"Real life use" of troponin in the emergency department: a survey of over 3000 cases

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Abstract

Introduction: The aim of this study was to identify clinical variables which may be independently associated with positivity of a cardiac troponin I (cTnI) assay in a large population of patients admitted to the emergency department (ED).

Materials and methods: 3166 subjects, with at least two troponin I tests ordered within 6 hours in the ED, were studied. Patient data were statistically analyzed to identify clinical associations with increased values of Troponin I.

Results: Although patients with diagnosis of acute coronary syndrome displayed troponin I values significantly higher than those of other groups, positivity to troponin I (> 40 ng/L) was also observed in patients with other clinical conditions. In multivariate analysis, age, elevated heart rate and electrocardiographyc changes were independently associated with troponin I positivity at admission. In the whole study population troponin I positivity exhibited high sensitivity and negative predictive value, counterbalanced by low specificity and limited positive predictive value.

Conclusions: Troponin I positivity should be combined with history and clinical evaluation and cautiously interpreted in the ED, especially in patients exhibiting factors associated with higher troponin I levels such as older age, elevated heart rate or ECG changes.

Key words: troponin I; acute coronary syndrome; emergency service, hospital; chest pain

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Introduction

The clinical diagnosis of ST-elevation myocardial infarction (STEMI) and of non ST-elevation MI (NSTEMI), according to the universal definition of myocardial infarction (MI), is based on the detection of a rise and/or fall of cardiac biomarker values, preferably cardiac troponins (cTn), with at least one value above the 99th percentile upper reference limit (URL) (1). Guidelines usually recommend that blood samples for the measurement of cTn should be drawn on first assessment and repeated 3–6 h later (1-3). Patients with suspected acute coronary syndrome (ACS) typically present to the Emergency Department (ED) within a few hours or even minutes after symptom onset (4). Therefore, delay of blood sampling may increase costs for hospital observation and/or admission, whereas early cTn negativity may lead to missing some diagnoses of MI.

The new and more (i.e., "highly") sensitive cTn assays can detect myocardial injury substantially earlier than the previous generation of assays (5), due to the improved analytical sensitivity. Nevertheless, since cTn is a general biomarker of myocardial

injury, a variety of different causes of myocardial damage such as inflammation (6) pulmonary embolism (7) and heart failure (8) may cause increased level of plasma cTn. On the other hand, these assays should be regarded as significant step forward for diagnosing patients with stable cardiovascular disease and to anticipate their prognosis (9). The availability of new, high-sensitivity (HS) cTn tests, along with the more extensive use of this test in ED as universal "screening for MI", has remarkably increased the number of patient testing positive for cTn (i.e., cTn value over the 99th percentile of a reference population) (10). The obvious consequence is a further increase in the workload necessary to rule out ACS in cTn positive patients. Emergency physicians have therefore been faced with the paradox of increasing efforts to troubleshoot the causes of potential positivity of this marker due to conditions other than myocardial ischemia. The aim of this study was to identify clinical variables which may be independently associated with positivity of a cTnI assay in a large population of patients admitted to the emergency department (ED).The main novelty of this study resides in providing valuable information about cTnI in order to help emergency physicians to appropriately use and interpret this test in a day-to-day clinical setting of an ED.

Materials and methods

Subjects

Between April 2012 and March 2013, 33,496 cTnI tests were performed in the local hospital laboratory, corresponding to 11,470 different patients. A total number of 5,596 out of these patients, having at least 2 cTnI tests ordered within 6 hours, were further selected. Among these patients, 3,188 were admitted to the ED, and complete clinical data were available in 3,166 subjects who were hence finally included in the study.

Median basal (t1) and following (t2) cTnI values (expressed as ng/L, following IFCC recommendations) were classified according to ED discharge diagnosis. Nevertheless, additional information was acquired in order to perform a statistical analysis in the population sample and in specific subgroups, as follows:

Electrocardiograms (ECG) obtained at presentation were retrospectively re-interpreted, by three expert physicians, in a blinded fashion as 1) normal or non-diagnostic: paced rhythm or old left bundle-branch block (LBBB), non-specific ST-T changes; 2) as suggestive of ACS: ST-segment depression or elevation (≥ 1.0 mm in more than two contiguous leads), new onset of LBBB or new T-wave inversion.

Chest pain was retrospectively classified as typical or atypical by two expert physicians using the following criteria (11,12): typical chest pain was diffuse at the entire chest, localized under sternum or epigastric, gradual or waxing and waning onset, duration ranging from few minutes to 2 hours, spontaneous or provoked by activity, not influenced by respiration or changes in body position, described as squeezing, tightness, pressure, constriction, crushing, strangling, burning, heartburn, fullness in the chest, band-like sensation, knot in the center of the chest, lump in throat, heavy weight on chest, toothache. Irradiation to epigastrium, shoulders, arms, wrist, neck and throat, lower jaw and teeth or interscapular region was instead considered atypical.

Data were also retrospectively re-evaluated by two expert physicians and patients were considered as "unequivocal ACS" if they were admitted to ED with chest pain, with ECG changes suggestive of ACS and with a coronary angiography showing stenosis > 70% of lumen diameter of 1 or more coronary arteries (13).

The study was planned according to the guidelines of the local ethical committee in conformity to the principles of the Declaration of Helsinki.

Methods

Blood samples were collected in Becton Dickinson Vacutainer Plastic tubes containing lithium heparin (Vol. 4.5 mL, Ref. 366567) (BD Diagnostics, Franklin Lakes, New Jersey, USA). cTnI concentration was measured with the TnI-Ultra method, on ADVIA Centaur®CP platform (Siemens Healthcare Diagnostic, Erlangen, Germany). The threshold val-

ue of this assay, which is the value beyond which the concentration of cTnI is considered clinically significant and corresponding to the 99th percentile, is 40 ng/L (CV 10%). The TnI test was hence classified as "positive" in the presence of values > 40 ng/L, whereas values equal or lower than this threshold were considered as "negative".

Statistical analysis

Statistical analyses and graphs were performed by SPSS statistical software v. 15.0 (SPSS Inc., Chicago, IL, USA) and R software v. 2.15.1 (R Foundation for Statistical Computing). Differences between groups were estimated by non-parametric Kruskal-Wallis (with Bonferroni correction for multiple comparisons) or Mann-Whitney tests. Differences in proportions were estimated by Chi-squared or Fisher's exact test. Confidence intervals (CI) were calculated using CIA software v. 2.1.1 (by T Bryant, University of Southampton, UK). Distribution of basal and subsequent cTnI data, assessed by the Kolmogorov–Smirnov and the Shapiro-Wilk tests, and visually by histogram and kernel density plot, was found to be highly skewed. Predictors for positive cTnI test (> 40 ng/L) were estimated by univariate and multivariate logistic regression. Sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) to detect "unequivocal ACS" were calculated in the whole sample and in three subgroups (see column 1 in Table 2) and were provided with their 95% confidence intervals, according to the efficient-score method (corrected for continuity).

Results

cTnI values and ED diagnosis

The study population included 3,166 patients, 1,757 males (55.5%) and 1,409 females (44.5%), with a median age of 72 years (interquartile range [IQR] 57-82 years, min-max 16-104 years). The patients were classified in 16 groups according to discharge diagnosis from the ED. Table 1 shows basal (time 1: admission) and following (time 2: within 6 h) cTnI values. Patients with ACS (group 3; N = 303) displayed both basal and subsequent cTnI values significantly higher than those of other groups (Bonferroni correction; group 3 *vs*. all other groups: $P < 0.01$).

Table 1 shows also the change of cTnI positivity (% of values > 40 ng/L) between the two time points. In all groups, but not 8, the rate of cTnI positivity increased from time 1 to time 2, with larger increase for groups 1 (from 62.0 to 74.1%), 2 (from 26.2 to 35.3%) and 3 (from 76.2 to 93.7%). Interestingly, 230 out of 231 positive basal cTnI values in group 3 (ACS) were confirmed as positive also at time 2.

cTnI and clinical presentation: chest pain and admission heart rate

Among all patients admitted to the ED, 1,629 (51.5%) did not report chest pain, 657 (20.7%) and 666 (21.0%) respectively reported typical and atypical chest pain, whereas 214 (6.8%) reported a chest pain that was not classified as typical/atypical. Patients without chest pain displayed basal and subsequent cTnI values significantly higher than patients with typical or atypical pain (Bonferroni correction; $P < 0.003$).

In the ACS group (N = 303), 73 patients (24.1%) did not report chest pain, 131 (43.2%) and 54 (17.8%) respectively reported typical and atypical chest pain, whereas 45 (14.9%) reported a chest pain that was not classified as typical/atypical. In this group, no association between chest pain type and cTnI positivity at either time point was observed. However, patients without chest pain (N = 73) showed significantly higher basal cTnI values than patients with chest pain (N = 230) ($P = 0.022$). Surprisingly, no difference was found in cTnI values of the second time point ($P = 0.216$).

Patients with elevated admission heart rate (HR > 100 bpm, 18.1%) displayed significantly higher basal cTnI values (Bonferroni correction, $P < 0.0015$) and larger prevalence of cTnI positivity ($P < 0.001$) than patients with lower HR. No difference was found between patients with admission HR < 60 bpm (6.1%) and HR between 60 and 100 bpm (75.8%).

Table 1. Median basal (t1) and subsequent (t2) cTnI values (ng/L) in patients subdivided by ED discharge diagnosis.

	ED Diagnosis group N of patients (%)	cTnI t1 median (IQR), N of patients (%)	cTnI t2 median (IQR), N of patients (%)
1	Congestive cardiac failure, acute pulmonary edema 255 (8.1)	60 (30-130) POS 158 (62.0)	90 (40-300) POS 189 (74.1)
		POS at both times: 151 (59.2)	
2	Atrial fibrillation, arrhythmia 225 (7.1)	20 (10-50) POS 59 (26.2)	30 (10-90) POS 80 (35.6)
		POS at both times: 54 (24.0)	
3	Acute coronary syndrome (STEMI, NSTEMI, unstable angina) 303 (9.5)	240 (50-1850)* POS 231 (76.2)	3520 (370-24800)* POS 284 (93.7)
		POS at both times: 230 (75.9)	
4	Chest, epigastric pain 992 (31.3)	10 (10-20) POS 120 (12.1)	10 (10-20) POS 145 (14.6)
		POS at both times: 109 (11.0)	
5	Pneumonia, COPD, dyspnoea, respiratory failure, pulmonary embolism, other conditions affecting respiratory system 290 (9.2)	50 (10-130) POS 162 (55.9)	60 (20-240) POS 172 (59.3)
		POS at both times: 154 (53.1)	
6	Stroke, TIA, other conditions affecting CNS 117 (3.7)	20 (10-90) POS 44 (37.6)	20 (10-130) POS 46 (39.3)
		POS at both times: 43 (36.8)	
7	Trauma, contusion, bone fracture 102 (3.2)	10 (10-60) POS 33 (32.4)	20 (10-70) POS 38 (37.3)
		POS at both times: 31 (30.4)	
8	Salt and water derangements, metabolic disorders 87 (2.7)	60 (20-240) POS 54 (62.1)	80 (20-250) POS 52 (59.8)
		POS at both times: 50 (57.5)	
9	Hypertensive emergency 75 (2.4)	10 (10-20) POS 13 (17.3)	10 (10-30) POS 16 (21.3)
		POS at both times: 13 (17.3)	
10	Syncope, pre-syncope 253 (8.0)	10 (10-30) POS 40 (15.8)	10 (10-30) POS 47 (18.6)
		POS at both times: 31 (12.3)	
11	Shock, hypotension 34 (1.1)	40 (10-130) POS 16 (47.1)	70 (10-180) POS 18 (52.9)
		POS at both times: 16 (47.1)	
12	Psychosis, drug abuse, intoxications 48 (1.5)	10 (10-10) POS 4 (8.3)	10 (10-20) POS 7 (14.6)
		POS at both times: 4 (8.3)	
13	Gastritis, vomiting, abdominal pain, diarrhea, acute abdomen, cholangitis, other conditions affecting digestive system 189 (6.0)	10 (10-50) POS 47 (24.9)	10 (10-60) POS 52 (27.5)
		POS at both times: 45 (23.8)	

	ED Diagnosis group N of patients (%)	cTnI t1 median (IQR), N of patients (%)	cTnI t2 median (IQR), N of patients (%)
14	Sepsis, fever 55 (1.7)	80 (10-260) POS 35 (63.6)	100 (30-240) POS 38 (69.1)
		POS at both times: 34 (61.8)	
15	Other conditions affecting heart 81 (2.6)	20 (10-160) POS 30 (37.0)	30 (10-330) POS 34 (42.0)
		POS at both times: 27 (33.3)	
16	Other conditions 60 (1.9)	20 (10-70) POS 23 (38.3)	20 (10-100) POS 24 (40.0)
		POS at both times: 22 (36.7)	

IQR - interquartile range; COPD - chronic obstructive pulmonary disease; TIA - transient ischemic attack; CNS - central nervous system.
In each cell, median and IQR of cTnI at t1 and at t2 (first raw) are reported together with the absolute frequency and percentage of cTnI positivity (second raw). Percentages of cTnI positivity at each time are calculated within each "discharge diagnosis" group (second column)
*: $P < 0.01$ *vs*. all other groups

cTnI, coronary angiography and ECG

The 303 patients discharged from ED with ACS (STEMI or NSTEMI) were admitted to cardiology department for further examinations. 250 out of 303 (83%) underwent coronary angiography, whereas the remaining 53 (18%) were considered at highest risk for the procedure. Conversely, 135 patients without STEMI or NSTEMI were subjected to coronary angiography, most of them having persistent chest pain (85) or acute cardiac failure (21). Stenosis over 50% lumen diameter of 1 or more coronary arteries was present in 225/250 (90%) patients with ACS, 62/85 (73%) patients with persistent chest pain and 9/12 (43%) patients with acute cardiac failure, respectively. Patients with stenosis > 50% lumen diameter of 1 or more coronary arteries showed significantly higher cTnI values both at time 1 and 2 than patients with lower degree of arterial obstruction ($P < 0.001$).

ECG data were available in 1,404 patients. At admission, 455 patients (32.4%) displayed no ECG alterations, 262 (18.7%) and 203 (14.4%) showed ECG changes suggestive of ACS or atrial fibrillation, while 484 (34.5%) showed other ECG changes. Patients without ECG changes displayed significantly lower cTnI values at both times than all other groups (Bonferroni correction: $P<0.003$). Conversely, patients with ECG changes suggestive of ACS showed significantly higher cTnI values at both times than all other groups (Bonferroni correction: $P < 0.003$).

cTnI, co-morbidities or history of cardiac disease

Patients with hypertension and/or diabetes and/or renal insufficiency displayed basal and following cTnI values significantly higher than patients without comorbidities ($P < 0.001$). Accordingly, patients with 1 or more comorbidities showed cTnI concentrations ($P < 0.001$) significantly higher than patients without comorbidities.

Patients with positive cardiac history (any type) displayed cTnI values at both times significantly higher than patients who did not report any previous cardiac disease ($P < 0.001$).

Predictive power of cTnI to detect "unequivocal ACS"

In the whole sample population, cTnI positivity showed sensitivity and specificity of 74% and 62% for basal cTnI, and 94% and 57% for subsequent cTnI, respectively (Table 2). Although the negative

predictive value (NPV) was found to be high at both time points (98% t1 and 99% t2), the positive predictive value (PPV) appeared overall modest (10% t1 and 11% t2). cTnI performance was also investigated in different subgroups of patients: those with chest pain, in the subgroup with ECG changes related to ACS, as well as in the subgroup with both chest pain and ECG changes related to ACS (Table 2). A progressive increase of diagnostic performance was hence observed in parallel with the presence of clinical signs and ECG findings suggestive of MI.

Predictors of cTnI positivity at time 1

In the cohort of patients (N = 3,166), age, absence of chest pain, presence of hypertension, diabetes or renal insufficiency, elevated HR (> 100 bpm), presence of ECG changes were significantly associated with basal cTnI positivity in univariate analysis. However, only age, elevated HR and presence of ECG changes remained independently associated with cTnI positivity at admission in multivariate analysis (Table 3).

Table 2. Sensitivity (Se), specificity (Sp), predictive positive (PPV) and negative values (NPV) of cTnI to detect "unequivocal ACS".

Group	Se (%)	Sp (%)	PPV (%)	NPV (%)
cTnI positivity (time 1)				
Whole population	74 (66-82)	62 (60-64)	10 (8-12)	98 (97-98)
Patients with chest pain	74 (66-82)	77 (73-80)	41 (34-47)	93 (91-95)
Patients with ECG changes related to ACS	74 (66-82)	42 (32-54)	65 (57-73)	53 (41-65)
Patients with chest pain AND ECG changes related to ACS	74 (66-82)	56 (23-85)	96 (89-99)	14 (5-30)
cTnI positivity (time 2)				
Whole population	94 (87-97)	57 (55-59)	11 (9-13)	99 (98-100)
Patients with chest pain	94 (87-97)	71 (67-74)	41 (35-47)	98 (96-99)
Patients with ECG changes related to ACS	94 (87-97)	35 (25-46)	68 (60-75)	79 (62-90)
Patients with chest pain AND ECG changes related to ACS	94 (87-97)	44 (15-77)	96 (90-98)	33 (11-65)

Values are expressed as percentages and 95% confidence interval.

Table 3. Univariate and multivariate analysis of the predictors of cTnI positivity at admission in the whole population investigated.

	Univariate		Multivariate	
Predictor	**P**	**OR (95%CI)**	**P**	**OR (95%CI)**
Age, years	<0.001	1.054 (1.048-1.060)*	<0.001	1.032 (1.023-1.042)*
Gender (M *vs*. F)	0.304	0.925 (0.798-1.073)		
Chest pain (YES *vs*. NO)	<0.001	0.424 (0.364-0.494)*	0.754	0.961 (0.748-1.234)
Hypertension (YES *vs*. NO)	<0.001	1.352 (1.165-1.569)*	0.738	1.043 (0.814-1.338)
Diabetes (YES *vs*. NO)	0.005	1.317 (1.088-1.594)*	0.174	1.241 (0.909-1.693)
Renal insufficiency (YES *vs*. NO)	<0.001	3.128 (2.298-4.259)*	0.238	1.329 (0.829-2.131)
Heart Rate	<0.001		<0.001	*
60-100 *vs*. <60	0.764	1.052 (0.756-1.463)	0.086	1.543 (0.941-2.532)*
>100 *vs*. <60	<0.001	2.022 (1.411-2.898)	0.001	2.598 (1.514-4.458)*
ECG changes (YES *vs*. NO)	<0.001	3.570 (2.733-4.664)*	<0.001	2.557 (1.916-3.413)*

OR – odds ratio; CI - confidence interval.
*: significant predictors

Discussion

As predictable, patients with a diagnosis of ACS in the ED displayed median cTnI values significantly higher than other groups of diagnosis. Moreover, as previously described, significantly higher median cTnI level was also observed in patients with infections (14). A large number of patients with other conditions displayed cTnI positivity, and this evidence is attributable to the fact that the patient population presenting to the ED is different from the normal population used to establish the diagnostics specification of cTnI (15), wherein an increased rate of cTnI positivity may be caused by minimal myocardial injury that is typically lacking in the reference population. In our study population (median age 72 years), a relative 5% increased risk of positivity to cTnI was observed for any one-unit age increase. The remarkable rate of increased values observed in the elderly are probably due to higher prevalence of left ventricular strain, impaired sub-endocardial perfusion, inflammation or other undetermined factors, which lead to myocardial injury or cellular myocyte membrane leakage (16,17). As regards non-ACS causes of increased values of cTnI in elderly, these findings pose a considerable diagnostic problem due to the frequent presence of ECG abnormalities (LBBB, cardiac device induced rhythm, chronic ischemic ECG findings, etc.) that challenge the rule out process or the diagnosis of MI. The evidence that age is an independent predictor of cTnI positivity emerged from our and other studies (16-18) suggests that the adoption of age-specific cTnI cutoffs may be regarded as a potentially useful approach for increasing the specificity of this test.

It has been reported that up to 100% of patients with stable chronic heart failure and CAD have detectable levels of cTnT when measured with a HS assay (19). HS-TnT was also detectable in approximately 25% of adults in the general population (17). Interestingly, detectable HS-TnT levels were also found to be associated with diabetes, hypertension, impaired renal function, increased left ventricular mass, wall thickness and heart chamber dilation. Although similar associations were observed in our study in univariate analysis, these variables were not independently associated with cTnI values in multivariate analysis. Despite increased levels of cTns are frequently encountered in subjects with progressive decline of renal function (20-21), whether the adjustment of cTnI values for renal function could be a viable approach for increasing its diagnostic specificity, still remains to be elucidated, since our multivariate model does not support these data.

Supraventricular tachycardia has been associated with a troponin elevation without severe CAD (22). An increase of high-sensitivity cTn levels has also been observed after strenuous exercise (23). We demonstrated that positivity for cTnI was independently associated with heart rates. More specifically, compared to patients with HR < 60 bpm, we found that those with heart rate between 60 and 100 bpm or > 100 bpm had a 1.5 and 2.6 higher risk of having increased cTnI levels, respectively.

Since elderly patients have increased ACS-attributable morbidity and mortality, the presence of signs and symptoms other than chest pain or dyspnea may justify cTnI testing (24). Nevertheless, if considering the large number of patients (1,629 or 51.5%) admitted to the ED without chest pain but with serial cTnI measurements, it is conceivable that at least some of cTn tests were inappropriately and unnecessary requested. In our population, 1,537 (49%) patients presented to the ED with chest pain but only 230 (15%) were diagnosed as having ACS. Conversely, up to 73 out of 303 patients with an ACS diagnosis (24%) did not report chest pain. As such, it is not surprising that the presence of chest pain was found to be inversely associated (Risk < 1) with cTnI positivity in univariate but not in multivariate analysis (Table 3).

Despite in our study population cTnI positivity exhibited sensitivity and specificity of 74% and 62% (for basal cTnI) and 94% and 57% (for subsequent cTnI assay); the PPV at both times was very modest (10% at time 1 and 11% at time 2, respectively). This is probably attributable to the low prevalence of "unequivocal ACS" in our cohort of patients. Therefore, we could confirm that the cTnI positivity should not be straightforwardly considered as indicative of ACS in the ED setting, where the prev-

alence of ACS is typically low. Given the very high NPV (98% at t1 and 99% at t2 in the whole population), ED physician should hence preferably use a cTnI test to exclude ACS diagnosis in this population of patients. It is also noteworthy that the PPV of cTnI increased substantially in patients with higher probability of myocardial ischemia, reaching 96% in those reporting chest pain and showing ECG changes suggestive of ACS. In agreement with previous evidence, our results confirm that cTnI assay exhibits better performance in two extremes of patient population, and it should hence be used to rule out ACS in patient with low pre-test probability and confirm this diagnosis in patient with high pre-test probability (25,26).

We can hence conclude that the diagnostic accuracy of HS cTnI assays can be considerably improved when used in patients with a high clinical suspicion for MI. Nevertheless, these methods display lower specificity and increased rate of false positive diagnoses of MI, particularly in subjects with a low likelihood of MI, with older age, elevated heart rate or ECG changes. Current guidelines recommend more intensive treatment for patients with suspected ACS who also display increased cTn levels (27). Therefore, the indiscriminate use of HS assays without integrating clinical reasoning and new approaches to stratify patients with suspected acute MI is likely to expose some patients to unnecessary clinical risk and unjustified expenses for the health care system.

Potential conflict of interest

None declared.

References

1. *Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581-98. http://dx.doi.org/10.1016/j.jacc.2012.08.001.*
2. *Ebell MH, Flewelling D, Flynn CA. A systematic review of troponin T and I for diagnosing acute myocardial infarction. J Fam Pract 2000;49:550–6.*
3. *Cooper A, Calvert N, Skinner J, Sawyer L, Sparrow K, Timmis A, et al. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. 2010. Clinical Guideline. London: National Clinical Guideline Centre for Acute and Chronic conditions. Available at http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0034162/pdf/TOC.pdf. Accessed December 8, 2014.*
4. *Goodacre SW, Bradburn M, Cross E, Collinson P, Gray A, Hall AS. The Randomised Assessment of Treatment using Panel Assay of Cardiac Markers (RATPAC) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. Heart 2011;97:190-6. http://dx.doi.org/10.1136/hrt.2010.203166.*
5. *Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–67. http://dx.doi.org/10.1056/NEJMoa0900428.*
6. *Smith SC, Ladenson JH, Mason JW, Jaffe AF. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation 1997;95:163–8. http://dx.doi.org/10.1161/01.CIR.95.1.163.*
7. *Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jäckle S, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002;106:1263–8. http://dx.doi.org/10.1161/01.CIR.0000028422.51668.A2.*
8. *Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 2003;108:833–8. http://dx.doi.org/10.1161/01.CIR.0000084543.79097.34.*
9. *Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. J Am Coll Cardiol 2008;52:450-9. http://dx.doi.org/10.1016/j.jacc.2008.04.033.*
10. *High-Sensitivity Cardiac Troponin for the Rapid Diagnosis of Acute Coronary Syndrome in the Emergency Department: A Clinical and Cost-Effectiveness Evaluation. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2013 Mar. (CADTH Optimal Use Report, No. 2.1.) Available at: http://www.ncbi.nlm.nih.gov/books/NBK168953/. Accessed December 8, 2014.*
11. *Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. The rational clinical examination. Is this patient having a myocardial infarction? JAMA 1998;280:1256-63. http://dx.doi.org/10.1001/jama.280.14.1256.*
12. *Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. JAMA 2005;294:2623-9. http://dx.doi.org/10.1001/jama.294.20.2623.*

13. Fioretti PM, Pozzoli MM, Ilmer B, Salustri A, Cornel JH, Reijs AE, et al. Exercise echocardiography versus thallium-201 SPECT for assessing patients before and after PTCA. Eur Heart J 1992;13:213–9.
14. Lippi G, Margapoti R, Aloe R, Cervellin G. Highly-sensitive troponin I in patients admitted to the emergency room with acute infections. Eur J Intern Med 2013;24:e57-8. http://dx.doi.org/10.1016/j.ejim.2013.01.019.
15. Haq SA, Tavakol M, Silber S, Bernstein L, Kneifati-Hayek J, Schleffer M, et al. Enhancing the diagnostic performance of troponins in the acute care setting. J Emerg Med 2011;40:367-73. http://dx.doi.org/10.1016/j.jemermed.2008.02.049.
16. Normann J, Mueller M, Biener M, Vafaie M, Katus HA, Giannitsis E. Effect of older age on diagnostic and prognostic performance of high-sensitivity troponin T in patients presenting to an emergency department. Am Heart J 2012;164:698-705. http://dx.doi.org/10.1016/j.ahj.2012.08.003.
17. De Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503-12. http://dx.doi.org/10.1001/jama.2010.1768.
18. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J 2011;32:1379-89. http://dx.doi.org/10.1093/eurheartj/ehr033.
19. Omland T1, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361:2538-47. http://dx.doi.org/10.1056/NEJMoa0805299.
20. Chen S, Huang C, Wu B, Lian X, Mei X, Wan J. Cardiac troponin I in non- acute coronary syndrome patients with chronic kidney disease. PLoS One 2013;8:e82752. http://dx.doi.org/10.1371/journal.pone.0082752.
21. Lippi G, Cervellin G. High-sensitivity troponin T is more susceptible than high-sensitivity troponin I to impaired renal function. Am J Cardiol 2013;112:1985. http://dx.doi.org/10.1016/j.amjcard.2013.10.003.
22. Ben Yedder N, Roux JF, Paredes FA. Troponin elevation in supraventricular tachycardia: primary dependence on heart rate. Can J Cardiol 2011;27:105-9. http://dx.doi.org/10.1016/j.cjca.2010.12.004.
23. Lippi G, Cervellin G, Banfi G, Plebani M. Cardiac troponins and physical exercise. It's time to make a point. Biochem Med (Zagreb) 2011;21:55-62. http://dx.doi.org/10.11613/BM.2011.012.
24. Goodman DA, Kavsak PA, Hill SA, Worster A. Presenting characteristics of patients undergoing cardiac troponin measurements in the emergency department. CJEM 2014;16:1-5.
25. Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. Circulation 2011;124:2350-4. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.023697.
26. Newby LK, Jesse RL, Babb JD, Christenson RH, De Fer TM, Diamond GA, et al. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2012;60:2427-63. http://dx.doi.org/10.1016/j.jacc.2012.08.969.
27. Chatterjee S, Kim J, Dahhan A, Choudhary G, Sharma S, Wu WC. Use of high-sensitivity troponin assays predicts mortality in patients with normal conventional troponin assays on admission-insights from a meta-analysis. Clin Cardiol 2013;36:649-53. http://dx.doi.org/10.1002/clc.22196.