In Reply

E. Smith has pointed out that the use of cryocrit in the investigation of cryoglobulinemia has analytical and clinical limitations, an observation with which we concur in general. The emphasis of our case study, however, was not to make a judgment on which technique should be used, but rather to focus on the importance of including cryocrit in the differential and to address the need for standardization between laboratories. We reported a schema of sample collection and analysis that merely reflects a practice that many laboratories still conduct today. Vermeersch et al. reported that up to 37% of the 140 surveyed laboratories included cryocrit or other estimates (e.g., total protein) in their patient reports (1). The lack of standardization of practice appears, at least in part, to be related to a difference in opinion on the usefulness of estimating cryoglobulin quantities. Although some investigators reported no relationship between cryoglobulin concentration and the severity of symptoms and disease activity (2), cryoglobulin concentrations have, nevertheless, been found to correlate with response to treatment with plasmapheresis, cytotoxic agents, and/or interferon α (3). Moreover, we did indicate in our report that cryocrit does not differentiate type 1 and type 2 cryoglobulinemia, and we recommended that serum protein electrophoresis and immunofixation should be conducted on resolubilized cryoprecipitate (4). Certainly, laboratories that do not have specialized equipment or a test in place to screen for cryoglobulins should consider at minimum estimating the cryocrit.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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Kareena L. Schnabl
P. Cheung Chan
Khosrow Adeli*

* Address correspondence to this author at:
Hospital for Sick Children
555 University Avenue
Toronto, Canada M5G1X8
Fax 416-8136257
E-mail khosrow.adeli@sickkids.ca

Previously published online at DOI: 10.1373/clinchem.2009.137109

What Criteria Should Be Used to Assess Troponin Assays?

To the Editor:

Since the introduction of cardiac troponin testing in the 1990s, troponin measurement has become the main diagnostic criterion for the diagnosis of myocardial infarction. Multiple improvements have been made in the available commercial assays, with lower detection limits, improved imprecision at low concentrations, and improvements in standardization. Because troponin has been shown to be a powerful predictor of death and requirement for revascularization in patients presenting with the acute coronary syndrome, the analytical performance of assays is very important. Frequently, clinical decisions are based on increased troponin concentrations, and the performance of different assays is difficult to assess objectively.
To allow better evaluation for the clinical and laboratory community, Apple suggested a scorecard for cardiac troponin assays (1), with the value of the troponin assay being based on 2 criteria. The main criterion is the imprecision of the assay at the 99th percentile of a reference population. A good assay was defined as one with a 10% CV at the population’s 99th percentile, a clinically usable assay was defined as one with a CV between 10% and 20% at that percentile, and a CV >20% at this cutoff point was deemed unacceptable. Apple further differentiated assays on their ability to detect troponin in healthy control individuals. We have concerns with some aspects of his scorecard.

Our major point of disagreement with Apple is that he uses the 99th percentile of a reference population and the imprecision of the assay for assessing assay quality but gives no consideration to the clinical value of that assay. This latter point is of particular importance. For example, Venge et al. used samples from the FRISC (Fast Revascularisation during Instability in Coronary Artery Disease) study to compare the performance of the Liaison cardiac troponin I assay (DiaSorin) in unstable coronary artery disease (2). The Liaison assay showed good imprecision, with a 10% CV at 0.027 μg/L and a 99th percentile reference population value of 0.041 μg/L. This assay would have been qualified as acceptable; however, comparison with another troponin assay, the Access AccuTnI from Beckman Coulter, showed that the Liaison assay missed about 10% of patients with unstable angina and an increased risk of death or acute myocardial infarction within 6 months. More recently, a large prospective cohort study of patients presenting with chest pain to the emergency department showed similar results (3). In this study, assays that were more sensitive for troponin I show an improved diagnostic performance for acute myocardial infarction compared with a so-called standard assay (Roche fourth-generation troponin T assay). Assays with superior diagnostic performance in the recent cohort study were the Abbott Architect, the Siemens Centaur Ultra, and the Roche Elecsys high-sensitivity troponin T assays. Assays that were less sensitive included the fourth-generation troponin T assay; however, according to Apple’s scorecard, the Abbott Architect assay is ranked as “clinically usable” at his level 1 designation, similar to the rank of the fourth-generation Roche Elecsys troponin T assay. The use of assay imprecision defined as a 10% CV and the 99th percentile of healthy individuals falls short in judging assay performance.

A better way forward to compare assay performance might be to use patient serum pools with different cardiac troponin concentrations, as was done in a 2004 study (4). In this study, the Abbott AxSYM assay was unable to measure troponin in the pool with the lowest concentration, as were other analyzers at the time: the Immuno 1 analyzer (Bayer Diagnostics), the Vidas analyzer (bioMerieux), the Dimension RXL analyzer (Siemens), the Opus analyzer (Dade Behring), and the Vitros ECI analyzer (Ortho Clinical Diagnostics). In contrast, other analyzers measured detectable troponin down to the pool with the lowest concentration. Clearly, these findings illustrate the different analytical sensitivities of the different assays. This consideration translates into the recognition of additional patients at risk.

In his scorecard, Apple uses the 10% CV as an important point of assay differentiation. However, there is no evidence to support the use of the 10% CV; in fact, the opposite is true. There currently is a wealth of evidence showing that in the setting of acute coronary syndrome, troponin concentrations corresponding to assay CVs well above the 10% CV are informative for a worse prognosis (5).

What is the way forward? Although we agree that assays can and should be scored objectively on their technical characteristics, we also believe that assays can and should be compared for their clinical performance. Useful information for comparing troponin assays includes clinical cohort studies that use chest pain patients in the emergency department, patients with a high pretest probability for unstable angina, and patient populations from the glycoprotein IIb/IIIa inhibitor trials. Additional clinically relevant information can be obtained from the exchange of patient pools and measuring troponin in these pools with different analyzers and assays. This matter needs further debate.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: H.G. Schneider, Amgen.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: None declared.
Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Clinical Chemistry 56:1 (2010) 141
References


Hans G. Schneider1,2*
Jillian R. Tate3
Peter E. Hickman4,5

1 Alfred Pathology Service
Melbourne, Australia
2 Monash University
Melbourne, Australia
3 Chemical Pathology
Pathology Queensland
Royal Brisbane and Women’s Hospital
Brisbane, Australia
4 ANU Medical School
Canberra, Australia
5 Chemical Pathology
ACT Pathology, Canberra Hospital
Garran, Australia

* Address correspondence to this author at: Alfred Pathology Service
55 Commercial Rd.
P.O. Box 315, Prahran 3181
Victoria, Australia
E-mail schneiderh@alfred.org.au

Previously published online at DOI: 10.1373/clinchem.2009.137422