

Evaluation of Imprecision for Cardiac Troponin Assays at Low-Range Concentrations

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Background: The European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction (MI) has recommended that an increased cardiac troponin should be defined as a measurement above the 99th percentile value of the reference group. A total imprecision (CV) at the decision limit of $\leq 10\%$ is recommended. However, peer-reviewed data on assay imprecision are lacking. The purpose of this study was to construct the clinically relevant imprecision profiles for each of the commercially available cardiac troponin assays. Pools of human sera containing cardiac troponin concentrations around the MI decision limit were assessed to identify the lowest concentration associated with a 10% CV.

Methods: Eight serum pools targeting different concentrations of cardiac troponin (I and T) were prepared and stored at -70°C until usage. The cardiac troponin measurement protocol consisted of two replicates per specimen per run, and one run per day for 20 days, using two

reagent lots and three calibrations. Manufacturers of each cardiac troponin assay directly performed the measurements. Data analysis for each assay was centralized and performed according to the NCCLS EP5-A guideline.

Results: The lowest concentrations ($\mu\text{g/L}$) providing a 10% CV were as follows: AxSYM, 1.22; ACS:180, 0.37; Centaur, 0.33; Immuno 1, 0.34; Access, 0.06; Vidas, 0.36; Liaison, 0.065; Dimension, 0.26; Opus, 0.90; Stratus CS, 0.10; Immulite, 0.32; Vitros ECi, 0.44; Elecsys, 0.04; AIA 21, 0.09.

Conclusion: No cardiac troponin assay was able to achieve the 10% CV recommendation at the 99th percentile reference limit defined by the manufacturer.

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Cardiac troponins are currently the most sensitive and specific biochemical markers of myocardial necrosis. National and international scientific organizations have suggested the use of these markers when implementing new diagnostic strategies in patients with acute coronary syndrome (1–4). As a result, increasing numbers of clinical laboratories are in the process of switching to these new markers, and more physicians can be expected to rely increasingly, or solely, on cardiac troponin measurements when myocardial infarction (MI)⁹ is suspected on clinical grounds (5–9). In particular, the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction has recommended that an increased concentration of cardiac troponin be defined as a measurement exceeding the 99th percentile of the distribution of cardiac troponin concentrations in the reference group, a very low threshold (3). A total imprecision (CV) at this decision limit of $<10\%$ is

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⁹ Nonstandard abbreviations: MI, myocardial infarction; and cTnI and cTnT, cardiac troponin I and T, respectively.

recommended (1–3, 9, 10). However, the analytical imprecision obtained with different commercial immunoassays for cardiac troponins is not uniform, mainly at the low concentration range (11).

Consistent data on cardiac troponin assay imprecision are often lacking in the peer-reviewed literature. Many reports state the imprecision only for increased concentrations of cardiac troponins and do not address the low range, which is of greatest importance for clinical decision making. Furthermore, the imprecision frequently mentioned in published studies usually reflects assay performance under ideal, nonroutine laboratory conditions. No study has simultaneously determined the total imprecision for a large number of cardiac troponin assays based on the same samples and the same experimental protocol. The aims of the present study were (a) to construct clinically relevant imprecision profiles for commercially available cardiac troponin assays by assessing samples containing cardiac troponin concentrations covering the range around the assay-dependent MI decision limit; (b) to determine the lowest concentrations giving a 10% CV (total imprecision) in the various assays; and (c) to determine whether the concentration associated with a 10% CV corresponds to the manufacturer's stated 99th percentile reference limit.

Materials and Methods

SAMPLES

Eight serum pools (A–H) were prepared in the laboratory of one of the authors (K.T.J.Y.) by selectively pooling fresh sera (leftover) from patients to target different concentrations of cardiac troponin I (cTnI) and T (cTnT) spanning the 99th percentile reference limits to ROC curve-based MI cutoffs. The Bayer ACS:180 was used to preset pool concentrations [range, 0.10–3.15 $\mu\text{g/L}$ (12)]. Institutional Review Board approval was not necessary because samples were stripped of patient identifiers, and no medical records or patient-specific information were obtained. Before aliquoting and freezing, each pool was filtered and centrifuged to carefully remove particulate debris and fibrin strands. Pools were then stored (as 0.5-mL aliquots) at -70°C until they were shipped (on dry ice) to participating companies for analysis.

PARTICIPANTS

All companies manufacturing platforms/assays for cTnI and/or cTnT were invited to participate. The imprecision experiments were performed directly by the manufacturers. A total of 13 companies agreed to participate, but 2 of these companies did not return their results: Innotrax Diagnostics did not explain why the data were not sent, and Biosite Diagnostics specified that their system (Triage) was designed only for plasma and whole-blood samples. Eleven manufacturers submitted results; 4 of them used two or three different analytical systems (Table 1).

Table 1. Participating cardiac troponin assay manufacturers and systems.

Manufacturer	Platform
Abbott Diagnostics, Inc.	AxSYM
Bayer Diagnostics	ACS:180 Centaur Immuno 1
Beckman Coulter, Inc.	Access, second generation Access 2, second generation
BioMerieux	Vidas
Byk-Sangtec Diagnostica	Liaison
Dade Behring, Inc.	Dimension RxL, second generation Opus, second generation Stratus CS
Diagnostic Products Corporation	Immulite One
First Medical Inc.	Alpha Dx
Ortho Clinical Diagnostics	Vitros ECI
Roche Diagnostics ^a	E170 Elecsys 1010, third generation AIA 21, ^b second generation
Tosoh Corp.	

^a The Roche assays are the only cTnT assays on the market; all other assays are for cTnI.

^b AIA Nex IA on US market.

STUDY DESIGN

On receipt, the eight pools were stored at -70°C until measurement, which occurred within 30 days. Vials of each aliquot were thawed, allowed to equilibrate to room temperature, and centrifuged to eliminate possible fibrin strands. Manufacturers were directed to analyze two replicates of each specimen in each run and to perform one run per day for 20 working days with their respective analytical systems. Two reagent lots (10 working days per lot) and at least three calibrations were to be used. Participants were instructed to randomly analyze pools to reflect any carryover effect. The manufacturer's recommended controls, assayed at the beginning and at the end of each run, were used to validate measurements.

DATA ANALYSIS

Measurements were reported on a special electronic form prepared by the IFCC Committee and sent to the Committee's chairman (M.P.). The original instrument printouts with raw data were also submitted. The total imprecision of troponin assays at different concentrations was estimated using the ANOVA method described in NCCLS EP5-A guideline (13). The CV values reported for the pools were used to construct imprecision profiles for each method. The troponin concentration associated with a 10% CV was determined from the intercept of the total CV (y axis) equal to 10% on the imprecision profile curve.

Results

The mean cardiac troponin concentrations for pools A–H, with the exclusion of pool F, are shown in Table 2. Results for this pool were excluded from all analyses for technical reasons; i.e., out-of-proportion imprecision data and atyp-

Table 2. Mean cardiac troponin concentrations ($\mu\text{g/L}$) obtained from the evaluated pools by different measurement systems.^a

Pool	Bayer			Beckman		Dade Behring			Roche							
	Abbott AxSYM	ACS:180	Centaur	Immuno 1	Access 2	BioMerieux Vidas	Byk-Sangtec Liaison	Dimension RXL	Stratus CS	Opus	DPC ^b Immulite	First Medical Alpha Dx	Ortho ECI	Elecsys	EI 70	Tosoh AIA 21
A	<0.3 ^c	0.085	0.182	<0.05 ^c	0.052	0.051	0.019	<0.04 ^c	0.047	<0.1 ^c	0.126	<0.09 ^c	<0.02 ^c	0.028	0.030	0.100
B	0.785	0.151	0.301	<0.05 ^c	0.164	0.163	0.036	0.131	0.212	0.309	0.319	<0.09 ^c	0.137	0.026	0.031	0.219
C	0.948	0.198	0.368	0.107	0.166	0.165	0.052	0.149	0.210	0.313	0.454	<0.09 ^c	0.197	0.023	0.028	0.277
D	1.708	0.383	0.608	0.242	0.293	0.295	0.076	0.293	0.393	0.538	0.703	<0.09 ^c	0.359	0.058	0.064	0.526
E	2.088	0.462	0.713	0.370	0.422	0.418	0.097	0.457	0.614	0.706	0.719	<0.09 ^c	0.438	0.052	0.061	0.675
G	3.720	1.164	1.558	0.691	0.761	0.747	0.145	0.788	0.956	1.160	1.656	<0.09 ^c	0.982	0.134	0.147	1.168
H	8.080	2.673	3.512	1.299	1.793	1.709	0.360	2.328	2.715	2.784	2.278	0.399	2.041	0.256	0.290	2.131

^a All data are cTnI values except Roche (cTnT).^b DPC, Diagnostic Products Corporation.^c Result lower than the detection limit of the assay.

ical behavior in several assays. Marked differences were detected between the results obtained with the cTnI and cTnT assays, as well as among different assays measuring cTnI. The analytical response for each pool varied >20-fold for the 15 participating cTnI assays, underscoring the need for standardization. The data also indicated that the different methods had different sensitivities for measurement of cTnI in the pools with the lowest concentrations of this biomarker. Seven methods were unable to measure cTnI in pool A, and two methods were unable to measure cTnI in pool B. An extreme case was represented by the Alpha Dx method, which was unable to measure cTnI in all but one tested pool.

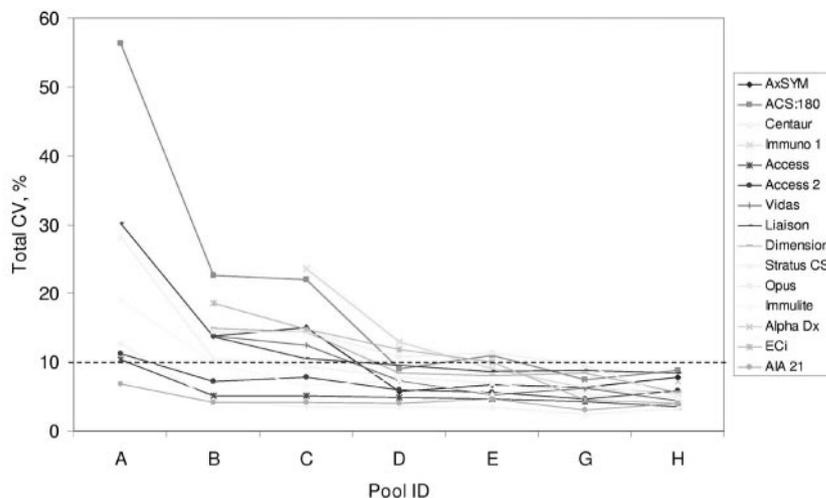
The imprecision profiles (total CV vs pools A–H, which had increasing cTnI concentrations) obtained for each cTnI method are shown in Fig. 1. Because it was impossible to directly compare cTnT with cTnI concentrations in the evaluated pools, the CV data for the two Roche platforms are reported in Fig. 2. Differences in imprecision were clear, which allowed us to categorize assays according to performance as good, moderate, and less than ideal.

The 10% CV concentrations together with the corresponding upper reference limits for each evaluated assay are reported in Table 3. There were no cardiac troponin assays that can achieve an imprecision (CV) of 10% at the 99th percentile reference limit. Six systems achieved a 10% CV at concentrations that were approximately twofold higher than the concentration corresponding to the 99th percentile of the value distribution in a reference population. A second group of nine platforms achieved a 10% CV at concentrations approximately fourfold higher than the 99th percentile cutoff. In two cases, the concentration was very high (ninefold higher than the 99th percentile cutoff; Opus) or even impossible to calculate (Alpha Dx).

Discussion

Despite the overt clinical advantages, important analytical and preanalytical obstacles to cardiac troponin analysis and interpretation remain, such as assay standardization, antibody specificity, interferences, preanalytical factors, and assay imprecision (9, 14). The 99th percentile reference limit for MI diagnosis proposed by the European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction was largely driven by the demonstration that any amount of detectable cardiac troponin release is associated with an increased risk of new adverse cardiac events (3). Currently available clinical data demonstrate no threshold below which increased cardiac troponin concentrations do not pose an increased risk and do not have negative implications for prognosis (15–17). However, to avoid diagnostic misclassification arising from assay imprecision in clinical practice, the decision limit should be measured with a total imprecision (CV) $\leq 10\%$ (4, 9, 10). A recent study showed that only use of cardiac troponin concentrations that meet the goal of 10% CV as an MI

Fig. 1. Imprecision results for human serum pools measured with different cTnI assays. The 10% total CV is shown by the dashed line.



cutoff provide a misclassification rate <1% in a population of patients with suspected acute coronary syndrome (18).

With regard to this point, many cardiac troponin assays have not been appropriately validated, and the absolute performance of some commercially available assays is not easily discerned (19). To date, clinical users have frequently had to rely on the manufacturers' claims and package inserts, even if data provided by manufacturers often portray better precision than is achieved in clinical practice (9). The current study is unique in that it demonstrates the imprecision at the low concentration ranges of the commercially available assays for cTnI and cTnT based on the use of the same experimental protocol performed over a clinically relevant timespan (4 weeks), use of the same human sera analyzed randomly with more than one lot of reagents and calibrations, and direct comparisons among assays independent of the commercial information provided with each assay. Pools of human sera were used. Because the imprecision for cardiac troponin measurements in modified protein matrices may be significantly different from that for measurements in human serum pools, a clinically realistic precision esti-

mate is obtained only when unmodified human sera are tested.

Our data confirm the large diversity among cardiac troponin assays with respect to total imprecision and underscore the need for introduction of improved cardiac troponin assays that comply with the redefined MI definition and imprecision requirements. There currently are no commercial assays that can achieve a 10% CV at the 99th percentile reference limit, which would allow accurate differentiation between "minor" myocardial injury and analytical noise. The demand for very precise cardiac troponin assays undoubtedly presents a difficult chal-

Table 3. Concentrations corresponding to 10% CV imprecision and 99th percentile reference limit for the evaluated troponin assays.

Platform	99th percentile limit, ^a µg/L	10% total CV concentration, µg/L	Ratio of 10% CV concentration to 99th percentile limit
AxSYM	0.30	1.22	4.1
ACS:180	0.10	0.37	3.7
Centaur	0.10	0.33	3.3
Immuno 1	0.10	0.34	3.4
Access	0.04	0.06	1.5
Access 2	0.04	0.09	2.3
Vidas	0.10	0.36	3.6
Liaison	0.03	0.065	2.2
Dimension RxL	0.07	0.26	3.7
Opus	0.10	0.90	9.0
Stratus CS	0.07	0.10	1.4
Immolute One	0.20	0.32	1.6
Alpha Dx	0.15	ND ^b	
Vitros Eci	0.10	0.44	4.4
E170	0.01	0.04	4.0
Elecsys 1010	0.01	0.04	4.0
AIA 21	0.06	0.09	1.5

^a Data obtained from manufacturer's package insert or through personal communications with manufacturers.

^b ND, not determined.

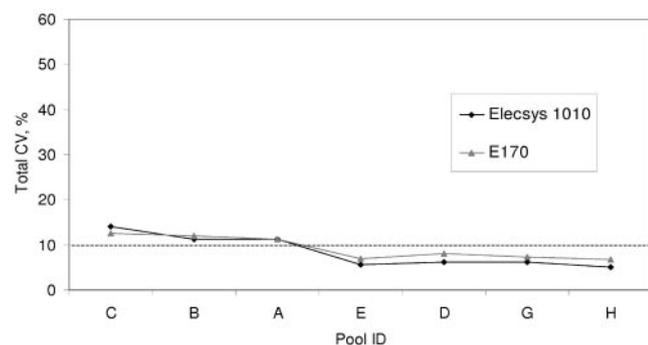


Fig. 2. Imprecision results for human serum pools measured with different cTnT assays.

The 10% total CV is shown by the dashed line.

lenge, but results obtained with more recently released next-generation assays show that there has been substantial improvement in the precision and sensitivity offered by the newer assays. This type of low-end improvement is considered by manufacturers as the main goal in the design of new assays (14).

According to previous suggestions (9, 20, 21), in the context of clinical practice a predetermined cardiac troponin concentration that meets the imprecision goal should be used as the cutoff for MI until the assays are improved. The results from the present study may help laboratories by identifying the lowest cardiac troponin concentrations that give the 10% CV required for implementation of the recommended clinical strategies in acute coronary syndrome patients. The use of the actual 10% CV concentration instead of the 99th percentile reference limit as a decision cutoff could slightly decrease the clinical sensitivity of the biochemical criterion used for the MI diagnosis, but should permit physicians to reduce the occasional increase in serum cardiac troponin in the absence of myocardial damage. Although higher precision at lower cardiac troponin concentrations does not automatically equate with higher clinical sensitivity, it has been shown that the use of a high-sensitivity cardiac troponin assay would allow identification of a substantial and additional proportion of patients with MI compared with a less sensitive cardiac troponin assay (22, 23). Use of the new diagnostic criteria for MI could lead to a mean increase in the number of infarcts in patients with acute coronary syndrome from 20% to 30%, but the percentage of patients recategorized from angina to MI may also be critically dependent on the performance of the cardiac troponin assay used.

Decision limits other than the 99th percentile and 10% CV have been clinically defined for some of the evaluated methods and used for risk stratification of patients with acute coronary syndrome (15–17). Although the data from these clinical trials are compelling, the use of cardiac troponin for MI diagnosis is different from its use for risk stratification. As discussed previously (24), it is important to consider differences in the prevalence of acute coronary syndrome in different populations. If the purpose of measuring cardiac troponin is only to risk-stratify patients with acute coronary syndrome for adverse events, consideration should be given to lowering the cardiac troponin cutoff below the 10% CV value. However, these low cardiac troponin cutoffs are not likely appropriate for the diagnosis of MI in a cohort of patients with chest pain and a low prevalence of disease, where false-positive results produced by a cardiac troponin assay as a result of analytical imprecision could have a much larger negative impact (18).

The limitations in our study should be noted. One limitation is that because each method was assessed in only one (manufacturer) site, it was not possible to definitively determine the effect, if any, on the imprecision of an assay by type of clinical laboratory (emergency

or centralized) or by type of healthcare worker (laboratory technician or ward nurse) performing measurements. Furthermore, although human serum pools are better than artificial protein matrices, pooling may mask problems related to the performance for individual samples because interfering compounds in individual sera, e.g., heterophilic antibodies, are diluted and their effects may escape attention. Another limitation is that it could be difficult to accurately estimate the 10% CV concentration based on an interpolation between relatively few points. However, there was no alternative way to derive this information from our findings. Furthermore, looking at the peer-reviewed literature, imprecision studies on individual assays using robust experimental approaches have obtained results very similar to ours (18, 25). Finally, use of the 99th percentile limits information obtained from the manufacturers for calculation of the ratio of the 10% CV and 99th percentile concentrations, and the ranking of tests could influence the results, if aspects such as statistical data analysis, sample sizes, or criteria for individual selection were not correctly considered in the production of data by each company. However, for fairness to all manufacturers, we decided to use only what their claim.

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