Cardiac biomarkers in patients suspected of acute myocardial infarction: Where do we stand and where do we go?

Biomarqueurs chez les patients suspects d’infarctus du myocarde; où sommes-nous et dans quelle direction aller?

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One year ago, in this journal, I questioned whether by using the actual biomarker (mainly sensitive cardiac troponin [cTn] assays) we were close to reaching the Holy Grail \cite{1} — and I thought we were. In fact, major advances in the field of biomarkers have occurred in the past few years: cTn assays have been refined, making it possible to measure and quantify small cardiomyocyte injury and to determine the 99th percentile of a reference population with high precision. Everyone was, therefore, able to conform to the third universal definition of acute myocardial infarction (AMI) \cite{2}. In addition, evidence existed that the use of sensitive cTn assays instead of contemporary assays improved the detection of patients with AMI \cite{3}, and that the change in the management of these patients facilitated by these sensitive assays made a clinically significant difference \cite{4}.

Instead of there being a rapid and broad consensus about the use of these sensitive or high-sensitivity cTn assays (hs-cTn), and an optimal protocol to recommend, important uncertainties were raised about their clinical value, the threshold value to use in routine practice, the optimal timing of serial measurements, and the possible need for a refinement of our classification of acute coronary syndrome. These questions are not yet fully resolved and some experts are already recommending that we rely on a combination of biomarkers.

\textbf{KEYWORDS}
Troponin; Copeptin; Biomarker; Acute myocardial infarction

\textbf{MOTS CLÉS}
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Abbreviations: AMI, acute myocardial infarction; cTn, cardiac troponin; hs-cTn, high-sensitivity cTn.
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While most cTn assays used in Europe are sensitive or high-sensitivity (hs-cTn) assays, conventional cTn assays are still in use in the USA. Although the European Society of Cardiology, the American Heart Association and the American College of Cardiology have endorsed the third universal definition of acute myocardial infarction (AMI), many institutions and physicians continue to use higher cut-off values for cTn than the 99th percentile, arguing that the 99th percentile has very low specificity, especially in the elderly. This is correct, but I also think that encouraging such an attitude is of major concern, as it will inevitably lower the performance of the assay and possibly harm patients [5,6]. As the 99th percentile has been recently confirmed in large studies of unselected patients as the optimal threshold value, whatever the time from onset of chest pain to presentation [7], it ought to be used. However, the 99th percentile might be slightly different (more elevated) in some very specific populations. At least two studies focused on elderly patients, and suggested that the 99th percentile may be higher in this group than in a generally younger population; this is particularly relevant for patients aged over 80 years [8,9]. In a recent study, our group reported that advanced age was more related to hs-cTn concentrations than to renal failure [8], but this study excluded patients with end-stage renal failure. One should, however, keep in mind that using too low a cut-off value will not alter the rule-out procedure, but will only reinforce the need for a second measurement, and that the presence/absence of a significant rise/fall will help to differentiate AMI from other causes of chest pain [10].

I assume that we will progressively rely more and more on biomarkers, without omitting clinical evaluation and the electrocardiogram to estimate the pretest probability. A good goal might be not only to rule out AMI but also to be able to rule out any severe cardiac conditions. To optimize cost and resources, we should move to new algorithms that allow both a rule-out and a rule-in decision. Whether we will be able to draw a conclusion using a single marker measured twice or will need to measure a combination of biomarkers is unknown as yet. Reichlin et al. [11] suggested the first hypothesis, as they demonstrated the ability to solve the problem adequately using a 1-hour protocol. This is very encouraging, but needs confirmation; their results have just been confirmed by the High-Sensitivity Cardiac Troponin T Assay for Rapid Rule Out of Acute Myocardial Infarction (TRAPID-AMI) study [12].

Measuring a second biomarker that reflects cardiomyocyte damage, endogenous stress or even plaque rupture might be very challenging. Recent studies have demonstrated that markers of plaque rupture and/or inflammation are not helpful when added to the actual standard of care [13]. Thus, copeptin is the marker that provides most hope today. Copeptin is a marker of endogenous stress, and previous studies have demonstrated that endogenous stress and myocyte damage/necrosis are reciprocal. The Biomarkers in Cardiology-8 (BIC-8) study was a randomized study that demonstrated that a combination of cTn and copeptin measured at presentation was not inferior to cTn alone (but measured twice), and allowed more patients to be discharged safely [14]. This study had important limitations, including a lower than anticipated number of observed events and the combination of conventional and hs-cTn assays. While being very meaningful, the results of this study have to be confirmed in a dedicated study that uses the actual optimal standard of care (i.e. hs-cTn assays).

Lastly, but importantly, will these new markers/protocols force us to refine our classification of acute coronary syndrome, and should this limit their broad use? From a theoretical point of view, the condition named unstable angina may not disappear. However, the new hs-cTn assays allow the reclassification of patients who were previously classified as having unstable angina to AMI [15]. These sensitive assays also allow the identification of three categories of patients with acute chest pain: those at high risk of events during a short follow-up period (patients with AMI); those at very low risk (patients in a stable condition, possibly with chronic angina); and those at low risk during a short follow-up period, but at higher risk if the follow-up period is prolonged [16]. Whether we should go on labelling these conditions as unstable angina is unknown as yet. However, the possible refinement of the old classification should not lead to a reluctance to use the new definitions.

To conclude, sensitive cTn assays carried out at presentation and repeated after 3 hours are the actual standard of care, and their use (including the 99th percentile as the cut-off value) has to be encouraged. More rapid protocols will emerge soon, and will be the strategies of the future—with or without the additional use of copeptin. Whether we will have to consider a specific cut-off value for very elderly patients remains unknown.

Disclosure of interest

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References

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