Combining Natriuretic Peptides and Necrosis Markers in Determining Prognosis in Heart Failure

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Despite significant advances in medical therapy, patients with heart failure remain at increased risk of overall mortality, progressive ventricular dysfunction, and sudden cardiac death. Although a number of individual clinical and laboratory variables have been identified as being associated with increased mortality risk in heart failure, there remains a clear need for an integrated, accurate method of determining prognosis. Elevated plasma B-type natriuretic peptide (BNP) has been demonstrated to be a powerful marker for prognosis and risk stratification in the setting of heart failure. Patients with elevated BNP levels have been shown to be at significantly higher risk for heart failure admission or death, and higher BNP levels are associated with progressively worse prognosis. Although cardiac troponins are a well-established diagnostic and prognostic marker in acute coronary syndromes, emerging data suggest that cardiac troponins also provide independent prognostic information in heart failure. Detection of cardiac troponins in the serum of patients with heart failure has been shown to be associated with an impaired hemodynamic profile, progressive decline in left ventricular systolic function, and shortened survival. Combining a marker of myocyte injury—cardiac troponin—with BNP in a multimarker strategy appears to be a useful tool for improving risk assessment and triage in patients with heart failure. Heart failure patients with detectable cardiac troponin I and high BNP levels have been shown to have a 12-fold increased mortality risk compared with those with both undetectable cardiac troponin I and lower BNP. Integrating this multimarker approach into the routine assessment of heart failure patients will allow clinicians to more accurately identify high-risk patients who may derive increased benefit from intensive management strategies.
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Key words: B-type natriuretic peptide • Troponin • Heart failure

Heart failure (HF) is a significant cause of morbidity and mortality, with a current U.S. prevalence of 5 million and a 5-year survival near 50%.[1] More than 1 million patients are hospitalized with acutely decompensated HF, with as many as 50% of these patients being rehospitalized in the first

6 months after discharge. HF also results in a substantial burden on health care expenditures. It is estimated that in 2002, more than $24 billion was spent on the direct costs for the care of patients with HF.[1] Although considerable progress has been made in the pharmacologic management of patients with HF, many remain at increased risk of HF-mediated death. Although some patients have significant improvement in left ventricular function over time in response to HF medical therapy, other patients do not respond or have progressive left ventricular dysfunction. Newer therapeutic modalities, including cardiac resynchronization therapy, internal cardioverter-defibrillators, and left ventricular assist devices, have been increasingly utilized in attempts to further improve outcomes in patients with HF.[2] Heart transplantation has also been employed in selected patients, but severe limitations in donor supply make this therapy obtainable to fewer than 2500 patients a year.[1] Because devices are expensive and transplants are in such limited supply, there is strong incentive to determine the prognosis of patients with HF so that these limited and/or expensive therapies can be applied to the HF patients who would derive the greatest benefit. There exists a clear need to develop strategies to accurately identify those patients with HF who are at increased risk of mortality.[3] Reliable biomarkers to predict which patients are likely to have improvement in left ventricular systolic function and lower risk of mortality would be particularly helpful in managing HF.

In a recent study of patients with HF with left ventricular ejection fraction < 35%, plasma BNP levels >130 pg/mL were associated with a significantly higher risk of sudden cardiac death than were lower BNP levels.

Ideal Biomarkers for Heart Failure

An ideal biomarker for HF would be highly sensitive and specific, provide accurate prognostic information independent of other variables, and would be reproducible and standardized.[4] The coefficient of variation would be sufficiently low so that changes in the level of the biomarker reflect true changes in the clinical status of the patient. The assay would be relatively easy to perform and analyze so that the results are readily available to the clinician while the patient is still in the treatment area. The biomarker results would be applicable to patients with multiple HF etiologies, of all ages, both sexes, and all racial/ethnic backgrounds. In addition, changes in the level of the biomarker for HF would accurately reflect changes in the patient's clinical status, as well as changes in the patient's prognosis. With such a biomarker it would be expected that optimizing the level of the biomarker through changes in therapy would translate into improved clinical outcomes.

There exists a clear need to develop strategies to accurately identify those patients with HF who are at increased risk of mortality.

B-type Natriuretic Peptide and Prognosis

B-type natriuretic peptide (BNP) is a cardiac neurohormone that is synthesized in ventricular myocardium and released in response to increased ventricular wall stress.[5] Its diverse actions include arterial and venous vasodilation, natriuresis, inhibition of the renin-angiotensin-aldosterone system, and inhibition of sympathetic nerve activity. BNP acts through the natriuretic peptide receptors, which are transmembrane proteins containing an intracellular particulate guanylate cyclase domain.[5] BNP is produced in the form of a precursor, prepro-BNP, which is cleaved to pro-BNP and released into the blood, where it is finally processed into the 32–amino acid active form (BNP) and an inactive metabolite, N-terminal pro-BNP.[5] The most important stimulus for the synthesis of BNP in the heart is an increase in wall stress.[6] It is well established that circulating BNP levels are increased in patients with chronic HF in proportion to the severity of the disease and that the BNP assay can facilitate the diagnosis of HF. Elevated plasma BNP has also been shown to be a powerful marker for prognosis and risk stratification in the setting of HF and has many characteristics of an ideal biomarker for HF.[7]

A number of studies have demonstrated that the BNP assay provides independent prognostic information regarding clinical outcomes. Harrison and colleagues[8] followed 325 patients for 6 months after an index visit to the emergency department for dyspnea (Figure 1). The relative risk of 6-month HF admission or death in patients with BNP levels > 230 pg/mL was 24 times the risk of patients with levels < 230 pg/mL. Higher BNP levels were associated with a pro-

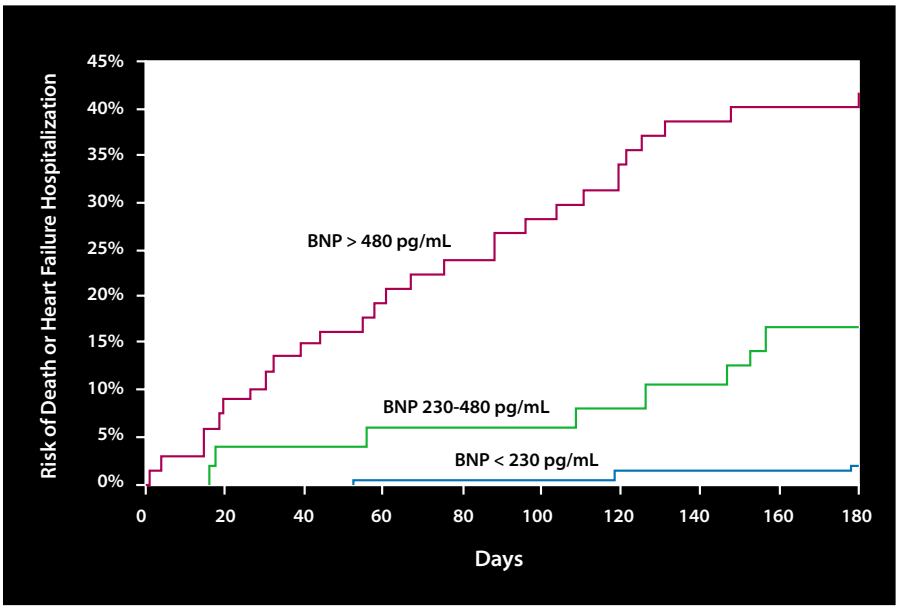
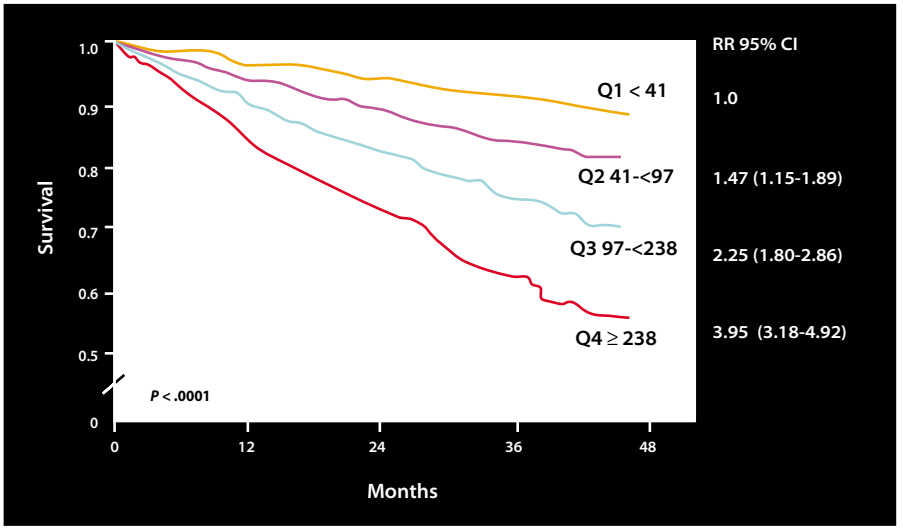


Figure 1. *Kaplan-Meier curves showing cumulative risk of any hospitalization or death from heart failure, stratified by B-type natriuretic peptide (BNP) levels at the time of initial visit to the emergency department. Higher BNP levels are associated with progressively worse prognosis. Patients with BNP levels > 480 pg/mL had a 6-month cumulative probability of 42% for heart failure hospital admission or death. Patients with BNP levels < 230 pg/mL had only a 2% risk of an event. Adapted with permission from Harrison et al.*[8]

gressively worse prognosis. Patients with BNP levels > 480 pg/mL had a 42% 6-month cumulative probability of HF admission or death. In a recent study of patients with HF with left ventricular ejection fraction (LVEF) < 35%, plasma BNP levels > 130 pg/mL were associated with a significantly higher risk of sudden cardiac death than were lower BNP levels.[9] It has also been shown that a significant elevation of BNP levels was associated with increased all-cause, cardiac, and pump-failure mortality rates.[10] The prognostic information provided by the BNP assay was shown to be as powerful in predicting functional deterioration as that derived from the Heart Failure Survival Score predictive model, which incorporates multiple clinical characteristics and peak oxygen consumption from cardiopulmonary exercise testing.[11] In a study of 72 patients admitted with decompensated HF, Cheng and colleagues[12] found that patients who had good outcomes were characterized by decrease in both New York Heart Association (NYHA) class and BNP levels during hospitalization, whereas patients who were readmitted within 30 days of discharge had only a minimal decrease in their BNP levels during hospitalization, despite improvement in NYHA classification. Subjects who died in the hospital were characterized by increasing BNP levels. Plasma BNP and norepinephrine were measured before randomization and during follow-up in 4300 patients in the Valsartan Heart Failure Trial.[13] BNP was demonstrated to be highly predictive of mortality or first morbid event (Figure 2). This study also showed that BNP is a more sensitive predictor than norepinephrine and that changes in BNP over time are associated with corresponding changes in subsequent mortality and morbidity. Morbidity and mortality were lowest in those patients with greatest decrease in BNP levels, whereas the morbidity and mortality were greatest in those patients with the greatest percent increase in BNP levels during the course of the trial (Figure 3).[13] Therefore, the degree of BNP elevation remains a powerful predictor of all-cause, pump-failure, and sudden death in HF patients, independent of extensive clinical and laboratory variables.

Figure 2. *Kaplan-Meier curves for all-cause mortality and first morbid event in subgroups by quartiles for B-type natriuretic peptide (BNP) in the Valsartan Heart Failure Trial (Val-HeFT). The baseline values for BNP in quartiles were <41, 41–<97, 97–<238, and ≥238 pg/mL. Adapted with permission from Anand et al.*[13]



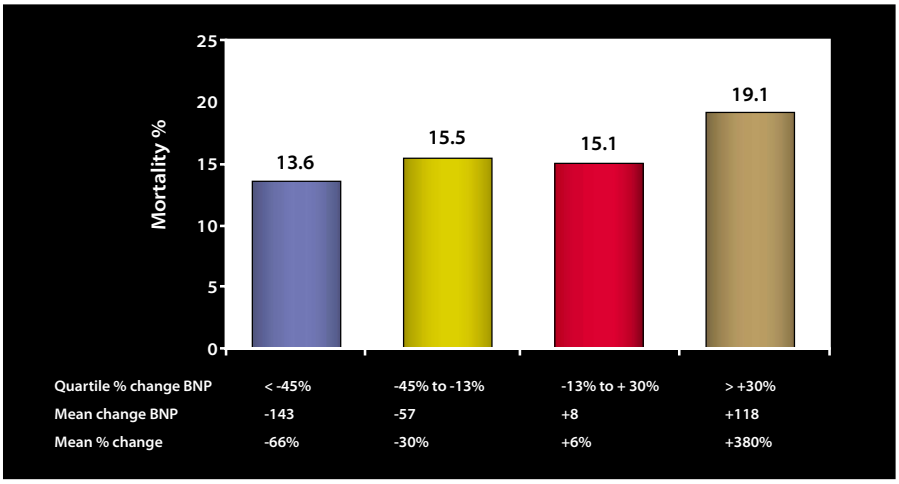


Figure 3. *Change in B-type natriuretic peptide (BNP) (pg/mL) from baseline to 4 months in quartiles and total mortality in the Valsartan Heart Failure Trial (Val-HeFT). The mean baseline BNP, the mean change from baseline, and the mean percent change from baseline to 4 months for each quartile are also shown. Data from Anand et al.*[13]

Although first studied as a diagnostic and prognostic marker among patients with HF, BNP has also been subsequently shown to predict outcomes in patients with acute coronary syndromes. When measured between 1 and 4 days after presentation of acute myocardial infarction, an elevated plasma concentration of BNP was associated with increased mortality risk.[14] After adjustment for independent predictors of mortality, including age, left ventricular function, and ST segment deviation, increased BNP remained highly predictive of mortality at 10 months. The adjusted overall risk (95% CI) was 3.8 (1.1-13.3) for the second quartile, 4.0 (1.2-13.7) for the third quartile, and 5.8 for the fourth quartile (1.7-19.7). Increased BNP levels were also predictive of nonfatal myocardial infarction ($P < .004$) and new or worsening HF ($P < .0001$) at 10 months.[14]

Unlike vasoconstricting neurohormones, which play a maladaptive, pathophysiologic role in the progression of HF, cardiac natriuretic peptides are believed to participate in adaptive responses that limit the pathophysiologic sequelae of HF.[15] Persistent elevation in left ventricular filling pressures has been associated with an increased risk of progressive HF death, sudden death, and overall mortality in patients hospitalized with decompensated HF.[16] Elevations in BNP may have prognostic significance by identifying patients with persistent congestion. BNP elevation may also reflect a response to greater activation of the sympathetic and renin-angiotensin-aldosterone system.[6] Thus, in contrast to hemodynamic markers or other neurohormones, the circulating concentration of a single BNP might provide information on multiple constituents of the pathophysiology of HF, reflecting the complex interplay of several factors contributing to the course of the disease. The association of changes in BNP over time and mortality have been shown to correspond with adverse structural and functional changes in the heart.[17] Elevated BNP may be reflective of patients with ongoing pathologic remodeling and may also reflect a greater degree of hyporesponsiveness to BNP. One study indicated a dissociation of increasing BNP levels with levels of its second messenger, cyclic guanosine monophosphate, in patients with subsequent mortality, indicating a potential relationship between increased BNP levels, impaired BNP activity, and mortality in HF.[18] Further studies are needed to elucidate the underlying mechanisms responsible for the progression of HF and hyporesponsiveness to natriuretic peptides.

The close correlation between BNP levels and HF status has raised the possibility of using BNP levels as a guide to optimize HF therapy. The Australia-New Zealand Carvedilol Heart Failure Trial showed that carvedilol reduced mortality rates and HF admissions in patients with higher baseline BNP levels.[19] Treatment with spironolactone resulted in a decrease in BNP levels that paralleled the effects of spironolactone on mortality in the Randomized Aldactone Evaluation Study (RALES).[20] Smaller, single-center studies have confirmed the utility of BNP measurements in assessing clinical outcomes and have shown that changes in BNP levels track clinical outcomes in patients hospitalized for HF. As BNP identified patients at increased risk of sudden death, the BNP assay may help guide which patients require prophylactic placement of implantable cardioverter-defibrillators. In a pilot study in an HF center, BNP-guided

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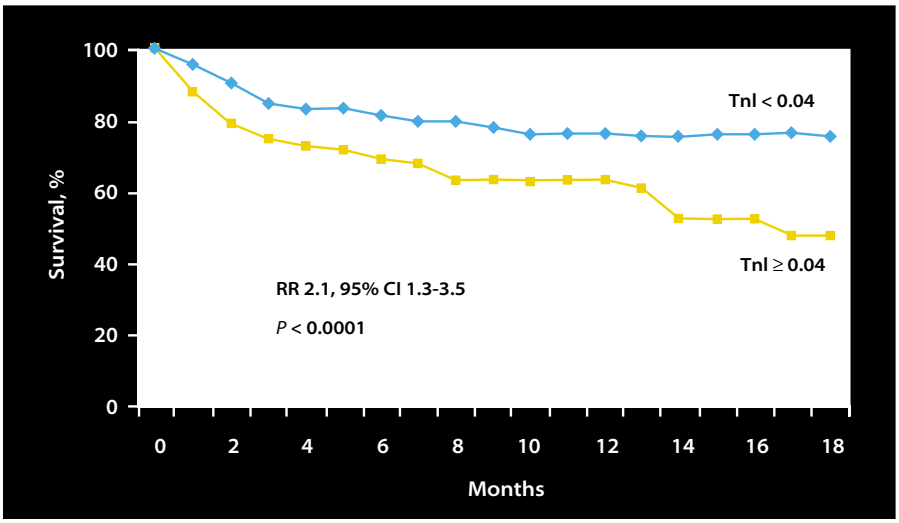

Figure 4. *Cumulative survival of advanced heart failure (HF) patients with detectable and undetectable cardiac troponin I (TnI) levels (<0.04 ng/mL). Reprinted wtih permission from Horwich et al.*[30]

treatment for HF was shown to reduce total cardiovascular events, including cardiovascular death, and to delay time to first cardiovascular event when compared with clinically guided treatment in a randomized study.[21] Further studies are needed to confirm data regarding using BNP to guide HF therapy.

Taken together, the existing data demonstrate a consistent relationship between BNP levels and mortality risk in patients with HF. In addition, there is a significant correlation between changes in BNP levels and clinically meaningful outcomes, such as death and/or change in patient symptom status. Thus, current data are compelling enough to support a role for the BNP assay as a diagnostic and prognostic marker for HF in routine clinical practice.[7] If ongoing studies confirm the initial pilot studies, the BNP assay may also be used to guide HF therapy.

Cardiac Troponins and Prognosis in Chronic Heart Failure

Troponins are proteins involved in the regulation of cardiac and skeletal muscle contraction. The presence of cardiac troponins in the serum indicates myocardial injury or loss of cell membrane integrity. Although the cardiac troponins—troponin I and troponin T—are well-established diagnostic and prognostic markers in acute coronary syndromes,[22,23] a role for cardiac troponins in the evaluation and risk stratification of patients with HF has recently emerged.

Several small studies have reported elevated cardiac troponin levels in patients with decompensated HF in the absence of acute coronary syndromes and furthermore have correlated troponin elevation with poor prognosis.[24–28] Sato and colleagues[24] studied 60 patients with dilated cardiomyopathy and found cardiac troponin T was increased in 27 patients. Persistently elevated levels were associated with decline in LVEF and higher mortality. In another study, elevated cardiac troponin I was found in 10 of 34 patients (29%) hospitalized with HF and was a predictor of mortality at 3 months.[25] A study of 98 patients hospitalized with class III and IV HF found that a cardiac troponin T level > .033 mcg/L on admission was associated with an increased risk of cardiac mortality.[29]

A recent study evaluated 238 advanced HF patients referred for cardiac transplant evaluation who had cardiac troponin I assay drawn at the time of initial presentation.[30] Patients with acute myocardial infarction or myocarditis were excluded from analysis. Cardiac troponin I was detectable (troponin I ≥ 0.04 ng/mL) in the serum of 117 patients (49.1%). Patients with detectable cardiac troponin I levels had more impaired hemodynamic profiles, including higher pulmonary wedge pressures (P = .002) and lower cardiac indices (P < .0001).[30] A significant correlation was found between detectable cardiac troponin I and progressive decline in ejection fraction over time. Detectable levels of cardiac troponin I were significantly associated with mortality in this cohort of advanced HF patients. On univariate analysis, detectable cardiac troponin I conferred a doubling of mortality risk (RR 2.1; 95% CI, 1.3-3.5; P < .0001) (Figure 4).[30] After adjustment for other factors associated with adverse prognosis, including age, sex, ejection fraction, and coronary artery disease, cardiac troponin I remained a significant predictor of mortality (Table 1). Receiver operator curve (ROC) analysis identified a cardiac troponin I level of 0.04 ng/mL as the optimal inflection point for mortality risk. Higher levels of cardiac troponin I were not associated

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Table 1
Cardiac Troponin I as Predictor of Mortality in Advanced Heart Failure

	Troponin I < 0.04 ng/mL	Troponin I ≥ 0.04 ng/mL
Patients, n	121	117
Death or urgent transplant, n (%)	22 (18.2)	42 (35.9)
Age- and sex-adjusted RR (95% CI)	—	2.09 (1.26-3.48)
Multivariate* RR (95% CI)	—	1.85 (1.04-3.26)

*Multivariate adjusted for sex, age, heart failure etiology, and left ventricular ejection fraction. Data from Horwich et al.[30]

with higher risk in HF. Thus, any detectable level of cardiac troponin has been associated with an increased risk of mortality in HF, a finding which makes risk assessment easier to standardize across hospitals using a variety of different troponin assays.

Patients with detectable levels of cardiac troponins have also been shown to be more likely to have progressive worsening of left ventricular systolic function, as quantified by follow-up echocardiography.[24,30] In the study by Horwich and colleagues,[30] of patients with detectable levels of cardiac troponin I on initial referral, 44% had a decrease in LVEF on follow-up echocardiography compared with only 18% of patients with undetectable cardiac troponin I levels ($P < .01$). Furthermore, in patients with cardiac troponin I values above 0.04 ng/mL, ß-blocker therapy was associated with significantly lower mortality compared with patients not receiving ß-blocker therapy (34% vs 74%, $P < .003$).[30] Thus, elevated troponins appear to identify HF patients with increased risk of progressive left ventricular dysfunction who derive particular benefit from ß-blocker therapy. Patients in whom initially detectable levels of cardiac troponins became undetectable over the next 3 months had improvements in LVEF and a good prognosis.[24] Interestingly, a preliminary study found that troponin T was significantly elevated in HF patients with prolonged QRS duration, suggesting a role for troponins in identifying patients with more severe wall stress associated with ventricular dyssynchrony, who may benefit from cardiac resynchronization therapy (biventricular pacemakers).[31]

Although elevation of serum cardiac troponins is a well-validated marker of necrotic myocyte injury during myocardial infarction, the pathophysiology behind serum cardiac troponin elevation in HF is likely distinct from that seen during myocardial infarction. The lesser elevations of serum cardiac troponins in chronic HF could indicate the presence of limited, irreversible myocyte injury and death, or alternatively could represent leakage of the cytosolic pool of cardiac troponins during reversible injury, as a result of loss of cell membrane integrity.[32] Progressive myocyte loss via necrotic and apoptotic cell death is increasingly recognized as a prominent pathophysiologic mechanism in the evolution of cardiac dysfunction in HF.[33–35] The mechanisms believed to be responsible for ongoing myocyte injury and/or cell death in HF include activation of adrenergic, renin-angiotensin-aldosterone or endothelin signaling pathways, calcium handling abnormalities, inflammatory cytokines, nitric oxide, oxidative stress, and mechanical stress.[33]

Release of cardiac troponins into the serum in HF has been strongly correlated with elevation of cardiac filling pressures and BNP. In vitro experiments with cardiac muscle cells have identified a link between myocardial wall stretch and myocyte functional injury and cell death,[36] and increased troponin proteolysis has been identified in volume-overloaded rat hearts.[37] At a cellular level, multiple intracellular signaling cascades are activated in the heart in response to changes in mechanical loading. Several reports propose a relationship between cardiac troponin elevation and mortality in clinical scenarios other than HF in which ventricular wall stress increases, such as pulmonary embolism, acute medical illness requiring intensive care, and infusion of cardiotoxic chemotherapy.[38–40]

Cardiac troponin elevations in HF patients thus appear to provide significant, independent prognostic information regarding mortality risk. They also identify patients with more severe hemodynamic abnormalities and increased risk of progressive left ventricular dysfunction. The prognostic power of cardiac troponins appears to be additive to other mortality predictors in HF. The association between cardiac troponins and increased mortality has been demonstrated in patients with ischemic and patients with non-ischemic cardiomyopathy.[28–30] Additional research is needed to elucidate the pathophysiologic connections between elevated levels of cardiac troponins and the associated higher mortality risk in HF.

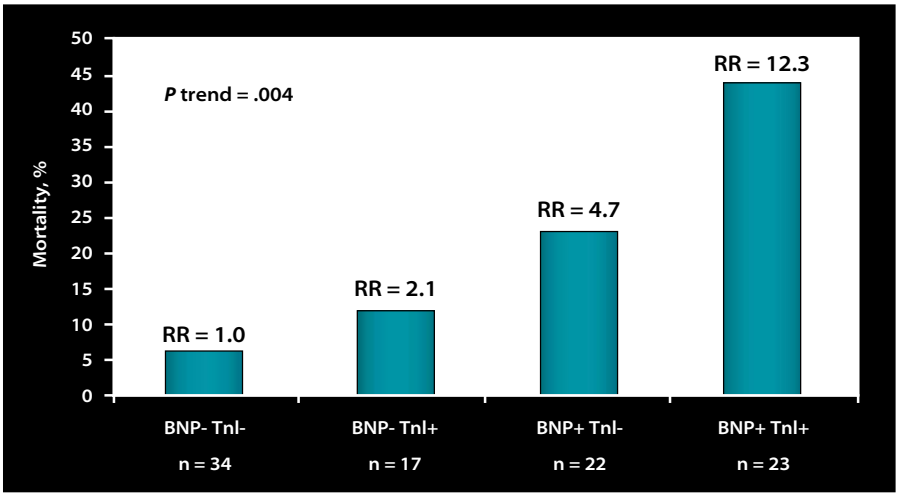

Figure 5. *Mortality rates stratified by cardiac troponin I (TnI) and B-type natriuretic peptide (BNP). TnI–, TnI < 0.04 ng/mL; TnI+, TnI ≥ 0.04 ng/mL; BNP–, BNP < 485 pg/mL; BNP+, BNP ≥ 485 pg/mL. Reprinted wtih permission from Horwich et al.*[30]

Multimarker Strategy for Prognosis in Heart Failure

Because both BNP and cardiac troponin appear to provide independent prognostic information in patients with HF, an integrated approach of measuring both biomarkers would be expected to further improve determination of mortality risk. In the study by Horwich and colleagues,[30] HF patients with detectable troponin had a 2.1-fold increased risk of death or need for urgent heart transplantation. Patients with BNP > 485 pg/mL (optimal cut-off for this cohort based on ROC analysis) had a 4.7-fold increased risk. Using the cardiac troponin I results in conjunction with BNP further improved prognostic value (Figure 5). In patients with detectable cardiac troponin I, those with BNP > 485 pg/mL had a 5.9-fold increase in risk compared with those with detectable cardiac troponin I and lower BNP. In patients with BNP > 485 pg/mL, those with detectable cardiac troponin I had a further 2.6-fold increase in risk over patients with higher BNP and undetectable cardiac troponin I. Patients with detectable cardiac troponin I and BNP > 485 pg/mL had a 12-fold increased mortality risk compared with those with both undetectable cardiac troponin I and BNP < 485 pg/mL (Figure 5). In a study of 98 patients hospitalized with HF, Ishii and colleagues[29] found that a cardiac troponin T level > 0.033 mcg/L and/or a BNP level > 440 pg/mL on admission was correlated with an incremental increase in in-hospital cardiac mortality, overall cardiac mortality, and cardiac event rate. Kaplan-Meier analysis revealed that the combination of troponins and BNP could reliably stratify the patients into low-, intermediate-, and high-risk groups for cardiac events.

When used together in a combined biomarker strategy, these two markers provide independent prognostic information and are more effective for identifying HF patients at increased risk. The combination of elevated cardiac troponin I and elevated BNP identified HF patients with a markedly increased mortality risk (12-fold increase);[30] this multimarker approach to risk stratification is similar to recent observations in patients with acute coronary syndromes in which cardiac troponin I, BNP, and C-reactive protein provided additive prognostic information.[41] Because point-of-care analyzers are available that combine BNP and cardiac troponin I on a single testing platform, clinicians can now obtain valuable prognostic information within 15 minutes of a blood sample being drawn.

Clinical Implications

Despite significant advances in medical therapy, patients with HF remain at increased risk of overall mortality and sudden cardiac death. There clearly is a clinical advantage over existing HF care strategies in being able to use combinations of different biomarkers that reflect different aspects of the disease process to optimize multiple facets of HF patient care. When used together in a combined strategy, these two markers (BNP and cardiac troponin) provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF. Such information is likely to enhance our ability to appropriately triage higher-risk HF patients and more reliably identify low-risk HF patients who may be candidates for less intensive evaluation and therapy. Patients with abnormalities of both cardiac troponins and BNP biomarkers are at significantly higher risk for mortality

Because point-of-care analyzers are available that combine BNP and cardiac troponin I on a single testing platform, clinicians can now obtain valuable prognostic information within 15 minutes of a blood sample being drawn.

and may derive particular benefit from more aggressive management strategies such as cardiac transplantation or HF device therapy.

Conclusion

Cardiac troponins and BNP are both significant independent predictors of increased mortality in patients with HF, irrespective of etiology. There is a consistent relationship between BNP levels and mortality risk in patients with HF, and there is a significant correlation between changes in BNP levels and clinically meaningful outcomes. Cardiac troponin adds substantially to risk assessment for mortality based on BNP alone in patients with HF. Patients with detectable cardiac troponin and elevated BNP were at particularly high risk for morbidity and mortality, whereas patients without detectable cardiac troponins and lower BNP levels have a substantially lower risk of adverse outcome. The multimarker strategy of combining assessment of cardiac troponin and BNP appears to be a novel, useful tool in identifying HF patients at increased risk for progressive ventricular dysfunction and mortality, who will likely benefit from aggressive management strategies and HF device therapy. By using such an integrated multimarker approach, clinicians will be able to accurately identify subgroups of patients with HF who are at increased risk and subgroups of patients at decreased risk of overall mortality, sudden cardiac death, and death due to pump failure. Prospective studies of BNP and cardiac troponins as predictors of therapeutic response are warranted. ■

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Main Points

- Because devices are expensive and transplants are in such limited supply, reliable biomarkers that predict which patients are likely to have improvement in left ventricular systolic function and lower risk of mortality would be particularly helpful in managing heart failure (HF).
- An ideal biomarker for HF would be highly sensitive and specific, provide accurate prognostic information independent of other variables, and would be reproducible and standardized. The assay would be relatively easy to perform and analyze and results would be applicable to patients with multiple HF etiologies, of all ages, both sexes, and all racial/ethic backgrounds.
- It is well established that circulating B-type natriuretic peptide (BNP) levels are increased in patients with chronic HF in proportion to the severity of the disease and that the BNP assay can facilitate the diagnosis of HF. Elevated plasma BNP has also been shown to be a powerful marker for prognosis and risk stratification in the setting of HF and has many characteristics of an ideal biomarker for HF.
- The existing data demonstrate a consistent relationship between BNP levels and mortality risk in patients with HF. In addition, there is a significant correlation between changes in BNP levels and clinically meaningful outcomes, such as death and/or change in patient symptom status. Thus, current data are compelling enough to support a role for the BNP assay as a diagnostic and prognostic marker for HF in routine clinical practice.
- Although the cardiac troponins—troponin I and troponin T—are well-established diagnostic and prognostic markers in acute coronary syndromes, their role in the evaluation and risk stratification of patients with HF has recently emerged.
- Cardiac troponin elevations in HF patients appear to provide significant, independent prognostic information regarding mortality risk. They also identify patients with more severe hemodynamic abnormalities and increased risk of progressive left ventricular dysfunction.
- When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF. Such information is likely to enhance our ability to appropriately triage higher-risk HF patients and more reliably identify low-risk HF patients who may be candidates for less intensive evaluation and therapy.

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