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# A practical approach for the validation and clinical implementation of a high-sensitivity cardiac troponin I assay across a North American city ☆, ☆☆

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ABSTRACT

*Objectives:* Despite several publications on the analytical performance of high-sensitivity cardiac troponin (hs-cTn) assays, there has been little information on how laboratories should validate and implement these assays into clinical service. Our study provides a practical approach for the validation and implementation of a hs-cTn assay across a large North American City.

*Design and methods:* Validation for the Abbott ARCHITECT hs-cTnI assay (across 5 analyzers) consisted of verification of limit of blank (LoB), precision (i.e., coefficient of variation; CV) testing at the reported limit of detection (LoD) and within and outside the 99th percentile, linearity testing, cTnI versus hs-cTnI patient comparison within and between analyzers (Passing and Bablok and non-parametric analyses). Education, clinical communications, and memorandums were issued in advance to inform all staff across the city as well as a selected reminder the day before live-date to important users. All hospitals switched to the hs-cTnI assay concurrently (the contemporary cTnI assay removed) with laboratory staff instructed to repeat samples previously measured with the contemporary cTnI assay with the hs-cTnI assay only by physician request.

*Results:* Across the 5 analyzers and 6 reagent packs the overall LoB was 0.6 ng/L ($n=60$) with a CV of 33% at an overall mean of 1.2 ng/L ($n=60$; reported LoD = 1.0 ng/L), with linearity demonstrated from 45,005 ng/L to 1.1 ng/L. Precision testing with a normal patient-pool QC material (mean range across 5 analyzers was 3.9–4.4 ng/L) yielded a range of CVs from 7% to 10% (within-run) and CVs from 7% to 18% (between-run) with the high patient-pool QC material (mean range across 5 analyzers was 29.6–36.3 ng/L) yielding a range of CVs from 2% to 5% (within-run) and CVs from 4% to 8% (between-run). There was agreement between hs-cTnI versus cTnI with the patient samples (slope ranges: 0.89–1.03; intercept ranges: 1.9–3.8 ng/L), however, the median CV on patient samples $<100$ ng/L across the analyzers was 5.6% for hs-cTnI versus 18.7% for the contemporary assay ($p<0.001$). Following the switch to hs-cTnI testing, no requests for repeat measurements were received.

*Conclusions:* Validation and implementation of hs-cTnI testing across multiple sites requires collaboration within the laboratories and between hospital laboratories and clinical staff.



## 1. Introduction

The introduction of high-sensitivity cardiac troponin (hs-cTn) assays into clinical use has had varied success within Canada [1–3]. This partly may be explained by insufficient analytical, clinical and educational material widely available to efficiently and effectively institute

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such a change within a North American city. There are, however, national and international materials published on the analytical aspects [4–6], and there has been excellent evaluation studies, both single center [7,8] and multicenter studies [9,10] on the two clinically approved hs-cTn assays in Canada (Roche Diagnostics hs-cTnT and Abbott Diagnostics hs-cTnI).

So why has there been problems, considering the reported analytical and clinical performance of the hs-cTn assays has always been demonstrated to be superior to the contemporary assays [11–14]? One contributing factor could be the lack of consensus on the most appropriate cutoff and interpretation for hs-cTn concentrations [3]. Another, more practical aspect for clinical laboratories, could be the lack of published data on the key elements required for internal validation and implementation of hs-cTn assays. Locally, within the city of Hamilton (population > 500,000) after clinical consultation, consensus and support, all four acute-care hospital core laboratories proceeded to implement hs-cTn testing. Detailed below is the step-by-step procedure followed by all laboratories for the validation and implantation of a hs-cTnI assay with materials and supplies readily available in all the laboratories.

## 2. Material and methods

### 2.1. Hospital laboratories, quality control, reagents

The four hospital core laboratories were the Juravinski Hospital and Cancer Centre (JHCC; Abbott ARCHITECT $i2000_{SR}$ analyzer), the Hamilton General Hospital (HGH; two Abbott ARCHITECT $i2000_{SR}$ analyzers), St. Joseph's Hospital (SJH; Abbott ARCHITECT $i2000_{SR}$ analyzer) and McMaster Children's Hospital (MCH; Abbott ARCHITECT i1000 analyzer). The laboratory practice for all four core hospital laboratories has been to prepare patient-pool quality control (QC) material (e.g., citrate phosphate dextrose plasma pool from Canadian Blood Services spiked with cTn) [15,16] to monitor cTn at the 99th percentile. In preparation for transitioning to a hs-cTn assay, a "normal" low patient-pool QC material was also prepared. Two different size hs-cTnI reagent packs (100-test and 500-test) were evaluated on the JHCC analyzer as this analyzer was the first to identify the first replication outlier effect present with the 500-test pack size for the contemporary Abbott cTnI assay on certain analyzers [17]. MCH was the only other site which evaluated the hs-cTnI 100-test pack (i1000 only supports 100-test packs), with HGH and SJH laboratories both evaluating the 500-test packs.

### 2.2. Limit of the blank and precision testing

Each site was instructed to run water as a patient 10 times on each instrument and reagent pack size ($n=60$ in total, as 10 water tested on 500-test pack and 100-test pack at JHCC). The limit of the blank (LoB) was determined by the mean concentration of the water ($n=60$)+3SD. Patient-pool EDTA plasma with a measured concentration of approximately 1 ng/L (to reflect the reported limit of the detection (LoD) for this assay) [8] at the JHCC was aliquoted, frozen (−20 C) and distributed for testing on each analyzer and reagent pack size ($n=60$ in total measurements; performed as within-run). The normal patient-pool QC and high patient-pool QC material (frozen aliquots below −70 C) were measured for within-run ($n=10$ tests) and for between-run precision (over 4 weeks) on the 5 different analyzers.

### 2.3. Linearity and patient comparison testing

An extremely high cTnI concentration EDTA patient-pool (approximately 50,000 ng/L, frozen below −20 C) was distributed to each site for linearity testing. Each site performed 16 serial dilutions with the Abbott Diagnostic multi-assay diluent (manufacturer recommended diluent for the hs-cTnI assay). Each site performed duplicate testing on each serial dilution (exception JHCC with the 100-pack). Linearity was achieved if the site's measured concentrations at all 17 levels were within 2SD of the average measurement for each level. Forty frozen (below −20 C) EDTA patient-pools ($n=8$: < 10 ng/L, $n=10$: 10–30 ng/L, $n=13$: 31–300 ng/L; $n=9$: > 300 ng/L) were distributed to each site to run for hs-cTnI and cTnI. The JHCC measured the 40 samples on the hs-cTnI 500-test pack, 100-test pack and the cTnI 100-test pack; SJH measured the 40 samples on the hs-cTnI 500-test pack and the cTnI 100-test pack; MCH measured the 40 samples on the hs-cTnI 100-test pack and the cTnI 100-test pack; and the HGH measured the 40 samples on analyzer 1 in duplicate: hs-cTnI 500-test pack and cTnI 500-test pack and on analyzer 2 in duplicate for the hs-cTnI 500-test pack. Passing and Bablok regression analyses were performed with Analyse-it software with proportional or absolute differences noted only if the 95%CI of the slope or intercept did not include 1.00 or 0 ng/L, respectively. The average concentration of each sample across all analyzers for both hs-cTnI and cTnI were calculated as well as the CV, with differences between hs-cTnI and cTnI measurements and imprecision assessed by Mann–Whiney non-parametric testing (Statsdirect software, with two-sided $p < 0.050$ considered significant).

### 2.4. Implementation of hs-cTnI

After clinical agreement and support for the hospitals' core laboratories to proceed to switch cTnI testing to hs-cTnI testing, extensive education and dissemination of this forthcoming change occurred via various educational activities and documents (targeted to all hospital staff, trainees, and students). The day before the switch a targeted communication to the emergency departments, internal medicine and cardiology services at the hospitals also occurred as a reminder. Each laboratory concurrently stop the contemporary cTnI testing (reported in μg/L to two decimal places) and proceeded with hs-cTnI testing (reported in ng/L, and in whole numbers). The practice of reporting hs-cTnI in whole numbers has been previously advocated and supported [6,18] and the following comment "*Units (ng/L) as high-sensitivity assay" was appended to the hs-cTnI results for further clarity.

As the stability of cTnI as measured by the Abbott hs-cTnI assay has already been documented [19], the core laboratory staff at all hospitals were instructed after the switch to hs-cTnI testing to repeat samples previously measured with the contemporary cTnI assay with the hs-cTnI assay only by physician request. To assess the impact on repeat testing; queries in the laboratory information system databases were performed to identify if a previous specimen number with a cTnI result also had a hs-cTnI result. Finally, to assess overall how the implementation proceeded, the Biochemist (PK) the following day asked each laboratory as well as directly following up with the