National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Utilization of Cardiac Biomarker Testing in Heart Failure

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A. Context of Biochemical Marker Testing in Heart Failure

Biochemical marker testing has revolutionized the approach to diagnosis and management of heart failure over the past decade. There is an unsurpassed excitement in the heart failure community that significant advances in our understanding of currently available and future cardiac biomarkers will facilitate improved characterization of heart failure disease states and promote individualized therapy in heart failure and beyond. However, like most novel diagnostic tests, the promising findings from pivotal trials have met with ongoing challenges when applied in the clinical setting.

The material discussed in this guidelines document addresses clinical use of BNP/NT-proBNP and cardiac troponin testing in the context of heart failure diagnosis, risk stratifi-

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cation and management, including therapeutic guidance in adult (>18 year-old) patients. Together with the associated document titled "*National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biomarkers of Heart Failure*", these recommendations are aimed at appropriate utilization of this testing by both practicing clinicians and laboratorians. The committee feels that dissemination of this guidance to the clinical and laboratory communities will improve communication and ultimately care and outcomes of patients with heart failure. Although providing specific tools for implementation is complicated, the guidelines are designed to be direct and succinct to facilitate implementation. The committee feels that education and dissemination are the major barriers to over- or under-use of natriuretic peptide testing. For this reason, there are plans for wide dissemination of the recommendations contained herein; the committee believes such dissemination will assist in educating users on the advantages and caveats of BNP and NT-proBNP measurement. Regarding costs as an example, the direct per-test cost for BNP or NT-proBNP measurement is approximately $50 (2007 United States [US] currency). Although somewhat controversial, there is evidence that use of natriuretic peptide testing in the context of heart failure decreases cost without increasing patient risk.[1,2] Costs were considered by the committee in formulating recommendations; however, the costs were considered modest compared with the total care of heart failure patients, and this view is supported by evidence.[1,2]

It is most important to emphasize that validity of test results must complement clinical findings to define a disease process. Thus, biochemical marker testing (such as BNP and NT-proBNP measurement) is not a stand-alone test, and must be used and interpreted in a larger clinical context, with confounding factors taken into account. Used appropriately in this context, the health benefits of testing far outweigh the side effects and risks of having knowledge of BNP and NT-proBNP levels. Use of cardiac troponin testing as it pertains to the heart failure population will also discussed primarily in its role for risk stratification.

B. Background and Definition of Terms

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood.[3] It is a growing and costly problem, affecting 2% to 3% of the total US population. Moreover, it is estimated that only 50% of all patients survive up to 4 years.[4] The increasing prevalence of heart failure is due to the aging population as well as the marked increase in survival of patients who suffered from myocardial infarction. Conservative estimates suggest that over 50% of cases have an ischemic origin, while up to 75% of cases have hypertension as a major contributing factor. The cost of heart failure is estimated to be $100 billion a year in Europe and the US, 70% of which is due to hospitalization.[3–5]

The diagnosis of heart failure is a bedside diagnosis based on clinical signs and symptoms *rather* than any stand-alone test results. However, a substantial proportion of the patients referred to cardiologists from primary care physicians have been originally misdiagnosed with conditions other than heart failure. Therefore, clinical biomarker testing in the setting of heart failure has three important goals: 1) to identify possible underlying (and potentially reversible) causes of heart failure; 2) to confirm the presence or absence of the heart failure syndrome; and 3) to estimate the severity of heart failure and risk of disease progression.

Over the last decade, natriuretic peptides, particularly BNP and its amino-terminal co-metabolite, NT-proBNP, have been shown to be particularly useful in confirming or refuting the diagnosis of heart failure as well as stratifying long-term risk profiles. Several novel cardiac, metabolic and inflammatory biomarkers have emerged in the heart failure literature, such as C-type natriuretic peptide,[6] endothelin-1,[7] cardiac troponin,[8] high-sensitivity C-reactive protein (hsCRP),[9,10] apelin,[11,12] myotrophin,[13] urotensin-II,[14–16] adrenomedullin[17,18] and mid-regional pro-adrenomedullin,[19] cardiotrophin-1,[20,21] urocortin,[22] soluble ST2 receptor,[23] myeloperoxidase (MPO),[24] copeptin,[19,25] growth differentiation factor-15 (GDF-15),[26] lymphocyte G-protein coupled receptor kinases (GRK-2),[27] galectin-3,[28] mid-regional pro-A-type natriuretic peptide and other circulating forms,[19,29] and many others. However, their clinical role remains to be determined and validated (Table). Therefore, we will focus our discussion on the utility of testing BNP and its associated metabolite NT-proBNP in heart failure, with some mentioning of other cardiac biomarkers in specific contexts.

C. BNP and NT-proBNP Metabolism and Measurement

Since a large body of knowledge in biochemical marker testing specific to patients with heart failure will involve BNP and NT-proBNP, we will specifically discuss the metabolism and measurement of these markers. BNP and NT-proBNP belong to a family of naturally occurring hormones known as natriuretic peptides. Although BNP is co-expressed in secretory vesicles with A-type natriuretic peptide and the stimuli for expression is complex, BNP expression is augmented primarily by increase in wall tension in response to pressure (and volume) overload in both the atria and the ventricles. Therefore, elevated blood BNP and NT-proBNP levels occur in the setting of elevated filling pressures in patients with cardiac dysfunction, and can provide relatively reliable diagnostic and prognostic information.[30]

It is clear from the existing literature that blood natriuretic peptide levels are reduced following long-term treatment with angiotensin converting enzyme (ACE) inhibitors,[31,32] angiotensin-II receptor blockers[33] and spironolactone.[34,35] This finding is most likely due to reduction in filling pressures and/or reversal of the pathological remodeling process that occurs following neurohormonal blockade. However, responses in natriuretic peptide levels to beta-adrenergic blockers have been mixed – while the majority of the literature points to reduction of blood natriuretic peptide levels with long-term treatment with beta-adrenergic blockers, transient elevation of blood natriuretic peptide levels have been observed with their initiation.[36]

Several commercial laboratory platform-based and point-of-care assays have become available for BNP testing in the clinical setting as an aid to the diagnosis of heart failure and

Selected Biochemical Markers Currently Available or Under Study for Clinical Diagnosis, Management, and Risk Stratification of Heart Failure

Standard laboratory markers
Sodium
Blood urea nitrogen
Serum creatinine
Hemoglobin
Leukocyte count
Total lymphocyte count
Serum albumin
Total bilirubin
Uric acid
Red blood cell distribution width
Neurohormones
Catecholamines (norepinephrine, epinephrine)
Renin, ACE activity, angiotensin II, and aldosterone
Natriuretic peptides (ANP, BNP, C-type, N-terminal proANP, N-terminal proBNP, mid-regional pro-ANP)
Endothelin-1
Vasopressin/copeptin
Cardiotrophin-1
Novel vasodilators (adrenomedullin and mid-regional pro-adrenomedullin, urotensin-II, urocortin)
Inflammatory biomarkers
High-sensitivity C-reactive protein
Myeloperoxidase
Galectin-3
Fatty acid binding protein
Soluble ST2 receptor
Tumor necrosis factor-alpha (TNF-α) and receptors
Interleukin-6 (IL-6)
Growth differentiation factor 15 (GDF-15)
Osteopontin
Metabolic biomarkers
Leptin
Adiponectin
Ghrelin
Apelin
Insulin-like growth factor-1 (IGF-1)
Other miscellaneous biomarkers
G-protein coupled receptor kinase-2 (GRK-2)
Cardiac troponin I or troponin T
Myotrophin

for providing prognostic information (Table). For example, blood BNP of $<$100 pg/mL or a blood NT-proBNP of $<$300 pg/mL have high negative predictive values in ruling out the diagnosis of heart failure among patients presenting with dyspnea.[37,38] As stated earlier, in this document, the term "natriuretic peptide" in subsequent discussions will refer to both BNP and NT-proBNP unless otherwise specified.

There are several practical considerations in the use of blood natriuretic peptide testing in the clinical settings. First, the reference ranges for natriuretic peptides assays vary depending on the assay method employed and the nature of the control population. The units expressed in the natriuretic peptide literature including mol/L and pg/mL, and the commonly used research assay (Shionogi) often reports values that are 15% to 20% below that of the commercial assays (Biosite and Abbott).[39] Differences in results between these assays have been attributed to the different epitopes identified by antibodies used in different immunoassays.[40] These variations have made direct comparison among study results difficult, and careful consideration of the type(s) of assay used when interpreting values reported in the literature is warranted (see *National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biomarkers of Heart Failure*).

Second, a wide variety of clinical factors have been shown to influence blood natriuretic peptide levels, including age and sex,[39,41–43] renal function,[43–48] body habitus,[49–51] thyroid function,[52,53] and anemia.[54] Obesity, in particular, has been associated with lower blood BNP and NT-proBNP levels across the spectrum of heart failure, and should be interpreted with caution, especially in ruling out cardiac causes of dyspnea. Preexisting cardiac conditions such as prior history of heart failure,[55] rhythm abnormalities,[42,56–58] and underlying etiology of heart failure[59] may also influence the diagnostic accuracies. The relative influence of these factors in relation to the degree of cardiac dysfunction remains highly debated, and can be different in various clinical settings (overall, confounding effects are less apparent in the setting of acute exacerbation of heart failure). Furthermore, diastolic dysfunction, mitral regurgitation, right ventricular dysfunction, recent heart surgery, and other cardiac structural or functional abnormalities can significantly influence blood natriuretic peptide levels.[60–63]

Third, although several studies have demonstrated excellent statistical correlations between the BNP and NT-proBNP assays,[64,65] there were noticeable differences. particularly with regard to their half-lives, intra- and inter-individual variability,[66,67] and differences in their production and renal clearance. However their overall diagnostic and prognostic abilities appeared to be comparable in the clinical setting. There are also differences in peptide stability. Currently, there is no direct "conversion" between the two assay types, let alone between different assays within the same peptide.

When applied in conjunction with the clinical history, physical examination and other tools available to physicians, cardiac biomarkers are valuable in achieving clinical objectives as outlined below.

II. Use of Biochemical Markers in the Initial Evaluation of Heart Failure

A. Diagnosis of Heart Failure

Recommendations for Use of Biochemical Markers for Diagnosis of Heart Failure

Class I

1. BNP or NT-proBNP testing can be used in the acute setting to *rule out* or to *confirm* the diagnosis of heart

failure among patients presenting with ambiguous signs and symptoms. (Level of Evidence: A)

Class IIa

1. BNP and NT-proBNP testing can be helpful to exclude the diagnosis of heart failure among patients with signs and symptoms suspicious of heart failure in the non-acute setting. (Level of Evidence: C)

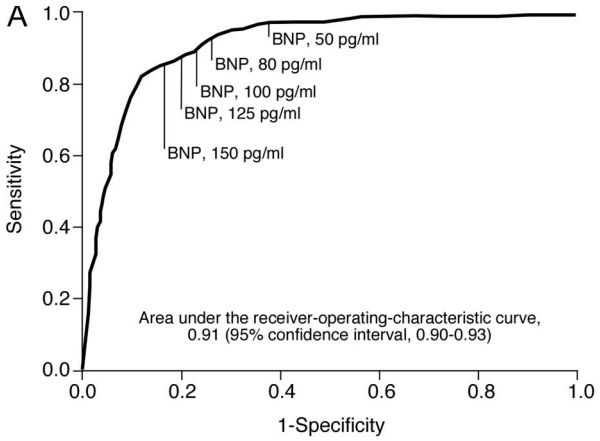
Class III

1. In diagnosing patients with heart failure, *routine* blood BNP or NT-proBNP testing for patients with an obvious clinical diagnosis of heart failure is not recommended. (Level of Evidence: C)

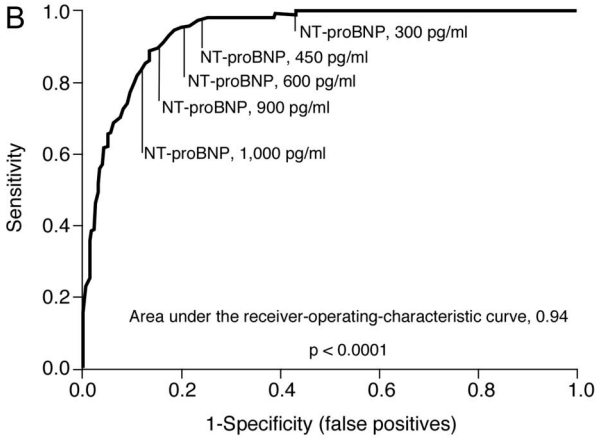
2. In diagnosing patients with heart failure, blood BNP or NT-proBNP testing should not be used to *replace* conventional clinical evaluation or assessment of the degree of left ventricular structural or functional abnormalities (eg, echocardiography, invasive hemodynamic assessment). (Level of Evidence: C)

1. BNP and NT-proBNP for Diagnosis of Acute Decompensated Heart Failure

Most of the early studies of natriuretic peptides have focused on the diagnostic role of BNP or NT-proBNP testing among patients presenting with signs and symptoms of heart failure. The utility of blood BNP or NT-proBNP testing in the initial evaluation of patients with heart failure in the acute setting has been well established by several prospective multi-center clinical studies. In the multicenter Breathing-Not-Properly Study, using a BNP level of 100 pg/mL as a diagnostic "cut-off" gave a sensitivity of 90%, specificity of 76% and a diagnostic accuracy of 81% in determining a heart failure etiology of acute dyspnea, which was superior to clinical assessment alone in a series of 1,586 patients presenting to the emergency department with acute dyspnea[68] (Figure, A). In a recent randomized controlled trial comparing a diagnostic strategy involving blood BNP testing versus clinical assessment alone, blood BNP testing in the emergency department improved the evaluation and treatment of patients with acute dyspnea, reducing the time to discharge and the total cost of treatment.[1] Similar findings were reported in the primary care setting in which blood NT-proBNP testing improved the diagnostic accuracy of acute heart failure by general practitioners.[69] The equivalent role of NT-proBNP testing was confirmed in the PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) study, in which blood NT-proBNP testing was performed in 600 patients presenting to the Emergency Department with acute dyspnea. NT-proBNP at cut-points of >450 pg/mL (ages <50 years) and >900 pg/mL (ages ≥50 years) were highly sensitive and specific for the diagnosis of acute heart failure, while <300 pg/mL was optimal for ruling out acute heart failure (negative predictive value of 99%, Figure, B).[70] Comparing natriuretic peptide levels longitudinally in previously stable patients with preexisting heart failure is logical, although the precise extent of an increase that might be deemed clinically significant has not been established. At present, there are no national guidelines for the diagnosis and management of acute heart failure syndromes in North America.



BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
50	97%	62%	71%	96%	79%
80	93%	74%	77%	92%	83%
100	90%	76%	79%	89%	83%
125	87%	79%	80%	87%	83%
150	85%	83%	83%	85%	84%



Cut Point pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
300	99%	68%	62%	99%	79%
450	98%	76%	68%	99%	83%
600	96%	81%	73%	97%	86%
900	90%	85%	86%	94%	87%
1000	87%	86%	78%	91%	87%

A, Receiver operator characteristic (ROC) curve for B-type natriuretic peptide testing in the diagnosis of heart failure with acute dyspnea. Reprinted from Maisel et al,[68] with permission. Copyright © 2002 Massachusetts Medical Society. All rights reserved. B, Receiver operator characteristic (ROC) curve for aminoterminal proB-type natriuretic peptide testing in the diagnosis of heart failure with acute dyspnea. Reprinted from Januzzi et al,[70] with permission. Copyright © 2006 Elsevier.

There has been some skepticism regarding the clinical indications for *routine* use of blood natriuretic peptide testing in the initial evaluation of patients presenting with signs and symptoms heart failure, particularly in the non-acute setting.[71] Moreover, a single-point measurement of blood natriuretic peptide with levels between 80 and 300 pg/mL using the Biosite assay has been reported to be less reliable in the setting of acute heart failure with "flash" pulmonary edema as the level of blood BNP or NT-proBNP may not have had

sufficient time to rise.[72] These natriuretic peptide "grayzones" in the diagnosis of heart failure may also be influenced by the presence of underlying history of heart failure, where the "dry" blood natriuretic peptide level may fall within this range.[55,73,74] There are also challenges with the specific "cut-offs" in certain populations such as in the elderly.[75] Furthermore, absolute values as well as changes in blood natriuretic peptide levels may correlate with clinical or echocardiographic parameters, but such correlations may vary considerably. There have been reports illustrating the lack of a tight relationship between blood natriuretic peptide levels and blood volume assessment,[76] left ventricular ejection fraction,[60] and hemodynamic parameters.[77–79] Therefore, at this time, natriuretic peptide testing should still be considered only as part of the diagnostic evaluation in heart failure, and not *the* diagnostic definition.

2. BNP or NT-proBNP for Confirmation of the Heart Failure Diagnosis

There is a consensus among the latest American College of Cardiology (ACC)/American Heart Association (AHA), Heart Failure Society of America (HFSA), and other guidelines regarding the management of *chronic* heart failure that blood natriuretic peptide testing should be performed to confirm the diagnosis of heart failure among patients with suspected diagnosis of heart failure, but only in those who present with signs and symptoms that are ambiguous or which occur in the setting of confounding disease states (such as chronic obstructive pulmonary diseases[80]). Such levels can be valuable to improve the diagnostic accuracy for detecting heart failure. Furthermore, blood natriuretic peptide testing has found to be useful in differentiating different mechanisms of cardiac dysfunction (restrictive cardiomyopathy versus constrictive cardiomyopathy[81]), and in identifying cardiac involvement in systemic diseases.[82,83]

Careful prospective evaluation of the utility of blood natriuretic peptide testing has not been conducted in the non-acute ambulatory care setting. By deduction, the clinical utility of natriuretic peptide testing in confirming the diagnosis of heart failure in symptomatic patients in the ambulatory care setting should be comparable to the acute setting, where more of the existing data regarding natriuretic peptide testing are derived from. It is important to point out that among minimally or chronically symptomatic patients in the non-acute, ambulatory care setting, blood natriuretic peptide levels may vary, and the diagnostic ranges may be different from that in the acute setting (see Section III on "Screening"). Hence, the cut-off values used in the acute setting may not reliably translate into the ambulatory care setting among patients with chronic stable heart failure. There also have been reports that in the ambulatory care setting, patients with stable but symptomatic chronic heart failure can have blood natriuretic peptide levels that are relatively lower than would normally considered to be "diagnostic" of heart failure (eg, Biosite BNP <100 pg/mL).[59] This is in direct contrast to the over 90% of patients presenting with blood BNP levels >100 pg/mL in the acute care setting.[84] Nevertheless, this cut-off is still likely to be helpful in excluding a diagnosis of heart failure when verified by a careful history and physical examination.

B. Risk Stratification of Heart Failure

Recommendations for Use of Biochemical Markers for Risk Stratification of Heart Failure

Class IIa

1. Blood BNP or NT-proBNP testing can provide a useful addition to clinical assessment in selected situations when additional risk stratification is required. (Level of Evidence: A)

2. Serial blood BNP or NT-proBNP concentrations may be used to track changes in risk profiles and clinical status among patients with heart failure in selected situations where additional risk stratification is required. (Level of Evidence: B)

Class IIb

1. Cardiac troponin testing can identify patients with heart failure at increased risk beyond the setting of acute coronary syndromes. (Level of Evidence: B)

Class III

1. *Routine* blood biomarker testing for the *sole* purpose of risk stratification in patients with heart failure is not warranted. (Level of Evidence: B)

1. Risk stratification of Patients With and Without Heart Failure Using BNP or NT-proBNP

There is a growing body of consistent literature supporting the utility of blood natriuretic peptide testing for risk stratification among patients with heart failure, or even those without prior history of heart failure.[85] This applies to a wide variety of clinical settings, including acute coronary syndromes,[86–89] stable coronary artery disease,[90–92] decompensated heart failure,[93,94] stable chronic heart failure,[95] and even non-cardiac disorders such as pulmonary embolism[96,97] or in the general population with no prior history of heart failure[85] or those at risk of developing heart failure.[98] There have also been studies advocating the role of blood natriuretic peptide testing in selection for cardiac transplantation,[8,99,100] as well as implantation of cardiac defibrillators[101] or cardiac resynchronization therapy.[102–104] Furthermore, blood natriuretic peptide levels have been found to be an important independent predictor of sudden death[105] and equivalent in risk stratification to the Heart Failure Survival Score.[106] Natriuretic peptides also provide incremental prognostic value with standard clinical and laboratory prognostic indicators.[98,107]

It is important to also point out that changes in blood natriuretic peptide levels have been associated with differences in long-term clinical outcomes (see Section IV on "Guiding Management"). In addition, it is also worthwhile to recognize that the absolute values of the ranges in different risk strata reported in the literature vary considerably, depending on the patient population. Indeed, even when the blood natriuretic peptide levels were intermediate in the diagnosis of heart failure, their long-term prognostic values remained robust.[74,108] However, the prognostic value of natriuretic peptide testing is still limited by a lack of clear utility in guiding clinical management. The challenge is to

better define the specific situations in which risk stratification can be clinically beneficial, and what is deemed to be "false-positive" or "false-negative" may reveal underlying pathophysiologic manifestations that are still not clinically apparent.[109]

Current medical management of patients with heart failure relies on patients' and physicians' subjective clinical assessment and various non-specific laboratory measurements of organ dysfunction and fluid status. Blood natriuretic peptide levels fall rapidly following diuretic therapy in patients with decompensated heart failure,[131–133] although these changes may vary widely and can be independent of hemodynamic changes.[77] Furthermore, blood natriuretic peptides may correlate with symptom status in the outpatient setting.[134] The intra-individual variability of serial natriuretic peptide levels remains highly debated.[135–137] Recent literature from patient cohorts with chronic heart failure[138] and with acute coronary syndromes[139] have further illustrated that reduction in blood natriuretic peptide levels over time may be directly associated with corresponding reductions in long-term clinical events. Therefore, serial blood BNP or NT-proBNP concentrations may be used to track changes in risk profiles and clinical status among patients with heart failure in selected situations where additional risk stratification is required.

2. Risk Stratification of Patients With Heart Failure Using Cardiac Troponin

Detectable serum levels of cardiac troponin represent evidence of myocardial necrosis, and have been extensively used in the setting of acute coronary syndromes (ACS). In patients presenting with acute heart failure, cardiac troponin testing has been used as part of the clinical work-up in the acute setting to rule out myocardial ischemia as the primary etiology (refer to Chapter 1 for recommendations). However, in the setting of advanced heart failure[8,110] or in decompensated states,[111–113] some patients may present with transient or persistent elevation of serum cardiac troponin I or troponin T levels in the absence of any obvious myocardial ischemia. Elevated serum troponin levels have been associated with poor long-term prognosis. Several clinical series have further illustrated a strong adverse prognostic effect of sustained elevation of serial serum troponin levels, which may indicate ongoing myocardial damage.[114,115] However, the utility of routine assessment of serum troponin levels in patients with acute or chronic heart failure, as well as the appropriate diagnostic and therapeutic approaches to elevated serum troponin levels in non-ACS setting remains to be determined. This is in part due to the lack of understanding as to whether cardiac troponin levels as markers of myocyte necrosis represents a risk marker versus a risk factor.

III. Use of Biochemical Markers in Screening for Cardiac Dysfunction

Recommendations for Use of BNP and NT-proBNP in Screening of Heart Failure

Class IIb

1. Blood BNP or NT-proBNP testing can be helpful to identify selected patients with left ventricular systolic dysfunction in the post-infarction setting or to identify patients at high risk of developing heart failure (eg, history of myocardial infarction, diabetes mellitus). However, the diagnostic ranges and cost-effectiveness in different populations remain controversial. (Level of Evidence: B)

Class III

1. *Routine* blood natriuretic peptide (BNP or NT-proBNP) testing is not recommended for screening large asymptomatic patient populations for left ventricular dysfunction. (Level of Evidence: B)

A. BNP or NT-proBNP for Screening Heart Failure and Dysfunction

The diagnostic utility of blood natriuretic peptide levels in the acute heart failure setting has prompted interest in evaluation of these biomarkers as screening tools for patients with underlying cardiac dysfunction but no overt signs and symptoms – so-called "asymptomatic left ventricular dysfunction" (ALVD). According to the latest ACC/AHA guidelines for the management of chronic heart failure, a large majority of patients who develop heart failure may have preceding structural cardiac abnormalities ("Stage B heart failure") that can be recognized before disease progression.[116] Recent data from the general population from Olmsted County suggest that the prevalence of underlying cardiac structural abnormalities (including ALVD, diastolic dysfunction, valvular abnormalities, left ventricular hypertrophy, and regional wall motion abnormalities) was the highest among individuals within the highest tertile of both BNP and NT-proBNP. Higher NT-proBNP levels have also been associated with greater likelihood of detecting incident heart failure in a population with stable coronary artery disease.[117] However, there have been inconclusive data regarding the role of screening for ALVD using natriuretic peptide testing in several studies.[85,118,119] In general, the diagnostic accuracies are far lower compared with the detection of clinical heart failure, which is likely due to the relatively non-specific association with ALVD at ranges of blood natriuretic peptide levels observed in the general population.[120,121]

B. Approaches for Screening for Cardiac Dysfunction

There are two approaches to use of natriuretic peptide testing for screening purposes. In the first approach, blood natriuretic peptide testing may be useful in the setting of acute myocardial infarction in the absence of overt heart failure. In this setting, blood natriuretic peptide levels have been inversely associated with post-infarction left ventricular ejection fraction. However, due to the heterogeneity of study populations and the timing of sampling, the accuracy of natriuretic peptide screening has been variable. Echocardiography is likely to remain the main method of assessing LV structural and functional abnormalities after a myocardial infarction.

The second approach is to combine natriuretic peptide testing with other screening modalities to increase the diagnostic accuracy of any single test. This "multi-marker" approach has been broadly studied for risk stratification in the setting of acute coronary syndromes. In this context, combining natriuretic peptide testing with myeloperoxidase or elec-

trocardiography appeared to be promising,[122,123] but further studies are needed to better define these approaches. At this time, most guidelines do not support *routine* blood natriuretic peptide testing for screening large asymptomatic patient populations for left ventricular systolic dysfunction.

Some investigators have attempted to increase the yield to detect asymptomatic cardiac dysfunction by focusing on high-risk subgroups, a strategy that may be more cost-effective.[124] A high prevalence of elevated blood natriuretic peptide levels has been observed in a patient population at risk of developing heart failure ("Stage A heart failure"), particularly among those with a history of long-term hypertension, diabetes mellitus,[125,126] coronary artery disease,[92,127] and in the elderly.[128–130] It is conceivable that blood natriuretic peptide testing may be useful for screening these high-risk populations who may otherwise be referred for further echocardiographic screening for ALVD, although the "cut-off" levels may differ in different patient populations. Others have combined several cardiac biomarkers to increase the specificity of screening using inflammatory markers such as MPO or hsCRP.[122] Until prospective studies are conducted to establish evidence for stratifying patients according to natriuretic peptide levels or to validate a multimarker approach with clinically available assays with cost-effectiveness justifications, broad clinical application of these approaches are still not warranted.

IV. Use of Biochemical Markers in Guiding Management of Heart Failure

Recommendations for Use of Biochemical Markers in Guiding Management of Heart Failure Patients

Class III

1. *Routine* blood BNP or NT-proBNP testing is not warranted for making specific therapeutic decisions for patients with acute or chronic heart failure because of the still emerging but incomplete data as well as intra- and inter-individual variations. (Level of Evidence: B)

A. Monitoring Therapy Using BNP or NT-proBNP Guidance

The natural extension in natriuretic peptide testing beyond its diagnostic capabilities is to guide therapy in an objective manner. Indeed, this hypothesis has been tested in a small pilot study among patients with mild-to-moderate chronic heart failure. In this study ACE inhibitors and diuretic therapy were titrated to achieve a blood NT-proBNP level of $<$200 pmol/L by the Christchurch assay (equivalent to 1,680 pg/mL) without compromising other organ function (eg, hypotension, renal insufficiency).[140] This study found significantly fewer total cardiovascular events (deaths, hospital admissions, or episodes of decompensated heart failure based on modified Framingham criteria) in the group randomized to NT-proBNP-guided therapy. These results have been confirmed in a multicenter French study that indicated significant improvement in clinical events following a natriuretic peptide-guided approach compared with standard clinical assessment.[141] However, neutral results were also observed when a natriuretic peptide-guided approach was compared with standard clinical assessment.[142,143] Therefore, the concept of natriuretic peptide-guided management of heart failure is still being debated, and there is no general consensus in expert opinion regarding this issue.

Another potential use of blood natriuretic peptide testing in treatment monitoring is the assessment of adequacy of therapy in decompensated heart failure. Pre-discharge, but not initial blood natriuretic peptide levels have consistently been more strongly associated with post-discharge outcomes,[93,144] although the ranges of the changes in blood natriuretic peptides following therapeutic interventions also vary widely. However, the difficulty remains the determination of the "dry" natriuretic peptide levels, which is different from patient to patient. Over-aggressive diuresis based *solely* on blood natriuretic peptide levels may increase the risk of renal azotemia or extend length of stay without reducing morbidity and mortality.

Several problems have also emerged regarding the clinical feasibility of a natriuretic peptide-guided therapeutic strategy. The wide variation of single or sequential blood natriuretic peptide levels in chronic heart failure after long-term medical therapy have created difficulties in establishing a single "target" level.[59,60,136,145,146] The frequency of natriuretic peptide testing and the utility of natriuretic peptide testing in monitoring patients with heart failure remain to be determined.

The ability to guide therapeutic decisions using a biomarker-guided approach is highly promising. Several prospective studies are currently underway to confirm the utility of a natriuretic peptide-guided therapeutic strategy.[147,148] However, until these results are available, all clinical guidelines agreed that routine blood BNP or NT-proBNP testing is still not warranted for therapeutic decisions for patients with acute or chronic heart failure, primarily due to the mixed results from clinical studies and inter- and intra-individual as well as inter-assay variabilities.

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