High-sensitivity cardiac troponin – a double-edged sword

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The diagnosis of myocardial infarction requires careful evaluation of the presenting symptoms, electrocardiogram and evidence of myocardial necrosis. In recent years, high-sensitivity cardiac troponin assays have transformed our ability to diagnose myocardial infarction by enabling the detection of myocardial necrosis with much greater degree of sensitivity and precision. The Universal Definition of Myocardial Infarction recommends use of the 99\textsuperscript{th} centile upper reference limit as the threshold to define myocardial necrosis and provides distinct clinical criteria to differentiate between the different subtypes of myocardial infarction and myocardial injury. The importance of diagnosing type 1 myocardial infarction cannot be understated given the array of evidence-based therapies available. In contrast, there remains a dearth of evidence-based strategies guiding management for type 2 myocardial infarction or myocardial injury. Elevations in cardiac troponin concentrations in the high-sensitivity era is common in patients who do not have type 1 myocardial infarction.

Furthermore, the prevalence of troponin elevations in patients without type 1 myocardial infarctions is compounded by different healthcare systems having different approaches to patient selection for troponin testing. Less selective use of troponin testing can significantly impact on the positive predictive value for the diagnosis of type 1 myocardial infarction and increase the difficulty in interpreting the results.

Etaher et al conducted a large prospective cohort study of 2,734 consecutive patients presenting with suspected acute coronary syndrome to a tertiary hospital. The study included all patients who received serial cardiac troponin measurements using a high-sensitivity cardiac troponin T assay with an upper reference limit of 14 ng/L. The medical records of all patients were reviewed by three consultant cardiologists who retrospectively adjudicated the final diagnosis according to the Fourth Universal Definition of Myocardial Infarction. Patients were subsequently followed up for up to 4 years for mortality, non-fatal myocardial
infarction and stroke. Elevated cardiac troponin was common with over a third of patients having concentrations above the 99\textsuperscript{th} centile upper reference limit. The vast majority of patients had either myocardial injury or type 2 myocardial infarction with less than 1 in 10 having a type 1 myocardial infarction. Almost all patients with type 1 myocardial infarction received in-hospital coronary angiography. In contrast, a quarter patients with type 2 myocardial infarction or acute myocardial injury and approximately one in every 30 patients with chronic myocardial injury. The same pattern was also observed in the use of evidence-based pharmacotherapies across these patient groups. Patients with type 1 myocardial infarction had better outcomes compared to those with chronic myocardial injury or type 2 myocardial infarction. Conversely, those with type 2 myocardial infarction in this cohort had the worst outcome, with over 3-fold higher risk of all-cause mortality at 4 years compared to those with type 1 myocardial infarction. This association persisted in a cox-proportional hazards model that adjusted for patient demographics, co-morbidities and smoking.

Etaher et al should be commended for several important strengths in their study design. First, they recruited consecutive patients into the study. This approach avoided selection bias and ensured that the findings are representative of the broad patient population presenting to the Emergency Department with suspected acute coronary syndrome. Second, they conducted an exhaustive review of hospital and general practice medical records to achieve excellent phenotyping of the patient population. This is particularly important for patients with subtypes of myocardial infarction since they are more likely to have comorbidities. Such an approach also allowed the authors to include these variables into the Cox models to account for confounding when evaluating the relationship between subtype of myocardial injury and risk of death. Third, the authors had a robust adjudication process for the final diagnosis. In
particular, all patients in this cohort had serial high-sensitivity cardiac troponin measurements which allowed an accurate differentiation between acute and chronic myocardial injury.

This analysis is an important addition to the literature in this field, particularly as high-sensitivity cardiac troponin continues to be implemented more widely across the world. In this cohort, the prevalence of type 1 myocardial infarction was 3.5% (97/2738) and the corresponding positive predictive value of elevated cardiac troponin concentrations for the diagnosis of type 1 myocardial infarction was 9.7% (97/995). This was significantly lower compared to healthcare systems that use troponin testing more conservatively where positive predictive values have been reported to range between 45% and 65%.

Recent studies have demonstrated the utility of very low concentrations of high-sensitivity cardiac troponin assays in ruling out type 1 myocardial infarction in the Emergency Department. Conversely, implementing the 99th centile diagnostic threshold using a high-sensitivity assay to rule-in the diagnosis did not improve patient outcomes. One of the major reasons for this observation is that the majority of those reclassified by the high-sensitivity assay had either type 2 myocardial infarction or myocardial injury reducing the positive predictive value for type 1 myocardial infarction. So how can we improve the positive predictive value of troponin testing for type 1 myocardial infarction? Various studies including that of Etaher et al illustrates the importance of patient selection for troponin testing with an indiscriminate approach significantly impacting on the positive predictive value. Other measures such as the application of clinical risk scores and machine-learning algorithms have also been suggested to improve the application and interpretation of high-sensitivity cardiac troponin testing. It is also possible that the 99th centile upper reference limit may not be the appropriate diagnostic threshold for myocardial infarction as this was...
defined from a statistical approach from different reference populations rather than for biological or clinical reasons.\(^\text{11}\) There is now significant data demonstrating that troponin varies significantly with age, sex and comorbidities.\(^\text{12,13}\) Whether a more nuanced approach to defining the decision limit for cardiac troponin requires further investigation.

Consistent with many other observations, patients with type 2 myocardial infarction or acute myocardial injury in this cohort had poor outcomes.\(^\text{14,15}\) Etaher et al provided a useful breakdown of the final diagnosis of these patients which ranged from sepsis to acute heart failure and tachyarrhythmia. This is clearly a very heterogeneous group of patients with limited data at the moment to guide management of these patients. It is likely that the primary determinant of poor outcome in these patients is the severity of the acute illness coupled with significant underlying co-morbid status and frailty of these patients. Indeed, patients with type 2 myocardial infarction or acute myocardial injury in this cohort were on average 12 years older than those with type 1 myocardial infarction, with significantly more comorbidities such as heart failure (22% versus 5%), atrial fibrillation (25% versus 5%), stroke (16% versus 10%), chronic kidney disease (49% versus 15%) and chronic obstructive pulmonary disease (19% versus 4%), therefore opportunities to improve their outcomes may be limited. Furthermore, a significant proportion of patients (43%) with type 2 myocardial infarction or acute myocardial injury did not undergo coronary angiography. Of those that did undergo coronary angiography, over a third had evidence of obstructive coronary disease. Whilst, it is plausible that this subgroup of patients may benefit from secondary preventative therapy no evidence base currently exists in this subgroup of patients.

Conflict of Interest: Dr Shah and Dr Lee have both received speaker fees from Abbott Diagnostics.
References