DIAGNOSING ACUTE CORONARY SYNDROME IN THE EMERGENCY DEPARTMENT USING HIGH SENSITIVITY TROPONIN I

by

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Abstract

Timely diagnosis of acute coronary syndrome (ACS), the most lethal manifestation of ischemic heart disease, remains challenging. Due to limitations in the diagnostic accuracy and costs associated with current methods for diagnosing ACS, evaluating patients for ACS in the emergency department (ED) can last up to 24 hours. The consequences of such prolonged ED evaluation are: high personal cost to the patient, significant financial costs to the healthcare system (estimated at $3 to $4 billion annually), and additional strain on an already overstretched emergency medical care system.

Measurement of circulating levels of cardiac troponin (cTn) is central to the diagnosis of acute myocardial infarction. Recent advances in clinical chemistry have yielded significant improvements in the analytic performance of cardiac troponin assays (cTn), resulting in superior sensitivity and precision. These high sensitivity cTn (hsTn) assays are able to detect up to ten-fold lower concentrations of cTn than current generation cTn, resulting in earlier diagnosis of acute myocardial infarction (AMI), reclassification of some unstable angina patients as AMI and shortened duration of the rule out AMI period for some patients. However, they also result in an increase in the number of non-ACS patients who will have elevated hsTn values, amplifying the clinical challenge of determining which patients with elevated cTn warrant inpatient admission versus outpatient management. There are insufficient data to guide the use of hsTn for diagnosing ACS in the ED.

Chapter 1 is an introductory chapter that discusses the current paradigm of ACS evaluation in the emergency department (ED), and the promise and challenges associated with clinical use of hsTnI to diagnose ACS in the ED. Chapter 2 is a prospective cohort study that quantifies for the first time in an ED located in the United States of America (USA), the frequency and prognostic implications of new cTn elevations when a high sensitivity troponin I (hsTnI) assay is used. This chapter also characterizes factors associated with new cTn elevations and explores the effects of these new elevations on potential hospital admissions. Chapter 3 is a cross-sectional study that examines the frequency and determinants of high sensitivity troponin I (hsTnI) values in emergency department (ED) patients with a primary non-cardiac diagnosis. Chapter 4 is a cross-sectional study that determines whether hsTnI can be used as a screening test to identify suspected ACS patients who do not have significant coronary artery stenosis (candidates for early discharge). In the concluding chapter 5, I will discuss future directions of this work and propose a new paradigm for evaluating ACS in the ED using hsTnI.

Keywords from the Medical Subject Headings (MeSH) Database

1. Acute Coronary Syndrome
2. Diagnosis
3. Emergency Service, Hospital
4. Myocardial Infarction
5. Troponin (specifically cTnI)

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Diagnosing acute coronary syndrome

Timely diagnosis of acute coronary syndrome (ACS) in the emergency department remains challenging. Each year, about 5-7 million visits are made to emergency departments (ED) across the United States for chest pain and other symptoms concerning for acute coronary syndrome (ACS).[1,2] ACS, the most lethal manifestation of ischemic heart disease, occurs when there is acute disruption of coronary blood flow, leading to a mismatch between myocardial oxygen demand and supply, and ultimately resulting in myocardial ischemia and infarction.[3,4] The term ACS encompasses acute myocardial infarction (AMI) comprised of ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) , and unstable angina (UA).[5]

Initial diagnostic testing for ACS begins with an ECG (Figure 1.1). However, the sensitivity of the initial ECG for diagnosing AMI has been reported to be as low as 40-50%.[6,7] Even when used in combination, history and physical examination, initial ECG, cannot reliably exclude ACS.[8] Thus, suspected ACS patients with non-diagnostic ECGs undergo additional testing including serial biomarker measurements. In fact, the current definition of AMI is based on biomarker (cardiac Troponin [cTn]) measurements. The 2012 “universal definition” of AMI according to Global AMI Task force (endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF))[9] defines AMI as the detection of a rise and/or fall of cardiac biomarker

values (preferably cTn) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia.
- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

Patients with ECG and serial troponin measurements that are non-diagnostic for AMI, but have new onset or severe exertional angina (Canadian Cardiovascular Society grade III or higher[10]) are classified as having unstable angina. However, with recent improvements in the sensitivity of cTn assays this category of patients is becoming vanishingly small.[11]

The biology of cardiac troponins

The troponin complex, consisting of three structural proteins (Troponin C [TnC], Troponin I [TnI] and Troponin T [TnT]), plays an integral part in the contraction of cardiac and skeletal muscle but not smooth muscle. Muscle contraction occurs when intracellular calcium ions increase and bind to the high affinity calcium-binding site TnC, resulting in conformational changes in TnT and TnI. TnT binds to tropomyosin, which facilitates the formation of cross bridges between filamentous actin and myosin.[12] TnI is an inhibitory subunit which binds

actin-tropomyosin and prevents contraction in the absence of calcium binding (which is released when it binds to calcium-TnC resulting in crossbridge formation and contraction).

Human cTnT is a 38 kDa protein comprising of 298 amino acid residues, whereas cTnI is approximately 23 kDa and is made up of 210 amino acid residues, and cTnC is an 18 kDa protein made up of 161 amino acid residues.[13] Cardiac troponin C (cTnC) is identical to skeletal slow troponin C (sTnC) although distinct from skeletal fast cTnC, hence it is not a useful biomarker of myocardial disease. cTnT and cTnI are unique isoform that is only expressed in cardiac, while slow and fast skeletal muscle have their associated isoforms (cTnT, cTnI, ssTnT, ssTnI, sfTnT and sfTnI, respectively).[14] TnT is also complicated by the existence of a number of splice variants that can be expressed differentially. Importantly, there is 56.6% and 58.3% homology between cTnT and fsTnT and ssTnT respectively.[15] Cardiac (cTnI), fast-twitch skeletal muscle (fast cTnI) and slow-twitch skeletal muscle (slow cTnI) isoforms have about 40% amino acid sequence homology, and in particular cTnI have an 32 amino acid N-terminal extension that not present in either skeletal isoforms.[15] As a result, antibodies used in clinical enzyme-linked immunosorbent assay (ELISA) assays for cTnT and cTnI are selected based on their ability to recognize epitopes that have no sequence homology with skeletal TnI or TnT. However, there are still reports of falsely elevated cTnT secondary to diseased skeletal muscle, despite the use of fourth generation and high sensitivity cTnT assays.[16] During myocardial ischemia, changes in cell membrane integrity cause an initial

release of cTn, followed by a continuous release of cTn from disintegrating myocytes that occurs during myocyte necrosis (or potentially other cell death mechanisms).[17] It is worth noting that myocyte necrosis is not a requirement for troponin release.[18] Other factors such as cellular apoptosis, normal myocyte turnover,[19] preload induced caplain-mediated proteolysis,[20] integrin-mediated increased cellular wall permeability,[21] and formation and release of membraneous blebs.[22]

Rationale for serial measurements of cardiac troponins

cTnI or cTnT can be measured in serum by ELISA within 1-6 hours of onset of myocardial injury (or cellular membrane disruption).[23] Despite recent improvements in the sensitivity of cardiac troponin assays approximately 10-20% of patients with AMI have a negative cTnI or cTnT on presentation.[24,25] The mechanisms underlining NSTEMI patients with initial cTnI negative are likely related to the following: short time interval between onset infarction and ED presentation or blood draw;[24,26] incomplete occlusion of coronary vessels;[27] and conversion from unstable angina to NSTEMI after presentation.[26] Cullen *et al.* recently demonstrated that a combination of clinical characteristics and ECG findings can rule-out AMI patients in a subset of patients.[28] Although the optimal timing of serial cTn measurements remains unclear, it remains unlikely that a single criterion will be applicable to all patients. The optimal timing of serial cTn measurements will depend on assay characteristics, time of onset of symptoms, whether symptoms are constant or intermittent, and other evidence of ischemia (such as concerning clinical story or concerning ECG findings).

All troponin assays are not equal

Circulating troponin exists as a mixture of complex (trimer, dimer) and free monomers (or bound to other circulating proteins) [29,30]as the intact and modified forms including degraded, phosphorylated/un-phosphorylated, glycosylated, acetylated and oxidized/unoxidized forms; among others. Post-translational modifications of cTnI and cTnT (including selective degradation) occurs predominantly in the myocardium in response to ischemia, leading to a high number of modified cTn products[31 32] (See Figure 1.2). In a study of patients with AMI, a cTnI degradation product was identified as early as 90 minutes after onset of symptoms.[33] Up to 11 cTnI degradation products have been identified in AMI patients.[34] During ischemia, proteolysis of the C-terminal of cTnI occurs, followed by N-terminal proteolysis cleavages that subsequently occur with increasing degree of ischemia. Furthermore, numerous studies have demonstrated that cTn can be phosphorylated at multiple amino acid residues with resulting alterations in function.[35-37] Zhang *et. al.* demonstrated that selective and functionally significant phosphorylation alterations occur on individual residues of cTnI in heart failure.[38] The clinical implications of cTn phosphorylations are not well understood. Although several of the novel sites were identified by Zhang *et. al.,* they have not yet been investigated for their functional affects. The above mentioned post-translational modifications of cTn may affect its immunoreactivity and hence the results of cTn ELISA assays. Although standardization or harmonization of the various cTnI clinical ELISA have occurred, given the heterogeneity of cTn in circulation the ELISA values

obtained may not reflect the 'True" concentration for a particular individual . Owing to patent restrictions, cTnT assays are available from one company (Roche) and the current generation of cTnT assays (fifth generation) have been approved for clinical use in Europe. Like cTnI, cTnT also has known proteolytic and phosphorylation and other PTMs, which could affect this ELISA cTnI assays have been developed by a number of different manufacturers including: Abbott Laboratories, Beckman Coulture, Siemens, Singulex, Nanosphere, Ortho Clinical Diagnostics among others.[39] Each manufacturer uses their own set of proprietary antibodies and reference standards. Thus, cTnI values using assays from different manufacturers are not comparable. A first step towards cTnI standardization would involve a universal adoption of capture and detection antibodies.[40] Thus, the value obtained for each assay will depend on the exact epitopes of the two anti-cTnI antibodies and the amount of TnI or TnI fragments which contain both epitopes. Thus, if proteolysis or another PTM eliminates on the availability of one of the epitopes, it will not be measured. This extent to which this occurs will vary for each individual and for each assay.

High sensitivity troponin: the new generation of troponin assays.

Recently, clinicians have begun to use the recommended cut-off values for current generation cardiac troponin assays; the 99th % upper reference limit (URL). Previously, there was reluctance to use these cut off values because they are associated with frequent elevations in cTn not associated with acute ischemic heart disease (such as: tachy/brady arrhythmias, cardiac structural abnormalities, coronary vasculitis, renal failure, sepsis, severe acute neurological disease,

cardiotoxic agents, heart failure among others[9]). Thus there was a tendency to use cut-off values for troponin that equated with the prior gold standard diagnosis developed with less sensitive markers such as creatine kinase MB isoenzyme (CKMB) or the lowest value at which assay achieved a 10% co-efficient of variation (CV) which was thought to reduce false positive elevations. The use of the 99th% URL increases the ability of these assays to detect both acute myocardial infarction and structural cardiac morbidities.[41] This change in practice should not be confused with increasingly sensitive assays.

Preparing the United States for High Sensitivity Cardiac Troponin Assays Manuscript:

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Improvements in the analytic performance of cardiac troponin assays (cTn) have resulted in superior sensitivity and precision. Improved sensitivity occurs because of more sensitive antigen binding and detection antibodies, increases in the concentration of the detection probes on the tag antibodies, increases in sample volume, and buffer optimization.[15] Assays now are able to measure 10-fold lower concentrations with high precision [a co-efficient of variation (CV) <10% at the 99th % of the upper reference limit (URL)]. The high sensitivity cTnT (hs-cTnT) assay is already in clinical use throughout most of the world. It is only a matter of time before high sensitivity assays are approved for use in the United States. In preparation for this, there are a number of important

issues that deserve consideration. They will be helpful as well with the use of the 99th% URL with contemporary assays.

The need for a universally accepted nomenclature.

The literature is replete with terminologies used to refer to cTn assays. We advocate the use of the term “high sensitivity cardiac troponin assays” (hs-cTn) for cTn assays that measure cardiac troponin values in at least 50% of a reference population.[15,42] This is a policy we are informed has now been embraced by the journal Clinical Chemistry. High sensitivity assays can be further categorized as well.

Ideally, assays should have a CV of <10% at the 99th % value. Assays that do not achieve this level are less sensitive. However, they do not cause false positives and they can be used.[43]

Defining uniform criteria for reference populations

There is a lack of consistency in the types and numbers of subjects that should/can constitute a reference population.[15] Often, participants are included after simple screening by check list but without a physical examination, electrocardiogram, or lab work. At other times, a normal creatinine and/or a normal natriuretic peptide value is required. Imaging to detect structural heart disease is rarely used. It is known that gender, age, race, renal function, heart failure and structural heart disease, including increased left ventricular (LV) mass are associated with increased cardiac troponin concentrations, [44-46] and that an assay’s 99th % value depends on the composition of the reference group. Thus, the more criteria used, the lower the reference values (Figure 1.3).[44] The

appropriate reference value to use clinically also is far from a settled issue. It might be argued that using a higher 99th % value for the elderly allows comparison of the patient to his/her peers but in raising the cut off value, if the increases are due to comorbidities, those who are particularly healthy will be disadvantaged.[47] Gender and ethnicity are not comorbidities and we would urge should be taken into account. It is clear that regardless of the assay, there will need to be different 99th% values for men versus women.[15] The reference population for assay validation studies should ideally be based on demographic characteristics that mirror the United States population and include subjects whose blood pressure, serum glucose, creatinine and natriuretic peptide values are within the normal reference range and who take no cardiac medications. These subjects should be free from structural heart disease documented by echocardiography, cardiac MRI or CT angiography. Meeting these criteria will be a major challenge especially for older individuals although some initial studies have been performed.[48] A conjoint pool of samples collected with the support of commercial manufacturers so that all companies could use the identical patient population for their reference ranges would be a major advance. One large national effort would probably be more cost effective than multiple smaller efforts.

Regardless of reference values, solitary elevations of hs-cTn values (>99th %) will be inadequate for clinical decision making.[49] The exception may be very elevated values which are most often due to myocardial infarction or myocarditis once possible analytical confounds are eliminated. In other circumstances, serial

changes in hs-cTn values will be required to determine whether acute myocardial injury is present.

Discriminating acute from non-acute causes of hs-cTn elevations

With the ability to precisely measure small concentrations of cTn clinicians will be faced with the challenge of discriminating between patients who have acute problems from those with chronic elevations from other etiologies. Using the 4th generation cTnT assay, approximately 1% of patients in the general population in the US have modest elevations >99th% URL.[50] In the same population, this number was 2% with the hsTnT assay.[45] Of that number, only half had documentation (even with imaging) of cardiac abnormalities. If the prevalence of a positive cTnT is 2% in the general population, it will likely be 10 or 20% in the ED and even higher in hospitalized patients, since these patients often have cardiac comorbidities.

Measurement of changes in hs-cTn over time (δ hs-cTn) improves the specificity hs-cTn for the diagnosis of acute cardiac injury.[51,52] However, it does so at the cost of sensitivity. With contemporary assays, differences in analytical variation have been used to define an increasing pattern. At elevated values, the coefficient of variation (CV) for most assays is in the range of 5-7% so a change of 20% ensures that a given change is not due to analytical variation alone.[49] At values near the 99th % URL, higher change values are necessary.[52] The situation with hs-cTn assays is much more complex:

1. Change criteria are unique for each assay.

2. It will be easy to misclassify patients with coronary artery disease who may present with a non-cardiac cause of chest pain but have elevated values. They could be having unstable ischemia or elevations due to structural cardiac abnormalities and non-cardiac discomfort. If hs-cTn is rising significantly, the issue is easy but if the values are not rising, a diagnosis of AMI still might be made. If so, some patients may be included as having AMI without a changing pattern. This occurred in 14% patients studied by Hammarsten et al.[53] If patients with elevated hs-cTn without a changing pattern are not called AMI, should they be called patients with "unstable angina and cardiac injury" or patients with structural heart disease and non-cardiac chest pain? Perhaps both exist?
3. The release of biomarkers is flow dependent. Thus, there may not always be rapid access to the circulation. An area of injury distal to a totally occluded vessel (when collateral channels close) may be different in terms of the dynamics of hs-cTn change than an intermittently occluded coronary artery.
4. Conjoint biological and analytical variation can be measured. They are assay dependent and the reference change values (RCV) range from 35%-85%.[15] The use of criteria less than that (which may be what is needed clinically) will thus likely include individuals with changes due to conjoint biological and analytical variation alone. This has been

shown to be the case in many patients with non-acute cardiovascular diagnoses.[53,54]

5. Most evaluations have attempted to define the optimal delta, often with receiver operator curve analysis. Such an approach is based on the concept that sensitivity and specificity deserve equivalent weight. But higher deltas improve specificity more and lower ones improve sensitivity and it is not clear that all physicians want the same tradeoffs in this regard. ED physicians often prefer high sensitivity so that their miss rate is low (<1%), [55] whereas hospital clinicians want increased specificity. This tension will need to be addressed in defining the optimal delta.

6. The delta associated with AMI may be different from that associated with other cardiac injury.[53] In addition, women have less marked elevations of cTn in response to coronary artery disease[56] and in earlier studies were less apt to have elevated values.[57] Given their pathology is at times different, it may be that different metrics may be necessary based on gender.

7. Some groups have assumed that if a change is of a given magnitude over 6 hours, it can be divided by 6 and the one hour values can be used. This approach is not data driven and biomarker release is more likely to be discontinuous rather than continuous.[58] In addition, the values that one obtains with this approach are too small to be distinguished from a lack of change with most assays.

These issues pose a major challenge even for defining the ideal delta change value and provide the reasons why the use of this approach will reduce sensitivity.[59,60]

In addition, there is controversy in regard to the metrics that should be used with high sensitivity assays. The Australian-New Zealand group proposed a 50% change for hs-cTnT for values below 53 ng/L and a 20% change above that.[61] The 20% change is much less than conjoint biological and analytical variation. A number of publications have suggested the superiority of absolute δ cTn compared to relative δ cTn, in discriminating between AMI and non-AMI causes of elevated cTn.[62-64] However, the utility of the absolute or relative δ cTn appears to depend on the initial cTn concentration and the major benefit may be at higher values.[62] A recent publication by Apple et al calculates deltas in several different ways with a contemporary assay and provides a template for how to do such studies optimally.[65] If all studies were done in a similar fashion, it would help immensely. In the long run, institutions will need to define the approach they wish to take. We believe this discussion is a critical one and should include Laboratory, ED and Cardiology professionals.

Distinguishing between Type 1 and Type 2 AMI.

Although δ cTn is helpful in distinguishing between AMI and non-acute causes of troponin release, it may or may not be useful in discerning type 1 from type 2 AMI. As assay sensitivity increases, it appears that the frequency of type 2 AMI increases. However, making this distinction is not easy. Type 1 AMI is due to a primary coronary event, usually plaque rupture. It is managed acutely with

aggressive anticoagulation, and revascularization (percutaneous coronary intervention or coronary artery bypass).[49] Type 2 AMI, typically evolves secondary to ischemia from an oxygen demand/supply mismatch such as severe tachycardia, hypo or hypertension and the like with or without a coronary abnormality. These events usually are treated by addressing the underlying abnormalities. They are particularly common in patients who are critically ill and those who are postoperative.[66] However, autopsy studies from patients with post-operative AMI often manifest plaque rupture.[67] Thus, the more important events, even if less common, may be type 1 AMIs. Type 2 events seem more common in women who tend to have more endothelial dysfunction, more plaque erosion and less fixed coronary artery disease.[67-69] Additional studies are needed to determine how best to make this clinical distinction. For now, clinical judgment is recommended.

Analytical imprecision in cardiac troponin assays

All analytical problems will be more critical with hs-cTn assays. cTnI and cTnT are measured using Enzyme Linked Immunosorbent Assays (ELISA). As with all immunoassays, quantification of hs-cTn can be influenced by interferences between reagent antibodies and the analyte (cTn) leading to false positive or negative results.[70] Auto-antibodies to cTnI or cTnT are found in 5%-20% of individuals and can reduce detection of cTn [71,72] Additionally, fetal cardiac troponin isoforms can be re-expressed in diseased skeletal muscle and detected by the cTnT assays resulting in false positive values.[73] Several strategies including the use of blocking reagents, assay re-design and the use of antibody

fragments have been employed to reduce interferences.[74] However, these strategies do not completely eliminate them. Furthermore, there are differences in measured cTn values based on specimen type (serum versus heparinized plasma versus EDTA plasma)[75]. In addition, hemolysis may affect the accuracy of cTn measurement on some platforms [76] and it is hard to avoid especially with line draws which are common especially in intensive care units.

Ruling Out AMI

Studies evaluating the diagnostic performance of hs-cTn assays for the early diagnosis of AMI usually define AMI on the basis of a rising and/or falling pattern of current generation cTn values.[60,77] However, defining AMI on the basis of the less sensitive current generation assay, results in an underestimation of the true prevalence of AMI and an overestimation of negative predictive value of the experimental assay. It also shortens significantly the time it takes to rule in all the AMIs and thus to definitively exclude AMI since it ignores the new AMIs more sensitively detected by the hs-cTn assay. Thus, in the study by Hammarsten et al,[53] the time to exclude all AMIs was 8.5 hours when all of the AMIs detected with the high sensitivity assay were included whereas others that do not include these additional events report this can be done in 3-4 hours[60,68,77]. In our view, Hammarsten is correct.

This does not mean that hs-cTn cannot help in excluding AMI. Body has reported that patients who present with undetectable values (<than the LOB of the hs-cTnT assay) were unlikely to have adverse events during follow up. If one adds those patients to those who present later than 6 hours,[78] then perhaps a

significant proportion of patients with possible ACS could have that diagnosis excluded with the initial value. Studies need to continue to evaluate cTn values for at least 6 hours to define the frequency of additional AMIs detected in that manner. Using follow-up evaluations of patients with small event rates who are likely to have additional care during the follow-up period are likely to be underpowered. It may be that better up front risk stratification may help with this as recently reported.[55,79] Low risk patients who have good follow-up after ED visit, may be a group that can be released as early as 2 hours after presentation.[55]

Investigating the etiology of positive troponin values in non-AMI patients

Elevated troponin values (including those with high sensitivity assays) are associated with a 2 fold higher risk for longer term all-cause mortality and cardiovascular death than a negative troponin.[45,80-82] This association is dose-dependent. If values are rising, they are indicative of acute cardiac injury. Those patients should be admitted because the risk is often short term. However, if the values are stable, assuming the timing of any acute event would allow detection of a changing pattern, the risk, though substantive, in our view, often plays out in the longer term.[82] Many of these individuals, assuming they are doing well clinically can be evaluated outside of the hospital in our view. However, because such elevations are an indicator of a subclinical cardiovascular injury such evaluations should be early and aggressive. The data from several studies suggests that there may well be risk far below the 99th% URL value. Thus, it may

evolve that patients in the upper ranges of the normal range also require some degree of cardiovascular evaluation.

Risk stratifying patients with non-Acute Coronary Syndrome conditions

Patients who have a rising pattern of values have a higher risk of mortality than those with negative values regardless of the etiology. Investigations are ongoing to determine how well results from high sensitivity troponin testing help risk stratify patients with pulmonary embolism,[83] congestive heart failure,[84] sepsis,[85] hypertensive emergency[86], and chronic obstructive pulmonary disease[87]. At present, they suggest that troponin values classify patients into clinically relevant risk-subgroups. Studies are needed to evaluate the incremental prognostic benefit of high sensitivity cardiac troponin.

CONCLUSION

Routine use of hs-cTn assays in the United States is inevitable. These assays hold the promise of improving the sensitivity of AMI diagnoses, shortening the duration of AMI evaluation and improving the risk stratification of other non-cardiac diagnoses. However, to be able to fully realize their potential, additional studies are needed to address the knowledge gaps we have identified. In the interim, clinicians need to learn how to use the 99th% URL and the concept of changing values so when the day comes that hs-cTn assays are available, they will have experience with the important basic concepts

Figures

Figure 1.1: Evaluation of ACS in the emergency department

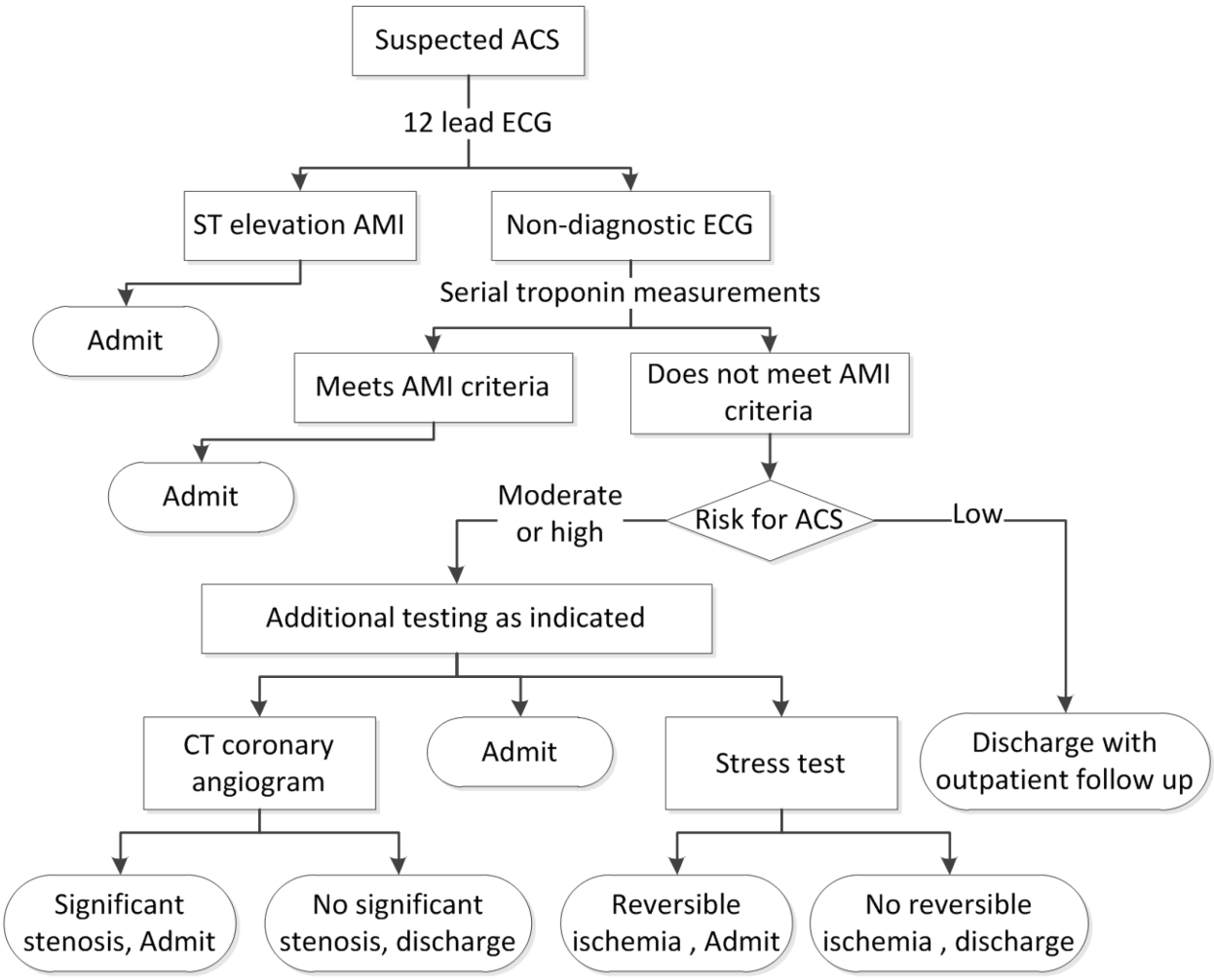


Figure 1.2: Degraded forms of cTnI in circulation

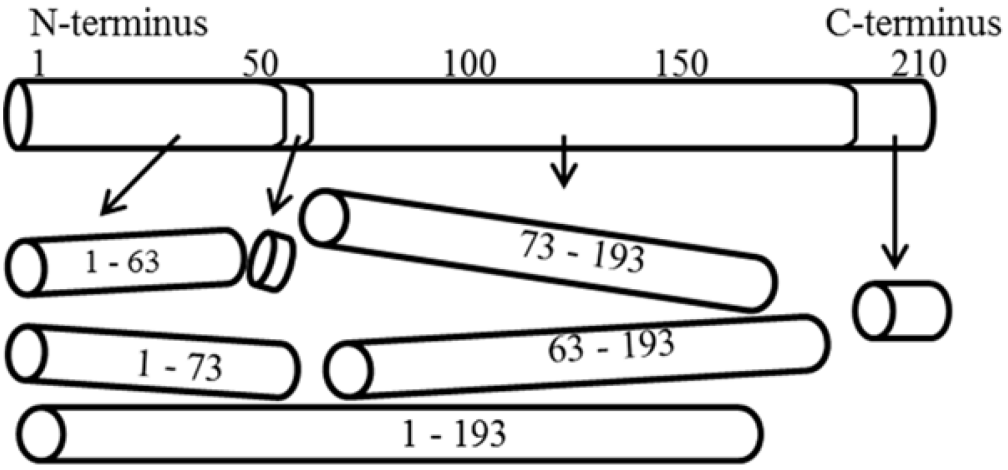
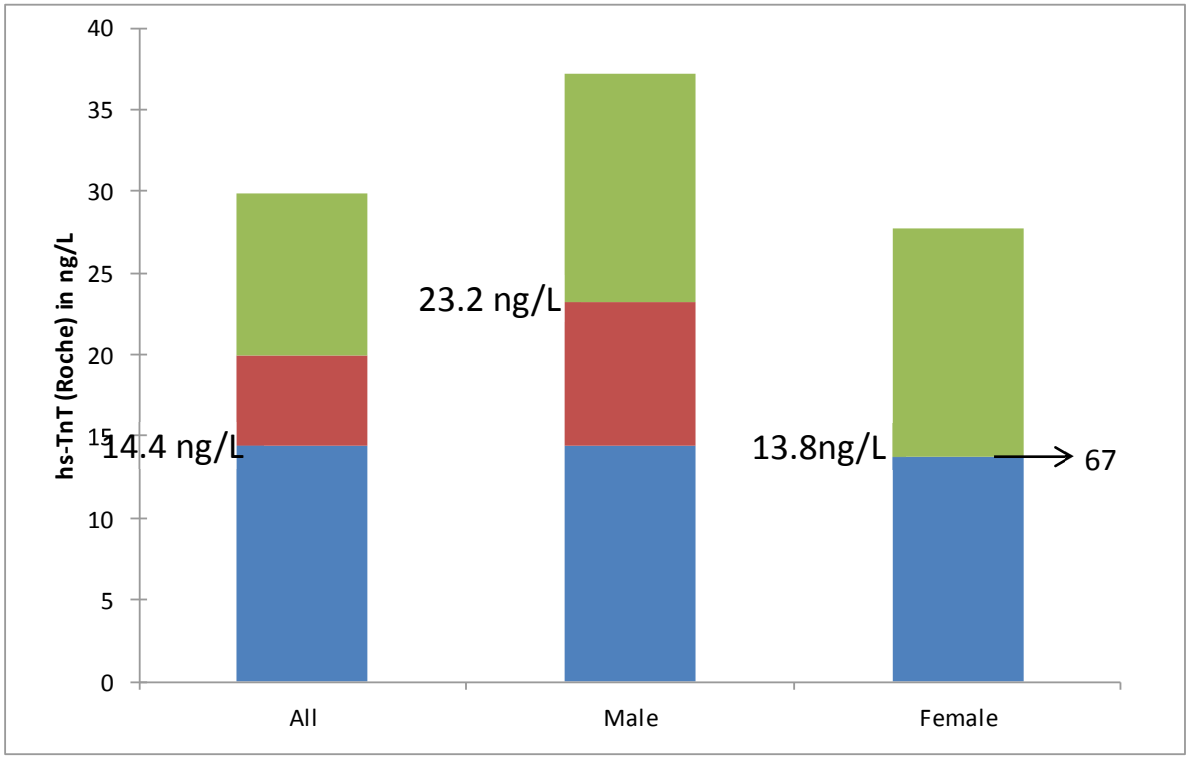


Figure 1.3: Relationship between patient characteristics and the 99% URL in healthy individuals.*



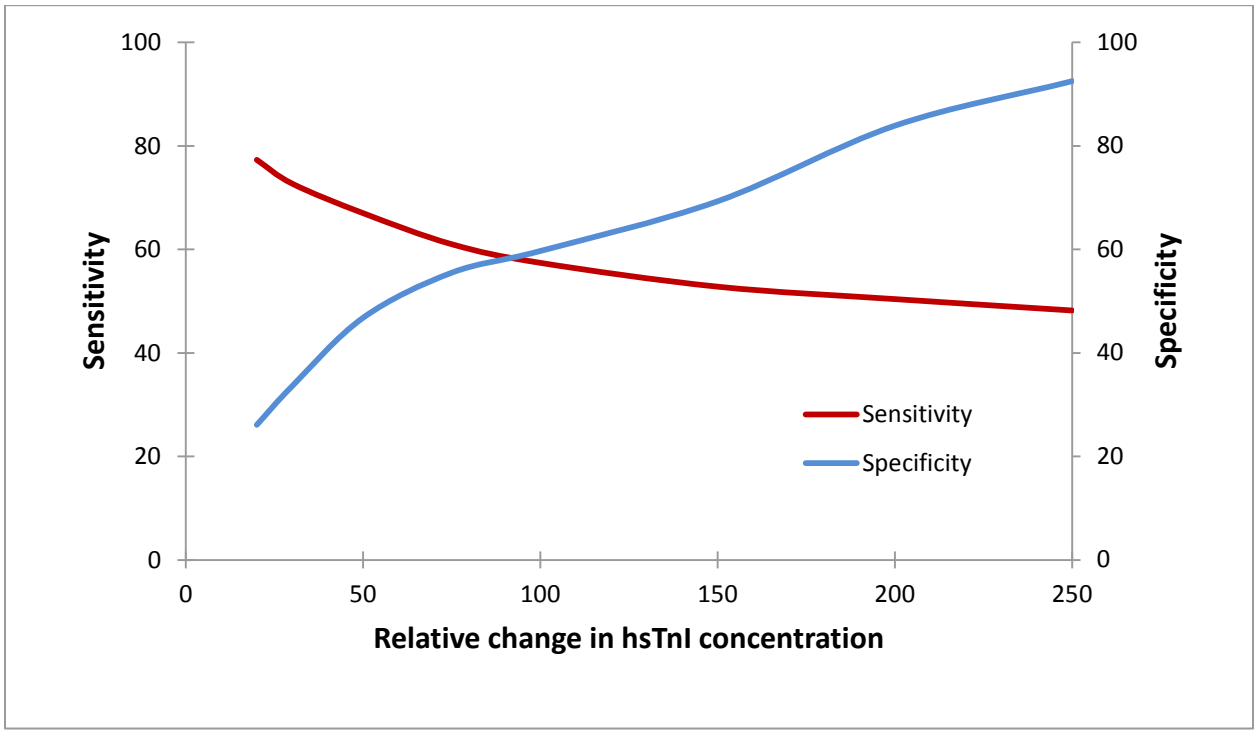
Data from Collinson *et. al.*[44]

- Healthy individuals who have comorbidities and hence did not pass questionnaire screen
- Questionnaire screened[a], but did not meet stringent BP, fasting glucose, GFR, or echocardiogram criteria
- True Normals[b]

a = No history of vascular disease or diabetes, and not taking cardioactive drugs
b = No history of vascular or cardiovascular disease, diabetes, hypertension, heavy alcohol intake, or cardiac medications AND had blood pressure ≤140/90mmHg; fasting glucose <110mg/dL; eGFR >60mL /min; LVEF > 50%; normal lung function; and no significant abnormalities on echocardiography.

* The number of observations in the normal group are not optimal for defining the 99th% URL

Figure 1.4: Defining the optimal delta: tension between sensitivity and specificity



Data from Keller et al.[59]

Chapter 2: Previously Unrecognized Elevations of High Sensitivity Cardiac Troponin I in the Emergency Department: How Frequent and How Important are They?

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Abstract

Objectives: Our aims were to quantify the prevalence of elevated high-sensitivity troponin I (hsTnI) in emergency department (ED) patients without elevated standard troponin I (cTnI), and to determine the association of these previously unrecognized hsTnI elevations with subsequent admission for a cardiac diagnosis and all-cause mortality.

Design: Prospective observational study

Setting: An urban ED that is part of a tertiary care academic institution.

Patients: ED patients evaluated for suspected acute coronary syndrome (ACS)

Interventions: HsTnI (Abbott) and cTnI (Beckman Coulter) levels were measured in 815 ED patients with chest pain, dyspnea or clinical suspicion for ACS. Treating clinicians were blinded to hsTnI measures.

Main outcome measures: Previously unrecognized hsTnI elevation (defined as hsTnI>99th% in a subject without a cTnI elevation on the initial sample). Secondary outcome was a composite of hospitalization for a cardiac diagnosis and all-cause mortality.

Results: The prevalence of previously unrecognized hsTnI on the initial sample was 10.5% (75/717) using a gender-neutral cut-off for the 99th%, and 12.7% (91/717) using a gender-specific cut-off. Patients with previously unrecognized hsTnI elevation were at higher risk for subsequent hospitalization for a cardiac diagnosis and all-cause mortality during the 1 year period following index discharge (Hazard Ratio 3.35 [95% CI: 2.22 – 5.05]) than those with no cTnI and hsTnI elevation. Additionally, their risk for subsequent hospitalization for a cardiac diagnosis and all-cause mortality was similar to those who had both cTnI and hsTnI elevations. The adjudicated diagnoses of patients with previously undetected hsTnI elevations (gender-neutral cut-off) were: 3 (4.0%) ACS, 15 (20.0%) acutely decompensated heart failure (ADHF) or 3 (4.0%) volume overload etiology unclear/non-cardiac, 4 (5.3%) cardiac (non-ACS), and 50 (66.7%) other.

Conclusions: With the use of the Abbott HsTnI, 10.5 – 12.7% of patients with previously unrecognized cTnI elevation (Beckman Coulter) had hsTnI elevations on the initial sample. Although only 4% were determined to have ACS, these patients were at higher risk for subsequent hospital admission for a cardiac condition or death during the year following discharge.

Introduction

High sensitivity cardiac troponin (hsTn) assays[88,89] including the novel hsTnI assay from Abbott are currently available for routine clinical use in Europe. Their use increases the proportion of non-ST myocardial infarctions (NSTEMI) that will have increased troponins at presentation,[25,90] and allows for novel ways of ruling out myocardial infarction (AMI).[28,91] However, hsTn assays also detect myocardial injury from many other disease conditions. Thus, clinicians will be challenged to determine the management and disposition of many more patients with cardiac injury. The frequency of this problem, the factors that lead to it and the prognosis associated with it are in part, assay and population dependent. The novel hsTnI assay from Abbott has been available since January 2013. It detects far more normal individuals than the hsTnT assay[39] and thus by that metric is more sensitive. There are very few data using this potentially more sensitive assay in ED patients. The selection of ED patients needing biomarker evaluation to rule out AMI varies according to geographic location, the size of the facility involved, and the needs of a given hospital but prior studies with hsTnT were performed in larger centers with pre-selected ED populations with high prevalence of AMI.[25,90,91] Therefore studies are needed in more heterogeneous ED populations, to better understand the impact of hsTn assays in general and specifically this new putatively sensitive assay. Thus, we sought to quantify the frequency of these previously undetected elevations and determine whether patients with these elevations are at higher risk of all-cause mortality and

subsequent hospital admission for a cardiac condition (after index discharge) than those with non-elevated troponin values.

Methods

Study design, setting and participants

A prospective observational study of patients evaluated for suspected acute coronary syndrome (ACS) was conducted after approval by the institutional review board. The study was conducted at an urban ED that sees 65,000 patients yearly and is part of a 1,000 bed academic, tertiary care institution. Patients with non-diagnostic initial ECGs, a chief complaint of chest pain or shortness of breath and cTnI ordered by treating clinicians were eligible. Such patients are routinely evaluated for possible AMI at our institution. In addition, patients with other complaints who had serial cTnI testing were eligible if their physicians confirmed that ACS was suspected. Written informed consent was obtained. Enrollment of patients occurred on weekdays from 9:00 am to 9:00 pm. Patients were excluded if they had ST elevation myocardial infarction (STEMI), left against medical advice, or if an initial blood sample was not obtained.

Data and sample collection

Research assistants interviewed subjects and their clinicians, and collected demographic and clinical information which was entered into a database via an online collection tool. [92] Blood samples were obtained at presentation and every 3 hours as dictated by the clinical care of the patient. Samples were centrifuged, and serum aliquoted and stored at -80°F within 2 hours of collection. The

hospital's cTnI assay (Beckman Coulter,Chaska, MN) Access II AccuTnI assay was used for clinical care. The 99th% upper reference limit (URL) for this assay is 40ng/L. The co-efficient of variation (CV) for this assay is 14% at 40ng/L: the 10% CV value is 60ng/L. Our clinical laboratory only reports values of cTnI≥60ng/L (the decision making cut-off for the institution). hsTnI was measured in batches using the Abbott Laboratories' (Abbott Park, IL) research-use ARCHITECT *STAT* hsTnI assay. The 99th% URL is 34.2ng/L for males, 15.6ng/L for females and 26.2ng/L overall. The limit of detection (LOD) is 1.2ng/L.[93] hsTnI data were used for research purposes only.

Estimated glomerular filtration rate was calculated from enzymatic creatinine results (Roche Modular and Cobas c701, Roche Diagnostics, Indianapolis, IN) and the IDMS-traceable 4-variable Modification of Diet in Renal Disease equation.

Outcomes and Definitions

An elevated local cTnI was defined as a value ≥60ng/L. An elevated hsTnI value was defined as >26.2ng/L. Gender-specific cutoff values were probed as well. We defined a previously unrecognized hsTnI elevation as an hsTnI>99th% in a subject with cTnI <60ng/L.

Clinical outcomes were adjudicated by a committee comprised of five board certified emergency physicians and two board certified cardiologists. ED physician reviewers blinded to hsTnI data reviewed all clinical information available and assigned the appropriate diagnosis. Disagreements between the ED physician reviewers were resolved by discussion among themselves or by a

cardiology arbitrator. AMI was defined according to the universal definition of AMI, except for the cTnI cutoff imposed at our institution.[49] A significant rising and/or falling pattern in the local cTnI values was defined as a change of at least 30% at the 10% co-efficient of variation level (18 ng/L or greater within 6-9 hours).[63] Unstable angina was defined based on the clinical history, objective ECG findings, a positive stress test or coronary artery stenosis on CT coronary angiography or coronary angiography catheterization of 70% or greater. Acutely decompensated heart failure (ADHF) was defined using modified Framingham criteria.[94] Patients with radiographic or clinical evidence of volume overload suspected from non-cardiac conditions such as end-stage renal disease were classified as volume overload, etiology unclear/non-cardiac. Patients diagnosed with myocarditis, pericarditis, valvular disorders and arrhythmia were classified as: cardiac (non-ACS).

A separate analysis was done with the investigational hsTnI assay (blinded to the cTnI assay), using criteria proposed by the ESC task force.[95] Patients diagnosed with unstable angina were considered to have NSTEMI if hsTnI values were elevated with a rising and/or falling pattern and a >20% change in the initial hsTnI within 3 hours (if the initial hsTnI was > URL) or a change of at least 50% of the URL within 3 hours if the initial hsTnI was $\leq$ URL.

We determined the time to the first occurrence of a composite of adverse events (death, or hospital admission for ACS, revascularization, ADHF or tachy/brady arrhythmia) during the year following index ED/hospital discharge. Hospital records were reviewed to ascertain these events. Additionally, a telephone

interview was conducted at least 30 days and 1 year after index ED/hospital discharge. For patients in whom follow-up could not be completed via phone or chart review, we queried the Social Security Death Master File (http://www.ssdmf.com) on August 30th, 2013, to ascertain their mortality status at 1 year after ED/hospital discharge.

Statistical Analysis

Differences between proportions were assessed with a χ^2 test. The frequency of elevated hsTnI was evaluated based on gender-neutral and gender-specific cutoffs for the 99th%. We also calculated 3 and 6 hour absolute and relative changes in hsTnI. To examine the association between hsTnI elevation and time to the first occurrence of an adverse event, we performed survival analyses using Cox proportional hazards models. We chose the day of discharge from the ED/hospital during the index visit as the origin, and follow-up time in days as the time metric. For all survival analyses, the proportionality assumption of the Cox model was confirmed by inspection of log(-log[survival function]) curves and Schoenfeld residuals. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed using STATA/MP statistical software version 11.2 (StataCorp, College Station, Texas), and RStudio statistical software version 0.97.312. Assuming the prevalence of new cTnI elevation is 9.0%, studying 815 patients allowed us to estimate the true prevalence within a ±2% confidence interval.

Results

Characteristics of enrolled patients (Table 2.1)

Between January 20th 2012 and July 31st 2012, 815 subjects were enrolled (Figure 2.1). Demographic characteristics of enrolled subjects and subjects with a troponin order, who presented on weekends or after 9pm on weekdays, during the same time period (Supplemental Table 2.2) were similar. The adjudicated final diagnoses are shown in Table 2.2. No patients initially diagnosed as having unstable angina were reclassified as having NSTEMI based on the hsTnI data.

Frequency of previously unrecognized hsTnI elevation

In the initial sample, 92.8% (756/815) of our study population had detectable hsTnI. 20.4% (166/815) had an elevated hsTnI (gender-neutral cutoff for the 99th%) and 22.0% (179/815) had elevated hsTnI (gender-specific cutoff for 99th%). With the local assay, only 12.0% (98/815) had an elevated cTnI in the initial sample. Thus, the frequency of previously unrecognized hsTnI elevation at presentation was 10.5% (75/717) with the gender-neutral cutoff, and 12.7% (91/717) with the gender-specific cutoffs. Patients with volume overload either from ADHF or from unclear/non-cardiac etiology had the highest frequency of previously unrecognized hsTnI elevation (Table 2.2). Similarly patients with a chief complaint of shortness of breath had the highest frequency of previously unrecognized hsTnI elevation (Table 2.3). Depending on the cut-off used for the 99th%, 11.8 – 17.6% ACS patients who previously had unrecognized cTnI elevation on the initial sample, had elevated hsTnI on initial measurement (Table 2.2).

Notably, 0.9% (7/815) had elevated cTnI but no hsTnI elevation. Six of these seven subjects had cTnI values of 60ng/L or 70ng/L with a 3-hour absolute

change (delta) of 10ng/L or less. The remaining patient had an initial cTnI of 329ng/L, and no change in cTnI in serial measurement. This patient had mild coronary artery disease on cardiac catheterization.

Adverse events during the year following ED/hospital discharge.

During the year following ED/hospital discharge, there were a total of 89 (11.0%) deaths and 87 (10.7%) hospital admissions for a cardiac condition (55 ADHF, 10 tachy/brady arrhythmia, 9 NSTEMI medically managed, 8 AMI with revascularization, 5 Unstable angina). Twenty-seven subjects were hospitalized for a cardiac condition prior to dying during the follow-up period. Four patients died during the index hospital admission and were excluded from the survival analyses. Subjects with previously unrecognized hsTnI elevation were at higher risk of having an adverse event during year following ED/hospital discharge than those with both un-elevated cTnI and hsTnI (hazard ratio: 3.35 [95% CI: 2.22 – 5.05]). Additionally, subjects with previously unrecognized hsTnI elevation had a similar risk of adverse events during follow up as those with both elevated cTnI and hsTnI (hazard ratio: 3.18 [95% CI: 2.12 – 4.78]). Kaplan Meier curves for the occurrence of adverse events during follow-up are presented in Figure 2.3.

Changes in hsTnI on serial measurement

Among enrolled subjects 76.1% (620/815) had serial cTnI measurement and 58.3% (475/815) had serial hsTnI measurements at 3 or 6 hours. Of the subjects with a previously unrecognized hsTnI elevation [gender-neutral cutoff] and no ACS, the median 3-hour relative change change in hsTnI was 9.1% (95%CI:5.4–13.5%), and the median absolute change was 3.7ng/L (95%CI:1.7–5.3). Based

on the ESC taskforce definition[95], 2.4% (8/337) of subjects diagnosed with "other diagnosis" who had serial samples, had a significant rise and or fall in hsTnI of 20% (or 50% if the initial hsTnI was≤URL) at 3 hours.

Sensitivity analyses

We conducted a number of analyses to determine whether our results were influenced by our definition of previously unrecognized cTnI elevation. First, previously unrecognized cTnI elevation was redefined non-elevated cTnI on the initial, 3, 6 and 9 hour samples who had elevated hsTnI on the initial sample. In this analysis, the prevalence of previously unrecognized hsTnI elevation was 8.8% (61/692). Secondly, we compared the Abbott cTnI (instead of the Beckman cTnI) to the Abbott hsTnI assay. In this analysis, the frequency of previously unrecognized hsTnI elevation was 9.3% (65/702). There were 7 patients with insufficient sample for Abbott cTnI measurement. In both analyses, subjects with previously unrecognized hsTnI were at higher risk of adverse events than those with both non-elevated cTnI and hsTnI. Additionally, their risk for adverse events was similar to subjects with both elevated cTnI and hsTnI (Table 2.4). We also probed whether the definition of elevated hsTnI using a gender-neutral or gender-specific cutoff influenced our results. In that analysis, 76.2% (618/811) of subjects had non-elevated hsTnI and 18% (146/811) had elevated hsTnI irrespective of the cutoff used. There were 30 subjects (all females) who had elevated hsTnI with the gender-specific cutoff only, and 17 subjects (all males) who had elevated hsTnI with the gender-neutral cutoff only. Patients with elevated hsTnI irrespective of the cutoff used, were at higher risk of adverse

events than those with non-elevated hsTnI irrespective of the cutoff used (Hazard ratio: 3.53 [95% CI: 2.51 – 4.97]). Furthermore, subjects who had elevated hsTnI only with the gender-specific cutoff and those who had elevated hsTnI only with the gender-neutral cutoff, were at higher risk of adverse events than those with non-elevated hsTnI irrespective of the cutoff used (Hazard ratios 2.21 [95% CI: 1.07 – 4.57] and 2.72 [95% CI: 1.18 – 6.23] respectively).

Discussion

This is the first report of hsTnI data using this newly approved highly sensitive assay in unselected ED subjects with possible ACS. Since this assay detects values in 96% of normal subjects,[39] these data may represent a better evaluation of the effects of the most sensitive hsTn assays when used in the ED, than assays that detect fewer subjects. Thus, it provides new guidance concerning the use of this assay in unselected ED subjects with possible ACS. Our data indicate that hsTn assays will assist in diagnosing ACS earlier in some subjects but the number of such subjects will not increase markedly. The preponderance of novel elevations which in this series is roughly 10% will be observed mainly in subjects with non-ACS conditions. Although all of the clinical implications of these elevations are not yet clear, patients with these new elevations have a risk of death or admission for a cardiac condition that is similar to those who currently have cTnI elevation. This suggests that at minimum, these patients will need additional evaluation to determine the etiology of hsTnI elevation and close follow-up to properly manage underlining conditions that may result in future hospitalization/death.

Most of those with elevations will have ADHF and other non ACS diagnoses such as volume overload from etiologies other than heart failure, cardiac (non-acs) conditions or cardiac conditions that complicate other primary diagnoses. The largest group (20% overall or 25% if the gender-specific cutoff is used) was ADHF. The causal mechanisms for elevations of hsTn in ADHF may include: increased wall stress, epicardial coronary artery disease, endothelial dysfunction, oxidative stress, neurohormonal activation, altered calcium handling and inflammatory cytokines.[96] It has also been suggested that elevated cTn may also be a mediator, leading to anti-cTn antibodies that result in worsening ADHF.[97] Thus, it is likely as in prior studies that hscTn elevations in subjects with ADHF will associated with increased short-term mortality and readmissions especially if the pattern of the values is rising.[84,98,99] Most of our subjects and especially those who were discharged did not have rising values. Larger future studies are necessary to determine if ADHF subjects with hsTnI elevations will benefit from more aggressive care.

The prevalence of elevated hsTnI will depend in part on whether a gender-specific or a single cutoff for the 99th % URL of the high sensitivity assay is used. We have argued for gender specific cutoffs because the 99th% URL for women with all hscTn assays is lower and because women have been reported to have lower hscTn values[56] and have been reported to less often have elevated cTn with ACS.[57] Our data further substantiate this important issue. The reported under treatment of women with ACS may be related in part to this issue. The use a gender-specific cutoff resulted in more new elevated hsTnI values compared to

a gender-neutral cutoff (91 [68 females] vs 75 [38 females]) including in subjects with ADHF. Our data demonstrates that patients who only have elevated hsTnI with either the gender-neutral or the gender-specific cutoff , are at high risk for adverse event. Additional studies are needed to better understand the optimal cutoff for clinical use.

It is also worth noting that 7 subjects had elevated cTnI with the standard assay but did not have elevations with the hsTnI assay. The one marked elevation may have been due to heterophilic antibodies which can cause elevations.[100] The other 6 reinforce the dictum that all cTn assays are different and one cannot extrapolate one to one from one assay to another.

Limitations

Our study has important limitations. First, our clinical chemistry laboratory only reported cTnI values of $\geq$60ng/L and not the 99th%. The use of the 99th% might have slightly reduced the prevalence of new positive hsTnI values. However, as reported in our sensitivity analyses, it is likely that the principles we report will be similar if the 99th% was used. Second, 6.5% (53/815) of enrolled subjects were lost to follow-up after their index discharge from the ED/hospital. They also did not have a death record in the Social Security Death Master file. It is unlikely that loss to follow up is associated with cTnI or hsTnI level, and thus it is unlikely to affect our conclusions. Third, in our cohort, only 58.4% of enrolled subjects had serial hsTnI measurements and 76.1% had serial cTnI. Some subjects with one cTnI measurement had onset of symptoms>8 hours, others had CT coronary angiography. Some subjects with cTnI but not hsTnI were missed for logistic

reasons. However, these data reflect a real world experience. Fourth, one could argue that the inclusion of subjects with shortness of breath biases the analysis. However, ED physicians feel an obligation to exclude ACS in certain subjects with shortness of breath since this symptom can be an angina equivalent. Had this group not been included the frequency of hsTnI elevations would have been lower. It should also be noted that a rising pattern of values in this group with ADHF has recently associated with adverse events.[101] Fifth, adjudication of final diagnoses was based on a current cTnI assay and all of the hospital records, potentially leading to an underestimation of AMI. However, for subjects with serial hsTnI samples, we re-analyzed the data for rising patterns in hsTnI using the ESC criteria. Finally, although the prevalence of ACS in this population was low, typical of an urban US ED population. Finally, although the frequency of ACS in reported in larger European studies is higher[102] due to different screening procedures, many smaller centers are likely to have to evaluate a more heterogeneous group such as we do in our center and we only included subjects whose physicians ordered a cTnI level to exclude ACS.

Conclusion

The frequency of previously unrecognized hsTnI elevation is URL-dependent and ranges between 10.5% and 12.7%. Patients with previously unrecognized hsTnI elevation have a higher risk for adverse event than those with non-elevated cTnI and hsTnI. Additionally, they have a similar risk for adverse events as those who have both cTnI and hsTnI elevation.

Table 2.1: Characteristics of enrolled subjects

Characteristic	Number (%)
Median Age in years (IQR)	55.4 (48.3–64.7)
Gender	
• Female	429 (52.6)
• Male	386 (47.4)
Ethnicity	
• Non-Hispanic Black	510 (62.6)
• Non-Hispanic White	222 (27.2)
• Hispanic	19 (2.3)
• Asian	18 (2.2)
• Native-American	43 (5.3)
• Native-Hawaiian	3 (0.4)
Insurance	
• Medicare	231 (28.3)
• Medicaid	219 (26.9)
• Commercial	270 (33.1)
• HMO	24 (2.9)
• VA	14 (1.7)
• None	57 (7.0)
Transportation	
• Self-transport	603 (74.0)
• Ambulance	206 (25.3)
• Transfer from other facility	6 (0.7)
Education	
• Did not complete high school	224 (27.6)
• Completed high school	251 (30.9)
• Some college	178 (21.9)
• Completed college	99 (12.2)
• Completed graduate or professional school	60 (7.4)
Currently employed	261 (32.1)
Current cigarette smoker	291 (35.7)
Current cocaine use	34 (4.2)
Family history of AMI or sudden cardiac death	260 (31.9)
History of hypertension	514 (63.1)
History of diabetes	242 (29.7)
History of high cholesterol	344 (42.2)
History of AMI or revascularization	206 (25.3)
History of congestive heart failure	173 (21.2)
History of stroke	118 (14.5)
Aspirin within last 7 days	559 (68.6)
Plavix	93 (11.4)
Nitroglycerin	110 (13.5)
Lipid lowering agent	297 (36.4)
Coumadin or warfarin	112 (13.7)

Median mean arterial pressure (IQR)	97 (86.3 – 111.3)

Table 2.2: Frequency of previously unrecognized cTnI elevation on initial blood draw (based on adjudicated diagnosis)

Adjudicated diagnosis	High sensitivity (Abbott Architect, single cutoff[a])	High sensitivity (Abbott Architect, gender-specific[b])
All (n=717)	75 (10.5%)	91 (12.7%)
Acute coronary syndrome (n=17)	3 (17.6%)	2 (11.8%)
Acutely Decompensated Heart Failure (n=47)	15 (31.9%)	22 (46.8%)
Volume overload, etiology unclear/non-cardiac (n=7)	3 (50.0%)	5 (83.3%)
Pulmonary embolus (n=7)	0 (0%)	0 (0%)
Cardiac, non-acute coronary syndrome[d] (n=35)	4 (11.4%)	4 (11.4%)
Others (n=605)	50 (8.3%)	58 (9.6%)

a = Single cutoff=26.2 ng/L
b = Gender specific cut-off: Males = 34.2 ng/L; Females = 15.6 ng/L
d = Cardiac, non-acute coronary syndrome defined as Myocarditis, Pericarditis, Valvular disorder and Arrhythmia

Table 2.3: Frequency previously unrecognized hsTnI elevations on initial blood draw (based on chief complaint)

Chief Complaint	High sensitivity (Abbott Architect, single cutoff[a])	High sensitivity (Abbott Architect, gender-specific[b])
All complaints (n=717)	75 (10.5%)	91 (12.7%)
Chest pain (n=337)	34 (10.1%)	34 (10.1%)
Shortness of breath (n=88)	13 (14.8%)	17 (19.3%)
Cardiac-related[c] (n=82)	5 (6.1%)	11 (13.4%)
Other (n=210)	23 (11.0%)	29 (13.8%)

a = Single cutoff=26.2 ng/L
b = Gender specific cut-off: Males = 34.2 ng/L; Females = 15.6 ng/L
c = Cardiac-related symptoms defined as: Dizziness, Syncope, Lightheadedness, Palpitations, Rapid heart beat, Irregular heart beat, Cardiac pacemaker and Hypertension.

Table 2.4: Sensitivity of results to changing definition of previously unrecognized cTnI elevation

	Any elevated cTnI on 0, 3, 6 or 9 hour sample instead of elevated cTnI on initial sample only		**Abbott cTnI instead of Beckman cTnI**	
	n	Hazard ratio (95% CI)	n	Hazard ratio
- cTnI, - hsTnI	631	1.00 (Reference)	637	1.00 (Reference)
+cTnI, - hsTnI	17	1.43 (0.45 – 4.53)	6	1.10 (0.15 – 7.91)
- cTnI, +hsTnI	61	3.14 (1.99 – 4.94)	65	2.96 (1.89 – 4.62)
+cTnI, +hsTnI	102	3.39 (2.32 – 4.96)	96	3.50 (2.38 – 5.16)

Figure 2.1: Derivation of study population

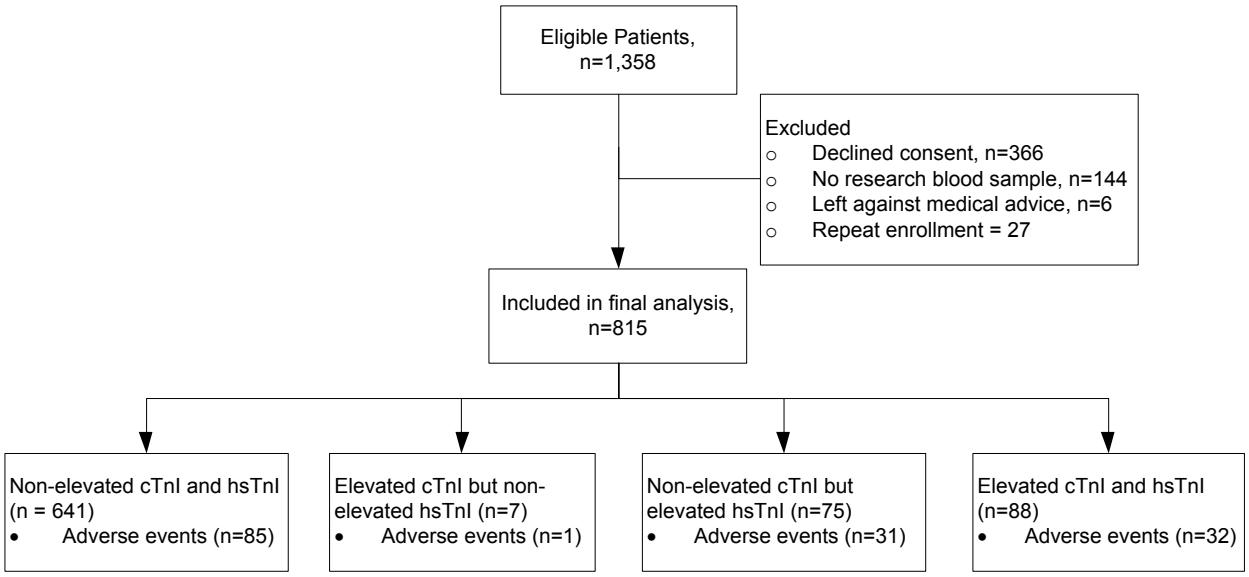


Figure 2.2: hsTnI values at ED presentation among subjects with non-elevated standard cTnI in initial sample.

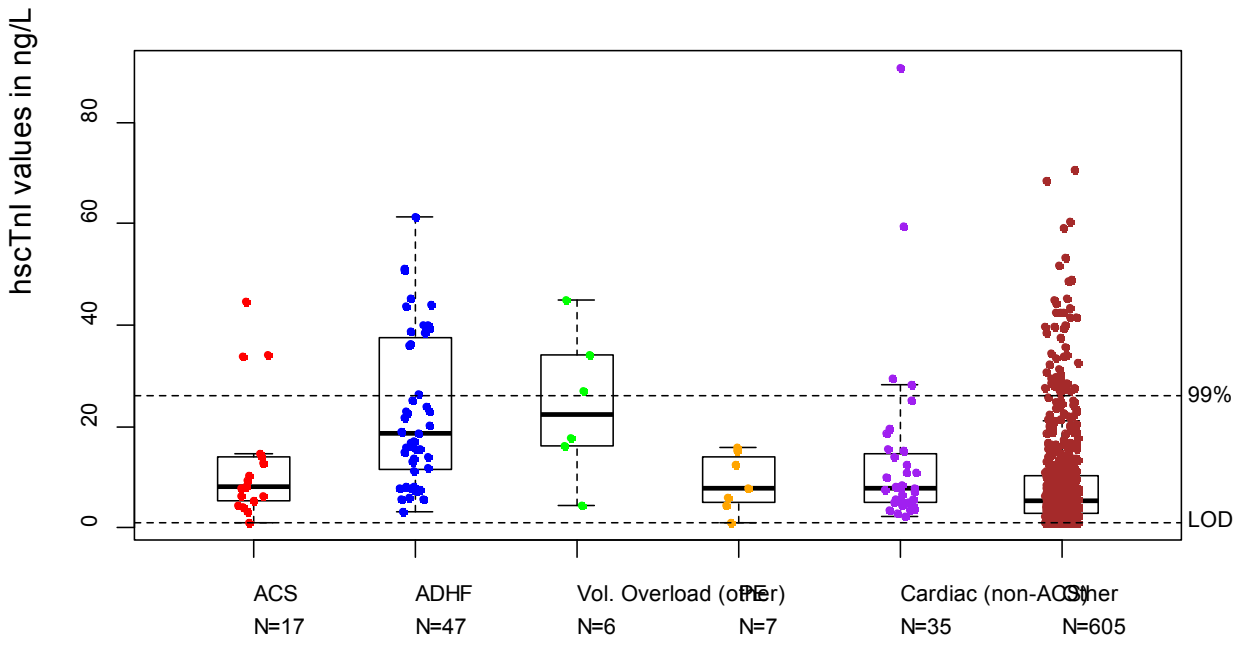
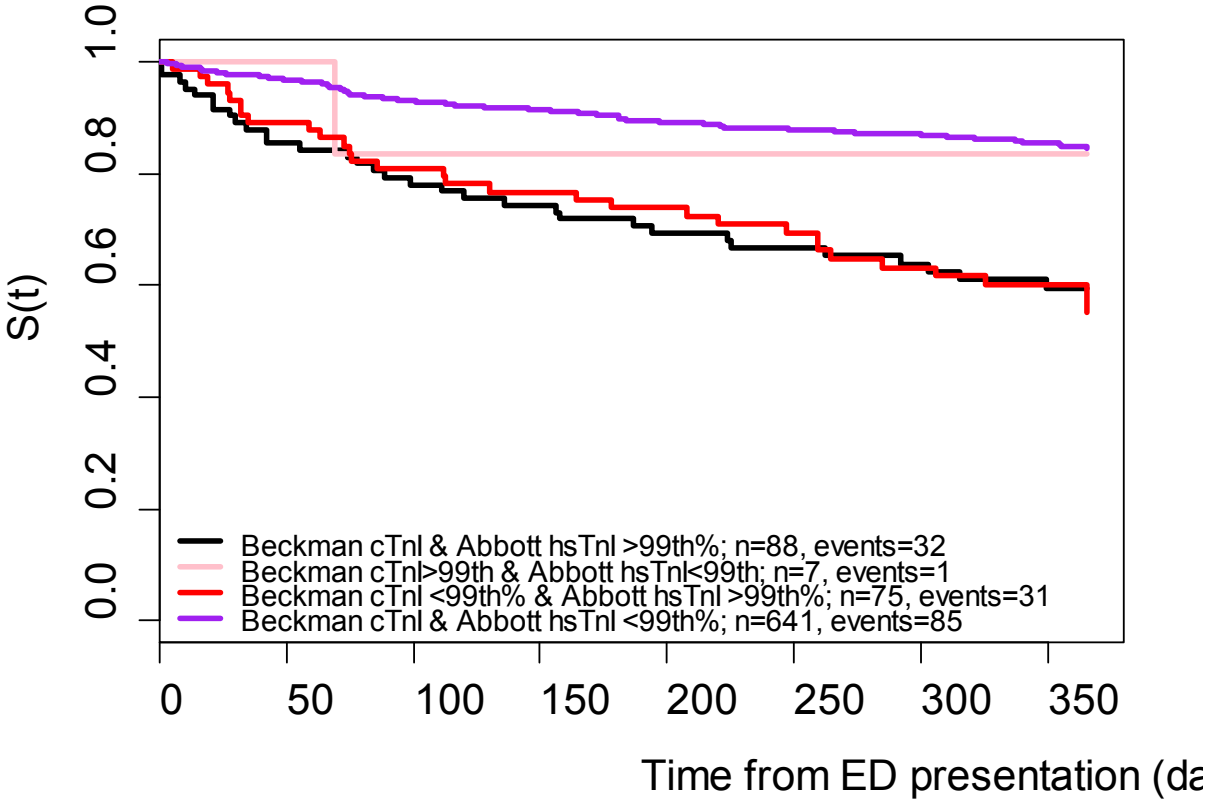


Figure 2.3: Occurrence of adverse events during the follow-up year



Supplemental Material

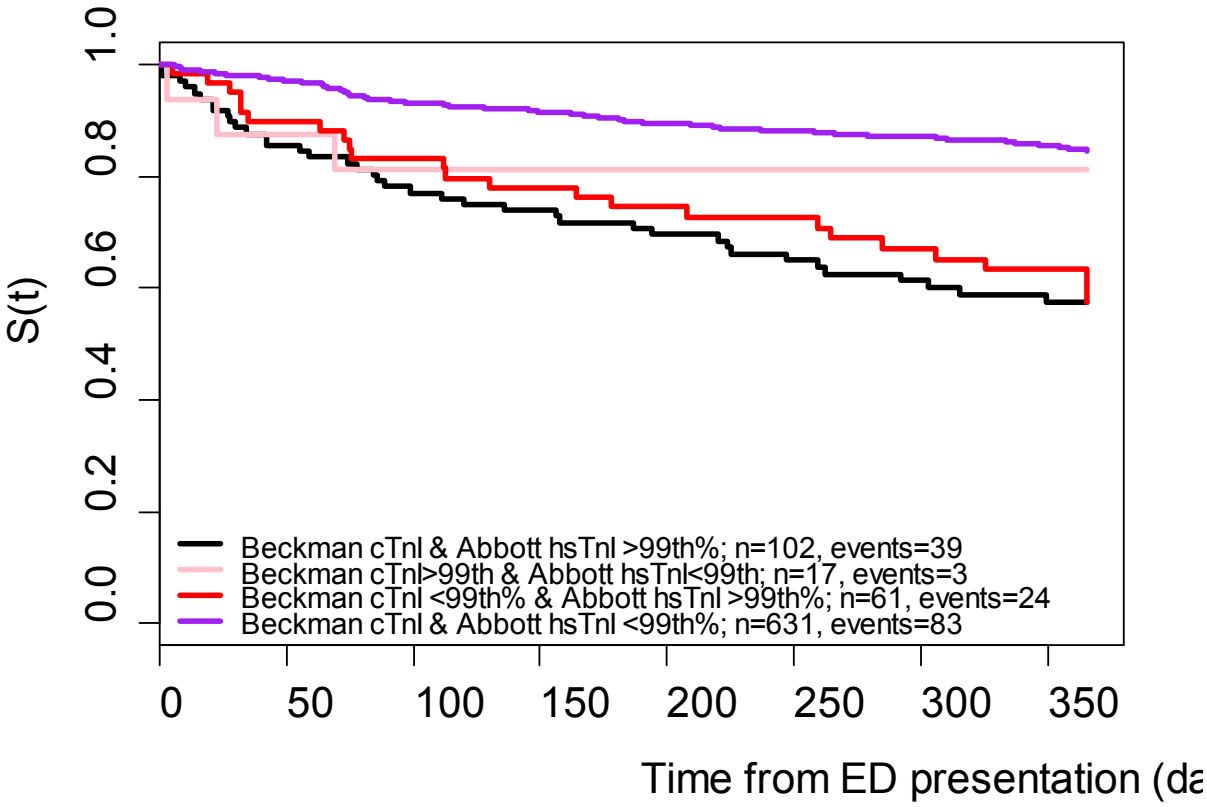
Supplemental Table 2.1: Comparison of enrolled to subjects with a troponin order who presented during outside enrollment hours.

Demographics	**Enrolled** n = 815	**Outside enrollment hours** n = 1724	**p-value**
Age in years	55 (48 – 64)	54 (53 – 55)	0.19
Gender			0.27
• Male	429 (52.6)	867 (50.3)	
• Female	386 (47.4)	857 (49.7)	
Race			0.55
• White	228 (28.0)	427 (24.8)	
• African-American	565 (69.4)	1242 (72.1)	
• Other	21 (2.6)	55 (3.1)	
Admitted to the hospital	393 (48.2)	890 (51.6)	0.11

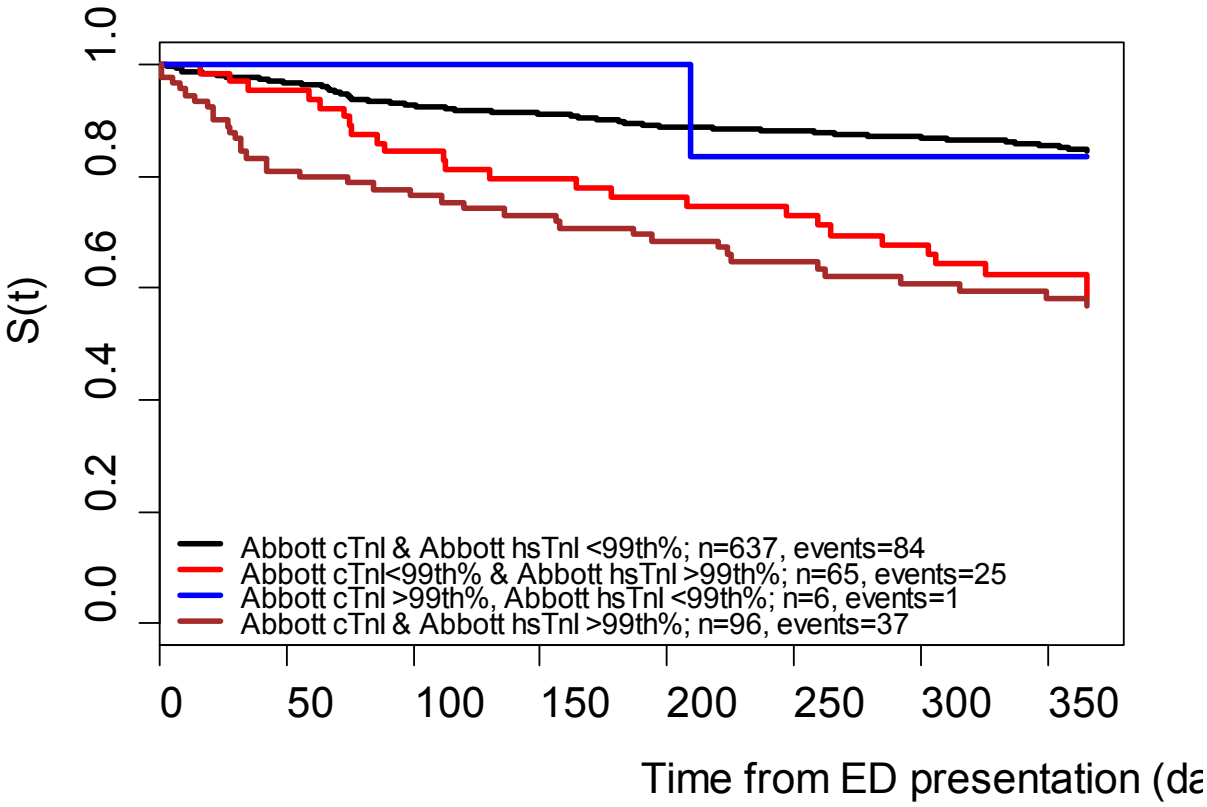
Supplemental Table 2.2: Adjudicated diagnoses according to cTnI (Beckman) and hsTnI values (Abbott)

Diagnosis	**-cTnI, -hsTnI** n=642	**+cTnI, -hsTnI** n=7	**+cTnI +hsTnI** n=91	**-cTnI, +hsTnI** n=75
Acute coronary syndrome	14 (2.2)	0 (0)	23 (25.3)	3 (4.0)
Acutely decompensated heart failure	32 (5.0)	1 (14.3)	14 (15.4)	15 (20.0)
Volume overload unclear etiology/non-cardiac	3 (0.5)	0 (0)	2 (2.2)	3 (4.0)
Pulmonary embolus	7 (1.1)	0 (0)	0 (0)	0 (0)
Cardiac, non-ACS	31 (4.8)	0 (0)	6 (6.6)	4 (5.3)
Other	555 (86.5)	6 (85.7)	46 (50.6)	50 (66.7)

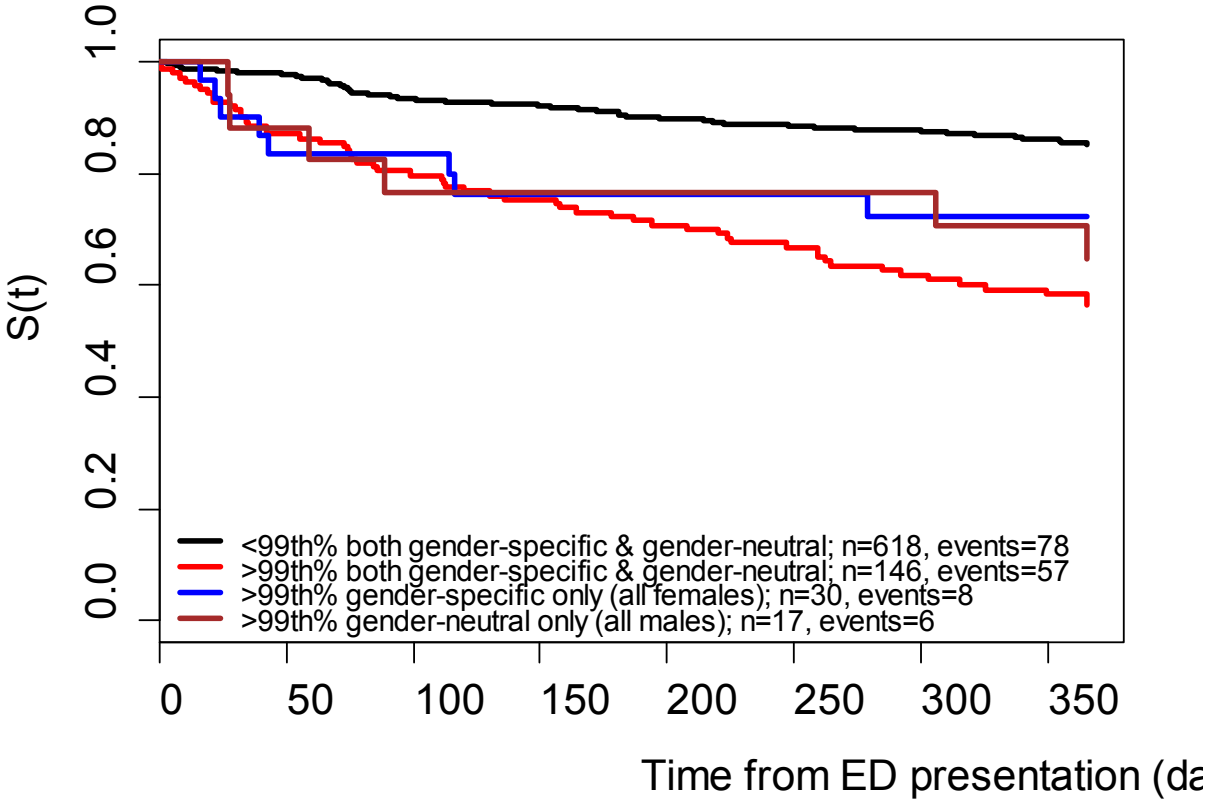
Supplemental Figure 2.1: Occurrence of adverse events during the year following ED/hospital discharge (previously undetected cTnI now defined as initial, 3, 6 or 9 Beckman cTnI <60ng/L)



Supplemental Figure 2.2: Occurrence of adverse events during the year following ED/hospital discharge (previously undetected cTnI now based on Abbott cTnI not Beckman cTnI)



Supplemental Figure 2.3: Occurrence of adverse events during the year following ED/hospital discharge (Gender-neutral vs Gender specific cutoff)



Supplemental Material: Criteria for Adjudication of a final diagnosis

Patients will be assigned one of the following final diagnoses:

a. Myocardial Infarction
b. Unstable Angina
c. Volume overload due to CHF
d. Volume overload due to ESRD
e. Volume overload due to CHF or ESRD
f. Pulmonary Embolism
g. Cardiac (non-ACS)
h. Other

Definitions

Myocardial Infarction: Subjects with no recent revascularization, in whom cardiac troponin I was never elevated or have been documented to return to normal after a prior elevation, who meet at least one of the following criteria:

1. Typical cardiac biomarker rise and/or fall (**a second troponin value drawn within 3 to 6 hours after the initial *positive* troponin value is at least 30% higher or lower than the initial positive troponin value**) AND at least one of the following:
    a. Ischemic discomfort at rest lasing ≥10 minutes
    b. ECG changes indicative of ischemia (ST elevation ≥0.1 mV or ST depression ≥0.05 mV, or new T-wave inversions. OR Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in >2 contiguous precordial leads or ≥2 adjacent limb leads;

or increase R amplitude in V1-V3 consistent with posterior infarction.

2. For patients with a baseline troponin elevation the appropriate delta criteria should be >20% and not 30% within 6 to 9 hours. Or at least a change of 0.02 ng/ml or more (30% of the 10% CV [0.06ng/ml])
3. Autopsy findings of an acute MI
4. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Unstable Angina:

1. Does not meet definition for myocardial infarction and has one of the following characteristics.
    a. Chest pain or angina equivalent at rest or in accelerating pattern AND at least one of the following objective signs:
        i. Positive stress test (imaging or ECG consistent with ischemia
        ii. Cath ≥70% stenosis or thrombus
        iii. CTA coronary with ≥ 70% stenosis
        iv. Patient has an acute myocardial infarction or sudden, unexpected cardiac death within 30 days after presentation.

b. History concerning for unstable angina as per inpatient documentation (has typical angina at rest or a deterioration of previously stable angina), however, optimal medical management pursued, instead of definitive testing and invasive management.

Volume overload most likely due to Congestive Heart Failure (CHF)

1. No ESRD
2. Patient complains of dyspnea, OR orthopnea, OR edema AND at least one of the following:
    a. Inpatient note or ED note strongly suggestive of chf exacerbation.
    b. Pulmonary vascular congestion on chest radiography
    c. New or worsening LE edema
    d. Pro-BNP >1000

Volume overload most likely due to End Stage Renal Disease (ESRD)

1. Pulmonary congestion on CXR
2. History of ESRD or GFR<30 mL/min/1.73m^2

And at least one of the following

1. History of missed hemodialysis, , less than normal volume take off during previous HD
2. CHF exacerbation not the most likely cause of volume overload

Volume overload may be due to CHF or ESRD

1. Pulmonary congestion on CXR
2. Can't tell if volume overload is due to CHF or ESRD

Pulmonary Embolism:

1. As per CT PE protocol read or high probability of PE per VQ scan

Cardiac (non-ACS):

1. Persons in this category are those whose most whose presenting symptoms are most likely due to a cardiac (non-ACS) condition, such as: Myocarditis, Pericarditis, Valvular disorder, Arrhythmia

Other: All others

Ascertainment of Adverse cardiac events on follow-up

Major Adverse Cardiovascular Events (MACE): Cardiovascular death, MI, unstable angina pectoris (UAP), coronary revascularization and/or re-hospitalization that are distinct from the qualifying event (after patient's initial ED presentation).

Myocardial infarction: As above

Unstable angina: As above

Cardiovascular Death: Any sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes. In addition, any death without a clear non-cardiovascular cause, or a death without known cause will be considered cardiovascular death.

Urgent Revascularization: Coronary revascularization during an unscheduled visit to healthcare facility or during an unplanned (or prolonged) hospitalization for these symptoms.

Note: Attempted revascularization procedures, even if not successful will be counted. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as urgent coronary revascularization.

Re-hospitalization: Coronary ischemia requiring re-hospitalization is defined as an event not meeting the definitions of myocardial infarction or urgent coronary revascularization and meeting the following criteria:

- Ischemic discomfort lasting ≥10 minutes at rest, or repeated episodes at rest lasting ≥5
- Prompting hospitalization (including overnight stay on an inpatient unit) within 48 hours of the most recent symptoms or prolonging hospitalization if occurring during existing hospitalization.

AND at least one of the following additional criteria for coronary artery disease and/or ischemia:

- New and/or dynamic ST-depression or ST-elevation
- Definite evidence of ischemia on stress echocardiography, myocardial scintigraphy
- Angiographic evidence of epicardial coronary stenosis of ≥70%

Note: If subjects are admitted with suspected myocardial ischemia, and subsequent testing reveals non-cardiac or non-ischemic etiology, this will not be adjudicated as meeting this definition. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as ischemia requiring hospitalization.

Coding of ECGs

ECGs will be reviewed by an independent ECG review committee supervised by Larisa Tereshchenko M.D., Ph.D.

- **ST Elevation Myocardial Infarction (STEMI)**
    - No LBBB or LVH
    - New ST elevation at the J-point in two contiguous leads with the cut-off points:
        - $\geq$ 0.1 mV in all leads except leads $V_2 – V_3$ in men and women
        - In leads $V_2 – V_3$, $\geq$ 0.2 mV in men $\geq$ 40 years and $\geq$ 0.25 mV in men <40 years
        - In leads $V_2 – V_3$, $\geq$ 0.15 mV in women
- **ST elevation in aVR or V1 only**
    - Does not meet STEMI criteria and ST $\geq$ 0.1mV
- **Isolated Posterior Myocardial Infarction**
    - Does not meet 2 criteria above
    - Isolated ST depression $\geq$ 0.05 mV in $V_1 – V_3$
- **Significant ST depression and T-wave changes**
    - Does not meet 3 criteria above
    - New horizontal or down-sloping ST depression $\geq$ 0.05 mV in two contiguous leads; and/or T inversion $\geq$ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1 (including pseudonormalization of T waves)
- **Non-specific ST changes**

- Does not meet any of 4 criteria above
- ST elevation ≥ 0.05mV in but does not meet STEMI criteria
- T wave changes <0.1 mV or not in contiguous leads

- **Normal ECG**
  - None of above pathologic findings

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	26
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	26
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	28
Objectives	3	State specific objectives, including any prespecified hypotheses	28
Methods			
Study design	4	Present key elements of study design early in the paper	28
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	29 and 30
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	29
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	29, 30, 31
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	29, 30, 31
Bias	9	Describe any efforts to address potential sources of bias	29, 30, 37

Study size	10	Explain how the study size was arrived at	32
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	31 and 32
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	31 and 32
		(*b*) Describe any methods used to examine subgroups and interactions	31 and 32
		(*c*) Explain how missing data were addressed	31
		(*d*) If applicable, explain how loss to follow-up was addressed	31
		(*e*) Describe any sensitivity analyses	31
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	32 and 42
		(b) Give reasons for non-participation at each stage	42
		(c) Consider use of a flow diagram	42
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	32 and 39
		(b) Indicate number of participants with missing data for each variable of interest	42
		(c) Summarise follow-up time (eg, average and total amount)	35
Outcome data	15*	Report numbers of outcome events or summary measures over time	35 and 46
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders	Supplement

		were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	30, 31
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	32
Discussion			
Key results	18	Summarise key results with reference to study objectives	11 and12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	35
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	35 and 36
Generalisabilit y	21	Discuss the generalisability (external validity) of the study results	37
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Chapter 3: Independent predictors of high sensitivity troponin I values in patients evaluated for acute coronary syndrome who are determined to have a primary non-cardiac diagnosis.

Korley FK, DeFilippis AP, Schulman SP, Sokoll LJ, Stolbach AI, Bayram JD, Omron R, Post WS, Fernandez, C, Jaffe AS.

Abstract

Objective: To investigate the factors associated with elevated high sensitivity troponin I (hsTnI) in emergency department (ED) patients with a primary non-cardiac diagnosis.

Methods: A cross-sectional study of patients in urban academic ED who were diagnosed with primary non-cardiac diagnosis was conducted. hsTnI was measured using the Abbott Laboratories' (Abbott Park, IL) research-use ARCHITECT *STAT* high sensitive Troponin I assay. Patient diagnoses were adjudicated by a panel of ED physicians and cardiologists blinded to hsTnI.

Results: Of 664 patients, 606 (91.3%) had detectable hsTnI and 96 (14.5%) had values >99th%. Patients with hsTnI >99th percentile were more likely to have a prior history MI/revascularization, congestive heart failure, poor renal function, hypotension or tachycardia. Of the 341 (51.4%) patients in whom initial and 3 hour hsTnI were measured, 8 (2.3%) had a significant change in hsTnI at 3 hours using criteria of the European Society of Cardiology.

Conclusions: Using the Abbott assay, hsTnI will be detectable in >90% of ED patients in whom a primary non-cardiac diagnosis is made and 14.5% will have

hsTnI>99th%. Prior history MI/revascularization, congestive heart failure, poor renal function, hypotension or tachycardia independently associated with elevated hsTnI.

Introduction

Background

High sensitivity troponin (hsTn) assays may be cleared by the Food and Drug Administration in the future, but are in use in other parts of the world.[103] Clinical use of more sensitive assays and the guideline recommended cut off values will result in earlier diagnosis of myocardial infarction (MI),[91] reclassification of a subset of patients currently diagnosed with unstable angina as non-ST elevation MI (NSTEMI), novel strategies for ruling out MI,[28,91] and improved risk-stratification of patients with other conditions that cause myocardial injury.[84,85,104] With hsTn assays, for the first time in clinical settings, clinicians will see measured hsTn values in most healthy individuals[15] and in many emergency department (ED) patients who have cardiovascular comorbidities. For example, prior studies have demonstrated that older age, male gender, higher systolic blood pressure, higher left ventricular mass and reduced renal function are each independently associated with higher hsTn values.[105,106] Accordingly, the diagnosis of AMI will require a changing pattern of values.[107]

Importance

To our knowledge, prior studies have not examined how these factors contribute to elevated high sensitivity troponin I (hsTnI) among undifferentiated US ED patients evaluated for acute coronary syndrome (ACS) have a primary non-cardiac diagnosis.

Goals of This Investigation

The goal of this study was to investigate the independent predictors of hsTnI in a subset of ED patients in whom a primary non-cardiac diagnosis was made.

Methods

Study design and setting

We conducted a prospective observational study of patients evaluated for ACS, who were diagnosed with a non-cardiac condition by adjudication committee of board certified clinicians. This study was nested in an ongoing prospective cohort study of ED patients evaluated for ACS (Korley et al, In press). The study was conducted at an urban academic ED seeing 65,000 patients a year, and was approved by our institutional review board.

Selection of Participants

Patients included in this cohort study had a recorded chief complaint of chest pain or shortness of breath, a non-diagnostic ECG and cardiac troponin I (cTnI) ordered by the treating clinician. Additionally, all patients with other chief complaints who had cTnI testing were considered eligible if their treating clinician confirmed when asked that ACS was a possible diagnosis. Eligible patients provided written informed consent. Continuous enrollment of consecutive patients occurred on weekdays from 9:00 am till 9:00 pm. Patients with the following were excluded: ST elevation myocardial infarction (STEMI), left against medical advice, initial research blood sample was missed or could not be obtained.

Methods and Measurements

Demographic and clinical information was collected by trained research assistants, and entered directly into an electronic database via an online data collection tool REDCAP.[92] The first documented blood pressure, heart rate and glomerular filtration rate were electronically extracted from patient charts. Each time blood samples were drawn for clinical cTnI testing, an additional 5 mL of blood was collected, centrifuged, and serum aliquoted and stored in a -80°F freezer. Sample storage occurred within 2 hours of blood draw. For clinical decision making, the hospital cTnI assay was the Beckman Coulter (Chaska, MN) Access II AccuTnI assay. The 99th% upper reference limit (URL) for this assay is 40 ng/L. The co-efficient of variation (CV) for this assay is 14% at 40 ng/L: the 10% CV value is 60 ng/L. Our clinical laboratory only reports values of cTnI > 60 ng/L (the decision making cut-off for the institution). hsTnI values were measured in batches, at least one month after initial presentation, using the Abbott Laboratories' (Abbott Park, IL) research-use ARCHITECT *STAT* high sensitive Troponin I assay. The 99th % (upper reference limit) for this assay is 34.2 ng/L for males, 15.6 ng/L for females and 26.2 ng/L overall. The limit of detection (LOD) for this assay is 1.2 ng/L.[93] hsTnI data were not available to clinicians for medical decision making.

Estimated glomerular filtration rate (GFR) was calculated using an enzymatic serum creatinine result (Roche Modular and Cobas c701, Roche Diagnostics, Indianapolis, IN) and the IDMS-traceable 4-variable Modification of Diet in Renal Disease equation.

Clinical diagnoses were adjudicated by a committee comprised of four board certified emergency physicians and two board certified cardiologists. Two members blinded to high sensitivity troponin data, reviewed the medical records and assigned one of the following diagnoses: AMI, unstable angina, acutely decompensated heart failure (ADHF), volume overload from other causes, cardiac (non-ACS), pulmonary embolism, and other. If there was disagreement between committee members, a third committee member arbitrated. AMI was defined according to the universal definition of AMI, except for the cTnI cutoff imposed at our institution.[49] A significant rising and/or falling pattern in cTnI was defined as a change of at least 30% at the 10% co-efficient of variation level (18 ng/L or greater within 6-9 hours).[63] Unstable angina was defined based on the clinical history, objective ECG findings, a positive stress test or coronary artery stenosis on CT coronary angiography or coronary angiography catheterization of 70% or greater. Acutely decompensated heart failure (ADHF) was defined using a modified Framingham criteria.[94] Patients with radiographic or clinical evidence of volume overload suspected from non-cardiac conditions such as end-stage renal disease were classified as volume overload and not ADHF. Patients diagnosed with myocarditis, or pericarditis, or valvular disorders or arrhythmia were classified as: cardiac (non-ACS). A board certified cardiologist also reviewed all subjects diagnosed with AMI or unstable angina to confirm diagnoses. This report includes only patients diagnosed as “Other”.

Outcomes

Our primary outcome was hsTnI analyzed both as a continuous variable and as a categorical variable (>99th% or <=99th%). Gender-specific cut off values were also probed. We also examined variations in hsTnI according to the primary diagnosis assigned by treating ED clinicians.

Analysis

Demographic and clinical characteristics of the study population have been summarized using descriptive statistics. Differences in demographic and clinical characteristics between patients with hsTnI>99th% and those with hsTnI<=99th% were examined using Student's t-tests for continuous variables (they all approximated a normal distribution) and χ^2 for categorical variables. To identify independent predictors of hsTnI and hsTnI >99th%, we used univariable and multivariable linear regression and logistic regression models. Blood pressure was categorized as hypotension (systolic <90 mmHg or diastolic <60 mmHg), severely elevated (systolic >180 mmHg or diastolic >120 mmHg) or neither, based on generally accepted definitions,[108,109] and a review of Lowess smoothing plots that examined the association between blood pressure and hsTnI. Similarly, heart rate was dichotomized into heart rate> or $\leq$110 beats per minute (bpm) based on biological plausibility and a review of lowess plots. Variables included in the final multivariable linear and logistic regression models (age; prior history of hypertension, diabetes, MI/revascularization, CHF; renal function measured by GFR; family history of M/sudden death; blood pressure; heart rate) were selected based on apriori literature review. Additionally, the final multivariable models included only variables whose univariate association with the primary outcome

approximated statistical significance ($p<0.2$). We measured collinearity among the variables included in the final models using the variance inflation factor (VIF). None of the included variables met our predetermined criterion for severe collinearity ($VIF \geq 10$). Since hsTnI values are not normally distributed, they were natural log transformed prior to including them in the linear regression models. The proportion of variability in hsTnI that can be explained by variables included in the multivariable linear regression model was estimated with the co-efficient of determination (R^2). All statistical analyses were performed using STATA/MP statistical software version 11.2 (StataCorp, College Station, Texas), and RStudio statistical software version 0.97.312. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Independent determinants of hsTnI

Between January 2012 and July 2012, 815 subjects were enrolled in the original cohort. This study focusses on 664 subjects within that cohort who were assigned a non-cardiac diagnosis by an adjudication committee (Figure 3.1). Demographic and clinical characteristics of the study population are presented in Table 3.1. hsTnI values were detectable in 91.3% (606/664) of the study population and 14.5% (96/664) had values> 99th%. Distribution of hsTnI values in the study population is presented in Figure 3.2. Additionally, the distribution of hsTnI according to the primary diagnosis assigned by treating ED clinicians is presented in Figure 3.3. Patients with hsTnI>99th% were more likely to be older, or on Medicare, or had a family history of a heart attack or sudden death, or had

a history of hypertension, or diabetes, or congestive heart failure, or prior MI/revascularization, or reduced renal function or an elevated heart rate at ED presentation. However, they did not have an increased likelihood of presenting with chest pain or shortness of breath (Table 3.1). However, after adjusting for confounders, only reduced renal function, hypotension and heart rate >110 bpm were found to be independent predictors of hsTnI>99th% (Table 3.2). The variables included in the final multivariable linear regression model (Table 3.3) explained 31% of the variability in hsTnI values. Of all the variables investigated, the strongest predictor of hsTnI was reduced renal function (Figure 3.4).

Three-hour hsTnI samples were available for 51.4% (341/664) of the study population and for 59.4% (57/96) of those with an initial hsTnI>99th%. Of those with an initial hsTnI>99th%, 12.3% (7/57) had a 20% or greater change in hsTnI (criterion for significant change in hsTnI proposed by the European Society of Cardiology [ESC][95]) in 3 hours. Similarly, of those with an initial hsTnI <= the 99th%, 0.4% (1/284) had a change of at least 50% of the 99th percentile i.e. 13.1 ng/L (ESC criterion[95]).

Effect of the definition of 99th% on the prevalence of elevated hsTnI

Assay manufacturers recommend using either a gender-neutral cutoff for the 99th% of all patients (26.2 ng/L) or gender-specific cut-offs (male: 34.2 ng/L, female: 15.6 ng/L). If a gender-specific cut-off is used, the number of elevated hsTnI (>99th%) would increase from 96 (14.6%; 52 males and 44 females) to 104 (15.7%; 41 males and 63 females). 85 patients had elevated hsTnI regardless of the cut-off used.

Discussion

Our data provide important new information for clinicians regarding the determinants of hsTnI among ED patients evaluated for ACS who are in whom a primary non-cardiac diagnosis was made. They demonstrate that when these assays are used, values will be measureable in 91% of patients with possible ACS in whom a primary non-cardiac diagnosis is made. Importantly, 14.5% of these patients will have hsTnI values greater than the 99th%. However, and a key to this analysis, very few (8 out of the 341 with serial samples) will have a rising pattern indicative of an acute event. This will further amplify the tension that has existed for some time concerning how ED physicians should response to elevated cTn values. Importantly, the use of gender specific cut off values will markedly reduce the frequency of elevations in men and markedly increase the frequency of elevations in women which may have a profound impact on the ability to properly refer such patients for subsequent appropriate care.

Because cTn is released into circulation after damage to cardiac myocytes, their near perfect specificity for myocardial injury has allowed for fairly straightforward clinical decision making in evaluating patients in the ED. If AMI was suspected, an elevated value was considered diagnostic in high risk patients and these individuals were admitted. Even in the absence of AMI, elevations of cTn indicative of cardiac injury in critically ill patients have been documented to be associated with increased risk for mortality in multiple settings, including the ED.[110,111] Thus, in many EDs, all such patients were immediately admitted

although this approach itself has been controversial and results in excessive testing and utilization of resources.[112]

With less sensitive assays, only higher values of troponin were detected and these values were associated with more severe cardiac injury and thus whether due to AMI or other cardiac abnormalities, such elevations were considered likely to be of clinical significance. With the increasing sensitivity of cTn assays, including many more sensitive assays currently in use in the U.S., which detect chronic structural abnormalities[45,105] well as acute events, this approach has become more and more problematic. This will be further accentuated with hsTn assays. Our data are reassuring however, that such patients will very infrequently have a changing pattern of values.

Our results are similar to many others. A recent study that used the Siemens hsTnI assay, reported measurable hsTnI values in 93% of a cohort of healthy community residents.[105] These data have been recapitulated with the Singulex hsTnI assay as well.[113] Although, numerous studies have demonstrated the dose-dependent association between hsTn values and long term adverse cardiac events,[45,46,113] it is unclear that such individuals are at increased short term risk, assuming they are clinically stable. Thus, an elevated hsTn value may not be sufficient to determine whether patients have an acute cardiac pathology. Serial sampling of hsTn to determine whether a rising pattern exists will be the key to distinguishing between acute and non-acutely elevated hsTnI.[58,62] In our cohort, the presence of such a pattern was rare.

Similar to prior studies[114], reduced renal function was highly associated with increased hsTnI. The reason for this is that renal disease and cardiac disease are frequently associated.[115,116] Potential contributors to elevations in hsTnI among patients with reduced renal function include an increased prevalence of multivessel coronary artery disease[117], volume overload with or without cardiac failure[118] left ventricular hypertrophy in this population,[119] and perhaps even the abnormal metabolic profile that exists in such patients.[120] Regardless of the etiology, in our multivariable linear regression model that identified independent predictors of hsTnI (Table 3.3), after adjustment for history of heart failure and history of prior MI, CABG and prior coronary stents, the influence of reduced renal function persisted. One explanation that has been advanced has to do with the clearance of cTn. More than 95% of the troponin I in human blood occurs as a binary troponin I and troponin C complex[15], a relatively large molecule (approximately 42KDa, albumin is 66 KDa) , making it less likely to be cleared by the kidney. It is possible but unproven that smaller molecular weight degradation products of troponin I[121] might be cleared by the renal system. Alternatively, cleavages of the protein may differ leading to reduced degradation.[122] Thus serial measurement of hsTnI will be especially important in patients with reduced renal function. Current ESC guidelines recommend that for patients with an elevated baseline hsTnI a change of >20% within 3 or 6 hours constitutes a significant change.[95]

Our data reveal that elevated blood pressure and elevated heart rate are both independently associated with higher hsTnI values. It has been well established

that the relationship between blood pressure and the risk of cardiovascular events is continuous and consistent, and independent of other risk factors.[123] However, many questions regarding the association between blood pressure and myocardial injury remain unanswered. Perhaps with the use of hsTnI, new understandings will be possible to more accurately define both risk and the mechanisms responsible for it.

A number of studies have reported significant differences in the 99th % value of hsTnI among males and females.[39,105,124] Our data demonstrates that the use of a gender-specific cut-off will increase the prevalence of elevated hsTnI. The majority of those with elevated hsTnI were females. Although data concerning these findings are unclear, it is likely that these elevations as with most others detected with hsTn assays define a group at enhanced risk.[93,125] If so, adhering to this approach will improve the care of female patients significantly and avoid over testing in their male counterparts. Additional studies are clearly needed to determine the proper approaches to these provocative findings.

Limitations

Based on our multivariable linear regression model (Table 3.3), the variables included in the model accounted for only 31% of the variability in hsTnI. This finding may reflect in part the fact that at least one known important predictor: left ventricular mass, was not included in our model. We unfortunately did not have imaging on all these patients which might be helpful in defining the presence of cardiovascular abnormalities.[44,105] Such data would assist ED physicians in

targeting appropriate follow up for these individuals given the known prognostic value of these elevations.[45,113]

Two other limitations are also clear. First, it is essential that it be confirmed that our assumption that these patients are not at increased short term risk is correct. The fact that the primary diagnosis in these patients was non cardiac does not suggest that they do not have cardiac disease marked by the elevated hsTn value. We are currently completing follow-up studies on this cohort to determine answer this critical question. A second important limitation is that the diagnoses made in these patients were made not with the hsTnI but with a solid contemporary assay. Indeed, the assay we used detects more normal subjects than others and thus is likely somewhat more sensitive than others[39] despite the use of the 10% CV value and not the 99th% URL value. Thus, many of the individuals who might have had a rising pattern of values may have been detected with the assay in use locally causing an underestimation of the frequency of this finding in our cohort. Such concern reinforces the suggestion of the importance of choosing the proper standards for evaluating hsTn assays.[107]

Conclusions

With the use of the Abbott hsTnI assay, more than 90% of ED patients in whom a primary non-cardiac diagnosis is made will have detectable troponin I values. Prior history MI/revascularization, congestive heart failure, poor renal function, hypotension or tachycardia independently associated with elevated hsTnI.

Figure 3.1: Derivation of cohort for current study

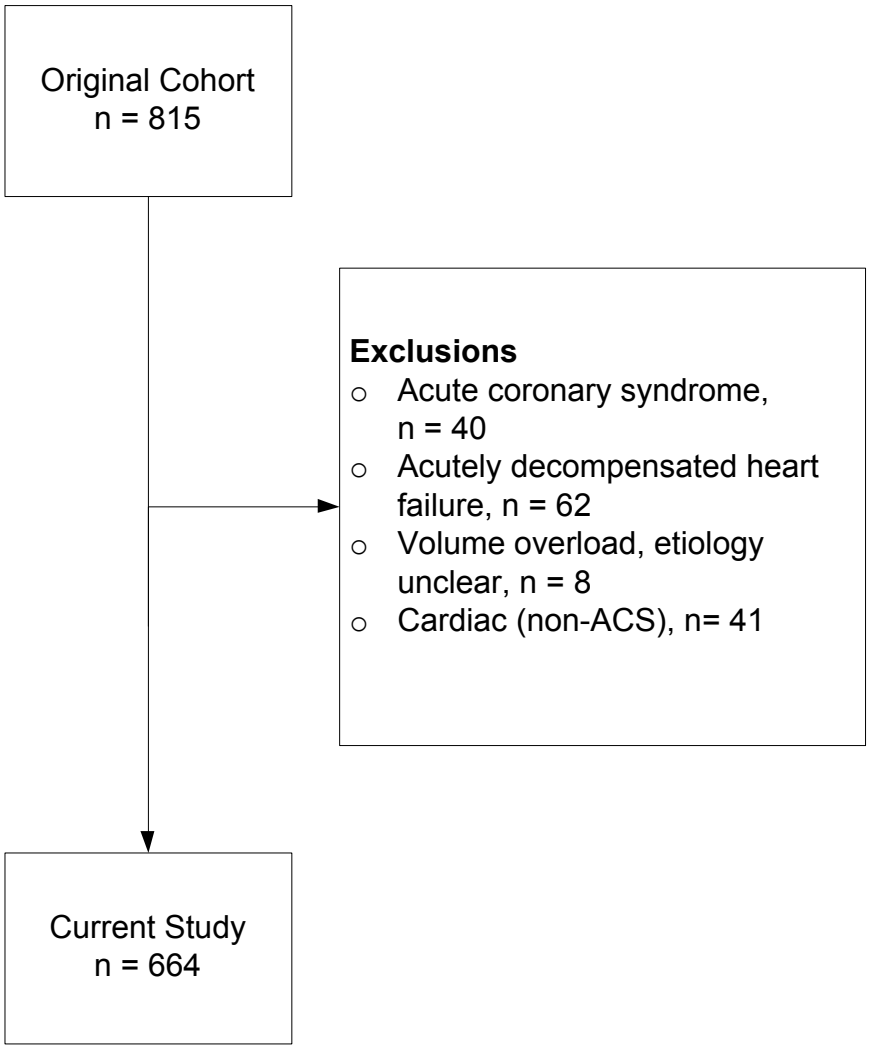


Table 3.1: Demographic and Clinical Characteristics of Study Population

	hsTnI <= 99th percentile n = 568	hsTnI > 99th percentile n = 96	P value
Mean age in years (95% CI)	54.7 (53.6 – 55.8)	59.8 (56.8 – 62.7)	<0.01
Gender (%)			0.11
• Male	258 (45.4)	52 (54.2)	
• Female	310 (54.6)	44 (45.8)	
Race (%)			0.64
• Non-hispanic Black	359 (63.2)	60 (62.5)	
• Non-hispanic White	154 (27.1)	23 (24.0)	
• Hispanic	14 (2.5)	4 (4.2)	
• Other	41 (7.2)	9 (9.4)	
Insurance (%)			0.07
• Medicare	138 (24.3)	34 (35.4)	
• Medicaid	167 (29.4)	22 (22.9)	
• Other	225 (39.6)	31 (32.3)	
• None	38 (6.7)	9 (9.4)	
Ambulance transport (%)	132 (23.2)	26 (27.1)	0.66
History of Hypertension (%)	331 (58.3)	70 (72.9)	<0.01
History of Diabetes (%)	140 (24.6)	36 (37.5)	<0.01
Prior MI or revascularization (%)	112 (19.7)	41 (42.7)	<0.01
History of CHF(%)	70 (12.3)	36 (37.5)	<0.01
History of high cholesterol (%)	218 (38.4)	39 (40.6)	0.68
Glomerular filtration rate (per mL/min/1.73m^2)			<0.01
• >60	470 (82.8)	41 (42.7)	
• 30-60	83 (14.6)	33 (34.4)	
• <30	15 (2.6)	22 (22.9)	
Current cigarette smoker (%)	352 (62.0)	63 (65.6)	0.49
Family history of heart attack or sudden death (%)	174 (30.6)	37 (38.5)	0.12
Blood pressure			<0.01
• Hypotension	32 (5.6)	16 (16.7)	
• Severely elevated	59 (10.4)	18 (18.8)	
• Neither	477 (84.0)	62 (64.6)	
Heart Rate >110 bpm	56 (9.9)	18 (18.8)	0.01
Probability that patient has non-cardiac cause of symptoms (determined by treating clinician)			0.02
• Low	84 (15.2)	25 (26.6)	

• Medium	204 (37.0)	31 (33.0)	
• High	263 (47.7)	38 (40.4)	
Had chest pain or shortness of breath	451 (79.4)	79 (82.3)	0.51

Table 3.2: Factors associated with elevated hsTnI (>99th%)

	Unadjusted Odds	Adjusted Odds
Age per 10 year increase	1.33 (1.13 – 1.56)	1.10 (0.90 – 1.33)
History of Hypertension	1.93 (1.19 – 3.11)	0.83 (0.46 – 1.50)
History of Diabetes	1.83 (1.16 – 2.89)	1.03 (0.59 – 1.81)
Prior MI or revascularization	3.04 (1.93 – 4.78)	2.07 (1.18 – 3.63)
History of CHF	4.27 (2.63 – 6.92)	2.24 (1.24 – 4.06)
Glomerular filtration rate (per mL/min/1.73m^2)		
• >60	Reference (1.0)	Reference (1.0)
• 30-60	4.56 (2.72 – 7.62)	3.59 (1.97 – 6.53)
• <30	16.81 (8.10 – 34.88)	11.34 (4.99 – 25.77)
Family history of heart attack or sudden death	1.42 (0.91 – 2.22)	1.28 (0.76 – 2.18)
Blood pressure		
• Hypotension	3.85 (2.00 – 7.41)	2.56 (1.17 – 5.59)
• Severely elevated	2.35 (1.30 – 4.24)	1.92 (0.96 – 3.91)
• Neither	Reference (1.0)	Reference (1.0)
Heart Rate >110 beats per minute	2.10 (1.17 – 3.78)	2.51 (1.27 – 4.98)

Table 3.3: Multivariable model to determine independent predictors of hsTnI

	% change in hsTnI (95% CI)
Age per 10 year increase	18.0 (9.8 – 26.8)
Gender (Reference is female)	42.2 (19.6 – 69.1)
History of Hypertension	40.9 (15.5 – 71.8)
History of Diabetes	19.2 (-3.4 – 47.2)
History of High Cholesterol	-13.4 (-28.7 – 5.1)
Prior MI or revascularization	25.3 (0.41 – 56.4)
History of CHF	63.4 (26.5 – 111.1)
Glomerular filtration rate (per mL/min/1.73m^2)	
• >60 (Reference)	
• 30-60	62.3 (26.9 – 107.5)
• <30	303.6 (173.3 – 496.0)
Blood pressure	
• Hypotension	53.9 (9.7 – 115.8)
• Severely elevated	51.1 (14.7 – 98.8)
• Neither (Reference)	
Heart Rate >110 beats per minute	94.0 (47.6 – 155.0)

Figure 3.2: Distribution of hsTnI in the study population

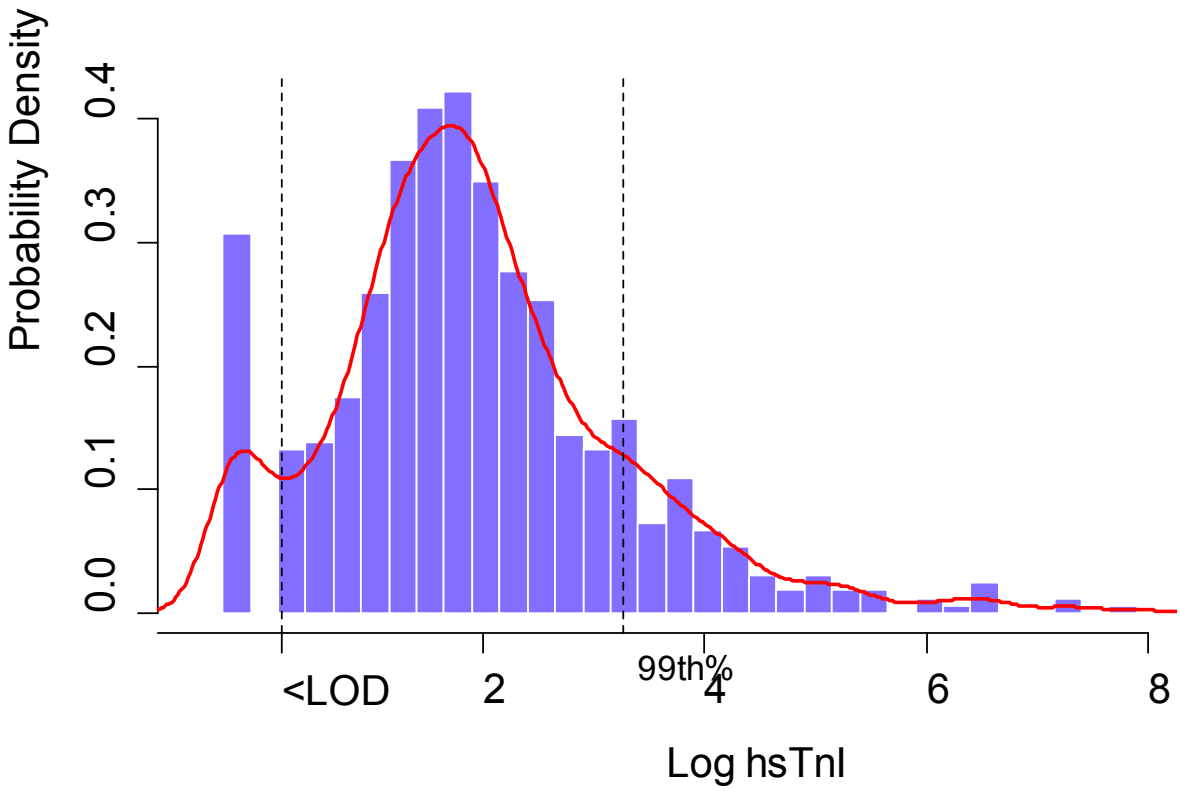
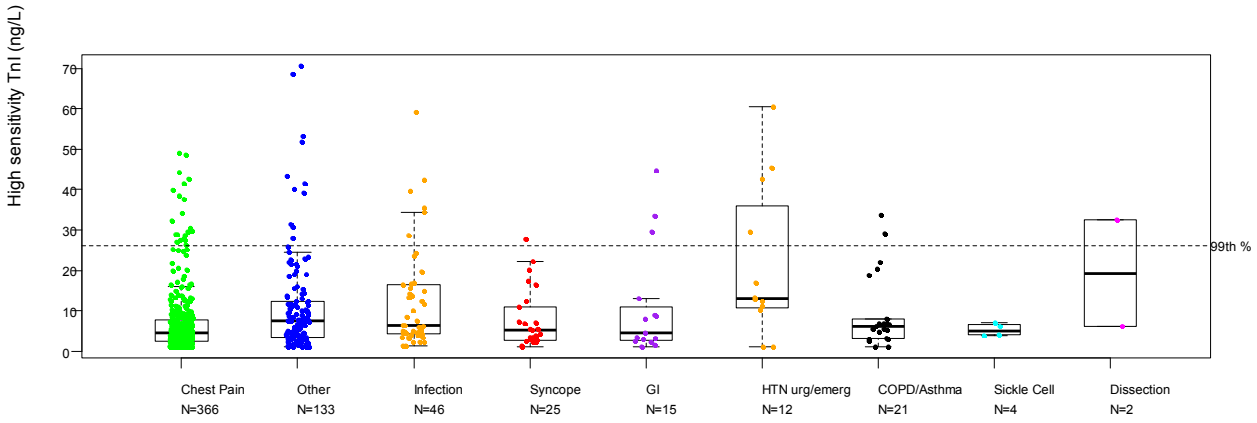


Figure 3.3: Distribution of hsTnI according to final diagnosis



Chapter 4: Rapidly Excluding Significant Coronary Artery Stenosis Using High Sensitivity Troponin I

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Oral presentation at the 2013 annual meeting of the Society of Academic Emergency Medicine (SAEM) in Atlanta, Georgia.

Background

Indiscriminate use of CT coronary angiography (CCTA) in evaluating emergency department (ED) patients for suspected acute coronary syndrome (ACS) may unnecessarily expose them to financial harm, ionizing radiation and the risks of IV contrast dye. High sensitivity troponin I (hsTnI) improves the risk stratification of ED patients with suspected ACS. We determined whether hsTnI can identify patients with non-significant coronary artery stenosis (<50%) on CCTA.

Methods

We conducted a cross-sectional study in which we measured hsTnI in ED patients who received a CCTA as part of their evaluation for suspected ACS. hsTnI was measured using the Abbott Laboratories' (Abbott Park, IL) research-use ARCHITECT *STAT* high sensitive Troponin I assay.

Results

Of the 206 patients studied, 51.5% (106/206) had coronary arteries without plaque or lumen narrowing, 39.3% (81/206) had maximal coronary artery stenosis of less than 50%, 6.3% (13/206) had maximal coronary artery stenosis

of 50-70% stenosis, and 2.9% (6/206) had at least one coronary artery with >70% stenosis. Median hsTnI values were higher among patients with maximal coronary artery stenosis of 50% or greater (median 6.4 [IQR: 5.1 – 11.2] ng/L) than in patients with maximal coronary artery stenosis <50% (median 3.1 [IQR: 1.5 – 5.3]), p<0.01. Avoiding CCTA in patients with hsTnI <=1.2 ng/L will result in avoiding 20.3% (38/187) of the CCTAs with <50% stenosis, without missing any patients with significant stenosis.

Conclusion:

hsTnI measured with the Abbott assay can identify CCTA candidates with low likelihood of having significant coronary artery stenosis.

Background

Diagnostic evaluation of Emergency Department (ED) patients suspected of having acute coronary syndrome (ACS) remains time consuming and costly.[126] In patients with ECG or biochemical evidence of myocardial infarction the diagnosis of ACS is fairly straight-forward.[9] However, those without these findings undergo either functional testing to evaluate for provocable ischemia or anatomic imaging to evaluate for flow-limiting coronary artery stenosis.[127] Coronary CT angiography (CCTA) visualizes coronary artery stenosis with excellent precision.[128,129] It can be used to safely expedite the discharge of low risk ACS patients.[130,131] However, as with all diagnostic tests, indiscriminate use of CCTA in a low to no risk population results in a decrease in its positive predictive value.[132] Additionally, CCTA use is associated with financial costs, and radiation and contrast dye exposure. Thus careful selection of candidates for CCTA is of utmost importance. However, the literature on appropriate identification of candidates for CCTA is scant.

High sensitivity troponin (hsTn) assays are able to measure up to 10 fold lower concentrations of troponin compared to contemporary assays. Prior studies using the high sensitivity troponin T (hsTnT) assay described an association between hsTnT and coronary artery disease (CAD) severity, and calcified and non-calcified plaque burden, resulting in a high diagnostic accuracy for the differentiation of patients by plaque composition.[133,134] To our knowledge no studies have investigated the association between high sensitivity troponin I (hsTnI) and the extent of coronary artery stenosis on CCTA. Additionally, it is not

known whether CCTA candidates who are unlikely to have significant coronary artery stenosis on CCTA (avoidable CCTA) can be identified using hsTnI. We hypothesized that median hsTnI values will be higher in patients with significant coronary artery stenosis than in those without. Additionally, we explored whether hsTnI as a screening test for CCTA candidates, can decrease the proportion of avoidable CCTAs (CCTAs with <50% stenosis) by 20% or greater, without missing patients with significant stenosis.

Methods

Study design and setting

We conducted a cross-sectional study of ED patients who received a CCTA as part of their diagnostic evaluation for ACS. This study was nested in an institutional review board approved prospective cohort of ED patients evaluated for ACS at an urban academic ED (HopACS). The details of the characteristics of this cohort have been previously published (Korley et al, Heart 2013 in press).

Selection of Participants

Patients included in the original cohort were 18 years or older ED patients who had a recorded chief complaint of chest pain or shortness of breath and a non-diagnostic ECG and cardiac troponin testing I (cTnI). Additionally, patients with other chief complaints who had cTnI testing were considered eligible if their treating physician confirmed when asked that ACS was a possible diagnosis. Enrollment of patients occurred on weekdays from 9:00 am till 9:00 pm. Patients were excluded from the study if they had ST elevation myocardial infarction

(STEMI), left against medical advice, or if the initial research blood sample was missed or could not be obtained. Within this cohort, patients with no known history of coronary artery disease, who had a cTnI <60 ng/L using the Beckman Coulter (Chaska, MN) Access II AccuTnI assay (the clinical assay), and no contraindication to receiving a CCTA (recent CCTA, IV contrast dye allergy, renal insufficiency, beta-blocker intolerance, persistent tachycardia, non-sinus rhythm, inadequate IV access) received a CCTA at the discretion of treating emergency physicians and mid-level providers. Eligible patients provided written informed consent.

Methods and measurements

Trained research assistants interviewed consented subjects and their clinicians, collected demographic and clinical information, and entered this information directly into an electronic database via an online data collection tool REDCAP [92]. Blood samples for hsTnI testing were drawn within 1-2 hours of ED presentation and prior to obtaining the CCTA. Samples were centrifuged and serum aliquoted and stored in a -80°F freezer. Sample storage occurred within 2 hours of blood draw. hsTnI values were measured in batches, at least one month after initial presentation, using the Abbott Laboratories' (Abbott Park, IL) research-use ARCHITECT *STAT* high sensitive Troponin I assay. The 99th % (upper reference limit) for this assay is 34.2 ng/L for males, 15.6 ng/L for females and 26.2 ng/L overall. The limit of detection (LOD) for this assay is 1.2 ng/L [93]. hsTnI data were used for research purposes only and not for clinical decision making.

CT Coronary Angiography

CCTA was performed using one of the following multidetector computed tomography scanning systems: first generation dual-source CT (Somatom Definition, Siemens), second generation dual-source CT (Somatom Definition Flash, Siemens), and a 320-row detector CT scanner (Aquillion ONE, Toshiba). Following scout images, a non-contrast image was obtained and a coronary calcium score was calculated using the Agatston method. CCTA was then acquired during the infusion of iodinated contrast at a rate of 4-6 ml/sec for a total of 50-100 ml. CCTA was performed with prospective ECG-triggering, when applicable, to maintain a low radiation dose.

CCTAs were read by board certified radiologists and cardiologists for clinical decision making. An emergency physician reviewed these clinical reads and categorized them into no stenosis (zero calcium score as calculated by the agatston method and no stenosis in any of the coronary arteries), 1-50% stenosis, 50 – 70% stenosis and stenosis of 70% or greater. Additionally, CCTA results were dichotomized into two categories: significant stenosis (50% or greater) and non-significant stenosis (less than 50% stenosis).

Outcomes

Our primary outcome was significant coronary artery stenosis. This was defined as coronary artery stenosis of 50% or greater in any coronary artery.

Statistical Analysis

Descriptive statistics were used to summarize study data. Continuous variables were summarized with means and corresponding standard deviations if normally

distributed, and with medians and corresponding interquartile ranges (IQR) if not normally distributed. Categorical variables were summarized as proportions. Differences between proportions were assessed with a χ^2 test. The differences in median hsTnI levels between patients with significant stenosis and those without, was tested using the Wilcoxon rank-sum (Mann-Whitney) test. We examined the association between hsTnI and coronary artery calcium score using a linear regression model, with log-transformed hsTnI as the dependent variable. A two-tailed p-value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA/MP statistical software version 11.2 (StataCorp, College Station, Texas), and RStudio statistical software version 0.97.312.

Results

Our study population comprised of 206 patients who received a CCTA. Of this population there were 114 females (55.3%) and 92 males (44.7%). The median age was 50.9 years (IQR: 45.3 – 57.6). Detailed description of the demographics of the study population is provided in Table 4.1. About half of study patients had coronary arteries without plaque or lumen narrowing (51.5% [106/206]), 39.3% (81/206) had maximal coronary artery stenosis of less than 50%, 6.3% (13/206) had maximal coronary artery stenosis of 50-70% stenosis, and 2.9% (6/206) had at least one coronary artery with >70% stenosis. hsTnI was detectable in 81.6% (168/206) of the study population, and 2.4% (5/206) had hsTnI > the 99th% of a reference population of healthy adults. Median hsTnI values were higher among patients with maximal coronary artery stenosis of 50% or greater (median 6.4

[IQR: 5.1 – 11.2] ng/L) than in patients with maximal coronary artery stenosis <50% (median 3.1 [IQR: 1.5 – 5.3]), p<0.01 (Figure 4.1). hsTnI values were higher with increasing severity of coronary artery stenosis (Figure 4.2). hsTnI discriminates between significant coronary artery stenosis (>=50%) and no significant coronary artery stenosis (<50%) with an area under the receiver operator curve (AUC) of 0.82 (95% CI: 0.74 – 0.89). Using ROC curve analysis, we determined that the optimal cut-off for discriminating significant stenosis (>=50%) is 3.2 ng/L. Avoiding CCTA in patients with hsTnI <=3.2 ng/L will result in avoiding 52.4% (98/187) of the CCTAs with <50% stenosis, without missing any patients with significant stenosis (Table 4.2). Similarly, avoiding CCTAs in patients with hsTnI at or below the limit of detection (LOD) will result in avoiding 28.3% (38/187) of CCTAs with <50% stenosis, without missing any patients with significant stenosis.

Discussion

Our study demonstrates that hsTnI are higher in patients with significant coronary artery stenosis (>50%) than in those without. Additionally, we found that by using a cut-off of either hsTnI<LOD or hsTnI<3.2 ng/L we can avoid CCTAs in 20 – 50% of patients who have no significant coronary artery stenosis. This finding has major implications for rapidly excluding significant coronary artery stenosis and ACS in a subset of ED patients. The idea of using undetectable or extremely low values of high sensitivity troponin to rapidly exclude AMI has been suggested by prior studies that used the high sensitivity troponin T (hsTnT) assay.[25,135] Our

study extends this idea by demonstrating hsTnI can be used to rapidly exclude significant coronary artery stenosis at ED presentation.

Our finding of higher hsTnI in patients with significant coronary artery stenosis is consistent with work done by prior authors. Korosoglou et al in a study of 124 patients with stable angina, described a strong correlation between hsTnT and total non-calcified plaque burden ($r=0.79$, $p<0.001$); and higher hsTnT values among patients with remodeled non-calcified plaque.[133] Similar findings using with the hsTnT assay were also reported by Januzzi et al.[136] It has also been established that hsTnT independently predicts 90-day adverse cardiac events after adjusting for cardiovascular risk profiling, calcium score and CCTA results.[137]

Our findings are well grounded in biological plausibility. Spontaneous coronary microembolization occurs in vessel with atherosclerotic plaques.[138] Additionally, subclinical episodes of plaque disruption and healing stimulate plaque growth resulting in high grade coronary stenosis.[139] Until the recent introduction of high sensitivity troponin assays, detection of micoinfarctions occurring secondary to coronary microembolization was achieved mainly by advanced magnetic resonance imaging (MRI) techniques[140] and the use of less sensitive biomarkers. Our findings of elevated hsTnI in patients with significant coronary artery stenosis suggest that coronary microembolization and microinfarction occurs with higher frequency in this group than in those without significant coronary artery stenosis.

The limit of quantitation of the hsTnI assay used in this study is 6.0 ng/L. Given the amount of uncertainty associated with the quantitation of values below the

limit of detection, the use of cut-off values between the LOD and the LOQ will be ill-advised.[141] For example, with the study assay a hsTnI value of 3.2 ng/L may not necessarily be different from a value of 5 ngL. Therefore, although according to our data, the use of 3.2 ng/L as the optimal cut-off for discriminating significant coronary artery stenosis results in avoiding about half of the CCTAs with no significant stenosis, it may also result in a misdiagnosis in patients with significant coronary artery stenosis. Therefore we recommend using the LOD as the optimal cut-off for discriminating significant coronary artery stenosis.

Limitations

Our study has two important limitations. First, our sample size is small. To be able to definitely state that patients with hsTnI<LOD have less than 1% chance of having significant coronary artery stenosis (the acceptable risk of major adverse cardiac events in chest pain patients discharged from the emergency department[142]), we need to study at least 370 patients with hsTnI<LOD, which translates to a sample size of about 6,100 total CCTA patients (if prevalence of hsTnI<LOD is 6%). Therefore a large multi-center study is needed to substantiate our study findings.

Secondly, since we enrolled only patients who received a CCTA at the discretion of their treating clinicians, our findings are applicable only to patients to CCTA candidates and not to the entire population of suspected ACS patients. Therefore, the use of hsTnI as a triage test for determining risk for significant coronary artery stenosis should be restricted to patients in whom a CCTA is being considered.

Conclusion

Our study demonstrates that hsTnI is higher in patients with significant coronary artery stenosis than in those without. Additionally, our results demonstrate that patients with undetectable hsTnI have low likelihood of significant coronary artery stenosis and may be candidates for expedited discharge, obviating the need for a CCTA.

Table 4.1: Demographic Characteristics of 206 Subjects Studied

Characteristic	Number (%)
Median Age in years (IQR)	50.9 (45.3 – 57.6)
Gender	
• Female	114 (55.3)
• Male	92 (44.7)
Ethnicity	
• Non-Hispanic Black	139 (67.5)
• Non-Hispanic White	49 (23.8)
• Hispanic	7 (3.4)
• Asian	3 (1.5)
• Native-American	7 (3.4)
• Native-Hawaiian	1 (0.5)
Insurance	
• Medicare	34 (16.5)
• Medicaid	54 (26.2)
• Commercial	89 (43.2)
• HMO	5 (2.4)
• VA	2 (1.0)
• None	22 (10.7)
Transportation	
• Self-transport	172 (83.5)
• Ambulance	28 (13.6)
• Transfer from other facility	6 (2.9)
Current cigarette smoker	90 (43.7)
Current cocaine use	7 (3.4)
Family history of AMI or sudden cardiac death	71 (34.5)
History of hypertension	102 (49.5)
History of diabetes	44 (21.4)
History of high cholesterol	64 (31.1)
History of congestive heart failure	7 (3.4)
History of stroke	17 (8.2)

Figure 4.1: High sensitivity troponin I values in those with significant vs non-significant stenosis

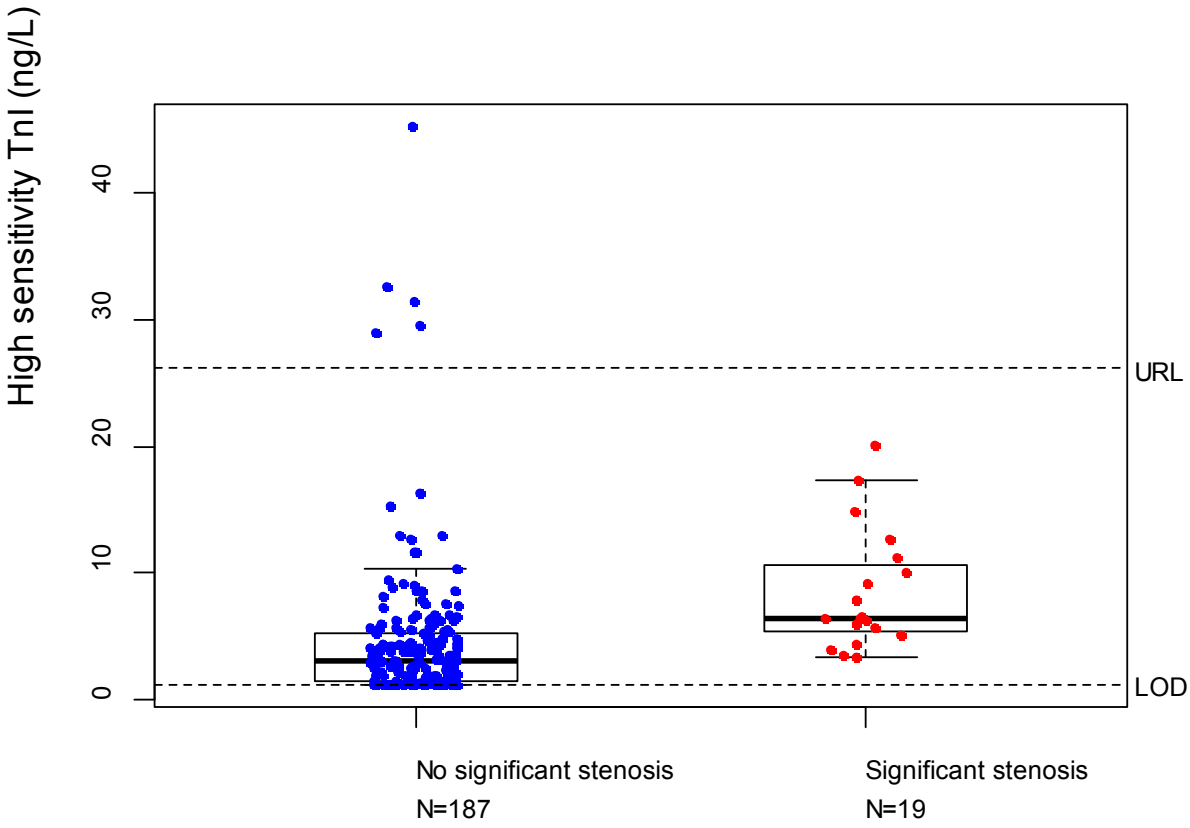

Figure 4.2: High sensitivity troponin I values in patients according to severity of CAD

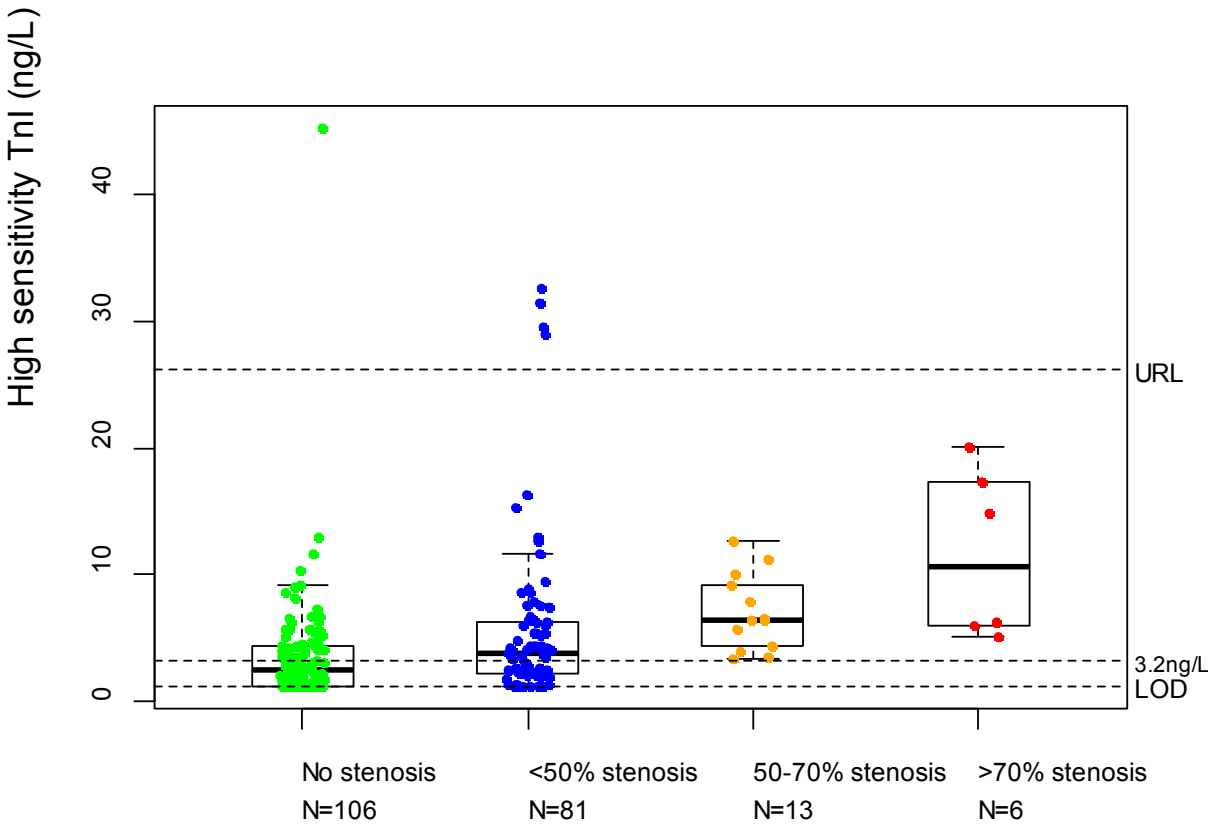

Table 4.2: 2 X 2 table at 3.2 ng.L cutoff for discriminating significant stenosis

	hsTnI>1.2 ng/L	hsTnI<=1.2 ng/L	
Stenosis >50%	19	0	19
Stenosis <50%	149	38	187
	168	38	206

Chapter 5: Future Directions

The duration of emergency department (ED) and hospital evaluation for acute coronary syndrome (ACS) remains problematic. In a recent report by the Office of the Inspector General on Medicare beneficiaries, chest pain was the most common reason for observation and short inpatient stays.[143] This finding can be explained by the fact that although evaluation for ACS often takes many hours, more than 85% of patients are often diagnosed with non-life threatening conditions and ultimately discharged.[2] My goal is to decrease the duration of ED evaluation for ACS by translating novel discoveries in biomarkers from bench to bedside. There are a number of barriers to rapidly ruling in or ruling out ACS within minutes to a few hours of ED presentation. These include: (1) the poor sensitivity of the traditional 12 lead ECG for diagnosing AMI;[6,7] (2) the need for serial measurements of cardiac troponins; and (3) the lack of biomarkers that can detect ischemic myocardial injury with acceptable diagnostic accuracy, resulting in the use of time and resource consuming tests such as coronary CT angiography, stress tests and cardiac catheterization. The next phases of this research will focus on the latter 2 barriers.

Circumventing the need for prolonged serial troponin measurements

Troponin measurements are central to the diagnosis of acute myocardial infarction (AMI).[9] Although clinical use of high sensitivity troponin I (hsTnI) assays will result improved diagnosis of AMI at ED presentation, we have demonstrated in Chapters 2 and 3 that the use of high sensitivity troponin I (hsTnI) will result in

an increase in the prevalence of elevated hsTnI among patients with a primary non-cardiac diagnosis. Thus, serial cTnI measurements will be needed to distinguish between acute and non-acute causes of elevated troponin. Recommendations for the duration of serial troponin measurements vary between expert groups. For example, the 2010 International Consensus on Cardiopulmonary Resuscitation recommends repeat troponin measurement between 6 and 12 hours after symptom onset, for patients who present within 6 hours of symptom onset.[144] The National Academy of Clinical Biochemistry and Laboratory Medicine 2007 Practice Guidelines recommend repeat measurements 6-9 hours after symptom onset.[145] Recommendations from the 2010 AHA Scientific Statement on testing of low-risk ED chest pain patients are for repeat cardiac biomarker measurements 6 to 8 hours after onset of symptoms.[127] With hsTn, the European Society of Cardiology recommends measuring hsTn at presentation and 3 hours after admission.[95] However, they acknowledge although the data is limited, some patients may still require a 6 hour sample for definitive diagnosis.[53]

In the next phase of this work, I will determine **whether serial sampling at presentation and 3 hours after presentation is adequate to safely rule out AMI using hsTnI**. Additionally, I propose an alternate approach to decreasing the duration of serial hsTnI sampling, which involves **quantification of both intact and degraded forms of cTnI, may reflect functional status of the heart and extent of intracellular damage in the infract and boarder regions. .**

As mentioned in chapter 1, prior studies have demonstrated that following myocardial injury, both cardiac troponin I (cTnI) and cardiac troponin T (cTnT) undergo degradation in a time-dependent pattern.[33,146] The amount of degraded fragments increases with increasing time from onset of injury. A recent study analyzed 18 patients with AMI and found intact cTnT present in only 3 patients within the first 8 hours after hospital admission. We hypothesize that patients with acute and ongoing myocardial infarction may have predominantly intact cTnI whereas those with old injuries or chronic troponin elevations may have predominantly degraded cTnI. Thus among those with an elevated hsTnI, those with predominantly intact cTnI will need acute intervention to treat the underlining cause of myocardial injury, whereas those with predominantly degraded cTnI and a non-rising hsTnI pattern, may benefit from expedited outpatient evaluation. Working with Dr. Pingbo Zhang in the Van Eyk lab, we will test our hypothesis on a cohort of ED patients evaluated for ACS, using a novel quantitative mass spectrometry assay that is able to quantify total cTnI and the N- and C-terminal regions. This allows determination of the extent of proteolysis in each sample along with providing a cTnI concentration.

Furthermore, we will also determine whether a combination of risk factors for CAD and hsTnI values allows the identification of a subset of the ED suspected ACS population with low risk for adverse cardiac events, who can be rapidly discharged.

Biomarkers of ischemic myocardial injury

Despite numerous attempts, the search for biomarkers of myocardial ischemia remains elusive. Prior studies have described associations between a number of biomarkers and myocardial ischemia. Ischemia modified albumin (IMA) is one of the most studied biomarkers of ischemia.[147] IMA levels are high is patients who develop chest pain and ST segment changes during PCI.[148] There are conflicting results regarding whether IMA adds diagnostic value to troponin and ECG results.[149,150] Although IMA have adequate negative predictive value,[149] there are many instances where elevated values cannot be easily explained, leading to a poor positive predictive value. In the coming months, I will be working with Dr. Christine Jelinek in Dr. Van Eyk's lab, to determine whether the quantification of post-translational modifications of albumin during myocardial ischemia may help improve the specificity of this candidate biomarker for myocardial infarction. Cysteine modifications to the N-terminus of albumin, as well as differences in the albumin-binding partners are being measured using the quantitative mass spectrometry method mentioned above.

Additionally a number of candidate biomarkers of ischemia have been discovered by work done in the Van Eyk lab. In the coming months to years, we plan to conduct clinical validation studies.

In conclusion, with the use of hsTnI, we AMI will be diagnosed earlier in a subset of patients who were previously initial cTnI negative. However, it will also result in a significant increase in the number of patients with elevated hsTnI values. Although majoriry of patients with new hsTnI elevations will not have AMI, they will be at higher risk of short and long-term adverse cardiac event than those who

remain hsTnI negative. There remains an unmet clinical need for novel methods of distinguishing between AMI and chronic hsTnI elevation. Quantification of cTnI disease-induced modified forms, albumin modified forms, or new markers of ischemia may offer a solution to this clinical challenge.

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149. Peacock F, Morris DL, Anwaruddin S, et al. Meta-analysis of ischemia-modified albumin to rule out acute coronary syndromes in the emergency department. *Am Heart J.* 2006;152:253-262; ( ) :.

150. Bhardwaj A, Truong QA, Peacock WF, et al. A multicenter comparison of established and emerging cardiac biomarkers for the diagnostic evaluation of chest pain in the emergency department. *Am Heart J.* 2011;162:276-282; e1; ( ) : . doi: 10.1016/j.ahj.2011.05.022.

Curriculum Vitae

CURRICULUM VITAE FOR ACADEMIC PROMOTION

(Signature) __Frederick Korley_____ 08/6/2013
(Typed Name) (Date of this version)

DEMOGRAPHIC AND PERSONAL INFORMATION

Current Appointments

The Johns Hopkins University School of Medicine

July 2007 – October 2007	Instructor, Department of Emergency Medicine
October 2007 to present	Assistant Professor, Department of Emergency Medicine
October 2007 to June 2012	The Robert E. Meyerhoff Junior Professor

The Johns Hopkins Medical Institutions

July 1, 2007 to present	Attending Physician, Department of Emergency Medicine

Personal Data

Office Address:

The Johns Hopkins University
Department of Emergency Medicine
5801 Smith Avenue
Davis Building, Suite 3220
Baltimore, MD 21209
Phone: 410-735-6450
Fax: 410-735-6440
Email: fkorley1@jhmi.edu

Education and Training

Undergraduate

Bachelor of Science, *summa cum laude*, 1999	Morris Brown College, Atlanta, GA	Biology

Doctoral

Doctor of Medicine, 2003	Northwestern University Feinberg School of Medicine, Chicago, IL	

Graduate

Ph.D.,	Johns Hopkins	Graduate Training Program in

Anticipated in 9/2013	Bloomberg School of Public Health	Clinical Investigation

Postdoctoral

2003 - 2007	Northwestern University McGaw Medical Center, Chicago, IL	Emergency Medicine Residency
2010 - 2012	Johns Hopkins Clinical Research Scholars Program	

Professional Experience

2006 - 2007	Chief Resident, Northwestern University Department of Emergency Medicine
2007 - present	Assistant Professor, The Johns Hopkins University School of Medicine, Department of Emergency Medicine
2007 - 2010	Member of Teaching College, The Johns Hopkins University School of Medicine, Department of Emergency Medicine

RESEARCH ACTIVITIES

Publications: **Peer-reviewed Original Science Research**

1. Gao P, **Korley** F, Martin J, Chen BT. "Determination of unique microbial volatile organic compounds produced by five Aspergillus species commonly found in problem buildings." AIHA J (Fairfax, Va). 2002 Mar-Apr;63(2):135-40.
2. Pins MR, Fiadjoe JE, **Korley F**, Wong M, Rademaker AW, Jovanovic B, Yoo TK, Kozlowski JM, Raji A, Yang XJ, Lee C. "Clusterin as a possible predictor for biochemical recurrence of prostate cancer following radical prostatectomy with intermediate Gleason scores: a preliminary report." Prostate Cancer Prostatic Dis. 2004;7(3):243-8.
3. Wang E.E., Quinones J., Fitch M.T., Dooley-Hash S., Griswold-Theodorson S., Medzon R., **Korley F**., Laack T., Robinett A., Clay L.. Developing technical expertise in emergency medicine-the role of simulation in procedural skill acquisition. Acad Emerg Med. 2008; 15(11):1046-1057.
4. Lammers RL, Davenport M, **Korley F**, et al. Teaching and assessing procedural skills using simulation: Metrics and methodology. Acad Emerg Med. 2008: 15(11):1079-1087.
5. **Korley FK**, Pham JC, Kirsch TD. Use of advanced radiology during visits to US emergency departments for injury-related conditions, 1998-2007. JAMA. Oct 6 2010;304(13):1465-1471.

6. Hymas E, **Korley FK**, Matlaga B. Trends in Imaging Utilization During the Emergency Department Evaluation of Flank Pain. J Urol. 2011 Dec;186(6):2270-4.
7. Leikin SM, **Korley FK**, Wang EE, et al. The spectrum of hypothermia: From environmental exposure to therapeutic uses and medical simulation. Dis Mon. 2012;58; 58:6-32.
8. Morton MJ, **Korley FK**. Head CT Utilization in the Emergency Department for Mild Traumatic Brain Injury: Integrating Evidence into Practice for the Resident Physician. Ann Emerg Med. Ann Emerg Med. 2012 Sep;60(3):361-7.
9. Pursnani S, **Korley F**, Gopaul R, Kanade P, Chandra N, Shaw RE, Bangalore S. Percutaneous Coronary Intervention Versus Optimal Medical Therapy in Stable Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Circ Cardiovasc Interv. 2012 Aug 1;5(4):476-90.
10. Hyams ES, Matlaga BR, **Korley FK**. Practice patterns in the emergency care of kidney stone patients: An analysis of the national hospital ambulatory medical care survey (NHAMCS). Can J Urol. 2012;19(4):6351-6359.
11. **Korley FK**, Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. J Am Coll Cardiol. 2013 Apr 30;61(17):1753-8
12. **Korley FK**, Jaffe AS. Reply to Letter to the Editor: Choosing troponin immunoassays in a world of limited resources. J Am Coll Cardiol. 2013 May 2.
13. **Korley FK**, Morton MJ, Hill PM et al. Agreement Between Routine ED Care and Clinical Decision Support Recommended Care in Patients Evaluated for Mild Traumatic Brain Injury. Acad Emerg Med. 2013 May;20(5):463-9.
14. Saber Tehrani AS, Coughlan D, Hsieh YH, Mantokoudis G, **Korley FK**, Kerber KA, Frick KD, Newman-Toker DE. Rising annual costs of dizziness presentations to US Emergency departments. Acad Emerg Med. 2013 Jul;20(7):689-96.
15. **Korley FK,** et al. Previously Undetected Elevations of High Sensitivity Cardiac Troponin I in the Emergency Department: How Frequent and How Important are They? Under Review. Heart

Editorial Work

1. Reviewer, Journal of the American Medical Association
2. Reviewer, Academic Emergency Medicine Journal
3. Reviewer, Circulation

Extramural Funding (current, pending, previous)

Current Grants:

7/2013 – 6/2014 Johns Hopkins Clinician Scientist Award

11/2012 – 12/2013 Improving current understanding of enhanced risk stratification of ED patients using high sensitivity cardiac troponin I.
Abbott Laboratories
PI: Korley, $170,046

9/2012 – 8/2013 NHLBI Proteomics Contract Minority Supplement Award
PI: Van Eyk, $50,000

7/2011 – 6/2013 NIH Student Loan Repayment Program
$70,000
PI: Korley

7/2012 – 6/2013 Johns Hopkins ED/Cardiology Readmissions Task Force
Co-investigator, 20%

Recent Grants:

7/2010 – 6/2012 Johns Hopkins Clinical Research Scholars Program
5KL2RR025006
Trainee: Korley

10/2007 – 6/2012 Robert E. Meyerhoff Endowed Professorship
PI: Korley, 10%

7/2008 – 6/2010 NIH Student Loan Repayment Program
$70,000
PI: Korley

EDUCATIONAL ACTIVITIES

Educational Publications

Book Chapters

1. Hackstadt D, **Korley F,.** "Thyroid Disorders." In Emergency Medicine. Adams JG et al.(eds.) Philadelphia, WB Saunders Company
2. **Korley F**, Leikin JB. "Disturbances Due to Cold." In Conn's Current Therapy 2008. Rakel RE, Bope ET (eds.) Philadelphia, WB Saunders Company.

3. **Korley F**, “Management of Increased Intracranial Pressure and Shunts.” In Clinical Procedures in Emergency Medicine, 5th ed. Roberts JR et al.(eds.) Philadelphia, WB Saunders Company
4. **Korley F**, “Venous Access”. In Handbook of Critical Care and Emergency Ultrasound. 1st ed. Moore et al. (eds) McGraw-Hill

Online Publication

1. **Korley F.** “Syncope: A case of torsades de pointes.” SAEM Simulation Interest Group, Simulation Case Library. 08/06. http://www.emedu.org/SimGroup/UploadFolder/syncope.doc.

Teaching

Classroom Instruction

1. Residency Conference: Bone and Joint Infections. Date: 7/2003. Role: Lecturer, Northwestern University Emergency Medicine Residency.
2. Trauma Conference: Penetrating Chest Trauma. Date: 8/2003. Role: Lecturer, Northwestern University Emergency Medicine Residency.
3. Residency Conference: Acute Presentation of G-6-P-D. Date: 9/2004. Role: Lecturer, Northwestern University Emergency Medicine Residency.
4. Toxicology Conference: Inhalant Abuse. Date: 8/2005. Role: Lecturer, Cook County Toxikon Consortium.
5. Residency Conference: Eye Trauma. Date: 10/2005 Role: Lecturer, Northwestern University Emergency Medicine Residency.
6. Residency Conference: Hemoptysis. Date: 1/2006. Role: Lecturer, Northwestern University Emergency Medicine Residency.
7. Chief’s Conference: Glaucoma. Date: 8/2006. Role: Lecturer, Northwestern University Emergency Medicine Residency.
8. Residency Conference: Emergency Delivery. Date: 9/2006. Role: Lecturer, Northwestern University Emergency Medicine Residency.
9. ED Rotator Resident Lecture Series: Ophthalmologic and ENT Emergencies. Date: 9/2006. Role: Lecturer, Northwestern University Emergency Medicine Residency.
10. Grand Rounds: Urinary Tract Infection. Date: 2/14/2007. Role: Lecturer, Northwestern University Emergency Medicine Residency.
11. Small groups session: Approach to Chest Pain. Date: 7/13/2007. Role: Instructor, Johns Hopkins University School of Medicine, Department of Emergency Medicine.
12. Cadaver ED skills lab: Orotracheal intubation, Chest tube insertion, ED thoracotomy, Central line placement. Date: 7/25/2007. Role: Instructor, Johns Hopkins University School of Medicine, Department of Emergency Medicine.

13. Toxicology Seminar: Opioid toxicity. Date: 8/25/2007. Role: Instructor, Johns Hopkins University School of Medicine, Department of Emergency Medicine.
14. Approach to the patient with altered mental status. Date: 9/28/2007. Role: Instructor, Johns Hopkins University School of Medicine, Department of Emergency Medicine.
15. Approach to the patient with syncope. Date: 2/15/2008. Role: Instructor, Johns Hopkins University School of Medicine, Department of Emergency Medicine.
16. The agitated patient. Date: 5/09/2008. Role: Instructor, Johns Hopkins University School of Medicine, Department of Emergency Medicine.
17. Cardiac Ultrasound Date: 7/23/2008 Role: Small group leader:
18. Hematuria Date: 9/19/2008 Role: Small group conference leader
19. Simulation case (Blunt abdominal trauma and hematuria) Date: 9/19/2008, Role: Instructor
20. Evidence Hour (Work-up of blunt abdominal trauma) Date: 9/19/2008 Role: Faculty leader
21. Simulation case (Post-concussive syndrome) Date: 10/3/2008 Role: Instructor
22. Evidence Hour (Hypertension) Date: 10/31/2008 Role: Faculty Leader
23. Hypotension Date: 3/20/2009, Role: Small group conference leader
24. Simulation case (sepsis) Date: 3/20/2009 Role: Instructor
25. Evidence Hour (Steroids and Sepsis) Date: 3/20/2009, Role: Faculty leader
26. Simulation case (Toxicologic Bradycardia) Date: 5/1/2009 Role: Instructor
27. Endocrine Emergencies Date: 6/5/2009 Role: Small group leader
28. Pediatric fractures Date: 11/6/2009 Role: Small group leader
29. Simulation-case (Conscious Sedation) Date:11/13/2009 Role: Instructor
30. Chairman's hour. Date: 1/14/2011 Role: Facilitator

<u>Simulation-based training courses</u>

1. August 15th, 2008, Instructor, Airway Course, 4 hours
2. November 17th, 2008, Course director and Instructor, Surgical and Emergency Department Physician Assistant Central Line Course, 4 hours
3. April 23rd, 2009, Instructor, Emergency Department Physician Assistant Central Line Course, 3 hours
4. May 8th, 2009, Course Instructor, Airway Course, 6 hours
5. June 23rd, 2009, Course Director and Instructor, Intern Central Line Course, 4 hours
6. February 19th, 2010, Instructor, Triple Course for medical students, 8 hours

7. April 8th, 2010, Instructor, Triple Course for medical students, 8 hours
8. 6/22/2010, Central line course. Emergency Medicine interns, 4 hours
9. 7/2/2010, Sepsis workshop, Emergency Medicine interns, 2 hour
10. 6/21/2011, Central line course, Emergency Medicine interns, 4 hours
11. 6/22/2012, Central line course, Internal Medicine interns, 4 hours
12. 7/01/2013, Central line course, Internal Medicine interns, 4 hours

<u>Emergency medicine residency simulation curriculum (1 hour sessions)</u>

1. 9/3/2008, Approach to Back Pain
2. 9/3/2008, Cocaine Toxicity
3. 9/3/2008, Chest tube
4. 9/3/2008, Syncope
5. 9/23/2008, DKA
6. 9/23/2008, Kidney Stone
7. 9/23/2008, Approach to Back Pain
8. 9/23/2008, Cocaine Toxicity
9. 2/4/2009, Sepsis: Infected Kidney Stone
10. 2/4/2009, Approach to Altered Mental Status (hepatic encephalopathy)
11. 2/5/2009, Approach to Altered Mental Status (hepatic encephalopathy)
12. 2/5/2009, Approach to Diabetic Ketoacidosis
13. 2/11/2009, Approach to Altered Mental Status (hepatic encephalopathy)
14. 2/11/2009, Sepsis: Infected Kidney Stone
15. 2/11/2009, Approach to Altered Mental Status (Tricyclic antidepressant poisoning)
16. 2/21/2009, Sepsis: Infected Kidney Stone
17. 3/3/2009, Approach to Back Pain
18. 3/3/2009, Approach to altered mental Status
19. 3/3/2009, Pediatric fever
20. 3/3/2009, Pediatric cardiac arrest
21. 3/3/2009, Pediatric cardiac arrest
22. 3/3/2009, Transvenous pacer placement
23. 3/18/2009, Pediatric fever
24. 3/18/2009, Pediatric arrest
25. 3/18/2009, Transvenous pacer placement
26. 3/12/2009, Pediatric fever
27. 3/12/2009, Pediatric arrest
28. 3/12/2009, Transvenous pacer placement
29. 5/5/2009, Approach to Altered Mental Status (Tricyclic antidepressant poisoning)

30. 5/5/2009, Sepsis: Infected Kidney Stone
31. 8/28/2009, Sepsis: Infected Kidney Stone
32. 8/28/2009, Clinical Diligence: Approach to patient with Thrombotic Thrompocytopenic Purpura
33. 9/9/2009, Sepsis: Infected Kidney Stone
34. 9/9/2009, Clinical Diligence: Approach to patient with Thrombotic Thrompocytopenic Purpura
35. 9/9/2009, Approach to Altered Mental Status (hepatic encephalopathy)
36. 9/9/2009, Approach to Back Pain
37. 9/17/2009, Transvenous pacemaker placement
38. 10/9/2009, Approach to Altered Mental Status (hepatic encephalopathy)
39. 10/9/2009, Approach to Back Pain
40. 11/17/2009, Approach to Altered Mental Status (hepatic encephalopathy)
41. 11/17/2009, 12/7, Sepsis II: Infected Kidney Stone
42. 12/7/2009, Approach to AMS I (Hepatic encephalopathy)
43. 12/15/2009, Transvenous pacemaker placement
44. 12/22/2009, Approach to back pain
45. 12/22/2009, Approach to AMS I (Hepatic encephalopathy)
46. 1/20/2010, Approach to AMS I (Hepatic encephalopathy)
47. 1/20/2010, Clinical diligence: Indentifying patient with TTP
48. 1/20/2010, Approach to AMS I (Hepatic encephalopathy)
49. 1/20/2010, Transvenous pacemaker placement
50. 1/20/2010, Clinical diligence: Indentifying patient with TTP
51. 1/20/2010, Transvenous pacemaker placement
52. 2/04/2010, Approach to AMS I (Hepatic encephalopathy) Approach to Back Pain

Educational Program Building / Leadership

7/1/2009 – 6/30/2010, Co-director, Education Fellowship, Johns Hopkins Department of Emergency Medicine

Educational Extramural Funding (current, pending, previous)

Dates: 7/1/2010 – 6/30/2011
Sponsor: The Women's Board of The Johns Hopkins Hospital
Total Direct costs: $27,980
Principal Investigator: Mr. Jim Scheulen
Role: Co-Investigator

CLINICAL ACTIVITIES

Certification

- Maryland Physician's License Number: D0065998
  Expiration Date: 9/30/2010
- American Board of Emergency Medicine Certification

ORGANIZATIONAL ACTIVITIES

Professional Societies

- Member, American College of Emergency Physicians, 2003 - present
- Member, Society for Academic Emergency Medicine, 2003 - present
- Member, SAEM Simulation Interest Group, 2005 - present
- Member, Society for Medical Simulation, 2005 – present
- Member, American Heart Association, 2011 - present

Conference Organizer, Session Chair

- Roundtable sessions chair, 2010 International Meeting on Simulation in Healthcare, Phoenix, Arizona

Consultantships

- 3/23/2010, Simulation Case Reviewer, Laerdal Corporation

RECOGNITION

- Presidential Merit Scholarship, Morris Brown College, 1996 - 1999
- Adolf F. Lange Scholarship, Northwestern University Feinberg School of Medicine, 1999 - 2001
- Goldberg Family Charitable Trust Travel Award, Northwestern Memorial Foundation, 2006
- **2009 Doctors Day donation by patient to JHH in my honor**
- Nominee, Attending of the year, Johns Hopkins University School of Medicine, Department of Emergency Medicine, 2007
- **Teacher of the Year**, Johns Hopkins University School of Medicine, Department of Emergency Medicine, 2010
- KL2 Clinical Research Scholar, Johns Hopkins Institute for Clinical and Translational Research, 2010
- Best presentation, Research Day, Johns Hopkins University School of Medicine, Department of Emergency Medicine, 2010

- **Attending of the Year**, Johns Hopkins University School of Medicine, Department of Emergency Medicine, 2011
- Scholar Abstract Award, 2012 Clinical Translational Science Annual meeting.