American Journal of Emergency Medicine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

High sensitivity troponin: The Sisyphean pursuit of zero percent miss rate for acute coronary syndrome in the emergency department

Shane M. Summers, MD [a], Brit Long, MD [a,*], Michael D. April, MD, DPhil [a], Alex Koyfman, MD [b], Curtis J. Hunter, MD [a]

[a] Department of Emergency Medicine, Brooke Army Medical Center, 3841 Roger Brooke Dr, Fort Sam Houston, TX 78234, United States
[b] Department of Emergency Medicine, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, United States

ARTICLE INFO

Article history:
Received 22 February 2018
Received in revised form 22 March 2018
Accepted 28 March 2018
Available online xxxx

Keywords:
Troponin
High sensitivity
Acute coronary syndrome
Diagnostic accuracy
Emergency department

ABSTRACT

Background: The United States Food and Drug Administration recently approved a high sensitivity troponin (hsTn) assay for use. Recent literature has investigated the diagnostic accuracy of hsTn for acute coronary syndrome (ACS) in the emergency department (ED) and its use in accelerated diagnostic protocols.
Objective: This article evaluates the existing literature and discusses incorporation of hsTn testing into ED clinical practice based on best available evidence.
Discussion: Interpretation of this literature for clinical application is challenging due to heterogeneity across studies with regards to the hsTn assays examined, time intervals for delta troponin tests, and study populations. The high sensitivity of these assays is predicated upon the ability of the physician to clinically determine a patient to have a low pre-test probability of disease. Physicians may further ensure maximal sensitivity by defining the cut-off for a positive value as the limit of detection and utilizing delta troponin testing. These assays do not obviate the need to consider follow-up for risk stratification for discharged patients. Higher sensitivity compared to standard troponin tests comes at the expense of lower specificity. Indiscriminate testing may translate to greater numbers of abnormal troponin results in patients with non-ACS syndromes, potentially leading to increased healthcare costs, hospital admissions, increased ED lengths of stay, and unnecessary interventions.
Conclusion: As hsTn becomes more widespread, it is imperative emergency physicians understand its potential and limitations. Knowledge of test characteristics is vital to ensure appropriate use. Further study of hsTn is required to optimize use.

Published by Elsevier Inc.

Contents

* Corresponding author.
E-mail addresses: shane.m.summers.mil@mail.mil, (S.M. Summers), brit.long@yahoo.com, (B. Long), michael.d.april.mil@mail.mil, (M.D. April), curtis.j.hunter.civ@mail.mil. (C.J. Hunter).

https://doi.org/10.1016/j.ajem.2018.03.075
0735-6757/Published by Elsevier Inc.

1. Introduction

After several years of international experience, the U.S. Food and Drug Administration recently approved a high sensitivity troponin (hsTn) assay for clinical use in the U.S. Proposed applications include the earlier identification of acute myocardial infarction (AMI), the assessment of myocardial injury in non-ACS syndromes such as pulmonary embolism, long term monitoring for drug cardiotoxicity, and prognostication of patients with chronic disease states such as congestive heart failure and renal insufficiency [1]. The application likely to be of the most interest to emergency physicians is achieving the rapid rule out of acute coronary syndrome (ACS) and identifying patients safe for discharge from the emergency department (ED).

The major concern with the widespread application of hsTn in the assessment of acute chest pain is the tradeoff of higher sensitivity at the expense of lower specificity. Indiscriminate use without consideration of the clinical context will undoubtedly lead to false positive results, unnecessary admissions, further invasive testing, and perhaps harmful interventions. Indeed, some cardiologists have voiced concerns about the "imminent plague of troponinitis" doomed to afflict EDs in the U.S. [2]. To avoid this, emergency physicians should utilize Bayesian principles and formulate a reasonable pre-test probability for ACS before applying test results [3,4]. In this article we will review existing literature, discuss potential pitfalls in the clinical use of these assays, and make recommendations for hsTn incorporation into ED clinical practice based on best available evidence.

1.1. Literature review methods

The objective of this narrative review is to determine the diagnostic accuracy of hsTn for AMI and 30-day major adverse cardiac events (MACE) in ED patients with possible ACS. We searched PubMed and Google Scholar with terms including "high sensitivity troponin," "emergency department," "acute coronary syndrome," "diagnosis," and "rule out". We included randomized controlled trials (RCT), prospective observational cohorts, and meta-analyses assessing diagnostic accuracy of hsTn in the ED setting for ACS. We excluded retrospective studies. Our final in-depth analysis included 18 studies (Table 2) of the 73 references utilized. Other included references detail test characteristics and background, guideline recommendations, and descriptions of troponin use in emergency medicine including editorials and review articles. We did not pool data for meta-analysis, and it is possible we missed studies evaluating hsTn in other settings or populations (such as in admitted patients to a medical floor or intensive care unit).

2. Discussion

2.1. Definition of hsTn assays and analytic characteristics

The term "high sensitivity" refers to the analytic characteristics of the assay and means the laboratory is capable of detecting the presence of traditional cardiac biomarkers (troponin I and troponin T) at much lower concentrations than previously achievable with standard assays. For a troponin assay to carry the label of "high sensitivity," certain analytical characteristic are required [5]. First, the assay must be sufficiently sensitive to detect the presence of circulating troponin *in at least 50% of healthy, asymptomatic individuals*. Second, the assay must be precise, as defined by a coefficient in variation (COV) of <10%. This precision ensures test reliability for delta (Δ) troponin testing [5].

Each assay has its own analytic characteristics as reported by the manufacturer. Manufacturers report these characteristics utilizing the following clinical chemistry nomenclature: limit of blank (LOB), limit of detection (LOD), and 99th percentile upper reference limit (URL) [6]. There is significant heterogeneity among assays, and because studies commonly report these terms when comparing them for use in clinical decision pathways, further explanation of these properties is needed.

First, the LOB is the highest *apparent* analyte concentration expected to be found when testing a sample containing no analyte [7]. If a chemist ran a sample with no troponin multiple times and recorded the results, the troponin concentration result should theoretically be zero. However, running a sample multiple times may on occasion falsely detect a troponin elevation in some samples devoid of troponin. The LOB is therefore set to the 95th percentile of analyte concentrations reported in samples without analyte. The remaining 5% of concentrations reported for a blank sample represent false positive (alpha, or type 1 error). On the other hand, it is possible that samples with analyte might produce concentration estimates less than LOB, representing false negatives (beta, or type II error) (Figs. 1 and 2).

The LOD is the lowest concentration of analyte reliably distinguishable from the LOB. Determination of the LOD entails repeated measurements of samples known to contain small but known concentrations of analyte. The LOD represents the mean of a Gaussian distribution of reported concentration values for which 5% of values are less than the LOB. The LOD is the concentration that defines positivity for detection *but does not necessarily define abnormal.*

The URL is the concentration of analyte that is greater than the 99th percentile in the reference population and is considered abnormal. Note that this abnormality does not necessarily imply ischemic heart disease, as there are other etiologies for troponin elevation (Table 1) [8]. A major challenge in determining the URL for high sensitivity troponin assays is establishing consensus on what defines the appropriate reference population. Predictably, there is much variability in the 99th percentile value depending on the population characteristics [9,10]. For example, a population with a high proportion of geriatric patients with chronic kidney disease would likely have a higher URL than a younger, healthier cohort [11,12]. Further complicating interpretation of the URL, 99th percentile values differ between men and women. Thus, for the Abbott Architect high sensitivity troponin I (hsTnI), several studies adopted gender-specific cutoffs [13-16].

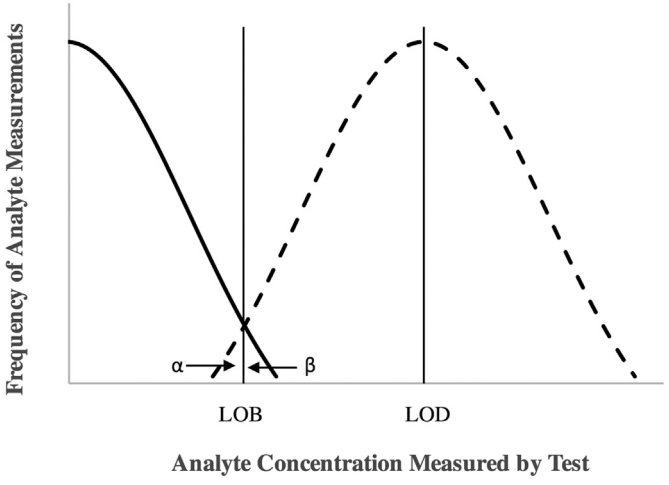

Fig. 1. Representation of LOB and LOD with analyte measurements. The horizontal axis represents the analyte concentration as measured by a test. The vertical axis represents the frequency of a particular analyte concentration measurement. The solid line represents the distribution of analyte concentration values for a population without any analyte. The dashed line represents the distribution of analyte concentration values for a population with a small but measurable concentration of analyte. The left vertical line represents the limit of blank, or the 95th percentile of the measured analyte concentration for samples not containing any analyte. The right vertical line represents the limit of detection, or the 50th percentile of the measured concentration of analyte in a population with a small but measured concentration of analyte. Alpha represents the probability of a false positive, or concluding there is measurable analyte in a sample without analyte. Beta represents the probability of a false negative, or concluding there is no measurable analyte in a sample with detectable analyte.

Please cite this article as: Summers SM, et al, High sensitivity troponin: The Sisyphean pursuit of zero percent miss rate for acute coronary syndrome in the emergency department, American Journal of Emergency Medicine (2018), https://doi.org/10.1016/j.ajem.2018.03.075