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Use of Troponin Assay 99th Percentile as the Decision Level for Myocardial Infarction Diagnosis

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Abstract

Background—The Universal Definition of Myocardial Infarction recommends the 99th percentile concentration of cardiac troponin in a normal reference population as part of the decision threshold to diagnose type 1 spontaneous myocardial infarction. Adoption of this recommendation in contemporary worldwide practice is not well known.

Methods—We performed a cohort study of 276 hospital laboratories in 31 countries participating in the National Heart, Lung, and Blood Institute sponsored International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial. Each hospital laboratory's troponin assay manufacturer and model, the recommended assay's 99th percentile upper reference limit (URL) from the manufacturer's package insert, and the troponin concentration used locally as the decision level to diagnose myocardial infarction was ascertained.

Results—Twenty-one unique troponin assays from 9 manufacturers were used by the surveyed hospital laboratories. The ratio of the troponin concentration used locally to diagnose myocardial infarction to the assay manufacturer-determined 99th percentile URL was <1 at 19 (6.6%) laboratories, equal to 1 at 91 (31.6%) laboratories, >1 to 5 at 101 (35.1%) laboratories, >5 to 10 at 34 (11.8%) laboratories and >10 at 43 (14.9%) laboratories. The variability in troponin decision

level for myocardial infarction relative to the assay 99th percentile URL was present for laboratories in and outside of the United States, as well as for high- and standard-sensitivity assays.

Conclusions—There is substantial hospital level variation in the troponin threshold used to diagnose myocardial infarction; only one-third of hospital laboratories currently follow the Universal Definition of Myocardial Infarction consensus recommendation for use of troponin concentration at the 99th percentile of a normal reference population as the decision level to diagnose myocardial infarction. This variability across laboratories has important implications both for the diagnosis of myocardial infarction in clinical practice as well as adjudication of myocardial infarction in clinical trials.

Introduction

Myocardial infarction (MI) is recognized by clinical symptoms and signs, electrocardiographic findings, and by elevated levels of biochemical markers of myocardial necrosis. In 2000, the European Society of Cardiology/American College of Cardiology provided recommendations for the use of biomarkers and their concentration thresholds for the diagnosis of MI.¹ Cardiac troponin (cTn) was recommended as the preferred biomarker, and a diagnosis of type 1 spontaneous MI required a rise and/or fall in cTn concentration with at least one cTn concentration exceeding the 99th percentile of a normal reference population (when baseline cTn concentration is less than the 99th percentile). This was done to establish consistency with regard to definition of MI among clinicians, laboratories, investigators and regulatory authorities. Currently, there is a paucity of data on implementation of this recommendation, with prior literature demonstrating adoption far from universal.^{2–4} Therefore, we sought to evaluate the extent to which the cTn 99th percentile upper reference limit (URL) has been adopted worldwide as the decision level to diagnose MI.

Methods

A questionnaire was administered to 314 activated sites participating in the ongoing National Heart, Lung, and Blood Institute sponsored International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial (NCT #01471522) between 01/2013 and 07/2015. Sites were asked to identify the cTn assay used at their laboratory, and the cTn concentration threshold used locally to diagnose MI. Email reminders were sent and telephone calls were scheduled as needed. The assay manufacturer-determined 99th percentile was recorded from the package insert for each assay. The ratio of the site laboratory cTn decision level for MI to the manufacturer-determined assay 99th percentile was calculated for each laboratory. A histogram was used to plot the variability across laboratories in this relationship. We also determined whether this relationship differed by region, and by cTn assay sensitivity. No extramural funding was used to support the research and creation of the paper. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

Results

Study data were submitted by 276 participating sites [101 from the United States (US), and 175 from outside of the US] from 31 countries. Sites reported employing 21 unique cTn assays from 9 manufacturers (Table 1). Twenty (7.2%) sites used 2 different assays. cTnI assays were employed in 181 (65.6%) sites, cTnT assays in 88 (31.9%) sites, and 7 (2.5%) sites used both a cTnI and cTnT assay. High-sensitivity assays were used by 71 (25.7%) sites; all from outside of the US. Non-quantitative point-of-care assays were used in 8 (2.9%) sites. Two cTn thresholds, a lower threshold suggestive for myocardial injury and a higher threshold for MI diagnosis were used in 49 (17.8%) sites. Sex-specific MI decision levels were used in 8 (2.9%) sites.

Overall, there was significant variability in the cTn MI decision level relative to the manufacturer-determined 99th percentile, with the cTn MI decision level equal to the 99th percentile in 91 (31.6%) laboratories (Figure 1). This variability in cTn decision level for MI relative to the manufacturer-determined 99th percentile was present for laboratories in and outside of the US, as well as for high- and standard-sensitivity cTn assays (Figure 2). High-sensitivity cTn assays were more likely to have the manufacturer-determined 99th percentile used as the MI decision level compared with standard-sensitivity cTn assays (49.3% vs. 25.8%, $p < 0.001$). For some cTn assays, there was a >20-fold variation in MI decision level between sites, e.g. the cTn MI decision limit ranged from 0.012ng/mL to 0.50ng/mL among laboratories using the Abbott Architect cTnI assay (manufacturer's recommended 99th percentile, 0.028ng/mL) (Table 1).

Discussion

There is substantial variability across hospital laboratories in the cTn concentration threshold used for diagnosis of MI in relation to the assay 99th percentile URL. Overall, only one-third of the hospital laboratories participating in this international clinical trial are in alignment with the Universal Definition of MI consensus recommendation to use the cTn assay 99th percentile URL as the decision level to diagnose MI. Adoption of this recommendation is greater for high- versus standard-sensitivity assays.

Given the use of different antibodies against troponin epitopes by different manufacturers, performance characteristics vary considerably between assays.⁵ The manufacturer determined 99th percentile for different assays are not biologically equivalent,⁶ and in one study, there was a 32-fold variation in 99th percentile value among contemporary cTnI assays.⁷ This poor correlation in performance does not allow for a correction factor that would adequately standardize results between different assays. Notwithstanding this limitation, it is felt that as long as absolute concentrations are not compared among different assays, and the 99th percentile URL is consistently applied as the decision level for diagnosis of MI, that clinical interpretation should be acceptable for all assays. In 2008, the CARDiac MARKer Uptake of Guidelines in Europe (CARMAGUE) study showed that only 35% of the 220 laboratories in 8 European countries used the assay 99th percentile URL as the decision level for MI.⁴ Although site reported use of the 99th percentile value for MI diagnosis was higher in 2013 (52.3% in European and 45.2% in North American laboratories), the

investigators reported that only a minority of sites claiming to use the 99th percentile used the appropriate value.⁸

Our study highlights a more concerning observation that for the same cTn assay, there was >20-fold variability across laboratories in the cTn threshold used for diagnosis of MI. Therefore, a patient with a cTn concentration 10-times the 99th percentile URL may be classified as MI by one hospital, but chest pain with “normal” cTn level or unstable angina by another hospital. This has considerable implications for patient management in clinical practice, as well as over and under-reporting of MI events in clinical trials.^{6, 9} Prior studies have demonstrated that even small elevations in troponin levels are associated with increased risk,^{10, 11} and the 99th percentile URL threshold stratifies well patients that may derive benefit from an early invasive strategy and more intensive antiplatelet therapy.^{12, 13} Lack of standardization of cTn threshold used for diagnosis of MI also has implications for rapid rule out protocols, with cost implications of over-testing, longer stays in the emergency department and delayed diagnosis.¹⁴ In a meta-analysis of 93 cardiovascular trials conducted between 2000 and 2012 that provided a definition for MI, only 7 specified 99th percentile as the MI decision limit.³ Standardized implementation of 99th percentile value as the threshold to adjudicate MI in cardiovascular trials is a key recommendation by the 2014 American College of Cardiology/American Heart Association Task Force on Clinical Data Standards.¹⁵ Implementation of this recommendation requires resolving how best to account for the wide variety of available cTn assays and their varying performance characteristics.³

Incomplete incorporation of 99th percentile URL as decision limit for MI diagnosis may reflect concerns about the precision of some assays at the 99th percentile. Current guidelines recommend assay imprecision [% coefficient of variation (CV)] of 10% at the 99th percentile URL, facilitating certainty that 2 values are unique.¹⁶ Since the diagnosis of MI requires a rise and/or fall in cTn value, assays without high precision make determination of a significant change more difficult. High-sensitivity assays lessen this concern because by definition these assays have a CV <10% at the 99th percentile value. In this context, we did observe greater, but far from universal adoption of 99th percentile URL as decision limit for MI with high- versus standard-sensitivity assays. In our study, the process by which each laboratory decided on their MI decision level was not ascertained. Some reasons hospital laboratories do not use the manufacturer-determined 99th percentile include (i) arbitrary adjustment of the manufacturer’s assay URL to be consistent with prior local experience, (ii) derivation of the cTn concentration at the 99th percentile from a local reference population, (iii) adoption of the URL from other cited publications. At the current time, there is not unanimous expert opinion or consensus about specific criteria for how the 99th percentile URL should be defined. For local hospitals, it is laborious, costly, and time intensive to study a sufficiently large and diverse age and gender normal population to derive the 99th percentile specific for a cTn assay. One approach to reduce heterogeneity in the cTn decision threshold for MI in clinical trials is to use the manufacturer’s recommended 99th percentile for the assay, an approach we have taken in the ISCHEMIA trial. This approach negates the issue of two hospitals using the same assay and platform with a 20-fold difference in the decision threshold for MI. With the recent approval of high-sensitivity assays in the US, many US laboratories are likely to switch troponin assays in the very near future. As more laboratories make this change, further efforts are required to encourage the adoption of 99th

percentile URL as the cTn threshold to diagnose MI, and for clinical societies/regulators to establish a recommendation for the best and universally accepted methodology to establish the 99th percentile for cTn assays.

Conclusions

There is large variability across hospital laboratories in the cTn threshold to diagnose MI relative to the assay manufacturer determined 99th percentile. Our findings underscore the pressing need to harmonize the clinical decision limit for MI across hospital laboratories to reduce inconsistency in practice, improve accuracy of clinical decision making, and standardize determination and reporting of MI endpoints in clinical trials.

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Figure 1.
Distribution of Ratios of Local Laboratory cTn Decision Level for Diagnosis of Myocardial Infarction to Manufacturer-determined Assay 99th Percentile Among Laboratories

Figure 2.
Distribution of Ratios of Local Laboratory cTn Decision Level for Diagnosis of Myocardial Infarction to Manufacturer-determined Assay 99th Percentile

- a. by Location
- b. by Assay Sensitivity

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Table 1

Troponin Assay, Manufacturer-Determined 99th Percentile and Myocardial Infarction Decision Level

Manufacturer	Assay Model	Assay Type (I or T)	Assay Sensitivity	Number of sites	Manufacturer-determined 99 th percentile	Lowest MI decision level	Highest MI decision level	Lowest MI decision level/99 th percentile ratio	Highest MI decision level/99 th percentile ratio
Abbott	Architect	I	Standard	39	0.028 ng/mL	0.012 ng/mL	0.5 ng/mL	0.4	17.9
	AXSYM ADV	I	Standard	1	0.04 ng/mL	0.04 ng/mL	0.04 ng/mL	1.0	1.0
	I-STAT	I	Standard	6	0.08 ng/mL	0.04 ng/mL	0.1 ng/mL	0.5	1.3
Alere	Architect	I	High	10	26 ng/L; (15.6ng/L for women; 34.2ng/L for men)	28 ng/L	300 ng/L	1.1	11.5
	Triage Cardio 3	I	Standard	4	0.022 ng/mL	0.02 ng/mL	0.1 ng/mL	0.9	4.5
	Accu Tnl	I	Standard	24	0.04 ng/mL	0.014 ng/mL	0.5 ng/mL	0.4	12.5
Beckman-Coulter	AccuTnl+3 Access	I	Standard	8	0.02 ng/mL	0.04 ng/mL	0.5 ng/mL	2.0	25.0
	AccuTnl+3 Dxi	I	Standard	3	0.03ng/mL	0.03 ng/mL	0.24 ng/mL	1.0	8.0
	VIDAS	I	Standard	4	0.01 ng/mL	0.01 ng/mL	0.16 ng/mL	1.0	16.0
bioMerieux	Vitros	I	Standard	17	0.034 ng/mL	0.12 ng/mL	0.034 ng/mL	0.9	3.5
Ortho Clinical Diagnostics	AQT90	T	Standard	1	0.017 ng/mL	0.03 ng/mL	0.03 ng/mL	1.8	1.8
	Cobas Elecsys	T	Standard	27	0.01 ng/mL	0.01 ng/mL	0.01 ng/mL	1.0	1.0
	Cobas h232	T	Standard	8	Not applicable/Qualitative assay *	–	–	–	–
Roche	Cobas 600	T	High	61	14 ng/L	14 ng/L	140 ng/L	1.0	10.0
	Advia Centaur	I	Standard	39	0.04 ng/mL	0.014 ng/mL	0.9 ng/mL	0.4	22.5
	Dimension Vista	I	Standard	30	0.045 ng/mL	0.021 ng/mL	0.135 ng/mL	0.5	3.0
Siemens	Dimension EXL	I	Standard	7	0.056 ng/mL	0.056 ng/mL	0.056 ng/mL	1.0	1.0
	Dimension RXL	I	Standard	4	0.070 ng/mL	0.070 ng/mL	0.1 ng/mL	1.0	1.4
	Immolute 1000	I	Standard	1	0.3 ng/mL	1.0 ng/mL	1.0 ng/mL	3.3	3.3
Tosoh	Immolute 2000	I	Standard	1	0.29 ng/mL	0.29 ng/mL	0.29 ng/mL	1.0	1.0
	AIA360	I	Standard	1	0.060 ng/mL	0.060 ng/mL	0.060 ng/mL	1.0	1.0

Lowest and highest MI decision levels refer to lowest and highest cardiac troponin concentrations used as the decision limit to diagnose myocardial infarction among all laboratories using that particular assay.

* For 8 laboratories that use sex specific troponin concentration thresholds for decision limit for myocardial infarction, the troponin concentration threshold used for men was used to determine the ratio of cardiac troponin decision limit to manufacturer-determined 99th percentile. For 20 sites that use 2 Tn assays, both assays are included in the table.