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ABSTRACT

Background: An analytical benchmark for high-sensitivity cardiac troponin (hs-cTn) assays is to achieve a coefficient of variation (CV) of ≤ 10.0 % at the 99th percentile upper reference limit (URL) used for the diagnosis of myocardial infarction. Few prospective multicenter studies have evaluated assay imprecision and none have determined precision at the female URL which is lower than the male URL for all cardiac troponin assays.

Methods: Human serum and plasma matrix samples were constructed to yield hs-cTn concentrations near the female URLs for the Abbott, Beckman, Roche, and Siemens hs-cTn assays. These materials were sent (on dry ice) to 35 Canadian hospital laboratories (n = 64 instruments evaluated) participating in a larger clinical trial, with instructions for storage, handling, and monthly testing over one year. The mean concentration, standard deviation, and CV for each instrument type and an overall pooled CV for each manufacturer were calculated.

Results: The CVs for all individual instruments and overall were ≤ 10.0 % for two manufacturers (Abbott CV_{pooled} = 6.3 % and Beckman CV_{pooled} = 7.0 %). One of four Siemens Atellica instruments yielded a CV > 10.0 % (CV_{pooled} = 7.7 %), whereas 15 of 41 Roche instruments yielded CVs > 10.0 % at the female URL of 9 ng/L used worldwide (6 cobas e411, 1 cobas e601, 4 cobas e602, and 4 cobas e801) (CV_{pooled} = 11.7 %). Four Roche

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instruments also yielded CVs > 10.0 % near the female URL of 14 ng/L used in the United States (CV_{pooled} = 8.5 %).

Conclusions: The number of instruments achieving a CV ≤ 10.0 % at the female 99th-percentile URL varies by manufacturer and by instrument. Monitoring assay precision at the female URL is necessary for some assays to ensure optimal use of this threshold in clinical practice.

1. Introduction

Since the first universal definition of myocardial infarction (MI) in 2000, acceptable imprecision for cardiac troponin (cTn) at the 99th-percentile of a healthy population (upper reference limit, URL) has been defined as a coefficient of variation (CV) ≤ 10 % [1]. Over the ensuing decade, improvements in the analytical performance of cTn assays led to the development of the high-sensitivity cTn (hs-cTn) assays [2]. The most recent laboratory recommendations for hs-cTn assays emphasize the importance of sex-specific 99th-percentile URLs [3,4].

Regarding monitoring assay performance, the only recommendations are to use quality control (QC) material at a concentration below the lower sex-specific URL and another concentration close to the highest sex-specific URL [3]. Monitoring performance near the lower limit of reporting (i.e., quantification within the normal range) for the hs-cTn assays has been a focus, with imprecision near the limit of detection being prospectively assessed in a clinical trial [5]. Specifically, this trial made use of a national QC program on the Abbott ARCHITECT to monitor the inter-laboratory variation using a patient serum pool with 3.5 ng/L of cTnI during the study [5]. Our objective was to prospectively assess the imprecision at the female URL in hospital sites across Canada as part of a randomized controlled study evaluating the impact of implementing the female URL on clinical outcomes (hs-cTn—Optimizing the Diagnosis of Acute Myocardial Infarction/Injury in Women (CODE-MI) trial; NCT03819894) [6].

2. Methods

2.1. Material for monitoring imprecision at the Female URL

The manufacturer stated female 99th URLs for hs-cTn are 16 ng/L for Abbott, 12 ng/L for Beckman, 39 ng/L for Siemens (ATELLICA and ADVIA Centaur) and 9 ng/L or 14 ng/L for Roche outside or inside the United States (US), respectively. Serum was chosen as the base material as this is an acceptable and approved sample type for all hs-cTn assays listed above, except for Abbott and Roche in the US where plasma is recommended by the manufacturer (https://ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/biomarkers-reference-tables/ see v052023). The serum base material was purchased from Millipore/Sigma (Product# H6914; 5x100 ml bottles) and was stored frozen (-20 °C) prior to use. For each diagnostic company (Abbott, Beckman, Roche, Siemens), a 100 ml bottle was thawed at 4 °C overnight, brought to room temperature and mixed (swirled by hand) prior to testing the serum base with the hs-cTn assay (n = 3 measurements). The Abbott hs-cTnI (ARCHITECT i1000, manufacturer's 20 %CV = 1.3 ng/L) yielded a mean value of 2.2 ng/L, the Beckman hs-cTnI (Access 2, manufacturer's 20 %CV = 1.0–2.3 ng/L) a mean of 1.5 ng/L, the Roche hs-cTnT (cobas e602, manufacturer's 20 %CV = 6 ng/L) a mean of 3.9 ng/L, and the Siemens hs-cTnI (ADVIA Centaur, manufacturer's 20 %CV = 2.5 ng/L) with all results < 2.5 ng/L (note the 20 %CV estimates were obtained from the IFCC website: High-Sensitivity Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer v052023 – see above).

Concurrent to this, high cTn plasma pools (EDTA plasma Pools A, B used previously to construct QC materials for the Abbott hs-cTnI assay where several different patients' EDTA plasma with cTnI values above 40,000 ng/L were pooled together) [7,8] were thawed at room temperature, mixed, and centrifuged (3000*g* for 10 min) prior to testing for all hs-cTn assays. Pool A was used for Abbott (hs-cTnI = 42011 ng/L) as the spike material and Pool B for Roche (hs-cTnT = 9052 ng/L), for Beckman (hs-cTnI = 70304 ng/L) and for Siemens (hs-cTnI = 82996 ng/L) as the spike material. The respective high cTn pools (i.e., spike materials) were then added to the human serum base material until the desired concentration was obtained (i.e., ±20 % from the manufactures stated URL). The final Abbott concentration was 14.1 ng/L, Beckman concentration was 9.8 ng/L, Roche concentration was 9.0 ng/L, and Siemens concentration was 37.1 ng/L [9]. The respective female URL materials were then aliquoted into cryovials with the first (Abbott 13.7, Beckman 9.5, Roche 8.7, Siemens 36.3 ng/L) and last (Abbott 13.4, Beckman 9.8, Roche 8.6, Siemens 36.7 ng/L) cryovial tested to confirm stability and the hs-cTn concentrations of the aliquots prior to storage below –70 °C. For Roche hs-cTnT at the US female URL (14 ng/L), a previous plasma pool (12.4 ng/L) was also assessed. Stability of cTn in this material has been demonstrated [7–9].

2.2. Testing of female URL materials at clinical laboratories

The respective female URL aliquots were sent on dry ice to clinical laboratories across Canada for testing to occur once per month in the 2022 calendar year. Instructions that were provided are listed in the online Method Supplement. Testing occurred for the Abbott hs-cTnI assay in Ontario (2 Alinity, 3 ARCHITECT i2000, 1 ARCHITECT i1000 instruments) and in Saskatchewan (2 Alinity and 2 ARCHITECT i2000 instruments); for the Beckman hs-cTnI assay in Ontario (2 DxI 600 instruments), in Quebec (1 Access 2, 1 DxI 600, 4 DxI 800 instruments) and in Alberta (1 DxI 800 instrument); for the Siemens hs-cTnI assay in Ontario (4 Atellica instruments); and for the Roche hs-cTnT assay in Ontario (4 cobas e602, 8 e801 instruments), in Quebec (2 cobas e411, 4 e602 instruments), in Nova Scotia (5 cobas e411 instruments), in New Brunswick (4 cobas e602), in Manitoba (1 cobas e411, 1 e601, 2 e602 instruments), in Saskatchewan (4 cobas e801 instruments), in Alberta (2 cobas e801 instruments) and in British Columbia (1 cobas e411 and 3 cobas e601 instruments). The mean, SD, and CV were determined for each individual instrument and overall for the hs-cTn assay with the pooled CV calculated (using mean and SD with one decimal place; see Supplemental Tables).

As this was a laboratory quality assurance study assessing imprecision at the female URL using non-identifiable human material, research ethics board approval was not required.

3. Results

The CVs for all individual instruments and overall were ≤ 10.0 % for the Abbott (CV_{pooled} = 6.3 %; n = 10), and Beckman (CV_{pooled} = 7.0 %; n = 9) hs-cTnI assays. The mean concentrations ranged from 11.5 to 13.1 ng/L for the Abbott hs-cTnI assay and from 10.6 to 12.3 ng/L for the Beckman hs-cTnI assay. For the Siemens Atellica instruments (n = 4), the mean concentrations ranged from 33.2 to 34.8 ng/L, with one instrument having a CV > 10.0 % (12.3 %), with the overall CV_{pooled} = 7.7 % (Fig. 1; Supplemental Table 1). Of the 41 Roche instruments, there were 15 instruments with CVs > 10.0 % on the serum sample (6 cobas e411, 1 cobas e601, 4 cobas e602, and 4 cobas e801; overall Roche CV_{pooled} = 11.7 %), with 4 of these Roche instruments (3 cobas e411 and 1 cobas e801) > 10.0 % on the plasma sample at the US URL (CV_{pooled} = 8.5 %). The mean concentrations for the serum samples ranged from 7.8 to 10.2 ng/L for e411, 8.0–9.4 ng/L for e601, 7.5–9.9 ng/L for the e602,

8.0–10.1 for the e801 and for the plasma samples 9.9–12.5 ng/L for e411, 10.9–12.4 ng/L for the e601, 10.6–12.8 ng/L for e602, and 11.5–13.9 ng/L for e801. The highest observed imprecision was from an e411 instrument with a CV of 30.3 % for the plasma and 19.2 % for the serum samples (Fig. 2, Supplemental Table 2).

4. Discussion

The findings from this prospective multi-center evaluation of imprecision at the female URL indicates differences between hs-cTn assays at this important cutoff with not all instruments achieving a 10 % CV. These differences could result in clinical misclassification. One-third of the instruments measuring hs-cTnT did not meet this precision target at the female URL recommended for use outside of the US. This may be why there is more controversy in regard to the value of using sex specific thresholds to evaluate possible MI with hs-cTnT.

A sex-specific URL cutoff for the diagnosis of MI is recommended by the Universal Definition of Myocardial Infarction based on studies that consistently demonstrate that cTnI and cTnT concentrations are lower in females than males [10]. Prospective studies of consecutive patients rather than selected ones demonstrate use of hs-cTnI sex-specific URLs result in a similar proportion of male and female patients being identified with myocardial injury [11]. Implementation of sex-specific URLs in some studies increase the proportion of female patients with myocardial injury [12]. The data with hs-cTnT is more mixed [13]. The retrospective nature of these studies meant female patients were not recognised with myocardial injury at the time of assessment as their cTnT concentrations were below the uniform URL used to guide care. Therefore, adoption of this guideline recommendation has been greater for sites using a hs-cTnI assay than for sites using a hs-cTnT assay [14]. This issue may also be important for the use of a single sample to exclude acute MI where the lower values in females present a more critical issue in regard to imprecision. This may be why studies often identify women as those in whom a rule-out strategy based on a single measurement may be less effective [15].

The CODE-MI trial is a stepped wedge, cluster randomized trial which aims to understand the impact of using a female-specific URL for all hs-cTn assays on the diagnosis, treatment, and outcomes of women with possible MI [6]. Based on our findings of assay imprecision here, it will be important to evaluate whether the impact of implementing a female specific 99th-percentile URL differs in those sites where the instrument performance did not meet the recommendations for a CV $\leq$ 10 %. Imprecision at this cutoff could result in over or under investigation at these sites.

Whilst our study is the first prospective, multi-center evaluation of assay imprecision at the female URL there are some limitations that merit consideration. First, there was unequal representation between instrument types and number of tests performed and thus it is difficult to assess those differences. Second, different sites had different instruments so the impact of the environment on the imprecision observed across the various instruments is unclear. Third, despite providing detailed instructions on handling and testing the aliquots, errors may have occurred which could have contributed to imprecision. Finally, a larger study is required to assess daily imprecision at the female URL.

In summary, this year long monthly testing prospective study highlights that not all assays and instruments consistently achieve the necessary precision required for accurate reporting of hs-cTn at the guideline recommended female URL cutoff.

Conflict of Interest / Disclosures:

Dr. Kavsak has received grants/reagents/consultant/advisor/ honoraria from Abbott Laboratories, Abbott Point of Care, Beckman Coulter, Ortho Clinical Diagnostics, Quidel, Randox Laboratories, Roche Diagnostics, Siemens Healthcare Diagnostics, and Thermo Fisher Scientific. McMaster University has the following patent with Drs. Kavsak and Worster listed as inventors "METHOD OF DETERMINING RISK OF AN ADVERSE CARDIAC EVENT". McMaster University has also filed the following patent: "QUALITY CONTROL MATERIALS FOR CARDIAC TROPONIN TESTING" with Dr. Kavsak and Ms. Clark being listed as inventors. Dr Mills has received research grants awarded to the University of Edinburgh from Abbott Diagnostics, Siemens Healthineers and Roche Diagnostics outside the submitted work, and honoraria from Abbott Diagnostics, Siemens Healthineers, Roche Diagnostics, LumiraDx and Psyros Diagnostics. Dr. Yip has received research support from Roche Diagnostics. Dr. Thiruganasambandamoorthy has received grant funds from The Physicians' Services Incorporated Foundation, Canadian Institutes of Health Research, Heart and Stroke Foundation Canada, The Ottawa Hospital Academic Medical Organization (TOHAMO), Ontario Centre of Innovation (OCI), and the Cardiac Arrhythmia Network of Canada (SRG-15-P10-001) as part of the Networks of Centres of Excellence (NCE). Dr. Thiruganasambandamoorthy is currently supported

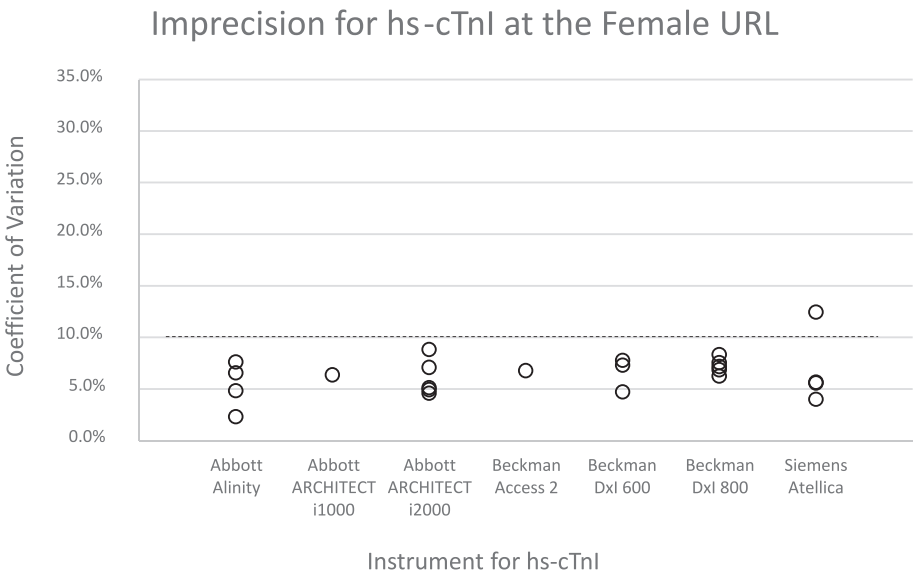

Fig. 1. The imprecision (circles representing %CV) for the Abbott hs-cTnI assay (Alinity, ARCHITECT i1000, ARCHITECT i2000), the Beckman hs-cTnI assay (Access 2, DxI 600, DxI 800) and the Siemens hs-cTnI assay (Atellica) at the Female URL (16 ng/L, 12 ng/L, 39 ng/L, respectively). The dashed line is the 10 %CV.

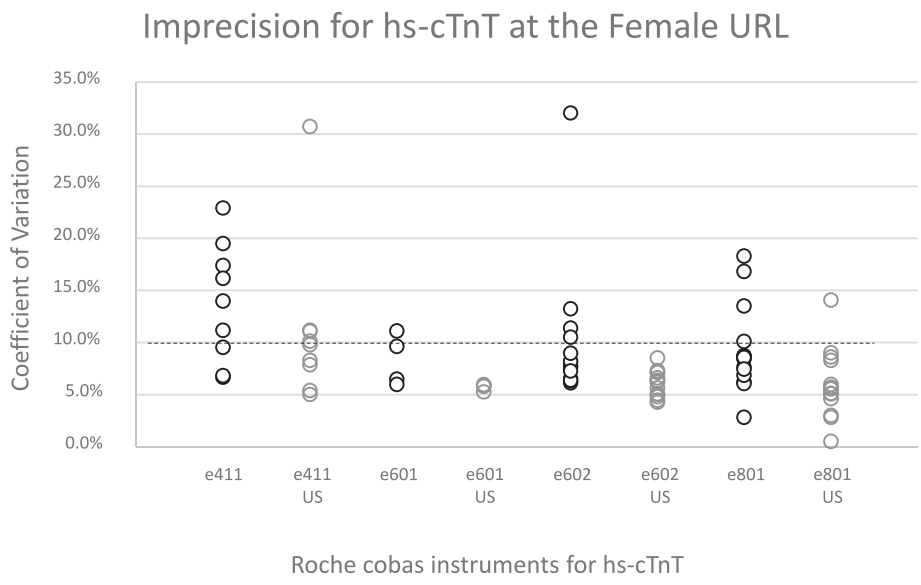

Fig. 2. The imprecision (circles representing %CV) for the Roche hs-cTnT assay with serum (black circles) at the Outside the United States (US) URL (9 ng/L) and with plasma (grey circles) at the US URL (14 ng/L) for the cobas e411, e601, e602 and e801. The dashed line is the 10 %CV.

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CRediT authorship contribution statement

Peter A. Kavsak: Conceptualization, Funding acquisition, Data curation, Writing – original draft, Formal analysis, Methodology, Supervision, Resources, Project administration, Software. **Lorna Clark:** Data curation, Writing – review & editing, Methodology. **Saranya Arnoldo:** Writing – review & editing, Resources. **Amy Lou:** Writing – review & editing, Resources. **Jennifer L. Shea:** Writing – review & editing, Resources. **Shaun Eintracht:** Writing – review & editing, Resources. **Andrew W. Lyon:** Writing – review & editing, Resources. **Vipin Bhayana:** Writing – review & editing, Resources. **Laurel Thorlacius:** Writing – review & editing, Resources. **Joshua E. Raizman:** Writing – review & editing, Resources. **Albert Tsui:** Writing – review & editing, Resources. **Rose Djiana:** Writing – review & editing, Resources. **Michael Chen:** Writing – review & editing, Resources. **Yun Huang:** Writing – review & editing, Resources. **Ali Haider:** Writing – review & editing, Resources. **Ronald A. Booth:** Writing – review & editing, Resources. **Chris McCudden:** Writing – review & editing, Resources. **Paul M. Yip:** Writing – review & editing, Resources. **Daniel Beriault:** Writing – review & editing, Resources. **David Blank:** Writing – review & editing, Resources. **Angela W.S. Fung:** Writing – review & editing, Resources. **Jennifer Taher:** Writing – review & editing, Resources. **Julie St-Cyr:** Writing – review & editing, Resources. **Sameer Sharif:** Writing – review & editing. **Emilie Belley-Cote:** Writing – review & editing. **Beth L. Abramson:** Writing – review & editing. **Steven M. Friedman:** Writing – review & editing. **Jafna L. Cox:** Writing – review & editing. **Marco L.A. Sivilotti:** Writing – review & editing. **Annabel Chen-Tournoux:** Writing – review & editing. **Jesse McLaren:** Writing – review & editing. **Susanna Mak:** Writing – review & editing. **Venkatesh Thiruganasambandamoorthy:** Writing – review & editing. **Frank Scheuermeyer:** Writing – review & editing. **Andrew Worster:** Writing – review & editing. **Dennis Ko:** Writing – review & editing. **Karin H. Humphries:** Writing – review & editing. **Kristin M. Aakre:** Writing – review & editing. **Nicholas L. Mills:** Writing – review & editing. **Allan S. Jaffe:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no other/known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2024.110731.

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