

Utilizing NT-ProBNP in the Selection of Risks for Life Insurance

Ramanathan K. Illango, MBBS, MBA

Brain natriuretic peptide (BNP) is a counter-regulatory hormone produced mainly by ventricular myocardium. Early research studies were performed to ascertain its value in the diagnosis of congestive heart failure in acute care settings. Subsequent studies have explored its utility in screening for asymptomatic left ventricular dysfunction in the community, determining prognosis in coronary artery disease, appropriate timing of surgery in valve disorders, and in evaluating many other cardiac diseases. This review summarizes the current status of medical literature, introduces a new test to the insurance industry.

Address: RK Illango Consulting, Inc, 21021 Goshen Rd., Gaithersburg, MD 200882; ph: 301-963-4650; fax: 301-963-4651; e-mail: rk@rkillango.com.

Correspondent: Ramanathan K. Illango, MBBS, MBA.

Key words: Brain natriuretic peptide, left ventricular dysfunction, congestive heart failure, coronary artery disease, life insurance.

Competing interests: Dr. Illango has a consulting arrangement with Clinical Reference Laboratory.

Received: June 1, 2007

Accepted: August 13, 2007

Amino-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) testing has been available as a risk selection tool from the insurance laboratories for 2 years. The use of NT-proBNP has resulted in documented significant mortality savings for at least one life insurance company.¹ The utility of brain natriuretic peptides (BNP) has been evaluated in clinical trials for more than a decade and its use in diagnosing and treating heart failure is now an accepted clinical practice.² It is evident from the examination of the medical literature that BNP has the potential to be a valuable cardiac biomarker that will have a major impact on care of cardiac

patients. This review is aimed at assessing the information from the major clinical studies and its potential role in insurance risk selection.

Natriuretic peptides are a family of counter-regulatory hormones that have a role in the body's defenses against hypertension and body fluid expansion.³ In addition to brain natriuretic peptide, the family of natriuretic peptides includes atrial natriuretic peptide (ANP) that is produced mainly by the atrium and C-type natriuretic peptide that is found in the several tissues. Brain natriuretic peptide is produced mainly by the ventricular myocardium in response to

ventricular wall stretch, ventricular dilatation and pressure overload. The actions of BNP include natriuresis, vasodilatation and inhibition of the renin-angiotensin-aldosterone axis, and sympathetic nerve activity. BNP is secreted by the myocyte as a prohormone containing 108 amino acids and is enzymatically cleaved into the biologically active 32 amino acid C terminal peptide (BNP) and a physiologically inactive 76 amino acid N-terminal proBNP (NT-proBNP). BNP has very short half-life of about 23 minutes in contrast to a half-life of 60 to 120 minutes for NT-proBNP. NT-proBNP also has better in vitro stability. It is stable in EDTA plasma for 3 days at room temperature or longer at 4 degrees centigrade.⁴

Initial clinical studies on the role of natriuretic peptides were done utilizing ANP and BNP. More recent clinical trials are being performed using the NT-proBNP assay as it has good analytical performance and better precision.⁴ This review will focus mostly on clinical trials performed utilizing NT-proBNP except when none is available for the topic under discussion.

Early studies of BNP were done on its utility in the diagnosis of congestive heart failure (CHF) in acute care settings. Since then studies have been done on its value in the detection of systolic and diastolic dysfunction and determining prognosis of acute coronary syndromes, stable coronary heart disease, valve disorders, pulmonary hypertension, hypertrophic cardiomyopathy, and many other cardiac disorders. Several studies have also been performed to assess its value in asymptomatic individuals in the community to screen for subclinical disease and to determine its impact on mortality.

CHF AND LEFT VENTRICULAR DYSFUNCTION

The clinical syndrome of congestive heart failure (CHF) affects nearly 5 million Americans with an incidence of 10/1000 popula-

tion among Americans over the age 65.⁵ Symptomatic heart failure confers a prognosis worse than most cancers, with a 1-year mortality of 45%. It is estimated that nearly half of those with heart failure have normal systolic function and in most of these cases there is moderate to severe diastolic dysfunction.⁷ It is also apparent that there is a significant number of individuals in the community with undiagnosed systolic and diastolic dysfunction who are at considerable risk of early death. NT-proBNP and BNP appear to be excellent diagnostic tools for the diagnosis of heart failure and undiagnosed systolic and diastolic dysfunction.

The Breathing Not Properly Multinational Study is a 7 center prospective study of 1586 patients that examines the use of BNP in the diagnosis of congestive heart failure (CHF) in those who presented to the emergency department with acute dyspnea.⁶ This particular article is an analysis of a subset of 452 patients with congestive heart failure who had an echocardiogram done within 30 days of the visit. Of this group of 452 patients, 36.5% had preserved LV function with a mean ejection fraction of 56%; the rest had abnormal systolic function and a mean EF of 28%. The median level of brain natriuretic peptide for the group without CHF was 34 pg/mL (from the main study), those with CHF and normal systolic function was 413 pg/mL and for the group with CHF and abnormal systolic function was 821 pg/mL. Brain natriuretic peptide was effective in separating all CHF from non-CHF patients with 90% sensitivity and area under the curve (AUC) 0.90 at a cutoff value of 100 pg/mL.

The prevalence of left ventricular dysfunction in the community is much higher than is recognized, and this condition is associated with considerable increased mortality. A study of 2042 randomly selected residents of Olmsted County (Minnesota) aged 45 and older during a 3-year period illustrates the magnitude of the problem of systolic and diastolic left ventricular dysfunction in the

Table 1. Prevalence of Systolic and Diastolic Dysfunction by Age⁷

	45 to 54	55 to 64	65 to 74	75 and older	Overall
Diastolic dysfunction					
Moderate (Pseudonormal)	1.4%	6.0%	9.9%	14.6%	6.6%
Severe (Restrictive)	0%	0.4%	0.7%	3.4%	0.7%
Systolic dysfunction					
EF ≤50	3.0%	4.8%	7.1%	12.9%	6.0%
EF ≤40	0.8%	1.3%	2.7%	4.4%	2.0%

community.⁷ In this community, the prevalence of any congestive heart failure diagnosis was 2.6%. Forty-one percent of those with a diagnosis of CHF had an ejection fraction (EF) greater than 50%. The prevalence of systolic dysfunction with ejection fraction of less than 50% was 6.0%, and EF of less than 40% was 2.0% (Table 1). The prevalence of diastolic dysfunction was similar with moderate dysfunction of 6.6% and severe dysfunction of 0.7%. There was marked increase in all-cause mortality in those with any left ventricular dysfunction.

A subsequent prospective study was done by the same group of investigators to evaluate the presence of diastolic dysfunction among patients with heart failure and its impact on mortality.⁸ The study included 556 patients with CHF from Olmsted County. Of this group with congestive heart failure, 308 patients (55%) had ejection fraction >50%; isolated diastolic dysfunction with preserved ejection fraction was present in 242 patients (44%). The median BNP for the whole group of 556 with CHF was 257 pg/dL, those with preserved ejection fraction was 183 pg/mL and the rest with abnormal ejection fraction was 388 pg/mL. In those

with isolated diastolic dysfunction and normal ejection fraction, BNP was higher when diastolic dysfunction was more severe. There was no difference in mortality rate between those with reduced and those with preserved ejection fraction.

Another study of these same 2042 residents of Olmsted County utilized NT-proBNP instead of BNP to detect LV dysfunction and to assess the impact of age and gender on NT-proBNP values.⁹ NT-proBNP test results were available in 1869 patients of whom 746 were clinically normal. An analysis of the NT-proBNP values of these normal patients reveals that the values were higher at the older ages and in females; however the normal ranges at ages 75 and older are unreliable because of small numbers of patients in this age group (Table 2).

Of the 1869 residents with NT-proBNP test results, 37 had ejection fraction of ≤40% and 115 had EF of ≤50%. It is important to note that of the 37 with ejection fraction of <40%, 45.9% had preclinical LV dysfunction. Table 3 summarizes the relationship between NT-proBNP values and ejection fraction of ≤40% and the cutpoints for diagnosis by age and gender.

Table 2. Age and Gender Specific Ranges for Plasma NT-ProBNP (pg/mL) in Normal Patients⁹

	Age	45–54	55–64	65–74	75–96
Women	Median	54(N=190)	77(N=137)	114(N=57)	124(N=18)
	5 th –95 th percentile	8–141	17–226	25–458	42–587
Men	Median	13(N=187)	25(N=114)	45(N=41)	57(N=2)
	5 th –95 th percentile	5–87	5–88	14–140	46–68

Table 3. NT-proBNP Cutpoints, Sensitivity and Specificity for Age and Gender Strata for the Detection of Ejection Fraction >40%⁹

Age	Men			Women		
	NT-proBNP	Sensitivity	Specificity	NT-proBNP	Sensitivity	Specificity
45–54	108	100	96	Not determined	Not determined	Not determined
55–64	234	100	94	246	100	90
65–74	462	91	94	773	100	98
≥75	1024	89	84	879	75	85

A well designed study by a group of investigators from Berlin provides guidance in the use of NT-proBNP in isolated diastolic dysfunction.¹⁰ This study compares NT-proBNP values of 68 symptomatic patients with isolated diastolic dysfunction (average age 51±9) with 50 patients (average age 49±10) with normal left ventricular function. All patients had echocardiography and ventriculography. NT-proBNP level in patients with isolated diastolic dysfunction was 189.54 pg/mL vs 51.89 pg/mL for controls. There was “no significant difference” in NT-proBNP values between men (164.3 pg/mL) and women (204 pg/mL). NT-proBNP levels increased significantly according to the severity of diastolic dysfunction: impaired relaxation was associated with NT-proBNP level of 151.6 pg/mL, pseudonormal filling was associated with NT-proBNP level of 308.1 pg/mL, and restrictive filling was associated with NT-proBNP level of 2307.1 pg/mL. ROC curve analysis revealed an area under the curve (AUC) for NT-proBNP of 0.83. This was in between AUC for left ventricular end diastolic pressure (0.84) and tissue Doppler imaging (0.81) indicating that it is comparable to other accepted methods for diagnosing diastolic dysfunction.

RISK OF CARDIOVASCULAR EVENTS AND DEATH IN GENERAL POPULATION

A community based prospective (Framingham Offspring) study of 3346 persons without heart failure with a mean follow up of

5.2 years explored the link between mortality and natriuretic peptide levels.¹¹ Increasing plasma BNP and NT pro-ANP levels were associated with increased risk of death. Values of BNP and NT-proANP above eightieth percentile were associated with increased risk of death of 62% and 76% and a 3 and 5 times the risk of heart failure, respectively. Elevated natriuretic peptide levels were also associated with the risk of atrial fibrillation and TIA or stroke but not the risk of coronary artery disease. This increased risk of death was noted across all tertiles of BNP. Excess risk was apparent at peptide levels well below the current threshold used to diagnose heart failure. This ability of natriuretic peptides to predict increased mortality in a population free of heart failure was confirmed in another Olmstead County study.¹²

STABLE CORONARY ARTERY DISEASE

Elevated NT-proBNP is a marker for cardiovascular morbidity and mortality even in the absence of systolic or diastolic dysfunction and other prognostic markers. It provides prognostic information above and beyond that provided by conventional risk factors and is independently associated with ischemia in those with stable coronary artery disease.

The Heart and Soul Study is a prospective cohort study of 987 ambulatory patients with stable coronary artery disease.¹³ The association of plasma NT-proBNP levels with cardiovascular events or death was assessed during a mean follow up of

3.7 years. A total of 256 participants developed cardiovascular events or died. Participants in the highest (≥ 460 pg/mL) quartile of NT-proBNP were older, were more likely to have clinical risk factors for cardiovascular events, including a history of hypertension, myocardial infarction or revascularization, higher systolic blood pressure and lower creatinine clearance. Other known poor prognostic markers such as low ejection fraction, diastolic dysfunction, increased left ventricular mass index, inducible ischemia, poor exercise capacity, elevated C-reactive protein, detectable troponin, and NYHA class III or IV were significantly associated with increasing levels of NT-proBNP. The cardiovascular event rate and death increased with each successive quartile of NT-proBNP. Individuals with NT-proBNP concentrations in the highest quartile had nearly an 8-fold increased rate of cardiovascular events and death compared to the lowest quartile.

The elevated levels of NT-proBNP predicted cardiovascular morbidity and mortality independent of other prognostic markers and identified at-risk individuals even in the absence of systolic or diastolic dysfunction by echocardiography. A prior study by the same group of investigators found that elevated levels of BNP to be independently associated with inducible ischemia among outpatients with stable coronary disease, particularly among those with a history of myocardial infarction.¹⁴

The effect of NT-proBNP level on long-term mortality from all causes was evaluated by a large prospective observational study of patients with angiographic evidence of coronary artery disease and normal left ventricular function.¹⁵ After a median follow up of 9.2 years, 288 of 1034 patients have died. The NT-proBNP level was significantly lower among patients who survived than those who died (120 vs 386 pg/mL). Kaplan-Meier estimates of survival showed a progressive decrease in survival from the first (< 64 pg/mL) to the fourth (> 455 pg/mL) quartile

even after adjusting for age, presence or absence of diabetes, smoking status, left ventricular ejection fraction, presence or absence of heart failure and severity of angiographic coronary artery disease.

ACUTE CORONARY SYNDROME

Acute coronary syndrome (ACS) encompasses a continuum of events ranging from unstable angina pectoris with no biochemical evidence of myocardial necrosis to ST elevation acute myocardial infarction (AMI). NT-pro BNP is a powerful indicator of mortality in ACS and provides prognostic information above and beyond the conventional risk markers.

The long-term value of NT-proBNP in assessing all-cause mortality was studied in an unselected consecutive series of patients admitted with ACS to a Scandinavian teaching hospital.¹⁶ The study population consisted of 609 patients, 204 with ST elevation acute myocardial infarction, 220 with non ST elevation acute myocardial infarction and 185 with unstable angina. Appropriate interventions were performed during the primary hospitalization.

After a median duration of 51 months, 86 patients had died. The median BNP concentration at baseline for the whole group was 545 pg/mL, 1034 pg/mL for those with ST-elevation AMI, 644 pg/mL for those with non ST-segment elevation AMI, and 174 pg/mL for those with unstable angina. Those who survived had a lower median NT-proBNP than those who died (442 pg/mL vs 1306 pg/mL; $P < 0.0001$). The unadjusted relative risk for those with supra median (> 545 pg/mL) NT-proBNP compared with infra median values was 3.9 for the whole group, 4.7 for those with ST segment elevation MI, 5.6 for those with non ST segment elevation MI and 3.0 for those with unstable angina. In a multivariate model adjusting for age, Killip class and LVEF, supra median NT-proBNP remained significantly associated with mortality in all groups.

The GUSTO-IV sub study, a study of 7800 patients with non ST-segment elevation acute coronary syndrome confirmed the findings of the Scandinavian study.¹⁷ Multivariate logistical regression analysis adjusting for a large number of predictors of long-term mortality found increasing quartiles of NT-proBNP still independently predictive of 1-year mortality.

LONE ATRIAL FIBRILLATION

Approximately 20% to 30% of atrial fibrillation occurs in the absence of objective evidence of structural heart disease and is known as lone atrial fibrillation. Atrial fibrillation is associated with NT-proBNP elevation even in the absence of demonstrable structural heart disease.

A study at Massachusetts General Hospital sought to characterize natriuretic peptide levels in subjects with lone atrial fibrillation.¹⁸ This study enrolled 150 subjects with electrocardiographic evidence of at least 1 episode of atrial fibrillation (average age 53.8 ±10.7) and structurally normal heart on echocardiography. Subjects were excluded if they had a history of myocardial infarction, rheumatic heart disease, cardiomyopathy, significant valvular heart disease and hyperthyroidism. Those with hypertension within 2 years of onset of atrial fibrillation were also excluded. Seventy five controls from healthy primary care population matched for age gender and ethnicity (average age 54.3 ±10.3) also had their NT-proBNP levels evaluated. Median NT-proBNP level was significantly elevated in those with lone atrial fibrillation (166 fmoL/mL vs 133 fmoL/mL) compared to healthy controls. Subjects with permanent atrial fibrillation had higher levels (197 fmoL/mL vs 157 fmoL/mL) than those with paroxysmal atrial fibrillation.

HYPERTENSION

Natriuretic peptides have a key role in regulation of blood pressure, yet clinical studies of natriuretic peptides and blood

pressure have yielded conflicting results.¹⁹ Large well controlled studies with the exclusion of those with structural disease by echocardiography are not available. Therefore, it is difficult to comment on the impact of hypertension with no demonstrable left ventricular dysfunction on NT-proBNP.

VALVE DISORDERS

Ventricular wall stress is a consequence of all valve disorders and elevation of natriuretic peptides is a frequent occurrence in valve disorders. Several studies have been done to assess the usefulness of NT-proBNP in managing valve disorders.

The risk of surgical intervention outweighs the risk of sudden cardiac death in asymptomatic patients with severe aortic stenosis. Onset of symptoms is associated with limited survival, averaging 2 to 3 years.²⁰ Thus, the onset of symptoms is a critical point in the natural history of aortic stenosis and the cardinal indication for valve replacement. Determining whether a patient is truly symptomatic is difficult because of the insidious nature of the disease or the patient's inactivity. Plasma NT-proBNP level increased with decreasing size of the aortic valve area and higher NYHA class. It was useful in separating symptomatic from asymptomatic patients.²² Preoperative NT-proBNP levels also predicted post operative outcome with regards to survival.²¹ Post surgery natriuretic peptide levels decreased over the next 6 to 12 months and correlated with regression of LVH.²³ Higher BNP levels after surgery may be indicative of smaller prosthetic valve size and higher transprosthetic gradient.

In isolated chronic aortic regurgitation, the serum natriuretic peptide level correlates directly with severity of the valve disorder and functional status.²³ Post valve surgery, there was a significant drop in natriuretic peptide level, and this correlated with reduction in LVEDD.

Echocardiography is the standard method for evaluating the severity of mitral regurgitation and assessing LV dysfunction. Methods to assess quantitatively the severity of mitral regurgitation are technically demanding and ejection fraction can be maintained in the presence of left ventricular dysfunction. This causes difficulty in determining the optimal time for surgery. A study of 49 patients with isolated mitral regurgitation and left ventricular ejection fraction of greater than 55% revealed that NT-proBNP and ANP levels increase with the severity of mitral regurgitation and are higher in symptomatic compared to asymptomatic patients even when the ejection fraction is normal.²⁵ Another study of 124 patients with organic mitral regurgitation noted lower survival and higher combined endpoint of heart failure and death in those with higher than median BNP.²⁴

HYPERTROPHIC CARDIOMYOPATHY

BNP levels were significantly higher in hypertrophic cardiomyopathy than patients with hypertensive heart disease.²⁸ Elevated levels correlated with the degree of hypertrophy and left ventricular outflow tract gradient.²⁶ BNP levels showed a statistically significant relationship to the degree of functional limitation.²⁷

DISORDERS AFFECTING THE RIGHT VENTRICLE

The response of the right ventricle to ventricular wall stretch, ventricular dilatation and pressure overload is similar to that of the left ventricle. Levels of BNP and related peptides increase in disorders that cause right ventricular dysfunction such as primary pulmonary hypertension, chronic obstructive pulmonary disease, pulmonary embolism and left to right shunts.²⁹

Plasma NT-proBNP is elevated in the majority of cases of pulmonary embolism resulting in right ventricular overload. Plas-

ma levels reflect the degree of overload and may predict short-term outcome.³⁰ In primary pulmonary hypertension, BNP elevation reflects changes in pulmonary hemodynamics and functional capacity.³¹⁻³² Progression of disease paralleled increasing levels of BNP, and favorable response to therapy was associated with reduction in BNP levels. In chronic obstructive pulmonary disease without significant pulmonary hypertension, BNP values are within the normal range.³³ In those with significant pulmonary hypertension (mean pulmonary artery pressure >35 mm Hg) BNP is elevated and is a marker for decreased functional capacity and reduced life expectancy.³⁴

In a study of 50 asymptomatic or minimally symptomatic patients post-surgery for tetralogy of Fallot (TOF), right ventricular dysfunction detected by echocardiography and plasma NT-proBNP determination correlate well with cardiopulmonary exercise capacity.³⁵ In the early stages of right ventricular dysfunction, left ventricular function is usually normal. Evaluation of right ventricle by echocardiogram is technically more difficult, and the standard report does not contain much information about the right ventricle. Therefore, NT-proBNP level is very valuable in the evaluation of these cases.

NON-CARDIAC CAUSES OF NATRIURETIC PEPTIDE ELEVATION

BNP and NT-proBNP are markedly influenced by renal dysfunction. Mild to moderate impairment of renal function leads to approximately 2-fold increase of both markers.³⁶ Low hemoglobin concentration and low body mass index are independently associated with elevated BNP level.³⁶ Both BNP and NT-proBNP are more closely associated with lean mass than fat mass.³⁷

INDUSTRY EXPERIENCE

The following is an analysis of the results of NT-proBNP testing performed on 23,869

Table 4. NT-proBNP by Age and Gender (Insurance Industry Data from CRL)

NT-proBNP pg/mL	Age											
	50 to 59				60 to 69				70 and up			
	F		M		F		M		F		M	
	N	%	N	%	N	%	N	%	N	%	N	%
≤100	3060	84.0	12,276	94.0	697	67.1	3714	83.1	192	35.0	576	52.3
101–200	479	13.1	581	4.4	223	21.5	501	11.2	162	29.6	249	22.6
201–300	67	1.8	113	0.9	70	6.7	122	2.7	77	14.1	120	10.9
301–400	14	0.4	28	0.2	22	2.1	36	0.8	33	6.0	39	3.5
401–500	12	0.3	19	0.1	7	0.7	24	0.5	33	6.0	19	1.7
501–600	3	0.1	14	0.1	11	1.1	17	0.4	6	1.1	18	1.6
601–700	2	0.1	10	0.1	2	0.2	14	0.3	8	1.5	8	0.7
701–800	1	0.0	5	0.0	3	0.3	9	0.2	8	1.5	9	0.8
801–900	1	0.0	3	0.0	0	0.0	4	0.1	4	0.7	10	0.9
901–1000	1	0.0	0	0.0	1	0.1	6	0.1	1	0.2	7	0.6
>1000	4	0.1	17	0.1	2	0.2	24	0.5	24	4.4	47	4.3
	3644	100	13,066	100	1038	100	4471	100	548	100	1102	100

insurance applicants as routine age and amount requirements at Clinical Reference Laboratory. Table 4 provides information on the distribution of NT-proBNP values by age and gender. Descriptive statistics, suggested normal ranges by age and gender are displayed in Table 5.

USE OF NT-PROBNP IN RISK SELECTION

The prevalence of sub clinical LV dysfunction in the community is significant (Table 1) and is associated with considerable excess mortality. Removing this group from the insured population or appropriately rating would result in significant mortality savings. The use of the echocardiogram to detect these cases is not practical, as the cost would be prohibitive. The electrocardiogram, which is widely used in the industry, is a poor screening tool for LV dysfunction.³⁸ The utility of NT-proBNP in detecting left ventricular dysfunction is well established based on multiple studies. Screening for left ventricular dysfunction with NT-proBNP utilizing age and amount guidelines may need to be considered according to the business needs of the individual company.

Mortality in coronary artery disease increases with rising level of NT-proBNP. Therefore, cases with low levels of NT-proBNP could be considered favorably or without required additional testing, and those with very high levels could be postponed for evaluation.

NT-proBNP is elevated in cases of atrial fibrillation even in the absence of demonstrable structural heart disease by echocardiography. All cases of atrial fibrillation with significant elevation of NT-proBNP need evaluation for associated cardiac disease if a recent echocardiogram is not available.

The utility of NT-proBNP in valve disease appears to be confined to cases of moderate to severe valve disorders. Lower levels of NT-proBNP predict a lower risk. Those with high levels and a severe valve disorder are at high risk as NT-proBNP appears to provide mortality information above and beyond that provided by the echocardiogram.

NT-proBNP is also useful in evaluating disorders affecting the right heart such as cor pulmonale, primary pulmonary hypertension, and congenital heart disease.

The level of NT-proBNP increases with age and is higher in females probably due to lower hemoglobin concentration. This

Table 5. Statistical Distribution of NT-proBNP (Insurance Industry Data from CRL)

Age	SEX	N	Min	Max	Mean	Std. Deviation	2 × SD	Normal Range
50–59	F	3633	3	495	61	54	108	0–169
60–69	F	1019	5	470	90	79	156	0–246
70>	F	497	5	499	160	117	234	0–394
50–59	M	13,019	3	497	37	42	44	0–81
60–69	M	4400	3	500*	60	64	128	0–188
≥70	M	1003	5	500*	115	98	196	0–310

* Trimmed at 500 to prevent a few large values distorting the SD computation.

should be considered when setting decision points for underwriters. The data from the literature (Tables 2 and 3) and from Clinical Reference Laboratory (Tables 4 and 5) should provide sufficient information for this purpose. In the long run NT-proBNP, if utilized appropriately, has the potential to simplify the underwriting process, reduce costs and improve cardiovascular mortality for insurance companies.

I would like to express my appreciation to Clinical Reference Laboratory for providing data on NT-proBNP testing on insurance applicants. I am grateful to Dr. Robert Stout, Dr. Robert Palmer and Dr. Robert Feingold for reviewing this article and providing valuable editorial comments and advice.

REFERENCES

1. Privileged communication.
2. Maisel A. The coming of age of natriuretic peptides: The emperor does have clothes! *J Am Coll Cardiol.* 2006;47:61–64.
3. Levin ER, Gardner DG, Samson WK. Mechanisms of disease: natriuretic peptides. *N Engl J Med.* 1998;339:321–328.
4. Yeo KJ, Wu AHB, Apple FS, et al. Multicenter evaluation of Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay. *Clin Chim Acta.* 2003;338:107–115.
5. Jessup M, Bozena S. Medical progress: heart failure. *N Engl J Med.* 2003;348:2007–2018.
6. Maisel AS, McCord J, Nowak RM, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction: Results from a Breathing Not Properly Multinational Study. *J Am Coll Cardiol.* 2003;41:2210–2017.
7. Redfield MM, Jacobsen SJ, Burnett JC, et al. Burden of systolic and diastolic function in the community: Appreciating the scope of heart failure epidemic. *JAMA.* 2003;289:194–202.
8. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. *JAMA.* 2006;296:2209–2216.
9. Costello-Boerrigter LC, Boerrigter G, Redfield MM, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. *J Am Coll Cardiol.* 2006;47:345–353.
10. Tschope C, Kasner M, Westermann D, et al. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. *Eur. Heart J.* 2005;26:2277–2284.
11. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide and the risk of cardiovascular events and death. *N Eng J Med.* 2004;350:655–663.
12. McKie PM, Rodeheffer RJ, Cataliotti A, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide: Biomarkers for mortality in a large community-based cohort free of heart failure. *Hypertension.* 2006;47:874–880.
13. Bibbin-Domingo K, Gupta R, Na B, et al. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-ProBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. *JAMA.* 2007;297:169–176.
14. Bibbin-Domingo K, Ansari M, Schiller NB, et al. B-Type natriuretic peptide and ischemia in patients with stable coronary disease: data from the Heart and Soul Study. *Circulation.* 2003;108:2987–2992.
15. Kragelund C, Gronning B, Kober L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart Disease. *N Engl J Med.* 2005;352:666–675.

16. Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long term mortality in acute coronary syndromes. *Circulation*. 2002;106:2913–2918.
17. James SK, Lindahl B, Siegbahn A, et al. 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;108:275–281.
18. Ellinor PT, Low AF, Patton KK, et al. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. *J Am Coll Cardiol*. 2005;45:82–86.
19. Freitag MH, Larson MG, Levy D, et al. Plasma brain natriuretic peptide levels and blood pressure tracking in Framingham Heart Study. *Hypertension*. 2003;41:978–983.
20. Patel DN, Bailey SR. Role of BNP in patients with severe asymptomatic aortic stenosis. *Eur Heart J*. 2004;25:1972–1973.
21. Berger-Klein J, Klaar U, Heger M, et al. Natriuretic peptides predict symptom-free survival and post-operative outcome in severe aortic stenosis. *Circulation*. 2004;109:2302–2308.
22. Gerber IL, Stewart RAH, Leggett ME, et al. Increased plasma natriuretic levels reflect symptom onset in aortic stenosis. *Circulation*. 2003;107:1884–1890.
23. Weber M, Arnold R, Rau M, et al. Relation of N-terminal pro B-type natriuretic Peptide to progression aortic valve disease. *Eur Heart J*. 2005;26:1023–1030.
24. Detaint D, Messika-Zeitoun D, Avierinos JF, et al. B-type Natriuretic peptide in organic mitral regurgitation. Determinants and impact on outcome. *Circulation*. 2005;111:2391–2397.
25. Sutton TM, Stewart RAH, Gerber IL, et al. Plasma natriuretic peptide levels increase with symptoms and severity of mitral regurgitation. *J Am Coll Cardiol*. 2003;41:2280–2287.
26. Briguori C, Betocchi, Manganelli F, et al. Determinants and clinical significance of natriuretic peptides in hypertrophic cardiomyopathy. *Eur Heart J*. 2001;22:1328–1336.
27. Maron BJ, Thollakanahalli VN, Zonovich AG, et al. Usefulness of B-type natriuretic peptide assay in the assessment of symptomatic state in hypertrophic cardiomyopathy. *Circulation*. 2004;109:984–989.
28. Ogino K, Ogura K, Kinugawa T, et al. Neurohumeral profiles in patients with hypertrophic cardiomyopathy: differences to hypertensive left ventricular hypertrophy. *Circ J Am Heart Assoc*. 2004;68:444–450.
29. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. *Circulation*. 2003;107:2545–2547.
30. Pruszczyk P, Kostrubiec M, Bochowicz A, et al. N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism. *Eur Respir J*. 2003;22:649–653.
31. Leuchte HH, Holzapfel M, Baumgartner RA, et al. Characterization of BNP in long-term follow-up of pulmonary arterial hypertension. *Chest*. 2005;128:2368–2374.
32. Leuchte HH, Neurohr C, Baumgartner R, et al. BNP and exercise capacity in lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med*. 2004;170:360–365.
33. Cabanes L, Richaard-Thiriez B, Fulla Y, et al. Brain natriuretic peptide blood levels in the differential diagnosis of dyspnea. *Chest*. 2001;120:2047–2050.
34. Leuchte HH, Baumgartner RA, Nounou ME, et al. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir Crit Care Med*. 2006;173:744–750.
35. Norozi K, Buchhorn R, Kaiser C, et al. Plasma N-terminal pro-brain natriuretic peptide as a marker of right ventricular dysfunction in patients with tetralogy of Fallot after surgical repair. *Chest*. 2005;128:2563–2570.
36. Knudsen CW, Clopton P, Westheim A, et al. Predictors of elevated B-type natriuretic peptide concentrations in dyspneic patients without heart failure: an analysis from the Breathing Not Properly Multinational Study. *Ann Emerg Med*. 2005;45:573–580.
37. Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. *Circulation*. 2005;112:2163–2168.
38. Talwar S, Squire IB, Davies JE, et al. Plasma N-terminal pro-brain natriuretic peptide and ECG in the assessment of left-ventricular systolic dysfunction in a high risk population. *Eur Heart J*. 1999;20:1736–1744.