological Q waves, evidence of new loss of myocardium consistent with an ischaemic aetiology seen on an imaging modality or coronary thrombus identified at angiography or autopsy (16).

There has been some discussion recently regarding the classification of those patients with a primary coronary event not related to acute atherosclerotic disruption as the cause of their presentation. These patients include those with spontaneous coronary artery dissection, coronary artery embolism and coronary vasospasm or microvascular dysfunction, all of whom are currently classed as a T2MI (99). This minor change has been suggested because these presentations result from an acute spontaneous coronary obstructive process and their initial management therefore has more in common with T1MI than T2MI (99). These conditions are relatively uncommon and in a recently published study evaluating the impact of these suggested changes to the Universal Definition of MI this classification resulted in 17 (6.8%) patients being reclassified from T2MI to T1MI (100).

The commonest aim when hs-cTn is used in front line clinical practice is to rule out or detect T1MI because the evidence base clearly demonstrates that these patients benefit prognostically from a fast track combination of pharmacological and invasive interventions (8). However, the assumption that a hs-cTn result above the ULN in an inpatient makes an automatic diagnosis of T1MI is commonplace and flawed, as well as being potentially dangerous. I will discuss this further.

1.3.2 Type 2 myocardial infarction and myocardial injury

A T2MI is defined as MI resulting from the mismatch between oxygen supply and demand which results in cTn release (16). The criteria for the diagnosis of a T2MI require a rise and fall of cTn with at least one result above the 99th percentile with evidence of imbalance between myocardial oxygen supply and demand along with at least one of these other features: symptoms of myocardial

ischaemia, new ECG changes, development of pathological Q waves or myocardial loss on imaging (16). Specifically, in order for a diagnosis of T2MI, the infarct must not be caused by acute coronary thrombosis as a result of atherosclerotic coronary artery disease. Further, if there is no clinical evidence of myocardial ischaemia and the only feature is a raised cTn then this should be classed as a myocardial injury, which can either be acute, as demonstrated by the rise and fall of cTn levels, or chronic if the cTn level is stable (16, 101). Repeat testing is therefore helpful to identify those patients in whom the cTn is chronically elevated due to continuous myocardial injury as opposed to those who have had an acute event (102). The use of the term myocardial injury may also help to reduce the inappropriate diagnosis of a T1MI (103).

The definition for the diagnosis of T2MI means that these patients represent a markedly heterogeneous population (102). This definition also highlights two issues with the commonly employed clinical algorithms for the diagnosis of a T1MI. Firstly, that an elevated cTn, or even a rise in cTn, indicates a T1MI by default is clearly flawed: both T1 and T2 MIs, as well as myocardial injury, are characterised in this way (8, 9, 13, 16, 104). Secondly, that the presence of chest pain does not inevitably mean that this is a T1MI, given that myocardial ischaemia precipitated by a physiological cause for an oxygen supply/demand mismatch can also cause chest pain (16). Importantly, the absence of chest pain does not exclude a T1MI as chest pain does not have to be present in the Fourth definition of an MI (16)

Furthermore, the distinction between a T1 and T2 MI is complicated by the observation that patients with a T2MI can have coronary artery disease, whether that be stable atherosclerotic disease, dissection or coronary artery spasm (16). In fact, coronary artery disease is a common finding in patients with T2MI that subsequently have coronary angiography (105-108). The diagnostic challenge in delineating patients with a T2MI from those with a T1MI is further complicated by the observation that ST-elevation is reported in between 3% and 24% of patients presenting with a T2MI (109). This variability in reported rates of ST elevation in T2MI reflects the wide range of mechanisms of a T2MI (109). To complicate this diagnostic dilemma further, patients, particularly those who are critically unwell, are at a higher risk of coronary thrombosis due to the imbalance of coagulation mechanisms and also the high prevalence of endothelial dysfunction related to these conditions (110). These factors make the distinction between T1 and T2MI particularly challenging in critical care, where the clinical picture is often unclear, particularly in the context of sepsis, other comorbidities, sedation use, inotrope requirement etc. However, of some help to the clinician is the observation that the higher the cTn concentration the more likely that a T1MI has occurred, but there is no definitive cut off level beyond which a diagnosis is certain and therefore even a very high cTn result can only be accurately interpreted in the light of the clinical context (8).

The previously suggested revision to the universal definition of MI highlights the difference between patients with T2MI who have no underlying CAD and those with T2MI who do have underlying CAD (99). They suggest that patients with fixed coronary artery disease be classed as T2aMI and those without coronary artery disease as T2bMI because this will create more homogenous groups when further research is undertaken and is likely to be of relevance when considering potential treatment strategies (99).

1.3.2.1 Incidence of T2MI and myocardial injury

There is a wide range in the reported incidence of T2MI which likely stems from both the different patient cohorts evaluated and the broad diagnostic criteria (16). Whilst T2MI has been defined in guidelines, the exact clinical interpretation of this definition can be challenging, and the reported incidence in the literature ranges between 2% and 64% depending on the inclusion criteria used and the population sampled (92, 111-114). The incidence is likely to increase because, until the end of 2017, the International Classification of Diseases did not have a code for a T2MI (109). In addition, given the aging population with increasing comorbidity, as well as the ever-increasing sensitivity of cTn assays, it is probable that the frequency of T2MI will rise further. Finally, in clinical practice, the vast majority of patients with a T2MI are not diagnosed as such, adding to the difficulty getting an accurate picture of the frequency of this condition (18, 113). More recently, in patients in whom a hs-cTn was taken for clinical reasons, the introduction of hs-cTn assays increased the diagnosis of MI and myocardial injury, but the biggest increase was in chronic myocardial injury (T1MI 11% increase, T2MI 22% increase, acute myocardial injury 36% increase and chronic myocardial injury 43% increase) (115). This, however, is still likely to be an underestimate of the true incidence because this study only included patients in whom the test was requested for clinical reasons.

A study of 231 patients with T2MI went on to reclassify these patients as either T2aMI or T2bMI and found a similar incidence of both (45.0% and 55.0% respectively) (100).

There are two main reasons why the true frequency of T2MI and myocardial injury is likely to be underestimated. Firstly, given that the majority of studies have only included patients in whom the test was clinically requested, there will be a group of patients who have suffered T2MI or myocardial injury as a result of a presentation for which cTn testing is not routinely indicated, such as sepsis or anaemia. Secondly, many of these studies were performed with standard cTn assays which, by their nature, are less sensitive for either myocardial injury or T2MI.

1.3.2.2 Causes of T2MI and myocardial injury

cTn elevation in association with the diagnosis of T2MI/myocardial injury occurs in a wide range of clinical conditions (116). Table 3 lists some of the potential causes of cTn elevation and divides them into direct cardiac causes and indirect causes. The range of conditions and differing mechanisms behind the cTn elevation is broad and consequently studies reporting T2MI have heterogeneous populations. For example, a patient with sepsis may have cTn elevation as a result of the haemodynamic consequences of the condition causing an oxygen supply/demand mismatch, whereas patients with chest trauma might have cTn elevation as a result of direct myocardial injury rather than a systemic mechanism (116). In addition, it has been suggested that some of the patients with sepsis that have a cTn elevation may have this as a result of the bacteraemia via direct (myocarditis) or indirect (free radical formation) mechanisms rather than the haemodynamic effects of sepsis (117, 118). These observations highlight the challenges that researchers face in attempting to evaluate the natural history of patients with cTn concentrations above the ULN outside the context of a T1MI.

Cardiac causes	Non-cardiac causes
Plaque rupture and intraluminal coronary artery thrombus formation	Sepsis
Coronary vasculitis	Extreme exertion
Severe valvular heart disease	Pulmonary embolism
Myocarditis	Renal failure
Acute or chronic heart failure	Severe acute neurological disease (including acute stroke and sub-arachnoid haemorrhage)
Stress induced (Takotsubo) cardiomyopathy	Acute respiratory failure
Hypertrophic cardiomyopathy	Severe anaemia
Infiltrative cardiomyopathy	Severe burns (affecting >30% of body surface area)
Tachy/brady arrhythmias	Cardio-toxic agents
Frequent defibrillator shocks	Critical illness / shock
Aortic dissection	Pulmonary hypertension
Cardiac contusion	Chronic obstructive pulmonary disease
Post cardiac surgery	Hypertension
Post PCI	Lab error/miss handling of specimen
Post ablation (radiofrequency or cryo-ablation)	

Table 3: Cardiac and non-cardiac causes of cTn elevation outside acute coronary syndromes

1.3.2.3 Prognosis of T2MI and myocardial injury

The increasing sensitivity of cTn assays has led to a gradual increase in clinical diagnoses of T2MI, but does this observation have clinical relevance? In this regard, the SWEDEHEART registry in 2011 compared the outcomes of all 20,138 patients that were diagnosed with an MI of any sort. This study demonstrated a significantly higher crude one year mortality amongst the T2MI patients compared with the T1MI patients (24.7% versus 13.5% respectively ($p<0.001$)) (119). However, the patients with T2MI were older, had more co-morbidities, worse renal function and were more likely to have anaemia than the T1MI group (119). This observation is perhaps unsurprising as all of these factors would reduce the threshold at which an oxygen supply/demand mismatch might occur.

Interestingly, once all of these factors were adjusted for, the hazard ratio (HR) for one year mortality for T2MI patients was no different to those with T1MI (HR 1.03, 95% CI 0.86-1.23) (119). Whilst these data suggest that there is no mortality difference between patients with T1 and T2MI, it is important to note that only 7.1% of the cohort were classified as a T2MI compared with 88.5% classified as a T1MI. As already discussed, the frequency of a T2MI is probably at least as high as a T1MI and therefore it would suggest that a significant group of patients that suffered a T2MI were either not captured in this cohort or were misdiagnosed. This is not surprising given that this cohort was from 2011 when cTn assays were less sensitive and the awareness of T2MI was lower. In a study of 5,460 patients who had a cTn concentration above the 99th percentile, the frequency of T2MI became similar to that of T1MI, not because the frequency of T2MI increased but because the frequency of T1MI decreased. However, the last year reported in this study was 2012 and it only included patients in whom the standard sensitivity cTn was performed for clinical reasons and hence the actual frequency may now be higher (114). At a median follow up of 5.5 years, the multivariate hazard for mortality for patients with T2MI was 1.4 (95% CI 1.2 – 1.6) compared with patients suffering T1MI (114). Interestingly, patients in whom arrythmia was the precipitating factor for T2MI have more favourable outcomes than those whose precipitating factor was hypoxia, hypotension or anaemia. Furthermore those patients who had more than one precipitant for T2MI had significantly worse survival with a hazard of mortality of 1.39 (95% CI 1.19 – 1.61) compared with those in whom only a single precipitant was present (114).

Two studies in 2014 reviewed the outcomes of all patients that had a cTn performed as part of their routine care on admission to hospital. Both of these studies found a much higher proportion of T1MI than T2MI (360 patients versus 119 patients and 2691 versus 127 patients) (106, 120). Further, both studies demonstrated significantly worse outcomes in patients that were diagnosed with a T2MI, with Saaby *et al* reporting that the mortality in T2MI patients reached 48.7% compared with 25.6% in patients with T1MI after two years (106, 120).

Some studies included myocardial injury, as defined by the Fourth Universal Definition, in their classification of causes of an elevated cTn. Patients classified as having myocardial injury were older and were more comorbid than the T1MI patients (101, 121, 122). Patients with T2MI or myocardial injury in all three of these studies had significantly worse long term outcomes compared with those patients with a T1MI. For example, in one study mortality at a median of 3.2 years follow up was 59% of those with a myocardial injury versus 39% in patients with MI and 23% in patients with cTn concentrations below the 99th percentile (101, 121, 122). Of further interest, Cediel *et al* found that whilst patients with myocardial injury or T2MI had a worse prognosis, they did in fact have lower future admission rates for acute coronary syndrome (ACS) than T1MI patients (HR 0.11 (95% CI 0.04 – 0.31)(121). Importantly, this study appropriately considered mortality to be a competing

event for presentation with ACS and hence this was accounted for using a competing risk model. This suggests that myocardial injury and T2MI are markers of general health and not necessarily of cardiovascular health.

Similar themes are seen in the work by Chapman *et al*, with 55.2% of the 2122 patients with elevated cTn levels diagnosed with a T1MI by the study team, 20.2% with a T2MI and 24.6% with myocardial injury (107). This study found that five year mortality was 36.7% for T1MI, versus 62.5% for both T2MI and myocardial injury (107). It is not surprising that the prognosis in patients with T2MI or myocardial injury is poor given that these patients tend to be older with greater comorbidity (123). However, this study also demonstrated that the majority of excess deaths in the T2MI and myocardial injury group were as a result of non-cardiovascular causes, and that the cardiovascular event rates were similar between the groups (107). These observations further suggest that myocardial injury and T2MI are potentially markers of general, rather than cardiovascular, health.

A recently published analysis of the HIGH-STEACS trial found that of the 9115 patients in whom the hs-cTnI was above the 99th percentile and a final diagnosis was known, T1MI was the most common cause (55%), followed by myocardial injury (32%) and T2MI (12%) (115). The composite of MI or cardiovascular death occurred in similar frequency across the types of MI and myocardial injury (T1MI 17%, T2MI 14%, acute myocardial injury 16%, chronic myocardial injury 16%)(115). The mortality from non-cardiovascular causes was, however, highest in patients with acute myocardial injury (HR 2.65 (95% CI 2.33 – 3.01)), followed by T2MI and chronic myocardial injury (HR 1.72 (95%CI 1.44 – 2.06) and HR 2.06 (95% CI 1.77 – 2.40) respectively) when compared with those patients with a hs-cTn below the 99th percentile (115). Interestingly, the mortality from non-cardiovascular causes was reduced in patients suffering from T1MI (HR 0.83 (95% CI 0.72 – 0.96)) (115). This suggests that the hs-cTn elevation associated with T2MI and myocardial injury may be more representative of overall health than in T1MI.

Singh *et al* reviewed the outcomes of 3,829 patients under the age of fifty who presented with a cTn above the 99th percentile. Whilst the majority had T1MI (55%), T2MI and myocardial injury were also frequently seen (32% and 13% respectively) (124). The mortality (over a median of 10.2 years) was highest in the patients with myocardial injury (45.6%), followed by T2MI (34.2%) and T1MI (12%) (124). On an adjusted model, these young patients with T2MI were at an increased hazard of both all cause and cardiovascular mortality compared with T1MI patients (HR 1.8 (95% CI 1.2 – 2.7) and HR2.7 (95% CI 1.4 – 5.1) respectively) (124).

The Schoepfer *et al* paper on the outcomes of patients with the proposed subclassifications of T2MI sheds some further light on the clinical relevance of the bystander coronary artery disease in

patients with T2MI. Patients with T2aMI (those with stable coronary artery disease) had higher two year all cause mortality (25.0% (95%CI 17.7 – 34.1%) compared with those with T2bMI (7.9% (95% CI 4.3 – 13.9%, P<0.001) (100). Whilst further work is required to support the findings of this relatively small study it does suggest that these groups should be considered separately in diagnostic classifications and that there could potentially be different treatment strategies given the different underlying aetiologies.

1.3.2.4 Management of T2MI and myocardial injury

Despite the poor prognosis of patients with a T2MI or myocardial injury there is little evidence to guide therapy in these patients. Furthermore, the data presented so far suggest that the excess mortality seen in these patients is not necessarily cardiovascular in origin. It is therefore unsurprising that patients with a T2MI or myocardial injury are less likely to be taking cardioprotective agents (antiplatelets, beta-blockers, statins) (107).

The CASABLANCA study enrolled 1251 patients undergoing angiography (coronary or peripheral), with or without intervention, and took cTn samples before and afterwards to assess for evidence of T2MI. Similar to previous work the study found that a T2MI was associated with increasing age and comorbidity (125). Interestingly, however, patients with a T2MI were significantly more likely to be taking cardioprotective medications including beta-blockers, statins and angiotensin receptor blockers or angiotensin converting enzyme inhibitors (125). At this stage further studies are needed to assess the role of cardioprotective agents in preventing T2MI or myocardial injury and to see whether they offer prognostic benefit following the event.

The MANAGE trial was designed to specifically assess whether dabigatran, a direct oral anticoagulant (DOAC) used in the anticoagulation of atrial fibrillation, would alter the natural history of patients with myocardial injury after non-cardiac surgery. The study randomised 1754 patients who had been identified as having had myocardial injury to either dabigatran 110mg BD or placebo. The primary endpoint (a composite of vascular mortality, non-fatal T1MI, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation or symptomatic venous thromboembolism) occurred in 15% of the placebo group compared with 11% of the dabigatran group (HR 0.72 (0.55-0.93) (126). Whilst these data are encouraging, the study has a number of potential flaws. Firstly, different centres used different cTn assays, some high sensitivity and others not. The centres were encouraged to check cTn post operatively as part of the routine standard of care, but this does not seem to have been consistent and patients could be included if their cTn was elevated within 35 days of the event. Whilst patients with other causes of cTn elevation were excluded, there is no information as to how thorough this assessment was. Furthermore, patients did not have a cTn performed at baseline prior to the surgery and, hence, it is probable that some

of these patients had chronic myocardial injury rather than one precipitated by the surgery. Perhaps the most important feature of the study that limits its applicability to clinical practice is the fact that in both arms the rate of discontinuation was very high (46% in the dabigatran arm and 43% in the placebo arm) (126). Furthermore, secondary analysis of the individual components of the primary composite endpoint demonstrated that there was a significant reduction in non-haemorrhagic stroke in the dabigatran arm, albeit with a wide confidence interval as a result of the small numbers of events (HR 0.20, 95% CI 0.04-0.90)(126). Stroke risk reduction using dabigatran for AF is well documented and therefore the observed stroke risk reduction in MANAGE is perhaps unsurprising given that this group of patients are at risk of AF as a result of their comorbidities (127).

The lack of effective therapies to alter the future cardiovascular risk in patients with either T2MI or myocardial injury are demonstrated by a secondary analysis of the HIGH-STEACS study which showed that despite the increased diagnosis of these conditions, there was no change in investigation, treatment or clinical outcomes (115).

1.3.3 Type 3, 4 & 5 myocardial infarctions

CTn, as already discussed, is key to the diagnosis of MI. Some patients, however, will present with symptoms and ECG findings consistent with an acute MI but may not survive long enough to have cardiac biomarkers taken (16). In this case they are classed as a T3MI, but, importantly, if autopsy findings demonstrate fresh/recent thrombus within the infarct artery then the T3MI should be reclassified as a T1MI (16). A T3MI is relatively uncommon, with between 3% and 4% of all MIs classified this way (128). In the Universal Definition, type four and five MIs result from events following PCI or coronary artery bypass grafting (CABG) respectively (16). Both of these will be discussed later in this thesis, but it is important to note that the cTn thresholds for the diagnosis of T4 and T5MIs are 5 and 10 times ULN, respectively (16). The Society for Cardiovascular Angiography and Interventions (SCAI) have a different threshold for the diagnosis of periprocedural MI, with a requirement for the cTn to rise more than seventy times the ULN, regardless of whether it is following PCI or CABG (129). The SCAI committee arrived at this threshold by consensus based on the observation that studies have not demonstrated a specific cTn beyond which there were worse clinical outcomes following either PCI or CABG. The committee therefore used the threshold seen using CK-MB studies and then factored in the difference between cTn values and CK-MB values to come up with 70 times the ULN (129). The difference between the SCAI definition and the Universal Definition clearly has important implications for patients and clinical investigators as it will markedly alter the frequency of MI following these procedures.

1.4 Troponin in the emergency department

1.4.1 High sensitivity troponin for the diagnosis of myocardial infarction

Whilst standard cTn (ScTn) assays required 10-12 hours in order to reach sufficient levels for diagnostic accuracy in clinical practice, high sensitivity assays demonstrate sufficient levels of accuracy within three hours. For example, hs-cTn assays have been shown to have excellent discriminative ability for AMI within a short timeframe with an AUC of 0.92-0.96 within three hours, compared with an AUC of 0.76 for ScTn assays within the same time frame (10-12, 68). In two studies of patients presenting with suspected ACS, reducing the ULN for a ScTn assay increased the rate of diagnosis of MI and identified a group of patients at substantially higher risk of future mortality than those who were still below this reduced ULN (7.4% 1.7% (at 12 months) and 16.4% versus 4.8% (at 30 months)) (130, 131). The identification of a cohort of patients at higher future risk by lowering the diagnostic threshold suggests that the introduction of hs-cTn assays may also identify a cohort of patients at higher risk of future events that may have been missed using ScTn assays. The introduction of these assays has resulted in improvements in the speed and cost efficiency of the patient pathway (8, 67, 132-136).

1.4.1.1 Clinical impact of the introduction of high sensitivity assays

Reichlin *et al* conducted a study to assess the impact of high sensitivity assays in clinical practice. Standard care, utilising ScTn assays, continued in 1142 patients presenting to ED with chest pain, whilst the research team also took hs-cTnT samples to compare the impact that the high sensitivity assays had on the final diagnosis. The introduction of hs-cTnT led to the diagnosis of a further 44 MIs (a relative increase of 22%), of which 35 were classed as T1MI and 9 as T2MI (137). The reclassified group of patients were more likely to be older, and have a history of coronary artery disease and coronary revascularisation than both the overall cohort and also those who were diagnosed with MI using the standard assay (137). Unsurprisingly, this was offset by a reduction in the number of patients diagnosed with unstable angina (29 less patients, relative reduction of 19%) (137). Further, there was also a marked increase in the number of patients diagnosed with a non-coronary cardiac cause for their myocardial injury (relative increase of 268%) (137). The total number of patients diagnosed with either AMI or unstable angina was similar when ScTn or hs-cTnT assays were used (364 vs. 349). Patients with a diagnosis of AMI or unstable angina are likely to be

treated in the same way and therefore, this study would raise uncertainty as to whether the introduction of the high sensitivity assays would have an impact on patient outcomes.

In terms of angiographic findings, there was no difference in the location or number of vessels involved when the patients diagnosed with MI using the ScTn assay were compared with the group that were reclassified as a result of the hs-cTn assay. However, patients with AMI diagnosed by high sensitivity assays alone were more likely to have subtotal occlusion (95-99% stenosis) and less likely to have chronic total occlusions compared with the patients originally diagnosed with AMI using the standard assay (69% vs. 35% and 8% vs. 41%) (137). It is therefore possible that the increased sensitivity of these assays leads to patients being picked up earlier in the trajectory of their coronary artery disease. Perhaps unsurprisingly the patients in whom a diagnosis of AMI was made on ScTn assays had the worst prognosis, because these infarcts were, by nature, larger than the ones detected by hs-cTn assays alone. However, the prognosis of the patients with MI only diagnosed using high sensitivity assays was significantly worse than those without an infarct (mortality at a mean 19+/-9months in: no MI – 4.8%; MI diagnosed by hs-cTnT alone – 16.4%; MI diagnosed using standard assays 23.9%) (137). This suggests that the introduction of high sensitivity assays may result in improved patient outcomes, given that the cohort with MI diagnosed only on high sensitivity assays would otherwise have been missed.

More recently, the High-STEACS study evaluated the implementation of high sensitivity assays in patients presenting to emergency departments with suspected acute coronary syndromes across 10 hospitals in Scotland (15). There was a six month validation phase, during which only the research team knew the hs-cTnI result. After this, five hospitals transitioned to hs-cTnI, whilst the other five waited a further 6 months before transitioning. The study enrolled 48,282 consecutive patients, in whom 21% (10,360 patients) had cTn (either ScTn or hs-cTn) above the ULN (15). Interestingly, the introduction of the hs-cTnI assay reclassified 17% as having AMI (1,771 patients) (15, 115). This clearly demonstrates the potential for high sensitivity assays to identify more patients that have had myocardial injury/infarction than the standard assays. These patients were older, twice as likely to be women (importantly, this study used a high sensitivity assay that has gender specific ULN, which, as previously discussed, has implications for the sensitivity and specificity of the assay across genders) and less likely to have evidence of myocardial ischaemia on the ECG. The groups otherwise had similar characteristics in terms of presentation, comorbidity, haemoglobin and renal function. However, only a third of the group that were diagnosed as a result of the hs-cTn assay had a final diagnosis of T1MI, compared with 60% of those identified by a standard assay. This highlights the “price” of the increased sensitivity for T1MI offered by the new assays: ie their reduced specificity for T1MI. The risk of cardiovascular mortality or myocardial infarction was similar across the patients in the validation (i.e. the clinicians were unaware of the

results) and the implementation (i.e. the clinicians were aware of the results) phases (15% vs. 12%, adjusted OR for implementation vs. validation phase 1.10 (95%CI 0.75-1.61 (15). This result suggests, perhaps surprisingly, that the current treatment of this group of patients that are only identified by high sensitivity assays is ineffective. This could be explained by the observation that the majority of the reclassified group did not have a T1MI and, as such, represent a heterogeneous group in whom there is no specific treatment that has as yet been demonstrated to improve outcomes, unlike the intensive pharmacological and invasive strategies that are offered, with considerable prognostic benefit, to T1MI patients (15).

Theoretically, based on these effects on sensitivity and specificity, the introduction of hs-cTn assays in routine clinical practice could either (a) increase admission rates as a result of the increased diagnosis of MI, or (b) decrease admission given the established ability (discussed below) to discharge patients who are hsTn negative early from ED. Bandstein *et al* specifically looked to assess the impact on admission rates and one year outcomes in 15,472 patients admitted to the emergency department with chest pain following the introduction of a high sensitivity assay. This study demonstrated that admissions for chest pain steadily decreased over the first four years of hs-cTnT use by 36% (138). The introduction of the high sensitivity assay also seemed to provide clinicians with more confidence to discharge patients, as evidenced by the observation that 92% of patients with a negative hs-cTnT level were discharged compared with 71% who were negative using the ScTn assay. Interestingly, during the course of the study the highest relative increase in discharges directly from the emergency department was in patients with an hs-cTnT level above the ULN, which doubled (15-32%) (138, 139). This suggests that clinicians in ED quickly adapt their clinical practice to consider the reduced specificity of the high sensitivity assays. Reassuringly, there was no increase in the cardiovascular death or MACE during the study but, curiously, there was an increase in the rate of non-cardiovascular death.

1.4.1.2 More rapid rule out with high sensitivity assays

Attempts have been made to further refine the investigation algorithm of patients presenting with chest pain to see if it is possible to risk stratify patients even faster than the current practice of three hours. To this end, Rubini Gimenez *et al* applied a one hour algorithm, whereby clinicians were able to categorise patients as (a) rule in MI, (b) rule out MI or (c) arrange further observation serial testing based on a one hour sample. The study demonstrated that this method provided an accurate rule in and out method for around 70% of patients presenting with suspected acute coronary syndromes (140). Reichlin *et al* found a similar result with a one hour algorithm, which was effective in ruling in or out MI in 77% of patients presenting with suspected acute coronary

syndromes (141). As a result of these data the ESC suggest that the 1 hour algorithm is an appropriate alternative to the 3 hour algorithm (142).

Rubini Gimenez *et al* went further still and assessed the negative predictive value of undetectable hs-cTn levels on admission across three assays in patients presenting with chest pain. They found negative predictive values (NPV) of between 98.8% - 100.0% (143). This is consistent with Boeddinghaus *et al*, who demonstrated that a very low hs-cTnI point of care test on arrival also provided excellent negative predictive value (100% (95% CI 99.4 – 100%) (144). These observations suggest that patients with undetectable hs-cTn levels on admission for chest pain can have acute MI robustly excluded. However, further work by Hoeller *et al* demonstrates that normal hs-cTn levels at admission should not be used as a single arbiter of MI because, in their study of 2072 patients, up to 23% of patients with a final diagnosis of T1MI (using the Universal Definition criteria) had normal hs-cTn levels initially which rose above the 99th percentile on repeat testing (145). A recent meta-analysis of 11,014 patients does raise doubt about the efficacy of a 0/1 hour algorithm as recommended by the ESC. This study showed that these algorithms can rule out MI in between 50 -55% of patients but that the sensitivity was not consistently high across all cohorts and may not be sufficiently robust if a 1% missed MI rate is desired (146).

As already discussed, when considering whether the diagnosis is a chronic versus acute myocardial injury, the change in hs-cTn can be helpful. This change in hs-cTn result has been evaluated in patients presenting to ED with chest pain. For example, Aldous *et al* performed serial hs-cTnT measurements in patients presenting to ED with chest pain. The team considered a change in troponin of ≥ 20% to be significant and found that, by using this cut off, specificity increased from 80.6% to 93.7% but at the cost of a reduction in sensitivity (90.9% to 71.8%) (68). This result has been widely replicated (135, 147-149). Whilst the increase in specificity is helpful, using a change in hs-cTn weighs against the original strength of the test; namely, its ability to exclude MI reliably. Thus, the change in hs-cTn concentration should not be used on its own in clinical practice.

The COMPASS MI investigators created a risk assessment tool which integrated hs-cTn concentration on presentation to ED, as well as its dynamic change during serial sampling between 45 and 120 mins after presentation (150). The study demonstrated that patients with both a low hs-cTn concentration on presentation and a small absolute change had a negative predictive value of 99.5% for MI and with a very low 30 day mortality (0.2%) (150). Furthermore, this study was able to classify over half of the patients (56.5%) as low risk (150). This suggests that algorithms based on the initial hs-cTn result and the relative change may provide diagnostic and prognostic improvements to the current pathway. However, it is important to consider that these algorithms are more complex than those in current use and as such this raises concerns about how this would

be utilised in clinical practice, particularly initially, some of the benefits maybe lost due to suboptimal integration with clinical practice.

1.4.2 Troponin outside the context of acute coronary syndromes in the emergency department

Patients presenting to the ED frequently have hs-cTn levels above the ULN, even in the absence of symptoms that would be suggestive of AMI (14, 151, 152). Furthermore, in patients managed in the resuscitation area, who could be assumed to be the sickest of the ED population, nearly 1 in 5 (19.5%) have an hs-cTn above the ULN (14). Whilst the Southampton CHARIOT study included consecutive patients presenting to ED, regardless of a clinical indication, the majority of the studies in this field have only included patients in whom a cTn was requested for clinical reasons. This is an important difference: a highly selected group in whom there was a high suspicion of MI is likely to have a different distribution of hs-cTn levels than a consecutive cohort included regardless of presentation. It would be expected that the explanation for an elevated hs-cTn in the consecutive group would more often be myocardial injury or T2MI than T1MI. The potential clinical value of the assay is also therefore likely to be different: in one group it is being used as a tool to rule out MI, whereas in the other, it is not yet clear what an elevated hs-cTn actually means, and, specifically, whether it represents a biomarker for cardiac risk.

Three studies have retrospectively evaluated the cause for ScTn elevation in patients presenting to ED in whom the tests were requested and the results known to the supervising clinician. Ilva *et al* reported that the majority (83%) of these patients had a T1MI, whilst 7.9% had a cardiac explanation and 9.1% had a non-cardiac explanation for the result (153). By contrast, Sandoval *et al* found a T1MI in only 6% of the population and T2MI in 17% (104). When interpreting the marked differences between these studies it is important to consider that Sandoval *et al* included patients with any level of ScTn (overall, 58.1% of their cohort had ScTn concentrations below the ULN) whereas Ilva *et al* only included those above the ULN. Further supportive evidence that T2MI is more frequent than T1MI comes from a smaller study of 249 ED patients with ScTn above the ULN, which found that 64% of these patients had T2MI (113). Even though the most frequently reported prevalence of T2MI in ED is nearly three times as common as T1MI, this is still likely to be an underestimate of the true frequency given that these studies only included patients in whom the suspected diagnosis was AMI and we know that T2MI and, also especially, myocardial injury, occur in a wide range of different presentations. Importantly, two of these studies demonstrated that T2MI had a significantly worse prognosis than T1MI, both in hospital and at 180 days (104, 153)

A number of studies have specifically evaluated hs-cTn levels in the elderly at presentation to hospital. Reiter *et al* found that among 1098 elderly patients (over 70 years of age) presenting to emergency medical services without a final diagnosis of MI, up to 51% had hs-cTn levels above the ULN (154). Similarly, Zhang *et al* found that 52% of 679 patients above the age of 65 that were admitted to elderly care services had an hs-cTn above the ULN (92). Furthermore, a larger study of 4118 consecutive patients admitted to the emergency department demonstrated an association between age and hs-cTn level in the absence of MI (93). This highlights the potential weakness of using hs-cTn as a method of excluding/diagnosing an MI in the elderly because the data presented reinforce the previously documented observation that hs-cTn is often raised in the elderly whether at baseline or in association with acute illness. Despite these data not covering the whole population presenting to ED, they do provide a useful picture of the frequency and impact of T2MI.

Part of the work by Shah *et al* included a cohort of 1054 unselected patients presenting to ED in whom a hs-cTnI test was added onto the biochemistry sample (152). In this cohort the clinicians were blinded to the hs-cTnI result unless it was clinically indicated, which occurred in 12.9% (152). The study found that a diagnosis of T2MI or myocardial injury was common (12.0%) in this unselected population (152). The study also included two additional cohorts of patients in whom testing was requested by the clinician and these demonstrated much higher rates of T1MI, T2MI or myocardial injury, as might be expected in a selected population (152). In the unselected population, the 30 day mortality was higher in patients with a diagnosis of either T2MI or myocardial injury (15.4% and 18.4% respectively) when compared with either T1MI or no myocardial injury (5.7% and 1.2% respectively) (152). It is this type of result that leads us to speculate about the potential role of hs-cTn as a biomarker for cardiovascular mortality.

A recently published study of over 250,000 patients in whom cTn (a mixture of ScTn and hs-cTn assays) was measured as part of routine clinical care across five centres in the UK again demonstrates that cTn concentrations steadily increase with increasing age, with 50% of those above the age of 90 having cTn concentrations above the ULN (155). The three year mortality hazard ratio for patients with cTn above the ULN was 3.2 (95% CI 3.1 – 3.2) and, notably, this effect was most profound in the youngest group of patients (HR 10.6 (95% CI 8.5 – 13.3) aged 18 – 29 years) and progressively declined with age (HR 1.5 (95% CI 1.4 – 1.6) in those over 90 years) (155). These data suggest that cTn above the ULN is a potentially effective method of identifying young patients with a disproportionate future risk relative to their peers, and demands further investigation. Of further interest, in patients who were admitted to hospital, there was an inverted "U"-shaped relationship between cTn concentration and mortality, with a peak hazard ratio of 2.4 (95% CI 2.3 – 2.4) at a concentration 70 times greater than the ULN, after which the hazard rapidly fell (155). The rate of clinically driven invasive angiography, within three months of the cTn result,

in patients without acute coronary syndromes was 6.4% and this steadily increased with increasing cTn concentrations (155). In addition, those patients without acute coronary syndromes who were managed with invasive coronary angiography had better outcomes than those managed non-invasively. Furthermore, the mortality risk of patients managed invasively didn't change with increasing cTn concentrations, whereas, by contrast, the mortality dramatically increased once the cTn was greater than 10 times the ULN in those managed medically (155). These data suggest that angiography may have a role in managing patients with elevated cTn concentrations outside the context of T1MI. It is important to note that these data are based on real world practice and therefore there will be a number of potential confounders which mean that these data should prompt further investigation rather than lead to a change in practice.

The utility of cTn has been evaluated in a number of specific conditions and this will be covered in detail later in the thesis.

1.5 Troponin use outside the acute coronary syndrome context

1.5.1 Utility of troponin in cardiac causes of elevation

Table 3 demonstrates the wide range of cardiovascular causes of cTn elevation. Outside the context of the intention to confirm or deny a diagnosis of T1MI, obtaining an alternative cardiovascular explanation for an elevated troponin result is important, but apart from avoiding inappropriate intensive therapy for Type 1 MI, the question is whether knowing the troponin level has any further clinical value or relevance?

1.5.1.1 Value of troponin in heart failure

Elevated concentrations of cTn are well described in heart failure (HF) and rarely related to a T1MI (156). CTn release in HF is frequently multifactorial but often results from supply/demand mismatch as well as non-coronary triggers such as increased wall tension, anaemia and the direct toxic effects of circulating neurohormones and toxins as a result of the inflammation that occurs in this condition (156). The observed rates of raised cTn concentrations in HF have markedly increased with the advent of the high sensitivity assays. For example, one of the earliest meta-analyses to compare early hs-cTn assays with ScTn assays found that hs-cTn assays were about twice as likely to be positive in patients with chronic HF (mean percentage of patients with chronic HF with hs-cTn above the ULN was 63.9% compared with 31.1%) (157). However, with the further development of hs-cTn

assays, nearly all patients with chronic HF will have levels above the manufacturer's ULN (158). Importantly, patients with a left ventricular ejection fraction (LVEF) below 40% have higher cTn levels (both ScTn and hs-cTn assays) than those with preserved LVEF (159).

These observations are consistent with the notion that hs-cTn might have a prognostic role in HF, and this has been borne out in the subsequent data: specifically, both ScTn and hs-cTn assays have been shown to be independently associated with both short- and medium-term mortality (157-160). For example, in a recent meta-analysis of 9289 patients, a hs-cTnT level above 18ng/L was found to be associated with a twofold hazard in all-cause mortality (HR2.28 (95% CI 2.03-2.57) (158). Importantly, this association was seen across multiple subgroups (gender, aetiology (ischaemic/non-ischaemic), renal failure) and also for cardiovascular death and hospitalisation (158). Despite these observations, the discriminative ability of hs-cTnT for mortality is modest with an AUC of 0.69. Whilst this offers some prognostic information, it falls far short of the discriminative ability of other risk scores for HF and, in particular, does not match the excellent discriminative ability of the assay in ACS (158, 159). The addition of hs-cTnT results to established prognostic models does, however, apparently offer some improvement to the discriminative ability (AUC 0.715 to 0.744 $p<0.001$) (158). A study of 1843 patients in the community with HF compared the prognostic utility of hs-cTnI and NT-proBNP. This study also demonstrated that elevated hs-cTnI concentrations were independently associated with mortality at a median of 10.7 years (161). Interestingly, the prognostic utility of hs-cTnI concentration was superior to that of NT-proBNP but the most benefit was derived when these two assays were evaluated together (161).

It is hardly surprising that patients presenting with acute decompensated HF (ADHF) are frequently found to have cTn levels above the ULN (over 50% with ScTn assays, rising to over 90% with hs-cTn assays) (162, 163). It is notable that in the group of patients with a clinical presentation of ADHF that have hs-cTnT concentrations below the ULN, there were no cardiovascular deaths within 180 days compared with 7.3% mortality in the group with an hs-cTnT above this threshold (163). This may prove to provide useful prognostic information to clinicians (163, 164).

1.5.1.2 Value of cTn in chronic coronary syndromes

There would be great clinical value in development of a biomarker that accurately predicts future acute events in patients with chronic coronary syndromes. Current stratification tools are relatively blunt, and this is compounded by the fact that the actual rate of cardiovascular mortality in this group is low (2.2% at 4.6 years follow up) (165). Given this low rate of mortality, it would be highly attractive to be able to further risk stratify these patients to allow high intensity therapy to be

targeted at the highest risk cohorts, and perhaps, just as enticingly, not to be targeted at the low risk patient at all. When ScTn assays have been measured in patients with chronic coronary syndromes, between 2% and 11% of patients have concentrations above the ULN (166-168). One of these studies demonstrated that there was also an association between increasing cTn levels and the incidence of cardiovascular death and heart failure, but no association was seen with the incidence of MI (167). Interestingly, the observed graded increase in risk was even seen in patients with ScTn concentrations below the ULN, thereby again calling into question the validity, in this context, of an artificial binary but off for such assays. (167). The addition of ScTn results into a predictive model did indeed increase the discriminative property of the model from 0.70 to 0.75 ($p<0.001$) (167). However, whilst this addition to the predictive model is highly statistically significant, its clinical relevance is less clear and, as yet, it has no implications for patient care. Another study followed cTn levels at six weeks, three months and six months after an NSTEMI and found that a cTn at six months above the lowest cut off (0.01µg/L using the Access AccuTnI assay (99^{th} percentile 0.04 0.01µg/L) was an independent predictor of mortality at five years (HR 2.1 (95% CI 1.3-3.3)) (166).

Given the observation that cTn levels, even below the ULN, may be predictive of future acute events in stable coronary artery disease, the development of hs-cTn assays, with their greater discriminative power at lower concentrations, has the potential to offer improved prognostic data. Interestingly, study data demonstrate marked variability in the prevalence of hs-cTn above the ULN ranging from 2.9% to 39% in patients with chronic coronary syndromes (169-174). Despite this wide range, all bar one of these studies demonstrated a prevalence above 20%. This variation is likely to be explained by two factors: firstly, the definition of chronic coronary syndromes varies across these studies, in particular whether it is newly diagnosed or pre-existing; secondly, different assays will demonstrate variable performance in different populations. This variability in assay performance is highlighted in the paper by Omland *et al*, in which two high sensitivity assays were tested in patients with stable coronary artery disease. It reported that 2.9% of this population were above the ULN with hs-cTnI assay compared with 10.9% with the hs-cTnT assay (169). Further, in adjusted models in this study population, current smokers had 12% lower hs-cTnT concentrations than non-smokers but there was no difference in the hs-cTnI concentration (175). It is unclear why smokers, who are clearly at increased cardiovascular risk, would have lower hs-cTnT concentrations, but it has been suggested that substances in the tobacco could interfere either with the analytical process or the kinetic patterns of hs-cTnT (175). This important observation needs to be further investigated, since, if it is shown to be consistent, then a different ULN for high sensitivity assays would to be considered for patients who are active smokers.

Studies to date have consistently found that elevated hs-cTn concentrations, regardless of the assay used, are independent predictors of future cardiovascular events in patients with chronic coronary syndromes (169-171, 173, 174, 176, 177). Furthermore, many studies have gone on to demonstrate a statistically significant increase in the discriminative ability of risk prediction models when hs-cTn concentration is factored into the model (169, 170, 173, 174, 176, 177). However, whilst these improvements are statistically significant they only provide a modest improvement in the ability to predict risk and, as is the case with the ScTn assays, it is uncertain whether this will translate into useful clinical benefit (178).

Interestingly, a sub-study of BARI 2D assessed whether patients that had hs-cTn levels above the ULN (897, 39.3%) with both chronic coronary syndromes and diabetes would benefit from the addition of prompt revascularisation compared with optimal medical therapy alone. The study found that there was no significant difference in the primary composite endpoint (death from cardiovascular causes, non fatal myocardial infarction or non fatal stroke), consistent with the overall results from BARI 2D (171). Furthermore, this observation was seen across all of the components of the composite endpoint, all quintiles of hs-cTn levels and regardless of the method of revascularisation (whether CABG or PCI) (171). It is important to consider a few factors that are likely to play a part in this result. Firstly, in order to be considered suitable for revascularisation patients did not need to have documented evidence of ischaemia. Given the large body of evidence demonstrating that ischaemia is the target for revascularisation, this leaves us uncertain as to whether there is an additive role for the measurement of hs-cTn in patients with documented myocardial ischaemia (179, 180). Secondly, this sub-study acknowledges that it was underpowered to detect a treatment effect of revascularisation (171).

1.5.1.3 The role of troponin in tachyarrhythmias of supraventricular origin

CTn elevation in the context of AF, particularly with uncontrolled ventricular rates has been well documented (8, 16). There are two large biomarker sub-studies of the trials comparing the DOACs with warfarin for stroke prevention in patients with AF, which demonstrate that at least 25% of these patients have hs-cTn concentrations above the ULN (181, 182). Furthermore, both studies found that the hs-cTn level was independently associated with future cardiovascular events (181, 182). Both these studies also demonstrated that the addition of hs-cTn to either the CHADSVASc or CHADS2 scores improved the ability to stratify the risk of stroke in these patients (181, 182). In addition, a smaller study of stable patients with AF demonstrated similar findings with hs-cTn being found to be an independent predictor of future cardiovascular events and adding to the predictive ability of the CHADSVASc and CHADS2 scores (183).

CTn is frequently found in patients presenting acutely with symptoms of AF. However there is discordance in the literature as to whether this observation is associated with an increased prevalence of significant coronary artery disease (184-187). Even so, the majority of studies demonstrate that cTn release in the context of an acute presentation with AF is associated with worse long term outcomes (184, 186). Fan *et al* performed a meta-analysis of over 22697 patients presenting either with AF for the first time or with stable AF. This study demonstrated that an elevated cTn (97% with high sensitivity assays) was independently associated with a twofold increase in all-cause mortality (HR 2.04 (95% CI 1.56-2.67)) (188). A similar hazard ratio (1.93 (95% CI 1.61-2.30)) was seen in terms of major adverse cardiovascular events (188).

Interestingly, a single study of previously healthy patients (with no history of AF) in Japan found that the future incidence of atrial fibrillation was significantly associated with the baseline hs-cTn level (incidence of 0% for patients within the lowest quartile of hs-cTn results and 15% for patients in the highest quartile) (189). Importantly, however, these results were not adjusted for age, which is both a key risk factor for the development of AF and also is associated with higher baseline cTn levels as already discussed.

Two studies, including one from the Southampton group, have documented hs-cTn levels in patients presenting with any supraventricular tachyarrhythmia (excluding sinus tachycardia) and report that between 45.2% and 50.7% of these patients had hs-cTn concentrations above the ULN (18, 190). There were only three patients in whom revascularisation was performed, at thirty days, in the 100 patients followed by Costabel *et al* and these events all occurred in patients without significant hs-cTn levels (190). By contrast, in the other study by Mariathas *et al*, which was four times the size and had a median follow up of 747 days, patients with a tachyarrhythmia and hs-cTn concentrations above the ULN were nearly twice as likely to die as those with normal hs-cTn levels (26.2% versus 14.5% p = 0.003) (18). Furthermore, this study compared the outcome of patients with tachyarrhythmias and elevated hs-cTn levels with patients who had suffered an NSTEMI and found that there was no difference in mortality between these groups (18). These data both indicate the potential prognosticative capability of hs-cTnI in tachyarrhythmia, and offer a reminder about the equally adverse outcome associated with a T2MI/myocardial injury in this context.

Direct current cardioversion (DCCV) is an effective method of terminating cardiac arrhythmias and, as such, is often used for the restoration of sinus rhythm, particularly in the elective setting for patients with AF (191). Historically, DCCV was performed with monophasic energy, but biphasic energy is now more commonly used. A number of studies assessed the impact of DCCV with these two waveforms using the standard cTn assays. Interestingly, the monophasic shocks were less effective at restoring sinus rhythm and were associated with higher cTn levels post procedure (192-

194). More recently, with the sole use of biphasic defibrillators, Lobo *et al* demonstrated that DCCV was not associated with myocardial injury as measured by hs-cTn (191). This observation is important, and possibly counter intuitive, because it means that raised cTn levels should not be ignored in patients because they have had a recent DCCV.

Electrical isolation of the pulmonary veins is an established treatment for AF which involves the application of either cryotherapy or radiofrequency energy to cardiac tissue. This application of energy is designed to cause myocardial injury and, therefore, as one would expect, studies have demonstrated that cTn always rises following the procedure, normally above the ULN (195-197). Interestingly, Yoshida *et al* demonstrated that the cTnT level was significantly higher in patients who responded to AF ablation, and that those patients requiring a further procedure also had significantly lower cTnT levels (195). This might be explained by longer ablation times resulting in a higher total energy applied to the myocardium, thus resulting in both greater cTn levels and a more successful procedure (198). The suggestion that the amount of energy delivered during the procedure may be correlated with cTn is not, however, supported by Rubenstein *et al* who found no correlation between ablation time, temperature or power (196). This is discrepant with the findings of a meta-analysis (199), which also showed that patients with a higher cTnT result post ablation were more likely to have recurrent AF (199). Interestingly, and counterintuitively, however, there was no such association when the cTnI assay was used rather than the cTnT assay (199).

1.5.1.4 The role of troponin in congenital heart disease

Three small studies have assessed the value of hs-cTn in congenital heart disease (CHD), which represents a markedly heterogeneous group of patients. Rybicka *et al* demonstrated that there was no difference in hs-cTnT concentration between simple and complex CHD as well as non-cyanotic and cyanotic CHD (200). There was, however, an association between hs-cTn levels and both left and right ventricular systolic dysfunction (200). This observation is replicated by Eindhoven *et al* who also found that higher hs-cTnT levels were associated with AF, age and NYHA class (201). This larger study did, however, unlike Rybicka *et al*, identify that patients with a systemic right ventricle or pulmonary hypertension consistently had the highest hs-cTnT levels (201). A third study found that the 16.4% of patients with an hs-cTnT level above the ULN had significantly worse cardiovascular outcomes (a composite of cardiovascular death, heart failure admission, arrhythmia or need for intervention) than either those with undetectable or normal hs-cTnT levels (202).

1.5.1.5 The role of troponin in myocarditis

cTn elevation has been shown to be useful to confirm a clinical diagnosis of myocarditis (203, 204). However, this elevation does not represent a marker of poorer prognosis in myocarditis and, in fact, some studies have demonstrated that patients with a normal or minimally elevated cTn have worse outcomes (205-207). This lack of a relationship between cTn and clinical outcomes has also been demonstrated, albeit in a case series, in patients with giant cell myocarditis, a rare and particularly aggressive form of myocarditis (208).

1.5.1.6 The role of troponin in cardiomyopathy

Until the advent of hs-cTn assays, cTn elevation was only infrequently seen in hypertrophic cardiomyopathy (HCM) (209, 210). However, with the advent of hs-cTn assays, between 42% and 54% of stable patients with HCM have been found to have levels above the ULN (211, 212). In one study, hs-cTnT levels were associated with markers of HCM disease severity including: NYHA class, degree of left ventricular outflow obstruction, left ventricular systolic dysfunction, abnormal blood pressure response to exercise, presence of gadolinium enhancement on MRI, maximal left ventricular wall thickness and left atrial diameter (212). Interestingly, a smaller study using a ScTn assay did not find any correlation between ScTn level and any echocardiographic parameters but ScTn elevation was associated with the presence of AF (210). Given the observation that hs-cTn levels are associated with markers of HCM disease severity, it is unsurprising that in one study, with a mean follow up of 4.1 +/- 2.0 years, 18% of the group with an elevated hs-cTnT level had an adverse cardiovascular event (cardiovascular death, unplanned heart failure admission, sustained ventricular tachycardia, embolic events or progression of heart failure to NYHA 3 or 4), compared to 0% of the group with a normal hs-cTnT level (211). Furthermore, once confounding factors were considered on multivariate analysis, hs-cTnT remained independently associated with outcomes in these patients (211).

Dilated cardiomyopathy (DCM) represents a specific subset of heart failure patients in whom the role of cTn has also been evaluated. The reported frequency of ScTn elevation amongst these patients is between 21% and 55% (213, 214). Sato *et al* classified patients with DCM into three groups: group 1, normal cTn level; group 2, high initial cTn concentration that normalised during follow up; group 3, high cTn concentration that remained elevated at follow up. Initial left ventricular ejection fraction and diastolic dimensions were the same across all groups, but at follow up (15.9+/-10.5 months), group 3 had significantly worse LVEF and left ventricular dimensions than the other two groups (213). Furthermore, whilst there was no difference in cardiovascular event

free survival between group 1 and 2, there was a significant difference between these groups and group 3 (213). A larger study of 310 patients followed up patients with DCM for a mean of 2.2 years found that there was a significant difference in the all-cause mortality between patients with a cTn above the ULN and those below it (37.5% vs. 15% P<0.001) (214). More recently, Kawahara *et al*, in a study of 85 patients with DCM followed up for a mean 4.1 years, also demonstrated that hs-cTnT was independently associated with the risk of cardiovascular death (215).

Two studies have assessed the value of hs-cTnT in patients with amyloidosis. Takashio *et al* compared patients with amyloid and those with left ventricular hypertrophy (in whom a diagnosis of amyloid was excluded by biopsy) and demonstrated that hs-cTnT had reasonable discriminative ability for amyloid (AUC 0.788) (216). Hs-cTnT level has also been demonstrated to be an independent predictor of adverse outcomes and significantly improves the risk assessment scores for patients with cardiac amyloidosis (216, 217).

1.5.1.7 The role of troponin in ventricular tachycardia

Like AF, ventricular tachycardia (VT) is frequently associated with a cTn rise (218). This is likely to result from a combination of the arrhythmia causing a supply/demand mismatch and the fact that these patients often have a previous history of coronary artery disease or cardiomyopathy. Interestingly, a single study of 218 patients with heart failure, having excluded those with an acute MI or myocarditis, measured an initial ScTn and then followed patients for ventricular tachyarrhythmias. The study demonstrated that the serum ScTn closely correlated with the occurrence of ventricular arrhythmias (218). The authors suggested that the elevated cTn might be the substrate for ventricular arrhythmias. However, we should also consider that patients with worse heart failure have higher ScTn levels and it is these patients that are more likely to have arrhythmias, so perhaps the ScTn level is merely a surrogate of a patient with more severe HF rather than the substrate for ventricular arrhythmias (218). Whilst this provides interesting data, there is no clear cut off beyond which the risk of ventricular arrythmia is high. What would potentially be helpful for future studies to investigate is whether the cTn concentration progressively increases before an episode of VT. This could potentially provide more useful prognostic data for clinicians.

Again, like patients with AF, none of the 27 patients undergoing a DCCV for ventricular arrhythmia precipitated in the electrophysiology lab had a subsequent ScTn rise, and so the authors suggested that an elevated ScTn following a cardioversion could indicate AMI or myocardial injury (219). Given the frequency of cardioversion in routine clinical practice, this finding should prompt further evaluation. It is important to consider that patients presenting spontaneously with VT may have

had a more prolonged arrhythmia than those precipitated during procedures and hence have longer to develop a supply/demand mismatch as a result of the arrhythmia. Similarly to AF ablation, ablation for VT has also been associated with a cTn rise but to a greater degree (198). However, unlike AF ablation, the cTn level does not seem to correlate well with the total amount of energy delivered (198).

1.5.1.8 The role of troponin in valvular heart disease

The timing of intervention in patients with severe, truly asymptomatic aortic stenosis with normal left ventricular function is an area of debate (220). In this situation, an elevated B-type natriuretic peptide, a marker of myocardial wall shear stress, has been recommended as an indication to consider aortic valve intervention (220, 221). Given that hs-cTn indicates myocyte damage it could be postulated that this biomarker might provide a better gauge of when intervention is required, rather than waiting for the development of either left ventricular dysfunction visible on echo or symptoms (221). A study of 57 patients with moderate to severe aortic stenosis and left ventricular hypertrophy found that 72% had a hs-cTnT level above the ULN (222). The hs-cTnT levels were positively correlated with the LV cavity size, peak velocity and pressure gradients across the aortic valve (222). Interestingly, there was no difference in hs-cTnT levels when patients with concomitant coronary artery disease were compared to those without (222). After multivariate analysis the only echocardiographic features that were associated with hs-cTnT levels were fractional shortening and LV mass (222). The prognostic accuracy of hs-cTnT to discriminate mortality was similar to the NT-pro-BNP, with areas under the curve of 0.72 and 0.74 respectively (p=0.87 for comparison)(222). Multivariate regression analyses did demonstrate that hs-cTnT concentrations greater than twice the ULN were independently associated with mortality during a median follow up of 769 days (HR 18.0 (95% CI 2.4 – 136.4)) (222).

A larger study of 253 patients with mild to severe aortic stenosis reported that 7.9% had hs-cTnI levels above the ULN (223). This study also found that hs-cTnI concentrations were positively associated with left ventricular mass, as well as myocardial fibrosis (as measured on cardiac MRI) on multivariate analysis (223). However, a study by Kim *et al* found no difference in the hs-cTnT levels when comparing those patients with myocardial fibrosis and those without in the context of severe aortic stenosis (224) Furthermore, Chin *et al* found that both cardiovascular death and the need for aortic valve intervention were associated with hs-cTnI levels on multivariate analysis (223).

Similarly, another study of 136 patients referred for evaluation of severe aortic stenosis found that hs-cTnT concentrations were associated with measures of aortic flow as well as left ventricular size

and function (225). As demonstrated before, the area under the curve for both hs-cTnT and NT-pro-BNP to discriminate mortality was similar (hs-cTnT 0.71, NT-pro-BNP 0.76). Interestingly, however, only when the hs-cTnT and NT-pro-BNP levels were combined were these biomarkers independent predictors of mortality (225).

In addition to the studies assessing whether cTn can guide the timing of surgery, a number of studies have also assessed the prognostic role of cTn before and after aortic valve intervention. For example, in a group of 60 patients who underwent surgical aortic valve replacement, the highest hs-cTnT tertial was found to be an independent predictor of major adverse cardiac events (hazard ratio 3.71, p=0.03) (226). Three studies have specifically evaluated the role of hs-cTn after transcatheter aortic valve implantation (TAVI). A study of 259 patients found that an elevated pre-procedural hs-cTnT was an independent risk factor for all cause death whilst the periprocedural hs-cTnT was not (227). A similar study of 198 patients demonstrated that post TAVI hs-cTnT levels rose significantly (about sevenfold) after the procedure and peaked at day 3 (228). This study also demonstrated that pre-procedural hs-cTnT concentrations were associated with one year mortality (228). However, in contrast to Kohler *et al*, this study demonstrated that post TAVI hs-cTnT levels were also associated with adverse outcomes at 1 year (228). This observation should, however, be interpreted with care given that multivariate analysis was not performed in this study. A study by Rodes-Cabau *et al* also reported that 99% of patients undergoing TAVI will have a degree of myocardial injury as a result of the procedure and that the size of this injury (as measured by hs-cTnT) was independently associated with cardiovascular mortality at 9 month follow up (229). Similarly, Yong *et al* found that myocardial injury after TAVI is common (17% with hs-cTnT >5 times the ULN) and that this, together with the pre-procedural hs-cTnT, were independent predictors of 30 day mortality (230).

Unlike severe aortic stenosis, there are no guideline recommendations for the use of cardiac biomarkers to aid the decision as to when to send patients for surgery in severe mitral regurgitation (220). The majority of studies in this area have assessed the merit of measuring cTn following mitral valve intervention to predict outcomes rather than to guide the timing of treatment. Monaco *et al* measured ScTn levels in 180 patients following mitral valve surgery and found that bypass time and the need for an infusion of adrenaline/noradrenaline during the operation independently predicted ScTn release (231). The association between ScTn levels and bypass time was also found in another small study of 24 patients after mitral valve surgery (232). More recently, a study of 34 patients undergoing MitraClip therapy measured their hs-cTnT prior to the procedure and found that the median hs-cTnT levels were higher at baseline in those that had a major cardiovascular event at follow up compared with those that did not (92.6ng/L vs. 25.2ng/L) (233). The area under the curve for hs-cTnT was 0.82, but this was outperformed by other biomarkers including NT-pro-BNP (233).

1.5.1.9 The role of troponin in coronary angiography and percutaneous coronary intervention

As already discussed, cTn elevation is frequently seen in patients with stable coronary artery disease and therefore it is unsurprising that this observation has been replicated in patients prior to elective PCI (234-236). An elevated pre-procedure hs-cTnI has only once been shown to be an independent predictor of outcome (234).

It is widely accepted that patients undergoing PCI will often have an isolated minor cTn rise and previously it had been thought that this was not related to prognosis and therefore routine testing is not supported by guidelines (237). In an early study comparing the use of CK-MB with cTnI in 3494 patients undergoing PCI without ST elevation, elevated cTnI levels were seen in 44.2% (238). Interestingly, however, this study demonstrated that elevated cTnI levels were not associated with two year mortality, but that the degree of CK-MB rise was (238). More recent studies, using high sensitivity assays, have found a higher frequency of hs-cTn elevation following PCI (77.6% - 78.6%) (234, 235). Interestingly, 22.9% of patients with stable coronary artery disease will have a hs-cTn concentration of more than five times the ULN, thus meeting the Universal definition biomarker threshold for T4aMI (235). This casts uncertainty on the true clinical value of the Universal Definition-defined T4aMI cTn threshold.

A study using ScTn found that the number of stents deployed during PCI is associated with increasing concentrations of cTn post procedure (239). Two large, more recent, studies utilising hs-cTn have also found that both the complexity of the procedure and the length of stent used, as well as baseline demographic features, were associated with higher hs-cTn (234, 235). Both these studies demonstrated that, on multivariate analysis, post PCI hs-cTn levels were not associated with an increased risk of mortality (234, 235). Furthermore, the area under the receiver operator curve was only 0.589 and, in particular, at 5 times the ULN the specificity was 77.2% but the sensitivity was just 28.6% (235). This is supported by the work of de Melo *et al*, who demonstrated that 32 patients (from a cohort of 56) had hs-cTnI concentrations above the T4aMI threshold following elective PCI even in the absence of any late gadolinium enhancement on cardiac MRI (240).

The idea that T4aMI is merely a biochemical diagnosis without clinical significance is challenged by the most recent study in this area. Zeitouni *et al* collected hs-cTnI data from 1390 patients attending for elective PCI, in whom the preprocedural hs-cTnT was below the ULN (241). Hs-cTnT rose to above five times the ULN in 27.6% of patients (241). However, associated features (new ischaemic ECG changes, development of new pathological Q waves, loss of viable myocardium in a pattern

consistent with ischaemia or angiographic findings consistent with a flow limiting coronary complication) required to confirm a diagnosis of T4aMI were only seen in a quarter of this group (16, 241). Higher risk procedural and patient characteristics were associated with an increased likelihood of hs-cTnT above the ULN (left main stenting, stent length greater than 30mm, chronic kidney disease and age over 75 years) (241). Unlike previous studies, the patients who had a hs-cTnT rise to above five times the ULN had a higher rate of subsequent cardiovascular events (HR 3.8 (95% CI 1.9 – 6.9)), mainly driven by ischaemic events (241). Furthermore, this increased risk continued out to one year, although the HR was lower by this time point (1.7, 95% CI 1.1 – 2.6) (241). Whilst it is difficult to directly compare this study with the contrasting findings of Ndrepepa *et al*, there are undoubtedly differences, albeit modest, between these two cohorts (235, 241, 242). In addition, the rate of adverse events in the study by Ndrepepa *et al* at three years was only 3.8% compared with 2.3% at one year seen in the work by Zeitouni *et al*. The suspicion must be that there might have been differences in the extent of revascularisation or optimal medical therapy (234, 235, 241, 242). The other point to note is that the relative risk of adverse events in the study by Zeitouni *et al* fell at one year (and was only just statistically significant) and therefore suggests that hs-cTnT may only provide short term prognostic utility post PCI but that this is lost over time.

Whilst the data on the prognostic role of a rise in hs-cTn after elective PCI are not clear, clinicians should be aware that cTn elevation is frequently seen post PCI. These data also highlight the reason behind the high profile controversy about the use of the Universal Definition of periprocedural MI in relation to the EXCEL trial (243).

1.5.1.10 The role of high sensitivity troponin after coronary artery bypass grafting surgery

A number of different factors can result in myocardial injury following CABG (16). It therefore seems likely that concentrations consistent with a diagnosis of a T5MI (a rise in cTn >10 times the 99th percentile within 48 hours of CABG with one of; new Q waves, new angiographic occlusion, new loss of myocardium in an ischaemic pattern) would almost be ubiquitous. For example, one study describes that the median cTnI concentration was 250 times above the ULN in a group of 99 patients post CABG (244). One study using a high sensitivity assay, in 560 patients following CABG, found that hs-cTnT rose to above the threshold for T5MI criteria in 93% of patients (245).

Like in the PCI setting, a similar combination of patient specific factors and procedural elements have been demonstrated to be associated with cTn concentrations above the T5MI threshold (previous bypass surgery, end stage renal failure, left main disease, three vessel disease, elevated

pre-operative hs-cTnT concentration and higher EuroScore II) (245). Furthermore, specific features of the operation were also seen to be associated with higher hs-cTnT concentrations including: on pump surgery, a larger number of bypass grafts and bypass time (245). Interestingly, in a study using a high sensitivity assay, the cross clamp time was not statistically different between those who had hs-cTnT concentrations above the T5MI threshold and those below, although in a study using ScTn the cross clamp time was a highly significant predictor of reaching T5MI cTn threshold (244, 245).

Three studies have specifically assessed the association between ScTn concentrations and the degree of myocardial injury, as assessed by cardiac MRI, post CABG. All three of these studies demonstrate that the degree of injury on MRI is closely associated with the ScTn concentration (246-248). However, another study found that 96% of patients with no evidence of MI on MRI (according to new gadolinium hyperenhancement) had a hs-cTnI above the diagnostic threshold for T5MI as specified by the Fourth Universal Definition (16, 249). Interestingly, at least half of these patients would also have been considered to have had MI by the SCAI criteria too (median hs-cTnI concentration post operatively was 78.7 times the ULN) (129, 249). These data raise questions about the underlying mechanism for the elevated troponin in these patients.

Selvanayagam *et al* also specifically assessed the impact of on- versus off-pump CABG and found that off- pump CABG was associated with better ventricular function but no difference in the incidence or extent of myocardial injury (248). This is consistent with the only study to date using a high sensitivity assay which found that there was no difference between on- and off- pump CABG (245). When interpreting this difference it is important to note that the study by Selvanayagam *et al* was small (60 patients) and used a ScTn assay, but above all neither of these studies accounted for confounders when considering the impact of on- versus off-pump surgery (244, 245, 248).

Wang *et al*, on multivariate analysis, demonstrated that a T5MI was associated with mortality at both 30 days and medium term (up to 1000 days post CABG) (OR 4.92 (95% CI 1.34 – 18.1) and 3.44 (95% CI 1.13 – 10.5) respectively) (245). This observation is also supported by work using ScTn assays in a smaller population (246). These data support the concept that the criteria used for T5MI as defined by the Fourth Universal Definition are of true clinical value, but further data are now required to confirm this and also to evaluate whether any medical intervention can alter the risk once these patients have been identified (16). Further, a study of 629 patients who had both hs-cTn and NT-proBNP testing before and after any cardiac surgery (66.1% isolated CABG) found that both of these biomarkers were higher preoperatively in non-survivors when compared to survivors at nearly three years follow up (250). However, only the post-operative NT-proBNP was higher in non-survivors when compared to survivors and this is reflected in the multivariable analysis which demonstrated that only the Euroscore II and post-operative NT-proBNP (HR 1.76 (1.33 – 2.33)) were

independently associated with outcome (250). This suggests that NT-proBNP may provide better prognostic data than hs-cTn following cardiac surgery. This study did not, however, use hs-cTn concentration alongside clinical features to diagnose T5MI, which as shown in the previous study, is possibly when hs-cTn assays may be of prognostic value after cardiac surgery.

1.5.1.11 The role of convalescent high sensitivity troponin following acute coronary syndrome

The EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care) trial randomised patients with type two diabetes mellitus and a recent acute coronary syndrome (between 15 and 90 days prior) to alogliptin or the standard of care (251). As part of this study, a hs-cTnI sample was taken at randomisation and then repeated at six months. Hs-cTnI concentrations above the ULN were seen in 16% at baseline (251). In addition, the proportion of patients with hs-cTnI above the ULN remained high (11.7%) at six months. Of further interest is the observation that 21.5% of patients had a 25% or higher rise in hs-cTnI concentrations across the six month period (251).

Importantly, the baseline hs-cTnI concentration was associated with worse outcomes on multivariate analysis (HR 4.26 (95% CI 2.10 – 8.65) for cardiovascular death, myocardial infarction or stroke and 9.39 (95% CI 2.29 – 38.67) for cardiovascular death or heart failure when those with hs-cTnI above the ULN were compared with those with undetectable hs-cTnI concentrations) (251). There was a gradual increase in adverse outcomes with increasing hs-cTnI concentration, suggesting that hs-cTnI concentrations, even below the ULN, may have a role in risk stratification. Furthermore, those patients who had an increase in hs-cTnI concentration of more than 50% had a hazard ratio of 2.04 (95%CI 1.43 – 2.90), suggesting that the temporal trend of hs-cTnI is equally important as a predictor for, or at least marker of, adverse prognosis. (251).

Similarly, PROVE IT-TIMI 22, which randomised patients after acute coronary syndrome to intensive versus moderate statin therapy, included 3,209 patients in whom a hs-cTnI test was performed at 30 days and at four months (252). In this cohort the frequency of hs-cTnI above the ULN at 30 days was higher (30.2%) than seen in EXAMINE (252). These patients had numerically higher cardiovascular death or heart failure compared with those with hs-cTnI concentrations below the ULN, but this was not statistically significant (6.2% vs. 2.9% p = 0.26). The number of patients with hs-cTnI above the ULN fell at four months (22.2%) but this group had an increased risk of cardiovascular death or heart failure compared with those with hs-cTnI below the ULN (HR 2.62 (95% CI 1.69 – 4.06) (252). Further supporting the potential value of hs-cTnI as a prognostic marker,

those with the highest hs-cTnI concentrations had the largest absolute reduction in risk with statin therapy (252). Whilst this observation is redundant because National Institute for Health and Care Excellence (NICE) recommends high dose statin therapy in all patients following acute coronary syndrome, it does lend credence to the concept that hs-cTn may allow us to target future therapies to higher risk cohorts in the future (253).

These observations are supported by the work of Adamson *et al*, who evaluated the association of hs-cTnI and clinical outcomes at 4 and 12 months after acute coronary syndrome in 1776 patients (254). Nearly one in ten patients (9.3%) had hs-cTnI concentrations above the ULN at 4 months, falling to 5.9% at one year (56). Interestingly, the AUC at ≥6ng/L (double the concentration at which the CoV is <10%) was 0.745 (95% CI 0.707 – 0.745). Hs-cTnI outperformed other prognostic markers including measures of infarct size and the LV ejection fraction observed at 4 months. Furthermore, even after adjustment for the Global Registry of Acute Coronary Events (GRACE) score, patients with an hs-cTnI above the ULN at four months had a fivefold increased risk of cardiovascular death compared with those with hs-cTnI ≤5ng/L (254). Whilst the majority of patients had a fall in hs-cTnI concentration at 12 months, 16.1% had at least a 20% rise, which was associated with the worst clinical outcomes (254). Thus, the identification of patients with evidence of ongoing myocardial injury after acute coronary syndrome highlights those at the highest risk of future events and therefore suggests that these patients should be considered for the most intense follow up and medical optimisation (254).

1.5.2 Utility of cardiac troponin in non-cardiac causes of elevation

Table 3 highlights that there are many non-cardiac causes of cTn elevation. Given that these are likely to precipitate cTn release via indirect mechanisms, does cTn have a role as a prognostic biomarker in patients without a cardiovascular diagnosis? This is one of the most recent, and potentially most exciting, roles for cTn in future clinical practice.

1.5.2.1 The role of troponin in pulmonary embolism

The reported short term mortality from acute pulmonary embolism (in those without haemodynamic instability where there is clear evidence in favour of thrombolysis) is variable, ranging from <1% to 15% (255, 256). A number of different strategies have been described to try to better identify the individual risk of these patients to guide further management. A range of biomarkers, including cTn, have been shown to be released into the circulation, probably as a result

of right ventricular myocardial strain due to the increased afterload associated with a large pulmonary embolism (255). Original studies using ScTn found that levels did not discriminate between normotensive patients with pulmonary embolism who were at high and low risk of mortality (257). However, a study by Lankeit *et al* compared the use of ScTn with hs-cTnT assays in normotensive patients with acute pulmonary embolism and found that ScTn misclassified around 50% of these patients as low risk (258). By contrast, Hs-cTnT concentrations above the ULN were associated with excellent prognostic sensitivity (258). Specifically, regression analyses demonstrated a twofold increase in the risk of adverse outcomes for each standard deviation increase of hs-cTnT (258). Another study provides reassuring data for patients with hs-cTn levels below the ULN since none of these patients had adverse events at 30 days (259). More recently, a meta-analysis of 7,303 patients confirmed that elevated cTn levels were associated with a higher risk of death (OR 4.8, 95% CI 2.95-7.44) compared to patients with normal levels (255). Only three of the studies included in this meta-analysis used high sensitivity assays, but these demonstrated a similar, potentially magnified, risk of adverse outcomes with elevated hs-cTn (OR 7.86, 95%CI 2.94-21.0) (255). However, in terms of identifying low risk patients, hs-cTn did not quite reach satisfactory performance with a negative likelihood ratio of 0.21 (255).

These observations were taken forward in the PEITHO trial which randomised haemodynamically stable patients with right ventricular dysfunction on echo, and myocardial injury as evidenced by cTn concentrations above the ULN, to either standard care of thrombolytic therapy (260). The use of thrombolysis in this group had no effect on mortality but did reduce the risk of haemodynamic decompensation, but at a price of increasing the risk of major haemorrhage (260).

1.5.2.2 The role of troponin in chronic obstructive pulmonary disease

Cardiovascular disease is more frequently found amongst patients with chronic obstructive pulmonary disease (COPD) than in the general population and is a more frequent cause of death than respiratory disease in these patients (261-264). In clinically stable patients with COPD, 65% have hs-cTnT levels above the ULN and this increases to between 74-78% of patients with an acute exacerbation (261-263). In the stable population, hs-cTnT elevation is associated with increased mortality, independent of the severity of the respiratory disease and cardiovascular risk factors (263). In acute exacerbations of COPD, 64% of patients had a rise and fall of hs-cTnT, which would classify them as having had myocardial injury (as long as there was no clinical evidence of ischaemia), according to the Fourth Universal Definition (16, 262). Interestingly, patients with chronic myocardial injury, as evidenced by persistently elevated hs-cTnT levels, had a worse prognosis than those patients that had evidence of an acute myocardial injury (262).

1.5.2.3 The role of troponin in acute ischaemic stroke

Patients with an acute thrombotic stoke have an increased cardiac risk, with a 4% risk of mortality as a result of an acute MI and 19% risk of a serious cardiac event in the next three months (265). The reported incidence of hs-cTn above the ULN varies widely, from 20.7% to 59.7% (266-269). Both the in-hospital mortality and longer term mortality (1.5 +/- 0.7 years) in patients with acute stroke have consistently been shown to be associated with the hs-cTn concentration (267, 270). For example, on multivariable analysis, patients with the highest quartile of hs-cTn results had a 65% increased hazard of mortality at 1.5 +/- 0.7 years (HR 1.65; 95% CI 1.04 – 2.63) (270). Furthermore, the addition of hs-cTn concentrations to multivariable modelling demonstrated a significant improvement in the AUC in two studies (0.819 to 0.834 ($p = 0.007$) and 0.863 to 0.889 ($p = 0.008$))(267, 270).

1.5.2.4 Troponin in the post operative period following non cardiac surgery

The frequency of T2MI or myocardial injury following non-cardiac surgery, using a standard cTn assay, is between 5.0% and 8.0% (271, 272). The thirty day mortality in patients with T2MI or myocardial injury post operatively is around 1 in 10 (9.8% - 11.6%) which is much higher than those patients without evidence of T2MI or myocardial injury (1.1% - 2.2%) (271, 272).

When specifically considering patients undergoing hip fracture surgery, a ScTn above the ULN has been shown to be associated with a one year hazard of mortality of 6.52 (95% CI 1.78 – 23.87) (273). However, once demographics, comorbidity and brain natriuretic peptide (BNP) data were included on multivariable analysis, there was no independent effect of ScTn on one year mortality (HR 2.457 (95% CI 0.862 – 7.008) (273).

The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study, in the largest series of non-cardiac surgical patients (21,842 patients) to date, found that nearly one in five had hs-cTn concentrations above the ULN following surgery, but clinical evidence of myocardial ischaemia was rarely (7%) seen (274). This study demonstrated a progressive increase in the risk of 30-day mortality with increasing hs-cTn concentrations, with the highest concentrations (>1000ng/L using the fifth generation Roche Elecsys assay) having an OR of 227.0 (95%CI 87.4 – 589.9ng/L) when compared with the lowest concentrations (<5ng/L) (274). This is supported by a smaller study of 605 patients which found that a hs-cTn concentration above the ULN was associated with a fivefold increased risk of mortality at six months regardless of whether there was

any clinical evidence of myocardial ischaemia (275). Interestingly, the VISION study also demonstrated that a rise in hs-cTn of >5ng/L, was independently associated with 30-day mortality (HR 4.69 (95% CI 3.52 – 6.25) (274), thereby further supporting the concept that a rise in hs-cTn is clinically important. A subset of the VISION study also highlighted the association between hs-cTn concentration following non-cardiac surgery and the risk of non-cardiovascular complications (including infectious complications, critical care utilisation and significant post-operative complications) with a near two fold increase in patients with a hs-cTn above the ULN following surgery (276). Noordzij *et al* demonstrated that a rise of more than two times the baseline concentration following abdominal surgery was independently associated with non-cardiovascular complications following non-cardiac surgery (OR 4.31 (95%CI 1.8 – 10.1) (277). The authors did not look at the association with cardiovascular complications.

Whilst these observations provide helpful prognostic data, there are not as yet any robust data to support a change in the clinical management of these patients (126). However, the results generally raise the possibility that hs-cTn assessment might, in the future, be of value in identifying individuals at high risk post-operative complications after non cardiac surgery: this could, in turn, lead to tests of introducing medical therapy and risk factor modification to prevent such outcomes.

1.5.2.5 The role of troponin in renal failure

Given that cTn is excreted via the kidney it is unsurprising that studies consistently demonstrate that hs-cTn levels are elevated in patients with both end stage renal failure (ESRF) and chronic kidney disease (CKD) (13, 14, 278-280) . Prior to the advent of high sensitivity assays, a single study of 733 patients with ESRF found that these patients were much more likely to have cTnT above the ULN compared with cTnI (82% vs. 6%), suggesting that the elimination of cTnT and cTnI are affected differently by ESRF (281). In asymptomatic patients with ESRF and CKD the ScTn evidence consistently indicates that patients with elevated concentrations are at higher risk of future cardiovascular events (281-283).

The difficulty interpreting results in patients with renal dysfunction in the era of hs-cTn assays is demonstrated by Gunsolus *et al*, who found that whilst sensitivity and negative predictive values remained the same, the specificity for AMI decreased from 93-95% to 57-61% in patients with severely impaired renal function and to 40-41% in those with ESRF (284). This observation is supported by Miller-Hodges *et al* who also demonstrated that the area under the curve decreases from 0.95 to 0.82 for hs-cTn to diagnose T1MI in patients with CKD presenting with possible acute coronary syndromes (285). Perhaps most notably, however, is that these two studies also reported

that mortality was positively correlated with hs-cTn concentration, regardless of the degree of renal impairment and the admitting diagnosis (284, 285).

The Chronic Renal Insufficiency Cohort provides insight into the characteristics of patients with CKD outside the context of an acute presentation. In this group, hs-cTn was detectable in 84% and was strongly associated with left ventricular hypertrophy (286). Furthermore, elevated hs-cTn concentrations were associated with higher risk demographic profile and greater cardiovascular risk factors (286). Elevated hs-cTnT at baseline was strongly associated (hazard ratio 4.77, 95%CI 2.49-9.14) with the development of heart failure within six years across categories of CKD severity from mild to severe (287). Of further interest, patients in the highest category of hs-cTnT were nearly twice as likely (hazard ratio 1.8, 95%CI 1.35-2.40) to have a rapid decline in renal function (288). This observation was also found prior to the development of high sensitivity assays, with Desai *et al* finding that cTnT enhanced the ability to predict the progression from CKD to ESRF (289).

An analysis of 8121 patients in the PREVEND study of patients with CKD stages 1-3 demonstrated that 6.7% had an hs-cTnT above the ULN which, given that these patients only have mild renal impairment, is important for clinicians to consider when these patients present to medical services (290). Furthermore, even though these patients only had mild CKD, hs-cTnT concentrations were associated with future cardiovascular risk even after adjustment for cardiovascular risk factors, demographics and renal function severity (290).

This is yet another strand contributing to the overall concept that rises consistently throughout the data presented in this Introduction: that a troponin level above the ULN “never means nothing”.

1.5.2.6 The role of troponin in chemotherapy and radiotherapy

Chemotherapeutic agents can have a wide range of cardiovascular complications including: cardiomyopathy, vasospasm, hypertension and QT prolongation (291). Whilst historically anthracyclines were the main cause of cardiomyopathy, trastuzumab has now also been shown to be a frequent cause of cardiomyopathy (291). The possibility of using a biomarker to predict left ventricular injury before this becomes manifest on echocardiography is obviously an attractive one; unfortunately, however, the evidence for the use of ScTn in this context is discrepant (292). The advent of high sensitivity assays has led to renewed interest in this context. A single study of 452 patients receiving trastuzumab found that patients with elevated hs-cTn concentrations prior to treatment were more likely to develop cardiomyopathy than those with hs-cTn concentrations below the ULN (hazard ratios 4.52 for hs-cTnI and 3.57 for hs-cTnT) (293). Three further studies have demonstrated that a rise in hs-cTn during therapy or afterwards is indeed associated with an

increased risk of developing cardiomyopathy as a result of either anthracyclines or trastuzumab (293-295).

The key issue is whether these observations provide an opportunity to intervene at an early stage before the development of clinical features of cardiomyopathy. The ICOS-ONE trial attempted to address this by randomising patients undergoing anthracycline therapy, in an open label fashion, to either continuous enalapril therapy or to start enalapril if the cTn was elevated (296). This study demonstrated that elevated cTn concentrations were seen in similar frequency (23% vs. 26% p=0.50) across the two groups, suggesting that enalapril does not affect the mechanism underlying the hs-cTn release (296). The actual rate of significant left ventricular function deterioration was low (1.1%) in this study using low doses of anthracyclines (296). There was no difference in the incidence of cardiotoxicity between the two groups, but, given the low numbers of patients affected, it is difficult to draw definitive conclusions from this study (296). The evidence so far does suggest that the routine measurement of cTns in this population may have a future role in raising an alarm about incipient drug-induced cardiomyopathy, but clearly further studies are needed.

Whilst the advent of check point inhibitors has revolutionised the treatment of a wide range of malignancies, there is around a 1% risk of cardiac complication, most commonly myocarditis, which has a high associated mortality (297). The data on the utility of cTn in this group is limited: two case series have demonstrated that, in patients with cardiac complications, higher cTn concentrations are indeed associated with worse clinical outcomes (298, 299).

Chest radiotherapy is known to increase the risk of future major cardiovascular events (300). Historical studies using ScTn found that there were no changes in their concentration during and after treatment (301, 302). More recently, however, a study using hs-cTnT found that levels increased during radiotherapy in 21% and that these were associated with higher myocardial radiation doses (300). Whilst this is an interesting observation, there are no data to inform clinicians as to whether elevated hs-cTn post radiotherapy predicts future outcomes at this stage.

1.5.2.7 The role of troponin in the general population

Cardiovascular risk stratification for the general population is currently performed using relatively blunt tools at the current clinical front line, dominated as it is by a crude assessment of individual risk factors. Given that such factors (for example, cholesterol, blood pressure etc) are relatively weak identifiers of those destined to have acute cardiovascular events like AMI and stroke, this leads to a primary prevention strategy that yields a huge number of individuals who must be committed to intervention (mainly with statins) in order to prevent a small proportion of them

having the acute CV event that most will not have anyway. The prospect of a blood biomarker that could contribute to a much more accurate risk stratification tool for the general population is therefore extremely attractive for logistic, financial and patient satisfaction reasons. Given the evidence that cTn is associated with cardiovascular risk factors and worse clinical outcomes in a range of specific circumstances, it would seem plausible that cTn could be a potentially useful screening tool.

Zethelius *et al* evaluated the ability of ScTn to predict cardiovascular events in 1203 men aged 70 years over a 10 year follow up period (303). On multivariate analysis, this study demonstrated that, in patients without prior cardiovascular disease, a ScTn concentration above the ULN was associated with double the observed hazard of mortality (hazard ratio 2.12 (1.06-4.22)) (303). Predictably, however, whilst the specificity of using the ULN threshold was good (98.2%), the sensitivity was poor (6.4%) (303).

Since then, a number of studies evaluated the role of high sensitivity assays in the general population. Table 4 shows that hs-cTn has been demonstrated to be an independent predictor of future cardiovascular events across a range of populations (71, 304-314). The JUPITER trial, for example, measured hs-cTnI concentrations in 12,956 patients with low-density lipoprotein cholesterol levels of less then 3.4mmol/L without established cardiovascular disease before randomising them to either rosuvastatin or placebo. In this study, an elevated hs-cTn level was an independent predictor of the primary composite endpoint (non-fatal MI, stroke, unstable angina, arterial revascularisation and cardiovascular death) (315). Interestingly, rosuvastatin was equally effective at reducing vascular events across the range of hs-cTnI results but, due to their higher overall risk, the absolute benefit of rosuvastatin rose with increasing hs-cTnI levels (315). The number needed to treat (NNT) to prevent one event at 5 years in the highest tertile of hs-cTnI concentrations was similar to the NNT for a Framingham Risk Score >10% (NNT 18 & 20 respectively) regardless of the low-density lipoprotein cholesterol level (315). Further, WOSCOPS (West of Scotland Coronary Prevention Study) randomised previously healthy males with hypercholesterolaemia to pravastatin or placebo and followed them up for five years. This cohort contained 3138 patients in whom the plasma hs-cTn was measured at randomisation and at one year. The baseline hs-cTn was independently associated with death from ischaemic heart disease or myocardial infarction (HR 2.3; 95% CI 1.4 - 3.7 for the highest quartile of hs-cTn compared with the lowest quartile) (316). Interestingly, pravastatin doubled the number of men whose hs-cTn concentration fell by more than a quarter versus placebo ($p<0.001$), which put them at the lowest risk of future coronary events (316). Interestingly however, the change in hs-cTn concentration only correlated weakly with the change in cholesterol (Pearson correlation coefficient 0.20) (316).

The ease of use and wide accessibility of hs-cTn, combined with these data, suggest that hs-cTn assays may provide a novel risk assessment tool for patients without known cardiovascular disease (314, 317, 318). It is important, however, to consider the limitations of hs-cTn in this role: there are, as yet, no clear clinical decision-making cut offs and there are, of course, no outcome data relating to using the assay to direct pharmacological intervention. (317).

Study	**Year**	**Population**	**Age group (years)**	**Assay**	**Follow up**	**Results**
Blankenberg *et al* (308)	2016	BiomarCaRE cohort (74,738)	Mean 52.2	Abbott ARCHITECT STAT hsTnI	Median 13.8 years	Hs-cTnI was an independent predictor of cardiovascular mortality, cardiovascular disease and all-cause mortality
de Lemos *et al* (71)	2010	Dallas Heart Study cohort (3,546)	30-65	Elecsys-2010 Troponin T hs STAT, Roche	Median 6.4 years	Hs-cTnT independently associated with all-cause mortality
Evans *et al* (309)	2018	Meta-analysis (67,063)		Multiple	Multiple	Hs-cTn was an independent predictor of first HF event
Everett *et al* (315)	2015	JUPITER cohort (12,956)	Median 66	Abbott ARCHITECT STAT hsTnI	Median 2 years	Hs-cTnI was independently associated with cardiovascular events and all-cause mortality
Jia *et al* (304)	2019	ARIC cohort (8,121)	54-74	Architect Stat Troponin-I, Abbott Elecsys Troponin T, Roche	Median 15 years	Hs-cTnT & hs-cTnI were strongly associated with incidence of cardiovascular disease
Lyngbakken *et al* (307)	2019	HUNT 2 & 3 cohorts	> 18 years	Abbot ARCHITECT STAT hsTnI	Median 9.6 years	Hs-cTnI independently associated with cardiovascular risk
Neumann *et al* (306)	2014	FINRISK 1997	Mean 47.8	Abbott ARCHITECT	14 years	Hs-cTnI independently associated with all MI, stroke,

		cohort (7,899)		i2000SR hsTnI		cardiovascular disease, HF & MACE
Than *et al* (313)	2018	ADAPT cohort (836)	Mean 64	Abbott ARCHITECT STAT hsTnI	Median 5.8 years	Hs-cTnT & hs-cTnI independently associated with all-cause mortality
Van der Linden *et al* (319)	2016	Meta-analysis (65,019)		Multiple	3.8-20 years	Hs-cTn elevation was independently associated with increased cardiovascular risk and all-cause mortality
Wang *et al* (311)	2012	Framingham Heart Study cohort (3,428)	Mean 59	Erenna hsTnI, Singulex	Mean 11.3 years	Hs-cTnI was independently associated with future HF and MACE but not mortality or death
Willeit *et al* (310)	2017	Met-analysis (154,052)		Multiple	Multiple	Hs-cTn was an independent predictor for cardiovascular death, cardiovascular event and stoke
Xiao *et al* (305)	2017	Pingguoyuan residents (1,831)	45-91	Elecsys Troponin T hs assay, Roche	Median 4.8 years	Hs-cTnT was independently associated with the risk of all case mortality and MACE
Welsh *et al* (314)	2019	Generation Scotland Sottish Family Health Cohort	35 – 65	Abbott ARCHITECT STAT High Sensitive Troponin I & Roche hs-cTnT	Median 7.8 years	Both hs-cTnI and hs-cTnT were independently associated with development of cardiovascular disease and mortality
Zhu *et al* (312)	2018	Busselton Heath Study cohort (3,939)	25-84	Abbott ARCHITECT STAT High Sensitive Troponin I	20 years	Hs-cTnI was an independent predictor of fatal and non-fatal cardiovascular events

Table 4: Use of hs-cTn assays in the general population

1.5.2.8 Troponin elevation during/following exercise

Population studies have consistently demonstrated that physical activity can improve cardiovascular risk as well as reduce cardiovascular mortality (320, 321). There is, however, uncertainty about whether this benefit is also seen at extreme levels of endurance exercise (320). ScTn has been shown to rise, and then fall again, following endurance cycling, marathon running and triathlons (322-324). Specifically, competitors with less experience and younger age have been shown to be associated with elevated ScTn concentrations (322). Interestingly the presence of cardiovascular risk factors and the duration of the race we not associated with elevated ScTn concentrations (322). Deriving common themes from these studies can be challenging given the varied inclusion factors and the type of endurance activity (324). A meta-analysis of 1120 cases of ScTn measurement following endurance exercise demonstrated that detectable ScTn was seen in around half of these athletes (325). This study gave different insights into those at higher risk of ScTn elevation than the study by Fortescue *et al*, with heavier individuals and shorter endurance events being more likely to result in ScTn elevation (325). Overall, the data on ScTn elevation following exercise suggest that this is a benign phenomenon (324).

However, the advent of high sensitivity assays led to further studies in this area with much more concerning outcome data in some cases. As with standard assays, hs-cTn has been shown to rise in a variety of exercise scenarios including; marathons, mountain marathons, prolonged treadmill exercise, long distance walking races and prolonged swimming (326-332). The frequency with which hs-cTn rises above the ULN varies from 9% - 98% (327-329, 332). This variation is unsurprising given the differences in the cohorts, the type of exercise in the studies and the different assays used. There is also variation in the reported factors associated with hs-cTn concentrations above the ULN, with some studies finding no associations, and others finding a range of features including: gender, age, presence of previous cardiovascular disease and length of time taken to complete marathon (326, 327, 332). Tian *et al* provide echo data demonstrating that whilst the left ventricular ejection fraction deteriorated immediately after exercise, reassuringly this recovered within six hours and there was no association between hs-cTn and the degree of left ventricular impairment (329). Furthermore, Leckie *et al* found that there was no difference in hs-cTn concentration in healthy volunteers, those with cardiovascular disease and those that collapsed in patients who collapsed during the marathon (327).

Despite a number of studies demonstrating the kinetics of hs-cTn following marked endurance exercise there was little data on the longer term prognostic utility of these data until recently. However, the recently published work of Aengevaeren *et al* provides insights into this area (332). The study measured the hs-cTnI before and after 725 participants (median age 61 years) undertook

30 to 55km of walking. Importantly, this study demonstrated that the mortality/development of MACE during a median 43 months of follow up was higher in participants whose hs-cTnI concentration rose above the ULN when compared with those in whom it did not (27% vs. 7% p<0.001) (332). This difference persisted on multivariate analysis with a hazard ratio of 2.48 (95% CI 1.29 – 4.78) (332). This study was conducted in an older population than most other studies in the area and participants did not increase their heart rate (68%+/-10%) as much as perhaps would be expected in other endurance disciplines, and so this study may not be generalizable. However, it does however add to the growing body of evidence that hs-cTn may be a marker of future cardiovascular risk, and that the presence of the protein in the blood "never means nothing".

1.5.2.9 Troponin elevation in the context of coronavirus-19 infection

There is emerging evidence from the coronavirus-19 (COVID-19) pandemic that hs-cTn elevations are frequently seen and may be associated with prognosis. Hs-cTn concentrations above the ULN have been frequently (7%-27%) reported in patients admitted to hospital with COVID-19 and up to 31% in those admitted to critical care units (333-339). A number of possible mechanisms have been put forward to explain these observations (direct viral myocardial toxicity, oxygen supply/demand mismatch, microvascular dysfunction, intense vascular inflammatory response, stress cardiomyopathy and precipitation of acute plaque event) with the final common pathway being non-specific myocardial injury (333, 340). The data consistently demonstrate that myocardial injury is more frequently seen in non-survivors (46 - 51% vs 1 - 4.5% for survivors (p<0.001) (335, 337). Furthermore, on multivariate analysis, patients with a hs-cTn concentration above the ULN had more than four times the hazard for mortality compared with those without a hs-cTn rise (HR 4.26; 95% CI 1.92 – 9.49)(337). These early studies are based on non-consecutive data which will mean that there is a risk that selection bias will could affect their interpretation. However, as demonstrated by a recent meta-analysis of 4631 patients, the data thus far consistently show that patients with elevated cTn (a range of different assays) have worse outcomes (severe disease, need for critical care admission and mortality) (relative risk 5.64 (95%CI 3.04 – 10.22) (341). Whilst these data are emerging, there is a signal that cTn may provide a marker of prognosis in these patients but there is debate as to whether these assays should now be used clinically in these patients (342, 343).

1.6 Troponin in critical care

1.6.1 Troponin in general critical care

Given that ScTn assays were introduced into clinical practice around twenty years ago there is a large body of evidence relating to their use in general critical care (GCCU) when compared with the more recent hs-cTn assays.

1.6.1.1 Incidence of ScTn elevation in general critical care settings

There is wide variation in the reported incidence of ScTn elevation *on admission* to GCCU, ranging from 15% to 61% (Table 5 (344-360)). This range includes data from retrospective, observational studies which have the advantage of larger sample sizes but also the disadvantage of uncontrolled selection (one retrospective study for example had a 97% male cohort (357)). The variation in incidence is also likely to be partly explained by heterogeneity of criteria for admission to critical care (CC) units, variability of case mix between cohorts and differences in ScTn assays between studies.

Study	**Type of study**	**Number of patients**	**Raised ScTn at admission %**	**Mortality (%) during admission unless otherwise stated**		**Multivariate mortality analysis**
				ScTn raised	ScTn normal	
Ammann *et al* 2003 (349)	Prospective	58	55	22	5 (P<0.01)	Not performed
Babuin *et al* 2008 (358)	Retrospective	929	61	13	30 (0<0.001)	ScTn remained independent
Docherty *et al* 2017 (355)	Prospective	1349	45	72	10% (p<0.001)	ScTn remained independent
Guest *et al* 1995 (350)	Prospective	209	15	41	15 (p<0.001)	Not performed
Kim *et al* 2005 (356)	Prospective	215	56	41 (@30 days)	21	Not performed

King *et al* 2005 (351)	Prospective	128	27	43 (@28 days)	10 (p<0.001)	ScTn not independent
Landesberg *et al* 2005	Prospective	101	38	66 (@ 2 years)	33 (p<0.001)	ScTn not independent
Lim *et al* 2005(345)	Prospective	104	42			ScTn not independent
Lim *et al* 2006 (346)	Prospective	198	44	44	35 (p=0.33)	ScTn not independent
Lim *et al* 2006 (347)	Meta-analysis	4492	53	37	14 (p<0.001)	ScTn remained independent
Lim *et al* 2010 (348)	Prospective	103	51	31	2	ScTn remained independent
Liu *et al* 2015 (353)	Prospective	90	44	35	12 (p=0.01)	Not performed
Ozsu *et al* 2011 (360)	Retrospective	158	61	63	29 (p<0.001)	ScTn remained independent
Poe *et al* 2015 (357)	Retrospective	19979	19 (above 10% CV)	14 (@30 days)	32 (above 10% CV)	ScTn remained independent
Quenot *et al* 2005 (354)	Prospective	217	32	51	16 (p<0.001)	ScTn remained independent
Reynolds *et al* 2012 (359)	Retrospective	663	52	31	4 (p (<0.001)	ScTn remained independent
Wu *et al* 2004 (344)	Prospective	108	55	24	13 (p=0.003)	ScTn remained independent

Table 5: ScTn elevation incidence and association with mortality in mixed general critical care (CV - coefficient of variation)

Interestingly, one retrospective study also looked at whether patients had ScTn elevation *at any point during their stay* and found a much higher overall prevalence, increasing from 38% *at admission* to 52% *at any point* (359). If cTn assays are found to represent a tool to help in the risk stratification of critical care patients, this observation highlights the importance of serial measurements and of interpreting abnormal values in the context of the timing and frequency of measurement.

1.6.1.2 General clinical factors associated with ScTn elevation in general intensive settings

A number of demographic and comorbid factors are known to be associated with elevated cTn including age, cardiovascular risk factors, previous cardiovascular disease, malignancy, renal dysfunction and COPD (344, 353, 358-362). The strength of these associations is, however, inconsistent between studies.

There is also variation in the incidence of ScTn elevation depending on the type of admission to ICU, whether that be medical (76%), unplanned surgical (54%) or planned surgical (32%) (359). This is intuitive as it could be postulated that patients with planned admissions are frequently admitted in anticipation of the possibility of adverse events, which may not actually occur, whereas unplanned admissions typically occur following a period of clinical deterioration before admission, often characterised by haemodynamic compromise that could result in ScTn elevation. In support of this notion, the Acute Physiology and Chronic Health Evaluation (APACHE) score, which combines indicators of acute physiological disturbance with long-term health inputs, has been shown to be closely associated with ScTn elevation on admission in a number of studies (351, 352, 355, 358, 361, 362). Further supporting the concept that ScTn elevation is associated with the magnitude of physiological disturbance on admission to critical care, Ammann *et al* found that patients were significantly more likely to have ScTn elevation if shock was present (71% compared to 44% P = 0.004) (349). In addition, Ostermann *et al*, in an CC population without a cardiovascular admitting diagnosis, demonstrated that cTnT was closely correlated with biochemical markers of systemic inflammation as well as NT-proBNP (362). Finally, a number of studies have reported that sepsis and bacteraemia are associated with the highest rates of ScTn elevation (344, 347, 351). By contrast, Liu *et al* failed to identify any association between sepsis or shock and cTn elevation, highlighting the heterogeneity of the existing data (353).

1.6.1.3 Cardiovascular associations with ScTn elevation in general critical care

A number of studies have assessed whether, in patients with ScTn elevation, there was any additional evidence to support the diagnosis of T1MI. On review of the ECG and ScTn, around a quarter of patients in three studies were classified as having MI, but the majority of these were classed as T2MI (345, 348, 363). Landesberg *et al* specifically looked for evidence of myocardial ischaemia in general CC by placing all patients on continuous 12 lead ECG monitoring. This demonstrated that the chance of ScTn elevation was indeed associated with the presence and

duration of ischaemia on the 12-lead ECG (38% had ScTn elevation overall, 67% had ScTn elevation with ischaemia for over 10mins but less than 60mins, 77% had ScTn elevation if there was ischaemia for over 60mins) (352). Whilst this observation is interesting, it does not, however, help to distinguish between T1MI and T2MI. In one small general ICU study, 25 of the 32 patients with ScTn elevation had a stress echo, angiogram or autopsy, which demonstrated that the overwhelming majority (23/25 patients) did not have evidence of flow limiting coronary disease (349). These observations highlight the difficulties of interpreting ScTn results in the context of critical illness and demonstrate that the incidence of important coronary disease is low, suggesting that in the majority of patients elevated ScTn indicates a T2MI or myocardial injury.

Ammann *et al* also demonstrated that there was an association between having a reduced ejection fraction (EF), less than 45%, and ScTn elevation, particularly in the context of sepsis. Specifically, all patients with sepsis and an EF <45% had ScTn elevation, whereas only 42% of patients with an EF>45% had elevated ScTn (349).

1.6.1.4 Outcome and level of support associations with ScTn elevation in general critical care

Current data are discrepant as to whether ScTn elevation in CC is associated with escalation in therapy and length of stay (350, 353). One highly cited meta-analysis reported that ScTn elevation was associated with increased length of CC stay (3 days extra, p=0.004) but not length of hospital stay (2.2 days extra, p=0.12)(347).

Despite the marked variation in outcome data (Table 5), patients with an elevated ScTn consistently have a worse outcome than those with a normal level. Poe *et al* performed a retrospective analysis of nearly 20,000 patients admitted to either a surgical or medical CC and split the peak ScTn results into four categories: negative, ScTn below the lowest level for detection; intermediate, ScTn between the lowest level for detection and the 10% of the CV; high, above the 10% CV (357). Notably, the conventional threshold for diagnosing ScTn "elevation" (i.e. levels above the 99th centile of the distribution for a reference population) lies within the intermediate group in this categorisation (357). Multivariate analysis demonstrated a 30-day mortality odds ratio of 1.82 (P<0.0001) for the high group and 1.18 (P=0.0021) for the intermediate group when compared with the negative group (357). A number of other studies have also demonstrated that the degree of ScTn elevation may be associated with hospital mortality (346, 358, 363, 364). For example, one single large retrospective study demonstrated an association between even minor ScTn elevation and mortality (odds ratio 1.33, p=0.003) (364). However, overall, the available data are inconsistent

with regard to a risk predictive value of ScTn. Perhaps unsurprisingly, the influence of elevated ScTn is attenuated in studies when multivariate analysis is undertaken compared with those using univariate models (355).

1.6.2 ScTn in sepsis in critical care

The data presented thus far support the concept that sepsis is associated with raised ScTn and as a result of this observation a number of studies have looked specifically at this relationship.

1.6.2.1 Incidence of ScTn elevation in sepsis in general critical care

As already described in the GCCU population, the reported prevalence of elevated ScTn at admission to critical care in patients with sepsis also varies greatly from 32% to 85% (Table 6 and Figure 2(365-379)). This variation is likely to be explained by a number of factors including the heterogeneous nature of these populations, the differing admission criteria to a critical care environment, variation in definitions of sepsis, the specific assay employed, small sample sizes, and selection bias regarding the indication for the ScTn test. This selection bias is illustrated by Vasile *et al*, who demonstrated that patients tested for ScTn on admission to ICU were older, had higher APACHE II scores, were more likely to have significant comorbidity (diabetes, hypertension, ischaemic heart disease, heart failure) and had higher predicted in-hospital mortality compared with patients that did not have ScTn assessment on admission (373).

Study	**Type of study**	**Number of septic patients**	**Raised ScTn at admission (unless otherwise stated) %**	**Mortality (%) during admission unless otherwise stated**		**Multivariate mortality analysis**
				ScTn raised	ScTn normal	
Ammann *et al* 2001 (365)	Prospective	20	85	29	33	Not performed
Arlati *et al* 2000 (366)	Prospective	19	58			Not performed

Bessiere *et al* 2013 (367)	Meta-analysis (175 studies)	1226	61	44	28	ScTn remained independent
Brivet *et al* 2006 (375)	Prospective	118	49			ScTn not independent
Fernandes *et al* 1999 (377)	Prospective	10	60	50	25	Not performed
John *et al* 2007 (378)	Retrospective	105	46	52	30 (p = 0.003)	ScTn remained independent
John *et al* 2010 (368)	Retrospective	598	75	32 (28 day)	14 (p<0.0001)	ScTn remained independent
Mehta *et al* 2004 (369)	Prospective	37	43	63	24 (p=0.04)	ScTn remained independent
Sheyin *et al* 2015 (370)	Meta-analysis (17 studies)	1857	61	39	22	ScTn remained independent
Scott *et al* 2008 (376)	Prospective	66	64	29	21	Not performed
Spies *et al* 1998 (379)	Prospective	26	69	83	63	Not performed
Tiruvoipati *et al* 2012 (371)	Retrospective	293	56	36	15 (p<0.01)	ScTn not independent
Vallabhajosyula *et al* 2017 (372)	Retrospective	944	90			ScTn remained independent
Vasile *et al* 2013 (373)	Retrospective	926	42	32	15 (p<0.01)	ScTn remained independent
Ver Elst *et al* 2000 (374)	Prospective	46	50	35	11 (p<0.05)	Not performed

Table 6: ScTn elevation incidence and association with outcome in the context of sepsis in critical care

Kalla *et al* prospectively checked ScTn in 159 patients with bacteraemia on blood culture, only a small proportion of whom were in a critical care environment (6%), and found that 43% had ScTn elevation (117). It has been suggested that bacteraemia causes both direct (via myocarditis) and indirect (via formation of free radicals) myocardial injury (117, 118).

Most studies only assessed ScTn on admission to CC, thereby being unable to detect any changes that could occur as a result of dynamic alterations in a patient's condition during that critical care admission. Importantly, in this regard, two studies measured ScTn at more than one point during the critical care admission. Klouche *et al* measured ScTn levels on days 0 – 5 and then again at day

15. The trend demonstrated that ScTn concentrations peaked on day 2, after which the levels steadily decreased until day 5 when average levels rose again (380). By the 15 day sample, the average ScTn had dropped significantly (380). Scott *et al* measured ScTn at admission to CC and then repeated these measurements every six to eight hours for up to 48 hours after admission if there was ongoing tachycardia, arrhythmia or hypotension (376). Interestingly, this study found that patients with a normal ScTn concentration on admission did not develop tachycardia, arrhythmia or hypotension requiring treatment during the first 48 hours and so did not have repeat ScTn measured (376). Whilst this is only a small study (66 patients, with 24 ScTn negative on admission) it raises the hypothesis that a ScTn level below the ULN on admission points to a lower likelihood of haemodynamic deterioration requiring treatment. Patients that had elevated ScTn levels on admission continued to have elevated ScTn levels during repeat testing (376).

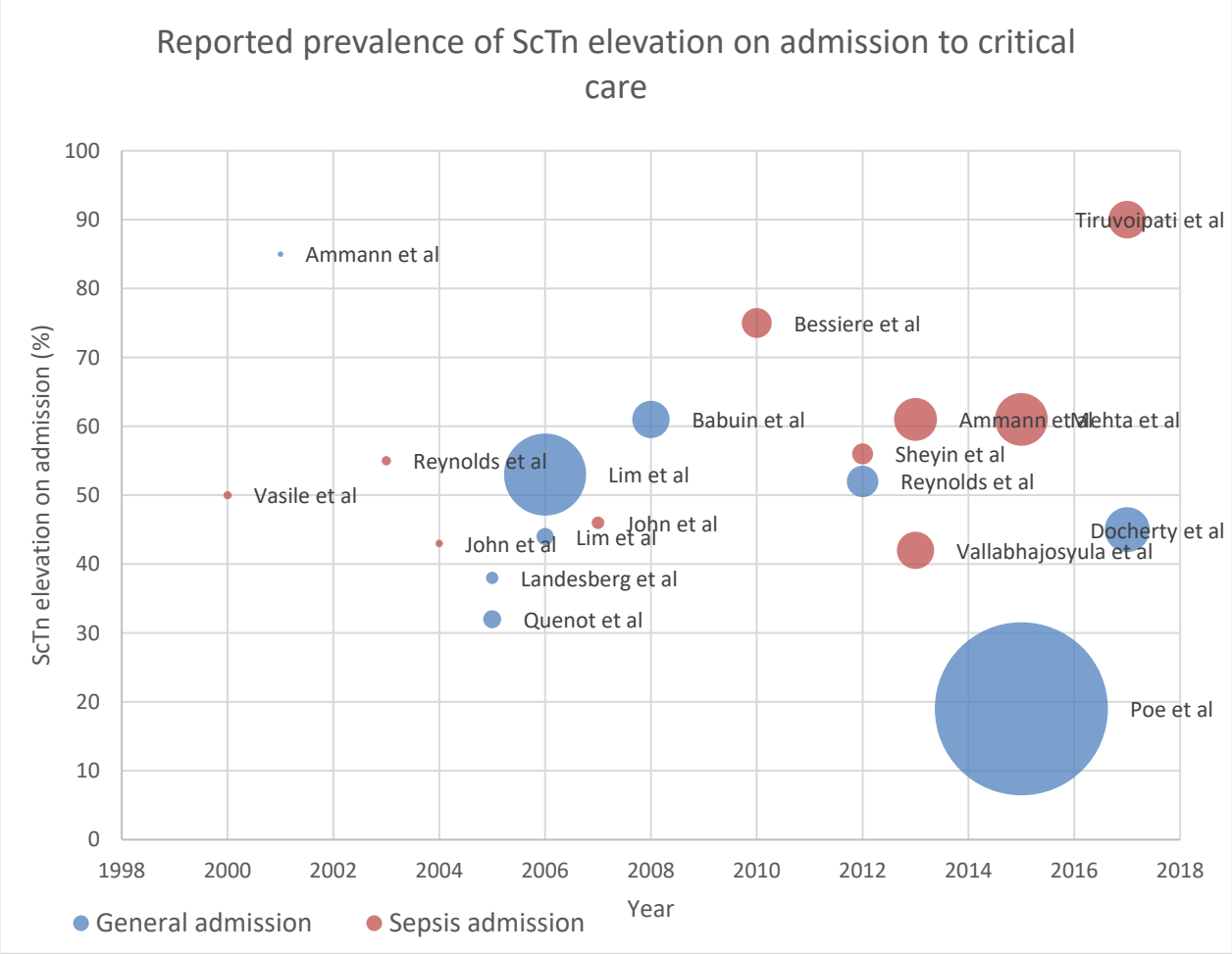

Figure 2: Scatter plot of the reported percentages of patients with a ScTn above the ULN on admission to CC (red = sepsis admission, blue = general admission, size of dot proportional to size of study)

1.6.2.2 Clinical association between ScTn elevation and sepsis in critical care

There is a similar association between ScTn concentrations in patients with sepsis as there is in the general CC population. More severe illness, mainly described by use of the APACHE score, was commonly associated with ScTn elevation in this group (368, 369, 372-374, 378). When considering premorbid state, increased age and comorbidity (diabetes, hypertension, pulmonary hypertension, and chronic kidney disease) were also associated with ScTn elevation in the septic group (368, 372-376). Ammann *et al* found that nine (53%) of ScTn positive cases were caused by gram negative bacteria whilst none of the ScTn negative patients had a gram positive bacteria (365). By contrast, ver Elst *et al* found no difference between the gram stain status of bacteria and ScTn elevation (374). The study by Kalla *et al*, whilst mainly not in a CC environment, is larger than both these studies and did not find an association between bacterial gram stain grouping and ScTn elevation, suggesting that it may be the inflammatory consequences of sepsis, rather than the nature of the organism, that is associated with ScTn concentrations (117). Interestingly, Scott *et al* demonstrated that septic patients with ScTn elevation had significantly reduced oxygen delivery compared to the septic patients without ScTn elevation (376).

1.6.2.3 Association between cardiovascular disease and ScTn concentration in sepsis in critical care

As expected, a number of studies also show that a previous history of cardiovascular disease (including previous MI, CABG and heart failure) is associated with ScTn elevation in sepsis (366, 372, 373, 376). Often, the primary clinical question in the circumstances of a raised ScTn in association with sepsis is whether it relates to a *new* cardiovascular event or whether it is a consequence of ongoing sepsis-induced myocardial injury. This diagnostic challenge is compounded by interpretation of other measures of cardiac wellbeing in this population, such as echocardiographic assessment of left ventricular function. Three studies found that left ventricular systolic dysfunction was more common in the ScTn positive groups early in the CC admission. Thus, Mehta *et al* described a higher prevalence of regional wall abnormalities in the ScTn positive group (56%) compared with the ScTn negative group (5%, P = 0.002) (369, 374, 377). Obviously, however, this snapshot observation cannot confirm whether this relates to a new event, and, if so, whether it is an ischaemic event or merely reflects the patient's cardiovascular history. In 2 studies, a baseline assessment was used to exclude patients with established LV dysfunction on their admission to CC, and then a further assessment made during the admission. The results, however, are discrepant, with Klouche *et al* finding no association between ScTn elevation and the development of left ventricular dysfunction, whereas Thiengo *et al* found a significant difference between ScTn levels

in patients with and without new left ventricular dysfunction at day 3 and 5 (p=0.001 and p=0.01 respectively) (380, 381).

Interestingly, a study of 106 patients admitted to CC with either severe sepsis or septic shock found a degree of echocardiographic dysfunction (LV systolic or diastolic dysfunction or right ventricular dysfunction) in 64% (382). Twenty of the twenty-eight patients who had repeat imaging (at day 5 or on discharge from CC if sooner) had complete normalisation of myocardial function with a significant average improvement in LV systolic function (42 +/- 15 % to 61 +/- 9 % (p=0.01)) and estimated right ventricular systolic pressures (44+/- 11mmHg to 34 +/-13mmHg (p=0.04))(382). Whilst this study did not analyse ScTn in any patients it does provide reassuring data that, for the majority, LV dysfunction is a consequence of sepsis rather than a T1MI.

Only one very small study attempted to assess whether ScTn elevation was associated with coronary disease in patients with sepsis, septic shock or systemic inflammatory response. The authors found no significant underlying coronary disease in 10 of 11 patients that had a further test (whether autopsy, coronary angiography or stress echo) (365). More data are clearly required to elucidate the frequency with which troponin elevation in CC is related to an acute coronary syndrome or other frequent causes of myocardial injury, a dilemma that will get even more frequent as more sensitive cTn assays are adopted.

1.6.2.4 Association between ScTn elevation in sepsis and both level of support and outcome in critical care

Two studies have demonstrated no difference in the requirement for mechanical ventilation according to ScTn elevation (369, 372). There is, however, discordance between studies as to whether ScTn elevation is associated with (a) the use and (b) level of cardiovascular support (369, 372, 374, 379). Meng *et al* recently compared the effect of adding levosimendan or dobutamine for 24 hours in 38 patients in CC with septic shock and an ejection fraction of less than 45%. Whilst there was no difference in clinical outcome the cTn was significantly lower in the levosimendan group (383). When considering length of stay, a single study demonstrated that patients with ScTn elevation have a significantly longer CC stay (9.8 days versus 4.7 days p=0.002) (369). Overall, there is a clear consensus that patients with ScTn elevation have a worse outcome (Table 6) (365-372, 375-379, 381, 384, 385). However, whether ScTn elevation is an independent predictor of outcome in sepsis remains unclear based upon inadequate and discrepant data.

1.6.3 ScTn in cardiac critical care

A substantial proportion of patients admitted to a specialist cardiac critical care unit would be expected to have an elevated cTn either as a result of the acute event leading to the admission (such as myocardial infarct, cardiogenic shock, acute heart failure etc) or as a result of cardiac surgery or percutaneous intervention. In common with data presented thus far, patients with a greater burden of cardiovascular risk factors (including hypertension and diabetes) had higher ScTn levels following mitral valve surgery (mainly for mitral regurgitation)(231). More complex surgical disease and longer cross clamp times are also associated with higher ScTn levels (in patients undergoing either mitral valve surgery or CABG) (231, 386). Furthermore, patients with higher ScTn levels post operatively have a longer length of stay and worse outcomes (231, 386-388). Given the potential for confounding factors it is interesting to note that the highest ScTn levels were independently associated with both increased length of stay and worse outcomes in hospital and at one year following mitral valve surgery or CABG (231, 386).

Platek *et al* conducted a relatively small study (106 patients) of all patients that had a cardiac arrest within the 12 hours prior to admission to cardiac CC, and this heterogeneous group demonstrated no association between the first ScTn level and survival (389).

1.6.4 ScTn in neurosciences critical care

ScTn elevation has also been described in the context of acute brain injury, possibly as a result of an adverse response to the catecholamine surge occurring as a consequence of the injury (390-395). In the context of intracerebral haemorrhage managed within neurosciences CC unit (NCCU), ScTn elevation was an independent predictor of outcome whether on admission or following surgery (391). However, in the context of subarachnoid haemorrhage (SAH), Deibert *et al* found no association between ScTn elevation and prior comorbidity, clinical and radiological severity of SAH or outcome (392). This study, which excluded patients with previous cardiac disease or abnormal echocardiograms, found that over half of patients with ScTn concentrations above the ULN had evidence of left ventricular dysfunction compared to none of the patients with normal ScTn levels (392). Of interest, this response was also transient: in all cases the LV dysfunction subsequently returned to normal during follow up (392). These data suggest that myocardial injury in such cases is transient and unlikely to be due to T1MI. Further evidence that ScTn elevation in critical care doesn't necessarily mean a T1MI, six (50%) of the patients with ScTn elevation went on to have clinically driven investigations which excluded significant coronary disease or myocardial ischaemia in all of them (392).

Salim *et al* conducted a retrospective study including 420 patients with blunt trauma and severe head injury, of whom 30% had ScTn elevation at admission and 41% had ScTn elevation at some point during their admission (393). Higher ScTn levels were associated with both more severe injuries and lower conscious level on admission (393). Whilst hospital mortality was significantly higher in both those with elevated ScTn at admission, and elevated peak ScTn, only peak ScTn elevation proved to be an independent predictor of outcome (OR 8.5, p<0.0001) (393). Another retrospective study including all trauma, found a significantly higher incidence of ScTn elevation in patients with severe head injury leading to brain death compared with the rest of the cohort (54% (of 43 patients) compared with 28% P<0.001) (396).

1.6.5 ScTn in acute liver failure in critical care

Whilst acute liver failure (ALF) is relatively uncommon, the prognosis remains poor in certain subgroups without liver transplantation (397). The King's Liver Critical care Unit (London, UK) reported that 62% of patients had a ScTn elevation on admission, which is of particular interest given their young age (median 36 years) (397). As previously seen in other settings, there is wide variation in the reported incidence of ScTn elevation in patients with ALF, ranging from 27% to 74% (398, 399). These studies demonstrate that ScTn elevation is associated with a more severe ALF and increased inotropic requirements (397-399). In terms of the association with mortality, there is again inconsistency (397, 399).Further, the King's group found a non-significant numerical association between ScTn elevation and left ventricular dysfunction (18% compared to 2% P = 0.051) but not in relation to regional wall abnormalities (397). This is consistent with the concept that the ScTn release is not due to T1MI.

1.6.6 Role of ScTn in other critical care settings

The reported incidence of ScTn elevation in major trauma admissions to CC, as with other presentations, varies from 12% to 29% (396, 400). There is also disparity in the observed associations with ScTn elevation in the trauma population, with one study reporting that ScTn elevation is associated with brain injury, blunt chest injury and shock, whilst another did not find this link (396, 400). Furthermore, Edouard *et al* found that ScTn elevation was not related to survival whilst Martin *et al* found that the highest category of ScTn elevation was an independent predictor of mortality (OR 2.3 p<0.001) (396, 400). Interestingly, Edouard *et al* divided their ScTn elevation into three categories and then performed coronary angiography in the majority of the patients (15

of 17) that had prolonged and significant ScTn elevation and found a coronary artery "injury" (which included dissections, rupture of a pseudo aneurysm or occlusion of distal obtuse margin branches) in seven of them (400). Martin *et al* found that beta-blocker usage in the ScTn elevation trauma group was associated with a 50% reduction in mortality (396). Given the very small number of patients involved, making meaningful interpretation of these data is difficult: there is a suggestion that coronary injury is a common cause of ScTn elevation in trauma and this may explain why beta-blockers have a possible role to play in management of ScTn elevation in trauma. Whilst this is potentially a plausible mechanism the data presented are not, however, convincing here and further research is required to evaluate this theory.

In one retrospective data set of 869 patients, in a surgical CC environment, the reported prevalence of ScTn elevation was 24% and this was associated with increased hospital and CC length of stay as well as mortality (401). Of note, this study also found that beta-blockade usage was associated with improved survival but this was only significant in the highest ScTn group (401).

Two studies have assessed the association between respiratory disease and ScTn elevation in a CC setting. In one retrospective study, 58% of patients with pneumonia requiring CC were ScTn positive and these patients were more likely to have a history of ischaemic heart disease, smoking or kidney disease, but there was no relationship with the APACHE II score (402). There was also an increased length of stay and reduced EF on echocardiogram in the ScTn positive group (402). Troponin elevation was an independent predictor of mortality (OR 1.4 p=0.047) on multivariate analysis (402). Lazzeri *et al* prospectively analysed 42 patients admitted to ICU with Acute Respiratory Distress Syndrome (ARDS) and found an incidence of ScTn elevation of 60% at some point during admission, with 26% of the group becoming ScTn positive during the CC stay having been negative on admission (403). ScTn elevation also remained an independent predictor of mortality (OR 3.6 p=0.042) in this cohort (403).

In the context of severe gastrointestinal bleeding, a single retrospective study of 754 patients demonstrated that 44% had ScTn elevation (404). As expected, ScTn elevation was associated with increasing age, cardiovascular risk factors (hypertension, dyslipidaemia, diabetes), previous diagnosis of ischaemic heart disease and end stage renal failure as well as the APACHE score (404). Whilst in hospital-, 30 day- and long term- (2 years +/-1.4) mortality was higher in the ScTn elevation group, ScTn elevation was only an independent predictor of mortality at the long term follow up (404). This suggests that ScTn has predictive value even once the bleed has resolved, which could point to a role for testing ScTn for long term outcome prediction.

1.7 Hs-cTn in critical care: a modern dilemma

As already discussed, the value of the troponin assay in critical care is uncertain. Specifically, the challenges of interpreting an elevated result are even more profound than in the emergency room or acute medicine settings, when many frontline staff assume a positive result is most likely to be due to T1MI. Whilst this assumption is often erroneous in those populations, the number of factors likely to combine to produce some troponin release in the critically ill mean that the value of hs-cTn to establish this diagnosis in critical care is diluted substantially more.

Given the increased sensitivity of the hs-cTn assays, the proportion of CC patients with hs-cTn elevation will inevitably expand further. However, a growing body of evidence suggests that hs-cTn measurement may have an alternative value in terms of risk stratification and possibly prognostication. The question is whether Hs-cTn measurement will translate into clinical value, perhaps in terms of improved prognostication, or just add confusion and further inappropriate testing when acute coronary syndrome is suspected in a cohort of patients who cannot provide a history. We have summarised the evidence available in the literature on the role of hs-cTn measurement in critical care settings in a review article (405).

1.7.1 Hs-cTn in general CC units

Baron *et al* retrospectively added a Hs-cTn onto the biochemical samples of 448 patients admitted to a non-cardiac CC and found detectable levels in the vast majority (98%) with 75% above the 99th centile (406). As has been frequently documented with ScTn there was an association between increasing age and hs-cTn (406). There was also an association between both increased length of stay (either on CC or in hospital) and mortality (406). Multivariate analysis was not, however, performed in this study.

A retrospective analysis of 243 patients admitted with major trauma demonstrated that the hs-cTnT level (taken in patients in whom it was clinically indicated) was significantly higher in those that died compared with survivors (42ng/L vs. 13ng/L, $p<0.0001$) (407). Furthermore, this study did demonstrate that the odds of mortality significantly increased as hs-cTnT increased and that this was independent of both age and APACHE II score (407).

An observational study of 145 patients presenting with any condition to CC, in whom a hs-cTnI was performed regardless of the clinical presentation, found that 91 (62.7%) had hs-cTnI concentrations above the 99th percentile. On univariate analysis there was an association between hs-cTnI and hospital mortality (OR 1.23 (95% CI 1.09 – 1.41) but this was attenuated in the multivariable model (OR 1.16 (95% CI 0.99 – 1.36) (355). It is possible that this study failed to find an association due to the small sample size.

Metkus *et al* performed a study of 1,057 patients presenting with acute respiratory distress syndrome. This study measured the hs-cTnI concentration within 24 hours of intubation regardless of whether there was a clinical indication for testing. In this population a hs-cTnI concentration above the 99th percentile was seen in 56% of patients (408). Hs-cTnI concentrations were associated with increasing age and markers of illness severity (heart rate, use of vasopressors tidal volume, creatinine and sequential organ failure assessment (SOFA) scores) (408). Interestingly, the relationship between hs-cTnI and 60-day mortality was lost when markers of illness severity were taken into account on multivariable analysis (408)

1.7.2 Hs-cTn in sepsis in critical care

Three studies to date have reported the incidence of hs-cTn elevation in sepsis in CC. One study of 207 patients, out of 470 patients admitted with sepsis, found hs-cTn levels detectable in all patients, with 80% above the 99th centile (409). A second study of 106 patients demonstrated detectable hs-cTn in 88% with 73% having an hs-cTn level above the 99th centile (410). A third prospective study, that performed hs-cTnI testing in all patients admitted to CC with sepsis, found that 60% of the 1124 patients had hs-cTn levels above the 99th centile on admission to CC with sepsis and an additional 7% developed elevated hs-cTn levels within four days (411).

All three of these studies found an association between hs-cTn and increasing age, comorbid state and severity of illness score (409-411). The discordant reported relationship between hs-cTn and outcome is also apparent in these studies. The larger study by Frencken *et al* demonstrated a steady increase in hazard ratio for 14-day mortality with increasing levels of hs-cTn up to 100ng/L (hs-cTnI Abbott ARCHITECT STAT assay, upper reference limit 26ng/l), at which point the risk plateaued (411). On multivariate analysis the moderate (100-500ng/L) and high (>500ng/L) hs-cTnI levels were independently associated with 14-day mortality (HR 1.72 (95% confidence interval 1.14 – 2.59) and HR 1.70 (95% confidence interval 1.11 to 2.6) respectively)(411). There was, however, no association between hs-cTn and one year mortality (411). Furthermore, both the smaller studies

and another study failed to demonstrate that Hs-cTn was an independent predictor of mortality (409, 410, 412).

Landesberg *et al* performed echocardiography, and, unlike a number of the ScTn studies, found no link between hs-cTn and left ventricular ejection fraction. It is notable, however, that there was an association between hs-cTn and indexed right ventricular end diastolic volume (410). Of further interest, Rosjo *et al* performed ScTn alongside hs-cTn to allow a comparison between these two cTns in 204 patients with sepsis managed in a CC environment. The prevalence of Hs-cTn elevation on admission was predictably higher than ScTn (80% compared to 42%) and, interestingly, Hs-cTn did differentiate between survivors and non-survivors, whilst ScTn did not (409). However, neither were significant predictors of outcome on multivariate analysis (409).

In an attempt to assess whether hs-cTn elevation was associated with longer term cardiovascular morbidity, Frencken *et al* reviewed usage of cardiovascular medications in a smaller subset of the patients after one year (122 with elevated hs-cTn and 78 with normal hs-cTn). This demonstrated that patients with hs-cTn elevation during their CC stay increased the number of cardiovascular medications in the following year (median increase of 1 medication $p = 0.002$), whereas the hs-cTn negative patients did not have an increase in cardiovascular medications (411). Interpreting these results is challenging as it is uncertain whether the hs-cTn positive group started the cardiovascular medications as a result of a genuine development of cardiovascular morbidity or as a result of misinterpretation of the hs-cTn result. (411).

1.7.3 Hs-cTn in Cardiac CC

A single study assessed the use of hs-cTn post aortic valve replacement in 79 patients. Unsurprisingly, it demonstrated that the hs-cTn level rose post procedure (413). Higher hs-cTn values were associated with longer cross clamp times, longer time on bypass and longer surgical procedures as demonstrated in the ScTn studies (413). Hs-cTn was, however, not independently associated with inotrope requirement or length of stay (413).

1.8 Future roles for hs-cTn: the "never means nothing" hypothesis?

Whilst cTn remains the gold standard tool for the exclusion/diagnosis of an "MI", this role is often oversimplified in acute medicine/emergency departments due to (a) low awareness of the frequency of T2MI and myocardial injury, and (b) uncertainty about the validity of the manufacturer's quoted 99th centile value as an "upper limit of normal". These factors limit the appropriate use of cTn assays as a binary arbiter of T1MI in front line clinical practice. The clear strength of the test, particularly true of the newer hs-cTn assays, is the ability to robustly rule out T1MI early. By contrast, interpretation of a positive test is becoming increasingly complex, especially in patients without a classical history of cardiac pain. Misdiagnosis of a patient with T2MI or some other reason for myocardial injury exclusive of T1MI can lead to inappropriate investigations and treatment. In critical care, in particular, the inflammatory and comorbid status of patients compounds the likelihood that a cTn elevation is due to multifactorial myocardial injury. Thus, the conventional use of cTn to diagnose T1MI is increasingly compromised outside the context of a patient with a classical history, but the clinical value of a negative result to rule out this diagnosis remains high. However, the data are clear that both T2MI and myocardial injury do not have benign outcomes either, so this diagnosis has value in its own right. Further, evidence is accumulating that in the general population an elevated hs-cTn is a biomarker for the risk of acute CV events. Furthermore, in critical care, there is a body of data to suggest that hs-cTn assays may also provide some risk stratification and even prognostication. More data are now required, particularly in patients in whom there was no clinical indication for performing hs-cTn testing, but this early data suggests that cTn elevation, in whatever context, may always be indicative of increased risk of events.

1.9 Aims and objectives

Hs-cTn has been shown to be elevated in a range of conditions not traditionally associated with T1MI and there is emerging evidence that it may also act as a marker of both cardiovascular and non-cardiovascular risk. In this thesis a series of studies will be described that: a) explore the expected hs-cTn range and factors associated with increased concentrations across ED and CC; b) assess whether hs-cTn has a role as a biomarker of future clinical risk in CC and a complete cohort of hospital patients (including inpatients (IPD), outpatients (OPD) and ED).

The overall objectives are as follows:

1. To assess whether hs-cTnI in ED could provide clinicians with useful information regarding the risk of inpatient mortality
2. To assess whether hs-cTnI concentrations taken in the 20,000 patients in the original CHARIOT study across a range of in- and out-patient settings are associated with one year mortality.
3. To describe the distribution of hs-cTnI concentrations across two different CC environments and the factors associated with increasing hs-cTnI concentrations
4. To determine whether hs-cTnI is associated with mortality in CC population and therefore may act as a biomarker of prognosis

Chapter 2 Method

The method of this thesis consists of three main sections: (a) analysis of the CHARIOT study (Is the Current Threshold of Diagnosis of "Abnormality", including Non ST Elevation Myocardial Infarction, using Raised Highly Sensitive Troponin Appropriate for a Hospital Population) population in the Emergency Department; (b) the one year outcomes of the CHARIOT study; (c) the Distribution of Highly Sensitive Troponin in the Critically Unwell & Associated Mortality study. The method of each of these will be described separately.

I am grateful to Dr Mark Mariathas for allowing me to use the original CHARIOT data for further investigation and analysis (14). He was the lead on the original CHARIOT study which, alongside collecting the hs-cTnI result from 20,000 patients, also recorded the location the sample was taken in, the reported clinical indication for the test, the eGFR, the sodium, the patient age and gender. The remainder of the data collected in this thesis was undertaken by me with the assistance of others as specifically documented in the methods section or in the acknowledgments. All the analyses in this thesis were performed by me.

2.1 CHARIOT Emergency Department sub-study

2.1.1 The design of the original CHARIOT study

The methods of the CHARIOT study have been previously described but the following is a summary of the key elements of the original study (14). CHARIOT was a prospective observational study of 20,000 consecutive patients over the age of 18 years undergoing a biochemistry blood test as part of their routine care in both the in- and out-patient settings between the 29th June and 24th August 2017. A hs-cTnI test was then added onto the first sample received for each patient during the study period as long as there was enough plasma left once the tests ordered by the requesting clinician were completed. Following extensive series of applications via Ethics and the National Confidentiality Advisory Group, the team had approval to proceed without either the patient or their requesting clinician either knowing that the assay had been performed or being told of the result. This study was performed by my predecessor, Dr Mark Mariathas, who kindly allowed me to use the data for further studies.

2.1.2 CHARIOT-ED population

This sub-study included 5708 of the CHARIOT cohort identified as in ED or eye casualty (EC) via the unique sample location details included on the blood sample. Basic demographics as well as the

hs-cTnI result and whether it was clinically requested were available as part of the original CHARIOT study. Clinical coding data (courtesy of Martin Azor) was used to ascertain whether the patient was admitted from ED/EC, the length of hospital stay and whether the patient was alive at discharge. Where there was insufficient data from coding, the electronic record was reviewed to provide these data.

2.1.3 Research approvals

The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The British Cardiac Patients Association was involved in the review of the study protocol and the study received relevant ethical and Health Research Authority UK approval (CAG reference 17/CAG/0083, IRAS number 215262, REC reference 17/SC/0042, Clinicaltrials.gov NCT03047785) (14). The application was unusual, given the lack of patient consent and nesting of the results and therefore involved review and approval by the Confidential Advisory Group.

2.1.4 Cardiac troponin assay

The Beckman Coulter Access AccuTnI+3 assay (Beckman Coulter, Brea, CA, USA) was used to measure hs-cTnI concentrations in CHARIOT because this was the higher sensitivity cTn assay used in our Trust for routine clinical care at the time of the study. The 99th percentile recommended by the manufacturer is 40ng/L and this was therefore used as the ULN in routine clinical practice in our institution. The CV at 40ng/L is less than 10%, the limit of quantification is 20ng/L, limit of detection 8ng/L and the limit of blank 5ng/L. Serum was collected and stored in serum separator tubes and stored at room temperature for up to 24 hours. Hs-cTnI concentrations were measured using the DxI800 platform (Beckman Coulter, Brea, CA, USA).

2.1.5 Statistical analysis

Statistical analysis was performed using SPSS v26.0 (SPPS, IBM Corporation, Armonk, New York, USA). Summary variables are reported as medians with IQRs, with percentages above the ULN and the actual 99th percentile (derived from the data) as appropriate. The Chi Squared test was used for comparisons between categorical variables across two different groups. The Mann-Whitney U test was used for comparison of two continuous variables without a normal distribution. The ability of hs-cTnI to predict survival was tested by calculating receiver operator curves and analysing the area under the curve (AUC). Multivariable analysis was performed to assess for variables independently associated with outcome.

2.2 One year follow up of the CHARIOT population

2.2.1 Study population

This study included all 20,000 patients from the original CHARIOT study (14), the methodology of which has been described previously.

2.2.2 Research approvals

To conduct this follow up study, a major amendment was submitted and subsequently approved by both the research ethics committee and the Confidentiality Advisory Group. Approval from the Confidentiality Advisory Group was required because in the original CHARIOT study patients were unaware that an additional hs-cTnI test was being performed and this would continue during the one year follow up.

2.2.3 Cardiac troponin assay

As already discussed, the Beckman Coulter Access AccuTnI+3 assay (Beckman Coulter, Brea, CA, USA) was used to measure hs-cTnI concentrations in CHARIOT because this was the higher sensitivity cTn assay used in our Trust for routine clinical care at the time of the study.

2.2.4 Data collection

An application to NHS Digital was completed to access one year outcome data for the entire CHARIOT cohort. NHS Digital were sent the NHS number, gender, date of birth and study specific ID for each study patient. NHS Digital then matched these to both the Health Episode Statistics and Office of National Statistics datasets in order to provide alive/dead status and cause of death at one year. NHS Digital then returned these data with the study specific ID to allow matching to the CHARIOT dataset.

2.2.5 Statistical analysis

Data were initially summarised based on whether they were continuous or categorical variables with appropriate statistical tests used to compare across groups. Kaplan Meier curves were used to compare the one year mortality depending on the hs-cTnI concentration. For this, two hs-cTnI variables were considered: firstly whether the hs-cTnI was above or below the ULN and secondly as an ordinal variable with categories defined by the ratio of hs-cTnI concentration to ULN (0, >0 to <0.25, 0.25 to 0.5, >0.5 to 1 and >1). Multivariable analysis was performed by fitting a Cox proportional Hazards model with hs-cTnI concentration as the variable of interest (primarily as log(10) transformed hs-cTnI). The proportional hazards assumption was evaluated for categories of hs-cTnI relative to the ULN using the log (-log(survival)) versus log (time) graph to ensure that this assumption was met. The area under the curve (AUC) was calculated from receiver operating characteristic curves (ROC) using hs-cTnI concentrations alone as a continuous variable.

2.2.6 Patient public involvement

As already discussed, patients included in this study were not contacted, but information, including a privacy notice, was placed on the research section of University Hospital Southampton's website. This explained the rationale for the study and described a study specific mechanism for patients to withdraw their data. The protocol for the CHARIOT study was reviewed by the Chairman of the British Cardiac Patients Society who was supportive of the methodology used.

2.3 Distribution of Highly Sensitive Troponin in the Critically Unwell & Associated Mortality

2.3.1 Study population

This was a prospective observational study (entirely separate from the CHARIOT study) of all adult patients (at least 18 years of age) admitted to one of two CC environments within our institution (University Hospital Southampton) over a six month period. The study enrolled consecutive adult

patients admitted to CC in whom at least one biochemistry sample was requested by the clinical team between 29th of January 2019 and 29th of July 2019. A hs-cTn test was added to the first biochemistry sample received and following this on day 1 and day 2 and then every alternate day until the patient was discharged from CC. Patients who did not have a hs-cTnI performed on admission were excluded from the analysis (specifically, this included patients who were already in CC at the start of the study and those who did not have a biochemistry sample requested within 24 hours of admission). Patients that remained in CC after the close of serial blood testing (30th of September) were excluded from further analysis. Patients who had suffered T1MI, as determined by clinical coding and admission criteria, were also excluded from the analysis.

2.3.2 Research approvals

The study received approval from the Confidentiality Advisory Group, part of the Health Research Authority. This was necessary for two reasons. Firstly, patients included in the study were not consented or informed that this extra blood test was being performed. Secondly, apart from patients in whom the clinical team requested hs-cTn testing as part of the patient's routine care, the results were nested and never revealed to either the patients or the clinical team, regardless of the magnitude of the result.

2.3.3 Cardiac troponin assay

The Beckman Coulter Access hsTnI assay (Brea, CA, USA) is now the hs-cTn assay in routine clinical use at our institution currently and, as such, was used to measure hs-cTnI concentrations in the study population. The manufacturer's recommended 99th percentile is 18 ng/L (at which level the coefficient of variation (CoV) is <10%) and this is the ULN used in clinical practice within our institution. The limit of detection is 2ng/L and the limit of quantification (10% of the CoV) is 6ng/L. This assay is a further iteration from the assay used in the CHARIOT study and has improved sensitivity as demonstrated by the improved discrimination at lower concentrations.

Study-requested hs-cTnI testing was only performed using serum that was left after all of the clinically requested tests were performed. An automated system was set up, with the help of the biochemistry team at our Trust, to add hs-cTnI testing to samples with a CC location code for the appropriate days and to ensure that study patients had hs-cTnI testing added only once on study testing days. The serum was collected in separator tubes and stored at room temperature for up to 24 hours before hs-cTnI levels were measured using the DxI800 platform (Beckman Coulter). Quality control was performed on the assay on a daily basis as part of routine clinical practice.

2.3.4 Data collection

Alongside the hs-cTnI result, the study team were informed as to whether the test was requested for clinical reasons on each of the study testing days. Specific comorbidity data (smoking status, BMI, hypertension, dyslipidaemia, diabetes, chronic kidney disease, asthma, chronic obstructive pulmonary disease, cerebrovascular disease, heart failure, ischaemic heart disease, previous percutaneous coronary intervention, previous coronary artery bypass grafting, atrial fibrillation, Crohns disease, ulcerative colitis, rheumatoid arthritis and peripheral vascular disease) were extracted from the online clinical record used within our institution (Metavision, iMD Software, Dusseldorf, Germany). The clinical coding system was also interrogated for the presence of these comorbidities in case the comorbidity was not entered contemporaneously in the electronic record. The type (elective/emergency, medical/surgical) and cause of admission was recorded from the online clinical record.

On admission, the determinants of the Acute Physiology and Chronic Health Evaluation (APACHE) II score (Table 7) and the Sequential Organ Failure Assessment (SOFA) score (Table 8) were recorded from the online patient record (414, 415). In addition, on admission, the haemoglobin, C-reactive protein (CRP) and lactate were recorded using the online patient record. The SOFA score, haemoglobin, CRP, lactate and white blood cell count were recorded on study blood test days.

The majority of the data was collected was collected using a bespoke data collection tool that we created which was linked to the online clinical record. I am grateful to Maclyn Augustine and Dr Lavinia Gabara for their help collecting some of the data during this study. Other than hs-cTnI testing, the research team did not perform additional testing, and so, any variables that were not performed as part of routine care were recorded as missing. Where there was no arterial gas result available, the partial pressure of oxygen was estimated based on the oxygen saturations using the previously defined estimates (416). The use of organ support was monitored throughout the CC stay. The clinical coding system was interrogated to define the length of stay and whether the patient died in CC.

	Score								
	4	3	2	1	0	1	2	3	4
Temperature (°C)	≥41	39 – 40.9		38.5 – 38.9	36 – 38.4	34 – 35.9	32 – 33.9	30 – 31.9	≤29.9
Mean arterial pressure (mmHg)	≥160	130 – 159	110 – 129		70 – 109		50 – 69		≤49
Heart rate	≥180	140 – 179	110 – 139		70 – 109		55 – 69	40 – 54	≤39
Respiratory rate	≥50	35 – 49		25 – 34	12 – 24	10 – 11	6 – 9		≤5
Oxygenation (PaO2 if FiO2< 50% otherwise A-a gradient (mmHg)					PaO2 >70	PaO2 61 – 70	PaO2 55 – 60		PaO2 <55

	A-a >499	A-a 350 – 499	A – a 200 – 349		A-a <200				
Arterial pH	≥7.7	7.6 – 7.69		7.5 – 7.59	7.33 – 7.49		7.25 – 7.32	7.15 – 7.24	<7.15
Sodium (mmol/L)	≥180	160 – 179	155 – 159	150 – 154	130 – 149		120 – 129	111 – 119	≤110
Potassium (mmol/L)	≥7	6 – 6.9		5.5 – 5.9					
Creatinine ((mmol/L) double if acute renal failure)	≥310	177 – 309	133 – 176		53 - 132		<53		
Haematocrit (%)	≥60		50 – 59.9	46 – 49.9	30 – 45.9		20 – 29.9		<20
White blood count (1000s/mm^2)	≥40		20 – 40	15 – 20	3 – 14.9		2.9 - 1		≤1
Glasgow Coma Score	= 15 – actual Glasgow Coma Score								
History of severe organ insufficiency/ immunocompromised	No – score = 0 Yes and non-operative or non-elective – score = 5 Yes and elective post-operative – score = 2								
Age score	6	5	3	2	0				
Age	>74	65 – 74	55 – 64	45 – 54	≤44				

Table 7: Acute Physiology and Chronic Health Evaluation (APACHE) score determinants (PaO2 - partial pressure of oxygen, FiO2 - Fraction of inspired oxygen, A-a - Alveolar-arterial gradient)

Parameter	**SOFA Score (sum of worst value in each parameter in 24 hours)**				
	0	1	2	3	4
PaO2/FiO2 mmHg	>400	400 – 300	299 – 200	199 – 100 With mechanical support	<100 With mechanical support
Platelets ($x10^3/mm^3$)	>149	149 – 100	99 – 50	49 – 20	<20
Bilirubin (µmol/l)	<20	20 – 32	33 – 101	102 – 204	>204
GCS	15	14 – 13	12 – 10	9 – 6	<6
Creatinine (µmol/l)	<110	110 – 170	171 – 299	300 – 440	>440
MAP (mmHg) & vasoactive medication (mcg/kg/min)	>70	<70 No support	Dopamine ≤5 or dobutamine any dose	Dopamine >5 Adrenaline ≤ 0.1 Noradrenaline ≤ 0.1	Dopamine > 15 Adrenaline > 0.1 Noradrenaline >0.1

Table 8: Sequential Organ Failure Assessment (SOFA) score determinants

2.3.5 Statistical analysis

Analysis was performed using SPSS 26.0 (SPSS, IBM Corporation, Armonk, New York, USA). Summary variables are reported as median with the interquartile range (IQR) as well as the percentage above the ULN. The Chi squared test was used for comparison between categorical variables across two groups. The Mann-Whitney U test was used for comparison of continuous

variables, without a normal distribution. Hs-cTnI was log (to the base 10) transformed due to the highly positively skewed distribution of this variable. Multivariable logistic regression analysis was performed with outputs presented as odds ratios (OR) with 95%CI.

2.3.6 Patient public involvement

The study protocol was reviewed with the patient public involvement research group at University Hospital Southampton. In particular the discussion focused on the planned lack of informed consent among the participants because a consecutive cohort was required to meet the study objectives. The patient public involvement research group were supportive of the study methodology including the lack of informed consent from participants because of the need for a consecutive cohort and because the research team were not performing any additional procedures or blood sampling beyond the standard clinical care.

Chapter 3 CHARIOT-ED Sub-study

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Distribution of contemporary sensitivity troponin in the emergency department and relationship to 30-day mortality: The CHARIOT-ED substudy

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ABSTRACT

Background
Contemporary sensitivity troponin (cs-cTn) concentrations above the upper limit of normal (ULN) are seen in a wide range of clinical conditions and evidence is growing that suggests cs-cTn may be a biomarker of future morbidity and mortality.

Objectives
Our aim was to test the hypothesis that cs-cTn, measured in the emergency department, may be a biomarker for 30-day mortality, irrespective of the patient's presentation.

Method
In all 5,708 consecutive cases, contemporary sensitivity troponin I (cs-cTnI) was measured either as requested by the clinical team or as part of the study, in which case both the clinical team and the patient were unaware of the result. Basic demographics were available from the original study and 30-day mortality was derived from NHS Digital data.

Results
In patients whose cs-cTnI test was requested solely as part of the study, 30-day mortality increased with increasing cs-cTnI concentrations (0% with undetectable concentrations to 14.7% with concentrations above the ULN). Multivariable Cox regression analysis showed that log(10)cs-cTnI concentration was independently associated with 30-day mortality.

Conclusion
Increasing cs-cTnI concentrations are associated with higher short-term mortality as well as length of stay. As such, cs-cTnI measurements may provide useful prognostic information.

KEYWORDS: Emergency department, myocardial injury, myocardial infarction, acute coronary syndrome, contemporary sensitivity troponin

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(417)

3.1 Abstract

Background: Contemporary sensitivity troponin (hs-cTn) concentrations above the upper limit of normal (ULN) are seen in a wide range of clinical conditions and evidence is growing that suggests cs-cTn may be a biomarker of future morbidity and mortality.

Objectives: Our aim was to test the hypothesis that cs-cTn, measured in the emergency department (ED), may be a biomarker for 30 day mortality, irrespective of the patient's presentation.

Method: In all 5708 consecutive cases hs-cTnI was measured either as requested by the clinical team or as part of the study, in which case both the clinical team and the patient were unaware of the result. Basic demographics were available from the original study and 30 day mortality was derived from NHS Digital data.

Results: In patients whose hs-cTnI test was requested solely as part of the study, 30 day mortality increased with increasing hs-cTnI concentrations (0% with undetectable concentrations to 14.7% with concentrations above the ULN). Multivariable Cox regression analysis showed that log(10)hs-cTnI concentration was independently associated with 30 day mortality.

Conclusion: Increasing hs-cTnI concentrations are associated with higher short term mortality as well as length of stay. As such, hs-cTnI measurements in patients presenting to ED may therefore provide useful prognostic information.

3.2 Introduction

The recommended criteria for the diagnosis of a type 1 myocardial infarction (T1MI) require a rise in cardiac troponin (cTn) above the 99th percentile derived from a reference population of normal individuals, in association with relevant symptoms and ECG changes (16). Around 6% of patients

arriving at the Emergency Department (ED) present with chest pain and the ability to manage these patients in a clinically effective and efficient manner is of paramount importance to healthcare systems (7). A key limitation with the initial cTn assays was that, in order to achieve acceptable levels of sensitivity and specificity, a sample was required 10 – 12 hours after the onset of chest pain. This stimulated the development of contemporary sensitivity cTn (cs-cTn) assays (11, 12). These assays now demonstrate improved diagnostic performance within a few hours of admission, and recently even earlier than this, which has led to their widespread adoption in both clinical practice and guideline recommendations (11, 12, 16, 133, 134). Consequently, cs-cTn assays have reduced the number of patients admitted from ED with chest pain by approximately a third, with no cost in terms of adverse clinical outcomes (15, 138).

Whilst the role of cs-cTn for rapid exclusion of MI in patients presenting to ED has been well established, the potential clinical value of cs-cTn as a biomarker outside this context is unknown (13). There is, however, evidence that both standard cTn and, to a greater degree, cs-cTn are frequently detected in patients presenting to ED, despite only a small proportion actually having a T1MI (14, 151-153, 418-420). In the CHARIOT study, we measured cs-cTn on 20,000 consecutive patients attending our institution for any reason, either inpatient or outpatient, with the aim of describing the true distribution and 99th percentile for cs-cTn in a hospital population (14). In the current study, we report the distribution of cs-cTn in the subpopulation of CHARIOT who attended ED, in whom the assay was taken *regardless of whether there was a clinical indication* and we assessed a possible association between the cs-cTn concentration and both 30 day mortality and length of stay. Our aim was to test the hypothesis that cs-cTn may be a biomarker for clinical outcome, irrespective of the indication for its measurement.

3.3 Materials and methods

3.3.1 Study population

This study included 5708 consecutive patients over the age of 18 years, presenting to ED or eye casualty (EC), who had a biochemistry sample performed for any reason as part of their routine clinical care as directed by the supervising clinician. These patients are a subset of the CHARIOT study that were identified as being seen initially in either ED or EC via the unique sample location originator details included on the blood sample (14). The sample location details are required in order to process biochemistry samples at our institution. This study included all locators from ED and EC; EC, clinical decisions unit (CDU), minor treatment area, major treatment area, resuscitation area and a generic ED code. Patients are triaged to these areas on arrival based on the perceived severity of their condition.

The method of the CHARIOT study (14) has been previously described but the key elements of this study are as follows: CHARIOT was a prospective observational study of 20,000 patients over the age of 18 undergoing biochemistry blood tests for any reason as part of their routine care in both the in- and out-patient settings. A hs-cTnI test was added on to the first sample received for each patient during the study period. The patients were unaware that this test was being performed, and, unless requested by the clinician, the hs-cTnI result was not revealed to patient or their doctor. This study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and the study received relevant ethical and Health Research Authority UK approval (IRAS 215262, REC 17/SC/0042, CAG 17/CAG/0022). In order to access the 30 day mortality for all patients, a major amendment was submitted and subsequently approved by both the Research Ethics Committee and the Confidentiality Advisory Group (IRAS 215262, REC 17/SC/0042, CAG 17/CAG/0083).

3.3.2 Troponin assay

The Beckman Coulter Access AccuTnI+3 assay (Beckman Coulter, Brea, CA, USA) was used to measure hs-cTnI concentrations in CHARIOT because this was the higher sensitivity cTn assay used in our Trust for routine clinical care at the time of the study. The 99th percentile recommended by the manufacturer is 40ng/L and this was therefore used as the upper limit of normal (ULN) in routine clinical practice in our institution.

3.3.3 Clinical outcome data

Basic demographic details, estimated glomerular filtration rate (eGFR), indication for the biochemistry sample and whether the hs-cTnI was requested by the clinical team were available from the original CHARIOT study. As prospectively planned, data from clinical coding were used to ascertain the following: whether the patient was admitted, the length of stay and the discharge diagnosis. Where there was insufficient coding data, the individual electronic patient record was interrogated to provide these data. Further, NHS Digital were sent each patient's NHS number, gender, date of birth and study specific ID to allow them to match each patient with national mortality data to provide 30 day mortality.

3.3.4 Statistical analysis

Statistics were performed using SPSS V26.0 (SPSS, IBM Corporation, Armonk, New York, USA). Summary variables are reported as medians with interquartile ranges, with the number (and percentage) above the ULN and the actual 99th percentiles as appropriate. The Chi squared test was used for comparison between categorical variables. The Mann-Whitney U test was used for comparison of continuous variables without a normal distribution. The primary outcome was 30-day mortality. The discriminatory ability of hs-cTnI for survival was tested by calculating receiver operator curves (ROC) and analysing the area under the curve (AUC). The sensitivity, specificity, positive and negative predictive values (PPV & NPV) of specific concentrations of hs-cTnI were

derived from the ROC analysis. Multivariable analysis was performed using a Cox proportional hazards model, with outputs presented as hazard ratios (HR) with 95% confidence intervals (95%CI). Hs-cTnI was log(10) transformed due to the highly positively skewed distribution of this variable. Covariables in this multivariable analysis were: gender, age, sample location, whether the hs-cTnI was requested and the eGFR (421). Separate mortality analyses were completed for the whole population and for the patients in whom the admitting clinician did not suspect acute coronary syndrome and, as such, did not request a hs-cTnI test.

3.3.5 Patient and public involvement

The protocol of the original CHARIOT study was reviewed by the British Cardiac Patients Association who wrote a letter of support to the Confidentiality Advisory Group. In particular, the group accepted that the lack of patient consent in the study was appropriate.

3.4 Results

3.4.1 Demographics of the whole cohort

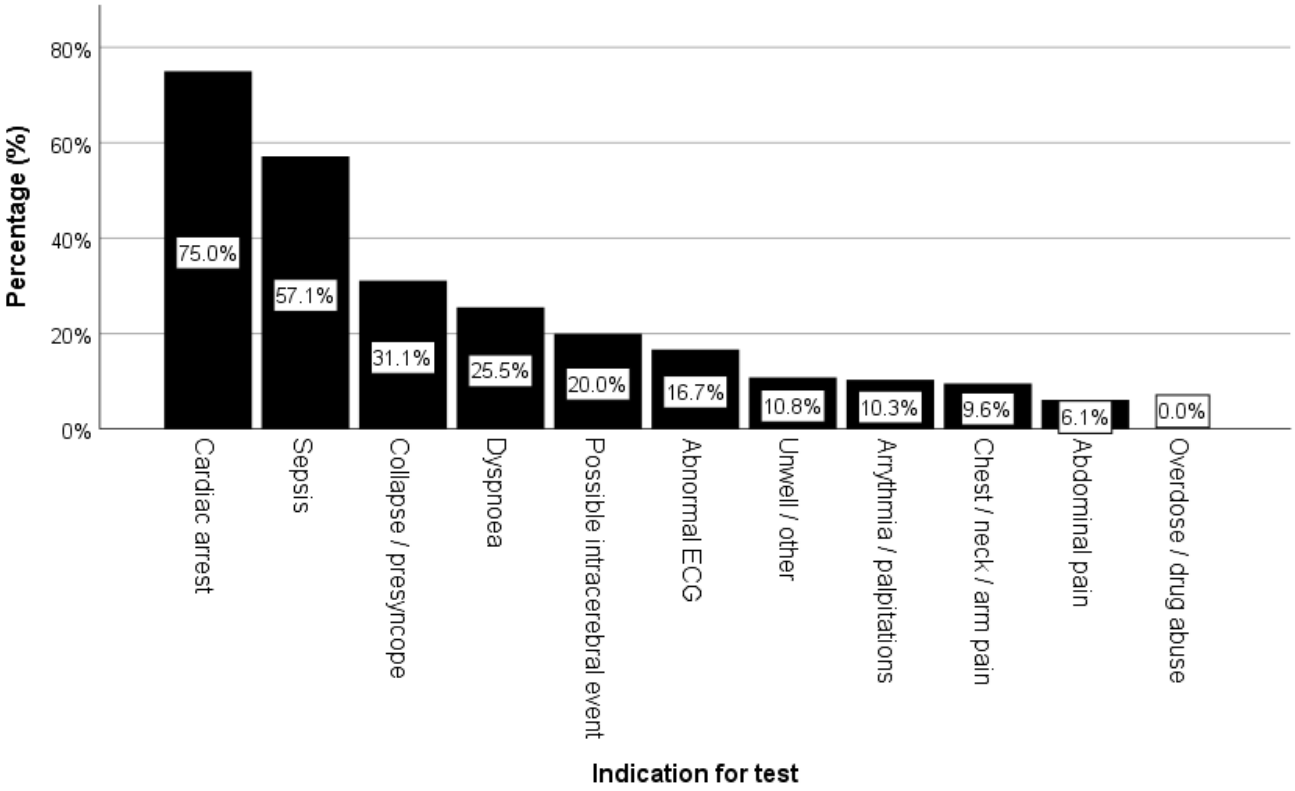
The median age of the whole cohort was 56 years (IQR 35 – 76 years). There were 63 (1.1%) samples from EC with the remainder from ED (resuscitation 554 (9.7%), majors 2551 (44.7%), minors 451 (7.9%), clinical decision unit (CDU) 23 (0.4%) with the rest from a “generic ED” location code 2066 (36.2%)). The median hs-cTnI for the whole population was 7 ng/L (IQR 3-13), with 681 (11.9%) having an undetectable hs-cTnI concentration and 491 (8.6%) having a hs-cTnI above the ULN. The 99th percentile for the whole cohort was 755ng/L. The frequency of hs-cTnI above the ULN increased with age (25 (1.4%) aged 18-39, 45 (3.3%) aged 40-59, 149 (10.4%) aged 60 – 79, 272 (23.2%) aged 80 and over).

3.4.2 Clinician-requested samples and study only samples

The clinical team requested hs-cTnI in 1551 (27.2%) of patients (0 (0%) in EC, 3 (13.0%) in CDU, 8 (1.8%) in minors, 688 (27.0%) in majors, 123 (22.2%) in resuscitation, 729 (35.3%) generic ED). The median hs-cTnI for patients who had their hs-cTnI test requested by the supervising clinician was 7ng/L (IQR 3 – 13). There were 512 (12.3%) with undetectable hs-cTnI concentrations and 309 (7.4%) with concentrations above the ULN. The 99th percentile for this cohort was 378ng/L. Table 9demonstrates the percentage of patients with hs-cTnI concentrations above the ULN based on their location and whether the test was requested by the clinical team. Figure 3 demonstrates the range of indications given for requesting hs-cTnI testing and the frequency with which the result was above the ULN.

Location	**Percentage of patients with hs-cTnI above 99th percentile**	
	Clinically requested	*Study requested*
Eye Casualty	n/a	0.0%
Minors	0.0%	2.0%
CDU	0.0%	5.0%
Majors	5.7%	7.2%
Generic ED	8.0%	6.2%
Resus	19.3%	28.8%

Table 9: Frequency of hs-cTnI above the 99th percentile across ED locations



Total number of tests	4	7	90	51	10	6	37	58	1234	49	5

Figure 3: Bar chart to demonstrate frequency of hs-cTnI above the ULN by clinical indication for testing

There was no difference observed in age distribution between patients in whom the test was clinically requested and those in whom it was only performed as part of the study (56 years (IQR 34 – 77 years) vs 56 years (IQR 34 – 77years)). There were fewer males in the clinically requested cohort (42.9% vs. 52.8%).

3.4.3 Outcome of ED visit

Five patients died in ED with a median age of 57: three of these had a hs-cTnI above the reference range (none of which were requested by the clinical team). Of the remaining 5703 patients, 3603

(63.2%) were admitted and 2100 (36.8%) were discharged from ED/EC. The median hs-cTnI for admitted patients was 9 ng/L (IQR 4 – 18 ng/L) with a 99th percentile of 1162ng/L and 439 (12.2%) were above the ULN, whilst for those patients not admitted the median was 5ng/L (IQR 2-9 ng/L) with a 99th percentile of 67ng/L and 49 (2.3%) were above the ULN (p<0.001). The rate of admission increased with increasing hs-cTnI concentrations regardless of whether the test was clinically requested or not (Table 10).

Hs-cTnI	**Admission rate (whole cohort)**	**Admission rate (clinically requested)**	**Admission rate (study requested only)**
0 ng/L	52.0%	49.7%	52.7%
1 - 9 ng/L	55.3%	54.9%	55.5%
10 - 19 ng/L	70.5%	69.6%	70.9%
20 - 40 ng/L	79.8%	79.7%	79.8%
>40 ng/L	90.0%	96.2%	86.3%

Table 10: Admission rate for hs-cTnI concentrations

Once patients in whom the hs-cTnI was clinically requested were excluded, the median hs-cTnI for admitted patients was 8 ng/L (IQR 4 – 17 ng/L) with a 99th percentile of 600ng/L and 264 (10.1%) were above the ULN, whilst for those patients not admitted the median was 5ng/L (IQR 2-9 ng/L) with a 99th percentile of 69ng/L and 42 (2.7%) were above the ULN (p<0.001).

3.4.4 Cause of hs-cTnI elevation

A cardiovascular diagnosis (27.5%) was the most frequent discharge diagnosis in those with an hs-cTnI above the ULN (Table 11). However, a neurological or a respiratory condition (13.6%) was most common in the patients in whom the test was only requested as part of the study and therefore the result was not available to the clinical team as there was no suspicion of an acute coronary syndrome. Table 12 highlights the mortality and distribution of hs-cTnI for each cardiovascular discharge diagnosis. Patients with a T1MI had higher hs-cTnI concentrations than the rest of the patients with hs-cTnI above the ULN (227 ng/L (101 – 1357 ng/L) and 69ng/L respectively (52 – 151ng/L) p<0.001).

Discharge diagnosis category	Number (%) of patients (whole population)	Number (%) of patients (only clinically requested)	Number (%) of patients (only requested as part of the study)
Allergy	2 (0.4%)	0	2 (0.7%)
Cardiovascular	135 (27.5%)	109 (59.9%)	26 (8.4%)
Endocrine	5 (1.0%)	1 (0.6%	4 (1.3%)
Ear, nose and throat / maxillofacial / dental	5 (1.0%)	0	5 (1.6%)
Fracture / dislocation	27 (5.5%)	0	27 (8.7%)
Gastrointestinal	36 (7.3%)	7 (3.9%)	29 (9.4%)
Neurological	46 (9.4%)	4 (2.2%)	42 (13.6%)
Non-specific chest pain	13 (2.7%)	13 (7.1%)	0
Obstetrics / gynaecology	2 (0.4%)	0	2 (0.7%)
Ophthalmology	1 (0.2%)	0	1 (0.3%)
Other	10 (2.0%)	1 (0.6%)	9 (2.9%)
Overdose / poisoning	5 (1.0%)	1 (0.6%)	4 (1.3%)
Psychiatric	3 (0.6%)	2 (1.1%)	1 (0.3%)
Renal / urology	27 (5.5%)	3 (1.7%)	24 (7.8%)
Respiratory	64 (13.0%)	22 (12.1%)	42 (13.6%)
Skin / joint / bone infection	6 (1.2%)	0	6 (1.9%)
Soft tissue injury / joint pain/injury/swelling / rashes	32 (6.5%)	6 (3.3%)	26 (8.4%)
Syncope / fall / postural hypotension	32 (6.5%)	8 (4.4%)	24 (7.8%)

Unspecified sepsis / infection	31 (6.3%)	4 (2.2%)	27 (8.7%)
Vascular disease	4 (0.8%)	1 (0.6%)	3 (1.0%)
Viral infection	5 (1.0%)	0	5 (1.6%)

Table 11: Discharge diagnosis categories in patients with a hs-cTnI concentration above the 99th percentile of all patients and then split by whether the supervising clinician requested the test or not

Diagnosis	**Number**	**Hs-cTnI (median) (ng/L)**	**Hs-cTnI (IQR) (ng/L)**	**Hs-cTnI>ULN no (%)**	**Mortality no (%)**
Arrhythmia	150	13	6 – 25	27 (18.0)	1 (0.7)
Heart failure	45	38	22 - 84	20 (44.4)	5 (11.1)
Acute coronary syndrome	90	112	29 - 657	63 (70.0)	7 (7.8)
Cardiac arrest / cardiogenic shock	5	70	41 - 787	4 (80.0)	3 (60.0)
Valvular heart disease	10	26	7 - 33	1 (10.0)	2 (20.0)
Pericardial diseases	17	11	6 - 55	5 (29.4)	0
Stable ischaemic heart disease	39	16	10 - 39	8 (20.5)	0
Hypertension	10	10	7 - 30	1 (10.0)	0
Aortic diseases	3	14	n/a	0	1(33.3)
Myocarditis	4	51	15 - 869	3 (75.0)	0
Device infection	5	37	13 - 368	2 (40.0)	1 (20.0)
Other	39	4	0 - 8	1 (2.6)	0

Table 12: Frequency of cardiovascular discharge diagnoses, the spread of hs-cTnI concentrations and the associated 30-day mortality

3.4.5 Hospital length of stay and 30-day mortality

150 (2.6%) patients died within 30 days of their presentation to ED. None of the patients that had an undetectable hs-cTnI died, but there was an associated increase in both mortality and length of stay with increasing hs-cTnI concentration in the whole cohort, and in those only having hs-cTnI testing as part of the study whose result was not available to the supervising clinical team

because there was no clinical suspicion of acute coronary syndrome (Figure 4 &Figure 5 respectively). The discriminatory ability of hs-cTnI concentration for 30-day mortality for the whole cohort was 0.863 (95% CI 0.838 – 0.888) and it was 0.859 (95% CI 0.830 – 0.888) for those in whom the test was only performed as part of the study. Table 13**Error! Reference source not found.** demonstrates the specificity, sensitivity, PPV and NPV derived from the ROC analysis for different hs-cTnI thresholds. The log(10) hs-cTnI was independently associated with 30 day mortality for the whole cohort (HR 3.836 (95%CI 3.211 – 4.583)). Furthermore, once all the patients in whom the hs-cTnI was requested on clinical grounds were excluded, hs-cTnI remained independently associated with 30 day mortality (HR 3.008 (95% CI 2.320 – 3.901)) (Table 14).

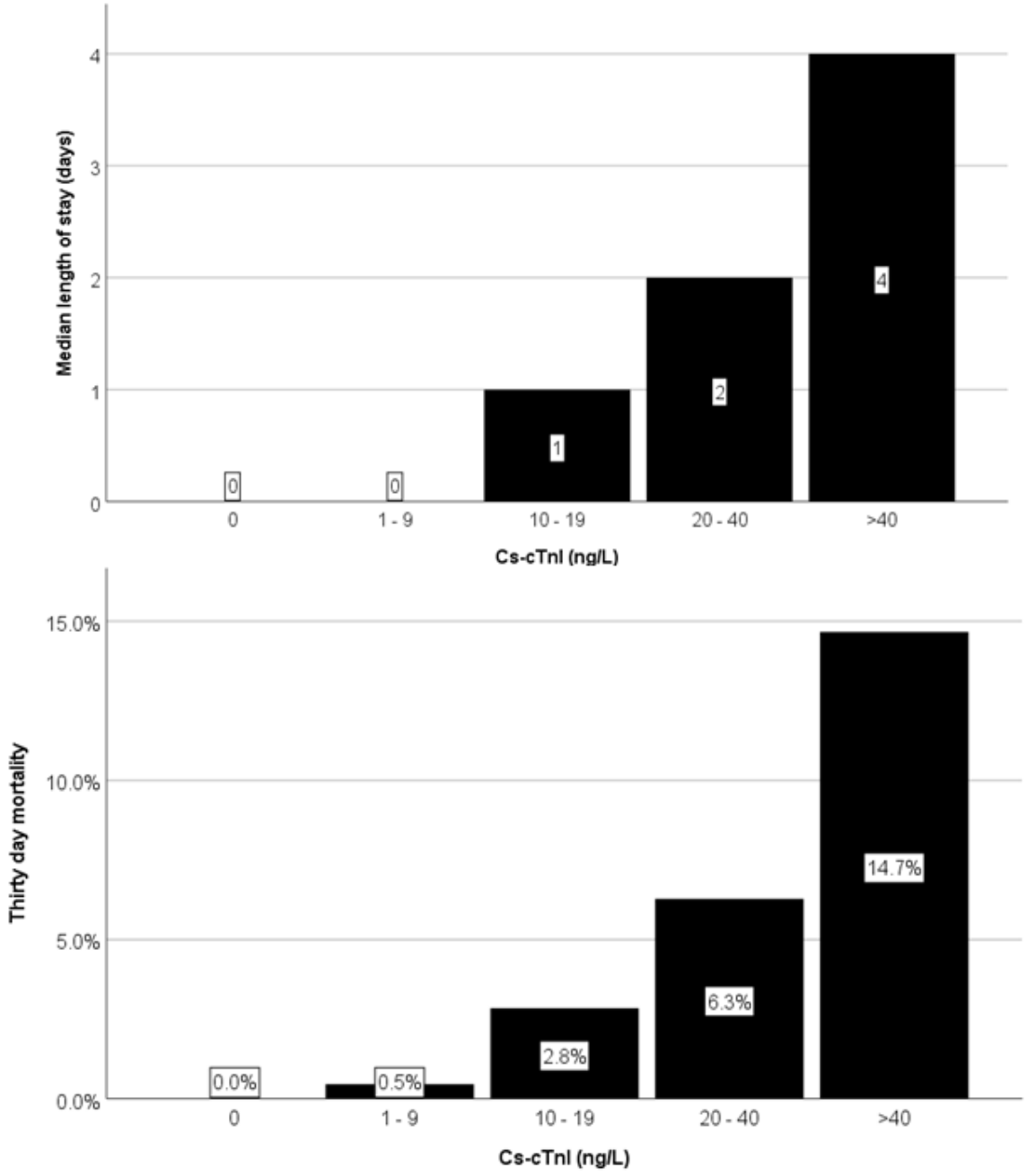


Figure 4: Length of stay and 30-day mortality across hs-cTnI groups for the whole cohort (panel A - median length of stay, panel B - 30-day mortality.

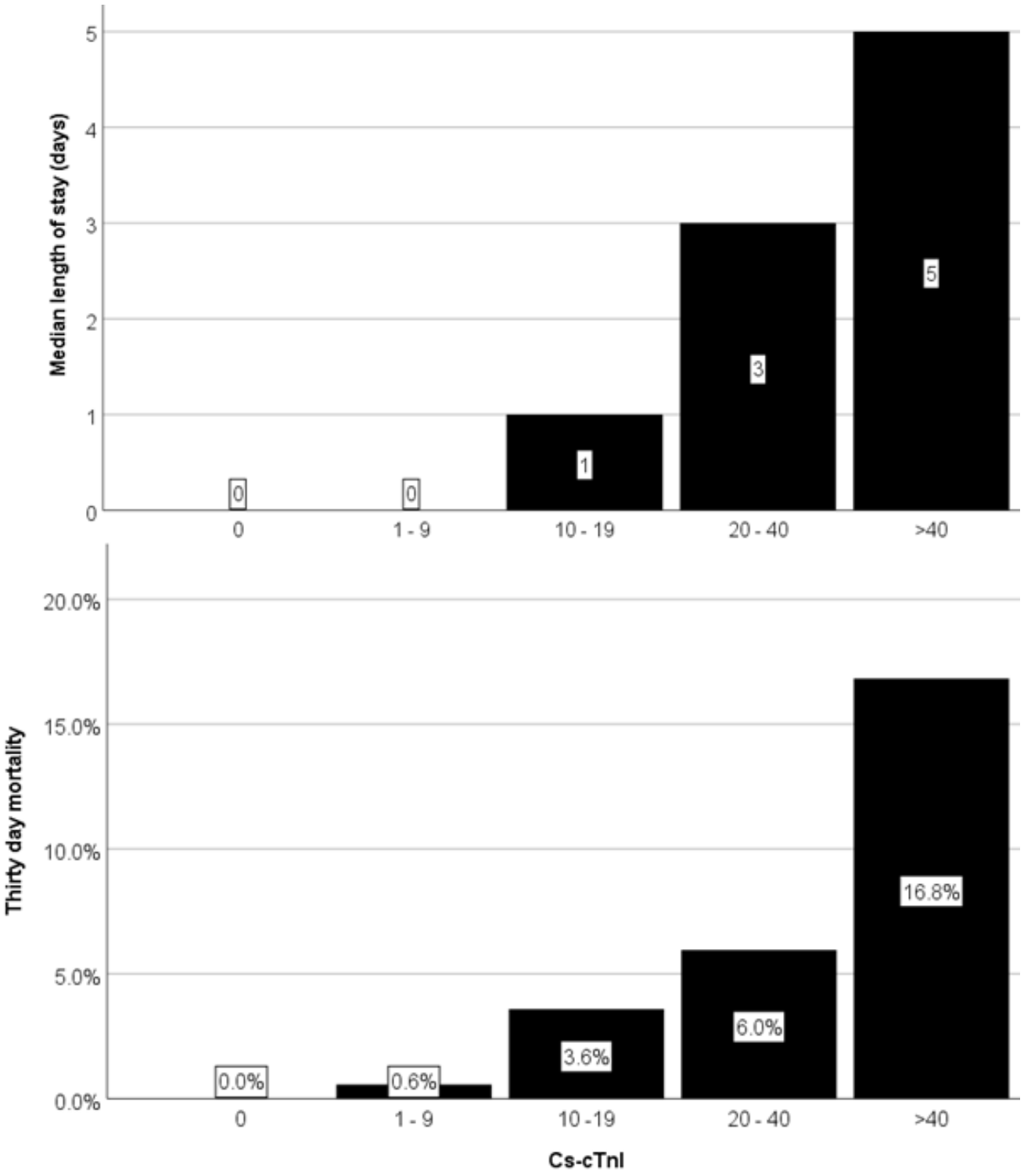


Figure 5: Length of stay and 30-day mortality across hs-cTnI groups for those in whom the test was only performed as part of the study (panel A - median length of stay, panel B - 30-day mortality

Cohort	Hs-cTnI threshold relative to ULN	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Whole population	>ULN	48.0%	92.5%	13.7%	98.4%
	>10 x ULN	13.3%	98.9%	24.7%	97.7%
Study requested cohort	>ULN	44.4%	93.6%	16.7%	98.3%
	>10 x ULN	9.4%	99.3%	27.5%	97.4%

Table 13: Discriminative performance parameters for hs-cTnI cut off thresholds for mortality

Covariable		Hazard ratio (HR (95%CI)) for the whole cohort	Hazard ratio (HR (95%CI)) for those in whom the cs-cTnI test was only performed as part of the study
Log(10)cs-cTnI		2.326 (1.872 – 2.892)	2.533 (1.932 – 3.321)
eGFR		0.989 (0.981 – 0.996)	0.992 (0.984 – 1.000)
Male gender		1.224 (0.883 – 1.697)	1.200 (0.828 – 1.739)
Age		1.043 (1.030 -1.057)	1.046 (1.030 – 1.061)
Sample requested by clinical team		1.676 (1.124 – 2.501)	n/a
ED Location	Generic ED code	REFERENCE	REFERENCE
	Eye casualty	0.980 (0.135 – 7.144)	0.852 (0.117 – 6.224)
	Clinical decision unit	n/a	n/a
	Majors	0.719 (0.461 – 1.121	0.567 (0.348 – 0.924)
	Minors	n/a	n/a
	Resus	4.054 (2.771 – 5.931)	3.104 (2.038 – 4.729)

Table 14: Cox regression covariables for the whole cohort and for those in whom the hs-cTnI test was performed solely as part of the study, in whom the clinicians had no suspicion of acute coronary syndrome

The relationship between the area of assessment within ED and subsequent mortality & length of stay is shown in Table 15.

Location	Median hs-cTnI (IQR) ng/L		P value	Median length of stay (IQR) days		P value	Mortality (%)		P value
	Clinically requested	*Study requested*		*Clinically requested*	*Study requested*		*Clinically requested*	*Study requested*	
Resus	21 (9 – 49)	11 (5 – 29)	<0.001	2 (0 – 7)	3 (1- 10)	0.112	17.9	10.9	0.039
Majors	7 (3 – 12)	6 (2 – 12)	0.203	0 (0 – 1)	0 (0 – 2)	<0.001	1.4	1.2	0.649
Generic ED	7 (3 – 12)	8 (3 – 14)	0.001	0 (0 – 1)	1 (0 – 4)	<0.001	0.1	3.4	<0.001

Table 15: Hs-cTnI spread, length of stay and mortality by ED location and whether the test was clinically requested (underlining highlights a statistically significant higher result)

3.4.6 Patients discharged with a hs-cTnI above the 99th percentile

There were 85 patients with hs-cTnI concentrations above the ULN who were either discharged within 24 hours of admission or direct from ED (Table 16). Specifically, seven patients were discharged direct from ED with hs-cTnI concentrations above the ULN that the clinicians had requested with the following discharge diagnoses; atrial fibrillation (2); supraventricular tachycardia; heart failure; abdominal pain; non-specific chest pain; general anxiety.

Discharge diagnosis category	Total number of patients (clinically requested) discharged from ED	Total number of patients (clinically requested) discharged within 24 hours of admission
Allergy	1 (0)	0
Endocrine	1 (0)	0
Ear, nose & throat / maxillofacial / dental	1 (0)	4 (0)
Fracture / dislocation	1 (0)	2 (0)
Gastrointestinal	5 (1)	3 (0)
Neurological	5 (0)	3 (0)
Non-specific chest pain	1 (1)	6 (6)

Obstetrics / gynaecology	1 (0)	0
Ophthalmology	1 (0)	0
Other	2 (0)	3 (0)
Overdose / poisoning	0	1 (0)
Psychiatric	1 (1)	0
Renal / urology	1 (0)	1 (0)
Respiratory	2 (0)	1 (1)
Syncope / fall / postural hypotension	8 (0)	3 (1)
Soft tissue injury / joint pain/injury/swelling / rashes	4 (0)	9 (1)
Unspecified sepsis / infection	0	1 (0)
Viral infection	3 (0)	0
Arrhythmia	7 (3)	0
Hypertension	1 (0)	0
Heart failure	2 (1)	1 (1)
Other cardiovascular	1 (0)	0

Table 16: Discharge diagnoses of patients with a hs-cTnI concentration above the ULN discharged from ED or within 24 hours of admission

3.5 Discussion

To our knowledge this is the largest study to assess hs-cTnI concentrations in a consecutive group of patients presenting to ED, regardless of clinical status and the first to report the association between hs-cTnI concentration and 30 day mortality in this population. Our study reports several key findings. Firstly, hs-cTnI concentrations above the ULN are frequently seen in patients

presenting to ED (7.6%) and this appears to be associated with the severity of their condition, as defined by the ED location, with nearly 1 in 5 patients above the ULN in the resuscitation area. Secondly, a wide range of cardiovascular and non-cardiovascular diagnoses are associated with hs-cTnI elevation. Thirdly, and most importantly, hs-cTnI concentrations on arrival to ED are associated with short term mortality and length of stay, regardless of whether there was a clinical indication to perform the assay.

Whilst this study demonstrates that, in patients presenting to ED, concentrations of hs-cTnI are frequently (7.6%) above the ULN, previous studies have reported much higher frequencies, even with non-contemporary-sensitivity assays (92, 93, 104, 152, 154). This is because the majority of these studies, in contrast to our study, included only patients in whom the test was clinically requested. There are two studies that have performed high sensitivity cTn testing regardless of the clinical indication, in consecutive patients in ED. The first of these, which excluded patients who were under 65 years of age and who were not admitted from ED, found a much higher prevalence (52% of 679 patients) of high sensitivity cTnT above the ULN, which is likely to be explained by the greater age (14, 92, 93, 154, 422). Shah et al studied a cohort of 1054 consecutive patients presenting to ED in whom a high sensitivity cTnI test was added onto their routine blood sample and this result was withheld from the clinical team (152). The prevalence of high sensitivity cTnI above the ULN was nearly twice as high (13.7%) in their cohort when compared to the current study. There are a number of potential reasons for this variation. Firstly, it maybe that the severity of illness was different between these populations, although the similar admission rates (63.2% vs 57.8%) suggest that this is not a major consideration. Secondly, and probably more importantly, the assays used in these studies were different and so it is possible that the variation in prevalence results from differences in the assay performance. The high prevalence of hs-cTnI above the ULN in patients presenting to ED highlights the potential flaws in the application of the manufacturer-supplied 99th percentile as a universal ULN across all patients (14, 15).

The observation that patients in the resuscitation department had the highest hs-cTnI concentrations is likely to be explained by these patients being the most unwell in the department, since increased illness severity has been demonstrated to be closely associated with cTn elevation, not only in ED, but also in the context of sepsis and patients admitted to critical care (349, 373, 405, 423, 424).

The most important observation of this study is that increasing hs-cTnI concentrations (regardless of the manufacturer's 99th percentile value) are associated with increasing 30 day mortality. Furthermore, the AUCs of 0.863 and 0.859 suggest that hs-cTnI testing on admission, outside of the context of acute T1MI, could provide useful prognostic information for clinicians about the patients newly presented to them. This concept is consistent with previous data from outpatient populations with chronic diseases suggesting that the cs-cTn concentration is associated with future cardiovascular events, and that the assay may therefore represent a biomarker for cardiovascular risk (13, 316, 425). These observations warrant further study to assess whether cs-cTn could represent a prognostic biomarker for patients presenting to ED.

3.5.1 Strengths and limitations of this study

This study provides a unique insight into the distribution of hs-cTnI within the population of patients presenting to ED as a result of its large, consecutive and prospective collection of the samples. The key limitation for this study is that the clinical data were collected using the coding system or the online clinical record. Clinical coding is key to the financial credibility of National Health System (NHS) institutions and therefore attempts are made to ensure that it is as accurate as possible. A large recent study, however, raises concern about its accuracy by demonstrating that in 16.8% of cases reviewed later the primary diagnosis was changed (426). Given the concern about the robustness of comorbidity coding, particularly within the ED environment, we have not included comorbidity data in the multivariable analysis. The recording of the length of stay and mortality is less subjective and therefore allows robust conclusions to be drawn. A second important limitation of this study is that we only added hs-cTnI testing onto the first sample

received for each patient in CHARIOT, but, given the evidence that more patients develop cTn elevation with time and the change in cTn may have further prognostic value, further studies are needed to assess whether these parameters provide better prognostic information (151). Finally, whilst the assay used in this study was in use as a high sensitivity cTn assay at our institution, and others, it only approaches the threshold to be classified as a true high sensitivity assay and as such could be considered a contemporary sensitivity assay. This may mean that the thresholds described in this study may not be directly transferable to a truly high sensitivity assay, but it seems unlikely that this would change the overall interpretation of the results.

3.6 Conclusions

In this consecutive population of patients presenting to the ED, in whom the assay was performed without the knowledge of the clinical supervising team unless it was specifically requested by them, hs-cTnI elevation is common and is associated with increasing age and illness severity. Furthermore, increasing hs-cTnI concentrations are associated with longer hospital admissions and short term mortality and may therefore provide useful prognostic information to clinicians. Given these data, further studies are now required to assess whether cs-cTn could represent a biomarker for prognosis in this and other populations presenting acutely to hospital.

Chapter 4 Relation of High-sensitivity Troponin to 1 Year Mortality in 20,000 Consecutive Hospital Patients Undergoing a Blood Test for Any Reason

Relation of High-Sensitivity Troponin to 1 Year Mortality in 20,000 Consecutive Hospital Patients Undergoing a Blood Test for Any Reason

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This was an observational study of the 1-year outcomes of the 20,000 patients included in the original CHARIOT study. The aim of the study was to assess the association between high sensitivity troponin I (hs-cTnI) concentration and 1 year mortality in this cohort. The original CHARIOT study included a consecutive cohort of in- and out-patients undergoing blood tests for any reason. Hs-cTnI concentrations were measured regardless of whether the clinician requested them. These results were nested and not revealed to the team unless requested for clinical reasons. One year mortality data was obtained from NHS Digital as originally planned. Overall, 1782 (8.9%) patients had died at 1 year. Multivariable Cox regression analysis showed that a hs-cTnI concentration above the upper limit of normal was independently associated with the hazard of mortality (HR 2.23; 95% confidence intervals 1.97 to 2.52). Furthermore, the log (10) hs-cTnI concentration was independently associated with the hazard of 1 year mortality (HR 1.77; 95% confidence intervals 1.64 to 1.91). In conclusion, in a large, unselected hospital population of both in- and out-patients, in 18,282 (91.4%) of whom there was no clinical indication for testing, hs-cTnI concentration was associated with 1 year mortality. **(Am J Cardiol 2021;158:124–131)**

(427)

4.1 Abstract

Objective: To assess the association between hs-cTnI concentration and one year mortality in a hospital cohort.

Method: This study included 20,000 consecutive patients that had hs-cTnI added onto their blood tests at a large teaching hospital, regardless of the clinical indication (CHARIOT population). One year mortality data was obtained by linkage with NHS Digital. The association between hs-cTnI concentration and one year mortality was evaluated using Kaplan-Meier plots and Cox proportional hazards analyses. After the cohort was considered as a whole, each of the clinical areas (inpatient (IPD), outpatient (OPD), emergency department (ED)) were considered separately.

Results: Overall, 1782 (8.9%) patients had died at one year. Multivariable Cox regression analysis showed that a hs-cTnI concentration above the upper limit of normal (ULN) was independently associated with the hazard of mortality (HR 2.23; 95% CI 1.97 – 2.52). Furthermore, the log (10) hs-cTnI concentration was an independent predictor of the hazard of one year mortality (HR 1.77; 95% CI 1.64 – 1.91). The discriminative ability of hs-cTnI for one year mortality was good with an AUC of 0.75 (95%CI 0.73 – 0.76). Further, the log(10) hs-cTnI concentrations were independently associated with mortality across all three locations and most strongly in the OPD cohort (IPD HR 1.49; 95% CI 1.33 – 1.67, OPD HR 2.44; 95% CI 1.95 – 3.04, ED HR 1.99; 95% CI 1.76 – 2.25).

Conclusion: In a large, unselected hospital population of both in- and out-patients, in 18,282 (91.4%) of whom there was no clinical indication for testing, hs-cTnI concentration was associated with one year mortality. These data suggest that hs-cTnI may have a role as a biomarker of future risk.

4.2 Introduction

High-sensitivity troponin (hs-cTn) assays are most effective when used to provide clinicians with a rapid and reliable mechanism for excluding myocardial infarction (MI), particularly in patients presenting to the emergency department (13, 16). As a result, these assays have been incorporated into international guidelines and have become embedded in clinical practice (16). However, given both the increased sensitivity and increased usage of these assays, elevated hs-cTn concentrations (above the 99th percentile, upper limit of normal (ULN) as defined by the manufacturer) are now frequently seen in both an in- and out-patient setting in the absence of clinical features of Type 1 MI (T1MI) (8, 9, 13, 14). In these cases, hs-cTn is released from the myocardium either as a result of a mismatch between oxygen supply and demand, which is categorised as a type 2 MI (T2MI) (in conjunction with symptoms of myocardial ischaemia, ischaemic ECG changes or new myocardial loss on imaging consistent with ischaemic origin), or as a consequence of myocardial injury (16).

There is increasing evidence that hs-cTn concentrations are associated with adverse outcomes across a range of specific conditions and even in the general population (9, 13, 18, 71, 161, 315-317, 405, 425, 428). As such, it is possible that these assays may have a role in prognostication (9, 13, 18, 71, 161, 405). Studies thus far have, however, either focused on specific conditions or been performed in patients in whom the hs-cTn test was requested for clinical reasons. Therefore, uncertainty remains as to the prognostic performance of hs-cTn assays across a broad range of conditions and clinical settings, particularly in those patients in whom there is no clinical indication for the test. These data are required not only to help clinicians interpret these results but also to assess whether hs-cTn assays provide a useful marker of prognosis across a complete cohort of hospital patients. Therefore, the aim of this study was to examine the hypothesis that hs-cTnI is a biomarker for clinical outcome by evaluating the association between hs-cTn concentration and mortality in an all comer hospital population, regardless of whether there was a conventional clinical indication to perform the assay.

We undertook this using one-year mortality data from the CHARIOT study, which had previously shown that 1 in 20 patients had a hs-cTnI greater than the ULN, and this varied according to age, sex and clinical setting (14).

4.3 Methods

4.3.1 Study population

This study included all patients from the CHARIOT population, the methodology of which has been described previously (14). In brief, CHARIOT was a prospective study of 20,000 consecutive and unselected patients, over 18 years of age, undergoing biochemistry blood tests for any clinical indication as part of their routine care at a teaching hospital in both the in- and out-patient settings. A hs-cTnI test was added onto the first sample received for each patient during the study period. Apart from cases where the hs-cTnI was requested for clinical reasons, both the patient and the supervising clinician were unaware that this was being performed and the result of the test was not revealed to the clinician or patient.

4.3.2 Research approvals

The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, and it received the appropriate approvals from the ethics committee and the Health Research Authority UK.

The original CHARIOT study received approval from the Confidentiality Advisory Group, part of the Health Research Authority. To conduct this follow up study, a major amendment was submitted, and subsequently approved, by both the Research Ethics Committee and the Confidentiality Advisory Group (IRAS 215262, REC 17/SC/0042, CAG 17/CAG/0083).

4.3.3 Cardiac troponin assay

The Beckman Coulter Access AccuTnI+3 assay (Beckman Coulter, Brea, CA, USA) was used to measure hs-cTnI concentrations in CHARIOT because this was the higher sensitivity cTn assay used in our Trust for routine clinical care at the time of the study. The 99th percentile provided by the manufacturer is 40ng/L and this was therefore used as the ULN in routine clinical practice in our institution.

4.3.4 Data collection

Following appropriate Ethical and Confidentiality Advisory Group approvals, each patient's NHS number, gender, date of birth and study specific ID were submitted to NHS Digital. NHS Digital then matched these to both the Health Episode Statistics ((HES) which contains data about all NHS admissions in the UK) and Office of National Statistics ((ONS) which contains data about mortality for all UK residents) data sets in order to provide mortality and cause of death at one year. NHS Digital returned these data with the study specific ID to allow matching to the CHARIOT dataset.

4.3.5 Statistical analysis

We summarised continuous variables using medians with the interquartile range (IQR) and categorical variables as the number (percentage) for each categorical group. The Chi squared test was used for comparison between categorical variables across two groups and the Mann Whitney U test for continuous variables across two groups. The hs-cTnI concentrations were split according to their relationship with the ULN: specifically, we defined categories of the ratio of hs-cTnI concentration/ULN of 0, >0 to <0.25, 0.25 to 0.5, >0.5 to 1 and >1. Kaplan-Meier curves were used to estimate cumulative mortality over one year, which were compared across strata (ratio of hs-cTnI concentration/ULN of 0, >0 to <0.25, 0.25 to <0.5, 0.5 to 1 and >1) using the log rank test. Multivariable analysis was performed by fitting a Cox proportional hazards model, with hs-cTnI as the covariate of interest, adjusting for age, eGFR, gender and clinical location (outpatient (OPD), inpatient (IPD) and emergency department (ED)). We considered three formulations of the hs-

cTnI covariate and re-fitted the models for each: first, as a binary variable (above/below ULN), second as an ordinal variable using the concentration relative to the ULN, and third, as a log(10) transformed continuous variable (due to the highly skewed distribution). Multivariable analysis outputs are displayed as hazard ratios (HR) with 95% confidence intervals (95% CI), where a HR greater than 1 implies an increased hazard of mortality. The proportional hazards assumption was evaluated for categories of hs-cTnI relative to the ULN using the log (-log(survival)) versus log (time) graph to ensure that this assumption was met. The area under the curve (AUC) was calculated from receiver operating characteristic curves (ROC) using hs-cTnI concentrations alone as a continuous variable.

Following this, each of the three clinical locations was considered individually to assess whether the relationship was the same across IPD, OPD and ED. The causes of death were ranked according to the frequency and then the association with cardiovascular and non-cardiovascular mortality was assessed using a Cox proportional hazards model. In addition, these analyses were repeated for the cohort of patients that remained after excluding those patients that had a hs-cTnI test requested by the clinical team.

All analysis was performed using SPSS v26.0 (SPSS, IBM Corporation, Armonk, NY, USA).

4.3.6 Patient public involvement

The original and follow up applications to ethics and confidentiality advisory group for CHARIOT were supported by the Chairman of the British Cardiac Patients Association. The patients making up the CHARIOT population by protocol did not know that they were in a study, but information, including a privacy notice, was placed on the research section of University Hospital Southampton's website in accordance to ethics and CAG approval.

4.4 Results

4.4.1 Demographics

A total of 20,000 patients over the age of 18 years were recruited between 29th June and 24th August 2017 and 1,085 (5.4%) had hs-cTnI above the ULN, as previously reported (14). All patients had all data fields present except for one patient who did not have eGFR available: this patient was excluded from all analyses requiring this variable. The median age of the cohort was 61 years (IQR 43 – 74 years) with 52.9% female (Table 17 demonstrates the baseline characteristics). 1,718 (8.6%) of patients had the hs-cTn measured according to a clinical request by the supervising clinician, whilst the remainder of the population (18,282 patients (91.4%) had the assay measured simply for the purposes of the research project and these results were nested in accordance with the study protocol.

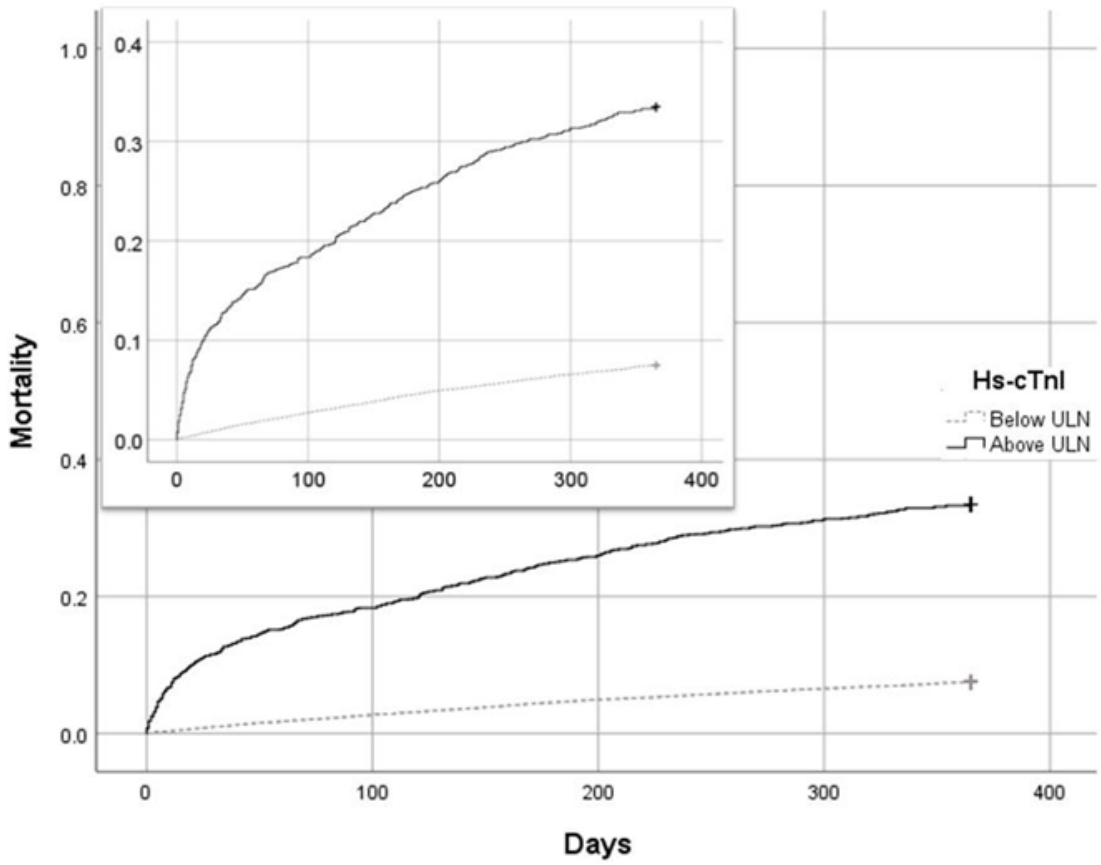
	Hs-cTnI ≤ULN	**Hs-cTnI >ULN**	**P for comparison**
Age	60 (42 – 73)	78 (66 – 87)	<0.001
Female	10117 (53.5)	463 (42.7)	<0.001
eGFR (ml/min/1.73m^2)	90 (73 – 90)	62 (39 – 85)	<0.001
Outpatient	9156 (98.0%)	189 (2.0%)	<0.001
Inpatient	4542 (91.8%)	405 (8.2%)	<0.001
Emergency department	5217 (91.4%)	491 (8.6%)	<0.001

Table 17: Baseline characteristics stratified by whether the hs-cTnI was above or below the ULN

4.4.2 Association between mortality and hs-cTnI concentration above or below the ULN

In total, there were 1782 (8.9%) deaths by one year of follow-up. The mortality of patients with a hs-cTnI concentration above the ULN at one-year was significantly higher than for those with a hs-

cTnI below the ULN (7.5% vs 33.5%, p<0.001) (Figure 6). On multivariable analysis, a hs-cTnI concentration above the ULN remained an independent predictor of one year mortality and increased the hazard of mortality by more than two fold (HR 2.23; 95% CI 1.97 – 2.52). The mortality was higher in patients who did not have their test requested for clinical reasons compared to those whose supervising clinician had requested it. This difference was significant both when the hs-cTnI result was below the ULN (mortality 7.7% for unrequested, research only vs 4.9 % for clinically requested samples, (p<0.001)) or above the ULN (35.5% in research only versus 26.1% in clinically requested (p=0.006)).

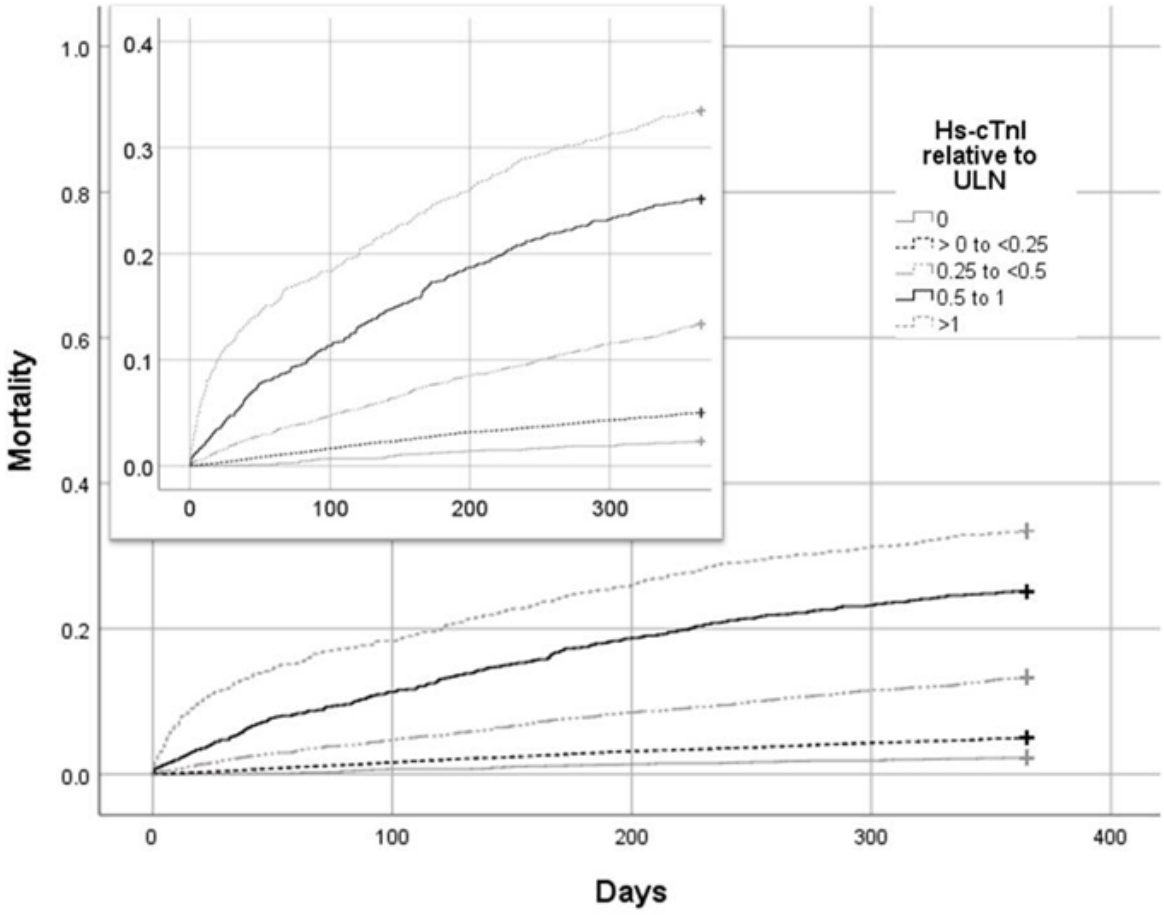


Hs-cTnI	0 days	100 days	200 days	300 days	365 days
≤ULN number at risk	18915	18402	17980	17675	17496
>ULN number at risk	1085	886	804	747	722

Figure 6:Kaplan-Meier curve of one year mortality by whether the hs-cTnI was above or below the ULN (log rank p<0.001).

4.4.3 Mortality for hs-cTnI concentrations across the whole population

Figure 7 demonstrates the positive association between increasing hs-cTnI concentrations relative to the ULN and mortality at one year (log rank p<0.001). The log(10) transformed hs-cTnI concentration, as a continuous variable, remained an independent predictor of mortality (HR 1.77; 95% CI 1.64 – 1.91) after adjusting for age, eGFR, patient clinical location and gender (Table 18). Further, the ratio of hs-cTnI concentration to the ULN was also independently associated with



Hs-cTnI relative to ULN	0 days	100 days	200 days	300 days	365 days
0	2609	2591	2573	2560	2549
>0 - <0.25	11576	11386	11207	11079	10997
0.25 - <0.5	3465	3303	3171	3065	3003
0.5 – 1	1265	1122	1029	971	947
>1	1085	886	804	747	722

Figure 7: Kaplan-Meier curve of one year mortality based on the ratio of the hs-cTnI concentration to the ULN (log rank test between each stratum p<0.001).

Variable		**Mortality HR (95% CI)**
Age		1.04 (1.04 – 1.05)
Male gender		1.19 (1.08 – 1.31)
eGFR		0.99 (0.99 – 1.00)
Clinical location	OPD	Reference
	IPD	2.26 (2.00 – 2.55)
	ED	1.62 (1.43 – 1.84)
Log(10) hs-cTnI concentration		1.77 (1.64 – 1.91)

Table 18: Hazard ratios for one year mortality for all covariates in the model for the whole cohort using log(10) hs-cTnI concentration

higher hazard of mortality (Table 19). The mortality steadily increased for hs-cTnI concentrations below the ULN until the hs-cTnI concentration was 17ng/L at which point the mortality stepped up. For hs-cTnI concentrations above the ULN, the mortality was around 30% and this did not increase with increasing concentrations (Figure 8). The discriminative ability of hs-cTnI for one year mortality was good with an AUC of 0.75 (95%CI 0.73 – 0.76).

Variable		**Mortality HR (95% CI)**
Age		1.04 (1.04 – 1.05)
Male gender		1.18 (1.07 – 1.29)
eGFR		1.00 (0.99 – 1.00)
Clinical location	OPD	Reference
	IPD	2.20 (1.95 – 2.47)
	ED	1.51 (1.33 – 1.71)
Hs-cTnI concentration relative to ULN	0	Reference
	> 0 to <0.25	1.470 (1.12 – 1.92)
	0.25 to <0.5	2.30 (1.74 – 3.03)
	0.5 to 1	3.20 (2.40 – 4.28)
	>1	4.74 (3.55 – 6.32)

Table 19: Hazard ratios for one year mortality for all covariates in the model for the whole population using the hs-cTnI concentration relative to the ULN

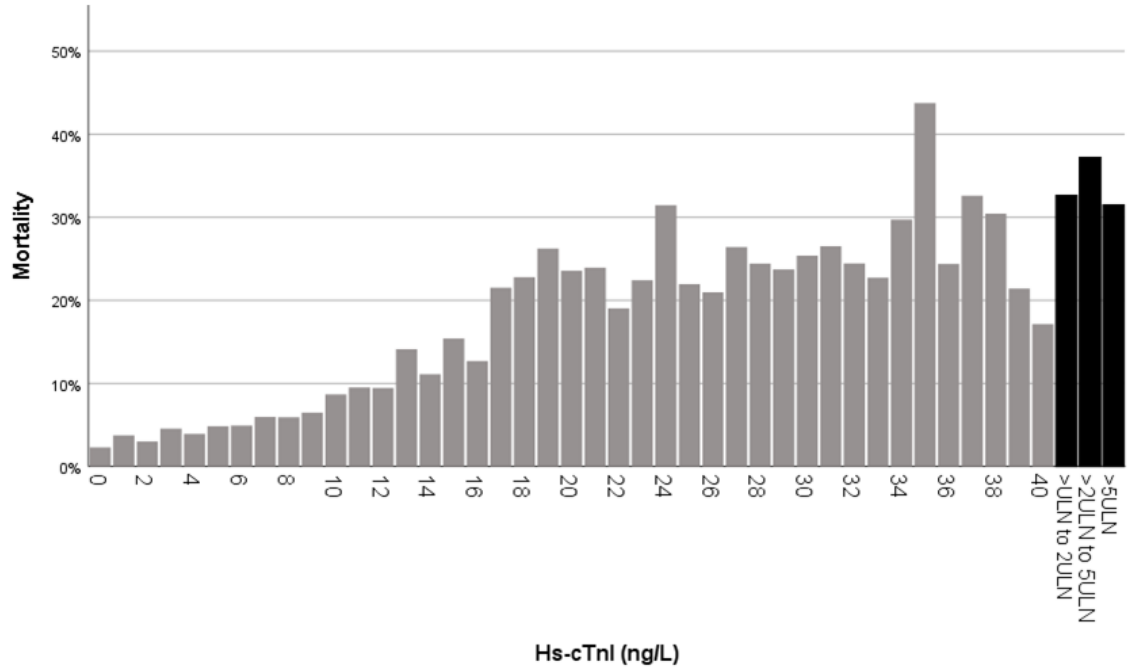


Figure 8: One year mortality by hs-cTnI concentration for each hs-cTnI concentration up to the ULN (grey bars) and then grouped by the degree above the ULN in black bars (>ULN to 2ULN, >2ULN to 5ULN, >5ULN).

4.4.4 One year mortality based on original sample location

At one year of follow-up, there were 728 (14.7%) deaths amongst in-patients (IPD), 484 (5.2%) deaths in out-patients (OPD) and 570 (10.0%) in emergency department (ED) patients. A hs-cTnI above the ULN was an independent predictor of mortality in the populations from all three locations (IPD HR 1.86; 95% CI 1.53 – 2.26, OPD HR 2.84: 95% CI 2.05 – 3.95, ED HR 2.28; 95% CI 1.89 – 2.76). The log(10) hs-cTnI concentration was independently associated with mortality across all three locations and most strongly in the OPD cohort (IPD HR 1.49; 95% CI 1.33 – 1.67, OPD HR 2.44; 95% CI 1.95 – 3.04, ED HR 1.99; 95% CI 1.76 – 2.25) (Table 20). Furthermore, the ratio of the hs-cTnI concentration to the ULN was independently associated with mortality (Table 21 & **Error! Reference source not found.**). Hs-cTnI appeared to have the best discriminatory power for predicting mortality in ED (IPD AUC 0.70; 95% CI 0.68 – 0.72, OPD AUC 0.69; 95% CI 0.66 – 0.72, ED AUC 0.82; 95% CI 0.80 – 0.83).

Variable	Mortality HR (95% CI) IPD	Mortality HR (95% CI) OPD	Mortality HR (95% CI) ED
Age	1.04 (1.03 – 1.05)	1.04 (1.04 – 1.05)	1.05 (1.04 – 1.06)
Male gender	1.16 (1.00 – 1.35)	1.32 (1.09 – 1.59)	1.15 (0.97 – 1.36)
eGFR	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	0.99 (0.99 – 0.99)
Log (10) hs-cTnI concentration	1.49 (1.33 – 1.67)	2.44 (1.95 – 3.04)	1.99 (1.76 – 2.25)

Table 20: Hazard rations one year mortality for all covariates in the model for each of the patient locations using the log(10) hs-cTnI

Variable		Mortality HR (95% CI) IPD	Mortality HR (95% CI) OPD	Mortality HR (95% CI) ED
Age		1.04 (1.03 – 1.04)	1.04 (1.04 – 1.05)	1.05 (1.04 – 1.05)
Male gender		1.17 (1.01 – 1.36)	1.30 (1.080 – 1.55)	1.10 (0.923 – 1.30)
eGFR		1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	0.99 (0.99 – 1.00)
Hs-cTnI concentration relative to ULN	0	Reference	Reference	Reference
	> 0 to <0.25	1.367 (0.93 – 2.01)	1.32 (0.88 – 1.98)	3.58 (1.32 – 9.74)
	0.25 to <0.5	2.09 (1.40 – 3.13)	2.10 (1.37 – 3.23)	6.02 (2.20 – 16.47)
	0.5 to 1	2.59 (1.70 – 3.94)	3.28 (2.02 – 5.31)	9.07 (3.29 – 25.02)
	>1	3.41 (2.25 – 5.18)	5.06 (3.05 – 8.41)	13.74 (5.00 – 37.77)

Table 21: Hazard rations one year mortality for all covariates in the model for each of the patient locations using the hs-cTnI concentration relative to the ULN

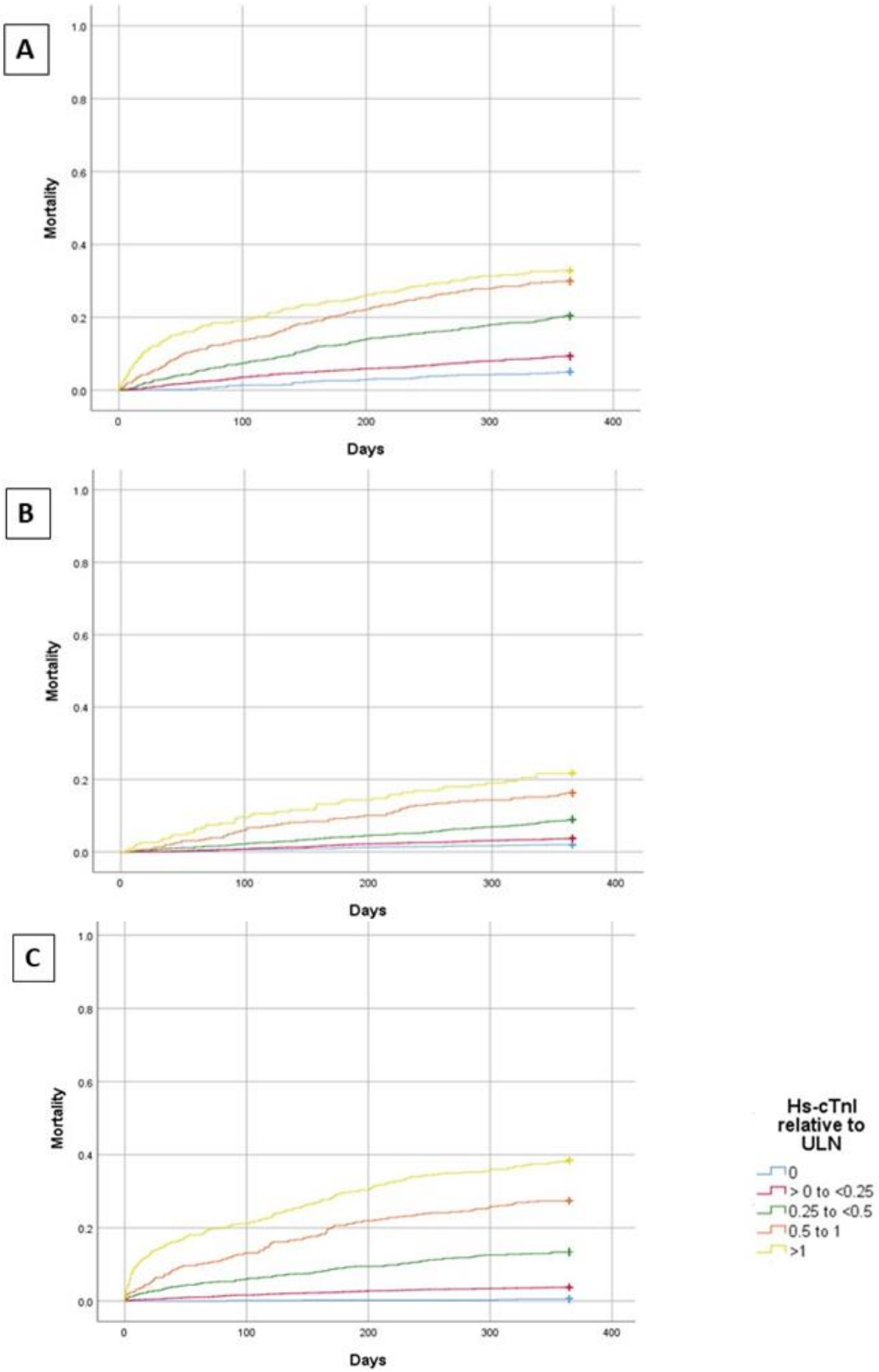


Figure 9: One year mortality Kaplan-Meier curves. Panel A: inpatients, panel B: outpatients, panel C: emergency department. Number at risk:

Hs-cTnI relative to ULN	0 days	100 days	200 days	300 days	365 days
0	567	559	551	543	538
0 - <0.25	2587	2495	2434	2380	2346
0.25 - <0.5	943	874	812	774	751
0.5 – 1	445	384	347	321	312
>1	405	328	300	278	272

IPD

Hs-cTnI relative to ULN	0 days	100 days	200 days	300 days	365 days
0	1361	1352	1343	1338	1334
0 - <0.25	5910	5862	5779	5725	5689
0.25 - <0.5	1529	1495	1460	1423	1392
0.5 – 1	356	335	320	305	298
>1	189	171	162	153	148

OPD

Hs-cTnI relative to ULN	0 days	100 days	200 days	300 days	365 days
0	681	680	679	679	677
0 - <0.25	3079	3029	2994	2974	2962
0.25 - <0.5	993	934	899	868	860
0.5 – 1	464	403	362	345	337
>1	491	387	342	316	302

ED

4.4.5 Cause of death

The most common cause of death in patients whose hs-cTnI test was not clinically requested was neoplastic disease (46.8%) followed by cardiovascular disease (13.4%) (Table 22). The log(10) hs-cTnI concentration was an independent predictor of one year non-cardiovascular mortality (HR 1.66; 95% CI 1.52 – 1.81) across the entire cohort and across all three locations (Table 23). The cardiovascular mortality was zero in patients with undetectable hs-cTnI concentrations and only 0.2% in patients with detectable hs-cTnI concentrations below 25% of the ULN (Figure 10). By contrast, the cardiovascular mortality was around 10% for patients with hs-cTnI concentrations more than two times the ULN (Figure 10).

Cause of death	**Number (percentage)**
Neoplastic disease	834 (46.8)
Cardiovascular disease	238 (13.4)
Respiratory disease	144 (8.1)
Old age/dementia	124 (6.9)
Neurological	99 (5.6)
Bacterial infection	73 (4.1)
Accidental	54 (3.0)
Other/unknown	44 (2.5)
Gastrointestinal disease	44 (2.5)
Hepatopancreatobiliary disease	34 (1.9)
Endocrine disease	27 (1.5)
Renal/urological	27 (1.5)
Viral infection	20 (1.1)

Multisystem disorder	11 (0.6)
Haematological disease	7 (0.4)
Substance abuse	2 (0.1)

Table 22: Cause of death for patients whose hs-cTnI test was not clinically requested or had a final diagnosis of MI.

Variable	**Mortality HR (95% CI) IPD**	**Mortality HR (95% CI) OPD**	**Mortality HR (95% CI) ED**
Age	1.04 (1.03 – 1.04)	1.04 (1.03 – 1.05)	1.05 (1.04 – 1.06)
Male gender	1.14 (0.97 – 1.34)	1.30 (1.07 – 1.59)	1.11 (0.92 – 1.32)
eGFR	1.00 (1.00 – 1.00)	1.00 (0.99 – 1.01)	0.99 (0.99 – 0.99)
Hs-cTnI concentration relative to ULN	1.40 (1.23 – 1.59)	2.18 (1.71 – 2.78)	1.86 (1.62 – 2.14)

Table 23: Mortality HR for non-cardiovascular death across all locations

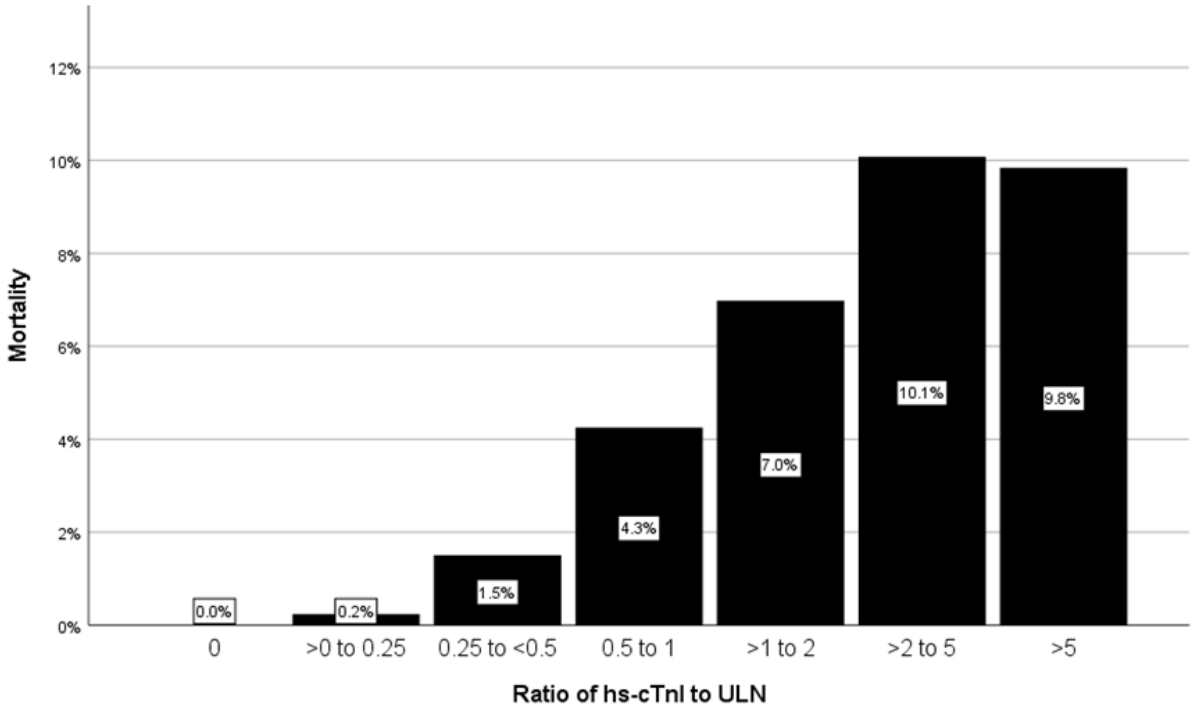


Figure 10: Cardiovascular mortality at one year by hs-cTnI concentration relative to the ULN

4.4.6 Patients without clinical indication for hs-cTnI testing

After excluding all the patients in whom the hs-cTnI test was requested on clinical grounds, there were 18,282 patients remaining. Of these, 1647 (9.0%) died within a year. Similar to the main results, a hs-cTnI above the ULN remained independently associated with one year mortality (HR 2.29; 95% CI 2.01 – 2.62). In addition, the log(10)hs-cTnI concentration was also independently associated with one year mortality in the population in whom the hs-cTnI test was not requested by the clinical team as a whole (HR 1.95; 95% CI 1.79 – 2.12) and across each of the locations (IPD HR 1.63; 95% CI 1.44 – 1.84, OPD HR 2.44; 95% CI 1.95 – 3.04, ED HR 2.33; 95% CI 2.00 – 2.73) (Table 24Table 25).

Variable		One year mortality HR (95% CI)
Age		1.04 (1.04 – 1.05)
Male gender		1.21 (1.10 – 1.34)
eGFR		1.00 (0.99 – 1.00)
Clinical location (compared to OPD)	IPD	2.31 (2.05 – 2.61)
	ED	1.79 (1.57 – 2.05)
Log (10) hs-cTnI concentration		1.95 (1.79 – 2.13)

Table 24: Hazard ratios for one year mortality for all covariates in the model for all patients after exclusion of those who were diagnosed with T1MI or had their hs-cTnI test requested on clinical grounds

Variable	One year mortality HR (95% CI) IPD	One year mortality HR (95% CI) OPD	One year mortality HR (95% CI) ED
Age	1.04 (1.03 – 1.04)	1.04 (1.04 – 1.05)	1.04 (1.04 – 1.05)
Male gender	1.18 (1.02 – 1.38)	1.30 (1.08 – 1.57)	1.81 (0.98 – 1.42)
eGFR	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	0.99 (0.99 – 1.00)
Log (10) hs-cTnI concentration	1.63 (1.44 – 1.85)	2.45 (1.96 – 3.05)	2.34 (2.00 – 2.73)

Table 25: Hazard ratios one year mortality for all covariates in the model for each of the patient locations after those who were diagnosed with T1MI or had their hs-cTnI test requested on clinical grounds

4.5 Discussion

The novel finding of this study is that, in 20,000 unselected, consecutive patients attending a large teaching hospital, there was a positive association between the level of hs-cTnI and one year mortality, regardless of whether there was any clinical indication for the assay to be performed. Specifically, on multivariable analysis, hs-cTnI was an independent predictor of mortality in the population as a whole and also separately in the in-patient, out-patient and ED cohorts. Furthermore, hs-cTnI concentrations predicted both cardiovascular and non-cardiovascular mortality at one year.

Our findings suggest that hs-cTnI may represent a biomarker for the risk of both cardiovascular and non-cardiovascular death in a consecutive population of hospital patients, the majority of whom had no clinical indication to have the assay taken. Uniquely, the design of this study meant that the hs-cTn was measured in the whole study population and, with the exception of those patients in whom the test was requested for clinical reasons, was never shared with the patient or their physician. While the concept that hs-cTn may be a biomarker for future cardiovascular risk is not new, it has not been explored in this way before.

The findings of this study are consistent with previous literature, although none of these studies share our methodology. For example, the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) study also found that hs-cTnI was independently associated with mortality (315). However, this study only included outpatients with known cardiovascular disease. Similarly, the Generation Scotland Scottish Family Health Study also demonstrated that hs-cTnI was independently predictive of cardiovascular mortality in an outpatient population with cardiovascular comorbidity (314). However, unlike our study, hs-cTnI was not associated with non-cardiovascular mortality. Further, the Dallas Heart Study found that hs-cTnT concentrations were associated with structural heart disease and all-cause mortality in the general population (71). Interestingly, a recent meta-analysis reported that the association with fatal non-cardiovascular events was stronger in studies using hs-cTnT compared with those

using hs-cTnI in the general population (310). It has been suggested that this may be because hs-cTnT is expressed in non-cardiac tissues and, as such, acts as a more comprehensive and sensitive marker of general ill health.

To our knowledge, this is the first study to evaluate the association between hs-cTn concentrations and one year mortality in patients in whom there was no clinical indication for the test. However, our results are consistent with previous data in intensive care, ED, post-operative patients and those with a variety of medical presentations (including tachyarrhythmia, chronic obstructive pulmonary disease and acute stroke) that all demonstrate an association between hs-cTn and various clinical outcomes (13, 18, 121, 272, 405). Furthermore, a study of over 250,000 patients across five UK centres, in all of whom the cTn test was requested on clinical grounds, found that even minor increases in cTn concentrations were associated with mortality (155). Our study also found an association between hs-cTn and mortality, even at concentrations below the ULN, but has more wide-ranging implications for troponin as a biomarker of mortality, given that, in the majority of our population, *there was no clinical indication to perform the measurement*.

The plausibility of hs-cTn as a biomarker for mortality is emphasised not just by the association between rising levels of the protein and increasing mortality, but also by our observation that mortality is extremely low in those with hs-cTnI concentrations <0.25 of the ULN. This may have considerable value, if further validated, because it has the potential to select outpatients who require less surveillance and, perhaps, even, less preventive treatment in the future.

This study, like previous studies whose method restricted patients to those in whom the hs-cTn was requested on clinical grounds, demonstrates that patients with hs-cTnI concentrations above the ULN outside the context of T1MI have the worst clinical outcomes (115). The data from this study demonstrate that hs-cTn concentrations do act as a marker of prognosis across a broad range of patient populations. Whilst these data are helpful to clinicians, the current lack of evidence demonstrating that hs-cTn can identify a group of patients in whom medical interventions can reduce future risk means that, at present, these assays do not have a clinically

relevant role for risk stratification. Further studies are therefore required to evaluate whether medical intervention can reduce the risk of future events in these populations before the widespread use of hs-cTn assays as a marker of prognosis could be considered (115).

4.5.1 Strengths and limitations

This study provides unique information about the potential associations between hs-cTnI and one-year mortality given the unselected and consecutive nature of enrolment across both the in- and out-patient contexts in whom the majority had no indication for the assay. This is testament to the unusual methodology, and regulatory approval, and hence raises the interesting possibility that hs-cTnI may be a biomarker for mortality in a hospital population.

The study does have a number of limitations. Firstly, given the size and consecutive nature of the cohort it was not possible to gather detailed demographic and comorbidity data to include in multivariable modelling. Specifically, this meant that we were unable to adjust for comorbidities that are known to be associated with chronically elevated hs-cTn concentrations, such as heart failure and diabetes. However, we do not intend for these findings to be interpreted in a causal manner, rather we report the potential association adjusting for the variables that were collected. Further, the study does not have details of whether patients were on disease-modifying cardiovascular therapy which could adjust the risk of mortality and potentially lead to reductions in the hs-cTn concentration.

Secondly, whilst the assay in this study was in clinical use within our institution (and others) as a "high sensitivity" assay, it only approaches the threshold to be classified as true modern high sensitivity and as such could be considered a contemporary sensitivity assay (429). However, whilst this may mean that the thresholds demonstrated in this study are not transferable to a truly high sensitivity assay, this does not change the interpretation of the results, which we could assume would be equally true of a more contemporary high sensitivity assay.

4.6 Conclusion

In 20,000 unselected and consecutive hospital patients, the majority of whom had no clinical indication for the assay, hs-cTnI concentrations were associated with one year mortality, both cardiovascular and non-cardiovascular. These data suggest that hs-cTnI may have a role as a biomarker of future mortality. Further studies are now warranted.

Chapter 5 Distribution of high sensitivity troponin taken without conventional clinical indications in critical care patients and its association with mortality

CLINICAL INVESTIGATION

Distribution of High-Sensitivity Troponin Taken Without Conventional Clinical Indications in Critical Care Patients and Its Association With Mortality

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OBJECTIVES: To describe the distribution of high-sensitivity troponin in a consecutive cohort of patients in critical care units, regardless of clinical indication, and its association with clinical outcomes.

DESIGN: Prospective observational study.

SETTING: Single-center teaching hospital.

PATIENTS: Consecutive patients admitted to two adult critical care units (general critical care unit and neuroscience critical care unit) over a 6-month period.

INTERVENTIONS: All patients had high-sensitivity troponin tests performed at admission and tracked throughout their critical care stay, regardless of whether the supervising team felt there was a clinical indication. The results were not revealed to patients or clinicians unless clinically requested.

MEASUREMENTS AND MAIN RESULTS: There were 1,033 patients in the study cohort (general critical care unit 750 and neuroscience critical care unit 283). The median high-sensitivity troponin was 21 ng/L (interquartile range, 7–86 ng/L), with 560 patients (54.2%) above the upper limit of normal as defined by the manufacturer. Admission high-sensitivity troponin concentrations above the upper limit of normal in general critical care unit and neuroscience critical care unit were associated with increasing age, comorbidity, markers of illness severity, and the need for organ support. On adjusted analysis, the high-sensitivity troponin concentration remained an independent predictor of critical care mortality in general critical care unit and neuroscience critical care unit.

CONCLUSIONS: High-sensitivity troponin elevation, taken outside the context of conventional clinical indications, was common in the critically ill. Such elevations were associated with increasing age, comorbidity, illness severity, and the need for organ support. Admission high-sensitivity troponin concentration is an independent predictor of critical care mortality and as such may represent a novel prognostic biomarker at admission.

KEY WORDS: high-sensitivity troponin; intensive care

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(430)

5.1 Abstract

Objective: To describe the distribution of high sensitivity troponin (hs-cTn) in a consecutive cohort of patients in critical care (CC) units, regardless of clinical indication, and its association with clinical outcomes.

Design: Prospective, observational study

Setting: Single centre teaching hospital

Patients: Consecutive patients admitted to two adult CC units (general (GCCU), neuroscience (NCCU)) over a six month period.

Interventions: All patients had hs-cTn tests performed on admission and tracked throughout their CC stay, regardless of whether the supervising team felt there was a clinical indication. The results were not revealed to patients or clinicians unless clinically requested.

Measurements and main results: There were 1,033 patients in the study cohort (GCCU 750, NCCU 283). The median hs-cTn was 21ng/L (IQR 7-86ng/L), with 560 (54.2%) patients above the upper limit of normal (ULN) as defined by the manufacturer. Admission hs-cTn concentrations above the ULN in GCCU and NCCU were associated with increasing age, comorbidity, markers of illness severity and the need for organ support. On adjusted analysis the hs-cTn concentration remained an independent predictor of CC mortality in GCCU and NCCU.

Conclusion: Hs-cTn elevation, taken outside the context of conventional clinical indications, was common in the critically ill. Such elevations were associated with increasing age, comorbidity, illness severity and the need for organ support. Admission hs-cTn concentration is an independent predictor of CC mortality and as such may represent a novel prognostic biomarker on admission.

5.2 Introduction

The development of high-sensitivity troponin (hs-cTn) assays has provided clinicians with a rapid and reliable test for exclusion of type 1 myocardial infarction (T1MI) (13, 16, 431). The increased

sensitivity of these assays has resulted in concentrations above the manufacturer-provided 99th centile value, commonly used as the upper limit of normal (ULN), being seen frequently in patients across a range of clinical settings that would not traditionally be associated with T1MI (8, 9, 13, 14, 428). The implications of these observations are currently unclear, but there is increasing evidence that hs-cTn elevation outside the context of a T1MI is associated with adverse clinical outcomes (9, 13, 18, 342, 405, 408, 428, 432).

Patients admitted to critical care (CC) units are likely to have a combination of reduced myocardial oxygen supply and increased demand as a result of their critical illness. It is therefore unsurprising that, in general CC units (GCCU), hs-cTn concentrations above the ULN are frequently seen (14, 17, 363, 406, 408-411, 433). The relationship between levels of hs-cTn and the severity of illness in CC, and the potential prognostic value of the hs-cTn assay in this population is unclear (355, 361, 363, 405, 433).

The data regarding the possible value of hs-cTn assays in neurosciences CC units (NCCU) are currently sparse.

The aims of this study are to: (a) describe the distribution of hs-cTn across two different adult CC environments (GCCU, NCCU); (b) highlight which factors are associated with higher hs-cTn concentrations; (c) to assess whether the admission, peak or change in hs-cTn concentration, are associated with worse clinical outcomes.

5.3 Materials and methods

5.3.1 Study population

This prospective, observational study enrolled consecutive adult patients admitted to either GCCU or NCCU in whom at least one biochemistry sample was requested by the clinical team between 29th of January 2019 and 29th of July 2019. A hs-cTn test was added to the first biochemistry sample received and, following this, on day 1 and day 2 and then every alternate day until the patient was discharged from CC. Patients who did not have hs-cTn performed on admission

(which included patients who were already in CC at the start of the study and those who did not have a biochemistry sample requested within 24 hours of admission), those that remained in CC after the close of serial blood testing and those with a diagnosis of T1MI were excluded from the analysis. Patients who remained in CC after the close of serial blood testing (30th of September) were also excluded from further analysis. Only the first admission for each patient to any of the CC units during the study timeframe was included.

5.3.2 Research approvals

In order to meet the objectives of this study, a consecutive cohort of patients was required, and, as such, it was not possible to obtain informed consent from each patient. The study was therefore reviewed and approved by the Confidentiality Advisory Group ((CAG), a national body that specifically reviews any research applications where informed consent is not possible), part of the Health Research Authority. This was required because informed consent was not possible and because, apart from patients in whom the clinical team requested hs-cTn testing as part of the patient's routine care, the results were never revealed to either the patient or the clinical team.

5.3.3 Cardiac troponin assay

The Beckman Coulter Access hsTnI assay (Brea, CA, USA) was used to measure hs-cTn concentrations in this study. The manufacturer's ULN is 18 ng/L (at which level the coefficient of variation (CV) was <10%). The limit of detection for the assay was 2ng/L and the limit of quantification (20% of the CV) was 2ng/L.

Study-driven hs-cTn testing was only performed using serum that was left after any clinically requested tests were performed. A bespoke, automated system was designed to add hs-cTnI testing to samples with a CC renal request code for each of the study testing days. The serum was collected in serum separator tubes and stored at room temperature for up to 24 hours before hs-

cTn levels were measured using the DxI800 platform (Beckman Coulter). Quality control was performed on the assay daily as part of routine clinical practice.

5.3.4 Data collection

Specific co-morbidity data (smoking status, body mass index (BMI), hypertension, dyslipidaemia, diabetes, chronic kidney disease, asthma, chronic obstructive pulmonary disease, cerebrovascular disease, heart failure, ischaemic heart disease, previous percutaneous coronary intervention, previous coronary artery bypass grafting, atrial fibrillation, inflammatory bowel disease, rheumatoid arthritis and peripheral vascular disease) were extracted from both the online clinical record (Metavision, iMD Software, Dusseldorf, Germany) and the coding system. A comorbidity was considered present if it was included in the current or historical (using the coding system) clinical record and as such, the study team did not define these comorbidities and relied solely on the clinical team's diagnoses. On admission the determinants of the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, haemoglobin, C-reactive protein (CRP) and lactate were recorded (414, 415). The use of inotropes/vasopressors (of any dose or agent), invasive ventilation and haemofiltration during the admission was also recorded. The research team performed no additional testing, so that any tests not performed by the clinical team were recorded as missing variables. If there was no arterial blood gas, the partial pressure of oxygen was estimated from the oxygen saturations using the European Prevalence of Infection in Intensive Care criteria (416). The length of CC stay and whether the patient died in CC was recorded.

5.3.5 Statistical analysis

For all analyses each CC was considered individually. Summary variables are displayed as either median with the interquartile range (IQR) where the variable was continuous, or as the number (percentage) in that group for categorical variables. Due to the highly skewed nature of hs-cTn distribution, a log(10) scale was used on histograms. Appropriate statistical tests were used to

compare groups depending upon the nature and distribution of the variable. Thus, the Chi squared test was used for comparison between categorical variables across two groups. For data that were normally distributed, the t-test was performed for comparison between two groups. Finally, for data that were not normally distributed, the Mann Whitney U test was performed for comparison between two groups. Patients who died in CC were excluded from length of stay multivariable analyses. For mortality analyses, two forms of the hs-cTn concentration were used; log(10)hs-cTn concentration and the relationship between the hs-cTn concentration and the ULN was categorised as follows; ≤ULN, >ULN to ≤5xULN , >5xULN to ≤20xULN and >20xULN. Variables with a significant association (at the 95% confidence level) with mortality on univariable analysis were taken forward and included in the multivariable analysis. Multivariable logistic regression was used to assess the relationship between both the hs-cTn variables and CC mortality, with outputs displayed as odds ratios (OR) and 95% confidence intervals (95% CI). Collinearity was assessed by calculating the variance inflation factor (VIF). The area under the curve (AUC) was calculated using admission hs-cTn concentration as a continuous variable and comparisons between AUCs were performed using a Chi^2 test in Stata (StataCorpLLC, Texas, USA). All other analyses were performed using SPSS v26.0 (SPSS, IBM Corporation, Armonk, NY, USA).

5.4 Results

5.4.1 Patient characteristics

There were 1033 patients remaining after exclusions (Figure 11). One patient in GCCU had an initial hs-cTn sample unsuitable for analysis. Table 26 demonstrates the baseline patient characteristics across the two CC units. Table 27Table 28demonstrate that increasing age and cardiovascular disease were more likely in patients with hs-cTn above the ULN in GCCU and NCCU.

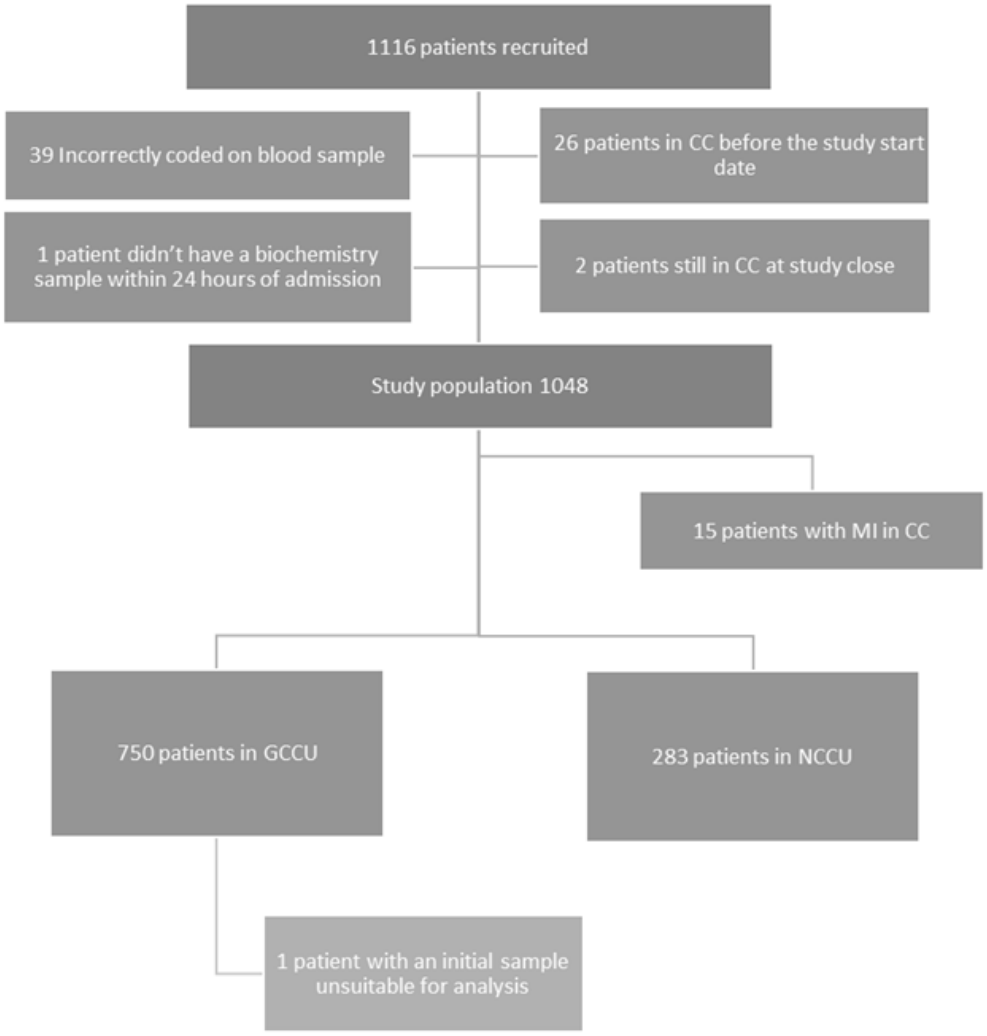

Figure 11: Study recruitment

Variable	GCCU (total 750)	NCCU (total 283)	p-value
Median age	64 (49 – 74)	59 (49 – 70)	0.040
Male	455 (60.7)	149 (52.7)	0.020
Smoking status Non-smoker Ex-smoker Current smoker	 220 (37.7) 68 (11.7) 295 (50.6)	 113 (53.3) 9 (4.2) 90 (42.5)	<0.001
Planned admission	129 (17.2)	86 (30.4)	<0.001
Body mass index	26.0 (22.9 – 30.2)	26.9 (24.0 – 30.0)	0.607
Hypertension	268 (35.7)	86 (30.4)	0.106
Hypercholesterolaemia	112 (14.9)	26 (9.2)	0.015
Diabetes mellitus	135 (18.0)	18 (6.4)	<0.001
Chronic kidney disease	60 (8.0)	9 (3.2)	0.009
Asthma	88 (11.7)	30 (10.6)	0.610
COPD	104 (13.9)	17 (6.0)	<0.001
Stroke or TIA	53 (7.1)	102 (36.0)	<0.001
Heart failure	60 (8.0)	6 (2.1)	0.001
Ischaemic heart disease	98 (13.1)	23 (8.1)	0.028
Previous PCI	8 (1.1)	10 (3.5)	0.007
Previous CABG	22 (2.9)	0 (0)	0.001
Atrial fibrillation	90 (12.0)	21 (7.4)	0.034
Inflammatory bowel disease	23 (3.1)	5 (1.7)	0.251
Rheumatoid arthritis	18 (2.4)	2 (0.7)	0.125
Peripheral vascular disease	46 (6.1)	5 (1.8)	0.004
Admission SOFA	5 (3 – 9)	4 (1 – 6)	<0.001

APACHE II	14 (9 – 20)	13 (7 – 20)	0.062
Creatinine	75 (58 – 119)	60 (45 – 73)	<0.001
WBC (10^9/L)	13.0 (9.4 – 17.4)	12.5 (9.9 – 15.7)	0.259
Haemoglobin (g/L)	114 (99 – 130)	125 (113 – 135)	<0.001
CRP (mg/L)	56 (11 – 161)	7 (3 – 24)	<0.001
Lactate (mmol/L)	1.3 (0.9 – 2.3)	1.0 (0.7 – 1.8)	<0.001
Invasive ventilation during admission (%)	325 (43.3)	145 (51.2)	0.023
Haemofiltration during admission (%)	70 (9.3)	2 (0.7)	<0.001
Vasopressor/inotrope use during admission (%)	336 (44.8)	112 (39.6)	0.131
Death in ICU (%)	86 (11.5)	32 (11.3)	0.943
Length of CC stay (days)	2 (1 – 5)	2 (1 – 7)	0.694

Table 26: Baseline demographics, admission characteristics and outcomes across the two CC environments (COPD=chronic obstructive pulmonary disease, TIA=transient ischaemic attack, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, SOFA=sequential organ failure assessment, APACHE=acute physiology and chronic health evaluation, WBC=white blood cell, CRP=C-reactive protein)

Variable	**Admission hs-cTnI ≤ ULN (total 306)**	**Admission hs-cTnI >ULN (total 443)**	**p-value**
Median age	58 (41 – 70)	67 (55 – 75)	<0.001
Male	172 (56.2)	283 (63.9)	0.035
Smoking status^ Non-smoker Ex-smoker Current smoker	 101 (40.9) 20 (8.1) 126 (51.0)	 118 (35.2) 68 (14.3) 295 (50.4)	0.051
Body mass index #	26.0 (22.7 – 31.0)	26.0 (23.0 – 30.0)	0.777
Hypertension	94 (30.7)	173 (39.1)	0.019
Hypercholesterolaemia	37 (12.1)	75 (16.9)	0.068
Diabetes mellitus	50 (16.3)	84 (19.0)	0.357
Chronic kidney disease	13 (4.2)	46 (10.4)	0.002
Asthma	42 (13.7)	46 (10.4)	0.163
COPD	40 (13.1)	64 (14.4)	0.593
Stroke or TIA	12 (3.9)	41 (9.3)	0.005
Heart failure	8 (2.6)	51 (11.5)	<0.001
Ischaemic heart disease	19 (6.2)	78 (17.6)	<0.001
Previous PCI	3 (1.0)	5 (1.1)	0.846
Previous CABG	1 (0.3)	21 (4.7)	<0.001
Atrial fibrillation	24 (7.8)	66 (14.9)	0.004
Inflammatory bowel disease	14 (4.6)	9 (2.0)	0.047

Rheumatoid arthritis	7 (2.3)	11 (2.5)	0.864
Peripheral vascular disease	12 (3.9)	34 (7.7)	0.035
Planned admission	92 (30.1)	37 (8.4)	<0.001
Admission SOFA	3 (2 – 6)	7 (4 – 10)	<0.001
APACHE II*	10 (7 – 16)	16 (11 – 22)	<0.001
Creatinine (μmol/L)	64 (52 – 80)	92 (65 – 146)	<0.001
WBC (10^9/L)	12.1 (9.1 – 16.1)	13.7 (9.7 – 18.6)	0.001
Haemoglobin (g/L)	117 (105 – 131)	113 (95 – 129)	0.003
CRP (mg/L)**	31 (9 – 119)	77 (13 – 196)	<0.001
Lactate (mmol/L)~	1.1 (0.7 – 1.8)	1.5 (1.0 – 2.7)	<0.001
Invasive ventilation during admission	116 (37.9)	209 (47.2)	0.012
Haemofiltration during admission	10 (3.3)	59 (13.3)	<0.001
Vasopressor/inotrope use during admission	90 (29.4)	246 (55.5)	<0.001
Length of CC stay	2 (1 – 3)	3 (2 – 5)	<0.001
Death in CC	4 (1.3)	82 (18.5)	<0.001

Table 27: demographics, comorbidity status, admission characteristics and outcomes for GCCU depending on whether the hs-cTnI was above or below the ULN. (COPD=chronic obstructive pulmonary disease, TIA=transient ischaemic attack, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, SOFA=sequential organ failure assessment, APACHE=acute physiology and chronic health evaluation WBC=white blood cell count, CRP=C reactive protein (^ smoking status unknown ≤ULN 59, >ULN 108; # BMI data unknown ≤ULN 16, >ULN 22, * APACHE II score unknown ≤ULN 7 >ULN 2; ** CRP data unknown ≤ULN 4, >ULN 5; ~ Lactate data unknown <ULN 4, >ULN 0)). All variables on admission to CC unless otherwise stated

Variable	**Admission hs-cTnI ≤ ULN (total 187)**	**Admission hs-cTnI >ULN (total 96)**	**p-value**
Median age	55 (45 – 67)	65 (54 – 74)	<0.001
Male	92 (49.2)	57 (59.4)	0.105
Smoking status^ Non-smoker Ex-smoker Current smoker	 83 (55.0) 5 (3.3) 63 (41.7)	 30 (49.2) 4 (6.6) 27 (44.3)	0.492
Body mass index #	26.6 (23.6 – 30.1)	27.0 (24.0 – 30.0)	0.681
Hypertension	45 (24.1)	41 (42.7)	0.001
Hypercholesterolaemia	14 (7.5)	12 (12.5)	0.167
Diabetes mellitus	12 (6.4)	6 (6.3)	0.957
Chronic kidney disease	8 (4.2)	1 (1.0)	0.142
Asthma	21 (11.2)	9 (9.4)	0.631
COPD	12 (6.4)	5 (.52)	0.685
Stroke or TIA	51 (27.3)	51 (53.1)	<0.001
Heart failure	3 (1.6)	3 (3.1)	0.400
Ischaemic heart disease	14 (7.5)	9 (9.4)	0.582
Previous PCI	6 (3.2)	4 (4.2)	0.679
Previous CABG	-	-	-
Atrial fibrillation	8 (4.3)	13 (13.5)	0.005
Inflammatory bowel disease	3 (1.6)	2 (2.1)	0.552
Rheumatoid arthritis	0 (0.0)	2 (2.1)	0.114

Peripheral vascular disease	2 (1.1)	3 (3.1)	0.341
Planned admission	80 (42.8)	6 (6.3)	<0.001
Admission SOFA	3 (1 – 6)	6 (4 – 8)	<0.001
APACHE II*	10 (6 – 16)	19 (11 – 22)	<0.001
Creatinine (μmol/L)	57 (45 – 70)	62 (47 – 78)	0.024
WBC (10^9/L)	12.1 (9.6 – 15.3)	13.1 (10.2 -17.8)	0.050
Haemoglobin (g/L)	126 (116 – 135)	124 (111 – 136)	0.552
CRP (mg/L)**	6 (2 – 14)	14 (4 – 58)	<0.001
Lactate (mmol/L)~	0.9 (0.7 – 1.9)	1.0 (0.7 – 1.6)	0.788
Invasive ventilation during admission	77 (41.2)	68 (70.8)	<0.001
Haemofiltration during admission	2 (1.1)	0 (0.0)	0.436
Vasopressor/inotrope use during admission	64 (34.2)	48 (50.0)	0.010
Length of CC stay	2 (1 – 4)	3 (1 – 10)	0.002
Death in CC	6 (3.2)	26 (27.1)	<0.001

Table 28: Demographics, comorbidity status, admission characteristics and outcomes for NCCU depending on whether the hs-cTnI concentration was above or below the ULN. (COPD=chronic obstructive pulmonary disease, TIA=transient ischaemic attack, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, SOFA=sequential organ failure assessment, APACHE=acute physiology and chronic health evaluation WBC=white blood cell count, CRP=C reactive protein (^ smoking status unknown ≤ULN 36, >ULN 35; # BMI data unknown ≤ULN 10, >ULN 6, * APACHE II score unknown ≤ULN 12 >ULN 4; ** CRP data unknown ≤ULN 2, >ULN 0; ~ Lactate data unknown <ULN 10, >ULN 3)).

5.4.2 Admission characteristics

The median admission hs-cTn across the two CCs was 21ng/L (IQR 7 – 86ng/L) with 560 (54.2%) above the manufacturer-defined ULN. Figure 12 shows that there is a positively skewed distribution of the log(10) admission hs-cTn concentrations across the two CC units (Table 29). Patients with a hs-cTn concentration above the ULN had worse markers of illness severity in GCCU and NCCU (Table 27Table 28).

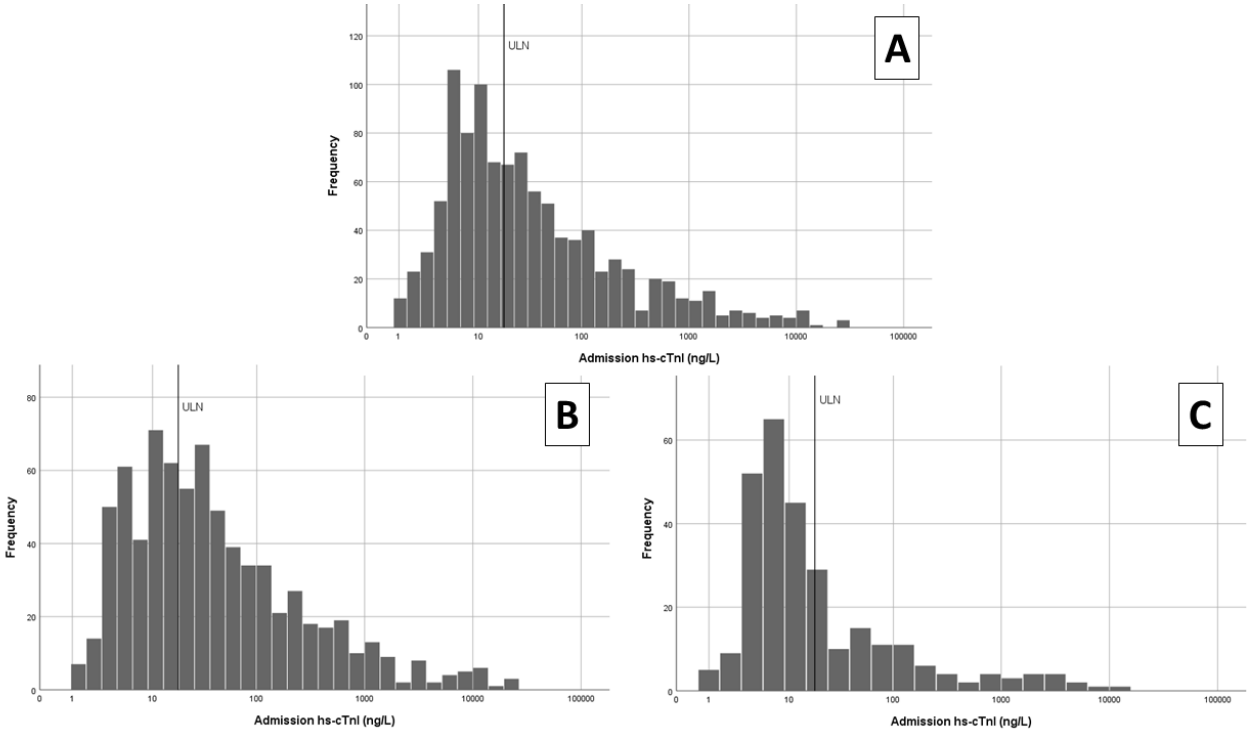

Figure 12: Distribution of hs-cTnI across the entire cohort (Panel A), GCCU (Panel B), NCCU (Panel C) with a log (10) scale for hs-cTnI concentration

Hs-cTn	GCCU (total 750)	NCCU (total 283)	p-value
Admission hs-cTn (ng/L)	27 (9 – 110)	9 (6 – 32)	<0.001
Number with admission hs-cTn above ULN (%)	460 (61.4)	100 (35.3)	<0.001
Peak hs-cTn (ng/L)	38 (12 – 198)	14 (7 – 47)	<0.001
Number with peak hs-cTn above ULN (%)	506 (67.5)	129 (45.6)	<0.001
Number >20% rise from admission (%)	23 (3.1)	4 (1.4)	0.075

Table 29: Hs-cTnI concentrations across the two CC environments

5.4.3 Peak hs-cTn and change in hs-cTn

The median peak hs-cTn was 28ng/L (IQR 10 – 143ng/L) across the two CC environments. In 54.8% of patients, the peak hs-cTn was on admission, with 26.2% on day 1, 10.3% on day 2 and 2.8% on day 4. There were, however, only 27 patients (2.6 %) across the two CC environments in whom the hs-cTn rose by more than 20% at any stage when compared with the admission hs-cTn (Table 29).

5.4.4 Organ support

Table 27Table 28 show that patients with a hs-cTn concentration above the ULN were more likely to need organ support compared with those below the ULN in GCCU and NCCU. Admission hs-cTn concentration demonstrated reasonable discrimination for haemofiltration in GCCU (Table 30).

Organ support	GCCU (AUC (95% CI)	NCCU (AUC (95% CI)
Invasive ventilation during admission	0.585 (0.543 – 0.626)	0.689 (0.651 – 0.727)
Haemofiltration during admission	0.725 (0.669 -0.780)	0.318 (0.145 – 0.480)
Vasopressor/inotrope use during admission	0.689 (0.651 – 0.727)	0.575 (0.505 – 0.645)

Table 30: Discriminatory ability of admission hs-cTnI concentration for organ support by CC unit (AUC – area under the receiver operator curve).

5.4.5 Length of critical care stay

Across the two CCs the median length of CC stays was 2 days (IQR 1 – 5 days). On multivariable analysis there was no association between length of CC stay and whether the hs-cTn concentration was above the ULN in either of the CC units.

5.4.6 Association with outcomes

Across the CC environments, 118 (11.4%) patients died during their CC admission (Table 27 Table 28). Mortality in GCCU and NCCU was significantly higher when the peak or admission hs-cTn was above the ULN (Figure 13). The discriminative ability of admission hs-cTn for in death in both GCCU and NCCU was strong (AUC 0.819 (95% CI 0.777 – 0.860) and AUC 0.828 (95% CI 0.757 – 0.900) respectively). Peak hs-cTn as a continuous variable performed similarly to admission hs-cTn (GCCU AUC 0.838 (95% CI 0.802 – 0.874), NCCU AUC 0.829 (95% CI 0.763 – 0.895)). For patients in GCCU and NCCU, admission hs-cTn performed as well as both the SOFA and APACHE II scores as a discriminator of in CC mortality (GCCU APACHE II AUC 0.807 (95% CI 0.763 – 0.851), SOFA AUC 0.791 (95% CI 0.745 – 0.836) and NCCU APACHE II AUC 0.892 (95% CI 0.847 – 0.937), SOFA AUC 0.812 (95% CI 0.757 – 0.867)). The level to which admission hs-cTn was above the ULN did not improve the discriminative ability of the APACHE II score in either GCCU or NCCU. Mortality increased with increasing admission hs-cTn concentrations relative to the ULN in GCCU and NCCU

(Figure 14). The admission hs-cTn remained independently associated with CC mortality on multivariable analysis for patients in GCCU and NCCU whether using the log(10) hs-cTn concentration or the hs-cTn concentration relative to the ULN (Table 31-35). There was no evidence of significant collinearity between variables included in these models (all derived VIFs were below three).

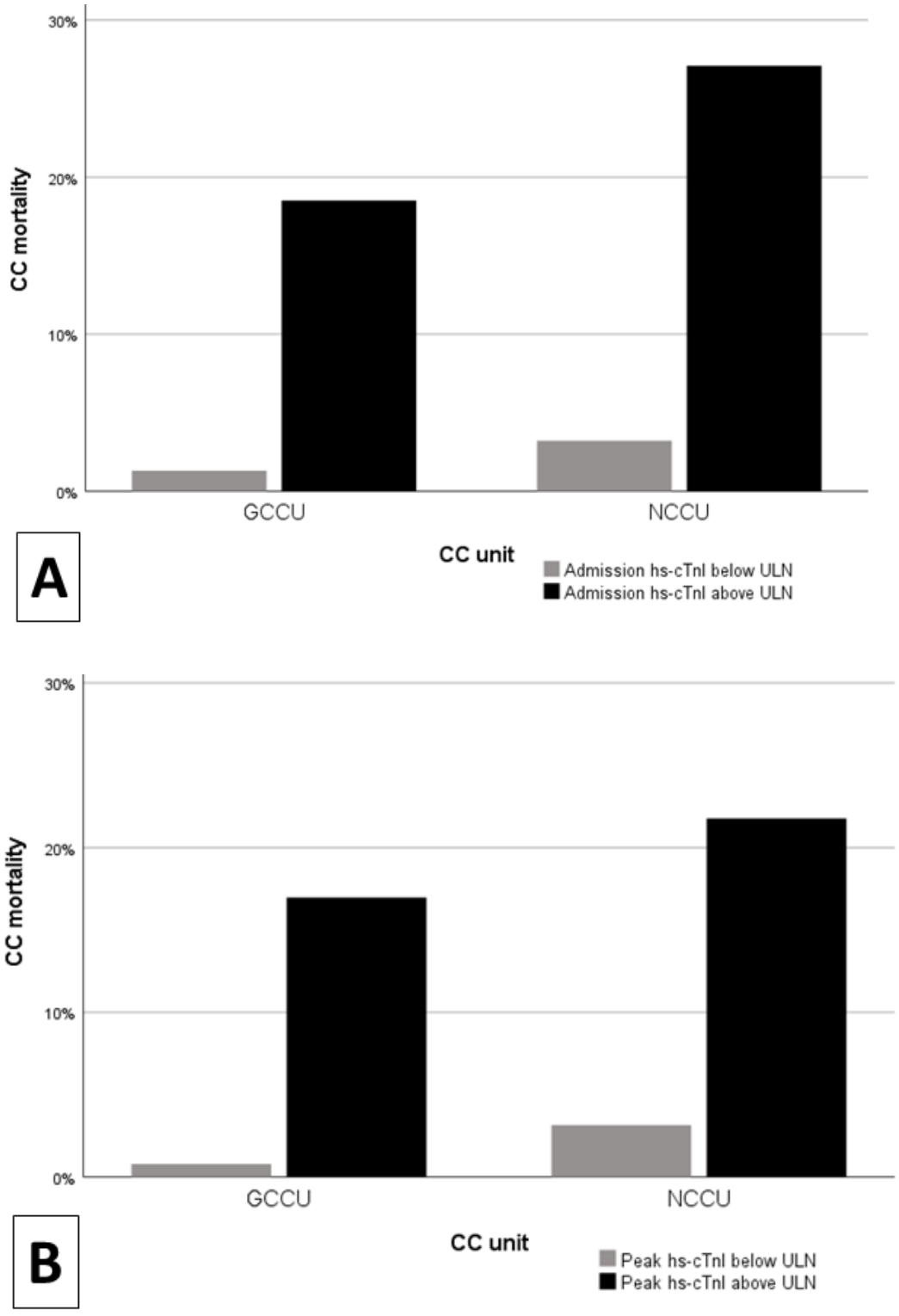

Figure 13: Mortality in CC across each CC environment. Panel A - mortality with admission hs-cTnI concentration above the ULN, Panel B - mortality with peak hs-cTnI concentration above the ULN

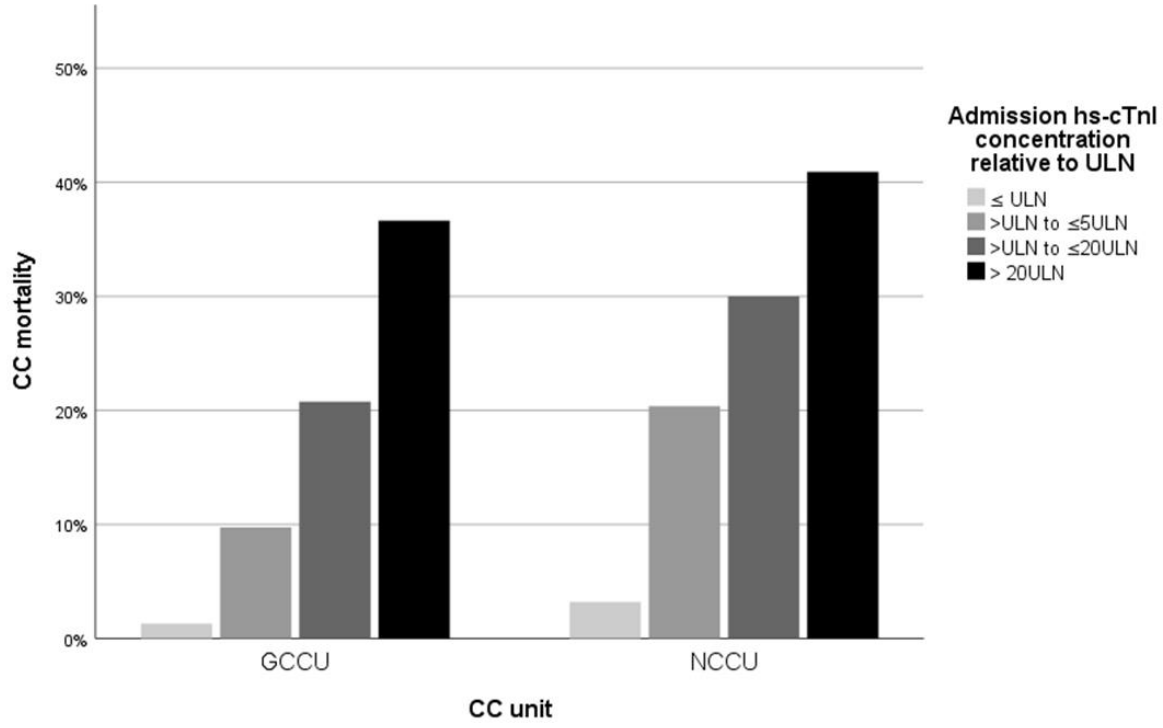

Figure 14: Mortality in each CC area according to the hs-cTnI concentration relative to the ULN

Variable	Number (%) death in CC with variable present	Number (%) death in CC with variable absent	p-value
Male	50 (11.0)	36 (12.2)	0.610
Smoking status^ Non-smoker Ex-smoker Current smoker	 15 (6.8) 11 (16.2) 30 (10.2)		0.065
Hypertension	28 (10.4)	58 (12.0)	0.514
Hypercholesterolaemia	13 (11.6)	73 (11.4)	0.960
Diabetes mellitus	10 (7.4)	76 (12.4)	0.102
Chronic kidney disease	6 (10.0)	80 (11.6)	0.710
Asthma	10 (11.4)	76 (11.5)	0.974
COPD	18 (17.3)	68 (10.5)	0.044
Stroke or TIA	8 (15.1)	78 (11.2)	0.390
Heart failure	6 (10.0)	80 (11.6)	0.710
Ischaemic heart disease	20 (20.4)	66 (10.1)	0.003
Atrial fibrillation	11 (12.2)	75 (11.4)	0.810
Inflammatory bowel disease	2 (8.7)	84 (11.6)	0.672
Rheumatoid arthritis	2 (12.2)	84 (11.5)	0.810
Peripheral vascular disease	6 (13.0))	80 (11.4)	0.792
Planned admission	3 (3.2)	83 (13.4)	<0.001

Invasive ventilation during admission	61 (18.8)	25 (5.9)	<0.001
Haemofiltration during admission	25 (35.7)	61 (9.0)	<0.001
Vasopressor/inotrope use during admission	66 (19.6)	20 (4.8)	<0.001
Hs-cTnI concentration relative to ULN ≤ULN >ULN≤5ULN >5ULN≤20ULN >20ULN	 4 (1.3) 23 (9.7) 22 (20.8) 37 (36.6)		

Table 31: Univariable association with mortality for categorical variables of demographics, comorbidity status, admission characteristics and organ support in GCCU (COPD=chronic obstructive pulmonary disease, TIA=transient ischaemic attack (^ smoking status unknown ≤ULN 59, >ULN 108))

Variable	Number (%) death in CC with variable present	Number (%) death in CC with variable absent	p-value
Male	22 (14.8)	10 (7.5)	0.053
Smoking status^ Non-smoker Ex-smoker Current smoker	 9 (8.0) 1 (11.1) 3 (3.3)		0.321
Hypertension	12 (14.0)	20 (10.2)	0.353
Hypercholesterolaemia	4 (15.4)	28 (10.9)	0.491
Diabetes mellitus	4 (22.2)	28 (10.6)	0.132
Chronic kidney disease	1 (11.1)	31 (11.3)	1.000
Asthma	1 (3.3)	31 (12.3)	0.222
COPD	1 (5.9)	31 (11.7)	0.703
Stroke or TIA	19 (18.6)	13 (7.2)	0.004
Heart failure	0 (0.0)	32 (11.6)	1.000
Ischaemic heart disease	2 (8.7)	30 (11.5)	1.000
Atrial fibrillation	5 (28.3)	27 (10.3)	0.073
Inflammatory bowel disease	1 (20.0)	31 (11.2)	0.454
Rheumatoid arthritis	0 (0.0)	32 (11.4)	1.000
Peripheral vascular disease	2 (40.0)	30 (10.8)	0.100
Planned admission	0 (0.0)	32 (16.2)	<0.001

Need for invasive ventilation	31 (21.4)	1 (0.7)	<0.001
Haemofiltration during admission	0 (0.0)	32 (11.4)	0.786
Vasopressor/inotrope use during admission	18 (16.1)	14 (8.2)	0.041
Hs-cTnI concentration relative to ULN ≤ULN >ULN≤5ULN >5ULN≤20ULN >20ULN	 6 (3.2) 11 (20.4) 6 (30.0) 9 (40.9)		

Table 32: Univariable association with mortality for categorical variables of demographics, comorbidity status, admission characteristics and organ support in NCCU (COPD=chronic obstructive pulmonary disease, TIA=transient ischaemic attack (^ smoking status unknown ≤ULN 36, >ULN 35))

Variable	**GCCU mortality odds ratio (95%CI)**	**NCCU mortality odds ratio (95%CI)**
Body mass index #	1.011 (0.979 – 1.043)	1.026 (0.969 -1.086)
APACHE II *	1.165 (1.125 – 1.205)	1.353 (1.218 – 1.503)
Haemoglobin (g/L)	1.007 (0.997 – 1.017)	1.001 (0.980 – 1.022)
CRP (mg/L)**	0.998 (0.996 – 1.001)	1.002 (0.995 – 1.008)
Lactate (mmol/L) ~	1.321 (1.213 – 1.439)	1.576 (1.173 – 2.117)
Log(10)hs-cTnI	3.660 (2.773 – 4.830)	3.594 (2.333 – 5.536)

Table 33: Univariable association with mortality for continuous variables of demographics, comorbidity statues, admission characteristics and organ support for GCCU and

NCCU (APACHE=acute physiology and chronic health evaluation CRP=C reactive protein (# BMI data unknown in GCCU ≤ULN 16, >ULN 22, in NCCU ≤ULN 10, >ULN 6; * APACHE II score unknown in GCCU ≤ULN 7 >ULN 2, in NCCU ≤ULN 12 >ULN 4; ** CRP data unknown in GCCU ≤ULN 4, >ULN 5, in NCCU ≤ULN 2, >ULN 0; ~ Lactate data unknown <ULN 4, >ULN 0))

Variable	**Mortality odds ratio (95%CI)**	**Mortality odds ratio (95%CI)**
Planned admission	0.544 (0.150 – 1.976)	0.406 (0.107 – 1.539)
Haemofiltration during admission	2.301 (1.168 – 4.532)	2.179 (1.101 – 4.312)
Invasive ventilation during admission	1.160 (0.563 – 2.387)	1.045 (0.506 – 2.157)
Vasopressor/inotrope use during admission	1.404 (0.705 – 2.798)	1.414 (0.705 – 2.836)
COPD	1.805 (0.904 – 3.607)	1.934 (0.971 – 3.852)
IHD	1.527 (0.789 – 2.956)	1.495 (0.764 – 2.927)
APACHE II	1.089 (1.036 – 1.145)	1.092 (1.038 – 1.148)
Lactate	1.090 (0.996 – 1.193)	1.093 (0.996 – 1.200)
Log (10)Hs-cTnI concentration	-	2.492 (1.804 – 3.443)
Hs-cTnI concentration relative to ULN ≤ULN >ULN≤5ULN >5ULN≤20ULN >20ULN	 Reference 4.915 (1.614 – 14.972) 8.061 (2.534 – 25.641) 13.978 (4.481 – 43.595)	-

Table 34: Multivariable outputs for GCCU using hs-cTnI concentration relative to the ULN and the log(10) hs-cTnI concentration separately

Variable	Mortality odds ratio (95%CI)	Mortality odds ratio (95%CI)
Planned admission	n/a	n/a
Invasive ventilation during admission	0.992 (0.085 – 11.595	0.832 (0.071 – 9.746)
Vasopressor/inotrope use during admission	2.110 (0.768 – 5.798)	2.259 (0.820 – 6.181)
Stroke or TIA	1.339 (0.498 – 3.602)	1.273 (0.470 – 3.441)
APACHE II	1.312 (1.135 – 1.517)	1.321 (1.143 – 1.527)
Lactate	1.562 (0.938 – 2.600)	1.579 (0.951 – 2.622)
Log (10)Hs-cTnI concentration	-	2.281 (1.292 – 4.026)
Hs-cTnI concentration relative to ULN ≤ULN >ULN≤5ULN >5ULN≤20ULN >20ULN	 Reference 2.529 (0.735 – 8.821) 5.056 (1.154 – 22.148) 5.799 (1.361 – 24.696)	-

Table 35: Multivariable outputs for NCCU using the hs-cTnI concentration relative to the ULN and the log(10) hs-cTnI concentration

5.5 Discussion

To our knowledge this is the largest study to enrol consecutive patients admitted to CC for any clinical reason and to follow hs-cTn concentrations throughout their admission, without a conventional clinical indication for testing. We present several key findings. Firstly, that hs-cTn concentrations above the ULN were frequently seen on admission to both GCCU (61.4%) and NCCU (35.3%). Secondly, that hs-cTn concentrations were associated with markers of illness

severity and the use of organ support during the CC admission. Thirdly, that admission hs-cTn concentrations were independently associated with mortality.

The findings of this study in GCCU are generally consistent with the previous literature demonstrating that hs-cTn concentrations are frequently above the ULN on admission (20% - 80%) (406, 408-411, 433). Furthermore, our study, similarly to previous literature, demonstrated that age, comorbidity status and markers of acute illness severity were closely associated with hs-cTn concentrations (406, 408-411). The present study is the first study to report hs-cTn concentrations in a consecutive cohort of NCCU patients and, perhaps surprisingly, given the increased sensitivity when compared to standard assays, the frequency of hs-cTn above the ULN in NCCU patients in this study was at the lower end of the previously reported range (30% - 65%) (392, 393). It is important to note, however, that these other studies only included specific patient subgroups admitted to NCCU and did not recruit consecutive patients. Across these studies, the comorbidity status and severity of illness were associated with the cTn concentration (393, 395).

The most important finding from this study is the independent association between hs-cTn concentration and CC mortality observed in both GCCU and NCCU. A similar study of 145 patients in GCCU found that hs-cTn was not associated with mortality on multivariable analysis (355). It is possible that their study failed to find an association due to the small sample size. The observations seen in our study are supported by Frencken et al, who performed hs-cTn testing in all patients presenting to GCCU with sepsis and similarly found that hs-cTn concentration was an independent predictor of mortality (411). Further, in patients with ARDS, the hs-cTn concentration was associated with mortality but this was not statistically significant after accounting for illness severity (408). Our study provides evidence for the prognostic value of hs-cTn concentrations across a broader population of GCCU and NCCU admissions. As such this study adds to the growing evidence that hs-cTn is a marker of prognosis across a range of cardiac and non-cardiac conditions (13, 342).

Interestingly, whilst following hs-cTn concentrations during admission does identify more patients with hs-cTn concentrations above the ULN, the peak hs-cTn concentration and the degree of hs-cTn rise do not add much additional prognostic information. These data suggest that serial hs-cTn testing in CC is not beneficial.

Given that in this study hs-cTn is a good discriminator of mortality, it is perhaps surprising that it was not associated with length of stay. This observation could be because the length of stay often results from bed pressure in the rest of the hospital limiting CC discharge or because some clinical scenarios prolong stay but are not in themselves predictive of CC-related mortality.

5.5.1 Strengths and limitations

This study provides a unique insight into the distribution, associations and discriminative ability of nested, non-clinically driven hs-cTn testing across two CC units. The study is strengthened by the prospective, consecutive nature of the recruitment and as such allows robust conclusions to be drawn.

The study does however have a number of weaknesses. Firstly, the study team could not ascertain the APACHE II score in all patients. Secondly, this is a single centre observational study and therefore carries the inherent limitations related to generalisability shared by all studies with such a design. In addition, our analysis does not consider the admitting diagnosis. This is potentially important because the admission diagnosis could give clinicians important prognostic data. However, the study does include markers of illness severity which allow evaluation of the performance of hs-cTn concentration against well validated illness severity scores. In particular, our study did not take into account whether patients had a diagnosis of sepsis, which as previously shown is an important predictor of mortality (411, 433). In addition, the lack of admission diagnoses means that patients who had an out of hospital cardiac arrest, in whom hs-cTn concentrations are likely to be high and outcomes poor, cannot be accounted for in the analysis. Finally, due to the fact that hs-cTn samples were drawn every 24 hours, it is possible that

the peak hs-cTn concentration may have occurred outside the sampling timeframe and so the study may have underestimated the true rise in hs-cTn concentration.

5.6 Conclusions

In this consecutive series of patients admitted to two adult CC units, and in whom hs-cTn concentrations were measured without any conventional clinical indication, values above the ULN were frequently seen and were associated with the comorbid status of a patient and the illness severity. In non-cardiothoracic settings admission hs-cTn concentration was independently associated with CC mortality and demonstrated similar discriminatory performance for mortality to well established risk scores, thus suggesting that they may have a role in routine clinical practice as a biomarker of risk.

Chapter 6 Conclusions

6.1 Summary of findings

Hs-cTn concentrations above the 99th percentile provided by the manufacturer (the threshold frequently used clinically as the ULN) are regularly seen in patients presenting to ED regardless of whether there is a clinical indication to perform this test and this appears to closely related to the severity of illness that the patients present with. Concentrations above the 99Th percentile are seen in a range of clinical conditions and not solely related to cardiovascular presentations. Furthermore, these tests are now frequently being used outside their original indication (as an aid in the diagnosis of T1MI) and the interpretation of the subsequent result is dependent upon a clear understanding of Types 1 & 2 MI as well as myocardial injury. These concepts, and the differentiation between Type 1 MI and the others, in particular, require greater education and training amongst frontline clinical staff, so that misdiagnosis and management do not occur. Outside the realm of the danger of misinterpreting a "positive" cTn to mean T1MI, a newer role for the assay may be emerging. Importantly, the hs-cTn concentration on presentation to ED is independently associated with short term mortality. Furthermore, the higher the hs-cTn concentration the longer the inpatient length of stay. These data suggest that hs-cTn concentrations on admission to ED could provide clinicians with additional prognostic data. Whilst further data are required before this can become the standard of care these data do add to the concept that hs-cTn elevation 'never means nothing.' Furthermore, these data will help aid clinicians in the interpretation of hs-cTn results when they are performed outside the context of T1MI [Chapter 3].

In a cohort of 20,000 hospital patients, including ED, IPD and OPD, the majority of whom had no clinical indication for hs-cTn testing, the hs-cTn concentration was independently associated with one year mortality. This relationship was seen regardless of the patient's clinical location at the

time of testing (ED, OPD,IPD) and as such suggests that hs-cTn concentrations may have a prognostic role in a range of different populations, including those who are acutely unwell (such as those in ED) as well as those who have a stable chronic health condition (such as those in the OPD cohort). Of further interest, the hs-cTn concentration was associated with both cardiovascular and non-cardiovascular mortality. In particular the cardiovascular mortality in those with low hs-cTn concentrations was negligible. This suggests that these assays may be useful to further refine the assessment of an individual patient's cardiovascular risk in the community, where, if concentrations are very low, potentially the clinical threshold for starting risk modifying medical therapy could be adjusted. In addition, the relationship between hs-cTn concentration and mortality appeared to persist for concentrations below the manufacturers 99th percentile. Thus, again, suggesting that the hs-cTn concentration, even if it is below the ULN, 'never means nothing' [Chapter 4].

In patients presenting to general or neurosciences CC units, hs-cTn concentrations are frequently above the manufacturer's 99th percentile even if there is no clinical indication for performing hs-cTn testing. Around a third (35.3%) of patients presenting to NCCU will have a hs-cTn concentration above the 99th percentile and two thirds (61.4%) of those presenting to GCCU. In general, the hs-cTn concentration was associated with increasing age, comorbidity and illness severity in GCCU and NCCU, thus suggesting that hs-cTn concentration is merely a reflection of these factors. However, the independent association between hs-cTn concentration and CC mortality suggests that hs-cTn concentration may be of use as a biomarker of risk on admission to these CC environments, particularly as it performs as well as previously validated risk scores [Chapter 5].

6.2 Overall limitations

Specific limitations relevant to each of the studies are discussed in the relevant results chapters. There are further limitations that are worth considering or rediscussing given their potential importance.

Firstly, all the studies in this thesis were performed in a single centre and as such there is potential uncertainty about the broader applicability of these findings. For example, in the CHARIOT-ED study, over a quarter of patients (27.2%) had hs-cTn testing performed on presentation to ED by the clinical team. The requested indications for these tests suggest that they are being performed outside the clinical guideline recommendations. It is likely that this practice may differ from other centres. However, whilst this may be the case, it does not affect the main results of that paper, that demonstrate that hs-cTn is a marker of prognosis regardless of whether there was a clinical indication for the test or not. Another potential instance where the single centre nature of this study may have an effect is in the CC study because it is likely that CC admission criteria vary across centres and countries. Whilst some units may only admit more or less unwell patients it is likely that the relationship between hs-cTn concentration and outcome seen in this study would persist because this relationship was present even after allowing for illness severity in the multivariable modelling.

The second limitation that is worth further discussion is the applicability of the assays used in this study. There are two elements to this. Firstly, as has been demonstrated elsewhere in the introduction of this thesis, different assays have been shown to have different performances and in particular have been shown to have different relationships with mortality in specific cohorts. The most important limitation for the CHARIOT studies is that the hs-cTn assay used in these does not quite meet the criteria for a high sensitivity assay and as such could be considered a contemporary sensitivity assay. Whilst this means that the thresholds demonstrated in the CHARIOT studies may not be specific to truly high sensitivity assays it is likely that this would not alter the relationship altogether. In fact, the increased sensitivity may allow discrimination at lower concentrations and thus allow improved prognostication at lower concentrations.

6.3 Proposed further work

The data as a whole undoubtedly demonstrate that hs-cTnI concentrations above the manufacturer's 99th percentile are frequently seen across a range of clinical scenarios and that these are related to prognosis. However, further data are now required in other inpatient cohorts and CC environments to support the findings of this thesis. Whilst improved prognostic data are clearly helpful to clinicians, the next step is to assess whether the identification of patients at high future risk, using hs-cTn assays, will guide intervention(s) that could alter this prognosis. However, at this stage there are limited data and it remains to be seen whether medical therapy will alter the future cardiovascular and non-cardiovascular risk of these patients. This is where the proposed modifications to the Universal Definition of MI are likely to be particularly relevant: the distinction between patients with T2MI who do and do not have underlying coronary artery

disease will clearly be important, because it seems likely that the use of proven disease-modifying agents will help those with T2MI and coronary disease but this seems less likely in those with T2MI and no underlying coronary artery disease. However ,it would be a reasonable starting point for trials to give these medications to those with and without underlying CAD. If it is shown that hs-cTn assays identify patients at risk, whose risk can subsequently be reduced using medical interventions, then this would set the stage for the widespread use of these assays outside the context of T1MI.

6.4 Summary

Hs-cTn assays do identify a group of patients at high risk of mortality across a range of clinical scenarios, from in- to out-patients as well as those presenting acutely in ED and those with critical illness states. These tests are already being used outside their original indication and the data from this thesis support the observation that whilst these results probably don't represent T1MI they 'never mean nothing'.

If data do go on to demonstrate that hs-cTn assays identify a group of patients at high risk of future events in whom a specific medical intervention alters that future risk it is likely that we will see a phase shift from the use of these assays as a primary diagnostic tool to them being used as a biomarker for future risk across a range of populations.

Appendix

A.1 Publications arising from work in this thesis

A.1.1 Reviews

- Hinton J, Gabara L, Curzen N. *Is the true value of high-sensitivity troponins as a biomarker of risk? The concept that detection of high-sensitivity troponin 'never means nothing'.* Expert Review Cardiovascular Therapy. 2020 18(12):843-857.
- Hinton J, Mariathas M, Grocott MPW, Curzen N. *High sensitivity troponin measurement in critical care: flattering to deceive or "never means nothing?"* Journal of the Intensive Care Society. 2020 Aug;21(3):232-240.

A.1.2 Original research papers

- Hinton J, Mariathas M, Gabara L et al. Relation of High-sensitivity Troponin to One Year Mortality in 20,000 Consecutive Hospital Patients Undergoing a Blood Test for Any Reason. American Journal of Cardiology 2021. 158 (1) 124-131
- Hinton J, Augustine M, Mariathas M et al. Distribution of high sensitivity troponin taken without conventional clinical indications in critical care patients and its association with mortality. Critical Care Medicine 2021 49 (9) 1451-1459
- Hinton J, Mariathas M, Gabara L, et al. *Distribution of contemporary sensitivity troponin in the emergency department and relationship to 30-day mortality: The CHARIOT-ED substudy.* Clinical Medicine 2020; 20 (6): 528-534

A.1.3 Abstracts

- Hinton J, Augustine M, Gabara L et al. Incidence and one year outcome of periprocedural myocardial infarction following cardiac surgery: are the universal definition and SCAI criteria fit for purpose? 2021 European Heart Journal 42, suppl 1 ehab724.1442
- Hinton J, Augustine M, Gabara L et al. the relationship between high-sensitivity troponin taken on admission to critical care, regardless of whether there was a clinical indication

for testing, and one year mortality. 2021 European Heart Journal 42, suppl 1 ehab724.1381

- Hinton J, Augustine M, Gabara L et al. The Incidence and Short-Term Outcomes of Periprocedural Myocardial Infarction Following Cardiac Surgery Across Two International Definitions Using the High-Sensitivity troponin Assay. European Medical Journal: Interventional Cardiology, EuroPCR 2021, 25
- Hinton J, Augustine M, Gabara L et al. The relationship between high-sensitivity troponin taken on admission to criticalc are, regardless of whether there was a clinical indication for testing and one year mortality: a novel biomarker for outcome? Heart 2021 107(suppl1) A41-42
- Hinton J, Mariathas M, Gabara L et al. Association between high-sensitivity troponin and one year mortality in 20,000 consecutive hospital patients undergoing a blood test for any reason. Heart 2021 107(suppl1) A143-144
- Hinton J, Augustine M, Gabara L et al. Incidence and one year outcome of periprocedural myocardial infarction following cardiac surgery troponin: are the Universal Definition and SCAI criteria fit for purpose? Heart 2021 107(suppl1) A32-33
- Hinton J, Augustine M, Gabara L et al. The frequency and short term outcomes of periprocedural myocardial infarction following cardiac surgery using high sensitivity troponin: are the Universal Definition and SCAI criteria fit for purpose? EuroPCR abstract book POS142
- Hinton J, Augustine M, Gabara L et al. Distribution of high sensitivity troponin taken without conventional clinical indications in critical care patients and its association with mortality. European Heart Journal 41 (suppl 2) e1688
- Hinton J, Mariathas M, Gabara L et al. Distribution of high sensitivity troponin levels in consecutive, unselected patients in the emergency department and relationship to in-hospital mortality. Heart 2020 106 (suppl 2) A21-A22
- Hinton J, Augustine M, Gabara L et al. Distribution of high sensitivity troponin taken without conventional clinical indications in critical care patients and its association with critical care mortality. Heart 2020 106 (suppl 2) A16-A17
- Hinton J, Mariathas M, Allan R et al. Real world high-sensitivity troponin levels in an entire hospital population: Insights from the CHARIOT study. Heart 2019; 105 (suppl 6) a45-46

A.2 Prizes resulting from work in this thesis

- Winner, Wessex Turner Warwick Lecture, Royal College of Physicians 2020.
    - The role of high sensitivity troponin assays outside the context of acute coronary syndromes
- Finalist Royal Society of Medicine Cardiology President's prize
    - Incidence and one year outcome of periprocedural myocardial infarction following cardiac surgery: are the Universal Definition and SCAI criteria fit for purpose?

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