
To the Editor:

We wish to raise several questions about the article by Newby et al.1 It purports to demonstrate that a quantitative multimarker strategy is better for chest pain patients than a single marker strategy because it identifies patients who are at risk for death earlier. (1) How would the results differ if the recent criteria advocated by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)2,3 were used [ie, the 99th percentile of the normal range or at a point with ≤10% imprecision2–4]? (2) Because local values were used for the single marker strategy, were the cut points similar to those used by the Dade-Behring Stratus CS analyzer? It appears to us that had that been the case, more patients would have been detected earlier than reported, especially with the single marker troponin strategy. (3) How would a myoglobin, troponin standard fare? Both Cardiology and Laboratory Medicine groups2–5 have recommended this standard. (4) Are there any statistical differences between the markers used in Table 1? (5) Since myoglobin and creatine kinase MB (CKMb) both can be released from skeletal muscle, if patients with false-positive CKMB values were included as having myocardial infarctions, they would have been detected with these assays but not troponin. How are the data affected if troponin is utilized as the gold standard?

The issues we pose are critical ones to this entire literature. The criteria any investigators chose (even if prospective) can markedly effect the results of studies as well as clinical results and lead to redundant and costly care. That may be the case with the present trial since the issue of cost was not addressed. The observation highlights the need to standardize marker testing and MI definition. The upper reference limit for each marker was the 99th percentile of a normal healthy population. Imprecision at this level was 5% for myoglobin; CK-MB, 4%; and troponin I (TnI), 9%. The SMLL strategy centered on CK-MB because not all sites used troponin testing. A variety of CK-MB assays were used. Site-specific cut-points varied and differed from the Dade-Behring Stratus CS STAT. Assays used and site-specific cutoffs are available from the authors. It is possible that more high-risk patients might have been detected with different cut-points or if troponin were used. These observations highlight challenges in standardizing biomarker use and diagnostic cut-points.

Since CHECKMATE’s design, cardiology and laboratory groups have indeed recommended a myoglobin/TnI standard. We evaluated this MMS post hoc. It performed similarly (death, 2.4% versus 0.0%; P=0.004 and death/MI, 20.6% versus 3.3%; P=0.001 for positive versus negative, respectively) to the MMSs tested prospectively.2 Differences in symptom duration by baseline marker status were not statistically significant, which may reflect small sample sizes.

Drs Apple and Jaffe raise the important difference between risk-stratification and MI diagnosis. CHECKMATE was not designed to study MMSs for index MI diagnosis relative to a gold standard. Rather, it asked whether near-patient, MMSs in chest pain units (CPU) could better identify patients with high 30-day cardiac risk. MI was determined centrally considering local CK-MB results, investigator report, and new ECG Q-waves. Defining MI using troponin may have identified fewer false-positives. However, because it was not uniformly used this is impossible to address. The observation highlights the need to standardize marker testing and MI definition.

We fully recognize the importance of cost and resource use related to cardiac marker testing in CPUs. However, with substantial interhospital variability, these analyses are complex and their discussion is beyond the scope of this reply.

In summary, our paper suggests that near-patient testing using MMSs is a better alternative than SMLL testing. In CPU settings, choosing the best marker combination and cut-points requires further research. When such studies are done, the new MI definition should be applied prospectively. This will lead to more consistent research and obviate concerns raised.

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Response

In the wake of the Joint ESC/ACC Committee for the Redefinition of Myocardial Infarction (MI) recommendations,3 Drs Apple and Jaffe raise interesting questions about our CHECKMATE results.2 However, it must be considered that CHECKMATE was designed and completed before publication of these recommendations. Further, we compared CHECKMATE near-patient, multimarker strategies (MMSs) with a single marker assayed in sites’ local laboratories (SMLL). Our rationale for adding myoglobin and also using near-patient testing was to shorten time to positive marker detection.

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