Editorial

Karl J. Lackner

Cardiac biomarkers – 2019

https://doi.org/10.1515/cclm-2019-0205

Cardiac troponins (cTn) and natriuretic peptides are two examples of extremely successful novel laboratory tests introduced in the last three decades. In particular cTn have profoundly changed our understanding of acute coronary syndrome and myocardial infarction and *Clinical Chemistry and Laboratory Medicine* (*CCLM*) has regularly published articles on this topic including thematic issues [1]. In fact, cTn have become part of the universal definition of myocardial infarction [2]. Starting with the early assay formats for cTnI and cTnT there has been continuous improvement of the analytical performance of the assays. For the central laboratories this means shorter times for analysis and increased analytical sensitivity leading to lower limits of detection (LoD) and improved coefficients of variation (CV) in particular in the low concentration range. At the same time numerous assays for the point-of-care have been devised. While these assay formats permit even shorter times to results they still lag behind in terms of sensitivity and precision. This has led to a plethora of commercially available assays for cTn which are very difficult to oversee for professionals in the field. About 10 years ago, before the advent of the current high sensitive (hs) assays, Jill Tate, our esteemed colleague who died much too early last year, undertook the task to compile the analytical characteristics of the cTn assays available at that time [3]. She summarized the information on 14 assays for automated platforms (13 cTnI and one cTnT) as well as four point-of-care tests (3 cTnI and one cTnT). At that time no assay was available which met the 10% CV-recommendation at the 99th percentile of a healthy reference population. In this issue the IFCC Committee on Cardiac Biomarkers (IFCC C-CB) presents a novel compilation of the currently available cTn assays with their analytical and diagnostic performances [4]. An immediate conclusion which can be extracted from the tables is the poor status of harmonization not to mention standardization of hs-cTnI assays. It is very obvious that clinical decision limits currently depend on the assay used. As a consequence diagnostic algorithms for rapid rule-out and/or rule-in of myocardial infarction which have been developed in recent years are assay specific [5–9]. In fact, currently there are many attempts underway to develop novel algorithms for patients presenting with symptoms suggestive of acute coronary syndrome. These are based on single or consecutive troponin measurements combined with clinical data and will provide meaningful and robust negative and positive predictive values in order to improve diagnostic and therapeutic pathways. The 99th percentile will become less important with these algorithms. Not surprisingly several thousand well-characterized patients are required for these purposes. The plethora of different assays for cTn makes this a formidable endeavor and also requires clinicians to adapt to different diagnostic algorithms depending on the locally implemented assays. This underlines the need for further efforts to harmonize the different assays which should be possible in principle [10].

A second article by IFCC C-CB also deals with the cardiac markers but focusses on two interferences – one very old, i.e. hemolysis, and one very recently observed, i.e. biotin [11]. The third article analyzes the effects of sample matrix on cTn [12]. Hemolysis is probably not only one of the longest known interferences but also the most common. In particular, emergency room blood samples are prone to hemolysis. While most laboratories will know the effect of hemolysis on their own methods, the data compiled by the IFCC C-CB are of great value, if decisions on new instrumentation have to be made or interpretations of results from point-of-care analyzers are concerned. A still rare but increasingly observed interference is biotin. As high-dose biotin supplementation enjoys growing popularity among health-conscious individuals and high-dose biotin has been evaluated for treatment of multiple sclerosis, laboratorians must be aware of this novel interference which affects assays relying on the biotin-streptavidin interaction. As interference is in theory inverse between sandwich type (commonly used for proteins) and competitive (commonly used for small molecules and metabolites) immunoassays this problem has been particularly cumbersome in endocrinology. As assays for TSH and free T4 are inversely affected, biotin supplementation has falsely led to a diagnosis of hyperthyroidism in the past [13]. Data collected by Saenger et al. show that biotin interference with biotin-streptavidin-based assays may be highly variable depending on the

assay format. It should be noted that biotin serum concentrations well above 100 µg/L may be achieved in real life by therapeutic biotin administration or self-administration. Thus, it should be mandatory that concentrations up to the mg/L range are tested. Currently, there is no simple solution to this problem, because biotin leads to falsely low cTn concentrations in the affected assays. In a patient presenting with chest pain cTn concentrations within the reference range are commonly observed and are used to rule out myocardial infarction. Accordingly, different from endocrine disturbances it will be unlikely that this combination will raise immediate suspicion of a false negative cTn result. In my view the only practical solution will be to ask patients routinely for biotin supplementation if biotin sensitive assays are used.

The third article in this issue deals with the matrix issue [12]. In emergency settings most laboratories nowadays rely on plasma as the preferred material, because clotting of serum samples delays analysis unacceptably. Heparin plasma is probably most widely used but EDTA plasma is also an option, in particular because brain natriuretic peptide is usually determined from EDTA plasma. The authors show that the Siemens Advia Centaur hs-cTnI measures lower concentrations of cTnI in EDTA plasma than in heparin plasma. This is similar to previous data with the Access hs-cTnI assay [14]. It is very likely that this bias between the two matrices will affect decisions based on the upcoming algorithms.

Taken together, these articles impressively underscore the tremendous progress made with cardiac biomarkers in the last three decades but also remind us that there are still many issues that should and hopefully can be optimized in the future. In particular, the overview presented by Collinson et al. [4] should motivate all stakeholders to advance harmonization of cTn assays with undiminished effort.

Author contributions: The author has 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.

References

1. Lackner KJ. High-sensitivity assays for cardiac troponins. Clin Chem Lab Med 2015;53:631–3.
2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237–69.
3. Tate JR. Troponin revisited 2008: assay performance. Clin Chem Lab Med 2008;46:1489–500.
4. Collinson PO, Saenger AK, Apple FS, on behalf of the 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;57:623–32.
5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.
6. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. J Am Med Assoc 2011;306:2684–93.
7. Rubini Gimenez M, Twerenbold R, Jaeger C, Schindler C, Puelacher C, Wildi K, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am J Med 2015;128:861–70.
8. Neumann JT, Sorensen NA, Schwemer T, Ojeda F, Bourry R, Sciacca V, et al. Diagnosis of myocardial infarction using a high-sensitivity troponin I 1-hour algorithm. JAMA Cardiol 2016;1:397–404.
9. Chapman AR, Anand A, Boeddinghaus J, Ferry AV, Sandeman D, Adamson PD, et al. Comparison of the efficacy and safety of early rule-out pathways for acute myocardial infarction. Circulation 2017;135:1586–96.
10. 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.
11. Saenger AK, Jaffe AS, Body R, Collinson PO, Kavsak PA, Lam CS, et al. Cardiac troponin and natriuretic peptide analytical interferences from hemolysis and biotin: educational aids from the IFCC Committee on Cardiac Biomarkers (IFCC C-CB). Clin Chem Lab Med 2019;57:633–40.
12. Kavsak PA, Roy C, Malinowski P, Clark L, Lamers S, Bamford K, et al. Sample matrix and high-sensitivity cardiac troponin I assays. Clin Chem Lab Med 2019;57:745–51.
13. Piketty ML, Prie D, Sedel F, Bernard D, Hercend C, Chanson P, et al. High-dose biotin therapy leading to false biochemical endocrine profiles: validation of a simple method to overcome biotin interference. Clin Chem Lab Med 2017;55:817–25.
14. Kavsak PA, Malinowski P, Roy C, Clark L, Lamers S. Assessing matrix, interferences and comparability between the Abbott Diagnostics and the Beckman Coulter high-sensitivity cardiac troponin I assays. Clin Chem Lab Med 2018;56:1176–81.

Karl J. Lackner, Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Mainz, 55101 Mainz, Germany, Phone: +49 6131 177190, Fax: +49 6131 176627, E-mail: karl.lackner@unimedizin-mainz.de