**High sensitivity troponins in contemporary cardiology practice: Are we turning a corner?**

Mark Mariathas1,2 BM, Bartosz Olechowski1,2 MD, Michael Mahmoudi1,2 MBBS, PhD, Nick Curzen1,2 BM(Hons), PhD \*

1Coronary Research Group, University Hospital Southampton NHS Foundation Trust, Southampton, UK

2Faculty of Medicine, University of Southampton, Southampton, UK

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\*corresponding author

Prof. N Curzen BM(Hons) PhD FRCP

Professor of Interventional Cardiology

E Level North Wing

University Hospital Southampton NHS Trust

Tremona Road

Southampton SO16 6YD

UK

00442381204972

nick.curzen@uhs.nhs.uk

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**Abstract**

***Introduction:*** Troponin is considered to be the gold standard biomarker for ruling out MI. There has been a drive to improve the diagnostic speed, and as such the high sensitivity cardiac troponin (Hs-cTn) assays have been introduced into clinical practice and are now part of international guidelines. Their novel value in clinical practice more generally is becoming apparent.

***Areas covered:*** In this review we will evaluate the evidence for the use of Hs-cTn assays in clinical practice, the issues with the assay and the how Hs-cTn can be utilized in the future as a biomarker of cardiovascular risk.

***Expert Commentary:*** The use of the Hs-cTn assays as a ‘rule out’ test for MI is compelling, as a ‘rule in’ there are significant issues relating the specificity of the assay for MI. The future of the assay may lie in population screening and risk modeling.

**Keywords**

Troponin, high sensitivity troponin, myocardial infarction, acute coronary syndromes, type 2 myocardial infarction, type 1 myocardial infarction

**1.1 What is troponin?**

Troponin is currently the gold standard biomarker used in clinical practice to help establish the diagnosis of myocardial infarction (MI)[1], defined as a rise in cardiac troponin (cTn) above the 99th percentile derived from a reference population associated with an appropriate clinical context[2]. The 99th percentile of a reference population of ‘normal’ individuals is generally regarded as the upper limit of normal (ULN) for troponin values[3, 4].

Myofibrils are the basic contractile apparatus of myocytes. Each myofibril is composed of a thick and a thin filament. The thick filament is made up of myosin whilst actin makes up the thin filament. Troponins are classified as cardiac regulatory proteins that control the calcium-mediated interaction between actin and myosin. There are three subunits of the troponin complex: Troponin C, I and T[5]. Cardiac troponin I (cTnI) is cardiac-specific and, although cardiac troponin T can also be found in skeletal muscle, this subtype is not usually detected in currently available assays[6]. As a consequence, the measurement of cTn is considered to be extremely specific for cardiomyocyte injury[7]. It is this concept that has cemented the use of cTn assays in the modern diagnosis and management of acute coronary syndromes (ACS).

**1.2 Troponin Assays**

***1.2.1 Background***

The primary role of cTn assays in ACS is in risk stratification. The evidence for early and aggressive treatment, including both pharmacological and invasive interventions, of ACS in medium-to-high risk individuals is robust, so that there is clinical outcome benefit for revascularisation in troponin positive patients.[8, 9] The serum cTn concentration in these patients is therefore plays a significant role in determining how these patients are managed[10-12].

However, plasma cTn concentrations can be raised in a variety of other conditions. (Table 1)

Table 1: Causes of raised cTn

|  |  |
| --- | --- |
| CARDIAC CAUSES | NON-CARDIAC CAUSES |
| Cardiac contusion | Pulmonary Embolism |
| Cardiac surgery | Pulmonary Hypertension |
| Cardioversion | Renal Failure |
| Acute and Chronic Heart Failure | Cerebrovascular disease |
| Aortic dissection | Sepsis |
| Hypertrophic cardiomyopathy | Drugs |
| Arrhythmias | Extreme exertion |
| Post PCI | Burns |
| Hypertension | Critical illness |
| Myopericarditis | COPD |

Given this, clinicians can be left in a dilemma when interpreting cTn serum concentrations in patients who have comorbidities such as chronic kidney disease, hypertension and heart failure. The obvious concern is therefore the potential that patients are inappropriately treated for “ACS” due to an elevated serum cTn concentration that is in fact due to an alternative aetiology. As well as a range of medications appropriate for ACS, *such patients could also undergo invasive diagnostic and revascularization procedures that are not appropriate*.

Pre-analytical factors that can affect c-Tn concentrations include the sample type required, appropriate handling, storage and transportation of samples[13]. Analytical issues include sensitivity and imprecision at low concentrations, antibody specificity and immunoreactivity of plasma isoforms[13]. Falsely increased and decreased troponin concentrations can occur due to factors affecting the antigen-antibody reaction[14]. This includes autoantibodies, heterophilic antibodies, rheumatoid factors, and human anti-mouse antibodies[15]

***1.2.2 Types of Assay***

The early cTn assays first came into clinical practice from 1995 onwards. These assays aided clinicians in the diagnosis of acute MI with the expectation that they would provide a ‘yes/no’ answer as to whether MI had occurred. However, due to limitations in terms of the early lack of sensitivity, they could usually only be helpful and reliable some 10-12 hours post infarction. Unsurprisingly, there has been a drive to develop more sensitive troponin assays that will allow rapid exclusion of MI, in particular, in order to facilitate the early discharge of patients, preferably from the Emergency Department. This has culminated in the advent of the new highly sensitive cardiac troponin (Hs-cTn) assays[16-20].The Hs-cTn assays are able to detect troponin at much lower concentrations than the previous assays[4]. This is in keeping with the universal definition of MI, which recommends that a troponin assay used to diagnose MI should have a coefficient of variation (CV) of ≤ 10% at the threshold concentration representing the 99th percentile upper limit of a “normal reference” population (ULN). *Modern Hs-cTn assays can detect troponin in more than 50% of the general population with some assays able to detect troponin in everyone*[21]. The implications for interpretation of the results of the assay by front line staff are important: no longer is the presence of troponin a binary indicator of MI/ACS. This may is not be fully appreciated in routine clinical practice[22]. The International Federation of Clinical Chemistry and Laboratory Medicine Task Force On Clinical Applications of Cardiac Bio-Markers (IFCC TF-CB) has proposed that for an assay to be defined as high-sensitivity (hs) the following criteria need to be met[23]:

1. The % CV at the 99th percentile value should be ≤10%.
2. The measurable concentrations should be measured above the limit of detection (LoD) in at least 50% of healthy individuals.

Examples of Hs-cTn assays available currently are shown in table 2[24]. Interestingly, the hs-cTnT assay (Roche) has shown lower than recommended rates of measurable concentrations when the IFCC TF-CB criteria for hs is used[24].

Table 2 : Hs-cTn assays (LoD = Limit of detection, ULN = 99th percentile, CV = Coefficient of variation)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Assay | LoD(ng/L) | ULN  M/F (ng/L) | %CV at ULN | 10% CV  ng/L |
| Abbott ARCHITECT  hs-cTnI | 1.2/1.9 | 34/16 | 5 | 3 |
| Roche E1 70  hs-cTnT | 5 | 20/13 | 8 | 13 |
| Beckman Coulter Access  hs-cTnI | 2.5 | 52/23 | <10 | 8 |

**2.1 Hs-cTn as a rule out test**

Perhaps the major advantage of the new Hs-cTn assays is the reduction in time to rule out a diagnosis of MI. This has influenced the algorithms that are available to use to adjudicate a diagnosis of MI. In 2015 the European Society of Cardiology (ESC) produced guidelines on the management of ACS[25], this included two algorithms, the 0/1h and the 0/3h, which both have a class I recommendation.

Specifically, the 0/3h ESC algorithm recommends that MI can be ruled out if the concentrations of Hs-cTn are below the ULN in blood samples taken at presentation and 3 hours later, if they fulfill clinical conditions. Patients should be pain free and be deemed “low risk” for in hospital mortality using the Global Registry of Acute Coronary Events (GRACE) score [25]. Where the time from onset of symptoms to presentation to hospital is over 6 hours, a single Hs-cTn concentration below the ULN is considered sufficient to rule out a diagnosis of MI. By contrast, a diagnosis of MI can be made if patients have a highly abnormal Hs-cTn with clinical correlation or if there a significant change in the 3-hour blood sample, which is assay dependent[25]. It is important to also acknowledge that there is also a cohort of patients who will not have an elevated Hs-cTn concentration at 3 hours but may nevertheless have a later elevation and be diagnosed with MI. When using the 0/3h algorithm, one study has shown that 56% of patients are directed towards outpatient management once a diagnosis of MI is excluded, with a median time of stay in the emergency department (ED) of 4.5 hours for the patients deemed suitable for outpatient management [26]. A recent meta-analysis (n=9241) has shown individuals presenting to the ED with a non-ischaemic ECG and a single low Hs-cTnT concentration (<0.005μg/L) can be classified as low risk. The pooled sensitivity for acute MI in this group was 98.7% (95% CI, 96.6% to 99.5%) and for 30 day MACE 98.0% (CI, 94.7% to 99.3%). No low risk patients died. On this basis these low risk patients can be discharged from the ED and managed on an outpatient basis[27].

The 0/1h ESC algorithm does not utilize scoring systems such as GRACE in the assessment of patients presenting with suspected MI[25]. The use of the 0/1h algorithm allows clinicians to make decisions on admission to hospital or outpatient management usually within 3 hours from presentation to the emergency department. A diagnosis of MI can be safely ruled out by a very low Hs-cTn concentration, which is again assay dependent, or a low Hs-cTn concentration followed by a minimal change at 1 hour, the detail of which is again assay dependent. To illustrate this the definitive figures currently used for the Architect Hs-cTnI assay (Abbott Laboratories) are a “very low” concentration of <2 ng/L or a “low” concentration of <5ng/L, followed by a change at hour of <2ng/L. In contrast, the values for the Elecsys Hs-cTnT (Roche Diagnostics) are 5ng/L for a very low concentration, 12ng/L for the low concentration, followed by a change at 1 hour of <3ng/L. To rule in a diagnosis of MI using either the Architect or Elecsys assay an admission value of ≥ 52ng/L or a change at 1 hour of ≥6ng/L (Architect) or ≥5ng/L (Elecsys) is recommended[25]. Use of this algorithm has been very effective with decisions made on patient destination in 75% of cases, with 15% of patients diagnosed as MI and 60% of patients in whom MI was ruled out. However, Kavsak et al[28] have demonstrated that repeat testing on the same sample used to determine the 0h hs-cTnI concentration can lead to the reclassification of more than 10% patients when using the ESC 0/1h algorithm in contrast to 2% of patients when using the 2h algorithm. Furthermore, Pickering et al[29] has shown that when the ESC 0/1h algorithm is utilized the sensitivity for the Hs-cTnT algorithm is 96.9%(91.5% to 100%) and for Hs-cTnI 98.8%(97.9% to 100%). This is below the 99% sensitivity, a safety level required by most physicians in the Emergency Department (ED) when investigating patients with suspected MI[30].

**2.2 Challenges: what is the “correct” 99th centile?**

The universal definition of MI advocates the use of the cTn 99th percentile (ULN) as the correct cut off concentration with which to diagnose MI[2]. This concentrationis unique for each Hs-cTn assay used in clinical practice. There are 2 different forms of MI commonly defined in patients presenting acutely. Type 1 MI (T1MI) is recognized as the classical “heart attack”and is defined as a troponin elevation related to an acute plaque rupture in a suspected ACS[2, 33, 34].The second form of MI or type 2 MI (T2MI) is defined as MI secondary to ischaemia due to increased oxygen demand or reduced oxygen supply. Examples of clinical scenarios giving rise to T2MI include anaemia, arrhythmias, hypertension, hypotension, coronary artery spasm and embolism[2, 34]. Other forms include MI presenting as sudden death (T3MI), myocardial damage associated with percutaneous coronary intervention (T4MI) or after coronary artery bypass grafting (T5MI). In addition, the third universal definition[2, 34, 35] introduces the diagnosis of myocardial injury, this is not defined as a subset of MI but is a cause of cTn concentrationsabove the ULN. In acute myocardial injury, cTn concentrations are elevated with dynamic change crucially in the absence of myocardial ischaemia. Chronic myocardial injury is used to describe scenarios where there are raised cTn concentrations but no dynamic change on serial testing. The diagnosis of myocardial injury is contentious, particularly given the considerable overlay in conditions that cause both T2MI and myocardial injury such as heart failure and sepsis[2, 34].

There are many variables that are correlated with an individual’s troponin concentration. This has a significant effect on the definition of the ULN for any particular assay. *This is particularly important as each manufacturer will have different inclusion and exclusion criteria used to define the reference population from which the 99th centile is derived*. For example, it has been shown that the younger the reference population is, and the stricter the criteria used to define cardiac health are, the lower the 99th centile will be.[36]

Gender specific normal ranges have been identified, with ULN for females being lower than males[37, 38]. Cullen et al[39] have shown that the use of gender specific cut points improves the identification of women at high risk of cardiovascular events, within a year of presentation to the ED with chest pain. In this study (n=2841), 25 out of the 1180 females recruited were reclassified from having a non-elevated troponin to having an elevated troponin, 7 (28%) of this group had a major adverse cardiovascular event (MACE) at 1 year. Shah et al[40] have also shown that gender specific cut points markedly increase the rate of MI in women from 11% to 22%. However, it has also been shown that the use of gender specific cut points in patients diagnosed with non-ST elevation acute coronary syndromes did not improve the accuracy for predicting the risk of 30 day acute MI or 1 year mortality[41]. Currently, the ESC does not recommend the use of gender specific cut-offs in the management of patients with suspected MI[25].

Furthermore, studies have shown different ULN have been defined for different sample populations when using the same assay.[42] A large number of clinical factors including eGFR, NT-proBNP, clinical criteria, history, examination and echocardiogram are all associated with an individual’s Hs-cTn concentration[42]. In fact, after correction for these factors in this study, the 99th centile for one assay in men aged less than 75 drops from 22.9 ng/L to 10.3 ng/L. These considerations inevitably lead to a fundamentally important question: “which concentration should clinicians use as the 99th centile”? The IFCC TF-CB now recommends a 2 fold approach in which both younger (<30 years) and older (>30 years, with a mean age of 60-65 years), apparently healthy individuals are used as reference groups to define the ULN for a specific assay[24]. Given what has been discussed about the sensitivity of the modern assays, and the list of clinical circumstances that can be associated with elevated troponin concentrations, this recommendation still leaves some questions unanswered.

Firstly, given that Hs-cTn assays are clearly more sensitive, is it appropriate that the assay is still being used by front line clinical staff used as a ’rule in’ / ‘rule out’ tool for the diagnosis of MI, using a simple binary cut off? Secondly, and more importantly, what is an “abnormal” Hs-cTn concentration and exactly which population should be used to define that concentration? This question has important implications for the use of Hs-cTn in clinical practice. The hospital population includes individuals with a very wide spectrum of comorbidities: from outpatients with autoimmune disease to patients in intensive care. *How likely is it that a single troponin concentration can be used appropriately as a binary cut off for the “ULN” in such a heterogeneous population?* Furthermore, should we be using the ULN derived from a healthy young population to determine the management of the hospital population? Thus, the concept that very low or absent absent troponin concentrations can help to exclude a diagnosis of T1MI remains robust, and based upon strong data (see below). However, the assumption of a diagnosis of T1MI based upon “elevation” of the concentration beyond the ULN is, by contrast, fundamentally flawed.

**2.3 Underlying reasons for variability in Hs-cTn concentrations**

The variation in Hs-cTn concentrations in individuals is dependent on many factors. One important factor is age: a significant proportion of studies used to define the ULN of a Hs-cTn assay have used reference populations with a substantially younger average age than the average age of patients who suffer MI[43]. Eggers et al[44] investigated the influence of cardiovascular disease, gender and age on the ULN. They found that 70 year olds who were free from cardiovascular disease had considerably higher ULN than previous studies describing younger reference populations. The same study also reported that men were found to have 24-46% higher median concentrations compared to women and, consequently, higher ULN. This is consistent with other studies[37, 45]. Furthermore, patients with chronic cardiovascular disease, such as congestive HF and hypertension, were found to have twice as high ULN than those without. , A study looking at Hs-cTnT concentrations in patients admitted to the emergency department has provided further evidence about the affect of age on Hs-cTnT concentrations[46]. In patients under the age of 65, the 99th centile was 12 ng/L with little age dependence whereas in those over 65 years the 99th centile was 82 ng/L and highly age dependent.

Another important association with Hs-cTn concentrations is heart failure. Hs-cTn concentrations have been shown to be raised in patients with heart failure (HF) and in patients who go on to develop HF. For example, Ergstrup et al[47], showed that 57% of outpatients (n=417) with chronic systolic heart failure have a Hs-cTnT concentration above the ULN, when sex-specific cut off values were used (male = 18ng/L, female = 8ng/L). Furthermore, Hs-cTnI is also a predictor of mortality in HF patients[48]. This includes both cardiac- and non cardiac-related mortality[49]. In addition, reductions Hs-cTnT concentrations have been found to closely correlate with improvements in the clinical status of HF patients[50]. Unsurprisingly, it has also been shown that patients presenting with decompensated HF with severe coronary artery disease (CAD) have a higher Hs-cTn concentration on admission when compared to patients without severe CAD. The explanation put forward for this is that patients with severe coronary stenosis are more liable to stress produced by an episode of acute decompensated HF[51].

Another chronic condition that can affect troponin concentrations is blood pressure. This is evident from the observation that higher Hs-cTn concentrations have been detected in patients with hypertension compared to the normotensive population. In addition to this, rising Hs-cTn concentrations have been associated in hypertensive patients undergoing cardiac remodeling from normal LV geometry to eccentric hypertrophy. This is independent of age, gender, diabetes mellitus and renal function[52]. In addition, Hs-cTn concentrations have been shown to increase with increasing left ventricular mass and left ventricular dilatation[53].

The effect of chronic kidney disease (CKD) on Hs-cTn concentrations has also been well described. Thus, studies consistently demonstrates degree of Hs-cTn elevation in asymptomatic patients with chronic and end stage renal impairment[54, 55].Furthermore, van der Linden et al [56]has shown that factors other than renal elimination contribute to elevated cTn in CKD. Diabetes has also been shown to be associated with elevated Hs-cTn concentrations in patients with CAD. For example, Segre et al[57] have shown that, in the absence of ACS, Hs-cTn concentrations are higher in diabetic patients with CAD than those without.

Patients who are critically ill also have elevated concentrations of troponin compared to a general population. One prospective observational study, for example, has shown 121 (84%) out of 144 critically ill patients had elevated Hs-cTn concentrations but only 40% of these patients had study-identified MI[58]. Another study has shown Hs-cTn concentrations are raised within 12 hours of admission to an Intensive Care Unit in 75% of patients (n = 451). Furthermore, there was a clear association between raised Hs-cTn concentrations and both morbidity and mortality. Specifically, no patients with Hs-cTnT concentration of < 3ng/L died in hospital whereas those with a concentration ≥ 50ng/L had an in hospital mortality of 31% (p<0.001). Notably, none of these patients were diagnosed as having an “ACS”[59]. In patients admitted to an intensive care unit labeled as having sepsis Hs-cTn concentrations have been shown to be raised above the ULN in the majority of cases (80%) and the concentration is associated with disease severity[60]. Interestingly, the elevated Hs-cTn concentrations were not associated with mortality in this population.

In patients with rheumatoid arthritis Hs-cTnT concentrations have been shown to be raised in comparison to healthy controls[61]: in the rheumatoid arthritis group 8% of patients had a Hs-cTnT concentration above 14ng/L versus 1% of the healthy controls (p<0.007). This was independent of cardiovascular risk factors.

Other conditions that are associated with elevated Hs-cTn concentrations include pulmonary emboli[62], chronic obstructive pulmonary disease[63], cerebrovascular disease[64] and radiation[65].

**2.4 So what *is* the ULN?**

The concept of using a single value for the 99th centile as a cutoff to diagnose ACS/NSTEMI/STEMI appears to be flawed, despite the fact that this is exactly how it is used by most front line clinicians in ED, acute medicine and cardiology. This has been highlighted in several studies. Petrie et al[66] prospectively looked at Hs-cTnT concentrations of 564 patients admitted to an acute medical unit in a district general hospital in the UK. 50% of these patients had their Hs-cTnT concentration measured, and of those measured 80% (n = 224) had a raised Hs-cTnT (≥14 ng/l). Only 44 (20%) had a final diagnosis of acute MI. The authors proposed the low actual MI rate is likely to reflect the increased sensitivity but reduced specificity of the assay. These data are consistent with Saad et al[67]. This study looked at 204 consecutive patients admitted to ED with symptoms suggestive of an ACS. 96 out of the 204 patients had Hs-cTn concentrations above the 99th centile cutoff, but only 26 of these patients had an ACS as ultimately defined by electrocardiogram changes and angiography. Stein et al[68] reported on Hs-cTn concentrations in 5,696 hospitalised patients. 61.6% of patients had a Hs-cTn concentration above the 99th centile, with a relative change of 50% or higher seen in 24% of patients. However, despite these relatively high numbers ACS accounted for only 6.1% of final diagnoses.

It is clear that the percentage of patients with “elevated” Hs-cTn concentrations is dependent on the population that is being studied and the derivation of the reference point. It is also clear that the “normal” reference population used to define the 99th centile cutoff for manufacturer’s Hs-cTn assay is likely to be different to the population that is admitted to hospital, particularly with regard to comorbidities and “general wellness”. It is this difference between the ‘normal’ population and the population admitted to hospital that could account for reduced specificity of the Hs-cTn assays. Furthermore, there is currently no policy for manufacturers on how to choose their normal reference population to determine the 99th centile for their specific Hs-cTn assay. It has been shown that the selection strategy for the reference population significantly influenced the 99th percentile reference values[43]. To address this the IFCC TF-CB now recommends a 2 fold approach in recruiting a younger(<30 years) and older (>30 years, with a mean age of 60-65 years) reference group of healthy individuals to define the 99th percentile of a specific Hs-cTn assay[24].

As described above, there are multiple factors that can influence an individual’s Hs-cTn concentration including age, renal function, sepsis, heart failure, and diabetes mellitus. One would expect that these factors to be more prominent in the population admitted to hospital than the relatively healthy reference population used to determine the 99th centile.

Currently, there are robust data to support the use of Hs-cTn concentrations of a patient as a ‘rule out’ test for ACS. For example, Shah et al[69] demonstrated that, in patients suspected of ACS, the Hs-cTn assays are able to identify two thirds of patients who are at very low risk of cardiac events and can therefore be safely discharged from hospital. This is a significant finding and, when implemented by clinicians can result in dramatic reductions in hospital admissions. As a ‘rule in’ test, however, the assays are of less value, and need to be interpreted carefully in the context of the clinical presentation.

**3. T1MI, T2MI and Myocardial Injury**

The third universal definition[2] has classified MI into T1MI, T2MI, T3MI, T4MI, T5MI and myocardial injury. This has been driven by the development of Hs-cTn assays and the lowering of thresholds to diagnose MI. This classification has been developed according to expert consensus. For most patients presenting acutely, the intention of clinical staff is to use Hs-cTn assays to accurately and rapidly diagnose or exclude T1MI. Unfortunately, for the reasons laid out above, many patients with raised Hs-cTn are actually in the T2MI category: this has important implications for their management unless the general concentration of awareness of this potential diagnostic confusion is high. The T2MI, in which there is myocardial ischaemia due to lack of oxygen supply or increased demand, can be related due to multitude of medical and surgical conditions. There is, however, a paucity of guidelines or diagnostic criteria available for clinicians to use to adjudicate whether patients have suffered a T2MI. As such, there is significant disparity in the literature over the incidence of T2MI with the proportion of MI being attributed to T2MI ranging from 1.6% to 29.6% [70-73]. The registry published by Baron et al [70] (n=20,138) has reported the incidence of T2MI in the MI population to be 7.1% and T1MI to be 88.5%. It should be noted, however, that there was considerable variation in the incidence of T2MI between different centres used (0-13%). There is also evidence to show that there is a greater increase in the diagnosis of T2MI in proportion to T1MI when Hs-cTn assays are used instead of cTnI assays [40, 74]. Inevitably, and appropriately, this raises concerns about the prospect that some patients whose true diagnosis of T2MI are being treated as T1MI: in particular, being exposed to aggressive invasive investigation and treatment for which there is no evidence base in T2MI. [75-77]. The study from Shah et al[78] has shown the utilization of lower thresholds and Hs-cTn assays reduces the risk of recurrent infarction and death in the T1MI population. By contrast, in the T2MI population, despite increasing the rates of detection and clinical investigations, there was no improvement in outcomes. This is certainly at odds with some definitions of T2MI that suggest significant coronary artery disease is required to cause T2MI as opposed to myocardial injury[79, 80]. However, it cannot be overlooked that patients diagnosed with T2MI are twice as likely to be readmitted at one year with a T1MI when compared to patients who have been diagnosed with myocardial injury[78].

Myocardial injury is defined as an acute or chronic rise in Hs-cTn, which occurs in the absence of myocardial ischaemia. The aetiology is multifactorial. There is considerable overlap between T2MI and myocardial injury, and, in fact both conditions can occur due to the same cause such as infection. This disparity and ambiguity is highlighted by the fact that infection is cited as a cause for T2MI [70, 78, 81], where as in others it is classified as myocardial injury[82]. Further confusion prevails when the reported incidences of T2MI and myocardial injury are evaluated. Sarkisian et al [83] have reported the incidence of myocardial injury in patients with a raised cTnI (n=1,577) to be 69% and T2MI to be 7.5%. This is in contrast to Shah et al[78] where the incidence of myocardial injury is 24% and T2MI 20%.

Irrespective of the issues relating to the classification of T2MI and myocardial injury and the considerable overlay, the outcome for both conditions is poor. Stein et al[81] have shown that at 30 and 1 year days there is an increased mortality in patients with T2MI compared to T1MI (30 days; 13.9% vs 4.9%, n= 2818, p<0.0001: 1 year; 23.9% vs 8.6%, p<0.0001 ). In the myocardial injury population Sarkisian et al have shown a greater risk of all cause mortality when compared to patients suffering a acute MI(59% vs 39%, p<0.0001). In this study, acute MI is defined as a cTn above the ULN alongside evidence of myocardial ischaemia, whereas myocardial injury is defined cTn above the ULN in the absence of myocardial ischaemia. Recent data from Chapman et al has shown at 5 years 60% of patients with T2MI and 75% of patients with myocardial injury were dead [84].

**4. Hs-cTn in the General Population: a novel biomarker for cardiovascular risk?**

The advent of the Hs-cTn assays now means that troponin can now be detected in over 50% of individuals, many of whom have no evidence of previous myocardial events or cardiovascular disease. This has led to observational research focused on the clinical significance of Hs-cTn concentrations in the general population. Recently, a series of such studies have shown that circulating troponin concentration in the general population are predictive of cardiovascular events[85-87]. Thorsteinsdottir et al[86] looked at the predictive power of Hs-cTn for cardiovascular events and mortality in large population of older community dwellers (n=5764). The study demonstrated that all cause mortality, the incidence of cardiovascular disease (CVD) and coronary heart disease (CHD), were significantly associated with increasing concentrations of Hs-cTn. Furthermore, this increased risk was found to begin with Hs-cTn concentrations well below to ULN. Thus highlighting the potential use of Hs-cTn as a primary predictor of heart disease[86].

There is evidence accumulating for the use of Hs-cTn assays in risk prediction in a variety of clinical settings. In 2015 the results from the SWEDEHEART registry (n=45,594) revealed that the introduction of Hs-cTn concentrations into clinical practice has led to the recognition of a large proportion of patients with minor troponin increases are at high risk with adjusted mortality rates beginning to increase at the concentration of the 99th percentile in healthy controls[88]. The majority of these patients did not have an MI. Furthermore, The West of Scotland Coronary Prevention Study (WOSCOPS)[89] revealed that troponin concentrations predicts coronary events and that in fact troponin concentrations can be reduced by statin therapy. This equates to a reduction in future coronary events, which is independent of cholesterol lowering. Thus illustrating the use of serial troponin monitoring in assessing cardiac risk and the efficacy of risk lowering therapies. The use of troponin as a marker of risk is not confined just to ischaemic heart disease. In a population of 8,153 elevated Hs-cTn concentrations were shown to predict the incident of diabetes in individuals without known diabetes or CVD[90]. Interestingly, Hs-cTn concentrations has been postulated to have a role in personalising preventative treatment strategies in the diabetic population[91]. In the acute ischaemic stoke population elevated troponin concentrations in the absence of myocardial infarction has been shown to be associated with increased mortality at 1 and 3 years[92]. Elevated Hs-cTn concentrations in individuals with stable chronic obstructive pulmonary disease without overt CVD has been shown to be associated with increased mortality, which is independent of COPD-severity and other cardiovascular risk factors[93].

A recently published large meta-analysis (n=154,052) describes the association between Hs-cTn concentrations and cardiovascular outcomes in a total of 28 primary prevention studies[94]. Hs-cTn was detectable in 80% of individuals. There was a clear association between the Hs-cTn concentration and acute cardiovascular events. Specifically, the data shows that individuals with Hs-cTn concentrations in the top third of the population distribution are at 43% increased risk of any CVD, 59% increased risk of CHD, and 67 increased risk of fatal CVD outcomes. This risk is independent of traditional risk factors for CVD. Importantly, the meta-analysis also observed significant positive associations with CVD outcomes and Hs-cTn concentration. This is despite the fact that 85% of individuals included in the study had Hs-cTn values below the ULN (≤14ng/L). This is of particular importance showing how Hs-cTn concentrations can be utilized in primary prevention of CVD in the general population where the majority of individuals will have a concentration below the ULN.

**5. Conclusion**

Recent data raise very important questions about the potential clinical utility of Hs-cTn assays. Whilst they represent excellent tools for the early exclusion of acute MI, their use by front line staff for attempting to diagnose T1MI is flawed and the subject of considerable confusion and suboptimal education. By contrast, a growing body of evidence suggests that Hs-cTn assays may represent biomarkers for prediction of future CV risk in the general population. If validated in this role, these assays could represent powerful tools in the search for personalized prevention therapy strategies.

**6. Expert Commentary**

The Hs-cTn assays are now able to detect troponin at much lower concentrations than previous assays [4], this has been reflected in the third universal definition of MI[2], which recommends that a troponin assay used to diagnose MI should have a coefficient of variation of ≤ 10% at the threshold concentration representing the 99th percentile upper limit of a “normal reference” population (ULN). The evidence for the use of the Hs-cTn assays as a rule out test for MI is compelling[31, 69], and is currently reflected in the ESC guidelines[25]. Hs-cTn assays now allow clinicians to safely discharge up to two-thirds of patients presenting with suspected MI, this decision is based on the patient’s Hs-cTn concentration in combination with their risk factors for MI and their clinical history. The implications for this is significant, particularly with regards to hospital admissions is significant and certainly relevant to the current climate of healthcare systems throughout the world.

As a ‘rule in’ test, however, the Hs-cTn assays now present clinicians with more questions when the ambition is to make a diagnosis of “heart attack”, on the assumption that this diagnosis falls into the category of T1MI. Interpreting a result of Hs-cTn concentration above the ULN particularly when the clinical history and presentation is not consistent with MI is problematic for clinicians. Furthermore, when the rise in Hs-cTn is due to either a T2MI or myocardial injury, it is clear that the outcome is poor, and as yet there is no specific intervention that is proven to alter this outcome[78, 81, 84], in contrast to T1MI.

**7. Five-year view**

We expect the use of Hs-cTn assays to evolve significant over the next five years, the future for the Hs-cTn assays as we see it is in risk modeling. This would include in the primary prevention for CVD and also in a variety of conditions. We expect the Hs-cTn assays to aid clinicians in deciding whether certain therapies, such as statins, will be beneficial for patients in the long term. As a rule in test for MI, we could see the emergence of new assays that are more specific for MI.

**8. Key Issues**

* The advent of Hs-cTn assays has allowed clinicians to make more timely management decisions on patients with suspected MI.
* Hs-cTn assays can now be detected in more than 50% of individuals.
* The improved analytical sensitivity of the assay has improved its clinical sensitivity, but has altered the specificity of the assay for MI.
* There is a greater proportion of patients being diagnosed with T2MI and myocardial injury with the use of the Hs-cTn assays, the outcomes in these groups is poor, with no treatment shown to alter these outcomes.
* The future of the Hs-cTn assays may lie in population screening and risk modeling.

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