Editorial

Detectable high-sensitivity cardiac troponin concentrations and risk stratification in the emergency setting

Peter A. Kavsak[1], Ola Z. Ismail[1], Stephen A. Hill[1], Andrew Worster[2]

[1]Department of Pathology and Molecular Medicine, [2]Division of Emergency Medicine, McMaster University, Hamilton, ON, Canada

Correspondence to: Dr. Peter Kavsak. Juravinski Hospital and Cancer Centre, 711 Concession Street Hamilton, ON L8V 1C3, Canada.
Email: kavsakp@mcmaster.ca.

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For nearly two decades' cardiac troponin (cTn) has been an integral component for the diagnosis of acute myocardial infarction (MI) in patients presenting with symptoms of acute coronary syndrome (ACS) in the emergency setting (1-4). The recommended cutoff to identify myocardial injury with cTn has been the upper limit 99th percentile concentration derived from a healthy population (4). Recent publications have, however, identified the complexity of deriving this metric when using high-sensitivity cTn (hs-cTn) assays (4-7). Accordingly, there have been many different 99th percentile cutoffs published for the same hs-cTn assay (5,8-11). This variation in reporting has also extended to the lower limit of reporting, where laboratories might use the limit of blank, or limit of detection (LoD), or limit of quantification, or some other cutoff to define undetectable hs-cTn concentrations (4,12-14). With divergence noted amongst laboratories on what concentration signifies myocardial injury and what concentration is used to define undetectable concentrations, one could question what is a "normal" cTn concentration? Perhaps the more appropriate question should be what cTn cutoffs are important for the diagnosis and the prognosis for future cardiac events (15,16)?

Prognostic studies using contemporary cTnI assays have demonstrated that detectable cTn concentrations (above the LoD and below the 99th percentile) provide important long-term risk stratification information for cardiovascular outcomes (17,18). These findings from both a community setting population (17) and a population with possible ACS in the emergency setting (18) have been confirmed with hs-cTn assays (19-21). But is this information still applicable for patients with symptoms suggestive of ACS in the emergency department (ED) who have not experienced or been diagnosed with a serious cardiac event? In this regard, Than and colleagues have provided further compelling data that detectable hs-cTn concentrations in patients ruled-out for serious cardiac events at ED presentation still provide important prognostic information (22).

Briefly, in 1,113 patients presenting with possible ACS to an ED in New Zealand, 277 patients had an index major adverse cardiac event [MACE; defined as a composite of cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, high-degree artrioventricular block, MI, emergency revascularization, or cardiac death in the study (22)], whereas 836 patients where ruled-out for MACE at ED presentation. In those patients without an index MACE (n=836), a concentration-dependent effect using the higher concentration from the 0/2 hours blood draws was observed with increasing hs-cTn concentrations reflecting a higher risk for future MACE (22). Intriguingly, in this observational study, the cumulative event rates (33% at 5 years) were equivalent between those patients with an index MACE versus those without if the following concentration cutoffs for Abbott's hs-cTnI assay $\geqslant$10 ng/L or Roche's hs-cTnT assay $\geqslant$16 ng/L in the non-index MACE group were utilized (22). These concentration cutoffs are similar to another Canadian study assessing hs-cTn risk cutoffs in patients presenting with symptoms suggestive of ACS to the ED; albeit the composite outcome (i.e., MI, unstable angina, heart failure, serious ventricular arrhythmia or cardiovascular death) and follow-up (i.e., 7 days) are different between the two studies (23).

Than and colleagues also evaluated the LoD with future MACE as a secondary analysis, and despite observing significant hazard ratios with higher hs-cTn concentrations relative to this lower analytical limit, they indicate caution in comparing assays using this approach "because the LoDs are not comparable between assays" (22). While this is true, there are several other important analytical considerations that lessen the enthusiasm for using the LoD in clinical decision making based on analytical performance (12-14). Notwithstanding the practical limitations of routinely (i.e., daily) monitoring of the LoD for hs-cTn assays (4), it is unclear if testing over different reagent lots and different analyzers demonstrates sufficient analytical robustness as to not misclassify patients at this lower analytical limit (14,24,25).

Collectively, Than and colleagues' study findings add to the accumulating data obtained over the last dozen years using either sensitive cTn assays or hs-cTn assays that have identified a clinical signal below the 99th percentile. The next steps are to further refine hs-cTn risk-cutoffs below the 99th percentile and to prospectively evaluate their effectiveness in patient care. In doing so, detectable and low hs-cTn concentration cutoffs can be established and monitored by quality processes in the clinical laboratory which should further limit patient misclassification due to analytical factors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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