Early diagnosis of myocardial infarction

Michael Marber
Department of Cardiology, Cardiovascular Division KCL, The Rayne Institute, St Thomas' Hospital, London, UK

Correspondence: Professor Michael Marber, Department of Cardiology, Cardiovascular Division KCL, The Rayne Institute, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK.
Tel: +44 20 7188 1008; fax: +44 20 7188 0970;
e-mail: mike.marber@kcl.ac.uk

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Early diagnosis of myocardial infarction with sensitive cardiac troponin* assays

Reichlin T, Hochholzer W, Bassetti S, et al. *N Engl J Med*. 2009;361:858–867.

The rapid and reliable diagnosis of acute myocardial infarction is a major unmet clinical need. We conducted a multicenter study to examine the diagnostic accuracy of new, sensitive cardiac troponin assays performed on blood samples obtained in the emergency department from 718 consecutive patients who presented with symptoms suggestive of acute myocardial infarction. Cardiac troponin concentrations were determined in a blinded fashion with the use of four sensitive assays (Abbott-Architect Troponin I, Roche High-Sensitive Troponin T, Roche Troponin I, and Siemens Troponin I Ultra) and a standard assay (Roche Troponin T). The final diagnosis was adjudicated by two independent cardiologists. Acute myocardial infarction was the adjudicated final diagnosis in 123 patients (17%). The diagnostic accuracy of measurements obtained at presentation, as quantified by the area under the receiver operating characteristic curve (AUC), was significantly greater with the four sensitive cardiac troponin assays than with the standard assay (AUC values: Abbott-Architect Troponin I, 0.96, 95% confidence interval [CI] 0.94 to 0.98; Roche High-Sensitive Troponin T, 0.96, 95% CI 0.94 to 0.98; Roche Troponin I, 0.95, 95% CI 0.92 to 0.97; Siemens Troponin I Ultra, 0.96, 95% CI 0.94 to 0.98; standard assay, 0.90, 95% CI 0.86 to 0.94). Among patients who presented within 3 h after the onset of chest pain, the AUCs were 0.93 (95% CI 0.88 to 0.99), 0.92 (95% CI 0.87 to 0.97), 0.92 (95% CI 0.86 to 0.99), and 0.94 (95% CI 0.90 to 0.98) for the sensitive assays, respectively, and 0.76 (95% CI 0.64 to 0.88) for the standard assay. We did not assess the effect of the sensitive troponin assays on clinical management. We conclude that the diagnostic performance of sensitive cardiac troponin assays is excellent, and that these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain. (ClinicalTrials.gov number, NCT00470587.)

Sensitive troponin I assay in early diagnosis of acute myocardial infarction

Keller T, Zeller T, Peetz D, et al. *N Engl J Med*. 2009;361:868–877.

Cardiac troponin testing is central to the diagnosis of acute myocardial infarction. We evaluated a sensitive troponin I assay for the early diagnosis and risk stratification of myocardial infarction. In a multicenter study, we determined concentrations of troponin I as assessed by a sensitive assay, troponin T, and traditional myocardial necrosis markers in 1818 consecutive patients with suspected acute myocardial infarction, on admission to hospital and 3 h and 6 h after admission. For samples obtained at the time of admission, the diagnostic accuracy was greatest with the sensitive troponin I assay (area under the receiver operating characteristic curve [AUC] 0.96), as compared with the troponin T assay (AUC 0.85) and traditional myocardial necrosis markers. With the use of the sensitive troponin I assay (cutoff value 0.04 ng/mL) on admission, the clinical sensitivity was 90.7% and the specificity was 90.2%. The diagnostic accuracy was virtually identical in baseline

and serial samples, regardless of the time of onset of chest pain. In patients presenting within 3 h after the onset of chest pain, a single sensitive troponin I assay had a negative predictive value of 84.1% and a positive predictive value of 86.7%; these findings predicted a 30% increase in the troponin I concentration within 6 h. A troponin I concentration of more than 0.04 ng/mL was independently associated with an increased risk of an adverse outcome at 30 days (hazard ratio 1.96; 95% confidence interval 1.27 to 3.05; $P = 0.003$). We conclude that the use of a sensitive assay for troponin I improves early diagnosis of acute myocardial infarction and risk stratification, regardless of the time of onset of chest pain.

Commentary

By coincidence, two very similar studies appear in this issue of the *New England Journal of Medicine*. Although the design of these studies differs, their conclusions are remarkably similar and consistent, and should have a significant impact on the way we use troponins to diagnose early acute myocardial infarction (AMI).

Troponins I, C, and T form a complex that regulates the interaction between myosin and actin in response to calcium. These proteins are embedded in the sarcomere, although there maybe a small cytosolic pool. Hence, compared with the release of cytoplasmic proteins traditionally used to mark myocardial infarction (creatine kinase, creatine kinase myocardial band [CK-MB], lactate dehydrogenase, and myoglobin), that of troponin is delayed, with a peak between 10 and 18 h after the onset of chest pain. However, the cardiac-specific expression of particular isoforms of troponins I and T confers such a significant advantage as markers that they have largely usurped creatine kinase and myoglobin, which are expressed more ubiquitously. Thus, since the late 1990 s, with the revised definition of myocardial infarction, the advantage of troponins as biomarkers of myocardial infarction has become widely acknowledged. The cutoffs we use clinically as our lower limit of normal for troponins are the result of a combination of early studies comparing troponins with CK-MB and of early assays that did not perform well at their lower limits of detection, having relatively high coefficients of variation. Since their clinical introduction, the commercial assay for troponin T and the various assays for troponin I have evolved through a number of generations. Consequently, the currently available assays have much lower coefficients of variation when measuring troponins in the sub-0.1 ng/mL range. This lower coefficient of variation allows the upper limit of the normal range to be set at the 99th centile of a reference ''normal'' population.

In the study by Reichlin et al, a number of the new ultrasensitive assays for troponins I and one for troponin T were compared with the standard assay for troponin T; in the study by Keller et al, only one vendor's assay for troponin I was compared with the standard assay from troponin T. In combination, the conclusions of the two studies are very clear, and they demonstrate that the newer assays perform well and hence are capable of reliably identifying the release of troponin at earlier timepoints after the onset of chest pain than is possible with the standard assay. This is likely to have a number of consequences for clinical practice.

The ability of the new assays to detect troponins reliably at an early point in their profile of temporal release should enable a more prompt ''rule out'' of AMI and reduce the needless waiting and overnight admissions that currently occur for many low-risk patients. In my view, this is likely to be their main benefit. Conversely, the earlier ''rule in'' of AMI will enable more prompt treatment of patients. However, by and large, these earlier diagnosed AMIs will be non ST-segment elevation myocardial infarctions, and towards the lower end of the risk spectrum where the benefits of early intervention are less clear. Perhaps the most daunting consequence of these new assays is their reduced specificity, which comes as an almost inevitable consequence of their greater sensitivity. The reduced specificity and greater false ''rule in'' rate of AMI are best illustrated in the study by Reichlin et al, in which the positive predictive value of the new assays was as low as 50%. What this actually means in real terms is complex. In both studies, AMI was defined by expert cardiologists and there were insufficient numbers of patients to analyze clinical outcome. It is quite possible that a patient in whom troponin release is detected using the new sensitive assays does not meet the clinical threshold for AMI but nevertheless has sustained cardiac damage and could be at increased risk of subsequent events. Moreover, this could still be the case when the coronary arteries appear angiographically normal. These new assays are likely to increase the prevalence of this group of patients with an indeterminate diagnosis or the default diagnosis of myocarditis.

Unfortunately, the amount of myocardial damage required to increased troponins above the 99th centile of a reference population is probably of too low a volume to be detected by magnetic resonance imaging with late gadolinium enhancement, unless the pathology is current or repetitive. Thus, for patients with detectable release of troponin, the benefit of these sensitive assays over those traditionally available is unclear. Furthermore, even if outcome studies confirm that low levels of troponin release confer a decrement in prognosis, it will be some time before intervention studies clarify the management of these patients.

Summary

These studies illustrate that we have a new tool with which reliably to exclude AMI as early as 3 h after the onset of chest pain. However, in those patients with normal hearts in whom low-level release occurs, we will have an increasing clinical dilemma and associated cost of investigation.

* see glossary for definition of this term.