



**EDUCATIONAL OBJECTIVE:** Readers will use measurements of cardiac biomarkers in conjunction with physical and electrocardiographic findings to assess chest pain

**WASSIM MOSLEH, HBSc**  
Trinity College, Dublin, Ireland

**HUSAM ABDEL-QADIR, MD**  
Division of Cardiology, Department of  
Medicine, University of Toronto, ON,  
Canada

**MICHAEL FARKOUH, MD, MSc**  
Chair, Peter Munk Centre of Excellence in Clinical  
Trials, and Director, Heart and Stroke Richard  
Lewar Centre of Excellence in Cardiovascular  
Investigation, University of Toronto, Toronto, ON,  
Canada

# Biomarkers in the emergency workup of chest pain: Uses, limitations, and future

## ABSTRACT

When patients present with chest pain, their levels of cardiac biomarkers are only one piece of the clinical picture, albeit an important one. Together with the history, physical examination, and electrocardiography (ECG), these levels help estimate the probability that the patient is experiencing an acute coronary syndrome and will have an adverse clinical outcome.

## KEY POINTS

Biomarkers of cardiac necrosis, particularly troponins I and T, can aid in risk assessment, but one must pay close attention to the underlying clinical context.

Stable patients at low risk with no evidence of ischemia on initial assessment can be admitted to a chest pain unit for observation with serial biomarker testing and ECG.

Highly sensitive troponin assays can improve the early diagnosis of acute myocardial infarction, but how best to use them is not yet defined.

Biomarkers, used alone or in combination, have the potential to complement or replace stress testing, permitting more timely, accurate, and cost-effective diagnosis and earlier discharge of patients at low risk.

Newer markers such as brain-type natriuretic peptide, cystatin C, and ischemia-modified albumin have shown promise but need to be thoroughly evaluated.

**E**ACH YEAR IN THE United States, more than 8 million people come to the emergency department with chest pain, but only a minority are eventually diagnosed with a heart attack.<sup>1</sup>

Confronted with signs and symptoms that could represent an acute coronary syndrome, clinicians need to know whether the patient has a benign condition and can safely be sent home or is in urgent need of hospitalization—and they need to do so in a safe, timely, and cost-effective manner.<sup>2,3</sup>

Testing for biomarkers of cardiac injury, especially troponins I and T, is an accepted part of the assessment of chest pain. However, the interpretation of these cardiac biomarkers is complicated by the fact they can be elevated from noncoronary causes of chest pain such as pulmonary embolism or renal impairment, and thus should be considered only as part of the patient's total clinical picture. This uncertainty can result in longer hospital stays and increased testing.

Thus, researchers are searching for new biomarkers that could allow for more rapid and accurate diagnosis and estimation of prognosis.

In this article we will examine the advantages and limitations of measuring cardiac biomarkers. We then discuss the emerging data on new biomarkers, including the very promising high-sensitivity troponin assays, cystatin C, and other markers, and the potential for biomarkers to be used instead of or in combination with stress testing in the evaluation of patients who have no initial evidence of ischemia.

**■ SCENARIO 1: ELEVATED TROPONIN AND ST-SEGMENT ELEVATION**

A 46-year-old woman presents to the emergency department with chest pain that started 2 hours earlier. Electrocardiography (ECG) initially shows sinus tachycardia with ST-segment depression and negative T waves in lead aVL. Her cardiac biomarker values (troponin I and creatine kinase MB) are normal. Repeated troponin I measurements show elevations of 250 ng/L, whereas her creatine kinase MB level is within the optimal range. Coronary angiography is unremarkable. Echocardiography shows right ventricular pressure overload in the pulmonary artery and the right ventricle. How should this patient be further evaluated?

**■ SCENARIO 2: ELEVATED TROPONIN AND LEFT VENTRICULAR HYPERTROPHY**

A 47-year-old man is admitted with worsening dyspnea and chest pain that worsens with coughing and inspiration. He has a history of end-stage renal disease secondary to poorly controlled hypertension and is being treated with hemodialysis, which he missed for the past 4 weeks while failing to take his hypertension medication. His blood pressure is 270/130 mm Hg. Chest auscultation reveals signs of pulmonary edema—ie, crackles at the end of inspiration. His troponin T level is 394 ng/L. ECG indicates left ventricular hypertrophy. How should this patient be further evaluated?

**■ TROPONIN IS SPECIFIC FOR INJURY, BUT NOT FOR INFARCTION**

American College of Cardiology and American Heart Association (ACC/AHA) guidelines<sup>4</sup> recommend that clinicians ask themselves two questions: what is the likelihood that the patient is truly having an acute coronary syndrome secondary to coronary artery disease, and what is the likelihood of an adverse clinical outcome? Clues come from the initial measurements of biomarkers of cardiac injury, history, physical examination, and ECG (TABLE 1),<sup>5</sup> and subsequent care is based on the estimated degree of risk.

Troponin revolutionized the diagnosis and risk stratification of chest pain. The ACC/

AHA guidelines call for measuring biomarkers—preferably troponin—in all patients who present with chest discomfort consistent with an acute coronary syndrome.<sup>4,6</sup>

Cardiac troponins I and T have been the biomarkers of choice for detecting myocardial injury,<sup>4,6</sup> since elevated concentrations are highly sensitive and tissue-specific.<sup>7</sup> Moreover, they identify patients at short-term and long-term risk of cardiac events.<sup>4,8</sup>

The introduction of troponin testing led to a substantial increase in the rate of diagnosis of myocardial infarction (MI), with an increase in cardiac care unit admissions of more than 20%.<sup>9,10</sup> This was partly because troponin is released into the blood with even minute myocardial damage, so that some patients who previously would have been diagnosed with unstable angina are now found to have non-ST-segment-elevation MI.<sup>10</sup> However, the increase in admissions may also represent an increase in misdiagnoses, with many clinicians equating an elevated troponin level with acute MI.<sup>11</sup>

Although an elevated troponin level is 100% specific for myocardial injury, it is not synonymous with MI.<sup>12</sup> Myocardial injury can be caused by a cardiac condition such as tachyarrhythmia, cardiac trauma, congestive heart failure, ventricular hypertrophy, myocarditis, or pericarditis, or by a noncardiac condition such as sepsis, respiratory failure, pulmonary embolism, pulmonary hypertension, cancer chemotherapy, or renal insufficiency.<sup>4,13</sup> Therefore, to avoid a misdiagnosis of MI, the troponin level must be considered in the clinical context.

In fact, Alcalai et al<sup>11</sup> noted that almost half of patients with elevated troponin did not really have an acute coronary syndrome. More importantly, in-hospital and long-term survival rates were significantly better for patients with an acute coronary syndrome than for those without, illustrating the importance of identifying and treating the true disease instead of mislabeling the problem as MI.

Bayesian theory predicts that patients with chest pain who have elevated troponin are less likely to truly have an acute coronary syndrome if the rest of their clinical presentation indicates a low probability for heart disease.<sup>14</sup> Indeed, when McDonald et al<sup>15</sup> used a risk-

**ACC/AHA guidelines call for measuring biomarkers—preferably troponin—in all patients with chest discomfort consistent with an acute coronary syndrome**

TABLE 1

**Unstable angina and non-ST-segment elevation myocardial infarction: Short-term risk of death or nonfatal infarction<sup>a</sup>**

FEATURE	HIGH RISK (AT LEAST ONE OF THE FOLLOWING MUST BE PRESENT)	INTERMEDIATE RISK (NO HIGH-RISK FEATURE, BUT MUST HAVE ONE OF THE FOLLOWING)	LOW RISK (NO HIGH- OR INTERMEDIATE-RISK FEATURE, BUT MAY HAVE ANY OF THE FOLLOWING)
<b>History</b>	Accelerating tempo of ischemic symptoms in preceding 48 hours	Prior myocardial infarction (MI), peripheral or cerebrovascular disease, or coronary artery bypass grafting surgery; previous aspirin use	
<b>Character of chest pain</b>	Prolonged ongoing pain at rest (longer than 20 minutes)	Prolonged angina at rest (> 20 min), now resolved, with moderate or high likelihood of coronary artery disease (CAD)  Angina at rest (> 20 min) or relieved with rest or sublingual nitroglycerine  Nocturnal angina  New-onset or progressive CCS <sup>b</sup> class III or IV angina in the past 2 weeks without prolonged pain at rest (> 20 min) but with intermediate or high likelihood of CAD	Increased frequency, severity, or duration of angina; angina provoked at a lower threshold; new-onset angina with onset 2 weeks to 2 months before presentation
<b>Clinical findings</b>	Pulmonary edema, most likely caused by ischemia  New or worsening mitral regurgitation murmur, S <sub>3</sub> , or new or worsening rales  Hypotension, bradycardia, tachycardia  Age > 75 years		
<b>Electrocardiographic features</b>	Angina at rest with transient ST-segment changes > 0.5 mm  Bundle-branch block, new or presumed new  Sustained ventricular tachycardia	T wave changes  Pathologic Q waves or resting ST depression < 1 mm in multiple lead groups (anterior, inferior, lateral)	Normal or unchanged ECG

<sup>a</sup> Estimation of the short-term risks of death and nonfatal cardiac ischemic events in unstable angina or non-ST-segment myocardial infarction is a complex, multivariable problem that cannot be fully specified in a table such as this. Therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms. Adapted from AHCPR Clinical Practice Guidelines No. 10, Unstable Angina: Diagnosis and Management, May 1994.

<sup>b</sup> CCS = Canadian Cardiovascular Society angina classification

FROM ANDERSON JL, ADAMS CD, ANTMAN EM, ET AL. 2011 ACCF/AHA FOCUSED UPDATE INCORPORATED INTO THE ACC/AHA 2007 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA/NON-ST-ELEVATION MYOCARDIAL INFARCTION: A REPORT OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION/AMERICAN HEART ASSOCIATION TASK FORCE ON PRACTICE GUIDELINES. CIRCULATION 2011; 123:E426–E579. REPRINTED WITH PERMISSION.

scoring index based on sex, a history of heart failure or coronary artery disease, the ECG, and use of aspirin, the positive predictive value of an abnormal troponin level was 83% at a risk score of 4 or greater, 63% at a score of 3, 52% at a score of 2, 32% at a score of 1, and 29% at a score of 0.

Thus, cardiac biomarkers are not a substitute for traditional clinical assessment, but rather should be used “in conjunction with the clinical history, physical examination, and interpretation of the ECG.”<sup>6</sup> Consequently, diagnostic protocols that incorporate pretest clinical features to identify low-risk patients have a higher negative predictive value.

This was illustrated in a study by Than et al<sup>16</sup> that aimed to prospectively validate the safety of an accelerated diagnostic protocol to assess chest pain suggestive of an acute coronary syndrome. The protocol included a structured pretest probability scoring method (ie, the Thrombolysis in Myocardial Infarction [TIMI] score), ECG, and a point-of-care biomarker panel of troponin, creatine kinase MB, and myoglobin. The protocol had a negative predictive value of 99.1%, whereas the use of biomarkers alone had a value of 96.1%.

**An elevated troponin is 100% specific for myocardial injury but is not synonymous with MI**

#### ■ HISTORY AND PHYSICAL EXAMINATION PROVIDE KEY INFORMATION

In a review, Heidenreich et al<sup>8</sup> noted certain demographic characteristics associated with worse outcomes—ie, older age and male sex; a history of medical conditions such as diabetes, MI, and hypertension; and heart failure on presentation.

A careful assessment of chest pain and associated symptoms helps narrow the differential diagnosis. Features that increase the likelihood of a cardiac origin of chest pain are:

- Chest pain at the time of presentation (likelihood ratio [LR] = 2.0)
- Radiation of the pain to the right shoulder (LR = 2.9), the left arm (LR = 2.3), or both arms (LR = 7.1)
- Nausea or vomiting (LR = 1.9)
- Diaphoresis (LR = 2.0).<sup>17</sup>

The physical examination can detect high-risk features such as new murmurs, hypotension, diaphoresis, pulmonary edema, and rales. It is more specific than sensitive and is useful

in identifying low-risk patients by targeting potential noncardiac causes of the patient's symptoms.<sup>18</sup>

The efficacy of clinical assessment was studied in 2,271 patients with chest pain presenting to the emergency department.<sup>19</sup> In this cohort, a low-risk group with a 30-day major cardiovascular event rate (death, MI, stroke, or revascularization) of 2.5% could be identified through the use of the US Agency for Health Care Policy and Research criteria.

#### Electrocardiography

ECG provides important diagnostic and prognostic information and independently predicts death or MI, even after adjustment for cardiac biomarker measurements,<sup>20,21</sup> making it pivotal in the evaluation.<sup>4</sup> The key features on ECG that increase the probability of MI are:

- New ST-segment elevation (LR 5.7–53.9)
- New Q waves (LR 5.3–24.8).<sup>17</sup>

One study<sup>20</sup> found that while the troponin T level was a powerful independent marker in patients presenting with MI, its value for risk stratification was enhanced when it was combined with a standard measure such as ECG.<sup>20</sup> While more than 90% of patients with ST-segment elevation had an adverse outcome, only 31.7% of those patients had an elevated troponin T level.

#### No component is sufficient by itself

Thus, in spite of the proliferation of cardiac diagnostic tests, the initial bedside assessment of chest pain remains paramount. In fact, in patients presenting to the emergency department with chest pain, low risk (ie, those with a < 5% probability of MI) may be identified by presenting symptoms, medical history, and ECG alone.<sup>19</sup>

Furthermore, although clinical assessment, ECG, and cardiac biomarker testing each provide incremental benefit in assessing chest pain, no component is sufficient by itself. Sanchis et al<sup>22</sup> found that even in patients with a normal troponin I level, the risk remained high in the case of ST-segment depression, and that even without signs of ischemia, the probability of cardiac events was 16% when the chest pain score was 11 points or higher.<sup>22</sup> Consequently, a normal troponin level, ECG,

or any other predictor alone would not ensure a good prognosis.

### ■ BIOMARKERS INSTEAD OF STRESS TESTING?

The ACC/AHA guidelines for the diagnosis of patients with unstable angina and non-ST-segment elevation MI say that stable patients at low risk with no evidence of ischemia on initial assessment can be admitted to a chest pain unit for observation with serial cardiac biomarkers and ECG.<sup>4</sup> At the end of the observation period, those who have reassuring results on ECG and normal cardiac biomarker measurements undergo functional cardiac testing or stress testing, or both.<sup>4</sup>

Exercise treadmill testing is a cornerstone of confirmatory testing in an accelerated diagnostic protocol because it is readily available, safe, and easy to do.<sup>18</sup> A low-risk result was shown to have a high negative predictive value,<sup>23,24</sup> so that the likelihood of an acute coronary syndrome is low enough for safe discharge.

However, the overall process is not ideal since it is time-consuming, generates additional costs, and can have false-positive results in patients who are otherwise deemed not to be at high risk. While some studies provided an optimistic view about discharging low-risk patients with negative biomarkers without stress testing,<sup>7,25</sup> others have discouraged omitting exercise treadmill testing from protocols.<sup>22,26</sup>

Others have proposed combining a biomarker with an imaging study such as coronary computed tomographic (CT) angiography.<sup>27</sup> Normal findings on this study have been shown to have a negative predictive value of up to 100% for ruling out an acute coronary syndrome and the occurrence of major adverse cardiovascular events in the long term.<sup>28,29</sup> Furthermore, it allows more-inclusive assessments of chest pain and can exclude other life-threatening causes such as pulmonary embolism and aortic dissection (referred to as the “triple rule-out”).<sup>30</sup>

However, 25% to 50% of patients presenting to the emergency department with chest pain may not be candidates for CT angiography because of obesity, contrast allergy, intolerance to beta-blockade, arrhythmia, renal

insufficiency, or a history of coronary artery disease.<sup>18</sup> Moreover, it may be more efficient and less costly to discharge some patients without coronary CT angiography<sup>31</sup> with the help of novel biomarkers without routine additional testing. This may spare patients the additional radiation exposure from CT angiography or nuclear imaging.<sup>27,32</sup>

New biomarkers may, it is hoped, better distinguish patients at low risk from those at high risk without resorting to stress testing. Several of these markers are moving toward mainstream clinical use. For a biomarker to be prognostically equivalent to stress testing, it must be able to tell us if the likelihood of an acute coronary syndrome is low enough for safe discharge—ie, it must have a significantly high negative predictive value. Also, it must be an independent predictor of adverse outcomes, particularly in patients deemed at low risk by initial low troponin measurements. Biomarkers that have shown promise in this regard include high-sensitivity troponin, brain-type natriuretic peptide (BNP), cystatin C, and ischemia-modified albumin.

### ■ HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

Although we speak of “high-sensitivity troponin,” these new assays detect the same molecule as do traditional troponin assays. The difference is that high-sensitivity assays can detect and measure troponin at concentrations much lower than the traditional assays can. In fact, high-sensitivity troponin assays can detect and measure troponin at very low levels in almost all healthy people.

Studies have shown that the high-sensitivity assays have better analytical accuracy and sensitivity than older assays.<sup>12</sup>

**Aldous et al**<sup>33</sup> reported that, in patients who presented to the emergency department within 4 hours of the onset of chest pain, an elevation in troponin T on a high-sensitivity assay had a positive predictive value of 53.8% and a negative predictive value of 98.3%.

**Weber et al**<sup>34</sup> found the diagnostic value of the high-sensitivity troponin T assay to be superior to that of a contemporary troponin T assay (area under the receiver-operating-characteristics curve [AUC] of 0.949 vs 0.929).

**Despite the proliferation of cardiac diagnostic methods, the initial bedside assessment of chest pain remains paramount**

Even when the contemporary troponin T assay was negative, the high-sensitivity assay provided strong diagnostic information (AUC 0.81). Furthermore, the high-sensitivity assay provided superior independent prognostic power for death within 6 months.

Hochholzer et al<sup>35</sup> reported a prognostic accuracy for death significantly higher (AUC 0.79) than that of contemporary troponin T (AUC 0.69). A concentration of high-sensitivity troponin T above 14 ng/L improved the prediction of death (hazard ratio 2.60) but not of subsequent acute MI in patients with acute chest pain. Therefore, a negative high-sensitivity troponin T assay identifies patients with a good prognosis and who may be discharged without further testing if their clinical presentation and ECG are also reassuring.

Keller et al<sup>36</sup> compared the diagnostic performance of the high-sensitivity cardiac troponin I assay against 11 other biomarkers, including a contemporary cardiac troponin I assay. The contemporary troponin I and the high-sensitivity troponin I assays performed best. The high-sensitivity troponin I assay at admission had a sensitivity of 82.3% and a negative predictive value of 94.7% for ruling out acute MI, whereas the contemporary troponin I assay had a sensitivity of 79.4% and a negative predictive value of 94.0%.

Using levels obtained at 3 hours after admission, the sensitivity was 98.2% and the negative predictive value was 99.4% for both troponin I assays. Combining the 99th percentile cutoff at admission with the serial change in troponin concentration within 3 hours, the positive predictive value for ruling in acute MI for high-sensitivity cardiac troponin I increased from 75.1% at admission to 95.8% after 3 hours; for the contemporary assay, it increased from 80.9% at admission to 96.1%.<sup>36</sup>

The authors concluded that performing either of the cardiac troponin I assays 3 hours after admission may help in ruling out MI early on, with a negative predictive value greater than 99%. Moreover, the relative change in concentration within the 3 hours after admission, combined with the 99th percentile diagnostic cutoff value on admission, improves specificity, allowing acute MI to be accurately ruled in.<sup>36</sup>

Of note, though studies have confirmed that a measurement at 3 hours identifies most cases of MI early, they have not used the recommended maximal sensitivity interval for troponin measurements (6 hours or more).<sup>6</sup>

**A proposed algorithm for diagnosing acute MI with a high-sensitivity assay**

While high-sensitivity troponin T assays can improve the early diagnosis of acute MI, how best to use them is yet to be defined. They still lack specificity for acute coronary syndromes, with positive predictive values as low as 50%.<sup>37</sup>

Reichlin et al<sup>38</sup> developed and validated an algorithm for rapidly ruling out or ruling in acute MI using a high-sensitivity cardiac troponin T assay, incorporating baseline values and absolute changes within the first hour. Using a baseline threshold of 12 ng/L or less and an absolute change of 3 ng/L or less, they found a sensitivity and negative predictive value of 100%, making these good criteria for ruling out acute MI.

Using a baseline threshold of 60 ng/L or greater and a change from baseline to 1 hour of at least 15 ng/L, the specificity was 97% and the positive predictive value was 84%, making these good criteria for ruling in acute MI.

Patients whose values were in between were classified as being in an “observational-zone group,” in which the prevalence of acute MI was 8%. The cumulative 30-day survival rate was 99.8% in patients in whom the test ruled out MI, 98.6% in the observational-zone patients, and 95.3% in patients in whom the test ruled in MI.<sup>38</sup> Using this simple algorithm allowed a safe rule-out as well as an accurate rule-in of acute MI within 1 hour in 77% of unselected patients with acute chest pain; thus, it may obviate the need for prolonged monitoring and serial measurements in three out of four patients.”

Newby<sup>39</sup> stated that such an algorithmic approach must be validated in a prospective study that assesses not only sensitivity, negative predictive value, specificity, and positive predictive value, but also the implications for clinical outcomes and the cost of widespread implementation.

In the meantime, clinicians must keep in mind that patient populations in clinical practice are less selected, the prevalence of MI may

**Brain-type natriuretic peptide appears useful for prognosis in acute chest pain but not for the diagnosis of acute coronary syndromes**

broadly vary, and confounding comorbidities such as heart failure and renal insufficiency are more common. Studies are also needed to verify whether other factors such as age, sex, and time from symptom onset should be considered.

### ■ BRAIN-TYPE NATRIURETIC PEPTIDE

BNP is a 32-amino-acid natriuretic peptide that is released from myocytes. The amount released depends on wall stress brought on by heart failure, ischemic heart disease, or other conditions.

In a study of the diagnostic utility of BNP in the workup of acute chest pain, Haaf et al<sup>40</sup> found that BNP levels at presentation were significantly higher in patients with acute MI than in patients with other diagnoses. However, the diagnostic accuracy of BNP was lower than that of cardiac troponin T at presentation, though its independent predictive value for all-cause mortality was more accurate than that of troponin T.

Elevation of the BNP<sup>41</sup> or the N-terminal pro-BNP<sup>42,43</sup> level was shown to also provide unique prognostic information in patients with suspected and confirmed acute coronary syndrome and was associated with higher rates of short-term and long-term mortality. Therefore, BNP appears useful for the prognosis but not the diagnosis of acute coronary syndromes.

### ■ CYSTATIN C

The protein cystatin C, widely used as a biomarker for kidney disease, has more recently been touted as a prognostic marker in acute coronary syndromes.

Jernberg et al<sup>44</sup> reported that, in patients with a suspected or confirmed acute coronary syndrome, a single measurement of cystatin C significantly improved the early stratification of risk.<sup>44</sup> Specifically, the cystatin C level was independently associated with mortality risk but not with the risk of subsequent MI.

In another study,<sup>45</sup> the cystatin C concentration independently predicted the risk of cardiovascular death or MI in non-ST-segment elevation acute coronary syndrome. However, the additive predictive value of cystatin C in these patients was found to be small when

clinical risk factors and biomarkers of MI were used in the prediction model. Therefore, cystatin C may predict global risk but does not appear to be useful in diagnosing MI.

### ■ ISCHEMIA-MODIFIED ALBUMIN

A major limitation of troponin is that it cannot detect reversible myocardial ischemia in the absence of cardiac necrosis, making stress testing necessary to unmask potential reversible ischemia.

Ischemia-modified albumin has been proposed as a means of detecting cardiac ischemia even if necrosis is absent. It is a product of the N-terminus alteration of albumin caused by myocardial ischemia, which reduces the ability of cobalt to bind to albumin and can be detected with the albumin cobalt binding test. This marker might have a high negative predictive value, ruling out acute coronary syndromes in conditions of low pretest probability with negative necrosis markers and ECG.<sup>13,46</sup>

Although ischemia-modified albumin does show promise, doubt remains as to its validity as a biomarker, as its mechanism of generation is not known. Some have suggested that it is in fact a marker of oxidative stress.<sup>47</sup>

### ■ PANELS OF MARKERS

The individual biomarkers we have discussed here have advantages and limitations in the emergency workup of chest pain. The concept of using a multimarker panel has been raised as a way of amplifying the positive attributes of individual biomarkers and compensating for their shortcomings.

Sabatine et al<sup>48</sup> tested this approach in patients with acute coronary syndromes who were at high risk of an adverse outcome. When patients were categorized at presentation on the basis of the number of elevated biomarkers such as cardiac troponin I, C-reactive protein, and BNP, the risk of death nearly doubled with each additional biomarker that was elevated.

The relationship was similar for the end points of MI, heart failure, and the composite at 30 days and 10 months. In a cohort of 1,635 patients, the number of elevated biomarkers remained a predictor of the composite end point after adjustment for known clinical pre-

**In one study, the risk of death nearly doubled with each additional biomarker that was elevated**

dictors. The risk of death, MI, or heart failure by 6 months was 2.1 times higher in patients with one elevated biomarker, 3.1 times higher in those with two, and 3.7 times higher in those with three.

The authors concluded that a multimarker strategy that categorizes patients on the basis of the number of elevated biomarkers at presentation allows risk-stratification of short- and long-term cardiac events.

**Tello-Montoliu et al**<sup>49</sup> tested this idea in patients with non-ST-segment elevation acute coronary syndromes using a panel consisting of cardiac troponin T, C-reactive protein, N-terminal pro-BNP, and fibrin D-dimer. The risk of a major event (death, new acute coronary syndrome, revascularization, or heart failure) at 6 months was associated with abnormal biomarker levels, especially with the presence of three positive biomarkers, even after adjustment for clinical characteristics and ECG findings.

**van der Zee et al**<sup>43</sup> showed that a positive biomarker panel consisting of C-reactive protein and N-terminal pro-BNP identified patients with chest pain and a normal or nondiagnostic ECG who have a high long-term risk of cardiovascular death.

**Glaser et al**<sup>50</sup> evaluated the combination of cardiac troponin I, BNP, homocysteine, C-reactive protein, placental growth factor, myeloperoxidase, choline, soluble CD40 ligand, ischemia-modified albumin, and lipoprotein-associated phospholipase A2 in patients with a suspected acute coronary syndrome. The combination of BNP, placental growth factor, and estimated glomerular filtration rate was the most accurate predictor of major adverse cardiovascular events compared with any other biomarker or clinical factor. With appropriate cutoff values, the negative predictive value for a major adverse cardiovascular event at 1 year was as high as 99.1%.

This study highlighted the importance of combining biomarkers, showing that with a negative predictive value of 97% for 30-day events, the combination of placental growth factor, BNP, and cardiac troponin I may help surmount the delay from symptom onset to cardiac troponin increase, thus permitting a more timely diagnosis and safe discharge within 12 hours.

**Comment.** These studies raise the promise that panels of biomarkers can be used in patients deemed to be at low risk after clinical assessment and troponin evaluation to enable them to be safely discharged early and to obviate the need for stress testing.

If we assume that unstable cardiac disease requiring hospitalization accounts for 35% of patients with chest pain, a hypothetical panel of biomarkers with a sensitivity and specificity of 95% for adverse cardiac outcomes would have a positive predictive value of 91% and a negative predictive value of 97%. The negative likelihood ratio of this hypothetical biomarker panel would be 0.05, while the positive likelihood ratio would be 19. This performance level means that in patients with a pretest probability less than 50%, the post-test probability can be reduced to below 10%, so that such patients can be safely discharged without further hospital evaluation.

Conversely, a positive test result in patients with pretest probability of 30% or greater raises the posttest probability to nearly 90%, meaning that such patients should be considered for aggressive intervention without the need for stress testing.

## ■ RETURN TO OUR SCENARIOS

Chest pain remains a nonspecific complaint, and the interpretation of biomarkers to find the cause presents clinicians with challenges, as illustrated by the cases introduced at the beginning of this article.

The cardiac troponin I elevation in scenario 1 led to an initial diagnosis of unstable angina. However, coronary angiography showed lesion-free coronary arteries, thus excluding ischemic heart disease. When other diseases that could cause elevated cardiac troponin I were considered and investigated with further diagnostic tests such as D-dimer, pulmonary embolism became the new working diagnosis, and this was confirmed by CT angiography.

Similarly, given the laboratory values for the patient in scenario 2, the condition could have been mistaken for an acute coronary syndrome. However, the absence of evidence on ECG to support this diagnosis would indicate an erroneously elevated biomarker secondary to his background of chronic renal insufficiency. ■

**Chest pain remains a nonspecific complaint, and the interpretation of biomarkers to find the cause presents clinicians with challenges**



## REFERENCES

- Pitts SR, Niska RW, Xu J, Burt CW. National hospital ambulatory medical care survey: 2006 emergency department summary. *Natl Health Stat Report* 2008; 1–38.
- Vucic R, Knezevic S, Lazic Z, et al. Elevation of troponin values in differential diagnosis of chest pain in view of pulmonary thromboembolism. *Vojnosanit Pregl* 2012; 69:913–916.
- Croitoru M, Taegtmeier H. Spurious rises in troponin T in end-stage renal disease. *Lancet* 1995; 346:974.
- Anderson JL, Adams CD, Antman EM, et al; 2011 Writing Group Members; ACCF/AHA Task Force Members. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; 123:e426–e579.
- Unstable angina: diagnosis and management. Guideline overview. Agency for Health Care Policy and Research. *J Natl Med Assoc* 1994; 86:649, 710–712.
- Morrow DA, Cannon CP, Jesse RL, et al; National Academy of Clinical Biochemistry. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation* 2007; 115:e356–e375.
- Hamm CW, Goldmann BU, Heeschen C, Kreyman G, Berger J, Meinerz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997; 337:1648–1653.
- Heidenreich PA, Go A, Melsop KA, et al. Prediction of risk for patients with unstable angina. *Evid Rep Technol Assess (Summ)* 2000; August: 1–3.
- Kontos MC, Fritz LM, Anderson FP, Tatum JL, Ornato JP, Jesse RL. Impact of the troponin standard on the prevalence of acute myocardial infarction. *Am Heart J* 2003; 146:446–452.
- Amit G, Gilutz H, Cafri C, Wolak A, Ilia R, Zahger D. What have the new definition of acute myocardial infarction and the introduction of troponin measurement done to the coronary care unit? Impacts on admission rate, length of stay, case mix and mortality. *Cardiology* 2004; 102:171–176.
- Alcalai R, Planer D, Culhaoglu A, Osman A, Pollak A, Lotan C. Acute coronary syndrome vs nonspecific troponin elevation: clinical predictors and survival analysis. *Arch Intern Med* 2007; 167:276–281.
- Thygesen K, Mair J, Katus H, et al; Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010; 31:2197–2204.
- Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol* 2006; 48:1–11.
- Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994; 271:703–707.
- McDonald MA, Holroyd B, Comeau A, Hervas-Malo M, Welsh RC. Clinical risk scoring beyond initial troponin values: results from a large, prospective, unselected acute chest pain population. *Can J Cardiol* 2007; 23:287–292.
- Than M, Cullen L, Reid CM, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. *Lancet* 2011; 377:1077–1084.
- Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. The rational clinical examination. Is this patient having a myocardial infarction? *JAMA* 1998; 280:1256–1263.
- Amsterdam EA, Kirk JD, Bluemke DA, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Cardiovascular Nursing, and Interdisciplinary Council on Quality of Care and Outcomes Research. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation* 2010; 122:1756–1776.
- Farkouh ME, Aneja A, Reeder GS, et al. Clinical risk stratification in the emergency department predicts long-term cardiovascular outcomes in a population-based cohort presenting with acute chest pain: primary results of the Olmsted county chest pain study. *Medicine (Baltimore)* 2009; 88:307–313.
- Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med* 1996; 335:1333–1341.
- Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; 335:1342–1349.
- Sanchis J, Bodi V, Llacer A, et al. Predictors of short-term outcome in acute chest pain without ST-segment elevation. *Int J Cardiol* 2003; 92:193–199.
- Gomez MA, Anderson JL, Karagounis LA, Muhlestein JB, Moores FB. An emergency department-based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: results of a randomized study (ROMIO). *J Am Coll Cardiol* 1996; 28:25–33.
- Diercks DB, Gibler WB, Liu T, Sayre MR, Storrow AB. Identification of patients at risk by graded exercise testing in an emergency department chest pain center. *Am J Cardiol* 2000; 86:289–292.
- Rahman F, Mitra B, Cameron PA, Coleridge J. Stress testing before discharge is not required for patients with low and intermediate risk of acute coronary syndrome after emergency department short stay assessment. *Emerg Med Australas* 2010; 22:449–456.
- Kontos MC, Anderson FP, Alimard R, Ornato JP, Tatum JL, Jesse RL. Ability of troponin I to predict cardiac events in patients admitted from the emergency department. *J Am Coll Cardiol* 2000; 36:1818–1823.
- Hoffmann U, Truong QA, Schoenfeld DA, et al; ROMICAT-II Investigators. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med* 2012; 367:299–308.
- Hoffmann U, Bamberg F, Chae CU, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol* 2009; 53:1642–1650.
- Goldstein JA, Chinnaiyan KM, Abidov A, et al; CT-STAT Investigators. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol* 2011; 58:1414–1422.
- White CS, Kuo D, Kelemen M, et al. Chest pain evaluation in the emergency department: can MDCT provide a comprehensive evaluation? *AJR Am J Roentgenol* 2005; 185:533–540.
- Redberg RF. Coronary CT angiography for acute chest pain. *N Engl J Med* 2012; 367:375–376.
- Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. *JAMA* 2011; 306:2128–2136.
- Aldous S, Pemberton C, Richards AM, Troughton R, Than M. High-sensitivity troponin T for early rule-out of myocardial infarction in recent onset chest pain. *Emerg Med J* 2012; 29:805–810.
- Weber M, Bazzino O, Navarro Estrada JL, et al. Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. *Am Heart J* 2011; 162:81–88.
- 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; 57:1318–1326.
- Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA* 2011; 306:2684–2693.
- Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009; 361:858–867.
- Reichlin T, Schindler C, Drexler B, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med* 2012; 172:1211–1218.

39. **Newby LK.** Myocardial infarction rule-out in the emergency department: are high-sensitivity troponins the answer?: Comment on "One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T". *Arch Intern Med* 2012; 172:1218–1219.
40. **Haaf P, Reichlin T, Corson N, et al.** B-type natriuretic peptide in the early diagnosis and risk stratification of acute chest pain. *Am J Med* 2011; 124:444–445.
41. **Sun T, Wang L, Zhang Y.** Prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *Arch Med Res* 2006; 37:502–505.
42. **Galvani M, Ottani F, Oltrona L, et al; Italian Working Group on Atherosclerosis, Thrombosis, and Vascular Biology and the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO).** N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation* 2004; 110:128–134.
43. **van der Zee PM, Cornel JH, Bholasingh R, Fischer JC, van Straalen JP, De Winter RJ.** N-terminal pro B-type natriuretic peptide identifies patients with chest pain at high long-term cardiovascular risk. *Am J Med* 2011; 124:961–969.
44. **Jernberg T, Lindahl B, James S, Larsson A, Hansson LO, Wallentin L.** Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. *Circulation* 2004; 110:2342–2348.
45. **Akerblom Å, Wallentin L, Siegbahn A, et al.** Cystatin C and estimated glomerular filtration rate as predictors for adverse outcome in patients with ST-elevation and non-ST-elevation acute coronary syndromes: results from the Platelet Inhibition and Patient Outcomes study. *Clin Chem* 2012; 58:190–199.
46. **Anwaruddin S, Januzzi JL Jr, Baggish AL, Lewandrowski EL, Lewandrowski KB.** Ischemia-modified albumin improves the usefulness of standard cardiac biomarkers for the diagnosis of myocardial ischemia in the emergency department setting. *Am J Clin Pathol* 2005; 123:140–145.
47. **Senes M, Kazan N, Coskun O, Zengi O, Inan L, Yücel D.** Oxidative and nitrosative stress in acute ischaemic stroke. *Ann Clin Biochem* 2007; 44:43–47.
48. **Sabatine MS, Morrow DA, de Lemos JA, et al.** Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation* 2002; 105:1760–1763.
49. **Tello-Montoliu A, Marín F, Roldán V, et al.** A multimarker risk stratification approach to non-ST elevation acute coronary syndrome: implications of troponin T, CRP, NT pro-BNP and fibrin D-dimer levels. *J Intern Med* 2007; 262:651–658.
50. **Glaser R, Peacock WF, Wu AH, Muller R, Möckel M, Apple FS.** Placental growth factor and B-type natriuretic peptide as independent predictors of risk from a multibiomarker panel in suspected acute coronary syndrome (Acute Risk and Related Outcomes Assessed With Cardiac Biomarkers [ARROW]) study. *Am J Cardiol* 2011; 107:821–826.

---

**ADDRESS:** Michael Farkouh, MD, MSc, Department of Medicine, University of Toronto, Toronto General Hospital, 585 University Avenue, 4N474, Toronto, ON M5G 2N2, Canada; e-mail: michael.farkouh@uhn.ca