description of such an association. Both patients had IgG-κ (8). Bisalbuminemia occurring with paraprotein has also been reported rarely in patients with myeloma and plasmacytoma, but the genetic origin was not investigated in these cases (8, 10). Bisalbuminemia in these cases may be a coincident finding. In our patient, myelodysplastic syndrome was also suspected; the occurrence of this disorder with bisalbuminemia has not been reported.

Our observations further support the previous report (11) that CZE has an advantage over agarose gel electrophoresis in albumin separation, allowing the detection of more cases of bisalbuminemia.

CZE is reported to be superior to agarose gel electrophoresis for the separation of albumin and to allow detection of more cases of bisalbuminemia (11). The present case of bisalbuminemia and benign monoclonal gammopathy appears to be the second...
mation was available on the clinical
tics, information on file). No infor-
the blood of healthy persons
protein that are reportedly present in
imperatives? Is it possible to reconcile these

gani et al. (5 ) could find no measur-
able troponin I in 120 healthy
persons. We would question the up-
per reference limit quoted for some troponin assays (Table 1).
How then should cardiac troponin concentrations measured by cur-
rently available commercial assays be reported? If we accept the clinical observation that any troponin detect-
able is of pathologic significance, then the question becomes at what concentration is cardiac troponin detectable? To answer this question for each assay, we can determine the apparent troponin concentration of 10 or more replicates of a zero cali-
brator (within-run) and calculate the troponin concentration at 2 or 3 SD above the mean of these results. Above this value, any cardiac troponin present would be considered clinically significant. Between this value and the concentration that cor-
responds to a day-to-day CV of 10%, the concentration should be reported as “detectable”; above the 10% CV value, the actual quantity should be reported. We choose 10% because expert opinions from the National Academy of Clinical Biochemistry Committee (6) and the IFCC Com-
mittee on Standardization of Mark-
ers of Cardiac Damage (C-SMCD) (2) recommend a CV of 10% at the clinical decision limit for troponin measurement. This is at variance with the increasingly common clinical prac-
tice of using the “functional sensitivity” (CV) of 20% as the practical cutpoint for reporting numerical values (7). The only concern with using a CV of 20% as the minimum requirement for a clinically relevant troponin value would be if it fell close to the detection limit. Reference to the data in Table 1 indicates that in all cases for which data were available, the 20% CV value is clearly above the detection limit. Although there is no evidence for the use of a CV of 20%, it has become established in clinical practice, at least for immu-
noassays. It would certainly be inap-
propriate to replace it with other criteria for which there is clearly op-
posing clinical evidence (8).

In practice, manufacturers of com-
mercial troponin assays determine the detection limit as the concentra-
tion corresponding to a signal 2 SD above the mean of replicate within-
assay measurements of a zero cali-
brator (Table 1). Another way sug-
gested by Panteghini et al. (2) is to
calculate the troponin concentration that is approximately one-fifth of the analytically valid clinical decision limit, i.e., one-fifth of the troponin concentration with a CV of 10% (Ta-
ble 1). Alternatively, the minimum detectable concentration can be de-
ferred from the imprecision data ob-
tained at low troponin concentra-
ations, including at least two troponin concentrations that cover the range between the detection limit and the clinical decision limit of the assay. Using the three-parameter variance function, \( \sigma^2(U) = (\beta_1 + \beta_2 U)^J \), where \( \sigma^2(U) \) denotes variance, \( U \) denotes concentration, and \( \beta_1, \beta_2, \) and \( J \) are the parameters, the between-run im-
precision data determined at six or seven troponin concentrations were used to calculate the parameters for an assay system. These were then substituted into the variance equa-
tion with \( U \) equal to zero to deter-
mine the minimum detectable con-
centration (9, 10). Using the Roche

Letters

Diagnostics cardiac troponin T system as an example, the minimum detectable concentration at the 99.9 percentile, which corresponds to the troponin concentration with a signal 3 SD above zero, was 0.009 \( \mu g/L \) (Table 1). This concentration was near the quoted detection limit of 0.01 \( \mu g/L \) and close to the troponin concentration that was one-fifth the concentration at the clinical decision cutpoint, i.e., 0.007 \( \mu g/L \).

In six other widely used cardiac troponin I systems, the detection limit values agreed reasonably well when estimated by the three meth-
ods (Table 1). The mathematical model gives added confidence to the reporting of troponin as “detectable” when the signal lies between those corresponding to the detection limit and the troponin concentration at a CV of 10%. Precision data obtained from our own field laboratories and applied to the mathematical model give a real-life measure of the detect-
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able concentration of troponin in current commercially available assays and highlight analytical and sub-
sequent clinical differences that exist between these assays (Table 1).

The reporting of any analyte de-
pends on the use of some valid criteria for the boundary between detection and nondetection, taking into account the degree of assay imprecision that does not affect clinical interpretation. For cardiac troponin, if we use a deci-
sion point of 3 SD above the zero cali-
brator, we might falsely label ~1 in 100 persons as having minor myocar-
dial injury. Is there a greater potential for harm or good as a consequence? Two potential benefits arise. One is that the patient is given life-saving therapy, using the rationale that any troponin in the setting of coronary ischemia is associated with a worse prognosis. The other is the ability to accumulate data that enable us to test the hypothesis that any cardiac tropo-
nin associated with ischemia carries a worse prognosis. The potential down-
side is that patients may be started on therapy and experience an adverse re-
action.

The old definition of myocardial in-
farction used decision thresholds for myocardial markers. This definition
Table 1. Reported characteristics of cardiac troponin I and T assay systems.

<table>
<thead>
<tr>
<th>Quality specification</th>
<th>Bayer Centaur cTnI, a µg/L</th>
<th>Dade Behring Dimension RxL cTnI, µg/L</th>
<th>Abbott AxSYM Access cTnI, µg/L</th>
<th>Beckman-Coulter Stratus CS cTnI, µg/L</th>
<th>Ortho Clinical Diagnostics Vitros ECI cTnI, µg/L</th>
<th>Roche Diagnostics Elecsys cTnT, µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection limit calculated as the mean cTn value of 10 or more replicates of the zero calibrator plus 2 SD</td>
<td>0.03 b</td>
<td>0.04 b</td>
<td>0.30 b</td>
<td>0.01 b</td>
<td>0.03 b</td>
<td>0.02 b</td>
</tr>
<tr>
<td>Minimum detectable cTn concentration calculated using a mathematical model (3 SD above zero)</td>
<td>0.10 f (1 SD, 0.032)</td>
<td>0.038 f (1 SD, 0.125)</td>
<td>0.38 f (1 SD, 0.128)</td>
<td>0.014 f (1 SD, 0.0046)</td>
<td>0.017 f (1 SD, 0.0057)</td>
<td>0.08 b (1 SD, 0.026)</td>
</tr>
<tr>
<td>IFCC C-SMCD recommendation for detection limit: cTn one-fifth the clinical decision value</td>
<td>0.06 b</td>
<td>0.28 b</td>
<td>0.3 g</td>
<td>0.012 b</td>
<td>0.016 b</td>
<td>0.07 b</td>
</tr>
<tr>
<td>cTn with a total imprecision (CV) of 20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFCC C-SMCD recommendation for clinical decision point: cTn concentration with a total imprecision (CV) of 10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturer’s quoted upper reference limit (95, 97.5, or 99 percentile)</td>
<td>≤0.07 (99)</td>
<td>0.05 (97.5)</td>
<td>0.07 (99)</td>
<td>0.03 (97.5)</td>
<td>0.07 (99)</td>
<td>0.10 (97.5) f</td>
</tr>
<tr>
<td>Suggested range: “detectable cTn”</td>
<td>0.2–0.5</td>
<td>0.07–0.13</td>
<td>0.6–1.5</td>
<td>0.04–0.05</td>
<td>0.07–0.08</td>
<td>0.10–0.35</td>
</tr>
</tbody>
</table>

a cTnI, cardiac tropinin I; cTnT, cardiac troponin T; NA, data not available.

b Data derived from manufacturer’s package insert or obtained directly from manufacturing representatives.

The mathematical model uses the between-run imprecision data determined at several troponin concentrations and substituted into the three-parameter variance function, \( \sigma^2(U) = (\beta_1 + \beta_2 U)^2 \), where \( \sigma^2(U) \) denotes variance and \( U \) denotes concentration, to calculate the parameters, \( \beta_1 \), \( \beta_2 \), and \( J \). At the 99.9 percentile, i.e., the value at 3 SD above zero, the minimum detectable concentration was calculated after substitution of \( \beta_1 \) and \( J \) into the variance equation at a concentration of \( U \) equal to zero (10).

d Data were obtained by local field laboratories from the daily repeat measurement of troponin using manufacturers’ controls and patient sera (Centaur) or heparin plasma (Dimension RxL and AxSYM) containing low concentrations of troponin \( n = 7–49 \) runs; imprecision was determined at six or seven troponin concentrations.

e Data from Quinn-Hall et al. (12).

f Based on serum samples.

g Based on heparin- and EDTA-plasma samples (upper reference limits for different specimen types are not available for other assay systems).
was flawed in that despite stratifying persons into those with myocardial infarction and those without (unstable angina), the death rates were identical after 2 years (11). The prognostic importance of a very low concentration of cardiac troponin has recently been confirmed by Morrow et al. (8), who found that troponin concentrations that were detectable but below that corresponding to an analytical CV of 10% had adverse prognostic significance. Thus the clinical evidence is in disagreement with the proposal from Apple and Wu (1).

The sole purpose of laboratory medicine is to provide clinically useful information. In this context, it appears that the clinically useful information is that any detectable cardiac troponin has pathologic significance. With the procedures we have outlined here, clinically significant low concentrations of cardiac troponin can now be defined with some confidence.

References


11. Schroeder JS, Lamb IH, Hu M. Do patients in whom myocardial infarction has been ruled out have a better prognosis after hospitalization than those surviving infarction? N Engl J Med 1980;303:1–5.

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Drs. Wu and Apple respond:

To the Editor:
The letter by Tate et al. attempts to resolve the issue of which cutoff concentration for troponin should be used in the diagnosis of myocardial infarction (MI) and risk assessment of acute coronary syndrome (ACS) patients. One of the underlying goals of the European Society of Cardiology (ESC)/American College of Cardiology (ACC) (1) and American Heart Association (AHA)/ACC guidelines (2) as well as the IFCC (3) recommendations for establishing a MI cutoff at a concentration with a 10% CV was to challenge manufacturers of cardiac troponin assays to improve the low-end analytical characteristics at the 99th percentile reference limit, to better identify ACS patients who are at higher risk of short- and long-term cardiac events. Our profession demands evidence-based studies to validate each troponin assay individually, addressing 99th percentile reference limits with appropriately powered numbers for gender and race, with MI diagnostic findings and risk-stratification information based on these reference limits. Clearly, the growing evidence-based literature supports the notion that any measurable troponin in ACS patients has pathologic significance for risk assessment independent of an assay’s analytical precision.

At present we suggest that both the laboratory medicine and clinical communities rally behind the ESC/ACC and AHA/ACC guidelines, which are supported by the IFCC Committee on Standardization of Markers of Cardiac Damage (CSMCD), which proposed the troponin 99th percentile reference limit for MI detection if a 10% CV can be attained. For assays for which the imprecision at the 99th percentile is >10%, we continue to support the lowest concentration that produces a 10% CV as the diagnostic cutoff (4, 5).

For the purposes of continuing debate, Tate et al. suggest the use of a mathematical model for calculation of the minimum detection limit for cardiac troponin assays and use of this value as the diagnostic cutoff. This model computes a limit from the mean plus 3 SD above zero. Use of this criterion for the cutoff will produce values that are necessarily below the 10% CV cutoff. Although the IFCC CSMCD has also recommended this analytical approach for determining the detection limit for troponin assays, the CSMCD endorsed a higher cutoff (i.e., 10% CV) as the decision limit (4). Tate et al. justified the lower cutoff by citing risk stratification studies such as Morrow et al. (6) in the TACTICS-TIMI Trial, where additional risk stratification was demonstrated for troponin concentrations between the detection limit and the 10% CV cutoff. Similarly, in the FRISC II trial, additional risk stratification data were produced when the cutoff for cTnT was low-