

Letter to the Editor

Elena Aloisio*, Sara Pasqualetti, Alberto Dolci and Mauro Panteghini

Daily monitoring of a control material with a concentration near the limit of detection improves the measurement accuracy of highly sensitive troponin assays<https://doi.org/10.1515/cclm-2019-0702>

Received July 10, 2019; accepted August 5, 2019

Keywords: accuracy; cardiac troponin; myocardial infarction; quality control.

To the Editor,

Rapid rule-out of acute myocardial infarction (AMI) in chest pain patients presenting to the emergency department (ED) is central in assuring adequate triage and optimizing ED length of stay. ED physicians consider safe rule-out strategies with a negative predictive value >99% [1]. Several studies have demonstrated that this diagnostic performance can be reached with a single value of highly sensitive cardiac troponin (hs-cTn) at patient admission lower than the limit of detection (LOD) of the assay [2, 3]. Accordingly, the LOD has been recommended as the lowest reportable limit of troponin results [4]. Accurate calibration of hs-cTn assays in the low range of concentrations is therefore of the utmost importance for this application, as even relatively small analytical variations may influence the proportion of patients who could be identified as suitable for discharge, potentially leading to clinical misdiagnosis or mismanagement [5]. However, commercial internal quality control (IQC) materials usually do not cover such low concentrations, leaving the assay vulnerable to potential drifts that could remain unnoticed. There is evidence that drifts over time are associated with reagent and calibrator lot changes, platform to platform variability, and different schemes of instrument maintenance, as well as instrument decline and malfunctioning [6, 7]. With these considerations in mind, in March 2017 we elected to use a low concentration serum pool with a concentration near to the LOD of the hs-cTn T assay

as an additional IQC material (IQC3), besides commercial control materials, both to identify any possible drift in the assay calibration and to monitor assay performance near the assay LOD. Here, we evaluated the impact of this additional quality tool on the performance of our laboratory in the external quality assessment (EQA) program.

In our laboratory, we measure hs-cTn T on two interchangeable Cobas e411 platforms (Roche Diagnostics). Limit of blank and LOD of this assay are 3 and 5 ng/L, respectively [8]. For routine checking of the platform alignment, we run Roche PreciControl Troponin 1 and 2 materials (cat. no. 05095107190). IQC3 is prepared by pooling fresh leftover human sera at a final hs-cTn T concentration of approximately 5 ng/L, stored at -20°C in 250 μL aliquots. A sufficient amount of IQC3 is prepared to run it on our two instruments for approximately 2 months. Before the introduction in use of each IQC3 new batch, batch-specific target value and acceptability range are determined by calculating the mean $\pm 30\%$ of 10 preliminary measurements, performed after verification of optimal instrumental conditions. IQC3 is then routinely assayed, together with the regular two level PreciControl Troponin material provided by the manufacturer, twice daily and after every new calibration. If IQC results, including IQC3, are “out of control”, immediate corrective actions, such as recalibration or technical interventions, are undertaken before reports related to the patient samples analyzed in the affected run are issued and measurements repeated. Accuracy of our hs-cTn T measurements is evaluated by participation to the EQA for cardiac markers organized by the UK National External Quality Assessment Service. This monthly scheme consists of the assessment of four different samples and always includes a “low concentration sample” (LCS) with cardiac troponin concentrations lower than the 99th percentile limit of the reference distribution, obtained by spiking with troponin complex a serum sample from a healthy female. Lacking however the definitive demonstration of the commutability of this material, we evaluate our EQA results by comparing them with the mean value of the Roche 411 module group, i.e. participants using the same model instrument/reagents/calibrator from one manufacturer, and applying

*Corresponding author: Elena Aloisio, Clinical Pathology Unit, ASST Fatebenefratelli-Sacco, Via GB Grassi 74, 20157 Milan, Italy, Phone: +39 02 39042683, Fax: +39 02 39042896, E-mail: elena.aloisio@unimi.it

Sara Pasqualetti, Alberto Dolci and Mauro Panteghini: Clinical Pathology Unit, ASST Fatebenefratelli-Sacco, Milan, Italy

the recommendations made by the Australasian Association of Clinical Biochemists, who recommended a maximum total error (mTE) of $\pm 22.5\%$ [9].

Figure 1 shows EQA results obtained by measuring LCS before (February 2015–February 2017) and after (March 2017–April 2019) the introduction of IQC3 in our daily practice. In the first period, 10 results out of 25 performed LCS measurements (40%) did not meet mTE, while in the second period only one out of 26 results (3.8%) did not (Fisher exact test, $p = 0.002$ between the two periods). The measured hs-cTn T in the failed scheme (September 2018) was 9.1 ng/L vs. a peer group mean value of 7.2 ng/L, resulting in a total error of $+26.4\%$, relatively close to mTE.

This marked improvement in the accuracy was obtained while the imprecision performance of the measuring systems, evaluated as previously described on a hs-cTn T concentration around the 99th percentile limit of the reference distribution [10], was substantially unchanged (fiscal year 2015 vs. fiscal year 2018 cumulative CVs were 5.7% [mean hs-cTn T, 16.9 ng/L] vs. 5.7% [mean hs-cTn T, 16.1 ng/L], respectively).

Our results show an overall significant improvement in the accuracy of hs-cTn T measurements at low but clinically relevant concentrations of the analyte since the introduction of IQC3. This is vital in order to assure the correct differentiation, after a single hs-cTn measurement

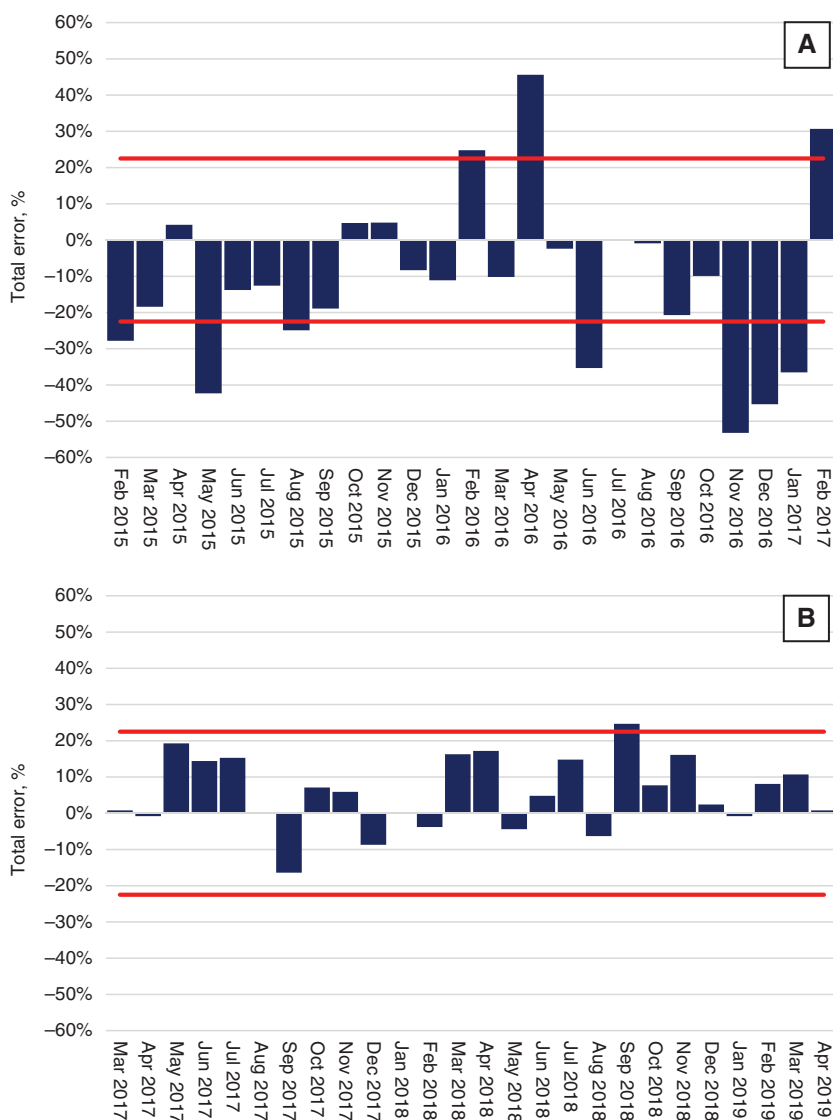


Figure 1: Results, expressed as total error in percentage, obtained by measuring “low concentration sample” of the UK National External Quality Assessment Service scheme before (A) and after (B) the introduction of the internal quality control material with a concentration near the limit of detection of hs-cTn T.

Red bars indicate the total error limits as recommended by the Australasian Association of Clinical Biochemists [9].

at ED admission, between patients with a negligible risk of cardiac adverse events who are potentially suitable for immediate discharge and those needing further evaluation in order to exclude/confirm AMI. It is widely accepted that concentrations of control materials should be chosen so that they reflect decision levels for a given analyte. Therefore, manufacturers of hs-cTn measuring systems should be encouraged to provide quality control materials that cover all the clinically relevant concentrations of the analyte, including those close to the LOD to monitor baseline drifts.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Than M, Herbert M, Flaws D, Cullen L, Hess E, Hollander JE, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department? A clinical survey. *Int J Cardiol* 2013;166:752–4.
2. Body R, Mueller C, Giannitsis E, Christ M, Ordonez-Llanos J, de Filippi CR, et al. The use of very low concentrations of high-sensitivity troponin T to rule out acute myocardial infarction using a single blood test. *Acad Emerg Med* 2016;23:1004–13.
3. Ferraro S, Dolci A, Panteghini M. Fast track protocols using highly sensitive troponin assays for ruling out and ruling in non-ST elevation acute coronary syndrome. *Clin Chem Lab Med* 2017;11:1683–9.
4. Wu AH, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, et al. 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.
5. Panteghini M. How clinical laboratories may improve their performance: the “high-sensitivity” troponin paradigm. *Clin Chem* 2018;64:621–3.
6. Kavsak PA, Don-Wauchope AC, Hill SA, Worster A. Acceptable analytical variation may exceed high sensitivity cardiac troponin I cutoffs in early rule-out and rule in acute myocardial infarction algorithms. *Clin Chem* 2016;62:887–9.
7. Kavsak PA, Worster A, Oliver R, Clark L, Parry D, Randell E, et al. Variability between reagent lots for high-sensitivity cardiac troponin I may affect performance of early rule out strategies. *Can J Cardiol* 2018;34:209.e5–6.
8. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chim Acta* 2011;412:748–54.
9. Panteghini M. Quality requirements for troponin assays – an overview. In: Troponin monograph 2012. The Australasian Association of Clinical Biochemists Inc., 2012:53–61.
10. Dolci A, Dominici R, Luraschi P, Panteghini M. 10% CV concentration for the fourth generation Roche cardiac troponin T assay derived from Internal Quality Control data. *Clin Chem Lab Med* 2006;44:1495–6.