High-sensitivity assays for cardiac troponins

Karl J. Lackner

This issue of Clinical Chemistry and Laboratory Medicine (CCLM) devotes a large section to the cardiac troponins (cTn) and in particular to the impact of the novel high sensitivity (hs) assays on clinical practice. Furthermore, several articles deal with known or novel pitfalls of hs-cTn in clinical diagnostics.

While there is no doubt that the hs-cTn assays constitute a significant analytical step forward, they obviously introduced a momentum of uncertainty for many clinicians. Perhaps this is common to all innovations which force people to leave their well known firm ground. In the case of hs-Tn the major changes relate to the rule-in and rule-out criteria of myocardial infarction. Already the first studies have provided robust data that early rule-out can be substantially improved and the ESC has adapted their guidelines accordingly [1–3]. However, many clinicians feel that rule-in has become more complicated not to say confusing. Since many of the traditional cTn assays had cut-offs far beyond the 99th percentile due to their relatively high limit of quantitation (LoQ) [4], the positive predictive value of an abnormal test result was high. In fact, it is important to keep in mind that the upper reference limit (URL) of most assays was not the 99th percentile but a significantly higher plasma concentration of cTn [4]. The novel hs-cTn assays provide reliable results between their 99th percentile and the cut-off of their predecessor tests [5]. This opens up a gray zone which was neglected in the past. Interpretation and clinical consequences derived from hs-cTn results in this gray zone are currently debated. For some but not all assays we have thorough data about positive and negative predictive values depending on individual patient characteristics and timing of cTn plasma concentrations [6]. Another issue that is profoundly influenced by the hs-cTn assays is the analysis of changes in cTn plasma concentrations over time and their diagnostic potential [7]. Many traditional cTn assays were not able to provide reliable time courses close to the 99th percentile. Therefore, the use of Δ-cTn generated with these assays was very limited. With the novel hs-cTn assays it is possible to reliably determine Δ-cTn even below the 99th percentile. However, the meaning of such changes is not clear and we will need more data from dedicated studies to interpret them [8–10].

In order to better appreciate these problems, it is helpful to remember the reasons for the new definition of myocardial infarction introduced in the year 2000 [11]. In the past we tended to differentiate between stable angina, unstable angina, and myocardial infarction. In the 1990s it became clear that patients with unstable angina with elevated cTn concentration had the same risk of adverse outcomes as patients with what was then considered myocardial infarction, while patients without cTn elevations had a much better prognosis [12]. Interestingly, this subgroup of unstable angina patients also benefited from the same interventions as patients with myocardial infarction [13]. This observation finally lead to the conclusion that unstable angina with a rise in cTn was in fact equivalent to myocardial infarction [11, 14]. One critical point here is the fact that the increase in cTn plasma concentration observed in these seminal clinical studies was usually far beyond the 99th percentile of the novel hs-cTn assays. Thus, it is still not clear whether the 99th percentile of the hs-cTn assays has the same clinical and prognostic meaning as the URL of the previous generations of cTn assays.

A completely novel question relates to the necessity of age- and sex-specific reference ranges. While it is obvious that cTn plasma concentrations measured by hs-cTn assays are higher in men than in women and in older individuals than in younger, it is by no means clear, whether the use of specific cut-offs would improve clinical diagnostics [15, 16]. However, the uncertainties go beyond this very obvious area. Many questions which had been addressed for the traditional cTn assays in the past need to be reanalyzed for the novel assays. One example is the interpretation of hs-cTn results in patients with impaired renal function. Firm evidence had accumulated that patients with severely reduced glomerular filtration rate and in particular patients on hemodialysis have increased plasma concentrations of cTn. While moderately elevated cTn beyond the URL in an individual renal patient was not necessarily diagnostic for myocardial infarction it was
clearly associated with a poorer cardiovascular prognosis [17, 18]. Currently, it is unknown whether this holds true with the hs-cTn assays [19]. In particular, it is also not clear, whether cTn concentrations within the reference range – also in individuals with normal renal function – may have prognostic implications. Data from large epidemiologic cohorts suggest that this may be the case [20].

Another issue relates to the question whether addition of other biomarkers may improve early diagnosis of myocardial infarction. While there was some evidence that some markers, e.g., copeptin and H-FABP improved early diagnosis and in particular early rule-out in the chest pain unit when combined with the traditional cTn assays, data with the novel hs-cTn assays are less clear [21]. Several studies show that copeptin can increase the sensitivity of laboratory testing on admission and therefore may permit very early rule-out.

Unfortunately, this increase in sensitivity is associated with a significant loss of specificity [22]. No study has yet been designed to analyze whether addition of copeptin to hs-cTn is superior to simply decreasing the cut-off of the hs-cTn assay. At least, post hoc analysis of the published ROC curves does not support superiority [23].

The hs-cTn assays also affect the role of point-of-care tests (POCT) for the diagnosis of myocardial infarction. Since most POCT have a lower analytical sensitivity, the question whether the shorter turn-around-time of such assays improves processes in chest-pain units has to be reevaluated. According to the current literature and ESC guidelines rapid rule-out of myocardial infarction within 3 h is only feasible with hs-cTn assays [3, 24].

And finally, the topic of standardization or harmonization of the assays is as urgent as it has been before the introduction of hs-cTn assays. In particular with hs-cTnI many different assays from different manufacturers are available. These assays have their specific reference ranges and cut-offs. Attempts to harmonize cTnI assays are underway, but pose a major challenge. Tate et al. report on the progress made by a working group of the IFCC [25].

The contributions of many researchers in the field assembled in this issue shall contribute to the ongoing discussion of the above mentioned topics. It will hopefully stimulate further clinical research to resolve the pertinent issues.

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References


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