Analytical Concordance of Diverse Point-of-Care and Central Laboratory Troponin I Assays

Albert K.Y. Tsui,[1,2*] Martha E. Lyon,[3] Sean van Diepen,[4] Bobbi Lynn Goudreau,[2] Dylan Thomas,[1,5] Trefor Higgins,[1,5] Joshua E. Raizman,[1,2] Anna K. Füzéry,[1,2] Karina Rodriguez-Capote,[1,5] Mathew Estey,[1,5] and George Cembrowski[1,2]

Background: Cardiac troponin I (cTnI) 99th percentile cutoffs, used in the diagnosis of acute myocardial infarction, are not standardized across cTnI assays. We compared 3 point-of-care (POC) and 1 central laboratory contemporary cTnI assays against the Abbott high-sensitivity (hs) cTnI to evaluate the analytical concordance and the feasibility of using a single cutoff value for all assays.

Methods: Fresh blood samples collected from 102 inpatients in the coronary care unit were measured on central laboratory instruments (Beckman Coulter DxI AccuTnI+3 TnI, Abbott Architect hs-TnI) and cTnI POC analyzers (Alere Triage Troponin I, Radiometer AQT90, Abbott i-STAT). Agreement and correlation between the contemporary cTnI assays and hs-cTnI assay were assessed using regression analysis. Proportional bias was assessed using Bland–Altman plots. Concordance between the contemporary cTnI and hs-cTnI assays was determined by diagnostic contingency tables at specific cutoffs.

Results: Most POC cTnI assays had excellent correlation with the Abbott hs-cTnI method (r^2 = 0.955–0.970) except for Alere Triage (r^2 = 0.617), while proportional bias is evident between all cTnI assays. Overall concordance between POC contemporary cTnI assays and hs-cTnI assay was 80% to 90% at their respective 99th percentile cutoffs. The concordance increased to 90% to 95% when a fixed cutoff of 0.03 to 0.05 ng/mL was used across the assays.

Conclusions: This study demonstrates poor analytical concordance between cTnI assays at the 99th percentile and supports the notion of a single clinical decision limit for cTnI and consequently standardization of diagnostic protocols despite the analytical differences among these assays.

IMPACT STATEMENT

This study compares the analytical concordance of 3 point-of-care (POC) and 1 contemporary central laboratory cardiac troponin I (cTnI) assays to a high-sensitivity cTnI assay using the 99th percentile and an alternative cutoff. These data can be used as an approach to harmonize troponin interpretation when 2 different troponin systems coexist. The evidence of the study will help laboratories decide on an optimized threshold with improved analytical concordance for the pair of POC and central laboratory troponin assays.

[1]Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada; [2]Department of Laboratory Medicine and Pathology, Alberta Health Services, Edmonton, AB, Canada; [3]Department of Pathology and Laboratory Medicine, Saskatoon Health Region,

Cardiac troponin (cTn)[6] is used as part of diagnostic and prognostic testing in patients with suspected acute myocardial infarction (AMI). In the past decade, refinement in the analytical performance of troponin assays has allowed the detection of very low cTn concentrations and has made determination of the 99th percentile more precise. Improvement of sensitivity and precision between the limit of detection and the 99th percentile has allowed high-sensitivity (hs) cTn assays to differentiate small but clinically significant changes from analytical noise, thereby facilitating a more rapid rule-out and rule-in of AMI. Many studies have evaluated rapid rule-in/rule-out protocols using hs-cTn with a second test at 1 to 3 h; this compares with contemporary cTn assays that require repeat testing at 6 to 12 h (*1*–*4*). Medical and laboratory associations endorse the 99th percentile cutoff for cTn as the clinical decision value as an aid to identify patients with AMI (*5*, *6*). Due to the use of different healthy populations, calibration, antibody, and method work flow, the heterogeneity of assays means that the 99th percentile cutoffs are not clinically identical between manufacturers, especially for cTnI assays (*7*). This raises concerns for patient safety when different troponin thresholds and/or different assays are used with different cutpoints in an integrated health region. This situation generates confusion for physicians working at multiple locations and increases the risk of result misinterpretation, leading to medical errors and ultimately poor patient care (*8*, *9*). A single harmonized cutoff could be advantageous if comparable analytical and clinical performance can be achieved between assays.

Point-of-care (POC) cTn testing is commonly used when the central laboratory cannot provide test results within 60 min, such as in emergency departments, ambulances, and rural areas where access to the main system laboratory is not readily available. Faster cTn results allow timely triage, disposition, and early discharge (*10*). However, most POC troponin assays are more expensive, less sensitive, and less precise compared with the central laboratory assays (*11*), and consequently, they are restricted to situations in which the risk of a delayed result outweighs the limitation of using POC devices, such as in rural areas and as backup to the main laboratory assay. The goals of this study are to (*a*) compare 3 POC and 1 central laboratory contemporary cTnI assays with an hs-cTnI assay and (*b*) evaluate the analytical concordance and establish an optimal cutoff for these assays.

METHODS

Study design

The study was approved by the Research Ethics Board at the University of Alberta (Pro00070032). Written informed consent was obtained from 102 patients admitted to the coronary care unit (CCU) at Mazankwoski Alberta Health Institute in Edmonton, Alberta, Canada, between March and June 2017. Patients admitted to the CCU were initially diagnosed with acute coronary syndrome, non–ST segment elevation myocardial infarction, ST segment elevation myocardial infarction, and unstable angina (Table 1). Demographic information including age, sex, and renal function was collected.

Saskatoon, SK, Canada; [4]Department of Critical Care Medicine, Division of Cardiology, University of Alberta, Edmonton, AB, Canada; [5]DynaLIFE Medical Labs, Edmonton, AB, Canada.
***Address correspondence to this author at:** Department of Laboratory Medicine and Pathology, University of Alberta, 4B1.18 Walter McKenzie Centre, University of Alberta Hospital, Alberta Health Services, 8440 112 St. NW, Edmonton, Alberta, T6G 2B7 Canada.
Fax 780-407-8599; e-mail atsui@ualberta.ca.
DOI: 10.1373/jalm.2018.026690

[6] **Nonstandard abbreviations:** cTn, cardiac troponin; AMI, acute myocardial infarction; hs, high sensitivity; POC, point of care; CCU, coronary care unit; TP, true positive; TN, true negative; FP, false positive; FN, false negative; CI, confidence intervals; ROC, receiver operating characteristic.

Table 1. Final diagnosis of study population and the hs-cTnI measurement at CCU.[a]

Final diagnosis	Number of patients	Abbott hs-TnI, ng/L
STEMI[b]	14	13933 ± 15260
NSTEMI	25	1759 ± 2614
Unstable angina	15	53 ± 70
Heart failure	13	28 ± 35
Cardiac, others	31	759 ± 2559
Non-cardiac	4	66 ± 61

[a] Troponin result is expressed mean ± SD.
[b] STEMI, ST segment elevation myocardial infarction; NSTEMI, Non–ST segment elevation myocardial infarction.

Three tubes of fresh venous whole blood (2 BD Vacutainer K_2EDTA and 1 BD Vacutainer lithium heparin plasma separator tubes) were collected from each patient, in addition to the routine morning blood draw. Immediately after blood collection, 1 EDTA tube of whole blood was analyzed on the Radiometer AQT90 and Alere Triage Troponin I, and 1 heparin plasma separator tube of whole blood was used for analysis on the Abbott i-STAT. Whole blood from the same EDTA and heparin tubes was centrifuged at 3000*g* for 10 min within 2 h after collection. Each plasma sample was measured on the Beckman Coulter DxI AccuTnI+3 and Abbott Architect hs-cTnI assays within the day of collection in accordance with stability claims.

Method comparisons and bias assessment

Manufacturer-defined 99th percentile values and specimen type for the cTnI assays used in this study are summarized in Table 1 of the Data Supplement that accompanies the online version of this article at http://www.jalm.org/content/vol3/issue5. Three POC cTnI assays (Radiometer AQT90, Alere Triage Troponin I, Abbott i-STAT) and 1 central laboratory contemporary cTnI assay (Beckman Coulter DxI AccuTnI+3) were compared with the Abbott Architect hs-cTnI assay. The Abbott hs-cTnI assay was designated as the reference method because of significantly improved precision profiles from the lower end of the measuring range and across the 99th percentile cutoff. Whole blood run on AQT90 and Triage was compared with EDTA plasma run on the Abbott hs-cTnI assay. Whole blood run on i-STAT was compared with heparin plasma on the Abbott hs-cTnI assay. Both heparin and EDTA plasma samples were used to compare the Beckman AccuTnI+3 and Abbott hs-cTnI assays. All quality control results were within the acceptable limit during the study period. Data within the linear range were assessed. Regression analysis (ordinary least squares) was used for each pairwise comparison. Proportional bias was assessed by Bland–Altman plots.

Diagnostic performance at the manufacturer's 99th percentile cutoff and fixed cutoffs for contemporary cTnI assays against the hs-cTnI assay

Four different cutoffs including the 99th percentile of each assay and fixed cutoffs across all assays of 0.03, 0.04, and 0.05 ng/mL were used to assess overall concordance, true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) rates. The Abbott hs-cTnI assay was assigned as the gold standard method to compare results from other assays. The concentration range in the Abbott hs-cTnI assay is 0 to 48 000 ng/L (i.e. 0 to 48 ng/mL). The choice to examine these specific cutoffs was based around the manufacturer-claimed 99th percentile cutoff for the central laboratory assays: Abbott hs-TnI (0.0262 ng/mL) and Beckman Coulter AccuTnI+3 (0.02 ng/mL for American population and 0.04 ng/mL for European population). At each troponin cutoff, a positive result was defined as greater than the specified cutoff value, whereas a result was deemed negative at or less than the defined cutoff. A 2 × 2 diagnostic table was generated to compare the test assay and hs-cTnI assay at a specific cutoff. TP and TN denote that both assays yield positive and negative results, respectively. FP indicates that the test assay is positive and the hs-cTnI

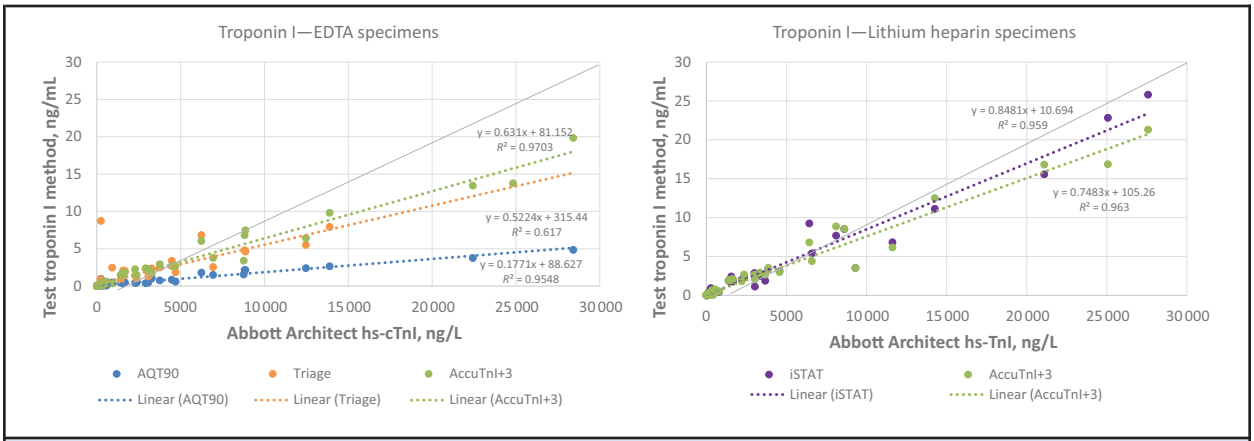

Fig. 1. Method comparison of contemporary cTnI assays with the Abbott hs-cTnI assay in EDTA (A) and lithium heparin (B) specimens across the analytical measuring range of the assays.
Bias is noted in all assays (largest bias for AQT90; least bias for i-STAT).

assay is negative. FN denotes that the test assay is negative but the hs-cTnI assay is positive. Analytical concordance is defined as the proportion of TP and TN between 2 assays to total specimen examined. The requirement for an optimal cutoff would be a high analytical concordance (>90%) between the 2 selected assays. In this analysis, specimens were grouped and evaluated by anticoagulant (heparin or EDTA) to control for any anticoagulant-related differences in troponin I results (*12*).

Statistical methods

Significance of discordant results in the 2 × 2 table between assays was assessed using McNemar's test (SigmaPlot 11). Significant discordant is defined as $P < 0.05$. Optimal cutoff is defined by the highest concordance between the test assay and reference assay (e.g., hs-cTnI). The 95% confidence intervals (CI) were calculated for the diagnostic test parameters in the contingency table (MedCalc version 18). Least-square regressions, Bland–Altman plots, and receiver operating characteristic (ROC) curves were generated with Analyze-It (version 4.81).

RESULTS

Method comparison demonstrated substantial interassay variability in troponin I assays

Assays had excellent correlation with the hs-cTnI method (r^2 = 0.955–0.970) except for Alere Triage (r^2 = 0.617) across the full measuring range. Bias was noted in all cTnI assays (Fig. 1; see also Fig. 1 in the online Data Supplement). Abbott i-STAT had the lowest average bias of all the POC cTnI assays (38%; 95% CI, 7%–69%; y = 0.8481x + 10.694), followed by Triage (44%; 95% CI, −66% to 154%; y = 0.522x + 315.44). Radiometer AQT 90 had the largest negative bias (−64%; 95% CI, −79 to −50%; y = 0.1771x + 88.627) of all the assays (see Fig. 1 in the online Data Supplement). For clinically relevant cTn concentrations of <0.1 ng/mL, correlation remained poor and variable among all POC assays. At this low range, Abbott i-STAT was the best (r^2 = 0.959) and Alere Triage had the poorest correlation (r^2 = 0.355) among the POC assays (Fig. 2). Significant proportional bias was also found between contemporary cTnI and hs-cTnI assays (Fig. 2; see also Fig. 2 in the online Data Supplement).

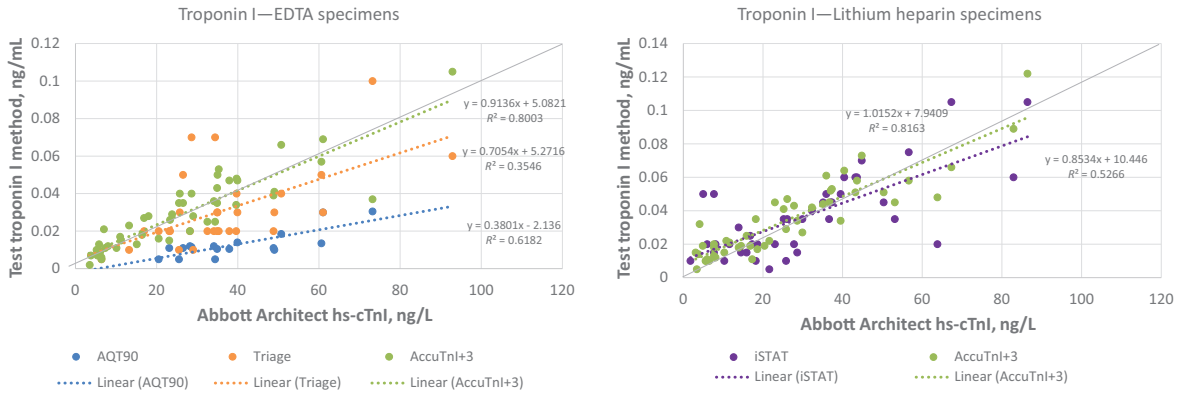

Fig. 2. Method comparison of cTnI assays with the Abbott hs-cTnI assay in EDTA (A) and lithium heparin (B) specimens at the clinically relevant cTnI levels (<0.10 ng/mL or <100 ng/L).
Like Fig. 1, bias is largest for AQT90 and smallest for i-STAT.

Diagnostic performance at the 99th percentile cutoff

Compared with the Abbott hs-cTnI assay, overall concordance at the 99th percentile of each assay was the highest for AccuTnI+3 (94%; 95% CI, 88%–98%), followed by Triage (90%; 95% CI, 83%–95%), AQT90 (80%; 95% CI, 70%–87%), and i-STAT (80%; 95% CI, 71%–88%) (Fig. 3). At the clinically relevant

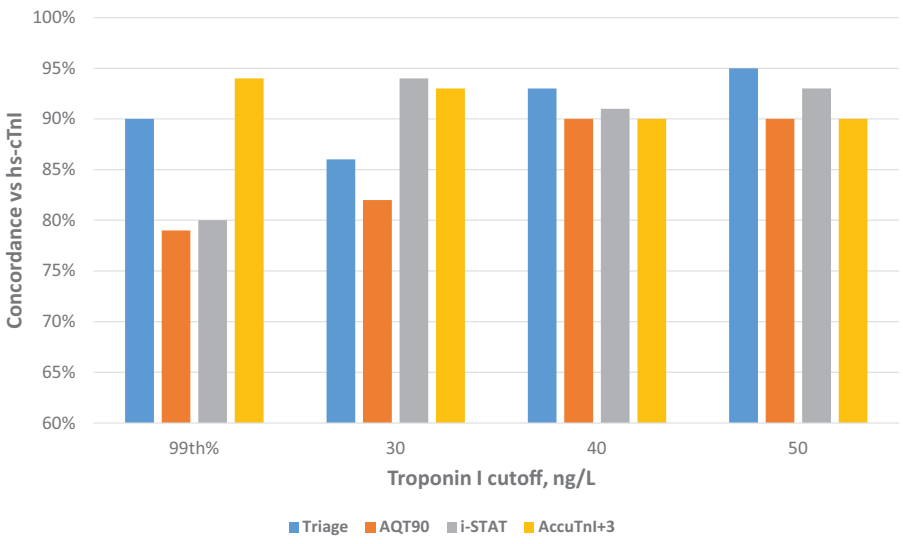

Fig. 3. Overall concordance of each cTnI assay against the Abbott hs-cTnI assay at their 99th percentile values and a fixed cutoff.
At the manufacturer's claimed 99th percentile of each assay, overall concordance is variable among cTnI assays and is lowest for AQT90 and i-STAT. At a fixed cutoff of 0.04 ng/mL or 40 ng/L, there is >90% concordance in all contemporary cTnI assays when compared with the Abbott hs-cTnI assay.

cTnI concentrations (<0.10 ng/mL), the FN rates were highest for both AQT90 and i-STAT at 33% (20 negatives of 60 results) (Table 2). Triage had an FN rate of 19% (9 negatives of 47 results). AccuTnI+3 had the lowest FN rate at 7% (3 negatives of 41 results).

Diagnostic performance at a fixed cutoff

Fixed cutoffs were used to compare the analytical diagnostic performance of the POC and central laboratory contemporary cTnI assays against the hs-cTnI assay (Fig. 3 and Table 2). The highest overall concordance was at the cutoff of 0.03 ng/mL for i-STAT [94% (88%–98%)], 0.04 or 0.05 ng/mL for AQT90 [90% (88%–98%)], 0.05 ng/mL for Triage [95% (89%–98%)], and 0.04 ng/mL (the 99th percentile) for AccuTnI+3 [94% (88%–98%)]. At 0.04 and 0.05 ng/mL cutoffs, the sensitivity (TP rate) and area under the ROC curve were also the greatest without compromising the specificity (TN rate) (Fig. 4; see also Fig. 3 in the online Data Supplement). The FN rate was reduced to 15% in AQT90, 5% in Triage, 3% in i-STAT, and 0% in AccuTnI+3.

DISCUSSION

This study has several important and novel findings. First, there is suboptimal analytical concordance at the 99th percentile cutoff compared with the fixed cTnI cutoffs for POC cTnI assays against the central laboratory hs-cTnI assay. Second, we identified the optimal cutoff based on analytical concordance for the specific POC and hs-cTnI assays. Lastly, this study examined an approach to harmonize cTnI cutoff when different cTnI assays are used in a health region.

A common problem with troponin I assays is the lack of comparability and harmonization resulting in substantial bias (*13*–*15*). Early attempts to standardize contemporary cTnI assays were unsuccessful because of poor commutability of the standard reference material among assays (*16*, *17*). Recent efforts using serum-based cTnI reference materials showed promise to achieve harmonization of cTnI results (*18*). Currently, assay-specific 99th percentile cutoffs are widely endorsed to help alleviate the lack of assay standardization; however, this value is not identical across different central laboratory cTnI and hs-cTnI assays (*7*, *19*). Our findings extend this concerning observation to the POC cTnI assays by demonstrating suboptimal analytical concordance and high FN rates against the central laboratory assays at the 99th percentile cutoff. The consequence of FNs in the POC troponin test can result in missed AMI, which would otherwise be diagnosed and managed appropriately. A resolution to the issue could repeat the POC test to improve confidence of the results. However, it would contradict the primary purpose of performing POC troponin I testing because it will lead to delayed reporting and additional costs.

It is important to appreciate that the establishment of the 99th percentile is also not standardized. First, different reference populations have been used to derive the 99th percentile cutoff. Second, sex- and age-specific influence on troponin assays have been recently identified especially for hs-cTnI. Third, the manufacturer-derived 99th percentile cutoff in hs-cTnI assays may not truly reflect certain populations, such as renal dysfunction patients or a so-called healthy population not reflective of the true patient cohort who present to the emergency department (*20*). Fourth, use of manufacturer-derived 99th percentile cutoffs are not clinically equivalent between assays, which can lead to a different clinical diagnosis if an alternate troponin assay is used (*7*). Fifth, differences in results are produced using different sample types, such as EDTA plasma vs heparin plasma. For these reasons, it is vital to understand the capabilities and suitability of the 99th percentile of the specific troponin assays applied to the local patient population. In the ideal situation, a direct reference interval study to establish the 99th

Table 2. Summary of the TP, TN, FP, FN, and overall concordance for different thresholds of cTnI assays when compared with the Abbott hs-cTnI assay.

	Cutoff, ng/mL	TP		TN		FP		FN		Overall concordance, % (95% CI)	McNemar *P* value	Optimal cutoff, ng/mL
		n	Rate, %	n	Rate, %	n	Rate, %	n	Rate, %			
Triage vs hs-TnI	99th% (0.02)	53	85	38	95	2	4	9	19	90 (83%–95%)	$P = 0.070$	0.04
	0.03	47	80	41	95	2	4	12	23	86 (78%–92%)	$P = 0.016$	
	0.04	44	92	51	94	3	6	4	7	93 (86%–97%)	$P = 1.000$	
	0.05	43	93	54	96	2	4	3	5	95 (89%–98%)	$P = 1.000$	
AQT90 vs hs-TnI	99th% (0.012)	42	68	40	100	0	0	20	33	80 (70%–87%)	$P < 0.001$	0.04
	0.03	41	69	43	100	0	0	18	30	82 (74%–89%)	$P < 0.001$	
	0.04	38	79	54	100	0	0	10	16	90 (83%–95%)	$P = 0.004$	
	0.05	36	78	56	100	0	0	10	15	90 (83%–95%)	$P = 0.004$	
i-STAT vs hs-TnI	99th% (0.08)	41	67	41	100	0	0	20	33	80 (71%–88%)	$P < 0.001$	0.03
	0.03	57	98	39	89	5	8	1	3	94 (88%–98%)	$P = 0.221$	
	0.04	49	96	44	86	7	13	2	4	91 (84%–96%)	$P = 0.182$	
	0.05	44	94	51	93	4	8	3	6	93 (86%–97%)	$P = 1.000$	
AccuTnI+3 (heparin) vs hs-TnI	99th% (0.02)	61	100	30	76	10	14	0	0	90 (82%–95%)	$P = 0.004$	0.04 (99th%)
	99th% (0.04)	58	95	38	93	3	5	3	7	94 (88%–98%)	$P = 0.683$	
	0.03	58	100	37	84	7	11	0	0	93 (87%–97%)	$P = 0.023$	
	0.04	51	100	41	80	10	16	0	0	90 (83%–95%)	$P = 0.004$	
	0.05	44	94	48	87	7	14	3	6	90 (83%–95%)	$P < 0.001$	
AccuTnI+3 (EDTA) vs hs-TnI	99th% (0.02)	62	98	31	79	8	11	1	3	91 (84%–96%)	$P = 0.046$	0.03
	99th% (0.04)	52	84	40	100	0	0	10	20	90 (83%–95%)	$P = 0.004$	
	0.03	57	97	39	91	4	7	2	5	94 (85%–97%)	$P = 0.683$	
	0.04	46	96	48	89	6	12	2	4	92 (85%–97%)	$P = 0.289$	
	0.05	45	98	55	98	1	2	1	2	98 (93%–100%)	$P = 0.480$	

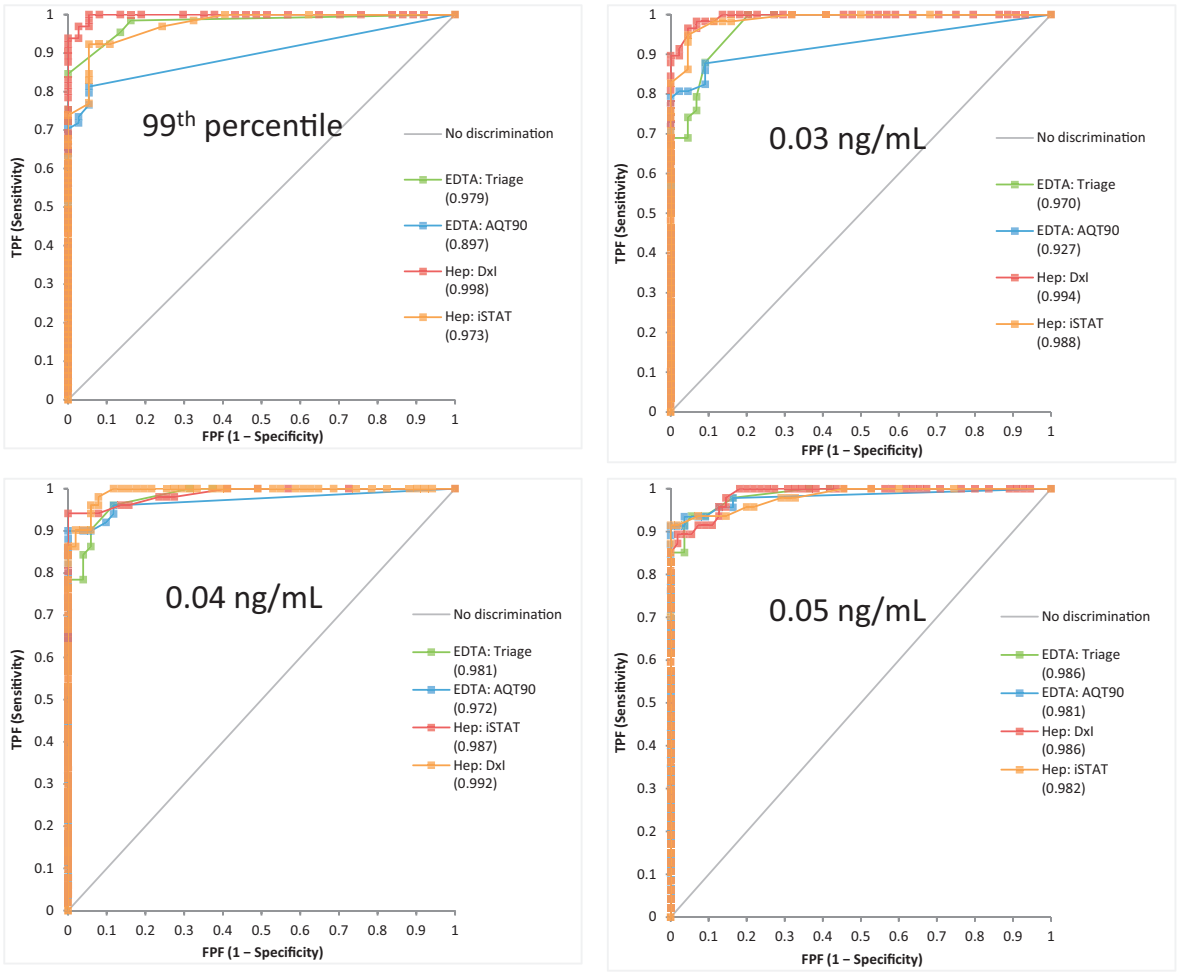

Fig. 4. ROC curve for each cTnI assay against the Abbott hs-TnI assay at their 99th percentile values and a fixed cutoff.
Area under the curve of comparison is stated in the bracket.

percentile using a local population is recommended but largely prohibitive because it is resource intensive.

Harmonization is difficult to achieve in an integrated health network consisting of multiple hospitals, laboratories, and a plethora of POC troponin assays with significant interassay variability and different 99th percentile cutoffs. We attempted using a single decision limit for all the cTnI assays used in our health region with the proviso of a high rate of concordant patient classification among the different assays. By applying a range of single cutoffs instead of the assay's 99th percentile, the analytical concordance is increased, as are the significantly improved TP rates and TN rates. For example, i-STAT's inferior TP rate and FN rates at 0.08 ng/mL (99th percentile) are dramatically improved with a cutoff of 0.03 ng/mL. An alternate 99th percentile cutoff (e.g., 0.04 ng/mL) for i-STAT was previously demonstrated to improve the sensitivity from 34% (at the 99th percentile cutoff of 0.08 ng/mL) to 81% (*21*, *22*). Similarly, overall analytical concordance with hs-cTnI is

improved with an optimized threshold of 0.04 ng/mL for AQT90 and Triage.

Our results suggested that a single harmonized cutoff of 0.03 to 0.05 ng/mL yields the greatest interassay agreement and could be used when POC and central laboratory assays coexist. POC cTnI assays are also used as a backup to the central laboratory assay. To achieve this goal, the performance of the POC cTnI test must be comparable with that of the central laboratory. Implementing a single cutoff avoids physician confusion associated with multiple reference intervals for the same laboratory test, especially for physicians working in multiple locations. Prospective clinical studies would also be desirable to assess the patient outcome, safety, and impact to the overall health system.

Although comparison studies have been published for a variety of central laboratory and POC troponin assays, most of these studies use frozen plasma samples for analysis, whereas few studies are performed using fresh whole blood and plasma samples (*13*, *14*). Although repeated freeze–thaw cycles and storage at −70 °C for 1 year did not have statistically significant changes to cTnI levels (*23*–*25*), frozen specimens could produce variable patterns for individual samples with up to a 50% change from baseline (*25*). While repeated freeze–thaw cycles produced a minimal change in cTnI with the new Beckman hs-cTnI assay, it was greatly affected using the Abbott hs-cTnI assay (*26*). Storage at −20 °C was also shown to produce a significant negative trend in cTnI with the Beckman AccuTnI+3 assay (*27*). For these reasons, we used fresh samples in the same matrix as intended in the clinical setting.

The current study has several limitations. First, this study was not designed to compare the optimized cutoffs with clinical diagnosis. The cutoff values were based on the analytical capabilities of the different cTnI assays compared with the hs-cTnI reference assay. Future studies will be required to assess the suitability of these cutoffs in the clinical settings (e.g., emergency department for strategies to rule in or rule out AMI) and cost-effectiveness of standardizing the cTnI cutoff between POC and central laboratory assays. Second, the CCU patients may not accurately reflect the population seen in the emergency department or rural areas in which the POC devices are predominately used. Third, the number of female subjects enrolled (n = 26) precludes evaluating sex-specific 99th percentile cutoff for the hs-cTnI assay. Finally, given our modest sample size (n = 102), this study would be underpowered to detect clinically meaningful differences.

In conclusion, this study demonstrates improved analytical concordance and TP rates but reduced FN rates by using a fixed optimal cutoff of 0.03 to 0.05 ng/mL as opposed to the 99th percentile of each assay. Our results also support the notion of a single clinical decision limit for cTnI to provide better analytical concordance and, consequently, standardization of diagnostic protocols despite the analytical differences among these assays.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements:* (*a*) *significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data;* (*b*) *drafting or revising the article for intellectual content;* (*c*) *final approval of the published article; and* (*d*) *agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form.* **Employment or Leadership:** T. Higgins, Alberta Health Services; G. Cembrowski, Laboratory Concision. **Consultant or Advisory Role:** A.K. Füzéry, Alere Canada, Radiometer. **Stock Ownership:** G. Cembrowski, Abbott Laboratories. **Honoraria:** M.E. Lyon, Radiometer Canada; G. Cembrowski, Abbott. **Research Funding:** None declared. **Expert Testimony:** None declared. **Patents:** None declared. **Other Remuneration:** M.E. Lyon, Radiometer Canada.

Role of Sponsor: No sponsor was declared.

REFERENCES

1. Cullen L, Mueller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. J Am Coll Cardiol 2013;62:1242–9.
2. Wildi K, Cullen L, Twerenbold R, Greenslade JH, Parsonage W, Boeddinghaus J, et al. Direct comparison of 2 rule-out strategies for acute myocardial infarction: 2-h accelerated diagnostic protocol vs 2-h algorithm. Clin Chem 2017;63:1227–36.
3. Papendick C, Blyth A, Seshadri A, Edmonds MJR, Briffa T, Cullen L, et al. A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: design of the rapid assessment of possible ACS in the emergency department with high sensitivity troponin t (rapid-TnT) study. Am Heart J 2017;190:25–33.
4. Jaeger C, Wildi K, Twerenbold R, Reichlin T, Rubini Gimenez M, Neuhaus JD, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am Heart J 2016;171:92–102 e1–5.
5. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, et al. National academy of clinical biochemistry laboratory medicine practice guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Clin Chem 2007; 53:552–74.
6. Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, Apple FS. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American Association for Clinical Chemistry and the task force on clinical applications of cardiac bio-markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2018;64:645–55.
7. Wildi K, Gimenez MR, Twerenbold R, Reichlin T, Jaeger C, Heinzelmann A, et al. Misdiagnosis of myocardial infarction related to limitations of the current regulatory approach to define clinical decision values for cardiac troponin. Circulation 2015;131:2032–40.
8. Miller WG, Horowitz GL, Ceriotti F, Fleming JK, Greenberg N, Katayev A, et al. Reference intervals: strengths, weaknesses, and challenges. Clin Chem 2016;62:916–23.
9. Plebani M. Harmonization of clinical laboratory information—current and future strategies. eJIFCC 2016; 27:15–22.
10. Ezekowitz JA, Welsh RC, Weiss D, Chan M, Keeble W, Khadour F, et al. Providing rapid out of hospital acute cardiovascular treatment 4 (PROACT-4). J Am Heart Assoc 2015;4:e002859.
11. Ho C, Cimon K, Weeks L, Mierzwinski-Urban M, Dunfield L, Soril L, et al. Point-of-care troponin testing in patients with symptoms suggestive of acute coronary syndrome: a health technology assessment. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016.
12. Lyon ME, Kavsak PA, Lyon AW. The effect of heparin on measurement of high sensitivity cardiac troponin I: influence on diagnostic misclassification at decision thresholds. 2017;63:A-064.
13. Palamalai V, Murakami MM, Apple FS. Diagnostic performance of four point of care cardiac troponin I assays to rule in and rule out acute myocardial infarction. Clin Biochem 2013;46:1631–5.
14. Christenson RH, Jacobs E, Uettwiller-Geiger D, Estey MP, Lewandrowski K, Koshy TI, et al. Comparison of 13 commercially available cardiac troponin assays in a multicenter North American study. J Appl Lab Med 2017; 1:544–61.
15. Mion MM, Bragato G, Casarotti A, Cosma C, Vigolo S, Vettore G, et al. Clinical performance of cardiac troponin I: a comparison between the POCT AQT90 Flex and the Dimension Vista analyzer in an emergency setting. Clin Biochem 2017;50:763–7.
16. Christenson RH, Duh SH, Apple FS, Bodor GS, Bunk DM, Dalluge J, et al. Standardization of cardiac troponin I assays: round robin of ten candidate reference materials. Clin Chem 2001;47:431–7.
17. Christenson RH, Duh SH, Apple FS, Bodor GS, Bunk DM, Panteghini M, et al. Toward standardization of cardiac troponin I measurements part II: assessing commutability of candidate reference materials and harmonization of cardiac troponin I assays. Clin Chem 2006;52:1685–92.
18. Tate JR, Bunk DM, Christenson RH, Barth JH, Katrukha A, Noble JE, et al. Evaluation of standardization capability of current cardiac troponin I assays by a correlation study: results of an IFCC pilot project. Clin Chem Lab Med 2015; 53:677–90.
19. Ungerer JP, Tate JR, Pretorius CJ. Discordance with 3 cardiac troponin I and T assays: implications for the 99th percentile cutoff. Clin Chem 2016;62:1106–14.
20. Gunsolus I, Sandoval Y, Smith SW, Sexter A, Schulz K, Herzog CA, Apple FS. Renal dysfunction influences the diagnostic and prognostic performance of high-sensitivity cardiac troponin I. J Am Soc Nephrol 2018;29: 636–43.
21. Schneider HG, Ablitt P, Taylor J. Improved sensitivity of point of care troponin I values using reporting to below the 99th percentile of normals. Clin Biochem 2013;46: 979–82.
22. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012;58:1574–81.
23. Wu AH, Shea E, Lu QT, Minyard J, Bui K, Hsu JC, et al. Short- and long-term cardiac troponin I analyte stability in plasma and serum from healthy volunteers by use of

an ultrasensitive, single-molecule counting assay. Clin Chem 2009;55:2057–9.
24. Uettwiller-Geiger D, Wu AH, Apple FS, Jevans AW, Venge P, Olson MD, et al. Multicenter evaluation of an automated assay for troponin I. Clin Chem 2002;48: 869–76.
25. Egger M, Dieplinger B, Mueller T. One-year in vitro stability of cardiac troponins and galectin-3 in different sample types. Clin Chim Acta 2018;476:117–22.
26. Kavsak PA, Worster A, Hill SA, MacRae AR, Jaffe AS. Analytical comparison of three different versions of a high-sensitivity cardiac troponin i assay over 10 years. Clin Chim Acta 2017;475:51–5.
27. Greene DN, Holmes DT, Liang J, Kwong SL, Lorey TS, Petrie MS. Challenges in harmonizing integrated healthcare network laboratories: multi-center evaluation of the AccuTnI+3 troponin assay. Clin Biochem 2015;48: 268–74.