



Brief Report

The Clinical Validation of a Common Analytical Change Criteria for Cardiac Troponin for Ruling in an Acute Cardiovascular Outcome in Patients Presenting with Ischemic Chest Pain Symptoms

Peter A. Kavsak ^{1,*} , Sameer Sharif ² , Isabella Globe ³, Craig Ainsworth ², Jinhui Ma ⁴, Matthew McQueen ¹, Shamir Mehta ², Dennis T. Ko ⁵ and Andrew Worster ²

¹ Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON L8S 4L8, Canada

² Department of Medicine, McMaster University, Hamilton, ON L8S 4L8, Canada

³ Faculty of Arts and Science, Queen's University, Kingston, ON K7L 3N6, Canada

⁴ Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON L8S 4L8, Canada

⁵ Sunnybrook Hospital, Toronto, ON M4N 3M5, Canada

* Correspondence: author: kavsakp@mcmaster.ca; Tel.: +905-521-2100



Citation: Kavsak, P.A.; Sharif, S.; Globe, I.; Ainsworth, C.; Ma, J.; McQueen, M.; Mehta, S.; Ko, D.T.; Worster, A. The Clinical Validation of a Common Analytical Change Criteria for Cardiac Troponin for Ruling in an Acute Cardiovascular Outcome in Patients Presenting with Ischemic Chest Pain Symptoms. *J. Cardiovasc. Dev. Dis.* **2023**, *10*, 335. <https://doi.org/10.3390/jcdd10080335>

Academic Editor: Krzysztof J. Filipiak

Received: 30 June 2023

Revised: 20 July 2023

Accepted: 1 August 2023

Published: 4 August 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Serial cardiac troponin (cTn) testing on patients with symptoms suggestive of acute coronary syndrome (ACS) is primarily to identify those patients with evolving myocardial injury. With the improved analytical performance of the high-sensitivity cTn (hs-cTn) assays, different change criteria have been proposed that are mostly assay dependent. Here, we developed and compared a new Common Change Criteria (3C for the combined criteria of >3 ng/L, >30%, or >15% based on the initial cTn concentration of <10 ng/L, 10 to 100 ng/L, or >100 ng/L, respectively) method, versus the 2 h assay-dependent absolute change criteria endorsed by the European Society of Cardiology (ESC), versus the common relative >20% change criterion. These different analytical change criteria were evaluated in 855 emergency department (ED) patients with symptoms of ACS and who had two samples collected 3 h apart. The cTn concentrations were measured with four different assays (Abbott hs-cTnI, Roche hs-cTnT, Ortho cTnI-ES, and Ortho hs-cTnI). The outcomes evaluated were myocardial infarction (MI) and a composite outcome (MI, unstable angina, ventricular arrhythmia, heart failure, or cardiovascular death) within 7 days of ED presentation. The combined change criteria (3C) method yielded higher specificities (range: 93.9 to 97.2%) as compared to the >20% criterion (range: 42.3 to 88.1%) for all four assays for MI. The 3C method only yielded a higher specificity estimate for MI for the cTnI-ES assay (95.9%) versus the absolute change criteria (71.7%). Similar estimates were obtained for the composite outcome. There was also substantial agreement between hs-cTnT and the different cTnI assays for MI with the 3C method, with the percent agreement being $\geq 95\%$. The Common Change Criteria (3C) method combining both absolute and different percent changes may be used with cTnI, hs-cTnT, and different hs-cTnI assays to yield similar high-specificity (rule-in) estimates for adverse cardiovascular events for patients presenting to the ED with ACS symptoms.

Keywords: high-sensitivity cardiac troponin; change criteria; myocardial infarction; acute coronary syndrome; emergency department

1. Introduction

For over 40 years, guidelines for the interpretation of laboratory biomarkers in the diagnosis of myocardial infarction (MI) have emphasized a change in biomarker concentrations with serial measurements [1–6]. With the redefinition of MI in 2000, the emphasis was placed on cardiac troponin (cTn), with serial determinations important to help interpret

concentrations near the upper reference limit (URL being the 99th percentile) [7]. The 2007 Universal Definition of MI recommended a relative (20%) change in cTn concentrations should be considered significant at higher concentrations where the coefficient of variation (CV) is approximately 5–7% [3]. Since 2007, analytical improvements in cTn precision and sensitivity have produced a newer, preferred generation of assays referred to as high-sensitivity cardiac troponin (hs-cTn) [5,6,8,9].

The early clinical validation of the hs-cTn assays assessed change using relative (%) or absolute cTn concentration changes, with early findings suggesting superior performance for the absolute change criteria [10–12]. The latest European Society of Cardiology (ESC) recommendations have provided assay-specific change criteria that can be used to rule-in MI, with the 4th Universal Definition of MI also stating a change of >20% in cTn concentrations being important for Type 4 and 5 MIs, with a cTn stable level being $\leq 20\%$ variation, which is important in order to distinguish chronic from acute injury [5,6].

Recently, common analytical criteria have been published for hs-cTn assays; specifically, allowable variation would be ± 3 ng/L for concentrations <10 ng/L and $\pm 30\%$ for concentrations slightly above and around the 99th percentiles [13]. At higher concentrations, there has been less emphasis on what is the acceptable analytical variation, with a recent long-term publication (data over 7 years) indicating a 15% cutoff would be suitable [14]. The objective of the present study was to evaluate cTn change alone for ruling-in an MI or a composite acute cardiovascular event across four different cTn assays using the 20% criterion, the ESC absolute cutoffs, and a new Common Change Criteria (3C) in patients presenting to the emergency department (ED) with symptoms suggestive of acute coronary syndrome (ACS).

2. Methods

2.1. Study Cohort

The study population has been previously described (Clinicaltrials.gov: NCT01994577) [15–18]. In brief, after obtaining Research Ethics Board (REB) approval, adult patients (18 years and older) who arrived at the ED (not transferred from another hospital) and had cTn ordered (Abbott ARCHITECT cTnI assay) by the ED physician were screened for study entry. Participants were excluded if they had an ST elevation MI at presentation, if their symptoms were not deemed to be due to ACS, had a previous MI or cardiac procedure/surgery or pulmonary embolus within 30 days, or history of malignancy or non-cardiac fatal disease or sepsis or ventricular fibrillation or sustained ventricular tachycardia at presentation. For this cohort, all participants had a least 2 samples (ED presentation and 3 h later) measured by 4 different assays (Abbott hs-cTnI, Roche hs-cTnI, Ortho cTnI-ES, Ortho hs-cTnI). The EDTA plasma samples were tested for the Abbott hs-cTnI and Roche hs-cTnI assays on fresh, not frozen samples [16]. An aliquot was frozen (below -70 °C) and thawed for the first time and tested for the Ortho cTnI assays, with data supporting stability after multiple freeze–thaw cycles and over 15 years when frozen below -70 °C [17,19]. The treating clinicians and the clinical adjudication team were blinded to the results of these 4 cTn assays [15–18]. It is important to note that the Ortho ES cTnI assay is not a high-sensitivity assay [17,20].

2.2. Outcomes

The 3rd Universal Definition of MI was used for the diagnosis of MI [4]. Clinically, cTnI (Abbott ARCHITECT) was reported in these patients with a cTnI concentration >99th percentile (0.03 $\mu\text{g/L}$) used to identify myocardial injury with an absolute change in concentration being ≥ 0.03 $\mu\text{g/L}$ for concentrations <0.1 $\mu\text{g/L}$ and a relative change in concentration $\geq 20\%$ for concentrations ≥ 0.1 $\mu\text{g/L}$, or new ST segment elevation or depression indicative of ischemia, new left bundle branch block, coronary artery intervention, or pathologic findings of acute MI [15]. For the composite outcome, in addition to MI, unstable angina, heart failure, serious ventricular arrhythmia, and cardiovascular death within 7 days of ED presentation were included, as previously described [15]. A team independently

adjudicated the outcomes, and in the event that consensus between two reviewers was not possible, a third reviewer was used. There was no distinction made for the type of MI, with the adjudicators being blinded to the Abbott hs-cTnI, Roche hs-cTnT, Ortho cTnI-ES, and Ortho hs-cTnI levels.

2.3. Statistical Analysis

Change in cTn concentrations were assessed as follows. For concentrations >20%, the difference between the 2nd from the 1st sample was divided by the 1st sample concentration, with an absolute percent >20% (i.e., rise or fall) being designated as positive for change. For the ESC absolute change, the published criteria for rule in was used based on the 2 h algorithm pathways with the absolute difference between the 2nd and 1st sample used to detect change: Abbott hs-cTnI ≥ 15 ng/L (or >14 ng/L) and Roche hs-cTnT ≥ 10 ng/L (or >9 ng/L) [6]. The Ortho hs-cTnI 2 h absolute change criterion was published after the ESC recommendations and is listed as ≥ 5 ng/L (or >4 ng/L) [21,22]. The same absolute change criterion was used for the Ortho cTnI-ES assay, and prior to calculating change, the Ortho cTnI-ES concentrations in $\mu\text{g/L}$ were multiplied by 1000 to yield ng/L values [17].

The new common change criteria or 3C utilized combined absolute and relative change criteria of >3 ng/L, >30%, or >15% based on the initial cTn concentration of <10 ng/L, 10 to 100 ng/L, or >100 ng/L, respectively. Briefly, if the 1st sample had a cTn concentration <10 ng/L, then a change would be detected if the difference between the 2nd from the 1st was >3 ng/L (absolute level) [13]. If the 1st sample had a cTn concentration between 10 ng/L and 100 ng/L, then a difference >30% (absolute percent) was needed to detect a change [13]. If either the first or second sample had a concentration >100 ng/L, then a difference >15% (absolute percent) was needed to detect change [14]. The 100 ng/L is equivalent to 0.1 $\mu\text{g/L}$ with the non-hs-cTn assays where a change of 20% was commonly used to detect change [23]. The 3C method was derived from analytical imprecision and accuracy estimates from laboratories that were and are involved in the CODE-MI (NCT03819894) and VISION Cardiac Surgery (NCT01842568) studies [13,14]. Descriptive analyses were performed with diagnostic estimates (specificity, positive predictive value (PPV), positive likelihood ratio (PLR), sensitivity, negative predictive value, and negative likelihood ratio) and kappa for agreement with 95% confidence intervals (CI) provided. For the kappa value calculation, each of the 3 change criteria was compared between the different cTnI assays and to hs-cTnT (i.e., change present and change absent for each cTnI assay compared to hs-cTnT). Each of the assays and change criteria was then assessed against the published benchmarks of a specificity $\geq 90\%$, PPV $\geq 75\%$, and a PLR ≥ 10 [24,25]. We performed all analyses using MedCalc for Windows, version 22.006 (MedCalc Software, Ostend, Belgium) and Graphpad prism software (QuickCalcs Web site: <http://www.graphpad.com/quickcalcs/ConfInterval1.cfm> accessed 30 June 2023).

3. Results

The cohort ($n = 855$), 53% of whom were female, that had all four cTn assays measured on both samples, had a median (interquartile) age of 68 years (56 to 80) (Figure 1). The Abbott hs-cTnI assay absolute change criterion (>14 ng/L) achieved a specificity of 98.6% (95% CI: 97.4 to 99.3%), a PPV of 83.1% (95% CI: 72.8 to 90.0%), and PLR of 46.9 (95% CI: 25.6 to 86.0) for MI (Table 1). No other assay nor change criteria exceeded the benchmarks for all three diagnostic parameters for MI. The highest observed specificity estimate when using the >20% criterion was with the Roche hs-cTnT assay for MI (specificity = 88.1%; 95% CI: 85.6 to 90.3%) (Table 2). The 3C method yielded high specificities in the range of 93.9% (Abbott hs-cTnI) to 97.2% (Roche hs-cTnT), with exactly the same estimates for Ortho cTnI-ES and Ortho hs-cTnI for MI (95.9%; 95% CI: 94.2 to 97.2%) (Tables 3 and 4).

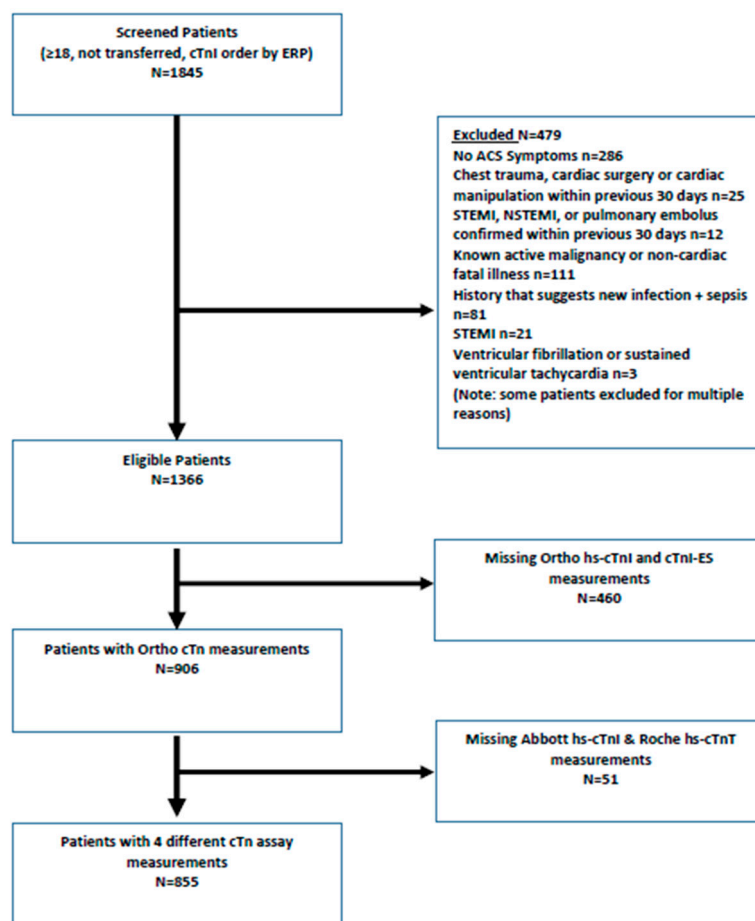


Figure 1. Flow diagram of study cohort. Abbreviations: ACS, acute coronary syndrome; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-STEMI; cTnI, cardiac troponin I; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T.

Table 1. Diagnostic parameters for the different analytical change criteria for MI and the composite outcome for the Abbott hs-cTnI assay.

ABBOTT hs-cTnI Criteria	MI			Composite Outcome		
	>20%	>14 ng/L	3C	>20%	>14 ng/L	3C
Specificity	66.5% (63.1–69.9%)	98.6% (97.5–99.3%)	93.9% (92.0–95.5%)	65.9% (62.2–69.5%)	99.1% (98.1–99.7%)	95.1% (93.1–96.6%)
Sensitivity	59.3% (47.8–70.1%)	66.7% (55.3–76.8%)	53.1% (41.7–64.3%)	42.5% (35.3–49.9%)	31.7% (25.1–38.9%)	30.7% (24.1–37.8%)
Positive Likelihood Ratio	1.8 (1.4–2.2)	46.9 (25.6–86.0)	8.7 (6.2–12.3)	1.2 (1.0–1.5)	35.4 (15.5–80.6)	6.2 (4.2–9.2)
Negative Likelihood Ratio	0.6 (0.5–0.8)	0.3 (0.2–0.5)	0.5 (0.4–0.6)	0.9 (0.8–1.0)	0.7 (0.6–0.8)	0.7 (0.7–0.8)
Positive Predictive Value	15.6% (13.1–18.5%)	83.1% (72.8–90.0%)	47.8% (39.3–56.4%)	25.7% (22.1–29.7%)	90.8% (81.2–95.7%)	63.3% (53.7–72.0%)
Negative Predictive Value	94.0% (92.3–95.3%)	96.6% (95.4–97.5%)	95.0% (93.8–96.0%)	80.5% (78.3–82.5%)	83.9% (82.6–85.2%)	83.1% (81.7–84.5%)

Abbreviations: hs-cTnI, high-sensitivity cardiac troponin I; MI, myocardial infarction; 3C, common change criteria.

Table 2. Diagnostic parameters for the different analytical change criteria for MI and the composite outcome for the Roche hs-cTnT assay.

ROCHE hs-cTnT	MI			Composite Outcome			
	Criteria	>20%	>9 ng/L	3C	>20%	>9 ng/L	3C
Specificity		88.1% (85.6–90.3%)	97.0% (95.6–98.1%)	97.2% (95.7–98.2%)	87.9% (85.2–90.3%)	97.8% (96.3–98.7%)	97.5% (96.0–98.5%)
Sensitivity		45.7% (34.6–57.1%)	54.3% (42.9–65.4%)	45.7% (34.6–57.1%)	25.8% (19.7–32.7%)	28.0% (21.6–35.0%)	22.6% (16.8–29.3%)
Positive Likelihood Ratio		3.8 (2.8–5.2)	18.3 (11.7–28.7)	16.1 (10.0–25.9)	2.1 (1.6–2.9)	12.5 (7.2–21.6)	8.9 (5.2–15.2)
Negative Likelihood Ratio		0.6 (0.5–0.8)	0.5 (0.4–0.6)	0.6 (0.5–0.7)	0.8 (0.8–0.9)	0.7 (0.7–0.8)	0.8 (0.7–0.9)
Positive Predictive Value		28.7% (22.9–35.3%)	65.7% (55.0–75.0%)	62.7% (51.1–73.0%)	37.2% (30.1–44.9%)	77.6% (66.6–85.7%)	71.2% (59.0–80.9%)
Negative Predictive Value		93.9% (92.7–95.0%)	95.3% (94.1–96.3%)	94.5% (93.3–95.4%)	81.0% (79.6–82.3%)	83.0% (81.7–84.2%)	81.9% (80.7–83.0%)

Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; 3C, common change criteria.

Table 3. Diagnostic parameters for the different analytical change criteria for MI and the composite outcome for the Ortho cTnI-ES assay.

ORTHO cTnI-ES	MI			Composite Outcome			
	Criteria	>20%	>4 ng/L	3C	>20%	>4 ng/L	3C
Specificity		42.3% (38.7–45.8%)	71.7% (68.4–74.9%)	95.9% (94.2–97.2%)	38.9% (35.2–42.7%)	71.8% (68.2–75.1%)	97.5% (96.0–98.5%)
Sensitivity		60.5% (49.0–71.2%)	79.0% (68.5–87.3%)	56.8% (45.3–67.8%)	46.8% (39.4–54.2%)	50.5% (43.1–57.9%)	29.6% (23.1–36.7%)
Positive Likelihood Ratio		1.0 (0.9–1.3)	2.8 (2.4–3.3)	13.7 (9.3–20.3)	0.8 (0.6–0.9)	1.8 (1.5–2.2)	11.6 (6.9–19.6)
Negative Likelihood Ratio		0.9 (0.7–1.2)	0.3 (0.2–0.4)	0.5 (0.4–0.6)	1.4 (1.2–1.6)	0.7 (0.6–0.8)	0.7 (0.7–0.8)
Positive Predictive Value		9.9% (8.3–11.7%)	22.6% (20.0–25.5%)	59.0% (49.4–68.0%)	17.5% (15.3–20.1%)	33.2% (29.2–37.5%)	76.4% (65.8–84.5%)
Negative Predictive Value		91.1% (88.5–93.1%)	97.0% (95.5–98.0%)	95.5% (94.3–96.5%)	72.4% (69.0–75.6%)	83.9% (81.7–85.9%)	83.3% (81.9–84.5%)

Abbreviations: cTnI, cardiac troponin I; MI, myocardial infarction; 3C, common change criteria.

Table 4. Diagnostic parameters for the different analytical change criteria for MI and the composite outcome for the Ortho hs-cTnI assay.

ORTHO hs-cTnI	MI			Composite Outcome			
	Criteria	>20%	>4 ng/L	3C	>20%	>4 ng/L	3C
Specificity		74.6% (71.3–77.6%)	93.9% (92.0–95.5%)	95.9% (94.2–97.2%)	75.0% (71.6–78.3%)	95.4% (93.5–96.8%)	96.6% (94.9–97.8%)
Sensitivity		59.3% (47.8–70.1%)	79.0% (68.5–87.3%)	56.8% (45.3–67.8%)	41.9% (34.8–49.4%)	43.0% (35.8–50.5%)	29.6% (23.1–36.7%)

Table 4. Cont.

ORTHO hs-cTnI	MI			Composite Outcome		
Positive Likelihood Ratio	2.3 (1.9–2.9)	13.0 (9.7–17.5)	13.7 (9.3–20.3)	1.7 (1.4–2.1)	9.3 (6.3–13.6)	8.6 (5.4–13.6)
Negative Likelihood Ratio	0.5 (0.4–0.7)	0.2 (0.1–0.3)	0.5 (0.4–0.6)	0.8 (0.7–0.9)	0.6 (0.5–0.7)	0.7 (0.7–0.8)
Positive Predictive Value	19.6% (16.4–23.2%)	57.7% (50.2–64.7%)	59.0% (49.4–68.0%)	31.8% (27.4–36.7%)	72.1% (63.8–79.1%)	70.5% (60.2–79.1%)
Negative Predictive Value	94.6% (93.1–95.8%)	97.7% (96.6–98.5%)	95.5% (94.3–96.5%)	82.3% (80.3–84.1%)	85.8% (84.1–87.2%)	83.1% (81.8–84.4%)

Abbreviations: hs-cTnI, high-sensitivity cardiac troponin I; MI, myocardial infarction; 3C, common change criteria.

For the composite outcome, the specificities for the 3C method were $\geq 95\%$, with the Ortho cTnI-ES assay diagnostic estimates exceeding the benchmarks for specificity (97.5%), PPV (76.4%), and PLR (11.6) (Table 3). The concordance between hs-cTnT and the other cTnI assays was substantial when the 3C method for change was used (i.e., 95% observed agreements) for MI (Table 5). The $>20\%$ criterion yielded the lowest kappa and percent agreements, with the highest observed PPV being 37.2% and PLR being 3.8 with the Roche hs-cTnT assay.

Table 5. Concordance between hs-cTnT (Roche) versus different cTnI assays for MI with the different analytical change criteria.

	Concordance Table								
	Roche and Abbott hs-cTnI			Roche and Ortho cTnI-ES			Roche and Ortho hs-cTnI		
	3C	Absolute Change	Percent Change	3C	Absolute Change	Percent Change	3C	Absolute Change	Percent Change
Kappa (95% CI)	0.671 (0.581–0.760)	0.704 (0.613–0.796)	0.256 (0.194–0.318)	0.659 (0.565–0.754)	0.234 (0.177–0.292)	0.124 (0.083–0.164)	0.659 (0.565–0.754)	0.564 (0.474–0.654)	0.260 (0.191–0.330)
Number of Observed Agreements (%)	810 (95%)	819 (96%)	600 (70%)	812 (95%)	621 (73%)	439 (51%)	812 (95%)	785 (92%)	633 (74%)

4. Discussion

The major finding of this study is the poor specificity for both MI and the composite outcome when using only the $>20\%$ change criterion. This contrasts with the newly derived Common Change Criteria (3C), where the specificities are similar across all assays and substantially higher (all $>90\%$) for MI and the composite cardiovascular adverse events outcome. Similar performances can be achieved when using the hs-cTn assays with the ESC absolute change criteria, which are assay dependent [6]. Here, the Ortho cTnI-ES assay (which is not a hs-cTn assay) achieves similar performance to the hs-cTn assays only when the 3C method to identify change is used. The findings from this study indicate that the common analytical change criteria may be applicable across all cTn assays. Additional strengths of our study are the prospective sample collection, health outcomes assessed, and measurements with four different cTn assays that have different analytical characteristics and interferences [26–28].

A few limitations are notable. First, there is a reasonable analytical and clinical agreement between the Abbott hs-cTnI assay and Abbott cTnI assay that was used clinically [11,29]. This, in part, could explain the high diagnostic performance when using the absolute change criterion for the Abbott hs-cTnI assay. Second, the ESC algorithms

and other pathways also incorporate a baseline value into the decision to rule-in MI in a patient [6,30]. The baseline level was used in the 3C method to select the appropriate change criterion and was not used alone to identify high-risk individuals. Third, the absolute cutoffs were used from the ESC 0/2 h algorithms, and our samples were collected 3 h apart. However, previous literature has suggested that early change criteria (i.e., 0/1 h or 0/2 h) can be applied to later sample draws (i.e., 0/3 h) with minimal impact on performance [18,31]. However, our study design would fall into the “late resampling” category with blood draws >120 to 210 min apart, and the performance for an “early resampling” (>45 to 120 min) protocol [30] using the 3C method would need to be evaluated. Fourth, longer-term cardiovascular outcomes using the 3C method were not assessed, and future studies should also evaluate if this change criteria can be used in convalescent settings following ACS for additional risk stratification [32,33]. Fifth, it is important to reiterate that the >20% criterion is recommended to distinguish acute from chronic myocardial injury, and the data from this study indicate that the application of this percent change across all concentration levels leads to lower specificity. However, the analytical change used in the 3C method finds support from recent studies assessing reference change values (RCV) for hs-cTn assays, where an RCV of 30% around the 99th percentile may be more suitable [34,35].

In conclusion, we have demonstrated that the Common Change Criteria (3C) method can yield similarly high specificity estimates for MI and an acute composite cardiovascular outcome which may be used rather than the relative >20% criterion or assay-specific absolute change values for samples that are collected 3 h apart. Additional evaluations and assessments of the 3C method for MI diagnosis in different and contemporary ACS populations with additional cardiac troponin assays are urgently needed to further demonstrate its generalizability.

Author Contributions: Conceptualization, P.A.K. and A.W.; methodology, P.A.K. and J.M.; software, P.A.K.; validation, P.A.K. and A.W.; formal analysis, P.A.K. and I.G.; investigation, P.A.K., S.S. and A.W.; resources, P.A.K. and M.M.; data curation, P.A.K.; writing—original draft preparation, P.A.K.; writing—review and editing, S.S., I.G., C.A., J.M., J.M., S.M., D.T.K. and A.W.; visualization, P.A.K.; supervision, P.A.K.; project administration, P.A.K. and A.W.; funding acquisition, P.A.K. and A.W. All authors have read and agreed to the published version of the manuscript.

Funding: For these secondary analyses, no additional funding was obtained with previous funding obtained via Canadian Institutes of Health Research, Abbott, Roche, and Ortho for performing testing in this study population.

Institutional Review Board Statement: Ethics approval was obtained by the Hamilton Integrated Research Ethics Board (REB# 13-277 and 2179). Patients were enrolled in NCT01994577 and agreed to follow up (REB#13-277).

Informed Consent Statement: Patients enrolled agreed to follow-up per Ethics approved studies (#13-277, 2179).

Data Availability Statement: The studies were conducted before data-sharing processes were in place, and thus individual data are not available. The data are not publicly available due to privacy.

Acknowledgments: Special thanks to the staff within the Clinical Research Laboratory and Biobank who performed the Ortho cTnI-ES and hs-cTnI testing.

Conflicts of Interest: P.A.K. has received grants/reagents/consultant/advisor/honoraria from Abbott Laboratories, Abbott Point of Care, Beckman Coulter, Ortho Clinical Diagnostics, Randox Laboratories, Roche Diagnostics, Quidel, Siemens Healthcare Diagnostics, and Thermo Fisher Scientific. McMaster University has filed patents with P.A.K. and A.W. listed as inventors in the acute cardiovascular biomarker field; in particular, a patent has been awarded in Europe on “A Laboratory Score for Risk Stratification for Patients with Possible Cardiac Injury”. No other disclosures were reported.

References

1. WHO. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. *Circulation* **1979**, *59*, 607–609. [[CrossRef](#)]
2. Alpert, J.S.; Thygesen, K.; Antman, E.; Bassand, J.-P. Myocardial infarction redefined—A consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction: The Joint European Society of Cardiology/ American College of Cardiology Committee. *J. Am. Coll. Cardiol.* **2000**, *36*, 959–969. [[CrossRef](#)] [[PubMed](#)]
3. Thygesen, K.; Alpert, J.S.; White, H.D.; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction; Jaffe, A.S.; Apple, F.S.; Galvani, M.; Katus, H.A.; Newby, L.K.; Ravkilde, J.; et al. Universal Definition of Myocardial Infarction. *Circulation* **2007**, *116*, 2634–2653. [[CrossRef](#)] [[PubMed](#)]
4. Thygesen, K.; Alpert, J.S.; Jaffe, A.S.; Simoons, M.L.; Chaitman, B.R.; White, H.D.; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction; Thygesen, K.; Alpert, J.S.; White, H.D.; et al. Third universal definition of myocardial infarction. *Eur. Heart J.* **2012**, *33*, 2551–2567. [[CrossRef](#)] [[PubMed](#)]
5. Thygesen, K.; Alpert, J.S.; Jaffe, A.S.; Chaitman, B.R.; Bax, J.J.; Morrow, D.A.; White, H.D.; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF). Task Force for the Universal Definition of Myocardial Infarction Fourth Universal Definition of Myocardial Infarction. *Circulation* **2018**, *138*, e618–e651. [[CrossRef](#)]
6. Collet, J.-P.; Thiele, H.; Barbato, E.; Barthélémy, O.; Bauersachs, J.; Bhatt, D.L.; Dendale, P.; Dorobantu, M.; Edvardsen, T.; Folliguet, T.; et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart J.* **2021**, *42*, 1289–1367. [[CrossRef](#)] [[PubMed](#)]
7. Jaffe, A.S.; Ravkilde, J.; Roberts, R.; Naslund, U.; Apple, F.S.; Galvani, M.; Katus, H. It's Time for a Change to a Troponin Standard. *Circulation* **2000**, *102*, 1216–1220. [[CrossRef](#)] [[PubMed](#)]
8. Kavsak, P.A.; MacRae, A.R.; Yerna, M.-J.; Jaffe, A.S. Analytic and Clinical Utility of a Next-Generation, Highly Sensitive Cardiac Troponin I Assay for Early Detection of Myocardial Injury. *Clin. Chem.* **2009**, *55*, 573–577. [[CrossRef](#)]
9. Giannitsis, E.; Kurz, K.; Hallermayer, K.; Jarausch, J.; Jaffe, A.S.; Katus, H.A. Analytical Validation of a High-Sensitivity Cardiac Troponin T Assay. *Clin. Chem.* **2010**, *56*, 254–261. [[CrossRef](#)]
10. Kavsak, P.A.; Ko, D.T.; Wang, X.; MacRae, A.R.; Jaffe, A.S. Increasing Cardiac Troponin Changes Measured by a Research High-Sensitivity Troponin I Assay: Absolute vs Percentage Changes and Long-Term Outcomes in a Chest Pain Cohort. *Clin. Chem.* **2010**, *56*, 1902–1904. [[CrossRef](#)]
11. Keller, T.; Zeller, T.; Ojeda, F.; Tzikas, S.; Lillpopp, L.; Sinning, C.; Wild, P.; Genth-Zotz, S.; Warnholtz, A.; Giannitsis, E.; et al. Serial Changes in Highly Sensitive Troponin I Assay and Early Diagnosis of Myocardial Infarction. *JAMA* **2011**, *306*, 2684–2693. [[CrossRef](#)]
12. Reichlin, T.; Irfan, A.; Twerenbold, R.; Reiter, M.; Hochholzer, W.; Burkhalter, H.; Bassetti, S.; Steuer, S.; Winkler, K.; Peter, F.; et al. Utility of Absolute and Relative Changes in Cardiac Troponin Concentrations in the Early Diagnosis of Acute Myocardial Infarction. *Circulation* **2011**, *124*, 136–145. [[CrossRef](#)] [[PubMed](#)]
13. Kavsak, P.A.; Clark, L.; Arnoldo, S.; Lou, A.; Shea, J.L.; Eintracht, S.; Lyon, A.W.; Bhayana, V.; Thorlacius, L.; Raizman, J.E.; et al. Analytic Result Variation for High-Sensitivity Cardiac Troponin: Interpretation and Consequences. *Can. J. Cardiol.* **2023**, *39*, 947–951. [[CrossRef](#)] [[PubMed](#)]
14. Kavsak, P.A. Lot-to-lot bias for high-sensitivity cardiac troponin I concentrations ≥ 1000 ng/L. *Clin. Chem. Lab. Med.* **2023**, *61*, e105–e107. [[CrossRef](#)] [[PubMed](#)]
15. Kavsak, P.A.; Worster, A.; Ma, J.; Shortt, C.; Clayton, N.; Sherbino, J.; Hill, S.A.; McQueen, M.; Mehta, S.R.; Devereaux, P.J. High-Sensitivity Cardiac Troponin Risk Cutoffs for Acute Cardiac Outcomes at Emergency Department Presentation. *Can. J. Cardiol.* **2017**, *33*, 898–903. [[CrossRef](#)]
16. Kavsak, P.A.; Neumann, J.T.; Cullen, L.; Than, M.; Shortt, C.; Greenslade, J.H.; Pickering, J.W.; Ojeda, F.; Ma, J.; Clayton, N.; et al. Clinical chemistry score versus high-sensitivity cardiac troponin I and T tests alone to identify patients at low or high risk for myocardial infarction or death at presentation to the emergency department. *Can. Med. Assoc. J.* **2018**, *190*, E974–E984. [[CrossRef](#)]
17. Kavsak, P.A.; Mondoux, S.E.; Sherbino, J.; Ma, J.; Clayton, N.; Hill, S.A.; McQueen, M.; Mehta, S.R.; Griffith, L.E.; Devereaux, P.; et al. Clinical evaluation of Ortho Clinical Diagnostics high-sensitivity cardiac Troponin I assay in patients with symptoms suggestive of acute coronary syndrome. *Clin. Biochem.* **2020**, *80*, 48–51. [[CrossRef](#)]
18. Kavsak, P.A.; Hewitt, M.K.; Mondoux, S.E.; Cerasuolo, J.O.; Ma, J.; Clayton, N.; McQueen, M.; Griffith, L.E.; Perez, R.; Seow, H.; et al. Diagnostic Performance of Serial High-Sensitivity Cardiac Troponin Measurements in the Emergency Setting. *J. Cardiovasc. Dev. Dis.* **2021**, *8*, 97. [[CrossRef](#)]
19. Kavsak, P.A.; Edge, T.; Roy, C.; Malinowski, P.; Bamford, K.; Clark, L.; Lamers, S.; Hill, S.; Worster, A. Analytical assessment of ortho clinical diagnostics high-sensitivity cardiac troponin I assay. *Clin. Chem. Lab. Med.* **2020**, *59*, 749–755. [[CrossRef](#)]
20. Collinson, P.O.; Saenger, A.K.; Apple, F.S.; IFCC C-CB. High sensitivity, contemporary and point-of-care cardiac troponin assays: Educational aids developed by the IFCC Committee on Clinical Application of Cardiac Bio-Markers. *Clin. Chem. Lab. Med.* **2019**, *57*, 623–632. [[CrossRef](#)]

21. Wildi, K.; Boeddinghaus, J.; Nestelberger, T.; Lopez-Ayala, P.; Sanchez, A.Y.; Okamura, B.; Shrestha, S.; Rohner, J.; Miró, Ò.; Martínez-Nadal, G.; et al. 0/2 h-algorithm for rapid triage of suspected myocardial infarction using a novel high-sensitivity cardiac troponin I assay. *Clin. Chem.* **2022**, *68*, 303–312. [[CrossRef](#)]
22. Kavsak, P.A.; Hulett, M.; Worster, A. Imprecision and Delta Criteria for a New ESC 0/2-Hour Algorithm. *Clin. Chem.* **2022**, *18*, 721–722. [[CrossRef](#)] [[PubMed](#)]
23. Kavsak, P.A.; Ko, D.T.; Wang, X.; MacRae, A.R.; Jaffe, A.S. 2007 Universal Myocardial Infarction Definition Change Criteria for Risk Stratification by Use of a High-Sensitivity Cardiac Troponin I Assay. *Clin. Chem.* **2010**, *56*, 487–489. [[CrossRef](#)]
24. Kavsak, P.A.; Cerasuolo, J.O.; Ko, D.T.; Ma, J.; Sherbino, J.; Mondoux, S.E.; Clayton, N.; Hill, S.A.; McQueen, M.; Griffith, L.E.; et al. Using the clinical chemistry score in the emergency department to detect adverse cardiac events: A diagnostic accuracy study. *CMAJ Open* **2020**, *8*, E676–E684. [[CrossRef](#)]
25. Than, M.P.; Pickering, J.W.; Sandoval, Y.; Shah, A.S.; Tsanas, A.; Apple, F.S.; Blankenberg, S.; Cullen, L.; Mueller, C.; Neumann, J.T.; et al. Machine Learning to Predict the Likelihood of Acute Myocardial Infarction. *Circulation* **2019**, *140*, 899–909. [[CrossRef](#)] [[PubMed](#)]
26. Kavsak, P.A.; Roy, C.; Malinowski, P.; Mark, C.-T.; Scott, T.; Clark, L.; Lamers, S.; Ainsworth, C. Macrocomplexes and discordant high-sensitivity cardiac troponin concentrations. *Ann. Clin. Biochem.* **2017**, *55*, 500–504. [[CrossRef](#)] [[PubMed](#)]
27. Kavsak, P.A.; Clark, L.; Martin, J.; Mark, C.-T.; Paré, G.; Mondoux, S.; Chetty, V.T.; Ainsworth, C.; Worster, A. Acute Phase Response and Non-Reproducible Elevated Concentrations with a High-Sensitivity Cardiac Troponin I Assay. *J. Clin. Med.* **2021**, *10*, 1014. [[CrossRef](#)]
28. Kavsak, P.A.; Mondoux, S.E.; Martin, J.; Hewitt, M.K.; Clark, L.; Caruso, N.; Mark, C.-T.; Chetty, V.T.; Ainsworth, C.; Worster, A. Disagreement between Cardiac Troponin Tests Yielding a Higher Incidence of Myocardial Injury in the Emergency Setting. *J. Cardiovasc. Dev. Dis.* **2021**, *8*, 31. [[CrossRef](#)] [[PubMed](#)]
29. Rezvanpour, A.; Shortt, C.; Clark, L.; Worster, A.; Kavsak, P.A. Analytical factors to consider when assessing a high-sensitivity cardiac troponin I assay compared to a contemporary assay in clinical studies. *Clin. Chim. Acta* **2014**, *429*, 6–7. [[CrossRef](#)]
30. Neumann, J.T.; Twerenbold, R.; Ojeda, F.; Sörensen, N.A.; Chapman, A.R.; Shah, A.S.; Anand, A.; Boeddinghaus, J.; Nestelberger, T.; Badertscher, P.; et al. Application of High-Sensitivity Troponin in Suspected Myocardial Infarction. *New Engl. J. Med.* **2019**, *380*, 2529–2540. [[CrossRef](#)]
31. Kavsak, P.A.; Mondoux, S.E.; Ma, J.; Sherbino, J.; Hill, S.A.; Clayton, N.; Mehta, S.R.; Griffith, L.E.; McQueen, M.; Devereaux, P.; et al. Comparison of two biomarker only algorithms for early risk stratification in patients with suspected acute coronary syndrome. *Int. J. Cardiol.* **2020**, *319*, 140–143. [[CrossRef](#)] [[PubMed](#)]
32. Adamson, P.D.; McAllister, D.; Pilbrow, A.; Pickering, J.W.; Poppe, K.; Shah, A.; Whalley, G.; Ellis, C.; Mills, N.L.; Newby, D.E.; et al. Convalescent troponin and cardiovascular death following acute coronary syndrome. *Heart* **2019**, *105*, 1717–1724. [[CrossRef](#)] [[PubMed](#)]
33. Kavsak, P.; Devereaux, P. High-sensitivity troponin testing months after an acute coronary syndrome: Noise or notable results. *Heart* **2019**, *105*, 1688–1690. [[CrossRef](#)]
34. Clerico, A.; Padoan, A.; Zaninotto, M.; Passino, C.; Plebani, M. Clinical relevance of biological variation of cardiac troponins. *Clin. Chem. Lab. Med.* **2020**, *59*, 641–652. [[CrossRef](#)]
35. Clerico, A.; Zaninotto, M.; Aimo, A.; Cardinale, D.M.; Dittadi, R.; Sandri, M.T.; Perrone, M.A.; Belloni, L.; Fortunato, A.; Trenti, T.; et al. Variability of cardiac troponin levels in normal subjects and in patients with cardiovascular diseases: Analytical considerations and clinical relevance. *Clin. Chem. Lab. Med.* **2023**, *61*, 1209–1229. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.