

Using single sex-specific high-sensitivity cardiac troponin cut-off values for ruling out myocardial infarction – Are we there yet?

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INTRODUCTION

Chest pain is the second most common emergency department (ED) presenting complaint.¹ Chest pain constitutes approximately 5% of all ED visits and, in the year 2012, an estimate suggests that there were approximately 600,000 ED visits for chest pain across Canada.² Given that chest pain is very common in the ED, improved efficiency in ED management of patients with suspected myocardial infarction (MI) is a key issue in alleviating ED crowding. Yet this improved efficiency should not compromise safety due to a false-negative diagnosis.

In acute care settings, women in comparison with men present with atypical symptoms, have fewer electrocardiogram abnormalities, and have lower cardiac troponin values for any extent of underlying coronary artery disease.^{3,4} Such differences in troponin values are extremely variable based on the type of assay with large differences with some assay types and negligible with others.⁵ Studies have reported that sex-specific cut-off values for high-sensitivity cardiac troponin (hs-cTn) assays improve diagnosis and classification performance of MI, particularly in women, leading to professional society guidelines recommending their use.^{3,6,7} While studies have previously focused on improving ruling-in MI with sex-specific cut-offs, in this issue, McRae and colleagues explore the concept of ruling-out MI with a single Roche Elecsys® high-sensitivity cardiac troponin T (hs-cTnT), using several cut-off levels relative to the limit of detection (< 5 ng/L) and the Food and Drug Administration–

approved limit of quantification (< 6 ng/L).⁸ The 99th percentile reference limit for this assay is 14 ng/L. The study found that sex-specific cut-offs may improve the classification performance and could lead to rule out MI among more patients on ED arrival. The authors were explicit in their discussion that their study was purely exploratory, and future research is needed in this area.

A few points merit discussions on this topic. The 99th percentile reference limit for a normal population is currently being used to define acute MI.⁷ However, these 99th percentile values are dependent on the population selected and the definition for healthy that is used in these studies.⁵ The study by McRae and colleagues introduces the concept of using sex-specific hs-cTnT cut-off values well below the 99th percentile normal population reference limit, particularly when using a single measurement within 60 minutes of ED arrival for ruling out MI. Hence, moving away from the 99th percentile reference cut-off and using specific values for each assay type that is confirmed in the target population is a step in the right direction for an improved diagnosis of MI. As detailed in the counterpoint argument by Giannitsis, the adoption of ruling in MI with sex-specific cut off values in previous studies has shown very little clinical benefit.⁹ The use of reclassification should be with caution due to inherent confirmation bias, as the troponin values are incorporated in the adjudication of MI outcome in these studies. Future studies are needed to confirm that sex-specific cut-offs improve the diagnosis of MI and specifically the impact on clinically

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important hard outcomes such as mortality, and revascularization procedures should be documented. Additionally, such new sex-specific cut-offs identified must be beyond the range of assay variability for adoption into clinical practice, unlike in the published study.

In summary, further large-scale studies that confirm sex-specific cut-offs beyond assay variability and clinical benefit are needed for the incorporation into day-to-day practice. Such sex-specific cut-offs will unfortunately have to be developed for each assay type in the intended target population.

Keywords: High-sensitivity troponin, myocardial infarction, sex-specific cut-off

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