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RESEARCH ARTICLE



High sensitivity cardiac troponin T in patients not having an acute coronary syndrome: results from the TRAPID-AMI study

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ABSTRACT

Purpose: To describe the baseline, 1 hr and delta high sensitivity cardiac troponin (hs-cTnT) values in patients with suspected acute myocardial infarction (AMI) but without a final acute coronary syndrome (ACS) diagnosis.

Materials and methods: hs-cTnT assay for RAPID rule out of acute myocardial infarction (TRAPID-AMI) was a prospective diagnostic trial that enrolled emergency department (ED) patients with suspected AMI. Final patient diagnoses were adjudicated by a clinical events committee and subjects placed in different clinical groups: AMI, unstable angina, non-ACS cardiac, non-cardiac and unknown origin. The baseline, 1 hr and delta hs-cTnT values were analysed in the 902 non-ACS patients.

Results: Amongst the 1282 studied the patient groups were 213 (17%) AMI, 167 (13%) unstable angina, 113 (9%) non-ACS cardiac, 288 (22%) non-cardiac and 501 (39%) unknown origin. The hs-cTnT values in the non-cardiac and unknown origin groups were combined. The median hs-cTnT values (ng/L) were higher ($p < 0.001$) in the non-ACS cardiac compared to the non-cardiac/unknown origin group at baseline (11.8, <5) and 1 hr (12.3, <5). Their negative predictive values were 0.955 (baseline) and 0.954 (1 hr) for predicting non-ACS cardiac versus non-cardiac/unknown origin diagnoses.

Conclusions: Hs-cTnT may help predict whether non-ACS ED patients have a final non-ACS cardiac or non-cardiac/unknown origin diagnoses.

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Context

Approximately 5%–10% of all emergency department (ED) visits are for possible acute myocardial infarction (AMI) (Goodacre *et al.* 2005). Thus, in the United States (US) 8–10 million patients are evaluated yearly in the ED with symptoms that might indicate the presence of an acute coronary syndrome (ACS) (Owens *et al.* 2010). However, up to 85% of these patients are ultimately diagnosed with a variety of non-ACS diagnoses (Hollander 1999, Chase *et al.* 2006, Pollack *et al.* 2006). There have been advances in technology that have increased the sensitivity of troponin assays with measurements reported below the 99th percentile (99th %) in over 50% of an apparently normal healthy reference population (Apple and Collinson 2011).

For the Roche high sensitivity cardiac troponin T (hs-cTnT) assay (Diagnostics Elecsys) the 99th % is 14 ng/L, the level of detection (LoD) 5 ng/L and the level of blank (LoB) 3 ng/L. The LoB is defined as the mean observed result plus 1.645 standard deviations when testing a sample containing no analyte. The LoD is defined as the LoB plus 1.645 standard deviation of results obtained from a low concentration sample and is thus the lowest troponin concentration that might reasonably be distinguished from the LoB (Armbruster and Pry 2008). The hs-cTnT assay has been reported in recent clinical trials to be useful in the ruling out of AMI using a single baseline draw if the result is below the LoD with no associated ECG ischemia (Carlton *et al.* 2015, Body *et al.* 2016). Additionally, the use of the baseline, 1 hr and resultant delta hs-cTnT measurements

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have been shown to be helpful in the very early rule in and out of AMI (Reichlin *et al.* 2012, Mueller 2012, Roffi *et al.* 2015).

Troponin measurements are commonly ordered in US EDs (14% of patients) and all abnormal values reported are those above the 99th % value for the contemporary assays currently utilized (Meigher *et al.* 2016). However, emergency physicians in the US will be seeing in the future very low hs-cTnT measurements (<99th %) reported, mostly in those patients who have been ruled out for ACS (the vast majority of those evaluated). There have been no studies to date analysing how these hs-cTnT values might be used to aid in making correct patient diagnoses.

Objectives

The objectives of this analysis were to describe the baseline, 1 hr and the resultant delta hs-cTnT values in ED patients enrolled in the hs-cTnT assay for RAPID rule out of AMI (TRAPID-AMI) trial and not having a final diagnosis of an ACS and to determine how these measurements might be used clinically to clarify patients' diagnoses. It was hypothesized that non-ACS-diagnosed patients having other cardiac diseases would have higher hs-cTnT levels than those with those with non-cardiac or unknown origin diagnoses.

Clinical significance

- With advances in technology hs-cTn levels below the 99th percentile will be reported in the majority of patients. The authors have analyzed the high sensitivity troponin (hs-cTn) T results in the TRAPID-AMI study in those patients NOT having a final acute coronary syndrome diagnosis. This paper is an initial analysis of this hs-cTnT data and makes preliminary conclusions and recommendations on how these measurements might be used clinically. Future hs-cTn trials should carefully document the comorbidities of all enrolled individuals as these will affect the hs-cTn values that are measured and what they might mean.

Materials and methods

Design and setting

This prespecified sub-study of the TRAPID-AMI trial (a prospective international multicentre diagnostic study conducted in 12 sites on 3 continents (Mueller *et al.* 2012, Reichlin *et al.* 2012)) was conducted to describe and evaluate the hs-cTnT values in patients who did not have a final ACS diagnosis. TRAPID-AMI was undertaken to externally validate the diagnostic accuracy of the hs-cTnT baseline and 1-hr algorithm for rapid rule in and out of AMI and thereby confirm its suitability for routine clinical use in the ED (Reichlin *et al.* 2012, Body *et al.* 2016).

Data collection and processing

Patients (>18 years of age) presenting to the ED with chest discomfort suggestive of AMI and onset within 6 hr of presentation or peaking within this time period were eligible to participate. Excluded patients included those on haemodialysis, with acute trauma, receiving cardioversion, defibrillation or

thrombolytic before inclusion, having coronary artery bypass grafting within the previous month, patients hospitalized with AMI within the prior 3 weeks, pregnant or breastfeeding women and those who had been previously been included in the study. Patients were enrolled in TRAPID-AMI once only. A threshold of <6 hr of symptoms was chosen in order to enrich the study population with early presenters. All participants provided written informed consent before enrolment, each participating institution obtained approval from the appropriate research ethics committee or institutional review board and the trial was conducted in accordance with the principles of the Declaration of Helsinki.

Patients underwent routine clinical assessments that included history, physical examination, and 12 lead ECG, blood testing and chest X-ray as per local practice. Clinical data were recorded in study-specific case report forms. Baseline blood samples were collected in ethylenediaminetetracetic acid plasma tubes within 45 min of ED arrival or within 45 min of initial physician assessment. Additional blood samples were obtained after 1 hr (± 30 min), 2 hrs (± 30 min) and 4–14 hrs (± 30 min). Within 30 min of blood collection, the samples were centrifuged at 2500 g for 15 min, plasma was separated and within 4 hrs of collection aliquots were frozen at -80° C. They were later assayed in a core laboratory in a blinded fashion for hs-cTnT with the Roche Diagnostics Elecsys 2010 (99th % 14 ng/L, coefficient of variation <10% at 13 ng/L, LoD 5 ng/L) and sensitive troponin I (s-cTnI) using the Siemens Healthcare ADVIA Centaur (99th % 40 ng/L, coefficient of variation <10% at 30 ng/L, LoD 6 ng/L).

Outcomes

To determine the final diagnosis causing the symptoms for each patient adjudication was performed by a clinical events committee comprised of two independent cardiologists with a third one used if there was disagreement. Patients were placed in 1 of 5 clinical groupings after review of all available medical records pertaining to the patient from ED presentation to 30-day follow-up. The first group included those with AMI, diagnosed according to the universal definition of AMI (Thygesen *et al.* 2012, Meigher *et al.* 2016). The s-cTnI assay was used for this adjudication (the ED physicians did not have access to these values) and there was complete blinding to hs-cTnT levels during the study period. The other predefined clinical grouping included unstable angina, non-ACS cardiac disease, non-cardiac disease and symptoms of unknown origin.

Given that the diagnosis of unstable angina utilized for this study was predominately made using clinical assessments (typical angina at rest, a deterioration of previously stable angina, a positive result on cardiac exercise testing, a cardiac catheterization showing stenosis of >70% or more of vessel diameter or when the patient had an AMI or sudden unexpected cardiac death within 30 days of study inclusion) we chose to look at the hs-cTnT levels in the non-ACS-diagnosed groups (non-ACS cardiac, non-cardiac and unknown origin).

Statistical analysis

Categorical data were summarized with frequencies and percentages and continuous data by the mean and standard

Table 1. Non-ACS group clinical variables comparisons.

Variable	Non-ACS Diagnosis Group			Overall Comparison <i>P</i> -value
	Cardiac (<i>N</i> = 113)	Other (<i>N</i> = 288)	Unknown (<i>N</i> = 501)	
Age	65.9 ± 16.0 69.0	57.9 ± 14.9 57.0	58.6 ± 14.2 57.0	<0.001
Male Gender	72 (63.7%)	166 (57.6%)	286 (57.1%)	0.427
Weigh in Kg	84.2 ± 21.1 82.0	81.3 ± 20.4 79.0	81.9 ± 17.8 79.0	0.389
Hx of Hypertension	90 (79.6%)	151 (52.4%)	278 (55.5%)	<0.001
Hx of Diabetes	34 (30.1%)	45 (15.6%)	88 (17.6%)	0.003
Current Smoker	21 (18.6%)	81 (28.5%)	108 (22.0%)	0.048
Past Smoker	41 (36.3%)	82 (28.9%)	177 (36.0%)	0.105
Hx of MI	24 (21.2%)	45 (15.6%)	93 (18.6%)	0.365
Hx of CHF	20 (17.7%)	15 (5.2%)	33 (6.6%)	<0.001
Hx of Cerebrovascular Disease	15 (13.4%)	25 (8.7%)	41 (8.2%)	0.218
Systolic Blood Pressure	143.5 ± 30.7 139.0	140.7 ± 21.7 139.0	142.1 ± 22.0 142.0	0.526
Diastolic blood pressure	85.2 ± 16.8 85.0	81.3 ± 13.5 81.0	81.5 ± 13.7 81.0	0.033
Heart rate	91.5 ± 24.1 87.0	77.7 ± 15.8 77.0	76.1 ± 13.6 75.0	<0.001
Creatinine reading	1.02 ± 0.64 0.88	0.86 ± 0.33 0.81	0.85 ± 0.29 0.81	0.004
Sinus rhythm	68 (60.2%)	273 (94.8%)	471 (94.0%)	<0.001

Numeric data is shown as the means ± standard deviation with the median below.

deviation (for normal data) and median and interquartile range (for non-normal data). Overall comparisons of the cardiac, non-cardiac and unknown origin patient groups were performed using the Chi-square test for categorical data, one-way analysis of variance for normally distributed continuous data and the Kruskal–Wallis test for non-normally distributed continuous data. The hs-cTnT measurements at baseline, 1 hr and the resulting delta values between the cardiac and non-cardiac/unknown origin groups were compared using the Wilcoxon Rank Sum test. ROC curves were plotted and the area under these curves used to evaluate the ability of hs-cTnT at baseline and 1 hr to predict a non-ACS cardiac diagnosis from the non-cardiac/unknown aetiology group. The optimal cut points for hs-cTnT at baseline and 1 hr were defined as those resulting in the maximum sum of the sensitivity plus specificity. The corresponding sensitivity, specificity and negative and positive predictive values were determined.

Results

From August 2011 to June 2013, 1458 patients with suspected AMI were enrolled of whom 1282 had sufficient data for inclusion in this analysis (Mueller 2012). The median time from symptom onset or peak to ED arrival was 2.7 hr (interquartile range 1.5–5.1 hr) and the median time to first study blood draw was 3.4 hr (interquartile range 2.1–6.0 hr). Clinically available data for each of the 3 non-ACS groups are compared in Table 1. While the non-ACS cardiac patients were significantly older with a more frequent history of hypertension (HTN), diabetes, smoking, myocardial infarction, congestive heart failure and had higher diastolic blood pressure, heart rate and sinus rhythm there was overlap in these variables within the non-cardiac and unknown origin groups.

The adjudicated final diagnosis in the clinical groups described was as follows: 213 (17%) AMI, 167 (13%) unstable angina, 113 (9%) non-ACS cardiac, 288 (22%) non-cardiac and 501 (39%) unknown origin. A more detailed breakdown of the diagnostic categories of the non-ACS cardiac group is shown in Figure 1. The majority of these patients (88%) were diagnosed with arrhythmia, HTN crisis and acute heart failure (AHF). A similar more detailed breakdown of the diagnostic categories of non-cardiac and unknown origin diagnosis is

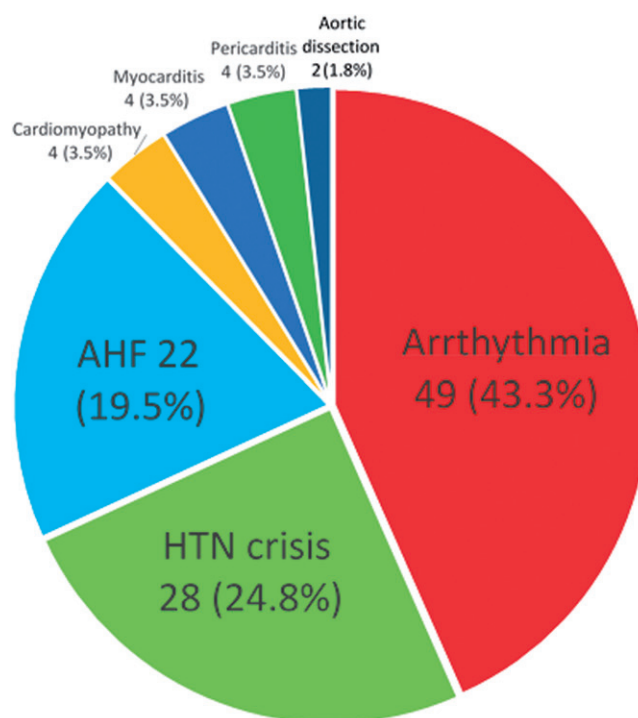


Figure 1. Non-ACS cardiac diagnoses.

shown in Figure 2. Most of these patients (64%) had an unknown origin and for the non-cardiac group the majority (34%) had musculoskeletal, gastrointestinal, anxiety and chronic obstructive lung disease (COPD) etiological as causes for their symptoms.

The distributions for the hs-cTnT values were initially completed for the non-ACS cardiac, non-cardiac and unknown origin groups. However, the non-cardiac and unknown origin groups had similar boxplots, quartiles and median values and so their hs-cTnT values were pooled for statistical analysis. Hs-cTnT measurements \geq LoD (5 ng/L) were found in 79.6% and 78.8% of patients with a non-ACS cardiac diagnosis and 37.4% and 38.1% of those with a non-cardiac/unknown origin diagnosis at baseline and 1 hr, respectively. Figure 3 shows the distribution of the non-ACS cardiac and non-cardiac/unknown origin groups' hs-cTnT levels at baseline, 1 hr and the resultant delta values. The median hs-cTnT measurements between

these 2 groupings at baseline and 1 hr were significantly different (11.8, <5; 12.3, <5 ng/L; all $p < .0001$) while the delta values were not (0.0, 0.0 ng/L; $p = 0.609$).

Receiver operator curves (ROCs) show that at baseline and 1 hr the areas under the curve (AUC) were 0.7653 (95% CI: 0.718–0.813) and 0.7672 (95% CI: 0.720–0.814) with optimal cut points of 5.49 and 5.35 ng/L, respectively, in differentiating

non-ACS cardiac from non-cardiac/unknown origin patients (Figures 4 and 5). The negative predictive values (NPVs) for a non-ACS cardiac diagnosis with values <5.49 ng/L (baseline) and <5.35 ng/L (hr 1) were 0.955 and 0.954, respectively.

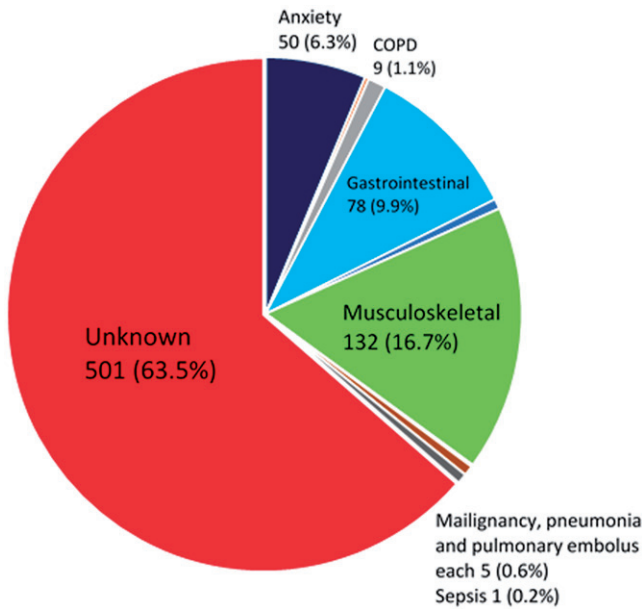


Figure 2. Non-cardiac/unknown aetiology diagnoses.

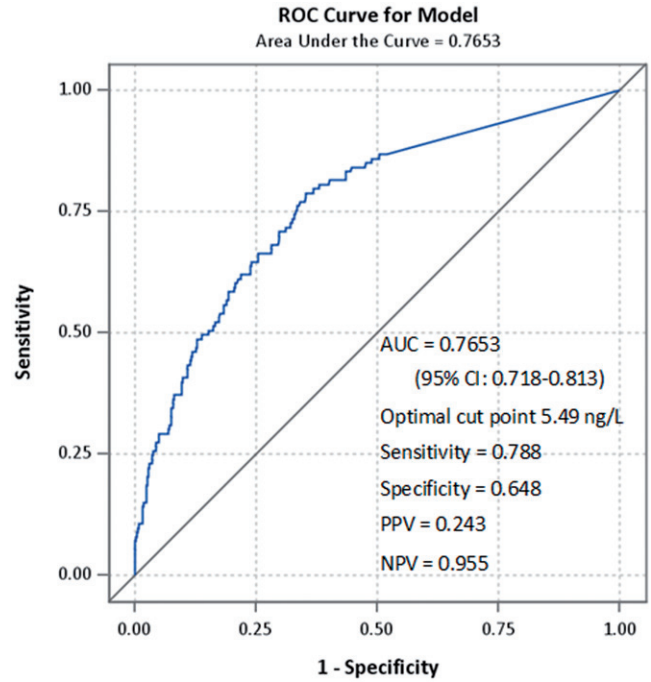


Figure 4. Prediction of non-ACS cardiac from non-cardiac/unknown aetiology diagnosis at baseline.

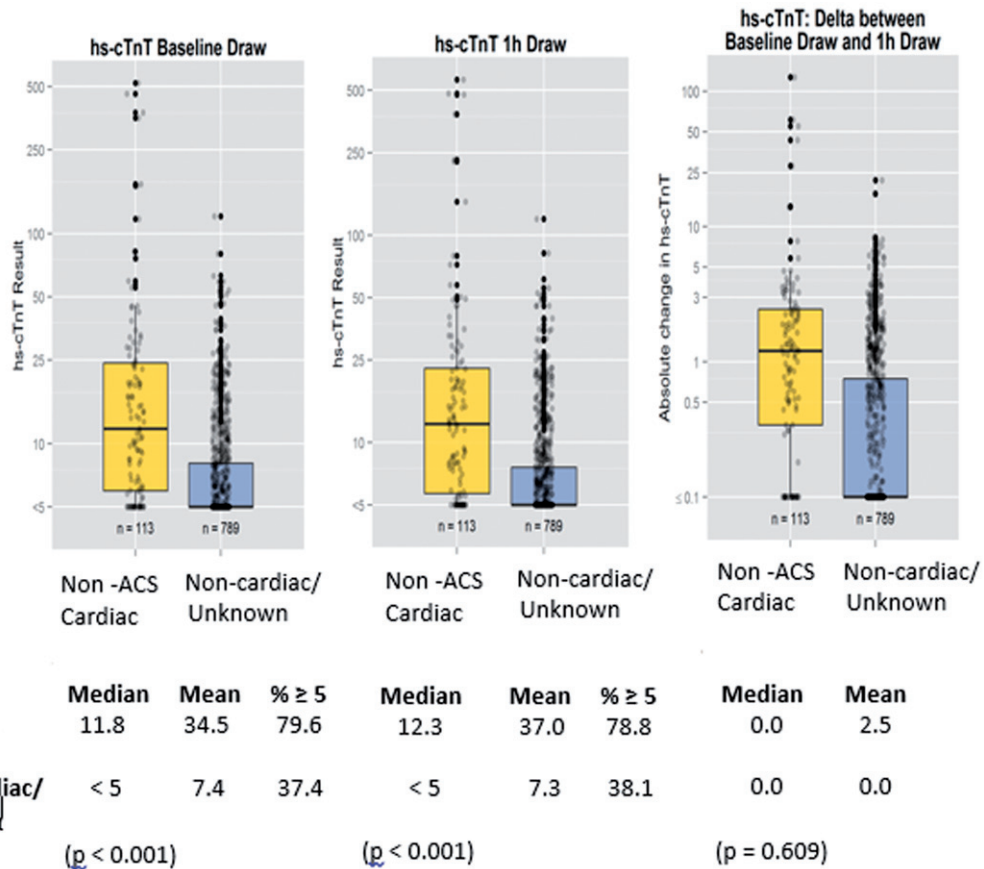


Figure 3. hs-cTnT measurements in the non-ACS cardiac and non-cardiac/unknown aetiology groups.

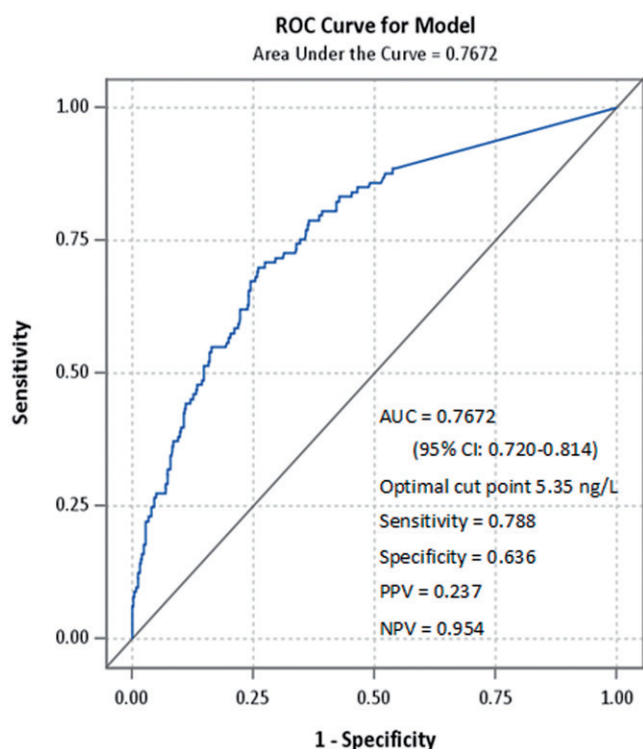


Figure 5. Prediction of non-ACS cardiac from non-cardiac/unknown aetiology at 1 hr.

When the cut-off points for the ROC analyses were changed to ≥ 5 ng/L (LoD) at baseline and 1 hr the sensitivities (0.796, 0.788), specificities (0.626, 0.619) and negative (0.956, 0.953), and positive predictive (0.234, 0.228) values changed marginally. The ROC analysis for the delta value between baseline and 1 hr had an AUC of 0.486 indicating that the hs-cTnT levels in these groups essentially remained very stable from baseline to 1 hr.

There were 23 patients (20%) who had hs-cTnT values $<$ LoD at baseline and had a final non-ACS cardiac diagnoses. These included 11 patients with arrhythmia, 10 HTN crises and 2 pericarditis. At 1 hr, 24 patients (21%) had values below the LoD and of these 11 had arrhythmia, 11 HTN crises and 2 pericarditis.

Discussion

This is the first report, to our knowledge, describing the measurements and possible clinical utility of hs-cTnT in patients enrolled in a large diagnostic AMI clinical trial but not having a final ACS diagnosis. This analysis is important as emergency physicians in the US will see in the near future many hs-cTnT levels reported that are below the 99th % in patients that do not meet current criteria for the early rule in/out of AMI and who are not thought clinically to have unstable angina.

Patients in the non-ACS cardiac group (113% or 9% overall) had final diagnoses mostly comprised of arrhythmia (43%), HTN crisis (25%) and AHF (20%) with a few having cardiomyopathy, myocarditis, pericarditis and aortic dissection. Patients in the non-cardiac group (288 or 23% overall) had diagnoses mostly of musculoskeletal (17%), gastrointestinal

(10%), anxiety (6%) and COPD with a few having pneumonia, sepsis, pulmonary embolus and malignancy. The unknown origin group was the largest comprising 501% or 39% of patients enrolled overall.

It can be difficult to determine clinically the diagnoses of the non-ACS patients and how accurate that final provisional ED diagnosis might be. Clinical assessments are utilized in making these alternate diagnostic decisions but the use of these alone do not reliably differentiate those with a non-ACS cardiac diagnosis from those with a non-cardiac/unknown origin categorization (Table 1). We have shown that patients with non-ACS cardiac disease have significantly ($p < 0.001$) higher median hs-cTnT levels than those in the combined non-cardiac/unknown origin group both at baseline and 1 hr. Additionally, the optimal hs-cTnT level to differentiate these groups at baseline was 5.49 and at 1 hr 5.35 ng/L. If the hs-cTnT values are less than these there is a NPV for non-ACS cardiac diagnosis of 0.955 at baseline and 0.954 at 1 hr. The NPVs (0.956 at baseline, 0.953 at 1 hr) remained similar when the LoD (≥ 5 ng/L) was used in the ROC analysis. Just as very low baseline hs-cTnT levels (below the LoD) strongly suggest the absence of AMI (Body *et al.* 2016) it appears that similar values $<$ LoD at baseline and 1 hr also suggest the absence of any alternative other non-ACS cardiac diagnoses. Patients with hs-cTnT levels below the LoD at either baseline or 1 hr are very unlikely to have a non-ACS cardiac diagnosis as the cause of the symptoms that brought them to the ED for evaluation, especially if they have no comorbidities that are associated with chronic troponin elevations. It is our thought that if all patient comorbidities had been known and those patients with a comorbidity that was associated with chronic hs-cTnT elevations (HTN, heart failure or renal insufficiency) were removed from the analysis then our NPVs at baseline and 1 hr predicting those with non-cardiac/unknown origin might have approached 100%. Our current results, although not definitive, may be helpful to ED physicians on their choices of early diagnostic workups for individual patients presenting with suspected ACS.

There were some patients with a final non-ACS cardiac diagnosis that had hs-cTnT measurement below the LoD at baseline and 1 hr (Figure 3). These were seen when the final diagnosis was arrhythmia, HTN crisis and pericarditis but not when the non-ACS cardiac diagnosis was AHF. This brings to question as to whether these final individual patient diagnoses were correct and if so could the hs-cTnT value $<$ LoD indicate a less malignant arrhythmia, a hypertensive crisis with no structural heart damage and thus management on an outpatient basis, or possibly a benign case of pericarditis.

This report comprises a prespecified and preliminary secondary analysis of the TRAPID-AMI study and hence requires large prospective trials that enrol all suspected ACS patients for verifications/alterations before our results can be routinely clinically implemented. The final non-ACS diagnoses provided by the adjudication committee were based mainly on the work up completed by the treating physicians and so the non-ACS diagnoses could have been in some cases not accurate. While there were some clinical variables (Table 1) that differed between the three non-ACS diagnostic groups these were not further studied as

our focus was on the potential use of hs-cTnT to differentiate between the non-ACS cardiac and non-cardiac/unknown origin groups. Future studies will require accurate documentation of patients' current comorbidities and chronically measurable troponin levels as these were not systematically recorded in TRAPID-AMI.

Conclusions

In ED patients being evaluated for possible ACS hs-cTnT measurements will be reported in approximately 80% of those with a final non-cardiac and 40% of individuals with non-cardiac/unknown origin diagnoses. Hs-cTnT levels < LoD at baseline and 1 hr may help in predicting whether these patients might have a non-ACS cardiac versus a non-cardiac/unknown origin cause for their symptoms. Also baseline and 1 hr levels of hs-cTnT < LoD in patients having a non-ACS cardiac diagnosis might help in determining the severity of that specific clinical presentation. As there will be continued increasing use of hs-cTnT testing in the US, ED setting further trials are necessary to clarify how best to incorporate these very low levels into the diagnostic and therapeutic approaches in patients who are suspected of but not having an ACS diagnosis.

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