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Letters to the Editor

Analytical Variation and Abbott Diagnostics High-Sensitivity Cardiac Troponin I Risk Categories in Asymptomatic Individuals

To the Editor:

Abbott Diagnostics released a product information letter (July 24, 2019) indicating new medical decision points using their high-sensitivity cardiac troponin I (hs-cTnI) assay for risk stratification for future cardiovascular events in asymptomatic individuals. Briefly, in agreement with recent study findings,[1] the updated package insert lists concentration ranges for future risk for both females (low-risk < 4 ng/L, moderate-risk 4-10 ng/L, elevated-risk > 10 ng/L) and males (low-risk < 6 ng/L, moderate-risk 6-12 ng/L, elevated-risk > 12 ng/L). Interestingly, the elevated-risk concentration ranges are similar to ones published previously on this assay when assessing risk stratification in an emergency department population for future cardiovascular events (ie, ≥ 14 ng/L).[2] Professional recommendations have opined that the 99th-percentile upper limit of normal be derived for both females and males,[3] yet no recommendation has been proposed for separate decision cutoffs in the normal range. At these low concentrations, analytical imprecision may vary due to suboptimal lots of reagents and analyser performance, thereby limiting the ability to use some diagnostic pathways in the emergency setting.[4] As sex-specific cutoffs in the normal range have now been included in the package insert, we sought to assess the impact of acceptable analytical variation on potential risk misclassification from low risk to moderate risk.

Briefly, quality control (QC) data from 3 different analysers all using the same lots of reagents and testing the same patient-derived QC materials from February 17, 2016, to July 17, 2019, were obtained from the Juravinski and Hamilton General Hospitals (Fig. 1). The rationale and procedure for constructing patient-derived QC have been previously published (Fig. 1). The overall mean concentrations ranged from 4.1 ng/L to 5.3 ng/L across the 3 analysers from 2 different patient-derived QC materials ($n_1 = 2418$, $n_2 = 2552$ for $n_{total} = 4970$) with the standard deviations below the recommended 0.8 ng/L limit.[3] These mean concentrations would therefore classify a female at moderate risk and a male at low risk. The percentage of results

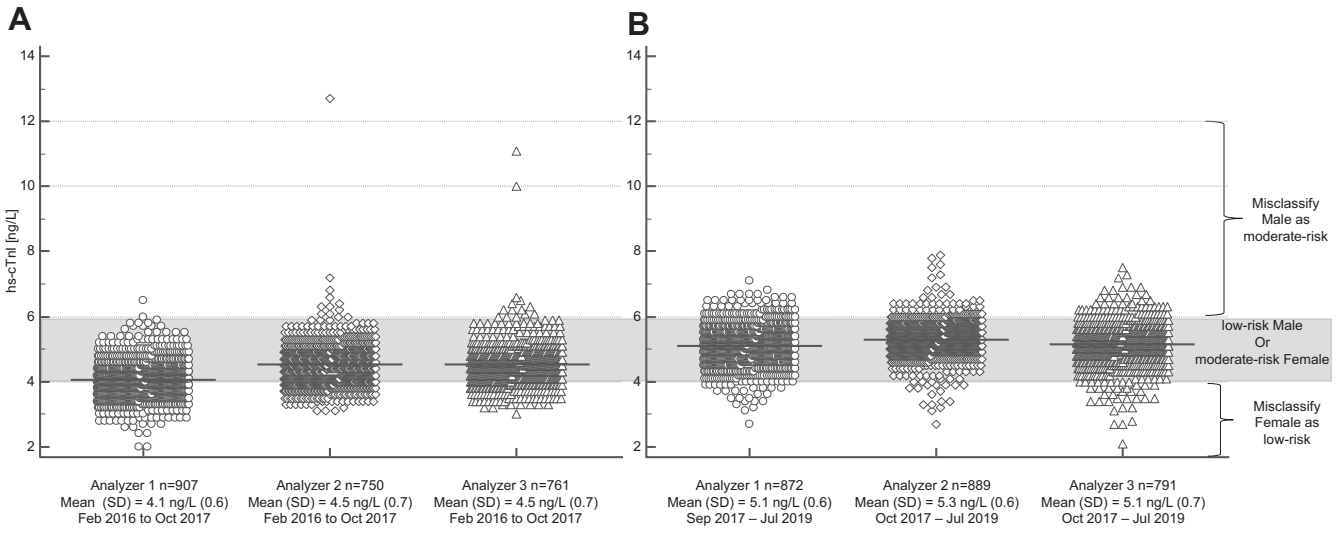

Figure 1. Analytical variation over 3 years in high-sensitivity cardiac troponin I (hs-cTnI) concentrations within a range that would classify asymptomatic women at moderate risk and men at low risk for future cardiac events (note: panels **A** [$n_1 = 2418$ results] and **B** [$n_2 = 2552$ results] represent 2 different lots of patient-derived quality control material). For the Abbott ARCHITECT STAT High Sensitive-I (package insert Outside United States G5-6634/R01 April 2015), the limit of the blank range of concentration is 0.7-1.3 ng/L, the limit of detection is 1.1 ng/L, and the limit of quantification (or 20% CV) is 1.3 ng/L; see the following website from the IFCC committee on Clinical Applications of Cardiac Biomarkers: https://www.ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/ (accessed August 11, 2019). The procedure for making the patient-derived quality control material has been to use an infectious free high-concentrate cardiac troponin human plasma pool material and spike this material in leftover frozen citrate phosphate dextrose plasma obtained from transfusion medicine, with the final stock aliquoted and frozen below −70°C. CV, coefficient of variation; SD, standard deviation.

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(with 1 decimal point) that were < 4 ng/L ranged from 1.8% to 45% and ≥6 ng/L ranged from 0.2% to 9.8%. Rounding the results and reporting as whole numbers (as recommended),[3] the percentage of results < 4 ng/L ranged from 0.8% to 15% and ≥ 6 ng/L ranged from 2% to 38%. Overall, reporting as whole numbers, only 77% of the results would repeat as 4 ng/L or 5 ng/L, with 23% yielding concentrations < 4 ng/L or ≥ 6 ng/L. These data reiterate that acceptable analytical performance may result in the patient's risk misclassification if using a low-normal hs-cTn concentration alone for decision making. Additional approaches besides one hs-cTnI measurement may be needed for appropriate risk stratification.

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Disclosures

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