Creatine Kinase–MB

The Journey to Obsolescence

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ABSTRACT

Objectives: To evaluate the clinical utility of and demand for the creatine kinase (CK)–MB assay.

Methods: We examined the number of CK-MB tests from 2007 through 2013 while we progressively deemphasized their use. We first removed CK-MB from the acute coronary syndrome (ACS) panel and then from the main menu and observed the demand for the test. We also reviewed patient medical records to assess the appropriateness of its use.

Results: After removing CK-MB from the ACS panel, the test volume dropped from around 12,000 per year to about 150 per year. In reviewing the records of 171 patients who had CK-MB determination done over a 28-month period, we discovered that CK-MB contributed to the diagnosis in only one patient, although it was not essential. Since removing CK-MB from the laboratory menu, two CK-MB tests were ordered in 4 months, and neither added value.

Conclusions: CK-MB determinations do not add value to information available from the troponin assay and can be safely removed from the laboratory menu.

Laboratory tests for the diagnosis of myocardial injury in general, and myocardial infarction (MI)/acute coronary syndrome (ACS) in particular, have been and still are in the process of evolving. Serum aspartate aminotransferase (AST), creatine kinase (CK), and lactic dehydrogenase, including isotypes of the latter, were used for diagnosis and served the purpose when no active interventions were taken for the treatment of ACS.1 Serum assay for myoglobin provides an early indication of ACS but has a large number of false positives and is not in common use.2 Introduction of the CK-MB assay provided a major advance in the early diagnosis of MI or ruling out MI. The test is a two-step process requiring determination of total CK and measurement of the MB fraction. An assay for the MB fraction has progressed to an immunoassay and does not require physical subfractionation of CK.3

Introduction of assays for troponins T and I has allowed slightly earlier diagnosis of ACS and improved the sensitivity over CK-MB. Some laboratories have stopped offering CK-MB in the workup of ACS.4,5 The search for better markers and panels of markers for myocardial injury is continuing.5-8

Just as there is a lag in introducing new tests and treatments even after the utility of the same has been demonstrated, there is a lag in discontinuing outdated tests and treatments. For example, bleeding time and erythrocyte sedimentation rate continue to be offered and used in some institutions. Experts have recommended discontinuing CK-MB testing for the diagnosis of MI.4,9 It appears that testing for CK-MB has reached obsolescence, and we present our experience in the journey of the change in CK-MB testing.
Materials and Methods

In 2009, the Cardiology Division of the internal medicine and pathology and laboratory medicine departments came to the agreement that, given the routine availability of an assay for troponin I, CK-MB testing was no longer needed for the workup of ACS. CK-MB was removed from the panel ordered routinely for patients with ACS, although the test was available as a stand-alone assay. Later in the same year, due to problems with the troponin I assay, the vendor withdrew the test from the market. During this process, CK-MB was reintroduced while we switched to a different vendor for the troponin assay, and the changeover was fully effective in August 2010, with CK-MB again removed from the ACS panel. However, CK-MB remained on the menu as a stand-alone test until May 10, 2013.

After noting the marked decline in CK-MB test volume, the pathology and laboratory medicine and cardiology departments jointly undertook a review of the medical records of the 171 patients who had CK-MB determinations done from January 1, 2011, through April 30, 2013. The pathology and laboratory medicine department conducted a primary review of all cases, and 10% of the randomly selected cases were audited by the cardiology department. Following discussion with other laboratory medicine departments in town and consultation with the cardiology department, the pathology and laboratory medicine department decided to remove CK-MB from the laboratory menu on May 10, 2013, but it could be ordered as a miscellaneous test.

The review of medical records was geared toward establishing the contribution of CK-MB test results in the diagnosis, treatment, and follow-up of patients, irrespective of the initial diagnosis. For each instance of the CK-MB test from January 1, 2011, through April 30, 2013, we reviewed the clinical presentation, problem list, differential diagnoses, results of electrocardiography, other laboratory test results (including troponin), treatments given, discharge diagnoses, and results of follow-up visits if any. Any discordance between CK-MB and troponin results was scrutinized for an explanation (eg, renal insufficiency, prior ACS, time since onset of symptoms, and results of additional tests during the same encounter). Physician notes were reviewed for comments about the laboratory test results in general and reference to the diagnosis of ACS in particular. Cardiology notes were analyzed for the contribution of laboratory test results in the diagnosis and implications for additional tests and treatments (eg, stress testing, angiography, or acute intervention).

We also examined the number of participants in the College of American Pathologists (CAP) proficiency testing (PT) survey in 2013—namely, the 2013 CAR-B. The number of participants in the CK-MB and troponin challenges was compared to assess the prevalence of CK-MB testing laboratories participating in the CAP PT program and differences in the number of laboratories participating in CK-MB and troponin challenges.

This study was conducted at a two-campus medical center in the Midwestern United States with about 520 beds. The main campus, a level 1 trauma center in the inner city, provides interventional cardiology services but does not perform open heart surgery. The medical center is affiliated with a medical school and serves as the primary teaching hospital for the school. The second campus, located in a suburb, provides mainly family medicine and long-term care services.

The Institutional Review Board of the University of Missouri–Kansas City and Privacy Board of Truman Medical Centers approved the study.

Results

When CK-MB was routinely a part of the ACS panel for laboratory tests, the yearly volume was about 12,000 tests, as shown in Figure 1, for 2007 and 2008. The volumes for 2009 and 2010 were lower but did not fully reflect the change, as CK-MB was reintroduced for parts of these years. The test volumes in 2011, 2012, and the first 4 months of 2013 were 113, 90, and 16 patient (billable) tests, respectively. These numbers are patient tests and do not include PT volume. The number of patients tested during these time frames was 92, 68, and 11, respectively. Despite the low volumes in 2011 onward, the laboratory continued to perform daily quality control and related procedures to ensure ready availability of the test in Table 1. The total number of tests, including PT, done in 2011, 2012, and the first 4 months of 2013 was 143, 159, and 36, respectively.

The creatine kinase (CK)–MB test volume from 2007 through 2013. The numbers for 2013 are extrapolated from the first 4 months. CK-MB was not on the acute coronary syndrome (ACS) panel for portions of 2009 and 2010 and not on the ACS panel in 2011 through 2013.
From January 1, 2011, through April 30, 2013, there were 16 instances in which the CK-MB test was done without any concurrent troponin testing. Thirteen of these 16 tests were ordered by an outreach clinic, ostensibly for the diagnosis of fibromyalgia. One patient was tested following coronary artery bypass grafting (performed at another hospital), and the reason for the CK-MB test could not be ascertained in the other two orders.

The review of medical records of the 171 patients revealed only one patient in whom the CK-MB test provided supporting information. This patient was seen in the emergency department, having been discharged 2 days earlier with a diagnosis of MI (and appropriate treatment). She had chest pain and elevated troponin levels, although the levels were lower than the values noted at discharge. The consultant cardiologist concluded that the troponin levels were consistent with resolving MI and did not comment on the CK-MB values. CK-MB was not elevated and thus could have contributed toward excluding a new MI, although troponin levels were considered sufficient for excluding a new MI or extension of an old MI. CK-MB values did not provide any additional information in the remaining 170 patients.

To ascertain the extent to which laboratories accredited by the CAP may have discontinued CK-MB testing, we examined the number of participants in the CAP PT program for cardiac markers in the 2013 CAR-B challenge. It was our assumption that the laboratories that would have discontinued performing CK-MB testing in-house would no longer be participating in the CK-MB PT program. For the 2013 CAR-B survey, there were 1,995 participants in the troponin I and T PT program and 1,558 participants in the CK-MB PT program. Thus, it would appear that around one-fourth (23%) of the laboratories have discontinued CK-MB testing as part of the cardiac testing menu, although, as discussed later, this figure may be an overestimate.

**Discussion**

CK-MB was a revolutionary test when introduced and served an important role in facilitating the diagnosis of MI. However, like many other tests, it has reached the end of its useful life and needs to be retired along with other tests, such as bleeding time, erythrocyte sedimentation rate, hemosiderin cells in urine, and prostatic acid phosphatase.10,11

Troponins T and I are more cardiac specific than CK-MB and have been shown to be sensitive and specific markers for myocardial injury in general and ACS in particular.12-15 Immunoassays for troponin have been adapted for point-of-care testing and have been deployed in emergency departments; however, given that even the point-of-care test is of moderate complexity, not all institutions have adopted this strategy.16 Serial testing is still done optimally in the main laboratory. The analytical process for troponins is still evolving, and methods are becoming more sensitive.13 On the other hand, assays from different vendors produce different results, and there is little likelihood of harmonization in the near future.12

The logistics of discontinuing a test are neither simple nor painless and require not only reviewing the relevant literature but also presenting the local data to the local stakeholders, who may have different perceptions about the value of a given laboratory test. The process of removing CK-MB from the routine ACS panel was facilitated by the close collaboration between the cardiology and pathology departments at the outset and by including the emergency medicine department early in the deliberations. This close collaboration also muted any reaction that may have occurred in response to the problems with the troponin assay soon after the change was implemented. When we proposed removing CK-MB from the routine menu, the suggestion was met with fierce response from one of the campuses. However, at the suggestion of the chief medical officer, the pathology department presented the data from the literature as well as utilization data from the particular campus to the medical staff of the hospital, and the opposition to the proposal dissipated, to the credit of the medical leadership of the campus. However, these events highlight the importance of close collaboration with clinical colleagues, gathering of local usage data, proactive discussions with medical staff, and engagement with medical leadership for implementing any change to an existing paradigm.

From the disparity in the number of laboratories participating in the CAP PT survey for troponins and CK-MB, it appears that around 23% of the laboratories are performing only troponin assays and not CK-MB. It is understood that the apparently higher number of laboratories participating in troponin PT may reflect PT for point-of-care testing sites, and the 23% gap may overestimate the number of laboratories that may have discontinued CK-MB for ACS testing. We understand that not all laboratories participate in the CAP PT program, and the data may not reflect the true prevalence of CK-MB testing laboratories in the United States. However, it is worth noting that a large number of laboratories participating in the CAP PT program for troponins and CK-MB.
the laboratories are still performing CK-MB testing despite questions about its clinical utility.

The only indication for the CK-MB assay is perhaps the circumstance, in which a new infarction or an extension of infarction is suspected in a person recovering from an ACS and has elevated troponin from the earlier episode. However, as we noted in the only case where this scenario prevailed, the cardiologist was comfortable with using the serial troponin values for excluding new infarction or extension of the prior infarct. Even this indication for the use of CK-MB is disputed, and institutions that have discontinued CK-MB testing have not experienced any ill effects from the change.

The paucity of orders for CK-MB since the item was removed from the ACS menu but still available as a stand-alone test listed in the laboratory menu suggests that most physicians understand the obsolescence of CK-MB. Since removing CK-MB from the ACS panel, there has been a 99.8% drop in the number of CK-MB tests ordered when the volumes in 2007 and 2008 were compared with test volumes in 2011 and 2012. Removal of a test from the laboratory menu is probably the most effective way to curtail the use of a particular test. Other maneuvers include adding pop-up warnings on ordering a test, and this technique is effective if used for a limited number of items. If such pop-up warnings occur too frequently, the value of this technique is lost since physicians often ignore the warnings.

Some of the CK-MB orders from January 1, 2011, through April 30, 2013, were likely inadvertently mistaken orders when the provider needed only total CK levels, as was likely to be the case in patients with fibromyalgia. From May 10, 2013, when we removed CK-MB from the laboratory menu (although it is available as a miscellaneous test), through September 5, 2013, we received orders for CK-MB for two patients, and the results did not add any meaningful information to the troponin values in either patient, as has been well emphasized by Saenger and Jaffe.

We are in the process of discontinuing the in-house testing for CK-MB, and the test will be available, if ordered, as a send-out test to the local reference laboratory.

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## References


