JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 73, NO. 1, 2019

PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

Cardiac Troponin Elevation in Patients Without a Specific Diagnosis

Kai M. Eggers, MD, PhD,[a] Tomas Jernberg, MD, PhD,[b] Bertil Lindahl, MD, PhD[a]

ABSTRACT

BACKGROUND Cardiac troponin (cTn) elevation is a common finding in acutely admitted patients, even in the absence of acute coronary syndrome. In some of these patients, no etiology of cTn elevation can be identified. The term troponinemia is sometimes used to describe this scenario.

OBJECTIVES This study aimed to investigate the associations of cTn levels with clinical findings and long-term outcome in acutely admitted patients with suspected acute coronary syndrome who had been discharged without a specified diagnosis.

METHODS Retrospective registry-based cohort study investigating 48,872 patients (SWEDEHEART [Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies] registry). Patients were stratified into cohorts with cTn levels less than or equal to the assay-specific 99th percentile and separated by assay-specific cTn tertiles in case of higher levels.

RESULTS A cTn level >99th percentile was noted in 9,800 (20.1%) patients. The prevalence of cardiovascular risk factors as well as cardiovascular and noncardiovascular comorbidities increased across higher cTn strata. In total, 7,529 (15.4%) patients had a major adverse event (MAE), defined as the composite of all-cause mortality, myocardial infarction, readmission for heart failure, or stroke (median follow-up 4.9 years). MAE risk was associated with higher cTn strata (hazard ratio for highest assay-specific cTn tertile: 2.59; 95% confidence interval: 2.39 to 2.80; hazard ratio in patients without cardiovascular comorbidities, renal dysfunction, left ventricular dysfunction, or significant coronary stenosis: 3.57; 95% confidence interval: 2.30 to 5.54).

CONCLUSIONS cTn elevation is associated with cardiovascular and noncardiovascular comorbidities and predicts major adverse events in acutely admitted patients, in whom no definite diagnosis could have been established. The term troponinemia is trivializing and should be avoided. Instead, careful work-up is required in these patients.
(J Am Coll Cardiol 2019;73:1-9) © 2019 by the American College of Cardiology Foundation.

Measurement of cardiac troponin (cTn) levels is a cornerstone in the assessment of patients with acute chest pain. An elevation in the cTn level together with a significant change in the setting of coronary ischemia indicates myocardial infarction (MI) (1). However, even other cardiac and noncardiac conditions may result in acute cTn increases (e.g., arrhythmias, severe hyper- or hypotension, pulmonary embolism, neurologic events, or endurance efforts) (2). Acute but subtle increases in cTn levels may also be difficult to distinguish from chronic cTn elevation which is a common

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; and the [b]Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden. The TOTAL-AMI project has received funding from the Swedish Foundation of Strategic Research. Dr. Eggers has received a research grant from Abbott Laboratories. Dr. Lindahl has served as a consultant for Roche Diagnostics, Thermo Fisher Scientific, bioMérieux Clinical Diagnostics, and Philips Healthcare; and has received research grants from bioMérieux Clinical Diagnostics. Dr. Jernberg has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received August 22, 2018; revised manuscript received September 28, 2018, accepted September 30, 2018.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.09.082

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

COPD = chronic obstructive pulmonary disease

cTn = cardiac troponin

eGFR = estimated glomerular filtration rate

ICD-10-CM = International Classification of Diseases-10th Revision-Clinical Modification

MAE = major adverse event

MI = myocardial infarction

finding in the elderly, patients with renal failure, or patients with chronic cardiac conditions (3).

Regardless of the underlying etiology, elevated cTn levels predict adverse outcome with a few exceptions (3,4). For this reason, an elevation in the cTn level, be it acute or chronic, warrants the search for the underlying cause. However, in some patients, no etiology can be identified. The proportion of patients discharged from the emergency department without a specified diagnosis but with cTn levels above the 99th percentile has been reported as 31% (5) and may be similarly high in those who are admitted (6). This often causes frustration among clinicians, and the term troponinemia has been coined to label this scenario. Using this term as search entry on PubMed yielded 2 published papers (7,8) but >2,000 links on Google, indicating that troponinemia is frequently discussed while scientific evidence is limited.

SEE PAGE 10

The aim of this retrospective registry-based cohort study was to closer investigate patients with cTn elevation of unknown etiology. In particular, we aimed to study the clinical characteristics of these patients and their long-term risk of fatal and nonfatal events.

METHODS

STUDY POPULATION. This study is part of the TOTAL-AMI (Tailoring Of Treatment in All comers with Acute Myocardial Infarction) project. The primary aim of the TOTAL-AMI project is to study the mechanisms and implications of different MI subtypes (1) and comorbidities (e.g., chronic obstructive pulmonary disease [COPD], atrial fibrillation, renal dysfunction) in MI. The TOTAL-AMI project uses data from the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry, which is a nationwide registry enrolling consecutive patients admitted to Swedish coronary care units or other specialized facilities because of suspected acute coronary syndrome. The SWEDEHEART registry prospectively collects information on >100 variables including the highest level of biomarkers of myocardial damage recorded during the hospitalization. On admission, patients receive written information about the registry, and have the right to deny participation and get their data erased upon request.

The population for the present study included all patients admitted between January 2005 and August 2013, who had been discharged without a specified diagnosis according to the diagnostic classification used within the SWEDEHEART registry framework. Only first-time admissions were considered. Patients with a planned admission, MI within 8 weeks before admission, and missing information on cTn results, and those who underwent coronary intervention during the hospitalization, were excluded. Patients were grouped into 4 strata: those with cTn levels less than or equal to the assay-specific cTn 99th percentile and the remaining patients separated by tertiles calculated separately for each assay.

All data had been made anonymous before the statistical analyses. The study was conducted according to the principles of the 1975 Declaration of Helsinki and had been approved by the Regional Ethical Review Board in Stockholm (2012/60-31/2).

cTn ASSAYS. cTnI results in patients included in this analysis had been obtained using the following assays: Stratus CS (Siemens, Erlangen, Germany) (99th percentile 70 ng/l), Architect (Abbott, Abbott Park, Illinois) (99th percentile 28 ng/l), and Access (Beckman Coulter, Brea, California) (99th percentile 40 ng/l). Other cTnI assays were not used frequently enough to be considered, and patients with cTnI results obtained using such assays were excluded from this analysis. cTnT levels had been measured using the conventional assay (99th percentile <10 ng/l) and the high-sensitivity assay (99th percentile 14 ng/l), both from Roche (Basel, Switzerland). For the purpose of this analysis, the 99th percentile for the cTnI (Architect) assay was set to 30 ng/l as hospitals utilizing this assay reported results as μg/l with 2 digits. We also set the 99th percentile of the conventional cTnT assay to 10 ng/l, as levels below this threshold had only been reported occasionally at some hospitals.

PROGNOSTIC EVALUATION. Information on patient outcome was obtained from the mandatory Swedish Patient Registry (hospitalization dates and discharge diagnoses based on International Classification of Diseases-10th Revision-Clinical Modification [ICD-10-CM] codes) and the Swedish Cause of Death Registry, both held by the Swedish Board of Health and Welfare. Patients were followed for events until the occurrence of death or December 31, 2013.

The outcomes for this analysis were all-cause mortality, MI (ICD-10-CM I21), cardiovascular mortality (primary cause of death: ICD-10-CM I00 to I99), noncardiovascular mortality (all other primary causes of death), and hospitalization for heart failure (ICD-10-CM I50) and ischemic stroke (ICD-10-CM I63).

In addition, we assessed major adverse events (MAE), defined as the composite of all-cause mortality and all nonfatal outcomes. During the first 30 days after the index hospitalization, it is not possible to separate a new MI from an index MI in the Patient Registry. Therefore, only MI occurring 30 days after the index hospitalization were counted.

STATISTICAL ANALYSIS. All continuous variables were skewed and are reported as median (interquartile range). Differences in continuous variables were assessed using the Kruskal-Wallis test. Categorical variables are expressed as frequencies and percentages with differences being analyzed with the chi-square test.

The associations of higher cTn strata with adverse outcome were investigated with Cox regression models. We separately assessed 3 clinically relevant subcohorts: patients without previous MI, previous coronary revascularization, previous stroke, and known congestive heart failure (subcohort 1); with additional exclusion of patients with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (subcohort 2); and with additional exclusion of patients from cohort 2 who had a left ventricular ejection fraction ≤0.50 or significant coronary artery disease, defined as ≥50% coronary stenosis according invasive angiography (subcohort 3). All Cox regressions were adjusted for age, sex, admission year, cTn assay, and hospital as a random effect in a mixed model. As sensitivity analyses, we conducted a Cox regression adjusted for all variables used to define subcohort 3 without and with adjustment for diabetes and hypertension. Cox regressions were also used to identify predictors of MAE among demographic data, cardiovascular risk factors, and various cardiovascular and noncardiovascular comorbidities. Cumulative hazard curves were constructed using the Kaplan-Meier method, and the log-rank test was applied to compare the incidence of MAE across cTn strata.

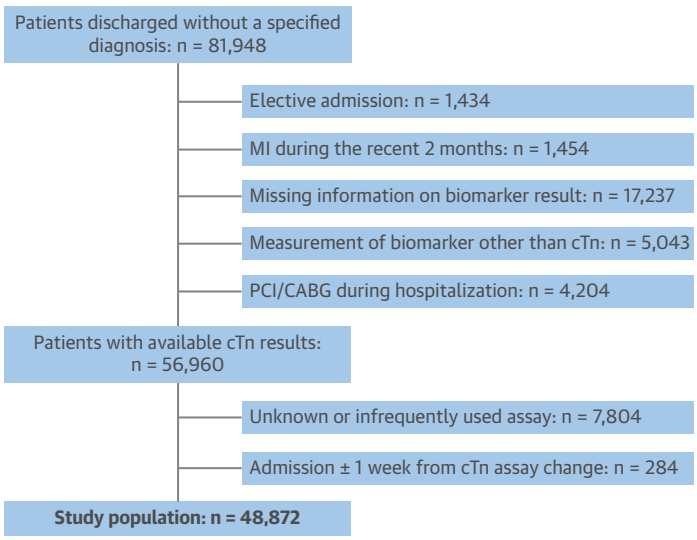
In all tests, a 2-sided p value <0.05 was considered significant. The software package SPSS 24.0 (IBM Corp., Armonk, New York) was used for the analyses.

RESULTS

The population of this analysis consisted of 48,872 patients following exclusions (**Figure 1**). The most common discharge diagnoses were unspecified chest pain, ICD-10 R07.4 (n = 38,589 [79.0%]), and observation for suspected MI, ICD-10 Z03.4 (n = 7796 [16.0%]). More detailed information on discharge diagnoses is provided in Online Table 1. Results for cTnI (Stratus CS) were available in 11,670 patients (cTnI strata: ≤70 ng/l, 71 to 100 ng/l, 101 to 130 ng/l, >130 ng/l), for cTnI (Architect) in 5,157 patients (cTnI strata: ≤30 ng/l, 31 to 50 ng/l, 51 to 60 ng/l, >60 ng/l), and for cTnI (Access) in 5,804 patients (cTnI strata: ≤40 ng/l, 41 to 60 ng/l; 61 to 90 ng/l; >90 ng/l). Results for cTnT (conventional assay) were available in 18,764 patients (cTnT strata: ≤10 ng/l, 11 to 30 ng/l, 31 to 50 ng/l, >50 ng/l) and for cTnT (high-sensitivity assay) in 7,417 patients (cTnT strata: ≤14 ng/l, 15 to 20 ng/l, 21 to 34 ng/l, >34 ng/l). In total, 9,800 (20.1%) patients had a cTn level above the 99th percentile. The numbers of patients with a cTn level >99th percentile in subcohorts 1, 2, and 3 were 6,952 (18.2%), 5,468 (17.2%), and 601 (30.8%), respectively. Online Figure 1 depicts the distribution of cTn levels.

Information on clinical characteristics and examination findings is presented in **Table 1**. The majority of patients (n = 46,029 [94.8%]) had been admitted because of acute chest pain. The prevalence of most cardiovascular risk factors tended to increase across strata with higher cTn levels apart from current smoking for which a decreasing prevalence was noted. Even the prevalence of previous manifestations of cardiovascular disease and noncardiovascular comorbidities increased across strata with higher cTn levels. Among patients who underwent echocardiography (n = 10,627), left ventricular dysfunction

FIGURE 1 Selection of Patients



Flowchart illustrating the selection of patients. Following exclusions, 48,782 patients were left for this analysis of a total of 81,948 potentially eligible patients admitted between January 2005 and August 2013 and discharged without a specified diagnosis. In some cases, patients met more than 1 exclusion criterion. CABG = coronary artery bypass grafting; cTn = cardiac troponin; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 1 Baseline Characteristics

	cTn ≤99th Percentile (n = 39,072)	Tertile 1 (n = 5,137)	Tertile 2 (n = 2,490)	Tertile 3 (n = 2,173)	p Value	Total (N = 48,872)
Demographics						
Male	19,456 (50.2)	2,716 (52.9)	1,351 (54.3)	1,156 (53.2)	<0.001	24,839 (50.8)
Age, yrs	60 (50–69)	63 (53–74)	66 (55–76)	68 (55–78)	<0.001	61 (51–70)
Year of admission						
2005–2007	16,587 (42.5)	2,914 (56.7)	1,046 (42.0)	640 (29.5)	<0.001	21,187 (43.4)
2008–2010	14,013 (35.9)	1,525 (29.7)	821 (33.0)	800 (36.8)		17,159 (35.1)
2011–2013	8,472 (21.7)	698 (13.6)	623 (25.0)	733 (33.7)		10,526 (21.5)
Risk factors						
Current smoking	7,066 (18.3)	839 (16.5)	401 (16.2)	296 (13.8)	<0.001	8,602 (17.8)
Hypertension	13,190 (34.1)	1,916 (37.5)	982 (39.7)	883 (40.8)	<0.001	16,971 (35.0)
Diabetes	4,086 (10.5)	685 (13.4)	376 (15.1)	375 (17.3)	<0.001	5,522 (11.4)
Hyperlipidemia	9,129 (23.5)	1,423 (28.0)	764 (30.8)	611 (28.2)	<0.001	11,927 (24.5)
BMI, kg/m^2	26.5 (23.9–29.7)	26.4 (23.8–29.6)	26.4 (23.7–29.4)	25.9 (23.3–29.0)	<0.001	26.4 (23.9–29.6)
eGFR, ml/min/1.73 m^2	88.0 (74.0–99.0)	81.3 (65.8–94.3)	79.6 (61.8–93.6)	75.3 (52.9–93.2)	<0.001	86.6 (71.8–98.2)
History						
Previous MI	4,698 (12.1)	884 (17.3)	504 (20.3)	482 (22.2)	<0.001	6,568 (13.5)
Previous PCI/CABG	4,366 (11.2)	742 (14.5)	417 (16.8)	370 (17.1)	<0.001	5,895 (12.1)
Previous heart failure	1,115 (2.9)	248 (5.0)	166 (6.7)	217 (10.1)	<0.001	1,746 (3.6)
Previous stroke	1,704 (4.5)	319 (6.6)	168 (6.9)	173 (8.3)	<0.001	2,364 (5.0)
PVD	751 (1.9)	170 (3.3)	100 (4.0)	134 (6.2)	<0.001	1,155 (2.4)
Previous or present cancer	541 (1.4)	105 (2.0)	58 (2.3)	87 (4.0)	<0.001	791 (1.6)
COPD	1,379 (3.5)	297 (5.8)	147 (5.9)	189 (8.7)	<0.001	2,012 (4.1)
Dementia	85 (0.2)	16 (0.3)	12 (0.5)	8 (0.4)	0.028	121 (0.2)
ECG findings						
Sinus rhythm	37,024 (95.3)	4,770 (93.1)	2,291 (92.3)	1,854 (85.6)	<0.001	45,938 (94.5)
Atrial fibrillation	809 (2.1)	238 (4.6)	130 (5.2)	183 (8.5)	<0.001	1,360 (2.8)
ST-segment elevation	1,451 (3.8)	251 (5.0)	114 (4.6)	114 (5.3)	<0.001	1,930 (4.0)
ST-segment depression	2,757 (7.1)	449 (8.9)	246 (10.0)	275 (12.8)	<0.001	3,727 (7.7)
Medication at admission						
Antiplatelets	10,829 (27.9)	1,776 (34.9)	932 (37.5)	794 (36.7)	<0.001	14,331 (29.5)
Oral anticoagulants	1,357 (3.5)	289 (5.7)	150 (6.0)	176 (8.1)	<0.001	1,972 (4.1)
Beta-blockers	10,501 (27.0)	1,734 (34.1)	851 (34.3)	775 (35.8)	<0.001	13,861 (28.5)
RAAS inhibitors	8539 (22.0)	1,396 (27.5)	773 (31.1)	683 (31.7)	<0.001	11,391 (23.5)
Statins	8857 (22.8)	1,358 (27.3)	753 (30.3)	598 (27.7)	<0.001	11,593 (23.9)
Echocardiography (n = 10,627)						
LVEF ≥0.50	7,740 (95.7)	985 (91.8)	596 (90.7)	688 (85.5)	<0.001	10,009 (94.2)
LVEF 0.40–0.49	264 (3.3)	66 (6.2)	38 (5.8)	67 (8.3)		435 (4.1)
LVEF 0.30–0.39	74 (0.9)	19 (1.8)	15 (2.3)	33 (4.1)		141 (1.3)
LVEF <0.30	14 (0.2)	3 (0.3)	8 (1.2)	17 (2.1)		42 (0.4)
Angiographic findings (n = 4,989)						
No significant stenosis	3,216 (92.8)	505 (91.5)	302 (92.1)	584 (90.8)	0.026	4,607 (92.3)
1- to 2-vessel disease	196 (5.7)	29 (5.3)	15 (4.6)	41 (6.4)		281 (5.6)
3-vessel disease	54 (1.6)	18 (3.3)	11 (3.4)	18 (2.8)		101 (2.0)

Values are n (%) or median (interquartile range). Patients with missing data were excluded from the analyses.

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; RAAS = renin-angiotensin-aldosterone system.

tended to be more common in case of higher cTn strata. In contrast, only a weak association between the extent of coronary artery disease and cTn strata emerged in patients who underwent coronary angiography (n = 4989).

In total, 7,529 patients (15.4%) experienced a MAE during a median follow-up of 4.9 years. The incidence rates for MAE and the assessed single outcomes increased in a stepwise fashion across strata with higher cTn levels (**Table 2**). Kaplan-Meier analysis demonstrated that MAE rates diverged early and constantly over time (**Figure 2**). Assessing subcohorts 1 and 2 yielded similar results (**Table 2**, Online Figures 2A and 2B). For subcohort 3, MAE rates were

particularly high in case of cTn levels in the highest assay-specific tertile (**Table 2**, Online Figure 2C). For lower tertiles, MAE rates did not differ significantly to those in patients with cTn ≤99th percentile (data not shown).

The risk pattern was similar when Cox regression analysis was applied (**Table 3, Figure 3**). MAE risk in the total cohort was mainly driven by the risks of cardiovascular mortality, MI and readmission for heart failure. Investigating subcohorts 1 and 2 revealed similar gradients of MAE risk. Compared with patients with cTn ≤99th percentile, the hazard ratios across increasing assay-specific cTn tertiles in subcohort 3 were 1.25 (95% confidence interval [CI]: 0.67 to 2.35), 1.26 (95% CI: 0.54 to 2.94), and 3.57 (95% CI: 2.30 to 5.54), respectively (**Figure 3**). The corresponding hazard ratios in the sensitivity analysis adjusted for all covariates used to define subcohort 3 were 1.01 (95% CI: 0.65 to 1.56), 2.13 (95% CI: 1.34 to 3.37), and 2.83 (95% CI: 2.08 to 3.87), respectively (n = 1,877). Additional adjustment for diabetes and hypertension yielded almost identical results (data not shown). The cTn assay used did not emerge as an independently predictive covariate in any of the applied models (data not shown).

Table 4 demonstrates that male and older patients as well as those with diabetes, renal dysfunction, lower body mass index, with previous manifestations of cardiovascular disease, COPD, or malignancies were at particular risk for experiencing a MAE.

TABLE 2 Event Numbers and Incidence per 10,000 Patient-Years

	cTn ≤99th Percentile	Tertile 1	Tertile 2	Tertile 3	Total
Single outcomes in the total cohort					
All-cause mortality					
Events/patients	3,485/39,072	796/5,137	447/2,490	586/2,173	5,314/48,872
Incidence rate	180.4	283.4	398.8	763.5	221.3
CV mortality					
Events/patients	1,317/39,072	353/5,137	229/2,490	297/2,173	2,196/48,872
Incidence rate	68.2	125.7	204.3	386.9	91.4
Non-CV mortality					
Events/patients	2,168/39,072	443/5,137	218/2,490	289/2,173	3,118/48,872
Incidence rate	112.2	157.7	194.5	376.5	129.8
Myocardial infarction					
Events/patients	839/39,072	216/5,137	128/2,490	127/2,173	1,310/48,872
Incidence rate	46.4	85.1	128.8	195.6	58.8
Heart failure					
Events/patients	878/39,072	256/5,137	122/2,490	173/2,173	1,429/48,872
Incidence rate	48.6	100.2	122.8	267.7	64.2
Stroke					
Events/patients	996/39,072	196/5,137	94/2,490	92/2,173	1,378/48,872
Incidence rate	55.3	77.6	94.2	143.1	62.2
Major adverse event					
Events/patients	5,077/39,072	1,122/5,137	595/2,490	735/2,173	7,529/48,872
Incidence rate	271.5	419.1	562.4	1046.1	325.4
Major adverse events in subcohorts					
Subcohort 1					
Events/patients	2,803/31,329	546/3,787	265/1,718	322/1,447	3,936/38,281
Incidence rate	182.5	257.6	330.8	606.4	209.3
Subcohort 2					
Events/patients	1,979/26,354	354/3,022	164/1,392	182/1,054	2,679/31,822
Incidence rate	152.8	207.7	237.7	445.9	170.1
Subcohort 3					
Events/patients	56/1,350	12/213	6/134	32/254	106/1,951
Incidence rate	103.7	134.2	138.3	360.7	139.2

Subcohort 1: patients with previous myocardial infarction, coronary revascularization, stroke or heart failure excluded; subcohort 2: as subcohort 1, excluding also patients with estimated glomerular filtration rate <60 ml/min/1.73 m^2; subcohort 3: as subcohort 2, excluding also patients with left ventricular ejection fraction ≤0.50 or significant coronary stenosis.

cTn = cardiac troponin; CV = cardiovascular.

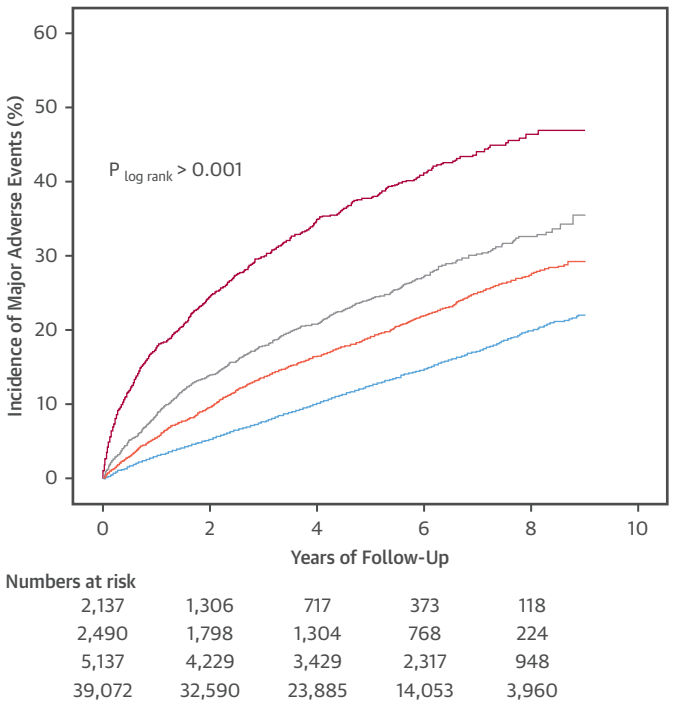
DISCUSSION

Our data demonstrate that cTn elevation is an important risk predictor in patients admitted with suspected acute coronary syndrome in whom no specific diagnosis could have been established. In our large retrospective cohort study, we noted that higher cTn levels were associated with various cardiovascular risk factors and cardiovascular and non-cardiovascular comorbidities. Moreover, higher cTn levels were associated with constantly increasing MAE rates during long-term follow-up. This was mainly driven by the risks of cardiovascular mortality, MI and readmissions for heart failure. About 1 in 3 patients with cTn levels in the highest assay-specific tertile suffered an event.

Stepwise exclusion of patients with previous cardiovascular disease and renal dysfunction (i.e., prognostically adverse conditions that may be associated with higher cTn levels) (3), resulted in lower absolute event rates in all cTn strata while the risk gradients remained fairly unchanged. Compared with patients with cTn levels ≤99th percentile, the MAE risk in those with cTn in the highest stratum was 2.5-fold increase in age- and sex-adjusted analyses. Even when considering the healthiest subcohort (i.e., patients without cardiovascular disease, renal dysfunction, impaired left ventricular ejection fraction, or significant coronary artery disease) (subcohort 3), cTn in the highest stratum was associated with a more than 3-fold increased MAE risk.

Our data are in line with results from studies investigating cTn levels in other populations without acute cardiovascular disease. cTn has been described as a powerful risk predictor in community-dwelling subjects (9), those with cardiovascular risk factors (10,11), and patients with stable coronary artery disease (12) and stable heart failure (13). A common denominator of these studies is the mediation of the

FIGURE 2 Unadjusted Kaplan-Meier Estimates of the Cumulative Incidence of Major Adverse Events



Unadjusted Kaplan-Meier analysis demonstrated that the rates of major adverse events increased across strata with higher cardiac troponin (cTn) levels. The event curves diverged early and constantly during the follow-up period (median 4.9 years). The **blue line** represents patients with cTn levels below the assay-specific 99th percentile. **Orange, gray, and red** lines represent patients with cTn levels in the assay-specific tertiles 1, 2, and 3, respectively.

prognostic importance of cTn through its association with cardiac abnormalities. These might possibly still be subclinical at the time point of cTn measurement. Accordingly, despite a possibly unidentified etiology of myocardial injury, cTn elevation appears to demask myocardial vulnerability that portends to an increased long-term risk. Along this line, even in subcohort 3, a more than moderate cTn elevation was associated with adverse outcome. This was not seen in the case of subtle cTn elevation and possibly relates to a preponderance of more adverse pathophysiologic mechanisms in case of higher cTn levels. A review on cTn release mechanisms has recently been published elsewhere (4).

Considerable proportions of patients admitted to the hospital with suspected acute coronary syndrome will be discharged without a specific diagnosis. The 30-day rate of MAE in these patients may be as high as 4.5% (14). This emphasizes that they do not represent a no-risk population. Higher age, diabetes, renal dysfunction, hypertension, heart failure, and previous manifestations of coronary artery disease have been reported as predictors of poor outcome in these patients (15,16). This corresponds with the findings from our investigation.

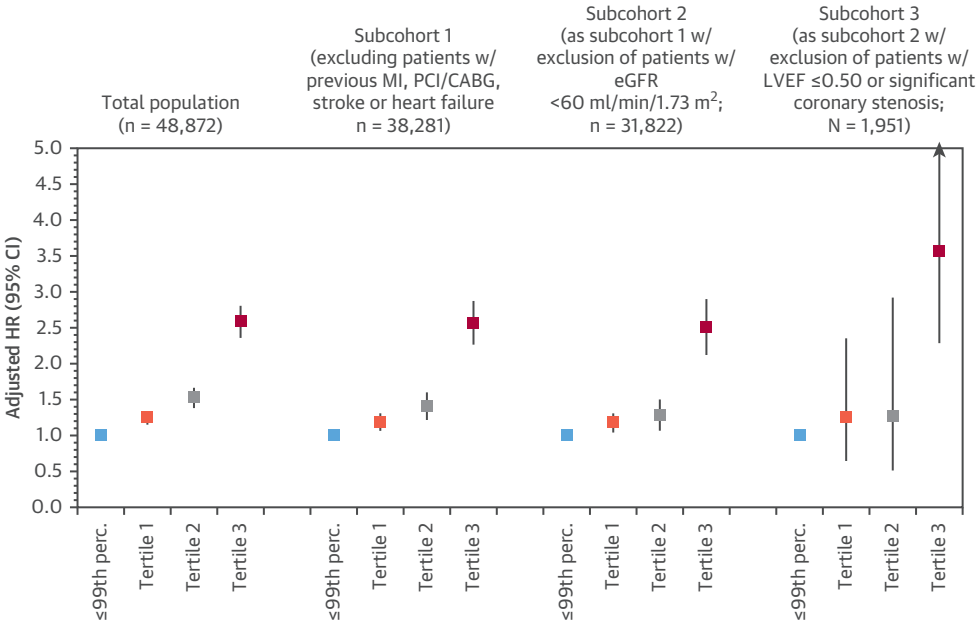
Nonetheless, with the implementation of high-sensitivity assays in routine diagnosis, clinicians will be more frequently confronted with patients having cTn elevation that is difficult to explain. The term troponinemia is sometimes used to describe this scenario. The high event rates noted in our analysis indicate that this term is misleading as it may tempt clinicians to trivialize cTn elevation. Instead, careful work-up is required (**Central Illustration**). This includes retesting of cTn to distinguish acute from chronic elevations, the use of an alternative assay in the same sample to exclude pre-analytical causes for cTn elevation (17), liberal referral for echocardiography and invasive or noninvasive coronary imaging, depending on the individual pre-test probability of coronary artery disease. Detected cardiovascular conditions should be treated consequently. For subjects regarded being cardiovascular healthy (corresponding to subcohort 3), caution still is warranted in case of moderate cTn elevation (i.e., levels corresponding to the highest assay-specific cTn tertile).

TABLE 3 Risk of Adverse Events in the Total Cohort

	cTn ≤99th Percentile		Tertile 1			Tertile 2			Tertile 3		
	n	HR (95% CI)	n	HR (95% CI)	p Value	n	HR (95% CI)	p Value	n	HR (95% CI)	p Value
All-cause mortality	39,072	Reference	5,137	1.24 (1.15–1.34)	<0.001	2,490	1.58 (1.43–1.75)	<0.001	2,173	2.76 (2.52–3.02)	<0.001
CV mortality	39,072	Reference	5,137	1.38 (1.23–1.56)	<0.001	2,490	2.00 (1.74–2.31)	<0.001	2,173	3.27 (2.88–3.72)	<0.001
Non-CV mortality	39,072	Reference	5,137	1.14 (1.03–1.27)	0.012	2,490	1.30 (1.13–1.49)	<0.001	2,173	2.37 (2.09–2.68)	<0.001
Myocardial infarction	35,918	Reference	4,444	1.43 (1.23–1.66)	<0.001	2,102	2.08 (1.72–2.51)	<0.001	1,671	2.85 (2.36–3.45)	<0.001
Heart failure	35,985	Reference	4,486	1.56 (1.35–1.79)	<0.001	2,112	1.77 (1.46–2.14)	<0.001	1,686	3.38 (2.86–4.00)	<0.001
Stroke	35,866	Reference	4,404	1.16 (0.99–1.35)	0.067	2,094	1.35 (1.09–1.68)	0.005	1,626	1.98 (1.59–2.46)	<0.001
Major adverse event	39,072	Reference	5,137	1.25 (1.18–1.34)	<0.001	2,490	1.53 (1.40–1.67)	<0.001	2,173	2.59 (2.39–2.80)	<0.001

The analyses were adjusted for age, sex, hospital, admission year, and cTn assay.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

FIGURE 3 Cox Regression Analysis: Risk of Major Adverse Events in the Total Cohort and Subcohorts



Multivariable-adjusted hazard ratios (with 95% CIs) of major adverse events in the total population and in the pre-defined subcohorts. In all cohorts, the risk of major adverse events increased in a stepwise fashion across higher assay-specific cardiac troponin (cTn) levels, with patients in the highest tertile being at particularly high risk. Patients with cTn ≤99th percentile were used as reference group. All analyses had been adjusted for age, sex, admission year, hospital, and cTn assay. CABG = coronary artery bypass grafting; CI = confidence interval; cTn = cardiac troponin; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

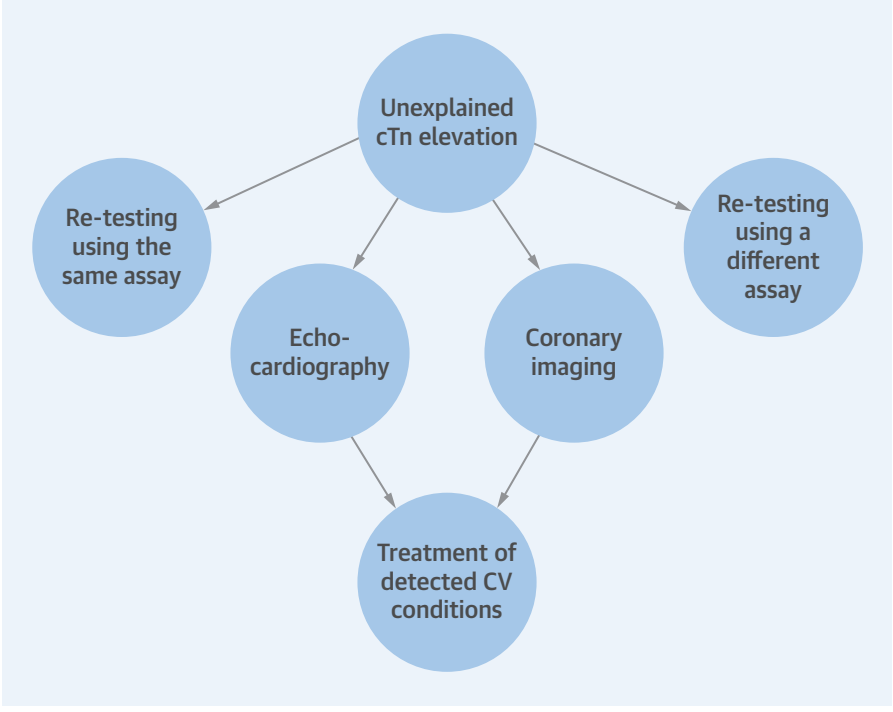
TABLE 4 Predictors of Major Adverse Events and Association With cTn Strata

	All Patients (n = 4,389/32,910)		Tertile 1-3 (n = 1,390/6,450)		Tertile 2-3 (n = 746/2,987)		Tertile 3 (n = 470/1,540)	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Male	1.44 (1.36-1.53)	<0.001	1.41 (1.26-1.57)	<0.001	1.38 (1.18-1.62)	<0.001	1.44 (1.18-1.76)	<0.001
Age (10 yrs)	2.01 (1.94-2.07)	<0.001	1.82 (1.72-1.92)	<0.001	1.68 (1.56-1.81)	<0.001	1.65 (1.51-1.81)	<0.001
Current smoking	1.72 (1.59-1.87)	<0.001	1.48 (1.26-1.73)	<0.001	1.33 (1.07-1.67)	0.012	1.24 (0.93-1.67)	0.145
Hypertension	1.11 (1.04-1.18)	0.001	1.07 (0.95-1.19)	0.261	1.00 (0.86-1.16)	0.963	0.99 (0.82-1.20)	0.947
Diabetes	1.63 (1.52-1.76)	<0.001	1.56 (1.37-1.77)	<0.001	1.62 (1.36-1.94)	<0.001	1.70 (1.36-2.12)	<0.001
Hyperlipidemia	0.92 (0.85-0.99)	0.021	0.94 (0.83-1.07)	0.345	0.87 (0.73-1.03)	0.103	0.83 (0.67-1.03)	0.093
Body mass index (ln)	0.74 (0.61-0.90)	0.003	0.57 (0.41-0.80)	0.001	0.47 (0.30-0.74)	0.001	0.53 (0.30-0.94)	0.031
1-eGFR (ln)	1.46 (1.42-1.51)	<0.001	1.47 (1.41-1.52)	<0.001	1.44 (1.36-1.50)	<0.001	1.40 (1.30-1.49)	<0.001
Previous MI	1.45 (1.33-1.57)	<0.001	1.43 (1.23-1.65)	<0.001	1.33 (1.10-1.61)	0.004	1.19 (0.93-1.51)	0.173
Previous PCI/CABG	1.03 (0.94-1.13)	0.488	0.97 (0.83-1.14)	0.719	0.99 (0.80-1.22)	0.917	0.92 (0.70-1.21)	0.553
Previous heart failure	1.61 (1.46-1.78)	<0.001	1.60 (1.37-1.87)	<0.001	1.72 (1.40-2.12)	<0.001	1.74 (1.34-2.25)	<0.001
Previous stroke	1.49 (1.36-1.64)	<0.001	1.41 (1.20-1.65)	<0.001	1.59 (1.28-1.96)	<0.001	1.58 (1.21-2.05)	0.001
PVD	1.74 (1.55-1.95)	<0.001	1.70 (1.42-2.05)	<0.001	1.90 (1.49-2.44)	<0.001	1.90 (1.41-2.56)	<0.001
Previous/present cancer	1.99 (1.73-2.29)	<0.001	1.61 (1.27-2.05)	<0.001	1.44 (1.04-2.00)	0.028	1.39 (0.94-2.05)	0.101
COPD	1.81 (1.65-2.00)	<0.001	1.86 (1.59-2.17)	<0.001	1.58 (1.27-1.96)	<0.001	1.54 (1.17-2.01)	0.002
Dementia	1.93 (1.30-2.87)	0.001	0.94 (0.42-2.11)	0.883	0.86 (0.27-2.68)	0.792	1.10 (0.27-4.48)	0.899
Atrial fibrillation	1.56 (1.42-1.75)	<0.001	1.30 (1.09-1.54)	0.003	1.29 (1.03-1.60)	0.025	1.22 (0.93-1.60)	0.157

The analyses were adjusted for all assessed variables including hospital, admission year, and in-hospital revascularization, if appropriate.

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; RAAS = renin-angiotensin-aldosterone system; other abbreviations as in Tables 1 and 3.

CENTRAL ILLUSTRATION **Work-Up of Patients With Unexplained Cardiac Troponin Elevation**



Eggers, K.M. et al. J Am Coll Cardiol. 2019;73(1):1-9.

In case of unexplained cardiac troponin (cTn) elevation, retesting of cTn is recommended to distinguish acute from chronic increases, the use of an alternative assay to exclude pre-analytical issues, and liberal referral for echocardiography or coronary imaging. Detected cardiovascular (CV) conditions should be treated consequently.

These patients have an estimated 10-year risk at which medical interventions to lower cardiovascular risk are recommended by current prevention guidelines (18,19).

STUDY LIMITATIONS. Some hospitals participating in the SWEDEHEART registry have not consistently quantified cTn levels below the 99th percentile, in particular when using the conventional cTnT assay. The modalities of reporting such low cTn levels (e.g., rounding of values, truncating at low values) have also differed between hospitals and changed during the observation period. Accordingly, we cannot exclude the possibility of some misclassification of patients with cTn levels at or below the 99th percentile. This together with partly narrow stratum boundaries might have contributed to variations in the sizes of assay-specific cTn strata. However, it is unlikely that this would have affected the associations of the highest cTn stratum with outcome. For the same reason, we are unable to comment on the prognostic importance of cTn levels below the 99th percentile which has been described in other studies (9-11). We cannot distinguish between acute and chronic cTn elevation as only the highest cTn level recorded during the hospitalization is documented in the SWEDEHEART registry. Despite multiple quality checks, there may be some erroneous registrations of cTn results or misdiagnosis, in particular as the diagnoses were set by the treating physicians without central adjudication. This might have contributed to the relative high proportion of patients who, despite an unspecified diagnosis, underwent coronary intervention during their hospitalization. Even though these patients had been excluded from our analysis, this indicates a weakness inherent all registry-based studies and rather emphasizes the need of a proper diagnostic assessment of patients with unexplained cTn elevation. In this context, we would like to point out that a monitor annually evaluates the correctness of the data entered in the SWEDEHEART registry, and the agreement with the medical records is around 96% (20). Finally, the SWEDEHEART registry documents only results from echocardiographies and

invasive coronary angiographies performed during the hospitalization. As such, we cannot comment on the results of other diagnostic methods or examinations performed after discharge which in some cases may have provided and explanation of cTn elevation.

CONCLUSIONS

Our results demonstrate that elevated cTn levels predict adverse outcome in patients admitted with suspected acute coronary syndrome in whom no definite diagnosis could have been established, even in the absence of significant coronary artery disease or left ventricular dysfunction. Careful work-up is required in these patients (**Central Illustration**). The term troponinemia, sometimes used to label this scenario, is trivializing and should be avoided.

ADDRESS FOR CORRESPONDENCE: Dr. Kai M. Eggers, Department of Medical Sciences, Cardiology, Uppsala University, S-751 85 Uppsala, Sweden. E-mail: kai.eggers@ucr.uu.se. Twitter: @UU_University.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Elevation of serum cardiac troponin on hospital admission is associated with cardiovascular and noncardiovascular comorbidities and predicts MAE even when no specific diagnosis is established.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether patients with unexplained troponin elevation benefit from specific preventive measures.

REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.

2. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. J Am Coll Cardiol 2017;70:996–1012.

3. Giannitsis E, Katus HA. Cardiac troponin level elevations not related to acute coronary syndromes. Nat Rev Cardiol 2013;10:623–34.

4. Mair J, Lindahl B, Hammarsten O, et al. How is cardiac troponin released from injured myocardium? Eur Heart J Acute Cardiovasc Care 2018;7:553–60.

5. Hochholzer W, Reichlin T, Twerenbold R, et al. Incremental value of high-sensitivity cardiac troponin T for risk prediction in patients with suspected acute myocardial infarction. Clin Chem 2011;57:1318–26.

6. Eggers KM, Lindahl B, Melki D, Jernberg T. Consequences of implementing a cardiac troponin assay with improved sensitivity at Swedish coronary care units: an analysis from the SWEDEHEART registry. Eur Heart J 2016;37:2417–24.

7. Stripe B, Rechenmacher S, Jurewitz D, Lee C, Schaefer S. The diagnostic yield of cardiac catheterization in low-risk troponinemia. JAMA Intern Med 2013;173:2088–90.

8. Arunachalam K. Troponinemia: an area that still needs to be explored. Am J Med 2016;129:e43.

9. Blankenberg S, Salomaa V, Makarova N, et al. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. Eur Heart J 2016;37:2428–37.

10. Ford I, Shah AS, Zhang R, et al. High-sensitivity cardiac troponin, statin therapy, and risk of coronary heart disease. J Am Coll Cardiol 2016;68:2719–28.

11. Pokharel Y, Sun W, Villareal DT, et al. Association between high-sensitivity troponin T and cardiovascular risk in individuals with and without metabolic syndrome: The ARIC study. Eur J Prev Cardiol 2017;24:628–38.

12. Omland T, White HD. State of the art: blood biomarkers for risk stratification in patients with stable ischemic heart disease. Clin Chem 2017;63:165–76.

13. Aimo A, Januzzi JL Jr., Vergaro G, et al. Prognostic value of high-sensitivity troponin t in chronic heart failure: an individual patient data meta-analysis. Circulation 2018;137:286–9.

14. Nejatian A, Omstedt Å, Höijer J, et al. Outcomes in patients with chest pain discharged after evaluation using a high-sensitivity troponin T assay. J Am Coll Cardiol 2017;69:2622–30.

15. Fabbri A, Ottani F, Marchesini G, Galvani M, Vandelli A. Predicting unfavorable outcome in subjects with diagnosis of chest pain of undifferentiated origin. Am J Emerg Med 2012;30:61–7.

16. Omstedt Å, Höijer J, Djärv T, Svensson P. Hypertension predicts major adverse cardiac events after discharge from the emergency department with unspecified chest pain. Eur Heart J Acute Cardiovasc Care 2016;5:441–8.

17. Mair J, Lindahl B, Müller C, et al. What to do when you question cardiac troponin values. Eur Heart J Acute Cardiovasc Care 2018;7:577–86.

18. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2935–59.

19. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–81.

20. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart 2010;96:1617–21.

KEY WORDS cardiac troponin, chest pain, risk prediction, troponinemia

APPENDIX For a supplemental table and figures, please see the online version of this paper.