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VIEWPOINT
Thrombosis and antithrombotic treatment

ESC Study Group on Cardiac Biomarkers of the Association for Acute CardioVascular Care: A fond farewell at the retirement of CKMB

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Transitions in medicine often are difficult especially when they involve diagnostic methods that are used widely. Clinicians may find some of the new tools hard to understand especially when they are comfortable with the approaches in use. This may particularly be the case with laboratory testing which often has far reaching consequences. The graphic of the changes in the biomarkers used to diagnose acute myocardial infarction (MI) over time is provided in *Figure 1*. The problems associated with incorporating new testing into clinical paradigms may reflect in part the fact that important elements of the analytics of laboratory testing are less emphasized during medical school and clinical training than they were in the past. In addition, there is a need for closer communication between laboratory professional and diagnosticians so that the technical and analytical advances with the testing and application of novel biomarkers are better appreciated.

The declining use of the muscle/brain (MB) isoenzyme of creatine kinase (CK) is a good example. Initially, the use of CKMB was a major advance in the ability to detect acute myocardial injury because it was more sensitive and specific than other markers that had been applied such as lactate dehydrogenase (LDH) serum glutamic oxaloacetic transaminase (SGOT or AST 3) and total CK.[1] Originally, it appeared that CKMB activity might be highly specific for injury of myocytes in the myocardium.[1] This was a function of the way in which CKMB activity was measured because in essence detection depended on CKMB being present as a high percentage of total CK activity. Otherwise it might be missed (Appendix 1). This problem was appreciated by those in the laboratory but was only unmasked for clinicians when CKMB mass concentration assays were developed, which were more sensitive.[2] It then became clear that increases in CKMB values were common especially after non cardiac surgeries where skeletal muscle was injured,[1] trauma,[1] exercise,[1] or with renal failure.[1] These increases were especially large when chronic skeletal muscle disease was present because damage to skeletal muscle results in a return to embryological patterns of isoforms and re-expression of the B chain of CK as part of the reparative process.[3] Because myocardium has a higher proportion of CKMB than most skeletal muscle,[1] there were a variety of attempts to use the percentage of CKMB relative to the absolute amount of total CK to distinguish cardiac release from skeletal muscle release.[1] This approach worked reasonably well when only cardiac injury or only skeletal muscle injury was present. However, when there was conjoint skeletal muscle and myocardial injury, the percentage of CKMB elevation was lowered by the high levels of total CK and thus, the sensitivity of CKMB was lost.[3] This imperfection was clearly shown early on with the use of cardiac troponin (cTn) assays.[4] In addition, spurious increases in CKMB values were detected in patients with renal failure, haemolysis, hyperbilirubinemia,[1] and in case of circulating

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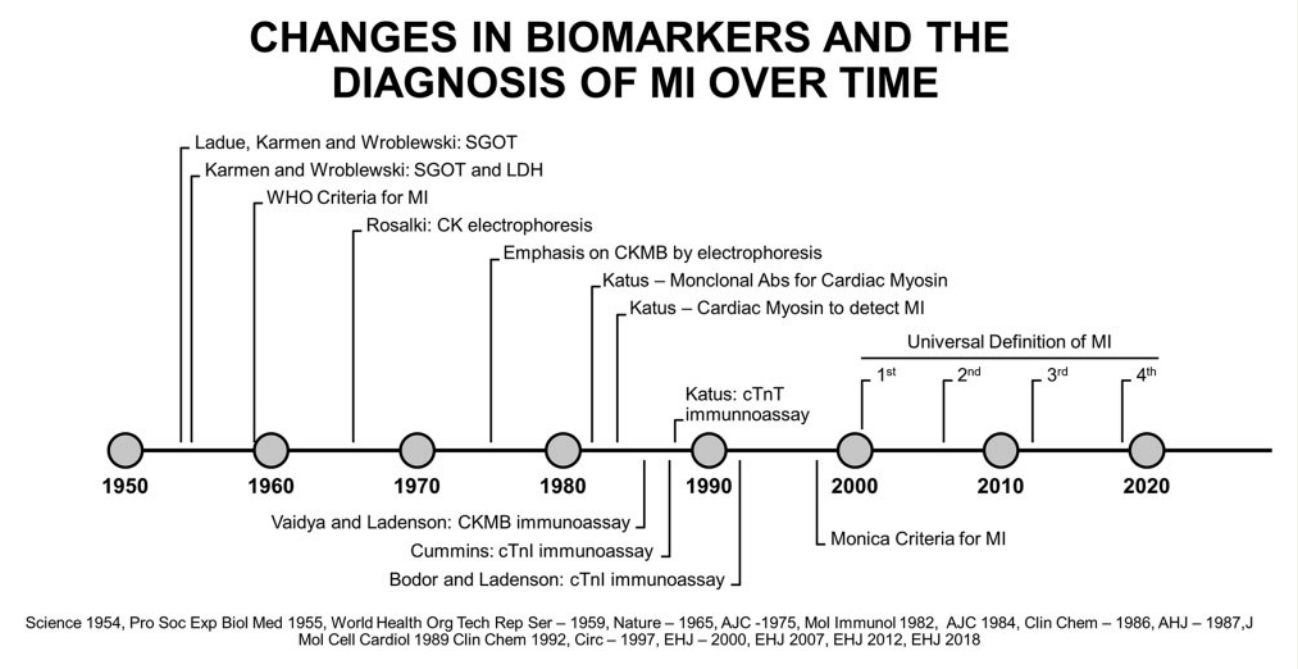

Figure 1 Timing of the initiation of the use of various biomarkers and the definition of myocardial infarction. Data predicated on the timing of publications. Full references can be found in Appendix 2.

macrokinases, i.e. immunoglobulins linked to CK.[1] In addition, there could be cross reactivity with the tags used for detection in the mass assays.[1]

Many clinicians were pleased with that state of the art. The fact that there were elevations of CKMB not due to cardiac abnormalities allowed them flexibility to determine which increases they would view seriously and which ones they could reasonably ignore. In the hands of good clinicians, this approach probably worked fairly well, although there likely were times when important diagnoses were missed even by astute clinicians. But problems occurred when there was conjoint skeletal muscle and cardiac injury became more common when CKMB was used to screen patients in the Emergency Department (ED) and after surgical procedures. Finally, a time lag of up to 4 h and sometimes even more from the onset of chest pain to the detection of increasing concentrations of CK and CKMB in plasma limited the possibility of a rapid diagnosis of acute myocardial infarction (AMI).[5] This has obviously be remedied with the use of high-sensitivity cTn assays.[6]

The use of CKMB diagnostically has diminished as a result of these problems and the development of cTn assays which are more sensitive and specific. Many now question whether there is still any role for CKMB at all.[7] Thus, in many places, the use of CKMB has been obsoleted. However, some clinicians particularly invasive cardiologists remain faithful to CKMB because, it is less sensitive and fluctuates less despite its many analytical confounds. Although one can have analytical problems with cTn, they are infrequent.[7] In addition, the release of cTn is highly specific and very sensitive for myocardial injury/necrosis and thus cTn has become the biomarker of choice for diagnosing and risk stratifying AMI.[8] Moreover, increases in CKMB not accompanied by increases in cTn values have been found not to be associated with adverse prognostic affects.[9] For that reason, the use of CKMB has no role in this setting as stated in the most recent ESC guidelines.[7]

Some clinicians might argue that there are other reasons where the measurement of CKMB might be useful. The original European Society of Cardiology/ American College of Cardiology (ESC/ACC) redefinition of MI document that over time became the Universal Definition of Myocardial Infarction (UDMI) included the use of CKMB for detection of possible reinfarction.[10] At that time, there were sparse data about this area and given that cTn increases persisted for days or weeks it was hypothesized that a marker that disappeared more quickly such as CKMB might be helpful. However, later, it was shown that this hypothesis was incorrect. In fact, diagnostically important re-elevations of cTn values despite an elevated level of cTn were easy to observe.[11] In contrast, when CKMB is increased, it can be difficult to see a changing pattern.

An additional area of controversy that persists even to this day is related to the desire of some interventionalists to use CKMB in the periprocedural period.[12] The initial reports in this area suggested that increases in CKMB were associated with complications related to the procedures that were done.[12] Their prognostic significance was not thought to be of importance. This changed when the studies began to include patients who had acute MI.[13] At that time, it was argued that CKMB elevations after percutaenous coronary intervention (PCI) imparted similar prognostic significance as that seen prior to the PCI.[14] Most importantly, the data seemed to suggest that despite the fact that even though the procedures were uncomplicated, the increases of CKMB were due to PCI. Subsequently, it was appreciated that CKMB was rising slowly, although it was still within the normal range in the majority of patients. This was hard to appreciate because of the lack of sensitivity of CKMB testing but when one sees other markers that are more sensitive like cTn rising, it is clear that

Table 1 Reasons why the use of CKMB should be discontinued

(1)	It is less sensitive to detect myocardial injury and infarction compared to cTn.
(2)	It does not add to diagnosis of risk stratification in patients with possible AMI.
(3)	It is not needed to diagnose reinfarction—cTn performs better.
(4)	The prolonged time lag before CKMB appearance delays the detection of myocardial injury compared to cTn and especially hs-cTn.
(5)	It is not required for detecting periprocedural myocardial injury—cTn accomplishes this with greater sensitivity.
(6)	It is no longer available in many hospitals in which cTn is measured routinely.
(7)	Its additional use adds unwarranted cost.

cTn, cardiac troponin.

CKMB likely is rising as well.[15] Consequently, the assumption that the adverse prognosis associated with this additional myocardial injury was due to the procedure itself was understandable but likely erroneous. Indeed, it is likely that in the vast majority of cases the poor outcomes in those with periprocedural increases were due to the original insult that led the patient to be admitted to hospital. In more elective situations, where the biomarkers are not rising prior to the procedure, an increased cTn value is associated with more extensive and more complex anatomy,[16] often not detected with CKMB. In both situations, whether the values are increasing or are simply elevated, including the baseline sample in the evaluation ablates the prognostic impact of post-PCI increases regardless of the biomarker used for detection.[17] Some clinicians have been reluctant to embrace this reality and the response has been to use cTn at higher than normal values as a baseline or to use CKMB.[12] Neither approach is desirable or helpful. This does not mean that important degrees of myocardial injury do not occur with procedures, only that most of the important prognostic information is contained in the baseline sample. It is for that reason that the UDMI has insisted on showing a normal cTn value or at least one that is stable prior to the procedure before one can attempt to define a significant procedural-related MI.[18] When the baseline cTn value is normal, increases of cardiac biomarkers post-procedurally are of prognostic significance whether with CKMB or with cTn.[12,16,17]

Similar claims have been made when dealing with postoperative cardiac surgical settings. More marked increases in CKMB and cTn are associated with a worse prognosis although cTn is a more robust predictor of mortality than CKMB.[19] Thus, cTnI had the strongest association with 5-year mortality compared with CKMB in a large study of CABG patients.[19]

Finally, there are issues of cost. In a recent ED analysis, by nearly eliminating CKMB ordering lowered costs by $47,000 per year.[20] Not included was personnel time nor charges to the health care systems. None of the 17 patients with increased CKMB and normal cTn had events. Given, its clinical efficacy is poor to non-existent and cost is significant, it is hard to understand the persistence of this marker in the armamentarium of laboratories.

Given the above (see *Table 1*), it is hard to define clinical scenarios where CKMB is helpful. It adds cost but not clinical benefit.[8,10,20] In addition, it may keep clinicians from learning how to use cTn for these clinical scenarios. Furthermore, the advent of high-sensitivity cTn (hsc-Tn) assays has increased the ability to detect myocardial injury at an even earlier phase permitting rapid rule-in of AMI[6] and so CKMB is no longer needed. Therefore, the ESC Biomarker Study Group of the Association for Acute Cardiovascular Care suggests that CKMB be eliminated from the menu of biomarkers available for use in the evaluation of patients with cardiovascular disease.

Conflict of interest: A.S.J. has in the past of presently consults for most of the major diagnostic companies. E.G. has received speaker honoraria from AstraZeneca, Roche Diagnostics, Bayer Vital, Boehringer Ingelheim, and Daiichi Sankyo; has received research funding from Brahms Thermo Fisher, Daiichi Sankyo, and Roche Diagnostics; and is a consultant for Brahms Thermo Fisher, Boehringer Ingelheim, AstraZeneca, and Bayer Vital. C.M. has received research support/grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the Cardiovascular Research Foundation Basel, the University Hospital Basel, the University of Basel, Abbott, Beckman Coulter, BRAHMS, Ortho Clinical, Quidel, Roche, Siemens, Singulex, Somalogic, and Sphingotec, as well as speaker/consulting honoraria from Acon, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, BMS, Osler, Novartis, Roche, and Sanofi. L.C. has received research support/grants from the Abbott, Beckman Coulter, and Siemens, as well as speaker/consulting honoraria from Abbott, Astra Zeneca, Osler, and Siemens. N.L.M. is supported by the Butler Senior Clinical Research Fellowship (FS/16/14/32023) from the British Heart Foundation. The University of Edinburgh has received research grants from Abbott Diagnostics and Siemens Healthineers, and N.L.M. has received honoraria from Abbott Diagnostics, Roche Diagnostics, Siemens Healthineers, and LumiraDx. The other authors report no conflict of interest,

Appendix 1. Electrophoretic separations for CKMB activity

To measure CKMB activity assessed by international units per litre (IU/L), the biochemical substrate conditions need to be optimized to make sure that reagents used in the assay are not depleted because of high CK activity. This meant that the total CK activity of the sample was diluted so it was no more than 300 IU/L. Then, the sample was run on an electrophoretic system a sensitivity of somewhere between 5 and 10 IU/L. If CKMB was not detected, the sample was viewed incorrectly as having no CKMB. For example, if the sample had been diluted 10-fold from the value of 3000 IU/L and the true value was 4 IU/L (below the sensitivity of the electrophoretic separation), then one would have had had an absolute value of 40 IU that was missed.

Appendix 2. Full references for *Figure 1*

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