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Biomarkers of acute myocardial infarction in the elderly: troponin and beyond

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Abstract: In the broadest context, biological markers, or biomarkers, are molecules that characterize a biological system or process. In the setting of cardiovascular disease, a number of biomarkers have become an integral part of diagnostic and risk stratification strategies. In this review, we will discuss classic and emerging biomarkers of cardiovascular disease and the role of these biomarkers in the diagnosis and prognosis of elderly patients presenting with acute myocardial infarction.

Keywords: cardiovascular disease, biological markers, diagnosis, prognosis

Acute coronary syndromes in the elderly

Ischemic heart disease (coronary artery disease, angina pectoris, and myocardial infarction) is commonly encountered in the current medical era. Data from the 2007–2010 National Health and Nutrition Examination Survey suggests 6.4% of all Americans >20 years old (15.4 million adults) have some form of ischemic heart disease. Not surprisingly, the prevalence of symptomatic ischemic heart disease increases with age. United States census data for 2012 revealed a total population of 313 million persons, with 61 million (~20%) being categorized as elderly (≥ 60 years).¹ Of these individuals, about 21% of men and 11% of women aged 60–79 years have ischemic heart disease; the numbers jump to 35% of men and 19% of women aged ≥ 80 years. In the United States, 180,000 men and 210,000 women over the age of 75 suffer an acute myocardial infarction (AMI) or die from coronary heart disease every year. The estimated direct and indirect cost of ischemic heart disease was \$195.2 billion in 2009. This number is projected to increase ~100% from 2013 to 2030.²

Biomarkers of myocardial necrosis

In the broadest context, biological markers, or biomarkers, are molecules that characterize a biological system or process. They are measured in a variety of situations and may indicate normal physiology, identify pathologic states, or be used to monitor a therapeutic response. Ideally, biomarkers affect therapy by identifying patients likely to benefit from a therapeutic intervention or in whom a more aggressive diagnostic strategy should be undertaken. In the setting of cardiovascular disease (CVD), biomarkers, particularly cardiac troponins (cTn) have become an integral part of diagnostic strategies. Other biomarkers alone or in combination have been shown to identify patients at high risk for subsequent adverse outcomes, but have not been shown to predict a response to a particular therapeutic strategy.

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Traditionally, creatinine kinase (CK), lactate dehydrogenase, and aspartate aminotransferase were used to evaluate for myocardial damage among patients presenting with chest pain. While sensitive for detecting cellular death, these biomarkers lacked specificity for myocardial injury. Later, the myocardial band (MB) isoform of CK (CK-MB) and serum myoglobin levels were utilized to improve specificity for cardiac damage and reduce the time to diagnosis (Figure 1). In the last two decades, the measurement of serum troponin level has become the predominant biomarker for the detection of myocardial necrosis. In this review, we will discuss the evolution of troponin as the quintessential biomarker for the diagnosis of AMI.

We will also discuss newer biomarkers being evaluated as part of a multimarker approach for the diagnosis of AMI.

Serum troponin and the diagnosis of AMI

Cardiac troponin I (cTnT) and troponin I (cTnI) are both structural proteins found in the contractile apparatus of cardiac myocytes (Figure 1). Both of these molecules are coded by single genes that are not expressed outside of the cardiac myocyte. In the myocyte, troponin is found in two “pools”; the majority (~95%) is bound to actin filaments in the sarcomere and is released into the systemic circulation

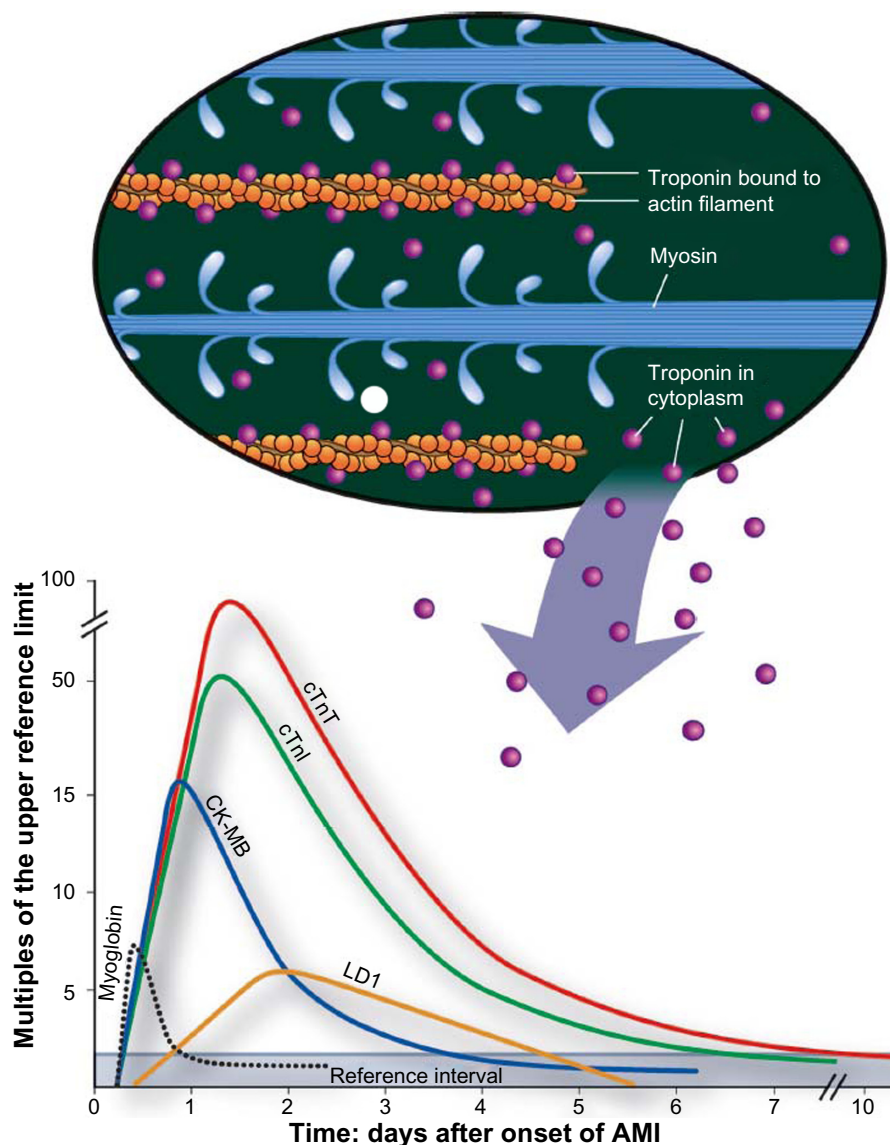


Figure 1 The cardiac sarcomere showing the sites at which troponin T and I are active.

Notes: The temporal release pattern of the classic biomarkers of myocardial infarction including cTnT, cTnI, CK-MB, myoglobin, and LD1. Reprinted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: *Anesthesiology*. Archan S, Fleisher LA. From creatine kinase-MB to troponin: the adoption of a new standard. 112(4):1005–1012.⁵⁰ Copyright © 2010 Wolters Kluwer Health. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information.

Abbreviations: AMI, acute myocardial infarction; CK-MB, creatine kinase myocardial band; cTnI, cardiac troponin I; cTnT, cardiac troponin T; LD1, lactate dehydrogenase 1.

when the myocyte dies. The “cytoplasmic” or “early appearing” pool of troponin is unbound and can be released into the circulation in the absence of cell death.³ Myocyte damage and cell death induces release of the “early pool” of cTn followed by release of the bound troponin. Levels usually peak 12–24 hours after injury, but may be present in circulation for weeks following a large AMI.⁴

Early studies identified troponin as a more sensitive marker of AMI than CK-MB.⁵ Subsequently, “troponin positive”, CK-MB “negative” patients were found to be at substantial short-term risk for recurrent myocardial infarction and mortality.⁶ Most importantly, troponin elevation alone was found to identify patients likely to benefit from intensive antiplatelet therapy or an early invasive management strategy.^{7,8} Eventually, elevated troponin levels were included in risk stratification schemes such as the TIMI-Risk Score and the GRACE-Risk Score.^{9,10}

The universal diagnosis of AMI

The importance of cTn in the diagnosis and management of AMI was recently underscored by the development of a new “definition” of myocardial infarction. This universal definition of myocardial infarction is based on the detection of a rise and fall in troponin, with at least one value greater than the 99th percentile of the upper reference limit (URL) for the assay. This biomarker elevation must be accompanied with at least one of the following: symptoms suggestive of ischemia, new or presumed new ST changes of left bundle branch block, pathological Q-waves, imaging that indicates the loss of viable myocardium or a new regional wall motion abnormality, or identification of intracoronary thrombus at autopsy.¹¹ With the advent and, now, routine use of biomarkers, the definition of an AMI has been transformed from a clinical diagnosis supported by electrocardiogram findings and biomarkers to a biomarker measurement supported by electrocardiogram and clinical findings.¹²

Troponin assays

There are several commercially available cTnI assays, but cTnT assays are produced by a single manufacturer. These assays are based on the affinity of an antibody for an epitope on the troponin molecule and vary significantly with respect to clinical performance, making it essential to understand the test characteristics of the specific product being used. To date, there is no agreement regarding the reference population used to characterize a particular assay; therefore, variability with respect to age, sex, and ethnicity is to be expected. Ideally, each hospital laboratory would perform

reference testing independently to determine the precision of the assay and local “cutoff” points. This is generally not possible, and so a reliance on published values for reference limits and reliability exists.

In general, there are three characteristics of troponin assays that should be considered. The point at which a troponin concentration is deemed abnormal or “elevated” is based on a determination of the 99th percentile URL for a given assay. Using this definition, the risk that a healthy person, selected at random from the general population, has an abnormal troponin level is 0.01 (1%). The coefficient of variability (CV) is a measure of the imprecision of a laboratory test if the same sample were repeatedly analyzed. With respect to serum troponin assays, a CV of <10% is considered ideal, and an assay with a CV of >20% should not be utilized, in general.¹¹ A CV between 10% and 20% may be of use, but may be associated with a few more misclassifications at low troponin concentrations.¹³ An ideal assay would then be characterized by a CV of <10% at the 99th percentile URL. Unfortunately, contemporary troponin assays are at the limits of their detection at low troponin levels and are often unable to deliver precise measurements at or below the 99th percentile URL (CV >20%). In such situations, it has been recommended that a cutoff be set at the lowest point that can be measured with a CV of <10%.¹⁴ Regardless, a solitary elevation in cTnI or cTnT is considered insufficient for the diagnosis of AMI. In most cases, serial measurements drawn 3–6 hours apart are performed, and the diagnosis of AMI is established when a rise and fall in the level of cTnI or cTnT is detected.¹¹

Troponin elevations outside the setting of AMI

It is important to note that the evidence substantiating the role of troponin in the diagnosis of AMI arises from studies in which the subjects had a relatively high pretest probability of having coronary artery disease and AMI. As with any diagnostic test, the reliability of the test decreases considerably when used in situations in which AMI is unlikely. At the time of development, it was hoped that elevations in cTn would be sensitive, but perhaps more importantly, exquisitely specific for myocardial injury.¹⁵ Unfortunately, experience with these assays has demonstrated numerous situations in which “elevated” cTn levels do not signal AMI. Specifically, it is known that patients with renal failure or chronic systolic or diastolic heart failure (HF) can have a persistently elevated cTn.^{16–18} Additionally, it has been noted that an elevated cTn can be associated with other life-threatening conditions such as

aortic dissection, pulmonary embolism, and sepsis.^{19–21} Despite this lack of specificity, the test is frequently ordered. In one analysis, a serum troponin level was ordered in 48% of patients presenting to an emergency department, only 29% of whom were admitted to “rule out” a myocardial infarction.²² Thus, it has become common for a cardiologist to be asked to evaluate a patient simply because of “an elevated troponin”.^{23,24}

Troponin elevations in the elderly

The current generation of troponin assays is poorly studied among elderly patients. The studies that established troponin as the diagnostic standard for AMI enrolled relatively young patients with a high pretest probability of AMI.⁶ Subsequent studies have found troponin elevations in “apparently healthy” subjects, especially those that are elderly. For example, in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVAS) study, 1,005 persons 70 years of age were evaluated for the presence of elevated cTnI levels. Using an assay with a lower limit of detection of 0.006 µg/L and “abnormal” cutoff value of 0.01 µg/L, the authors found that 21.8% of these patients had an elevated cTnI level. Predictors of elevated cTnI included the male sex, cardiac risk factors, and impaired left ventricular systolic function.²⁵ In contrast, in the Dallas Heart Study (DHS), 3,557 patients aged 30–65 years underwent a test for serum troponin using a cTnT assay with a lower detection limit of 0.01 µg/L. A detectable troponin level was found in only 1% of these younger subjects (0.7%; confidence interval 0.3%–1.1%).²⁶ Thus, the diagnostic characteristics of the traditional troponin assays among elderly subjects remains to be definitively determined.

Multiple biomarkers for the diagnosis of AMI

The increasing sensitivity of troponin makes it unlikely another marker of myocardial necrosis will add considerably to diagnostic or prognostic algorithms for AMI. However, there are still patients in whom troponin levels at presentation are undetectable and who proceed to be diagnosed with an AMI. Recently, diagnostic strategies using a combination of biomarkers have been evaluated in hope of identifying high risk patients with chest pain. The combination of troponin and a biomarker that does not arise from myocardial necrosis but by a different mechanism such as myocardial stretch, inflammation, or stress is appealing.

Natriuretic peptides

Brain natriuretic peptide (BNP) is a natriuretic hormone produced by myocytes and was initially identified in the brain.

A prohormone is released in response to increased wall tension or myocardial stretch. Cleavage of the prohormone in circulation releases BNP and the more stable N-terminal fragment (NT-proBNP). Plasma concentrations of both of these hormones are elevated in patients with left ventricular dysfunction (systolic or diastolic) and are frequently used to aid in the diagnosis of clinical HF.²⁷ The measurement of NT-proBNP and BNP levels have become commonplace in the setting of HF. It has become evident, however, that NT-proBNP and BNP levels are also elevated in a variety of other situations associated with myocardial dysfunction, such as pulmonary embolism, sepsis, and myocardial infarction.^{28–30}

BNP and NT-proBNP in the elderly

Plasma concentrations of BNP and NT-proBNP increase with increasing age. In fact, age appears to be the most important independent variable in explaining plasma levels of BNP and NT-proBNP.^{31,32} The reason for this increase is not entirely clear. Initial investigations suggested cardiac structural alterations (increased left ventricular mass, increased left atrial volume) and reduced renal clearance of the natriuretic peptides with aging. However, when BNP was studied in a population of more than 700 normal subjects in sinus rhythm without cardiovascular disease, renal disease, pulmonary disease, or diabetes, on no cardiovascular medications, and with normal cardiac function, age was still an independent predictor of BNP levels.³²

C-reactive protein

Inflammation plays a central role in the development of atherosclerosis. C-reactive protein (CRP) is a marker of inflammation. Elevations in CRP, especially when measured using highly sensitive assays (hs-CRP) have been shown to predict the presence of coronary disease among apparently healthy subjects and to predict adverse events in the setting of AMI.^{33,34}

Multimarker strategies

The potential of serum cTnI, BNP, and hs-CRP to predict outcomes in AMI was established by evaluating blood samples collected from a subset of patients enrolled in a large clinical trial. Samples were drawn in 450 patients within 72 hours of presentation with AMI and sent to a core lab for analysis. Multivariable analysis indicated each of these biomarkers was an independent predictor of subsequent adverse outcomes including death, recurrent myocardial infarction, and the development of HF. A scoring system

was developed that reflected the number of biomarkers that were elevated. The risk of mortality, recurrent myocardial infarction, or HF at 30 days increased in proportion to the number of biomarkers that were elevated. This scoring system was then validated in a larger cohort of patients enrolled in another clinical trial.³⁵

The prognostic utility of NT-proBNP, hs-CRP, and cTnT and several other candidate biomarkers has been studied in a group of patients presenting with chest pain. Both NT-proBNP and cTnT, but not hs-CRP, emerged as independent predictors of adverse events in the year following presentation (Figure 2). An elevated NT-proBNP ($\geq 1,371$ ng/L) was

associated with an adjusted odds ratio of 2.7 for death or AMI at 1 year. When the concentration of both NT-proBNP and cTnT exceeded the cutoff values, the risk of death or AMI at 1 year was 11.9% compared with 1.4% among patients in whom neither biomarker was elevated.³⁶

Future perspectives – emerging biomarkers

The next generation of troponin assays

Newer troponin assays promise to be significantly more sensitive. These newer assays are in use in Europe and await approval from the US Food and Drug Administration before

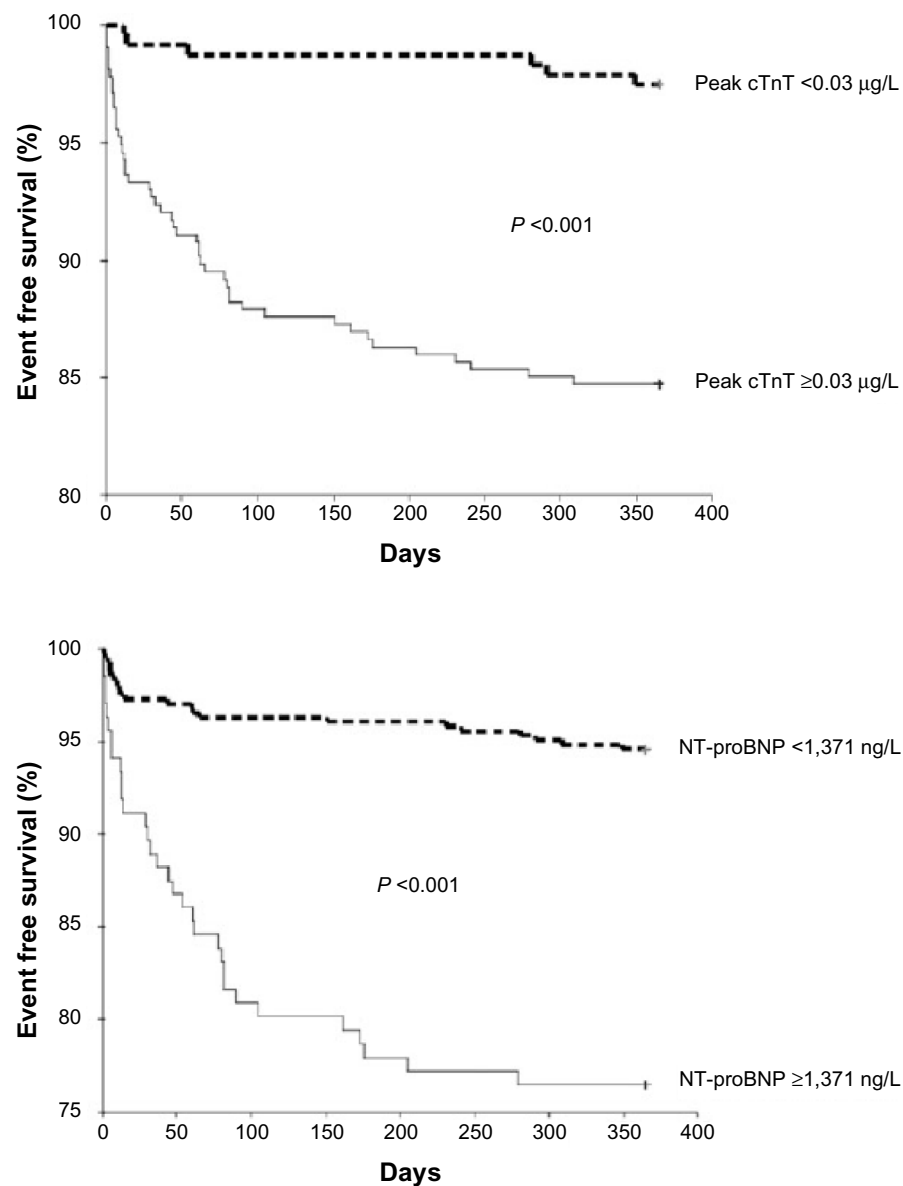


Figure 2 Kaplan–Meier curves demonstrating survival from death or myocardial infarction stratified by the level of cTnT ($\geq 0.03 \mu\text{g/L}$) or NT-proBNP ($< 1,371 \text{ ng/L}$).

Note: Reprinted from *Am J Cardiol* 103(1), McCann CJ, Glover BM, Menown IB, et al. Prognostic value of a multimarker approach for patients presenting to hospital with acute chest pain, pages 22–28.³⁶ Copyright © 2009 with permission from Elsevier.

Abbreviations: cTnT, cardiac troponin T; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

they enter the market in the United States. They have been given the name “high-sensitivity” troponin (hs-cTn) assays, as they detect troponin at concentrations tenfold lower than the currently utilized assays. That said, these assays are based on the same biochemistry as traditional troponin assays and are likely just the next, rather than the final, step along the path of improving sensitivity. The increased sensitivity will force providers to rethink how these assays are used (Table 1). For example, simply detecting troponin with these assays will not be suggestive of myocardial ischemia as there will be a measurable troponin level in many, if not most, persons admitted to emergency departments as well as a significant proportion of the general population.¹²

In the DHS, the ability of a traditional and highly sensitive cTnT assay to predict adverse events among a cohort of apparently healthy adults was compared. As noted above, ~1% of apparently healthy patients had a detectable troponin level using a traditional troponin assay. The same

samples were also analyzed using an hs-cTnT assay with a lower limit of detection of 3.0 ng/L and a 99th percentile URL of 1.4 ng/L. A detectable serum troponin was noted in 25% of these subjects. Elevated hs-cTnT was independently associated with all-cause and cardiovascular mortality in a concentration-dependent manner (Figure 3).³⁷

In emergency departments, hs-cTn measurements promise to change practice patterns. A large study by Reichlin et al was recently performed in which the effectiveness of four sensitive cTn assays were evaluated among 718 patients presenting to the emergency department complaining of symptoms consistent with AMI. The hs-cTn assays all performed well when compared with a standard troponin assay, especially among patients presenting within a few hours of the onset of symptoms. Perhaps as importantly, the negative predictive value of these assays was quite high. In fact, when the 99th percentile URL was used as a cutoff, the negative predictive value was 97%–99%.³⁸

Table 1 A comparison of contemporary and highly sensitive troponin assays

Characteristic	Current assays	High sensitivity assays
General	There is a variety of available troponin assays with unique test characteristics <ul style="list-style-type: none"> • The test characteristics and cutoff values will vary from assay to assay • Elevated levels uncommon in “apparently healthy adults” 	There is a variety of available troponin assays with unique test characteristics <ul style="list-style-type: none"> • Ten times more sensitive than conventional assays • Elevated levels common in “apparently healthy” adults • “Cutoff” values will vary significantly across reference populations and with age
Diagnosis of AMI	Elevated troponin levels in the appropriate clinical setting are required for the diagnosis of AMI <ul style="list-style-type: none"> • Serial measurements to detect a rise and fall in troponin concentration will likely remain an important part in the diagnosis of AMI 	Elevated troponin levels in the appropriate clinical setting are required for the diagnosis of AMI <ul style="list-style-type: none"> • Significantly improved sensitivity, which translates to earlier detection • Reduced specificity • Serial measurements may still be required
Exclusion of AMI	The absence of a measurable troponin on a single blood draw is insufficient to exclude AMI	The absence of a measurable troponin will likely exclude AMI
Non-cardiac disease	Troponin levels may be elevated in a variety of pathological states, some of which constitute medical emergencies <ul style="list-style-type: none"> • Aortic dissection • Pulmonary embolism • Shock • Heart failure • Chronic renal insufficiency 	Troponin levels may be elevated in a variety of pathological states, some of which constitute medical emergencies <ul style="list-style-type: none"> • Aortic dissection • Pulmonary embolism • Shock • Heart failure • Chronic renal insufficiency
Prognosis	Elevated serum troponin levels appear to be associated with a poor prognosis <ul style="list-style-type: none"> • Especially among hospitalized patients 	Elevated serum troponin levels appear to be associated with a poor prognosis <ul style="list-style-type: none"> • May prove true among “apparently healthy outpatients”
Pitfalls associated with the elderly	Limitations <ul style="list-style-type: none"> • Few studies evaluate an elderly population 	Limitations <ul style="list-style-type: none"> • Better studied in the elderly • Troponin levels “measurable” in the majority of elderly patients • Age specific “cutoff” values may be needed

Note: Data from Mohammed and Januzzi,⁵¹ and Korley and Jaffe.⁵²

Abbreviation: AMI, acute myocardial infarction.

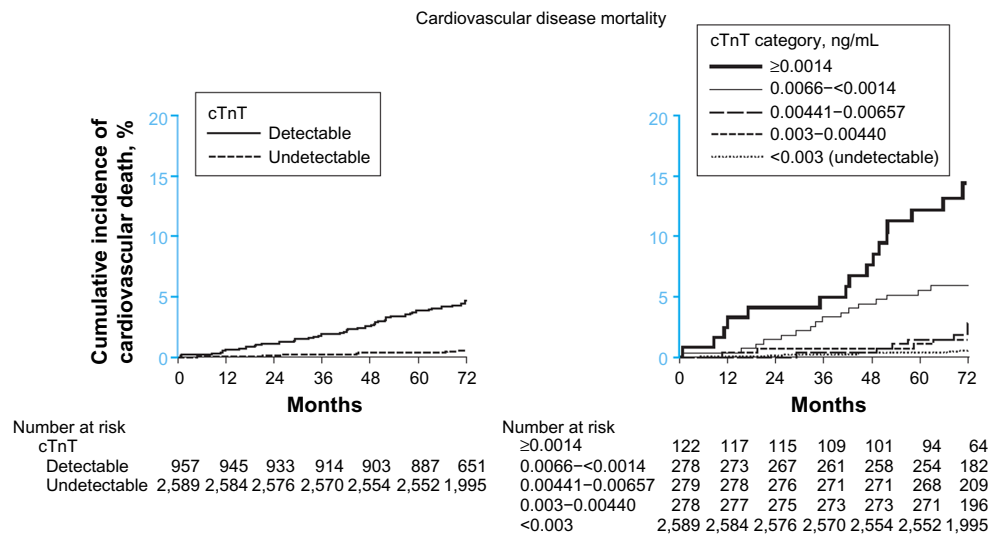


Figure 3 Cardiovascular disease mortality among a group of community-dwelling subjects enrolled in the Dallas Heart Study.

Notes: $P < 0.001$ for all between-group comparisons by the log-rank test. Reproduced from de Lemos JA, Drazner MH, Omland T, 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(22):2503–2512.³⁷ Copyright © 2010 American Medical Association. All rights reserved.

Abbreviation: cTnT, cardiac troponin T.

High sensitivity cTn assays and the elderly

High sensitivity cTn assays will detect troponin in a substantial number of asymptomatic elderly persons. In the DHS, age was found to be an independent predictor of a measurable hs-cTnT among asymptomatic adults.³⁷ In an Italian cohort of community dwelling subjects aged 65–84 years, circulating levels of hs-cTnT were detected in 18% of the females and 41% of the males. Correlation with echocardiographic data indicated an association between left ventricular mass, mid-wall fractional shortening, and diastolic dysfunction.³⁹ Eggers et al evaluated troponin in 940 elderly men, 379 of whom had an established diagnosis of coronary artery disease and 561 of whom did not. Using an hs-cTnT assay with a measurable range (3.0–10,000 ng/L), a detectable troponin level was found in 92.8% of the patients.⁴⁰ In another study, among patients >70 years old, the same group noted that hs-cTnT levels increased gradually with time and were on average 45% higher in the same patient after five years.⁴¹

Elderly persons presenting to emergency departments are also commonly found to have measurable troponin levels using hs-cTn assays. Menacer et al⁴² evaluated troponin levels among 362 patients presenting to an emergency department without chest pain or signs of CVD. They used four hs-cTn assays including an hs-cTnT assay (lower limit of quantification 13 ng/L) and three different hs-cTnI assays (lower limit of quantification 32, 40, and 30 ng/L). As expected, the hs-cTnT proved the most sensitive assay, detecting a measurable troponin level in 81% of the patients.

The hs-cTnI assays proved less sensitive, detecting troponin in 15%–56% of this cohort.⁴² It will be impossible using high-sensitivity assays to assign a working diagnosis of AMI using only a serum troponin concentration, especially among elderly patients.

Copeptin

Arginine vasopressin is released from the neurohypophysis in response to changes in plasma osmolality and is involved in osmoregulation and cardiovascular homeostasis. Activation of the arginine vasopressin system is part of the endogenous response to stress, such as is encountered in the setting of AMI. Vasopressin degrades rapidly in circulation and has not been found to be useful as a biomarker. Instead, copeptin, the more stable C-terminal fragment of provasopressin, has emerged as a promising surrogate for vasopressin in the characterization of the role of the arginine-vasopressin system in CVD. It has been hypothesized that the addition of copeptin levels to a diagnostic strategy for AMI might increase sensitivity and specificity. Reichlin et al⁴³ used a conventional cTnT assay and a novel copeptin assay to risk stratify 492 patients presenting to an emergency department with symptoms suggestive of AMI. They found that copeptin levels were elevated very early in relation to the onset of symptoms and when compared with cTnT (Figure 4). Furthermore, when cTnT and copeptin measurements were evaluated in combination, improved diagnostic sensitivity for AMI was noted. This was true when the combination was compared to either assay alone, or the combination of

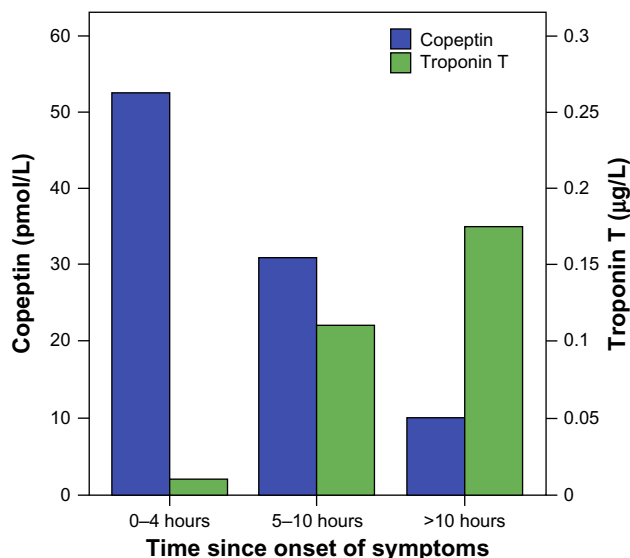


Figure 4 Copeptin (blue) and troponin T (green) levels at presentation in relation to the time since the onset of symptoms among patients found to have an acute myocardial infarction.

Note: Reprinted from *J Am Coll Cardiol*, 54(1), Reichlin T, Hochholzer W, Stelzig C, et al, Incremental value of copeptin for rapid rule out of acute myocardial infarction, pages 60–68.⁴³ Copyright © 2009 with permission from Elsevier.

cTnT and CK-MB. Of equal importance, the combination of cTnT and copeptin was very effective in identifying patients without AMI (negative predictive value 99.7%).⁴³

Growth-differentiation factor-15

Growth-differentiation factor (GDF)-15 is a member of the transforming growth factor-B cytokine superfamily. While GDF-15 is weakly expressed in most tissues under physiological conditions, its expression levels increase in response to pathological stress associated with inflammation or tissue injury. CVD and AMI are known to be inflammatory states.⁴⁴ GDF-15 concentrations are elevated in AMI and in chronic HF. In both cases, these elevations have been associated with a subsequent increase in mortality.^{45–48} Recently, GDF-15 was one of several biomarkers evaluated among a group of patients admitted with chest pain and an “undetectable” troponin. The study enrolled 1,247 patients, all of whom were admitted with concern for AMI, but who had undetectable serum cTnT levels measured by a conventional assay. The authors found that in this low risk cohort, a GDF-15 level of >1800 ng/L was associated with an increased risk of death or myocardial infarction on follow-up.⁴⁹

Conclusion

The practice of cardiovascular medicine has been forever changed by the ability to measure biomarkers.

Troponin measurements have become an integral part of contemporary diagnostic and patient management algorithms. The current generation of troponin assays has been shown to better identify patients with AMI who are at a high risk for adverse events. Additionally, patients with an elevated troponin seem to benefit from an aggressive therapeutic strategy. The prognostic power of other biomarkers such as NT-BNP has been established, but no link between these biomarkers and a therapeutic strategy has been established. Unfortunately, the studies upon which these conclusions were based enrolled relatively few elderly patients.

Research continues to find the next great biomarker for clinical practice and a few of the emerging candidates, as well as their potential utility, have been discussed in this paper. Elderly patients represent the largest portion of cardiovascular patients. There has been an increasing realization for the need to have algorithms that consider the patient’s age and other comorbidities rather than a one-size-fits-all approach to abnormal levels of biomarkers. With the increasing number of available biomarkers, the practice of medicine will depend more heavily on developing appropriate testing for all patients.

Disclosure

None of the authors have any conflict of interest in relation to this paper.

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