NACB: Recommendations for the use of Cardiac Biomarkers in Heart Failure

Prepared by W. H. Wilson Tang, MD (Cleveland Clinic Foundation)

Second Draft: February 27, 2004

I. Overview of Heart Failure

Heart failure is a clinical syndrome characterized in most patients by dyspnea and fatigue at rest and/or with exertion caused by underlying structural and/or functional heart disease[1]. Heart failure is a growing and costly problem, affecting 2-3 % of the total U.S. population, but only 50% of all patients would survive up to 4 years. It is the main cause of hospitalizations in the elderly population. The increasing prevalence in 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 suggested that over 50% of cases has an ischemia origin, while up to 75% of cases had hypertension as a major contributing factor.

Unlike acute coronary syndromes, the definition of heart failure is a bedside diagnosis based on clinical signs and symptoms *rather* than any stand-alone test results. However, as many as 50% of the patients referred to cardiologists from primary care physicians have been originally misdiagnosed with conditions other than heart failure. Therefore, the use of cardiac biomarkers in the diagnosis and management of heart failure may help to facilitate better clinical judgment.

Clinical laboratory testing in the setting of heart failure focuses on 2 goals: 1) to explore possible underlying (and potentially reversible) causes of heart failure; and 2) to

estimate the degree of severity and risk of disease progression. A partial listing of some commonly used laboratory tests is shown in Table 1.

II. B-type natriuretic peptides

Over the last decade, natriuretic peptides, particularly B-type natriuretic peptide (BNP), has introduced a new paradigm in the use of biomarkers in the evaluation and management of heart failure. Being a relatively specific biomarker for cardiac dysfunction, BNP and N-terminal proBNP (NT-proBNP) will be the main focus of this document. Several other novel cardiac, metabolic and inflammatory biomarkers, such as C-type natriuretic peptide[2], endothelin-1[3], cardiac troponin[4], C-reactive protein[5,6], apelin[7,8], myotrophin[9], urotensin-II[10-12], adrenomedullin[13,14], cardiotrophin-1[15,16], urocortin[17], have emerged in the heart failure literature, but their clinical role remains to be determined.

B-type natriuretic peptide and NT-proBNP belong to a family of naturally occurring hormones known as natriuretic peptides. Synthesized in the cardiac ventricles, elevated plasma BNP and NT-proBNP levels are highly specific for elevated filling pressures in patients with left ventricular dysfunction, and can provide relatively reliable diagnostic and prognostic information[18]. It is also clear from the existing literature that plasma BNP and NT-proBNP levels are reduced following long-term treatment with ACE inhibitors[19,20], beta-blockers[21,22], angiotensin-II receptor blockers[23] and spironolactone[24,25]. This is most likely due to the reversal of the pathologic remodeling process that occurs following neurohormonal blockade. Measurements of plasma BNP

or NT-proBNP have until recently been restricted to research laboratories, and the stability of plasma BNP and NT-proBNP has been well established[26,27]. Recently, several commercial assays have become available for BNP or NT-proBNP testing in the clinical setting as an aid to the diagnosis of heart failure (Table 1). Using the Biosite Triage® BNP assay system, a normal plasma BNP of < 100 pg/mL has a high negative predictive value in ruling out the diagnosis of heart failure[28]. For the Roche NT-proBNP assay, On the other hand, high plasma BNP levels (usually above 400-500 pg/mL) are related to a poor prognosis in patients with stable heart failure, but lack sensitivity and specificity.

There are several practical considerations in the use of plasma BNP or NT-proBNP testing in the clinical settings. First, the reference ranges for BNP and NT-proBNP assays vary depending on the assay method employed and the nature of the control population. The units expressed in the BNP literature varies from pmol/L to pg/mL, and the commonly used research assay (Shionogi) often reports values that are 15-20% below that of the commercial assays (e.g. Biosite Triage BNP assay)[29]. These variations have made direct comparison among study results difficult. Second, a wide variety of clinical factors have been shown to affect plasma BNP or NT-proBNP levels, including age and gender[29-32], renal function[32-36], body habitus[37], thyroid function[38,39], rhythm abnormalities[31,40-42], and underlying etiology of heart failure[43]. The relative impact of these factors in relation to the degree of cardiac dysfunction remains highly debated. Furthermore, diastolic dysfunction and other echocardiographic abnormalities significantly influence plasma BNP or NT-proBNP levels[44-47]. Third, there have been

very few studies directly comparing plasma BNP and NT-proBNP measurements. Although several studies have demonstrated their excellent statistical correlations between the two peptides[48,49], there were noticeable differences particularly with regards to their intra- and inter-individual variability[50,51].

III. Cardiac biomarkers in the initial evaluation of patients with heart failure

Most of the early studies on BNP have been focusing on the diagnostic role of plasma BNP and NT-proBNP in patients presenting with signs and symptoms of heart failure. The utility of plasma BNP and NT-proBNP testing in the initial evaluation of patient with heart failure has been well established by two prospective multi-center clinical trials. In the Multicenter Breathing Not Properly (BNP) Study, using plasma BNP level of 100 pg/mL as "cut-off" gave a sensitivity of 90%, specificity of 76% and a diagnostic accuracy of 81% which was superior to clinical assessment alone in a series of 1,586 patients presented to the emergency department with acute dyspnea[52]. In a recent randomized control trials comparing a diagnostic strategy involving plasma BNP testing versus clinical assessment alone, plasma BNP testing in the emergency department improved the evaluation and treatment of patients with acute dyspnea and thereby reduced the time to discharge and the total cost of treatment[53]. Similar findings have also been reported in the primary care setting where plasma BNP testing improve the diagnostic accuracy of acute heart failure by general practitioners[54].

However, there have been some skepticisms regarding the clinical implications for *routine* use of plasma BNP in the initial evaluation of every patient presenting with signs

and symptoms heart failure[55]. A single-point measurement of plasma BNP has been reported to be less reliable in the setting of acute heart failure with "flash" pulmonary edema between the ranges 80-300 pg/ml (using the Biosite BNP assay)[56]. There have also been reports that in the ambulatory care setting, patients with symptomatic chronic heart failure can have plasma BNP levels that are relatively lower than what would normally considered to be "diagnostic" (e.g. Biosite BNP <100 pg/ml)[43]. Therefore, there is consensus among heart failure specialists that plasma BNP or NT-proBNP testing should be performed to confirm the diagnosis of heart failure in patients with suspected diagnosis of heart failure but with presenting signs and symptoms that are ambiguous or with confounding disease states (such as chronic obstructive pulmonary diseases), and can be valuable to improve the diagnostic accuracy for detecting heart failure by non-specialists.

III. Recommendation 1: Plasma BNP or NT-proBNP testing should be performed to confirm the diagnosis of heart failure in patients with suspected diagnosis of heart failure but with presenting signs and symptoms that are ambiguous or with confounding disease states (such as chronic obstructive pulmonary diseases).

Strength/consensus of recommendation: Class IIa

III. Recommendation 2: Plasma BNP or NT-proBNP testing can be helpful (but not necessary) for non-specialists to confirm the diagnosis of heart failure in patients with obvious signs and symptoms of heart failure in the acute setting.

Strength/consensus of recommendation: Class IIa

III. Recommendation 3: In diagnosing patients with heart failure, routine plasma BNP or NT-proBNP testing for patients with an obvious clinical diagnosis of heart failure is not necessary.

Strength/consensus of recommendation: Class III (for routine use with clinically obvious heart failure)

III. Recommendation 4: In diagnosing patients with heart failure, plasma BNP or NT-proBNP testing should not be used to replace conventional assessment of the degree of left ventricular structural or functional abnormalities (e.g. echocardiography, invasive hemodynamic assessment).

Strength/consensus of recommendation: Class III (for replacement of echocardiography or invasive hemodynamic assessment)

IV. Cardiac biomarkers in the screening for asymptomatic left ventricular dysfunction

The diagnostic utility of BNP and NT-proBNP in the acute setting has prompted interest in evaluation these biomarkers as effective screening tools for asymptomatic left ventricular dysfunction (ALVD). According to the latest ACC/AHA clinical guidelines for the management of chronic heart failure, a large majority of patients who develop heart failure may have preceding risk factors (Stage A) or even structural abnormalities (Stage B) that can be recognized before disease progression.

There have been 2 major approaches in determining the utility of BNP and NT-proBNP in this setting. First, plasma BNP may be useful in the setting of acute myocardial infarction (MI) in the absence of overt heart failure, where plasma BNP levels have been inversely associated with post-MI left ventricular ejection fraction. However, due to the heterogeneity of study population and the timing of sampling, the accuracy of BNP screening has been variable. In this setting, echocardiography is likely to remain the main method of assessing LV structural and functional abnormalities after an MI.

Similarly, there have been inconclusive data regarding the role of screening for asymptomatic left ventricular dysfunction (ALVD) in several studies[57-59]. Also, there were limitations in detecting those with marginally impaired left ventricular abnormalities in the general population[60]. This may be due to the relatively non-specific association with left ventricular systolic dysfunction at lower levels of plasma BNP or NT-proBNP. Some investigators have attempted to increase the yield by focusing on high-risk subgroups which may be more cost-effective[61]. A high prevalence of elevated plasma BNP levels has been observed in a patient population at risk of developing heart failure (so-called “Stage A” heart failure), particularly in those with a history of diabetes mellitus[62,63] and in the elderly[64-66]. It is conceivable that plasma BNP and NT-proBNP may be useful to screening for these high-risk populations who may be referred for further echocardiographic screening for ALVD, although the “cut-off” levels may differ in different patient populations. There is also promising data suggesting the use of urinary N-terminal BNP measurements, which parallel the results obtained from measuring plasma N-terminal BNP levels[67]. However at this time, routine BNP testing remains not

appropriate for screening large asymptomatic patient populations for left ventricular systolic dysfunction.

IV. Recommendation 1: At this time, routine plasma BNP or NT-proBNP testing is not appropriate for screening large asymptomatic patient populations for left ventricular dysfunction.

Strength/consensus of recommendation: Class III (for routine screening in asymptomatic population)

IV. Recommendation 2: There is evidence to suggest that plasma BNP or NT-proBNP testing can be helpful to identify selected patients with left ventricular systolic dysfunction in the post-MI setting or in patients at high risk of developing heart failure (e.g. history of myocardial infarction, diabetes mellitus). However, the diagnostic ranges and cost-effectiveness remain controversial.

Strength/consensus of recommendation: Class IIb

V. Cardiac biomarkers in risk stratification and prognostication for patients with heart failure

There is a growing body of literature to support the consistent utility of plasma BNT or NT-proBNP testing in risk stratification and prognostication in patients with chronic heart failure, or even those without prior history of heart failure[58]. This applies to a wide variety of clinical settings, including acute coronary syndromes[68-71], decompensated heart failure[72], stable chronic heart failure[73], or even non-cardiac disorders such as

pulmonary embolism[74,75] or in the general population with no prior history of heart failure[58]. There have also been studies advocating the role of plasma BNP or NT-proBNP testing in patient selection for cardiac transplantation[4,76,77]. A recent study looking at ambulatory patients with cardiac dysfunction found plasma BNP levels to be the only independent predictor of sudden death[78], and at least equivalent in risk stratification to the Heart Failure Survival Score[79].

V. Recommendation 1: Plasma BNP and NT-proBNP can provide a useful addition to clinical assessment in selected situations when risk stratification is required. However, the adequacy of a single plasma BNP or NT-proBNP measurement for this purpose has to be determined.

Strength/consensus of recommendation: Class IIa

VI. Cardiac biomarkers in the management of patients with heart failure

Current medical management of patients with heart failure continues to rely on patients' and physicians' subjective clinical assessment and various non-specific laboratory measurements of organ dysfunction and fluid status. Plasma BNP concentrations are known to fall rapidly following diuretic therapy in patients with decompensated heart failure[80-82]. Furthermore, plasma BNP correlates with symptom status in the outpatient setting[83]. The Therefore, the natural extension in BNP testing beyond its diagnostic capabilities is to guide therapy in an objective manner. Indeed, this hypothesis has been tested in a small pilot study in patients with mild-to-moderate chronic heart failure where ACE inhibitors and diuretic therapy were targeted below a plasma NT-proBNP

level of 200 pmol/L by the Christchurch assay (equivalent to 1,680 pg/mL) without compromising other organ function (e.g. hypotension, renal insufficiency)[84]. This study found significantly fewer total cardiovascular events (deaths, hospital admissions, or episodes of decompensated heart failure based on a modified Framingham criteria) in the group randomized to NT-proBNP-guided therapy.

Another potential use of plasma BNP testing in treatment monitoring is the assessment of adequacy of therapy following decompensated heart failure. Pre-discharge, but not initial plasma BNP levels have consistently demonstrated better prediction of post-discharge outcomes[72,85]. However, the difficulty remains the determination of this "dry" BNP or NT-proBNP levels which is different from patient to patient, and over-aggressive diuresis based *solely* on plasma BNP or NT-proBNP levels may increase the risk of renal azotemia or extended length of stay without reducing morbidity and mortality.

Several other issues have also emerged over the feasibility of a BNP-guided therapeutic strategy. First, despite initial reports of a tight correlations between hemodynamic improvement and drop in plasma BNP levels following medical therapy, this relationship has not been consistent in patients with advanced heart failure[86]. Furthermore, changes in plasma BNP levels with beta-blocker therapy (proven to improve morbidity and mortality in this population) have been inconsistent[22,87-89]. The wide variation of single or sequential plasma BNP levels in chronic heart failure after long-term medical therapy have also created difficulties in establishing a single "target" level[43,44,90,91]. Two

larger studies are currently underway to confirm the utility of a BNP-guided therapeutic strategy.

IV. Recommendation 1: Although there is evidence from a pilot study to suggest that plasma BNP or NT-proBNP testing can be helpful to guide therapy in patients with mild-to-moderate heart failure, at this time, routine plasma BNP or NT-proBNP testing is *not* indicated for therapeutic decisions for patients with acute or chronic heart failure. Furthermore, the frequency of BNP or NT-proBNP testing and the utility of BNP or NT-proBNP testing in the monitoring patients with heart failure remain unclear.

Strength/consensus of recommendation: Class IIb

Conclusions

There is no doubt that plasma BNP and NT-proBNP testing has revolutionize the way we approach the diagnosis and management of heart failure over the last few years. However, like most diagnostic tests, the validity of the test results has to complement clinical findings to define a disease process. It is in this context that BNP is not a stand-alone test, and must be used and interpreted in a larger clinical context, with confounding factors taken into account. Nevertheless, there is an unsurpassed excitement in the heart failure community that significant advances in our understanding of how these present and future cardiac biomarkers can better characterize patients disease states and individualize therapy.

Table 1. Partial list of cardiac biomarkers in the clinical diagnosis, management and risk stratification of heart failure

Standard Electrolytes and Metabolic Markers
Sodium
Albumin
Total bilirubin
Hemoglobin
Uric acid
Neurohormones
Catecholamines (Norepinephrine, epinephrine)
Renin, angiotensin II and aldosterone
Natriuretic peptides (ANP, BNP, C-type, N-terminal proANP, N-terminal proBNP)
Endothelin-1
Novel biomarkers
High-sensitivity cardiac troponin
High-sensitivity C-reactive protein (hsCRP)
Apelin
Cardiotrophin-1
Urotensin-II
Adrenomedullin
Leptin
Ghrelin
Myotrophin
Insulin-like growth factor-1 (IGF-1)

References:

1. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldmanmd AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC, Jr. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. *Circulation*. 2001;104:2996-3007.
2. Kalra PR, Clague JR, Bolger AP, Anker SD, Poole-Wilson PA, Struthers AD, Coats AJ. Myocardial production of C-type natriuretic peptide in chronic heart failure. *Circulation*. 2003;107:571-3.
3. Kinugawa T, Kato M, Ogino K, Osaki S, Igawa O, Hisatome I, Shigemasa C. Plasma endothelin-1 levels and clinical correlates in patients with chronic heart failure. *J Card Fail*. 2003;9:318-24.
4. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108:833-8.
5. Berton G, Cordiano R, Palmieri R, Pianca S, Pagliara V, Palatini P. C-reactive protein in acute myocardial infarction: association with heart failure. *Am Heart J*. 2003;145:1094-101.
6. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agara M, Olaz-Preciado F, Urbieta-Echezarreta M, Gonzalez-Arencibia C. C-reactive protein as a predictor of improvement and readmission in heart failure. *Eur J Heart Fail*. 2002;4:331-6.
7. Chen MM, Ashley EA, Deng DX, Tsalenko A, Deng A, Tabibiazar R, Ben-Dor A, Fenster B, Yang E, King JY, Fowler M, Robbins R, Johnson FL, Bruhn L, McDonagh T, Dargie H, Yakhini Z, Tsao PS, Quertermous T. Novel role for the potent endogenous inotrope apelin in human cardiac dysfunction. *Circulation*. 2003;108:1432-9.
8. Foldes G, Horkay F, Szokodi I, Vuolteenaho O, Ilves M, Lindstedt KA, Mayranpaa M, Sarman B, Seres L, Skoumal R, Lako-Futo Z, deChatel R, Ruskoaho H, Toth M. Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure. *Biochem Biophys Res Commun*. 2003;308:480-5.
9. O'Brien RJ, Loke I, Davies JE, Squire IB, Ng LL. Myotrophin in human heart failure. *J Am Coll Cardiol*. 2003;42:719-25.
10. Ng LL, Loke I, O'Brien RJ, Squire IB, Davies JE. Plasma urotensin in human systolic heart failure. *Circulation*. 2002;106:2877-80.
11. Richards AM, Nicholls MG, Lainchbury JG, Fisher S, Yandle TG. Plasma urotensin II in heart failure. *Lancet*. 2002;360:545-6.
12. Douglas SA, Tayara L, Ohlstein EH, Halawa N, Giaid A. Congestive heart failure and expression of myocardial urotensin II. *Lancet*. 2002;359:1990-7.

13. Richards AM, Doughty R, Nicholls MG, MacMahon S, Sharpe N, Murphy J, Espiner EA, Frampton C, Yandle TG. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Australia-New Zealand Heart Failure Group. *J Am Coll Cardiol*. 2001;37:1781-7.
14. Richards AM, Nicholls MG, Yandle TG, Frampton C, Espiner EA, Turner JG, Buttimore RC, Lainchbury JG, Elliott JM, Ikram H, Crozier IG, Smyth DW. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation*. 1998;97:1921-9.
15. Talwar S, Squire IB, Downie PF, O'Brien RJ, Davies JE, Ng LL. Elevated circulating cardiotrophin-1 in heart failure: relationship with parameters of left ventricular systolic dysfunction. *Clin Sci (Lond)*. 2000;99:83-8.
16. Ng LL, O'Brien RJ, Demme B, Jennings S. Non-competitive immunochemiluminometric assay for cardiotrophin-1 detects elevated plasma levels in human heart failure. *Clin Sci (Lond)*. 2002;102:411-6.
17. Ng LL, Loke IW, O'Brien RJ, Squire IB, Davies JE. Plasma urocortin in human systolic heart failure. *Clin Sci (Lond)*. 2003.
18. Richards AM. The natriuretic peptides in heart failure. *Basic Res Cardiol*. 2004;99:94-100.
19. Murdoch DR, McDonagh TA, Byrne J, Blue L, Farmer R, Morton JJ, Dargie HJ. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison of the hemodynamic and neuroendocrine effects of tailored versus empirical therapy. *Am Heart J*. 1999;138:1126-32.
20. Brunner-La Rocca HP, Weilenmann D, Kiowski W, Maly FE, Candinas R, Follath F. Within-patient comparison of effects of different dosages of enalapril on functional capacity and neurohormone levels in patients with chronic heart failure. *Am Heart J*. 1999;138:654-62.
21. Kawai K, Hata K, Takaoka H, Kawai H, Yokoyama M. Plasma brain natriuretic peptide as a novel therapeutic indicator in idiopathic dilated cardiomyopathy during beta-blocker therapy: a potential of hormone-guided treatment. *Am Heart J*. 2001;141:925-32.
22. Hara Y, Hamada M, Shigematsu Y, Suzuki M, Kodama K, Kuwahara T, Hashida H, Ikeda S, Ohtsuka T, Hiasa G, Hiwada K. Effect of beta-blocker on left ventricular function and natriuretic peptides in patients with chronic heart failure treated with angiotensin-converting enzyme inhibitor. *Jpn Circ J*. 2000;64:365-9.
23. Latini R, Masson S, Anand I, Judd D, Maggioni AP, Chiang YT, Bevilacqua M, Salio M, Cardano P, Dunselman PH, Holwerda NJ, Tognoni G, Cohn JN. Effects of valsartan on circulating brain natriuretic peptide and norepinephrine in symptomatic chronic heart failure: the Valsartan Heart Failure Trial (Val-HeFT). *Circulation*. 2002;106:2454-8.
24. Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, Ohnishi M, Sawaki M, Fujii M, Matsumoto T, Matsui T, Kinoshita M. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J Am Coll Cardiol*. 2001;37:1228-33.

25. Rousseau MF, Gurne O, Duprez D, Van Mieghem W, Robert A, Ahn S, Galanti L, Ketelslegers JM. Beneficial neurohormonal profile of spironolactone in severe congestive heart failure: results from the RALES neurohormonal substudy. *J Am Coll Cardiol*. 2002;40:1596-601.
26. Buckley MG, Marcus NJ, Yacoub MH. Cardiac peptide stability, aprotinin and room temperature: importance for assessing cardiac function in clinical practice. *Clin Sci (Lond)*. 1999;97:689-95.
27. Nowatzke WL, Cole TG. Stability of N-terminal pro-brain natriuretic peptide after storage frozen for one year and after multiple freeze-thaw cycles. *Clin Chem*. 2003;49:1560-2.
28. Maisel AS. The diagnosis of acute congestive heart failure: role of BNP measurements. *Heart Fail Rev*. 2003;8:327-34.
29. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC, Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002;40:976-82.
30. Emdin M, Passino C, Del Ry S, Prontera C, Galetta F, Clerico A. Influence of gender on circulating cardiac natriuretic hormones in patients with heart failure. *Clin Chem Lab Med*. 2003;41:686-92.
31. Loke I, Squire IB, Davies JE, Ng LL. Reference ranges for natriuretic peptides for diagnostic use are dependent on age, gender and heart rate. *Eur J Heart Fail*. 2003;5:599-606.
32. McLean AS, Huang SJ, Nalos M, Tang B, Stewart DE. The confounding effects of age, gender, serum creatinine, and electrolyte concentrations on plasma B-type natriuretic peptide concentrations in critically ill patients. *Crit Care Med*. 2003;31:2611-8.
33. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis*. 2003;41:571-9.
34. Vesely DL. Natriuretic peptides and acute renal failure. *Am J Physiol Renal Physiol*. 2003;285:F167-77.
35. McCollough PA, Kuncheria J, Mathur VS. Diagnostic and therapeutic utility of B-type natriuretic peptide in patients with renal insufficiency and decompensated heart failure. *Rev Cardiovasc Med*. 2003;4 Suppl 7:S3-S12.
36. Herrmann Z, Uhl W, Steinberg HW, Dworschack R. The influence of renal function on NT-proBNP levels in various disease groups. *Clin Lab*. 2003;49:649-656.
37. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, Vasan RS. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;109:594-600.
38. Schultz M, Faber J, Kistorp C, Jarlov A, Pedersen F, Wiinberg N, Hildebrandt P. N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) in different thyroid function states. *Clin Endocrinol (Oxf)*. 2004;60:54-9.

39. Missouris CG, Grouzmann E, Buckley MG, Barron J, MacGregor GA, Singer DR. How does treatment influence endocrine mechanisms in acute severe heart failure? Effects on cardiac natriuretic peptides, the renin system, neuropeptide Y and catecholamines. *Clin Sci (Lond)*. 1998;94:591-9.
40. Albage A, Kenneback G, van der Linden J, Berglund H. Improved neurohormonal markers of ventricular function after restoring sinus rhythm by the Maze procedure. *Ann Thorac Surg*. 2003;75:790-5.
41. Inoue S, Murakami Y, Sano K, Katoh H, Shimada T. Atrium as a source of brain natriuretic polypeptide in patients with atrial fibrillation. *J Card Fail*. 2000;6:92-6.
42. Rossi A, Enriquez-Sarano M, Burnett JC, Jr., Lerman A, Abel MD, Seward JB. Natriuretic peptide levels in atrial fibrillation: a prospective hormonal and Doppler-echocardiographic study. *J Am Coll Cardiol*. 2000;35:1256-62.
43. Tang WH, Girod JP, Lee MJ, Starling RC, Young JB, Van Lente F, Francis GS. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation*. 2003;108:2964-6.
44. Troughton RW, Prior DL, Pereira JJ, Martin M, Fogarty A, Morehead A, Yandle TG, Richards AM, Starling RC, Young JB, Thomas JD, Klein AL. Plasma B-type natriuretic peptide levels in systolic heart failure: importance of left ventricular diastolic function and right ventricular systolic function. *J Am Coll Cardiol*. 2004;43:416-422.
45. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, Gardetto N, Wanner E, Maisel AS. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation*. 2002;105:595-601.
46. Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AH, Duc P, Omland T, Storrow AB, Krishnaswamy P, Abraham WT, Clopton P, Steg G, Aumont MC, Westheim A, Knudsen CW, Perez A, Kamin R, Kazanegra R, Herrmann HC, McCullough PA. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. *J Am Coll Cardiol*. 2003;41:2010-7.
47. Cheung BM. Plasma concentration of brain natriuretic peptide is related to diastolic function in hypertension. *Clin Exp Pharmacol Physiol*. 1997;24:966-8.
48. Masson S, Vago T, Baldi G, Salio M, De Angelis N, Nicolis E, Maggioni AP, Latini R, Norbiato G, Bevilacqua M. Comparative measurement of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in ambulatory patients with heart failure. *Clin Chem Lab Med*. 2002;40:761-3.
49. Yeo KT, Wu AH, Apple FS, Kroll MH, Christenson RH, Lewandrowski KB, Sedor FA, Butch AW. Multicenter evaluation of the Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay. *Clin Chim Acta*. 2003;338:107-15.
50. Wu AH, Smith A, Wieczorek S, Mather JF, Duncan B, White CM, McGill C, Katten D, Heller G. Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. *Am J Cardiol*. 2003;92:628-31.
51. Wang TJ, Larson MG, Levy D, Benjamin EJ, Corey D, Leip EP, Vasan RS. Heritability and genetic linkage of plasma natriuretic peptide levels. *Circulation*. 2003;108:13-6.

52. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161-7.
53. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004;350:647-54.
54. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, Gordon G, Bagg W, Oxenham H, Yandle T, Richards M, Sharpe N. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol*. 2003;42:1793-800.
55. Packer M. Should B-type natriuretic peptide be measured routinely to guide the diagnosis and management of chronic heart failure? *Circulation*. 2003;108:2950-3.
56. Logeart D, Saudubray C, Beyne P, Thabut G, Ennezat PV, Chavelas C, Zanker C, Bouvier E, Solal AC. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. *J Am Coll Cardiol*. 2002;40:1794-800.
57. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, Levy D. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. *JAMA*. 2002;288:1252-9.
58. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA, Vasan RS. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med*. 2004;350:655-63.
59. Nakamura M, Tanaka F, Yonezawa S, Satou K, Nagano M, Hiramori K. The limited value of plasma B-type natriuretic peptide for screening for left ventricular hypertrophy among hypertensive patients. *Am J Hypertens*. 2003;16:1025-9.
60. Luchner A, Burnett JC, Jr., Jougasaki M, Hense HW, Heid IM, Muders F, Riegger GA, Schunkert H. Evaluation of brain natriuretic peptide as marker of left ventricular dysfunction and hypertrophy in the population. *J Hypertens*. 2000;18:1121-8.
61. Nielsen OW, McDonagh TA, Robb SD, Dargie HJ. Retrospective analysis of the cost-effectiveness of using plasma brain natriuretic peptide in screening for left ventricular systolic dysfunction in the general population. *J Am Coll Cardiol*. 2003;41:113-20.
62. Epshteyn V, Morrison K, Krishnaswamy P, Kazanegra R, Clopton P, Mudaliar S, Edelman S, Henry R, Maisel A. Utility of B-type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. *Diabetes Care*. 2003;26:2081-7.
63. Silver MA, Pisano C. High incidence of elevated B-type natriuretic peptide levels and risk factors for heart failure in an unselected at-risk population (stage A): implications for heart failure screening programs. *Congest Heart Fail*. 2003;9:127-32.

64. Groenning BA, Raymond I, Hildebrandt PR, Nilsson JC, Baumann M, Pedersen F. Diagnostic and prognostic evaluation of left ventricular systolic heart failure by plasma N-terminal pro-brain natriuretic peptide concentrations in a large sample of the general population. *Heart*. 2004;90:297-303.
65. Alehagen U, Lindstedt G, Eriksson H, Dahlstrom U. Utility of the amino-terminal fragment of pro-brain natriuretic peptide in plasma for the evaluation of cardiac dysfunction in elderly patients in primary health care. *Clin Chem*. 2003;49:1337-46.
66. Hutcheon SD, Gillespie ND, Struthers AD, McMurdo ME. B-type natriuretic peptide in the diagnosis of cardiac disease in elderly day hospital patients. *Age Ageing*. 2002;31:295-301.
67. Ng LL, Geeranavar S, Jennings SC, Loke I, O'Brien RJ. Diagnosis of heart failure using urinary natriuretic peptides. *Clin Sci (Lond)*. 2004;106:129-33.
68. James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, Barnathan ES, Califf R, Topol EJ, Simoons ML, Wallentin L. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation*. 2003;108:275-81.
69. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton C, Turner J, Crozier IG, Yandle TG. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation*. 2003;107:2786-92.
70. Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J, Hartford M, Caidahl K. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation*. 2002;106:2913-8.
71. de Lemos JA, Morrow DA. Combining natriuretic peptides and necrosis markers in the assessment of acute coronary syndromes. *Rev Cardiovasc Med*. 2003;4 Suppl 4:S37-46.
72. Cheng V, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol*. 2001;37:386-91.
73. Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP, Glazer RD, Tognoni G, Cohn JN. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation*. 2003;107:1278-83.
74. Pruszczyk P, Kostrubiec M, Bochowicz A, Styczynski G, Szulc M, Kurzyna M, Fijalkowska A, Kuch-Wocial A, Chlewicka I, Torbicki A. N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism. *Eur Respir J*. 2003;22:649-53.
75. Kruger S, Graf J, Merx MW, Koch KC, Kunz D, Hanrath P, Janssens U. Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. *Am Heart J*. 2004;147:60-5.

76. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J*. 2003;24:1735-43.
77. Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P, Von Scheidt W. Clinical value of brain natriuretic peptide for candidate selection before cardiac transplantation. *J Heart Lung Transplant*. 2001;20:164.
78. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, Pacher R. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation*. 2002;105:2392-7.
79. Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P, vonScheidt W. Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. *J Am Coll Cardiol*. 2001;38:1934-41.
80. Richards AM, Crozier IG, Yandle TG, Espiner EA, Ikram H, Nicholls MG. Brain natriuretic factor: regional plasma concentrations and correlations with haemodynamic state in cardiac disease. *Br Heart J*. 1993;69:414-7.
81. Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Fail*. 2001;7:21-9.
82. Johnson W, Omland T, Hall C, Lucas C, Myking OL, Collins C, Pfeffer M, Rouleau JL, Stevenson LW. Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and vasodilators for class IV heart failure. *J Am Coll Cardiol*. 2002;39:1623-9.
83. Lee SC, Stevens TL, Sandberg SM, Heublein DM, Nelson SM, Jougasaki M, Redfield MM, Burnett JC, Jr. The potential of brain natriuretic peptide as a biomarker for New York Heart Association class during the outpatient treatment of heart failure. *J Card Fail*. 2002;8:149-54.
84. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet*. 2000;355:1126-30.
85. O'Brien RJ, Squire IB, Demme B, Davies JE, Ng LL. Pre-discharge, but not admission, levels of NT-proBNP predict adverse prognosis following acute LVF. *Eur J Heart Fail*. 2003;5:499-506.
86. O'Neill JO, Bott-Silverman C, McRae AT, Troughton RW, Ng K, Starling RC, Young JB. B-type natriuretic peptide levels are not a surrogate marker for invasive hemodynamics during management of patients with severe heart failure. *Am Heart J*. 2004:in press.
87. van den Meiracker AH, Lameris TW, van de Ven LL, Boomsma F. Increased plasma concentration of natriuretic peptides by selective beta1-blocker bisoprolol. *J Cardiovasc Pharmacol*. 2003;42:462-8.
88. Zugck C, Haunstetter A, Kruger C, Kell R, Schellberg D, Kubler W, Haass M. Impact of beta-blocker treatment on the prognostic value of currently used risk predictors in congestive heart failure. *J Am Coll Cardiol*. 2002;39:1615-22.
89. Stanek B, Frey B, Hulsmann M, Berger R, Sturm B, Strametz-Juranek J, Bergler-Klein J, Moser P, Bojic A, Hartter E, Pacher R. Prognostic evaluation of

neurohumoral plasma levels before and during beta-blocker therapy in advanced left ventricular dysfunction. *J Am Coll Cardiol*. 2001;38:436-42.

90. Melzi d'Eril G, Tagnochetti T, Nauti A, Klersy C, Papalia A, Vadacca G, Moratti R, Merlini G. Biological variation of N-terminal pro-brain natriuretic peptide in healthy individuals. *Clin Chem*. 2003;49:1554-5.
91. McGeoch G, Lainchbury J, Town GI, Toop L, Espiner E, Richards AM. Plasma brain natriuretic peptide after long-term treatment for heart failure in general practice. *Eur J Heart Fail*. 2002;4:479-83.