# Evaluation of Chest Pain and Heart Failure in the Emergency Department: Impact of Multimarker Strategies and B-Type Natriuretic Peptide

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*In the emergency setting, acute chest pain and shortness of breath represent common patient presentations. Cardiac biomarkers including myoglobin, creatine kinase (CK)-MB, troponin, and b-type natriuretic peptide provide diagnostic and prognostic information for patients with chest pain and shortness of breath. This article reviews the use of cardiac biomarkers in the emergency department to evaluate acute coronary syndrome and congestive heart failure.*

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**Key words:** Chest pain • Congestive heart failure • Creatine kinase-MB • B-type natriuretic peptide • Dyspnea • Troponin

Nearly 8 million patients with chest pain are evaluated each year in emergency departments (EDs) across the United States. Approximately 4 million of these individuals are admitted to inpatient units for further evaluation and treatment, but only 30% of these admitted patients ultimately will have the diagnosis of acute coronary syndrome (ACS). Previously, the initial evaluation of patients with chest discomfort presenting to the ED involved the

triad of history, physical examination, and the 12-lead electrocardiogram (ECG). Over the last decade, substantial evidence has demonstrated that a fourth element, cardiac biomarkers, serves as a valuable aid in not only determining initial diagnosis, but also providing risk stratification and dictating initial patient treatment in chest-discomfort presentations.

Chest pain units using serial biomarker determinations have been successful in a timely and cost-efficient manner in identifying patients with ACS who are at risk for adverse cardiac events. New point-of-care-testing for cardiac biomarkers at the patient's bedside allows for rapid determination, within 15 to 20 minutes after the sample is drawn.

Patients presenting with shortness of breath and possible congestive heart failure (CHF) also represent a significant challenge for emergency physicians. In the United States, over 500,000 new cases of CHF are diagnosed each year, with 1 million hospital discharges for this disease process. Patients with new cases of CHF and those with uncompensated disease both frequent EDs. Objective measures of cardiac dysfunction in CHF can improve the ability of emergency clinicians to diagnose and treat this common disease. B-type natriuretic peptide (BNP) measurement in patients presenting to the ED with shortness of breath represents an important new approach to evaluating these patients in the acute care setting.

This article will review the use of cardiac biomarkers in patients presenting to the ED with chest discomfort and possible ACS as well as shortness of breath and possible CHF, focusing on the use of such biomarkers for the risk stratification and initial treatment of these patients in the emergency setting.

## Cardiac Biomarkers in Risk Stratification of Chest Pain

Most previous chest-pain evaluation approaches in the ED have concentrated on ruling out myocardial infarction (MI). These evaluation protocols have been followed only to have patients released from the ED and later suffer an adverse cardiac event. ST-segment–elevation infarction represents an extreme manifestation of the condition now known as ACS. ACS encompasses the continuum from unstable angina through infarction and represents those patients at highest risk. The goal of the emergency physician is not just to identify patients with myocardial necrosis, but to rule out ACS and rule out the need for additional treatment using a combination of history, physical examination, a 12-lead ECG, and cardiac biomarkers.

Three cardiac biomarkers are readily available for routine use in the ED for the evaluation of chest discomfort: myoglobin, creatine kinase (CK)/CK-MB, and the cardiac troponins (cTns), cTnI and cTnT. Each of these biomarkers has well-known kinetics and should be carefully applied to each patient as directed by the onset of symptoms and presentation.[2] Myoglobin has been touted as an early biomarker with a high negative predictive value and low specificity. CK and its isoenzyme CK-MB represent the "gold standard" for the diagnosis of MI as currently defined by the World Health Organization criteria. The troponins are highly specific biomarkers that have proved valuable not only in the diagnosis of myocardial necrosis[1,2,13] but also in risk stratification in a variety of patient populations.

Initial studies on the risk-stratification utility of the troponins were performed on high-risk patients with known ACS, typical unstable angina with normal levels of CK-MB. Patients with elevated baseline cTnT levels in two studies had three to four times higher mortality than ACS patients with normal values (Figure 1).[4,5] A similar study using cTnI in ACS patients showed a statistically significant increase in mortality among those patients with levels greater than 0.4 ng/mL.[6] A meta-analysis of studies of high-risk patients performed by Wu and Lane[7] showed that the cumulative odds ratio of a positive cTnT for the development of acute MI or death in the follow-up period, defined as hospital discharge to 34 months, was 4.3 (95% CI, 2.8-6.8). Similarly, in the same analysis, the cumulative odds ratio of a positive cTnT for predicting need for cardiac revascularization within the same follow-up period was 4.4 (95% CI, 3.0-6.5). Another comprehensive meta-analysis involving over 18,000 patients in 21 ACS studies found that troponin-positive patients had an odds ratio of 3.44 for death or MI at 30 days. Additionally, troponin-positive patients without ST-segment elevation and patients with unstable angina carried odds ratios of 4.93 and 9.39 for adverse cardiac outcomes, respectively.[8]

Additional studies not represented in these meta-analyses include one by the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-II investigators comparing cTnT and cTnI in short-term risk stratification of ACS patients. In this model comparing the troponins collected within 3.5 hours of ischemic symptoms, Ohman and colleagues found that cTnT showed a greater association with 30-day mortality (chi square = 18.0, $P < .0001$) than cTnI (chi square = 12.5, $P = .0002$).[9] These authors concluded that cTnT is a strong, independent predictor of short-term outcome in ACS patients, and that serial levels were

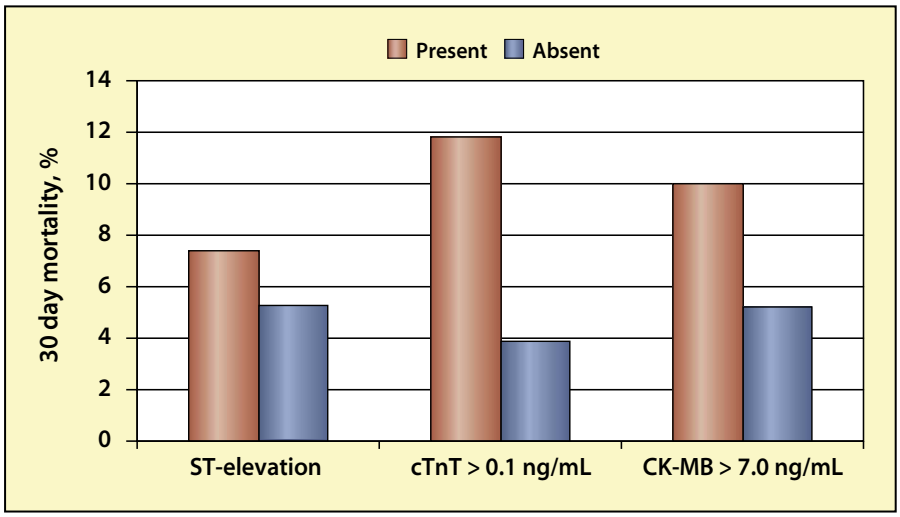


**Figure 1.** *Thirty-day mortality in Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa for patients with ST-segment elevation, troponin T (cTnT) elevation, and creatine-kinase (CK)-MB elevation.*

useful in determining the risk of adverse cardiac events.[10] While considerable effort has been made to determine the "better" troponin, most larger studies and analyses have determined that cTnI and cTnT both identify patients at risk for poor outcomes.[11]

Several studies have examined the value of cardiac markers in the risk stratification of heterogeneous patients with chest pain presenting to the ED. In a multicenter study of over 5000 patients in 53 EDs, the relative risk of ischemic complications and death for ED patients with positive CK-MB at 0 or 2 hours was 16.1 and 25.4, respectively.[12] Benamer and colleagues[13] compared the prognostic value of cTnI and C-reactive protein (CRP) in patients with unstable angina. They found that while 23% of patients with elevated cTnI had major in-hospital cardiac events, there was no such relation with CRP. Johnson and associates[3] studied a heterogeneous patient population admitted to an urban teaching hospital and found that cTnT was elevated in 31% of patients without MI who had major cardiovascular complications compared with 17% and 3% for CK-MB activity and mass, respectively.

Other authors have found that while patients with positive troponin levels are at higher risk for adverse cardiac events, the test in isolation lacks sensitivity. Polanczyk and colleagues[14] demonstrated that peak cTnI levels greater than 0.4 ng/mL were associated with a 47% sensitivity and an 80% specificity for a major cardiac event within 72 hours of presentation and that cTnI outperformed CK-MB in predicting major cardiac events among patients without MI. Similarly, Kontos and coworkers[15] found that while cTnI-positive patients were more likely than cTnI-negative patients to have significant complications (43% versus 12%), the sensitivity for this end point was low (14%).

In a similar chest pain unit population, Newby and associates[16] determined that more cTnT-positive patients than cTnT-negative patients had angiographically significant lesions (89% vs 49%) and positive stress testing (46% vs 14%). Long-term mortality was also higher in cTnT-positive patients (27% vs 7%).

## Cardiac Markers in Chest Pain Units and ED Evaluation Protocols

Chest pain units have proved to be efficient and cost effective for the evaluation of patients with low- to moderate-risk chest pain in the ED.[17] Many chest pain units and ED chest-pain–evaluation protocols use a system of cardiac marker determination combined with serial ECG determination, perfusion imaging, or provocative testing. Ideally, a chest pain unit will evaluate patients for myocardial necrosis, rest ischemia, and exercise-induced ischemia during the protocol.

The ideal chest-pain–evaluation protocol is different for each institution and chest pain population. Resource availability, physician preference, and patient volume all factor into this decision. Numerous studies have examined accelerated cardiac-marker regimens as an alternative to standard 18-hour rule-out protocols. One study found that a combination of carbonic anhydrase III and serum myoglobin was more sensitive than, and as specific as, CK-MB in patients presenting within 3 hours of symptom onset.[18] Similarly, serial myoglobin levels were 93% sensitive and 79% specific in detecting MI in patients within 2 hours of

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arrival.[19] Serial CK-MB results have also proved to be sensitive in MI detection when collected at 0 and 3 hours after ED presentation. Young and colleagues[20] found a 93% sensitivity and 95% specificity when combining CK-MB levels at 0 and 3 hours and net change in CK-MB level over the 3 hours. As expected, this sensitivity improved with increased time from symptom onset. Serial marker measurements and comparison of marker elevation over 3 to 6 hours also improved sensitivity for MI.[21-23] Specific marker regimens should be tailored to meet the objectives of diagnosing myocardial necrosis and providing risk stratification in the emergency setting.

## Cardiac Markers and Treatment

Recent investigation with cardiac markers suggests that not only are markers important for diagnosis and risk stratification, they also identify patients with ACS who will benefit from antiplatelet and antithrombotic pharmacologic management.

The Fragmin During Instability in Coronary Artery Disease (FRISC) study group determined that cTnT elevation identified a subgroup of patients who improved with prolonged antithrombotic treatment with dalteparin. Dalteparin significantly reduced short-term incidence of death or MI in patients with a positive cTnT from 6.0% to 2.5% ($P < .05$) as compared with a nonsignificant decrease from 2.4% to 0% in patients with normal levels of cTnT ($P = .12$). The incidence of death and MI in cTnT-positive patients at 40 days was 14.2% and 7.4% in the placebo and dalteparin treatment groups, respectively. There was no difference in long-term outcome in the troponin-negative patients.[24]

Platelet glycoprotein IIb/IIIa receptor antagonists are used in patients with ACS and those patients undergoing elective and emergent percutaneous coronary intervention. Several important studies such as the Chimeric 7E3 AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), and Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) collaboratives have demonstrated significant benefit of glycoprotein receptor antagonists in the setting of ACS by reducing death, MI, and refractory ischemia.[25-27] Cardiac biomarkers, specifically the troponins, help to identify ACS patients who may benefit from these agents. The PURSUIT trial investigated 10,948 ACS patients without ST-segment elevation. Primary endpoints included death and nonfatal MI within 30 days. Patients randomized to receive eptifibitide exhibited a 1.5% absolute risk reduction. Importantly, even small increases in CK-MB, just above the upper limits of normal, were associated with significant mortality increases.[28] The PRISM study investigators showed that tirofiban lowered the risk of death (adjusted hazard ratio 0.25) and MI (0.37) at 30 days in cTnI-positive ACS patients undergoing medical management or coronary revascularization. No significant treatment effect was evident for cTnI-negative patients.[29] The CAPTURE investigators correlated angiographic findings such a visible thrombus, lesion severity, and Thrombolysis in Myocardial Infarction (TIMI) flow with cTnT to determine which patients might benefit from abciximab therapy. In this study of 853 patients, cTnT was a more powerful predictor of cardiac risk and efficacy of abciximab treatment than were either lesion characteristics or thrombus formation alone. The authors suggested that cTnT was a sensitive marker for identifying patients with unstable angina who would benefit from antiplatelet therapy.[30] In another analysis of patients with refractory unstable angina, the relative risk of death or nonfatal MI in patients with elevated cTnT levels treated with abciximab was 0.32 (95% CI, 0.14-0.62) compared with cTnT-negative patients.[31]

Using an analysis of data from the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network B (PARAGON B) GUSTO IIa troponin substudies, and the CHest pain Evaluation by Creatine Kinase-MB, Myoglobin, And Troponin I (CHECKMATE) studies, Rao and associates[32] evaluated

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**Framingham Criteria**

**Major criteria**
Paroxysmal nocturnal dyspnea
Orthopnea
Neck-vein distention
Rales
Cardiomegaly
Acute pulmonary edema
$S_3$ gallop
Increased venous pressure > 16 cm of water
Circulation time
Hepatogugular reflux

**Minor criteria**
Ankle edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity decreased one half from maximum
Heart rate 120 beats/min

**Major or minor criteria**
Weight loss 4.5 kg in 5 d in response to treatment

**Figure 2.** *Framingham criteria for congestive heart failure.*

isolated troponin elevations in a spectrum of patients having low- to high-risk presentations of chest pain. Adverse clinical events, defined as death and MI at 24 hours and 30 days, were greatest in patients with elevations of both CK-MB and troponin. Isolated troponin elevation carried a higher risk of adverse clinical events in both high- and low-risk patients than did CK-MB alone.

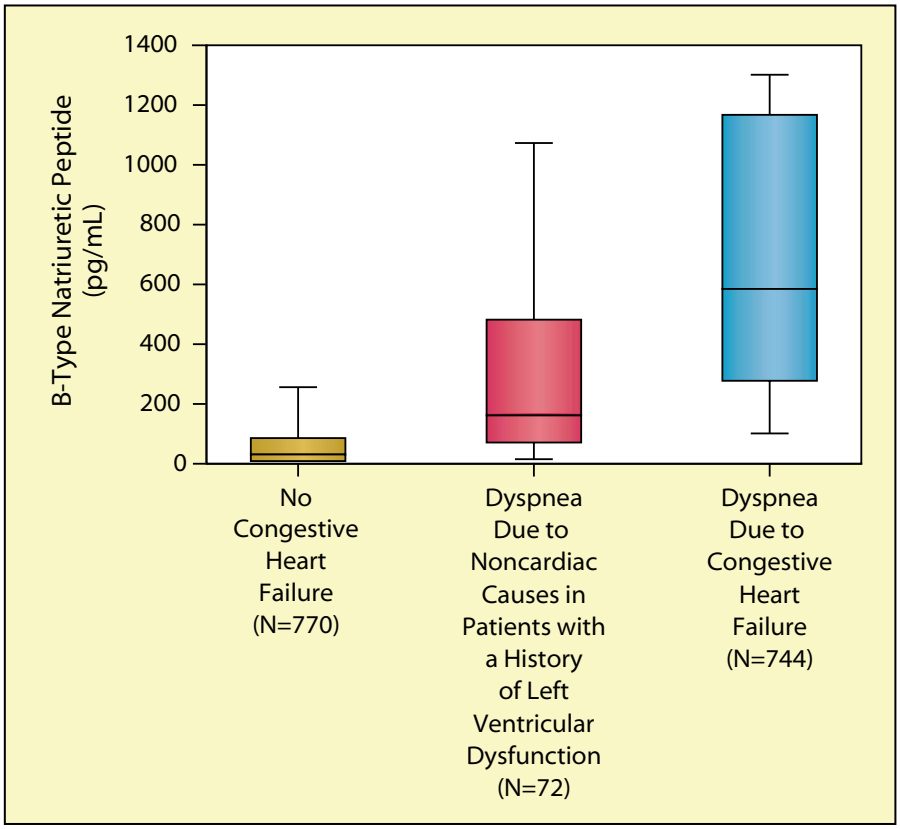
## Point-of-Care Testing

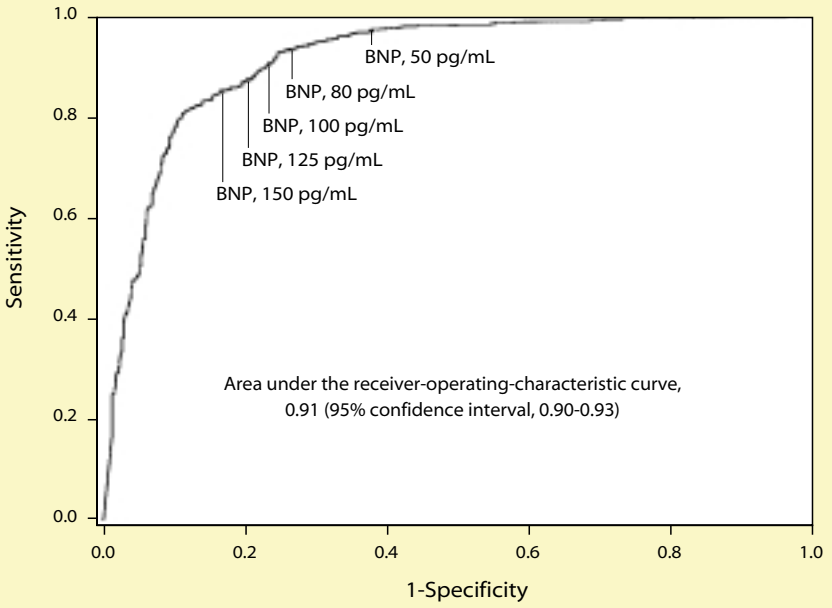
The important diagnostic and prognostic information of cardiac biomarkers of necrosis can now be obtained at bedside through point-of-care testing. In a substudy of TIMI IIA, Antman and colleagues[33] noted that within 14 days, 33.6% of patients with a positive bedside troponin T assay had an adverse clinical event, defined as death, nonfatal MI, or recurrent ischemia, as opposed to 22.5% in patients with a negative troponin T. In addition, length of hospital stay was 5 days in the troponin T–positive group versus 3 days in the troponin T–negative group. In a GUSTO III point-of-care substudy of over 12,000 patients receiving thrombolysis for acute ST-segment–elevation MI, Ohman and colleagues[34] reported that patients with bedside whole-blood elevation of troponin T had a 1 to 3 times higher incidence of death at 30 days. Finally, in a chest pain unit study, Newby and colleagues[35] observed that in 1005 patients with myoglobin, CK-MB, and troponin I measured over 24 hours, a bedside assay was more efficient than tests sent to a local laboratory at identifying patients at risk of 30-day mortality. Patients with a positive and negative baseline triple multimarker status determined at the bedside had an event rate of 18.8% and 3%, respectively, versus 13.6% and 5.5% when the tests were sent to the local laboratory.

## Congestive Heart Failure

As with the presentation of chest pain in the ED, shortness of breath is a common problem with severe potential consequences if appropriate diagnosis and treatment do not rapidly occur. In the recent past, CHF was diagnosed primarily on the basis of appropriate history and a physical exam consistent with cardiac dysfunction. In the emergency setting, evidence of increased ventricular filling pressures can include jugular venous distension and an S3 gallop. Lower-extremity edema and dyspnea can increase suspicion of CHF; however, these findings are not highly sensitive or specific. Chest radiography may reveal cardiomegaly

**Figure 3.** *Box plots showing median levels of b-type natriuretic peptide in three groups of emergency department patients. Boxes show interquartile range, and bars represent highest and lowest values. Adapted with permission from Maisel et al.[39] Copyright ©2002 Massachusetts Medical Society. All rights reserved.*






| BNP pg/mL | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value | Accuracy |
|---|---|---|---|---|---|
| | | (95 percent confidence interval) | | | |
| 50 | 97 (96-98) | 62 (59-66) | 71 (68-74) | 96 (94-97) | 79 |
| 80 | 93 (91-95) | 74 (70-77) | 77 (75-80) | 92 (89-94) | 83 |
| 100 | 90 (88-92) | 76 (73-79) | 79 (76-81) | 89 (87-91) | 83 |
| 125 | 87 (85-90) | 79 (76-82) | 80 (78-83) | 87 (84-89) | 83 |
| 150 | 85 (82-88) | 83 (80-85) | 83 (80-85) | 85 (83-88) | 84 |

**Figure 4.** *Receiver operating characteristic curve for various cut-off levels of b-type natriuretic peptide (BNP) in the Breathing Not Properly study of shortness of breath in the emergency department. Adapted with permission from Maisel et al.[39] Copyright ©2002 Massachusetts Medical Society. All rights reserved.*

and pulmonary congestion but remains unreliable. The electrocardiographic findings of anterior Q-waves and left bundle-branch block can also be present in patients with CHF. These various historical and physical examination elements are combined in the 1971 Framingham Criteria (Figure 2).[36]

## Diagnosis

The use of BNP in the evaluation of patients with shortness of breath in the ED can provide objective information to allow the clinician to help differentiate CHF from other causes of dyspnea. Initially isolated from the brain, BNP is secreted primarily from ventricular myocardium in response to the abnormal intraluminal pressure and stretching of the myocardial wall due to heart failure.[37] The impact of BNP use in the emergency setting was recently comprehensively reviewed.[38]

In the Breathing Not Properly Multinational Study, Maisel and colleagues[39] evaluated BNP in a large cohort of patients presenting to the ED with shortness of breath. Of 1586 patients from 5 centers in the United States, 1 in Norway, and 1 in France, 744 patients were given the diagnosis of CHF. In this trial, patients with a confirmed diagnosis of CHF had average BNP levels of 675 ± 450 pg/mL, whereas those individuals having shortness of breath due to other causes had mean BNP levels of 110 ± 225 pg/mL. Median BNP levels for these patients are shown in Figure 3. Left ventricular dysfunction without CHF exacerbation in 72 patients caused intermediate elevation of BNP (346 ± 390 pg/mL). Using a 100 pg/mL cut-off developed from a receiver operating characteristic curve, BNP had improved accuracy (83%) compared to the National Health and Nutrition Examination Survey (67%) and the Framingham Criteria (73%) in differentiating CHF from non-CHF causes of shortness of breath (Figure 4). BNP was the strongest predictor of CHF in the Breathing Not Properly study by multivariate analyses with an odds ratio of 29.6 (95% CI, 17.75-49.37).

The use of BNP measurements has improved the diagnostic capabilities of emergency physicians. McCullough and associates[40] found that levels of BNP above 100 pg/mL improved diagnostic accuracy over clinical judgment alone (74%–81.5%) for patients with a high probability of CHF (defined as 80%–100%). The BNP level was even more valuable in patients clinically considered at low risk for CHF by the emergency physician (<20% probability). Of 721 patients in this category, a cut-off level of 100 pg/mL would have correctly identified 90.2% of

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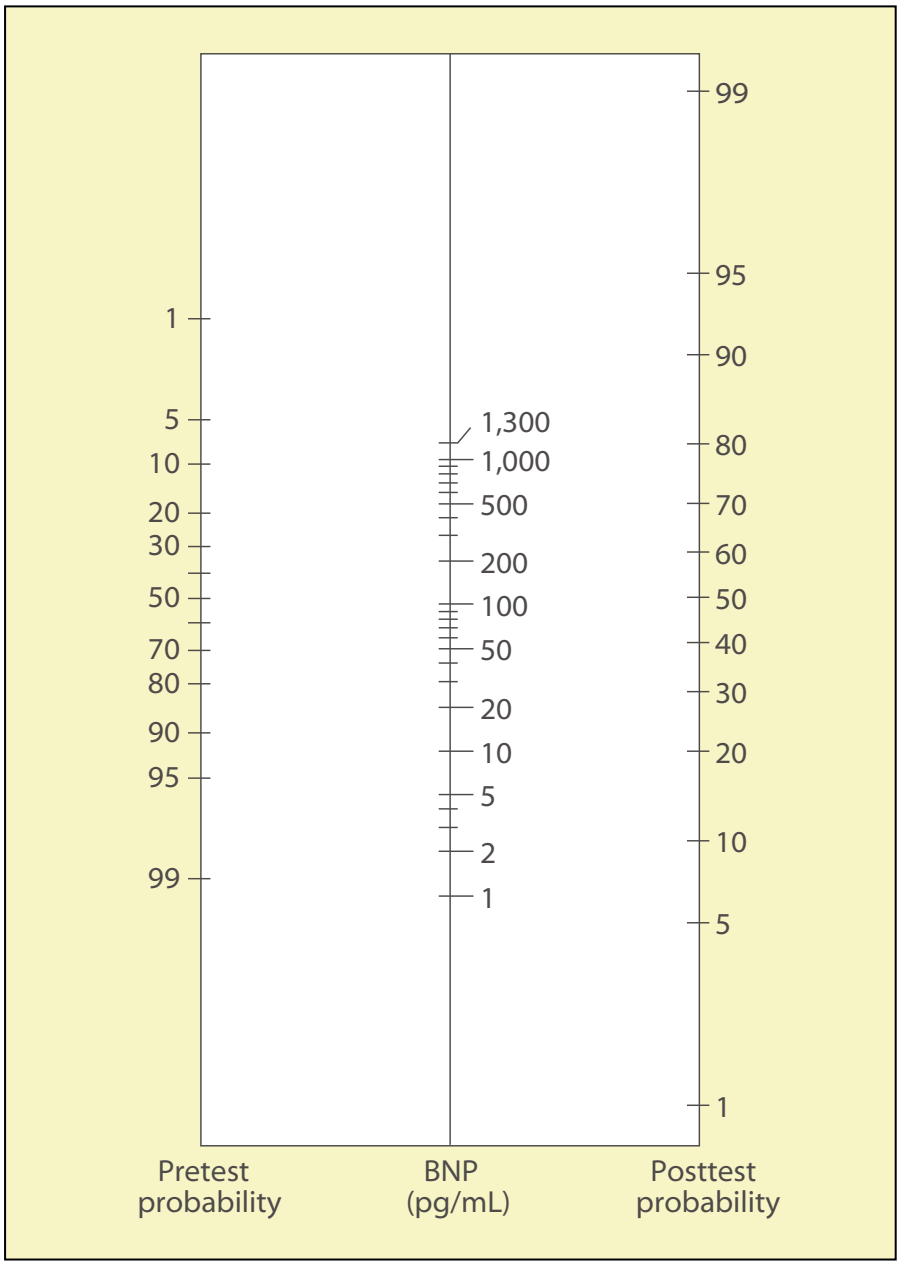


**Figure 5.** *Heart failure diagnosis nomogram. BNP, b-type natriuretic peptide.*

patients (111 of 123) ultimately found to have CHF as a cause of their presentation. A nomogram developed by the authors allows the clinician to use pretest likelihood and the BNP level to accurately identify the posttest likelihood of having CHF as a cause for the patient's presentation (Figure 5).

## Prognosis

The utility of BNP for prognosis in patients with CHF has also been evaluated. Harrison and colleagues[41] used a combined end point of death, hospital admission with a cardiac diagnosis, and recidivism for CHF to follow 325 patients from the ED for a 6-month period. An adverse-event rate of 51% was observed in 67 patients with a BNP level greater than 480 pg/mL, whereas a rate of 2.5% was seen in 205 patients with a BNP less than 230 pg/mL. In patients with BNP levels greater than 230 pg/mL, the relative risk of cardiac death within 6 months was 37.9 (95% CI, 5.7-755.8) and the relative risk of death due to CHF was 24.1 (95% CI, 3.5-491.1).

For patients with acute MI, BNP has proved to have prognostic abilities for identifying patients at high risk of remote death following infarction. In a substudy of the TIMI 16 trial, deLemos and associates[42] noted that BNP levels drawn at a mean of 40 ± 20 hours after symptom onset predicted increased mortality both at 30 days and 10 months. Elevated BNP levels of 137.9 to 1456.6 pg/mL increased the adjusted odds ratio for death to 5.8 (95% CI, 1.7-19.7) from 3.8 (95% CI, 1.1-13.3) when levels were 43.7 to 81.2 pg/mL. Using a multimarker strategy, Sabatine and colleagues[43] evaluated BNP with troponin I and CRP in TIMI 16 – Orofiban in Patients with Unstable Coronary Syndromes (OPUS) and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) – TIMI 18 for their ability to predict adverse events in patients presenting with ACS. Increasing the number of positive cardiac biomarkers proportionately increased the risk of death. In multivariate analyses, both BNP and troponin I proved independently predictive of the triple end point of death at 7 days, MI, or death at 6 months (BNP odds ratio = 1.6, $P = .019$; troponin I odds ratio = 2.1, $P = .001$).[44]

## Pulmonary Embolism

While multiple studies demonstrate that BNP levels have diagnostic and

prognostic implications for patients with CHF, BNP has also been evaluated in patients with pulmonary embolism. In a trial of 73 such patients with BNP measured within 4 hours of admission, Kucher and colleagues[45] found that 53 patients with benign clinical outcomes had a median BNP level of 131 pg/mL (range 16–34,802 pg/mL), whereas the patients with adverse clinical outcomes had a median level of 4250 (range 92–49,607 pg/mL; $P < .0001$). The authors suggested that patients with low BNP levels could be candidates for an abbreviated hospital stay. In another study, ten Wolde and colleagues[46] found that in 110 patients with pulmonary embolism, a BNP level greater than 21.7 pg/mL carried a 17% risk of death (95% CI, 6%-33%); a BNP value less than 21.7 pg/mL had a 99% negative predictive value for an uneventful course (95% CI, 93%-100%).

## Conclusion

The use of cardiac biomarkers including myoglobin, CK-MB, troponin, and BNP can provide important diagnostic and prognostic information for patients presenting to the ED with chest pain or shortness of breath. Point-of-care testing for these biomarkers allows appropriate therapy to be given to these often critically ill patients within minutes after presentation. ■

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## Main Points

- Chest pain and shortness of breath are common presentations in emergency departments, and cardiac biomarkers have become an important tool in determining diagnosis, providing risk stratification, and guiding treatment.
- Creatine kinase (CK) and its isoenzyme CK-MB represent the "gold standard" for the diagnosis of myocardial infarction as currently defined by the World Health Organization criteria.
- The cardiac troponins are highly specific biomarkers that have proved valuable in the diagnosis of myocardial necrosis and in risk stratification in a variety of patient populations, including high-risk patients with known acute coronary syndrome (ACS).
- The troponins have also identified patients with ACS who may benefit from antiplatelet and antithrombotic medications.
- B-type natriuretic peptide (BNP) has helped emergency-department physicians distinguish congestive heart failure from other causes in patients presenting with shortness of breath.
- Elevated BNP levels have been shown to predict both short- and long-term adverse events in patients with congestive heart failure and with pulmonary embolism.

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