Letter to the Editor

Ziwen Li*, Yong Yong Tew, Peter A. Kavsak, Kristin M. Aakre, Allan S. Jaffe, Fred S. Apple, Paul O. Collinson and Nicholas L. Mills, on behalf of the High-STEACS Trial Investigators

Impact of high-sensitivity cardiac troponin I assay imprecision on the safety of a single-sample rule-out approach for myocardial infarction

https://doi.org/10.1515/cclm-2024-1011
Received August 29, 2024; accepted September 4, 2024;
published online September 20, 2024

Keywords: imprecision; high-sensitivity cardiac troponin; myocardial infarction; single-sample rule-out

To the Editor,

High-sensitivity cardiac troponin (hs-cTn) assays facilitate identification of low-risk patients for immediate discharge and thus may help reduce emergency department (ED) overcrowding. The HiSTORIC trial evaluated implementation of a single-sample rule-out pathway using a hs-cTnI assay in 31,492 consecutive patients [1]. Following implementation, length of stay was reduced by 3 h and discharge from the ED increased by 21 % with no evidence of adverse events [1]. However, assay imprecision at the low hs-cTn thresholds deployed in single-sample rule-out pathways could impact performance [2]. There is presently little guidance on the allowable imprecision at lower concentration thresholds [3]. Here we model the impact of imprecision on misclassification and therefore the safety of a single-sample rule-out strategy for myocardial infarction (MI).

In 48,282 consecutive patients with suspected acute coronary syndrome (median age 61 [interquartile range 49–75] years, 47 % female) evaluated using a hs-cTnI assay (ARCHITECT$_{STAT}$, Abbott Laboratories; Abbott Park, IL, USA) in the HighSTEACS trial [4], we simulated the effect of imprecision for a range of CVs at the rule-out threshold of <5 ng/L: 10 % (±0.5 ng/L), 20 % (±1 ng/L), 30 % (±1.5 ng/L), 40 % (±2 ng/L), 50 % (±2.5 ng/L), 60 % (±3 ng/L), 70 % (±3.5 ng/L), 80 % (±4 ng/L), 90 % (±4.5 ng/L), and 100 % (±5 ng/L). The *rnorm* function in R was used, setting the mean to the initial cTn concentrations at presentation (ground truth) and the standard deviation to the absolute change corresponding to each CV. The resulting concentrations were then rounded to the nearest whole numbers as used in clinical practice. To model the impact of imprecision, we repeated the simulation 100 times and estimated the proportion reclassified to higher risk (from <5 ng/L to ≥5 ng/L), to lower risk (from ≥5 ng/L to <5 ng/L), and overall, in patients with cTn concentrations below the 99th percentile at presentation. We subsequently calculated the likelihood of (i) a primary outcome of an adjudicated index diagnosis of type 1 MI, type 4b MI or type 4c MI and (ii) a secondary outcome of any myocardial injury on serial testing, in those potentially misclassified as low risk at presentation due to assay imprecision. The 95 % confidence intervals (95 % CI) were estimated using a binomial likelihood with an equal-tailed Jeffreys prior using the *binom. bayes* function in R.

Based on our simulations, the effect of assay imprecision on the proportion reclassified from low to higher risk, which

***Corresponding author: Dr. Ziwen Li**, PhD, BHF/University Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh EH16 4SA, Edinburgh, UK, E-mail: ziwen.cass.li@ed.ac.uk. https://orcid.org/0000-0002-1668-0229
Yong Yong Tew, BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK. https://orcid.org/0000-0002-5423-3630
Peter A. Kavsak, Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada. https://orcid.org/0000-0003-4576-4744
Kristin M. Aakre, Department of Medical Biochemistry and Pharmacology and Department of Heart Disease, Haukeland University Hospital, Bergen, Norway; and Department of Clinical Science, University of Bergen, Bergen, Norway. https://orcid.org/0000-0002-7340-6736
Allan S. Jaffe, Departments of Cardiology and Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. https://orcid.org/0000-0003-1183-3959
Fred S. Apple, Department of Laboratory Medicine and Pathology, Hennepin Healthcare/ HCMC, Minneapolis, MN, USA; Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA; and Cardiac Biomarkers Trials Laboratory, Hennepin Healthcare Research Institute, Minneapolis, MN, USA. https://orcid.org/0000-0002-5920-6498
Paul O. Collinson, St George's University of London, London, UK. https://orcid.org/0000-0002-7000-5996
Nicholas L. Mills, BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK; and Usher Institute, University of Edinburgh, Edinburgh, UK. https://orcid.org/0000-0003-0533-7991

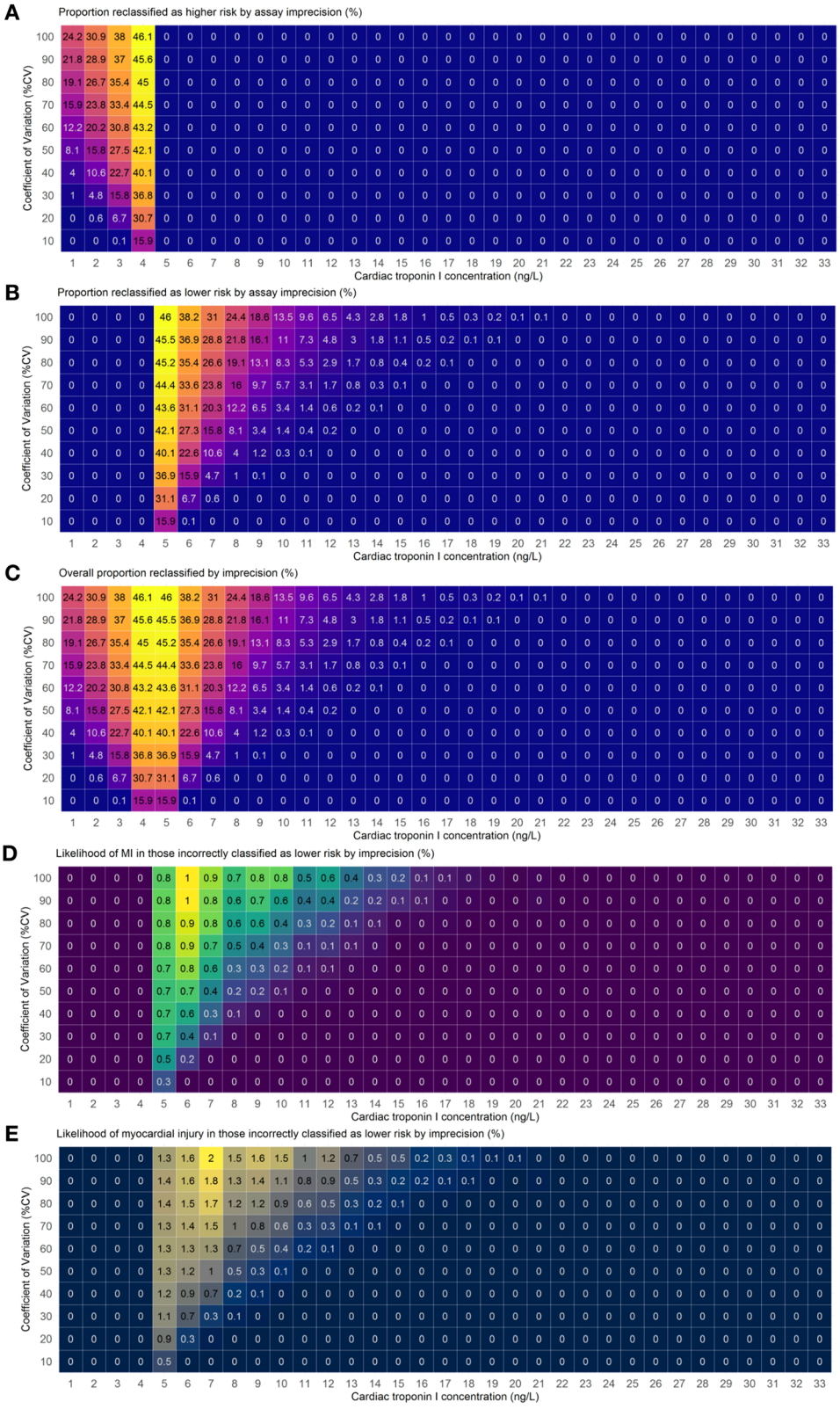

Figure 1: Estimated proportion of patients with suspected acute coronary syndrome reclassified due to hs-cTnI assay imprecision at the rule-out threshold of <5 ng/L and likelihood of MI or myocardial injury in those misclassified as a proportion of the total number of patients at each measured cardiac troponin concentration. (A) Proportion reclassified as higher risk by assay imprecision (%). (B) Proportion reclassified as lower risk by assay imprecision (%). (C) Overall proportion reclassified by imprecision (%). (D) Likelihood of MI in those incorrectly classified as lower risk by imprecision (%). (E) Likelihood of myocardial injury in those incorrectly classified as lower risk by imprecision (%). Patients with STEMI (n=925) were excluded from the modelling.

could result in unnecessary serial testing, increased as the CV and cTn concentrations increased from 1 to 4 ng/L (Figure 1). Similarly, the effect of assay imprecision on the proportion of reclassified from higher risk to low risk, which could result in harm, increased as the CV increased, and cTn concentrations decreased from 21 ng/L to 5 ng/L. Overall reclassification was depicted as a cone-shaped gradient. The likelihood of primary and secondary outcomes associated with reclassification from higher risk to low risk had a similar gradient.

For example, using an assay with a 10 % CV at the rule-out threshold of <5 ng/L, reclassification to low risk due to assay imprecision would occur in 15.9 % (95%CI 14.4%–17.5 %) and 0.1 % (95%CI 0%–0.4 %) patients with a measured cTn concentration of 5 ng/L and 6 ng/L, respectively (Table 1). The likelihood of having a MI in those reclassified due to imprecision who actually had a value of 5 ng/L when the measured concentration was<5 ng/L would be 0.3 % (95 %CI 0.1 %–0.5 %). Overall imprecision at this level would result in 0.01 % (95 %CI 0.01 %–0.03 %) of all patients evaluated being incorrectly classified as low risk who may have a missed index MI.

Whilst the proportion of patients reclassified due to hs-cTnI assay imprecision was high for all CVs evaluated, the likelihood of those misclassified having a missed diagnosis of MI due to assay imprecision was very low – just 1 in 10,000 patients tested if the CV is 10 % at the single-sample rule-out threshold of <5 ng/L. Our findings were consistent for the secondary outcome of any myocardial injury on serial testing. A recent study across 35 hospital laboratories in Canada showed that less than one-third of the laboratories achieved a ≤10 % CV at the very low cTn cut-offs recommended in clinical pathways, suggesting reclassification due to imprecision is common in practice [5]. Our study provides complimentary insights into the clinical implications of assay imprecision, suggesting that even with substantial reclassification when applying a single-sample rule-out threshold, the probability of an adverse outcome in the High-

Table 1: Estimated proportion of patients with suspected acute coronary syndrome misclassified due to hs-cTnI assay imprecision (coefficient of variation (CV) from 10 to 50 %) at the rule-out threshold of <5 ng/L and the proportion of all patients evaluated (n=47,357) with missed MI or myocardial injury due to imprecision.

CV	Measured hs-cTnI concentration, ng/L	Proportion misclassified as low risk by imprecision % (95 %CI)	Likelihood of MI in those reclassified % (95 %CI)	Proportion of all patients with missed MI due to imprecision % (95 %CI)	Likelihood of myocardial injury in those reclassified % (95 %CI)	Proportion of all patients with missed myocardial injury due to imprecision % (95 %CI)
10 %	5	15.9 (14.4–17.5)	0.3 (0.1–0.5)	0.01 (0.01–0.03)	0.5 (0.2–0.8)	0.02 (0.01–0.04)
	6	0.1 (0–0.4)	0 (0–0.2)		0 (0–0.2)	
20 %	5	31.1 (29.2–33.1)	0.5 (0.3–0.9)	0.03 (0.02–0.05)	0.9 (0.6–1.4)	0.05 (0.03–0.07)
	6	6.7 (5.5–8)	0.2 (0–0.5)		0.3 (0.1–0.6)	
	7	0.6 (0.3–1.2)	0 (0–0.2)		0 (0–0.3)	
30 %	5	36.9 (34.9–39)	0.7 (0.4–1.1)	0.05 (0.03–0.07)	1.1 (0.8–1.7)	0.08 (0.06–0.11)
	6	15.9 (14.2–17.7)	0.4 (0.2–0.8)		0.7 (0.3–1.2)	
	7	4.7 (3.6–5.9)	0.1 (0–0.5)		0.3 (0.1–0.7)	
	8	1 (0.5–1.7)	0 (0–0.3)		0.1 (0–0.4)	
	9	0.1 (0–0.6)	0 (0–0.3)		0 (0–0.3)	
40 %	5	40.1 (38–42.2)	0.7 (0.4–1.1)	0.06 (0.04–0.09)	1.2 (0.8–1.8)	0.11 (0.08–0.14)
	6	22.6 (20.6–24.7)	0.6 (0.3–1.1)		0.9 (0.5–1.5)	
	7	10.6 (9–12.5)	0.3 (0.1–0.7)		0.7 (0.3–1.2)	
	8	4 (3–5.3)	0.1 (0–0.4)		0.2 (0.1–0.7)	
	9	1.2 (0.6–2.1)	0 (0–0.4)		0.1 (0–0.5)	
	10	0.3 (0.1–0.9)	0 (0–0.4)		0 (0–0.4)	
	11	0.1 (0–0.6)	0 (0–0.4)		0 (0–0.4)	
50 %	5	42.1 (40–44.3)	0.7 (0.4–1.1)	0.08 (0.05–0.1)	1.3 (0.9–1.8)	0.14 (0.11–0.18)
	6	27.3 (25.1–29.5)	0.7 (0.4–1.2)		1.2 (0.7–1.8)	
	7	15.8 (13.9–17.9)	0.4 (0.2–0.9)		1 (0.5–1.7)	
	8	8.1 (6.6–9.8)	0.2 (0.1–0.6)		0.5 (0.2–1)	
	9	3.4 (2.4–4.8)	0.2 (0–0.6)		0.3 (0.1–0.9)	
	10	1.4 (0.7–2.5)	0.1 (0–0.5)		0.1 (0–0.7)	
	11	0.4 (0.1–1.1)	0 (0–0.4)		0 (0–0.5)	
	12	0.2 (0–0.8)	0 (0–0.5)		0 (0–0.5)	

STEACS trial as a consequence of misclassification is very low. Greater assay precision at these thresholds would reduce the likelihood of misclassification.

Acknowledgments: The authors thank the researchers from the Emergency Medicine Research Group Edinburgh and the British Heart Foundation Cardiovascular Biomarker Laboratory at the University of Edinburgh for their support during the conduct of the High-STEACS trial.

Research ethics: The study was approved by the Scotland A Research Ethics Committee, the Public Benefit and Privacy Panel for Health and Social Care, and by each National Health Service (NHS) Health Board.

Informed consent: Not applicable.

Author contributions: The corresponding author takes full responsibility that all authors on this publication have met the following required criteria of eligibility for authorship: (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. Nobody who qualifies for authorship has been omitted from the list. ZL, POC and NLM conceptualised the study. The High-STEACS Investigators acquired the data. ZL and NLM performed the analysis. ZL, POC, and NLM interpreted the data. ZL, POC and NLM drafted the manuscript. ZL, PAK, KMA, POC and NLM revised the manuscript for important intellectual content.

Competing interests: Dr Kavsak has received grants/reagents/consultant/advisor/ honoraria from Abbott Laboratories, Beckman Coulter, Ortho Clinical Diagnostics, Quidel, Randox Laboratories, Roche Diagnostics, Siemens Healthcare Diagnostics, and Thermo Fisher Scientific. McMaster University has the following patent with Dr Kavsak being a listed inventor "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 being a listed inventor. Dr Aakre has served on advisory boards for Roche Diagnostics, Siemens Healthineers and SpinChip, received consultant honoraria form CardiNor, lecturing honorarium from Siemens Healthineers, Mindray and Snibe Diagnostics, and research grants from Siemens Healthineers and Roche Diagnostics; she is Associate Editor of Clinical Biochemistry and Chair of the IFCC Committee of Clinical Application of Cardiac Bio-markers. Dr. Apple consults for Mindray, serves on advisory boards for Werfen and Abbott Vascular, is an Associate Editor at Clinical Chemistry, and has received research funding to Hennepin Healthcare Research Institute (non-salaried) from Abbott Diagnostics, Abbott POC, Beckman Dickenson, Beckman Coulter, Ortho-Clinical Diagnostics, Roche Diagnostics, Siemens Healthcare, Sysmex, and Quidel/Ortho. Dr Jaffe reports consulting for most of the major diagnostic companies. He also has an equity interest in RCE Technologies. Dr Collinson has consulted for Psyros, LumiraDx, Radiometer, Siemens Healthineers and QuidelOrtho and is Consultant to the IFCC Committee of Clinical Application of Cardiac Bio-markers. Dr Mills is supported by a Research Excellence Award (RE/24/130012) and a Chair Award (CH/F/21/90010) from the British Heart Foundation and reports honoraria or speaker fees from Abbott Diagnostics, Siemens Healthineers, Roche Diagnostics, LumiraDx, and Psyros Diagnostics over the last 3 years. The remaining authors have no conflicts of interest to disclose.

Research funding: This work was supported by a grant from the Canadian Institutes of Health Research (Kavsak), the British Heart Foundation through a Chair Award (CH/F/21/90010), a Programme Grant (RG/20/10/34966), and a Research Excellence Award (RE/24/130012; Mills). The funding organizations had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the final approval of the manuscript.

Data availability: Not applicable.

References

1. Anand A, Lee KK, Chapman AR, Ferry AV, Adamson PD, Strachan FE, et al. High-sensitivity cardiac troponin on presentation to rule out myocardial infarction: a stepped-wedge cluster randomized controlled trial. Circulation 2021;143:2214–24.
2. Pickering JW, Kavsak P, Christenson RH, Troughton RW, Pemberton CJ, Richards AM, et al. Determination of clinically acceptable analytical variation of cardiac troponin at decision thresholds. Clin Chem 2024;70:967–77.
3. Aakre KM, Apple FS, Mills NL, Meex SJR, Collinson PO, The International Federation of Clinical Chemistry Committee on Clinical Applications of Cardiac Biomarkers (IFCC C-CB). Lower limits for reporting high-sensitivity cardiac troponin assays and impact of analytical performance on patient misclassification. Clin Chem 2024;70:497–505.
4. Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet 2018;392:919–28.
5. Kavsak PA, Mills NL, Clark L, Ko DT, Sharif S, Chen-Tournoux A, et al. Assay precision and risk of misclassification at rule-out cutoffs for high-sensitivity cardiac troponin. Can J Cardiol 2024. https://doi.org/10.1016/j.cjca.2024.05.007.