Editorial

Does the LoD cutoff + the TIMI score = a NICE approach to rule-out a major adverse cardiac event in the emergency department?

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The literature is abundant with accelerated diagnostic pathways (ADPs) for early decision making in emergency department (ED) patients presenting with chest pain (1-10). By in large, this growth in the various ADPs has been possible due to the introduction of high-sensitivity cardiac troponin (hs-cTn) testing. Published data, nearly a decade ago, demonstrated the utility of how the more analytically sensitive and precise hs-cTn assays can lead to an earlier diagnosis and provide important prognostic information for patients presenting with chest pain to the ED (11-13). Yet despite all the data, no ADP has proven to provide better patient outcomes than the current standard of care. This is because these ADPs have not necessarily improved diagnostic performance or capture all the outcomes of interest for the physicians practicing in the ED (7-10). In fact, one could go further, and simply state that despite all the improvements made to hs-cTn, it is still just a diagnostic "test" and like any test there are errors, interferences and other variables that may affect its analytical performance and thereby affect its clinical performance (14). This point cannot be under-emphasized considering the bench mark most ED physicians consider safe for ruling-out major adverse cardiovascular events (MACE) is a sensitivity >99% (15).

The improvements to the hs-cTn tests now allow these assays to measure cTn concentrations in the majority of healthy individuals. However, the cutoff chosen for the majority of ADPs for ruling-out an event is the limit of detection (LoD), essentially reducing this test to a binary detected/not detected response. This approach is problematic on several fronts (16-20):

- First, there is no requirement that laboratories use the same lower reportable limit for the hs-cTn assays (thereby a "undetectable" result may be different between laboratories and studies);
- Second, there are no quality procedures in place to monitor test performance at the lower limit of reporting (thus the quality of measurements are unknown);
- Third, there are no accepted standard operating procedures to prevent drift of the assay at the lower reportable limit when changing lots of reagents (thus no guidance for unacceptable lots);
- Fourth, the repeatability and acceptable error estimates at the lower reportable limit can readily re-classify patients (thus a repeat measurement could change the decision to rule-out).

Reliance on more than just an undetectable hs-cTn result is, therefore, paramount and thus the coupling of this test with other validated tools. One such tool that has been used in ADPs is the Thrombolysis In Myocardial Infarction (TIMI) score (21). The latest 2016 National Institute for Health and Care Excellence (NICE) high-sensitivity troponin rule-out strategy suggests that physicians "consider performing a hs-cTn test only at presentation to rule-out non-ST elevation myocardial infarction (NSTEMI) if the test is below the limit of detect (LoD)' and "the patient is low-risk as indicated by a validated tool" (22). Carlton and colleagues study (publication in the journal *Heart*) evaluated such an approach in >3,000 patients

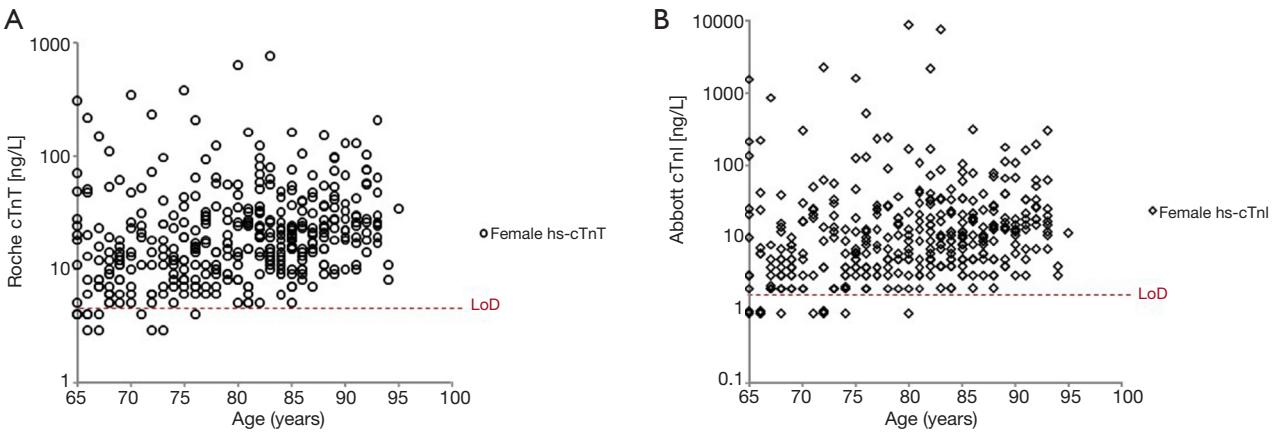

Figure 1 Presentation concentrations of hs-cTnT (A) or hs-cTnI (B) in females ≥65 years of age with symptoms suggestive of acute coronary syndrome with the limit of detection (LoD) indicated (dash line).

with hs-cTnT (Roche Diagnostics), hs-cTnI (Abbott Diagnostics), and TIMI scores (22). Their findings that a TIMI score of 0 coupled with the LoD cutoff, yielded a sensitivity of 99.5% (hs-cTnT) and 98.9% (hs-cTnI); supportive of the recommendation by NICE (22). This approach would limit this ADP to only patients <65 years of age (as age ≥65 years yields a TIMI score of 1). If, however, one accepts a lower sensitivity (range, 98.4–98.9%) by using a TIMI score ≤1, then this approach might be useful for those 65 years and older.

Intriguingly, neither the NICE guideline, nor other proposed rule-out pathways have incorporated sex as a variable (1,3-6,21,22); though there is data (for and against) that different cutoffs should be used for the sexes to rule-in MI (23,24). We have recently assessed the presentation hs-cTn concentration in a well characterized population presenting to the ED with symptoms suggestive of acute coronary syndrome for a composite acute cardiac outcome (similar to MACE but with additional cardiac outcomes; see ClinicalTrials.gov Identifier: NCT01994577) (25). In our analyses we found no difference in hs-cTn concentrations between women and men who experienced the composite outcome (25). Extending the analyses now to women 65 years and older (n=378, or 63% of the female population with at least a TIMI score of 1) to see if the LoD cutoff would be useful in this population to prevent misclassification we observed that <4% of women in this group had hs-cTn concentrations at presentation < LoD cutoff (see *Figure 1*). These data highlight the fact that despite gains in ruling-out patients for MI using the LoD, more sophisticated approaches are needed for patients who are at higher risk and who present with atypical symptoms before efficiency and safety in this setting can be realized.

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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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