JOURNAL OF INSURANCE MEDICINE

J Insur Med 2014;44:7–16

MORTALITY

NT-proBNP as a Predictor of All-Cause Mortality in a Population of Insurance Applicants

Michael Clark, MD, FACC; Valerie Kaufman, MD, FACC, DBIM; Michael Fulks, MD; Vera F. Dolan, MSPH; Robert L. Stout, PhD

Objective.—Quantify the independent value of NT-proBNP in predicting all-cause mortality for individual life insurance applicants and establish risk-based reference ranges.

Method.—By use of the Social Security Death Master File and multivariate analysis, relative mortality was determined for 144,027 life insurance applicants tested (almost all routinely rather than for cause) for NT-proBNP along with other laboratory testing and measurement of BP and BMI.

Results.—Risk increased substantially for NT-proBNP values >300 pg/mL in women and >200 pg/mL in men after age, smoking status and other cardiovascular risk factors were accounted for. The relative risk reached >10 fold at NT-proBNP levels >1000 pg/mL. For those age 50 to 89 and denying a history of heart disease, this level occurred in only 0.5% of applicants but was present in 7% of all deaths.

Conclusion.—NT-proBNP is a strong independent predictor of all-cause mortality but values associated with increased risk vary by sex.

Address of Correspondence: 454 Beltrami Drive, Ukiah, CA 95482; Fax: 707-463-3209; ph: 707-463-3200; dolanvp@consultancy.com

Correspondent: Vera F. Dolan, MSPH.

Author affiliation: Clark: VP and Medical Director, Swiss Re Life & Health America, NY; Kaufman: VP and Medical Director, Massachusetts Mutual Life, Springfield, MA; Fulks: Medical Director, Clinical Reference Laboratory, Jackson, CA; Dolan: Senior Research Scientist, Clinical Reference Laboratory, Ukiah, CA; Stout: President, Clinical Reference Laboratory, Lenexa, KS.

Key words: Cardiovascular disease, laboratory tests, life insurance, mortality, NT-proBNP.

Received: June 4, 2013

Accepted: July 16, 2013

INTRODUCTION

Primarily released by cardiac myocytes in response to wall stress, pro-B-type natriuretic peptide (proBNP) is cleaved into physiologically active brain natriuretic peptide (BNP) and the inactive fragment, NT-proBNP.

In the emergency ward setting, abnormal BNP levels at impressively low cut-points were able to differentiate those with cardiac dysfunction from patients with pulmonary insufficiency.[1] While some have questioned the value of B-type natriuretic peptide in older populations,[2] BNP has been shown to be useful in those with chronic heart failure,[3] particularly in those with preserved left ventricular systolic function.[4] It has also been found to be a powerful indicator of

short-term mortality after non-cardiac surgery by Karthikeyan et al in a review of 9 studies.[5] B-type natriuretic peptides have been shown to add clinical and prognostic value in other cardiac impairments, including hypertrophic cardiomyopathy,[6] mitral regurgitation,[7] atrial fibrillation,[8] as well as coronary artery disease.[9–11] In a population with 70% having albuminuria, NT-proBNP was predictive of mortality after a median follow-up of 7.5 years.[12]

With regard to other clinical variables, Frankenstein et al found minimal impact on B-type natriuretic levels associated with build or renal function[13] while Das et al found levels of NT-proBNP to be inversely correlated with body mass.[14] Interactions between NT-proBNP, serum creatinine level and body mass index (BMI) have also been found by Rogers et al.[15]

Both BNP and NT-proBNP have been effective in discriminating risk for cardiovascular and all-cause mortality, but NT-proBNP may be better suited for use as a screening tool due to an increased half-life and better stability in the circulation. In addition, it can be accurately measured in both serum and heparin plasma and can be collected in either glass or plastic tubes, whereas BNP requires collection in non-siliconized glass tubes and EDTA anticoagulation.[16]

Several studies have investigated the B-type natriuretic peptides as screening tools in asymptomatic populations showing that they can predict unrecognized cardiovascular disease,[17,18] as well as cardiovascular events and death even after adjustment for traditional risk factors.[19–23] This body of research led life insurers to question whether NT-proBNP could be used as a screening tool to identify unrecognized cardiovascular morbidity and mortality risk.

METHODS

The population for this study consisted of all applicants for individual life insurance age 50 to 89 (40 to 89 for distribution of values) who had a blood sample (obtained as part of the application process) tested for NT-proBNP at Clinical Reference Laboratory (CRL) between 2004 and 2010. The parameters for blood and urine screening were set by each insurance company; for NT-proBNP, typical criteria for testing include older ages and high coverage amounts. Applicants meeting the age and coverage criteria were routinely tested for NT-proBNP without regard to medical history.

Applicants for individual life insurance are typically ''healthy'' without life-threatening medical conditions such as diagnosed congestive heart failure or unstable coronary artery disease. Such conditions are associated with a markedly increased cost of insurance. Because both clients and insurance agents are aware of this, relatively few such applications are submitted. Additional NT-proBNP tests may have been performed on a ''for cause'' basis after certain applications were reviewed by insurers, but these constituted a tiny (but unknown) percentage of testing. All tests for NT-proBNP were conducted as part of the insurance application process at the request of insurers.

NT-proBNP testing was performed between 2004 and 2010 for 144,027 applicants age 40 to 89 who were all included in the study. To ascertain follow-up vital status, the applicants were matched to the Social Security Death Master File in September 2011 using Social Security number, name and date of birth. Partial matches were manually reviewed without knowledge of NT-proBNP value; if the only disparity appeared to be probable name misspelling or transposition of dates, such deaths were included as well. Test results were then de-identified before further analysis. The median duration of follow-up was 2 years (range 0 to 7 years) with a mean of 2.63 years.

Available information on all applicants included age, sex, NT-proBNP and other test results including total cholesterol, HDL and creatinine. Most applicants answered history questions including ''yes'' or ''no'' to any

Table 1. Distribution of Applicants by Sex and Decade of Age for Deaths, Total Studied, Heart Disease History, and Available Systolic BP and BMI Results

Sex, Age (years)	Number of deaths	Total tested	Heart disease history (%)			Results available (%)	
			Deny	Admit	Unknown	Syst. BP	BMI
Female							
40 to 49	7	4804	40.6	3.6	55.8	93.6	93.5
50 to 59	45	13,445	69.8	2.0	28.2	78.2	78.2
60 to 69	58	10,494	83.6	3.0	13.4	60.6	60.8
70 to 79	112	7695	88.4	4.5	7.1	56.3	57.0
80 to 89	41	1510	87.5	5.9	6.6	47.9	49.1
Total	263	37,948	74.4	3.2	22.5	69.7	69.9
Male							
40 to 49	15	6991	49.7	7.0	43.3	85.7	85.6
50 to 59	205	47,544	82.5	3.4	14.1	67.3	67.5
60 to 69	247	35,548	83.3	7.1	9.5	57.2	57.4
70 to 79	206	14,307	82.9	10.7	6.3	54.2	54.7
80 to 89	57	1689	77.9	13.7	8.3	45.5	46.3
Total	730	106,079	80.6	6.0	13.4	63.0	63.2

history of heart disease, hypertension or diabetes on the testing authorization form. For 65% of applicants, measured blood pressure, height and weight were also recorded. Smoking status was determined by the presence of urine cotinine >0.2 ng/mL (Microgenics DRI Cotinine assay) or by admission of tobacco use on the testing authorization form.

Testing for NT-proBNP was with Roche reagents on a Roche Hitachi E170 analyzer. The serum concentration of cholesterol, HDL and creatinine was determined with Roche reagents on Roche Hitachi Modular Chemistry Analyzers. All testing was per manufacturer's guidelines.

Cox regression was used to calculate relative mortality including the covariates noted in the text. Statistical analysis was performed with IBM SPSS Statistics, version 19.0.

RESULTS

Table 1 includes the distribution of our study population by decade of age and sex for number of deaths and total number studied, percent denying or admitting to heart disease (or not answering), and percent with systolic blood pressure (BP) and BMI results available.

The cumulative percent distribution of NT-proBNP values is shown in Table 2 by sex and decade of age for those applicants denying a history of heart disease. As a comparison, the statistical reference range for NT-proBNP was listed by the test manufacturer for age bands <45, 45–54, 55–64, 65–74, and >74 years with reference upper limits of 167, 174, 208, 318, and 717 pg/mL, respectively. In addition, the test manufacturer indicated large differences in statistical reference ranges by sex. We confirmed such large differences by sex from our data: the 95th percentile of values was almost 200 pg/mL for males age 60 to 69 (median value 40) and almost 300 for females age 60 to 69 (median value 66). Females had higher average NT-proBNP values than males below 400 pg/mL; values above 400 pg/mL occurred in near equal percentages by sex. We speculate this was because the physiologically higher values in females were matched by the pathologically higher values in males at these levels.

The relative mortality associated with various levels of NT-proBNP for those

Table 2. Cumulative Percent of Study Population by NT-proBNP Value for Those Denying a History of Heart Disease, Split by Sex and Decade of Age

Sex, Age (years)	NT-proBNP (pg/mL)							
	≤50	≤100	≤200	≤300	≤400	≤500	≤750	≤1000
Female								
40 to 49	60.6	86.5	97.6	99.4	99.7	99.9	99.9	99.9
50 to 59	53.5	84.0	96.7	99.0	99.4	99.6	99.7	99.9
60 to 69	37.4	68.8	90.3	95.8	97.6	98.3	99.4	99.7
70 to 79	18.6	46.2	75.6	87.4	92.8	95.3	97.9	98.6
80 to 89	10.3	27.2	55.7	74.3	83.9	88.9	93.9	96.4
Male								
40 to 49	88.6	97.6	99.5	99.7	99.8	99.8	99.9	99.9
50 to 59	79.2	94.5	98.7	99.4	99.6	99.7	99.8	99.9
60 to 69	60.6	85.1	95.4	97.8	98.5	98.9	99.4	99.6
70 to 79	33.6	63.7	85.4	92.1	94.6	96.4	98.0	98.7
80 to 89	17.8	39.9	66.2	80.1	84.2	88.1	91.8	94.5

applicants denying a history of heart disease is shown in Table 3 and graphically in Figure 1. This mortality analysis by multivariate Cox regression was split by sex and age group (50 to 69 and 70 to 89). It included age and smoking status as covariates. This combination of age-sex group and NT-proBNP bands was chosen after modeling of finer divisions of age and NT-proBNP (not shown) with or without a split by sex. The NT-proBNP band of 1–100 pg/mL was used as the reference group for calculating mortality ratios (MR) within all age-sex groups.

Table 3. Mortality Ratios (Cox Regression) by NT-proBNP Value for Those Denying a History of Heart Disease, Split by Age and Sex

Age-sex group	NT-proBNP (pg/mL)	Number of deaths	Total tested	MR (Cox)	95% CI	
					Lower	Upper
F 50 to 69	1–100 (ref)	54	13,920	1.0		
	101–300	18	3768	1.1	0.6	1.8
	301–1000	12	431	5.6	2.9	10.7
	1001+	2	35	9.6	2.3	39.9
M 50 to 69	1–100 (ref)	256	62,256	1.0		
	101–300	71	5697	2.7	2.0	3.5
	301–1000	19	742	5.3	3.3	8.5
	1001+	12	145	16.2	9.0	29.1
F 70 to 89	1–100 (ref)	34	3502	1.0		
	101–300	50	3425	1.3	0.9	2.1
	301–1000	31	1051	2.6	1.6	4.3
	1001+	16	144	10.1	5.5	18.5
M 70 to 89	1–100 (ref)	65	8083	1.0		
	101–300	69	3898	2.0	1.4	2.8
	301–1000	29	978	3.2	2.0	4.9
	1001+	24	222	10.5	6.4	17.2

Note: ref = reference group

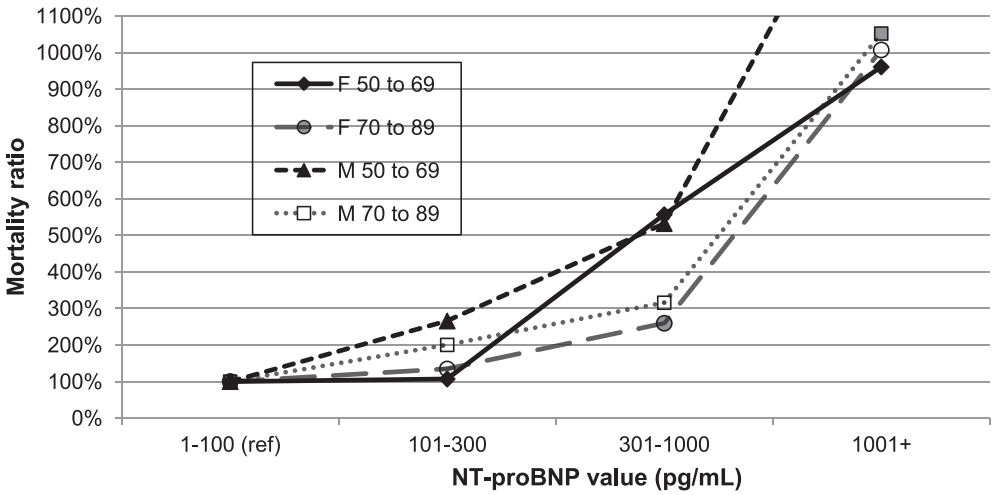

Figure. *Mortality Ratios for NT-proBNP Values for Those Denying a History of Heart Disease, Split by Age and Sex*

Relative mortality varied substantially by sex for lower NT-proBNP values and by age for higher values, requiring that these variables be split accordingly in the reported analysis. Even with the comparatively large number of deaths (n=762) for this age- and history-restricted study subpopulation, the number of NT-proBNP value groups was limited in order to support reasonably narrow 95% confidence intervals (CI). The analysis in Table 3 is supplemented by the Figure, which is a line graph showing relative mortality for each of the four age-sex groups. From this figure, relative mortality risk for intermediate NT-proBNP values can be more easily estimated.

Female relative mortality did not clearly increase until NT-proBNP values >300 pg/mL were reached, though there may have been some increase for age 70 to 89 (MR 1.3 with the lower 95% CI including 1) below that. In contrast, for men the relative risk doubled for NT-proBNP values of 101–300 pg/mL. Above a value of 300, risk increases at least 2.5 fold or more for all age-sex bands. For NT-proBNP values greater than 1000 pg/mL, the MR increased at least 10 fold for all groups.

A similar analysis shown in Table 4 was conducted comparing the mortality for those denying heart disease with NT-proBNP values 1–50 pg/mL (as the reference group)

Table 4. Mortality Ratios (Cox Regression) by NT-proBNP Value Ranges 1–50 vs 51–100 for Those Denying a History of Heart Disease, Split by Age and Sex

Age-sex group	NT-proBNP (pg/mL)	Number of deaths	Total tested	MR (Cox)	95% CI	
					Lower	Upper
F 50 to 69	1–50 (ref)	30	8301	1.0		
	51–100	24	5619	1.1	0.6	1.9
M 50 to 69	1–50 (ref)	172	49,007	1.0		
	51–100	84	13,249	1.7	1.3	2.2
F 70 to 89	1–50 (ref)	12	1400	1.0		
	51–100	22	2102	1.2	0.6	2.4
M 70 to 89	1–50 (ref)	33	4222	1.0		
	51–100	32	3861	1.0	0.6	1.6

Note: ref = reference group

Table 5. Mortality Ratios (Cox Regression) for Age 50 to 89 with Physical Measurements and eGFR and Not Admitting to a History of Heart Disease, With or Without Inclusion of CVD Tertile

			Age and smoking covariates			Age and CVD tertile covariates		
				95% CI			95% CI	
NT-proBNP (pg/mL)	Number of deaths	Total tested	MR (Cox)	Lower	Upper	MR (Cox)	Lower	Upper
1–300 (ref)	329	75,965	1.0			1.0		
301 to 700	41	1846	3.0	2.1	4.3	3.1	2.2	4.4
701+	37	665	7.1	4.9	10.2	7.0	4.8	10.0

Note: ref = reference group

vs those with values 51–100. Although all of these values fall within the commonly used statistical reference range, insurers are interested in potential use of NT-proBNP for differentiating risk within this ''normal'' group as well. There was no demonstrated difference in relative risk for any female age group or for males age 70 to 89. The only group showing increased risk for NT-proBNP values 51–100 pg/mL was males age 50 to 69, where the relative risk was 1.7 with a lower 95% CI >1. Given the statistical distribution of NT-proBNP values, this finding is not surprising because only males younger than 70 years and females younger than 60 years have a median NT-proBNP value below 51 pg/mL.

We also explored the association of NT-proBNP values with other cardiovascular risk factors, as well as the impact of BMI or renal function on the mortality ratios associated with bands of NT-proBNP values. To be included in this analysis, applicants needed to have eGFR, BMI and BP measurements available, which reduced the number of included applicants age 50 to 89 years to 78,476.

To maintain sufficient deaths for narrow 95% CIs, we included data from both applicants denying heart disease (80%) as we did above and applicants not answering the question (15%); we excluded only those who admitted a history of heart disease (5%). Because only 5% of applicants (with no missing physical measurements) admitted to heart disease, and because relative risk for NT-proBNP in those admitting to heart disease was similar (results based on few deaths, not shown) to those who denied it, adding this ''not answering'' group for this analysis seemed appropriate. Analysis excluding those ''not answering'' (not shown) for cardiovascular risk factors produced similar results but with wider CIs. NT-proBNP values were also split into three ranges of 1–300, 301–700 and 701+ pg/mL consistent with low, medium and high risk. The highest risk group began at 701 rather than 1001 pg/mL as done in the earlier analysis to include sufficient outcomes (deaths) to provide meaningful results with this reduced applicant pool.

Cardiovascular risk factors were stratified by the cardiovascular disease (CVD) score from D'Agostino et al[24] by using systolic BP (classifying all as ''not treated''), smoking status, diabetes (defined by HbA1c value ≥6.5%), cholesterol and HDL values. Age was not included in the CVD score since it was split in our analysis, as well as being a covariate in Cox regressions. CVD risk was split into approximate tertiles for women at CVD scores of −1 and 2 as the tertile breakpoints. CVD risk was split into approximate tertiles for men using CVD scores of 0 and 2 as the tertile breakpoints.

Results for age 50 to 89 were analyzed for relative mortality by Cox regression (with age and smoking as covariates) and then compared to the same analysis with CVD tertiles added as a covariate. Results are shown in Table 5 using

Table 6. Mortality Ratios (Cox Regression) for Age 50 to 89 with Physical Measurements and eGFR and Not Admitting to a History of Heart Disease, With or Without Inclusion of BMI and eGFR

			Age and smoking covariates			Age, smoking, BMI and eGFR covariates		
				95% CI			95% CI	
NT-proBNP (pg/mL)	Number of deaths	Total tested	MR (Cox)	Lower	Upper	MR (Cox)	Lower	Upper
1–300 (ref)	329	75,965	1.0			1.0		
301 to 700	41	1846	3.0	2.1	4.3	2.9	2.0	4.1
701+	37	665	7.1	4.9	10.2	6.4	4.4	9.3

Note: ref = reference group

sex to stratify the analysis (analyzed separately by sex but the hazard ratios merged). Additional analysis (not shown) was also conducted that split the results by sex; the results were similar to those using stratification only but with wider 95% CIs.

We found that including CVD tertiles had no impact on the predictive ability of NT-proBNP bands for mortality, even though the CVD score tertiles (when not including NT-proBNP as a variable) were predictive of elevated risk of 1.5 to 1.9 between the first and third tertiles (not shown).

To explore the interactions between NT-proBNP, kidney function and BMI, we repeated the analysis discussed above, substituting BMI and then BMI and eGFR as covariates instead of CVD tertiles. Results of the relative risk comparison with and without BMI and eGFR are shown in Table 6. Including both BMI and eGFR as covariates had almost no impact on the predictive ability of NT-proBNP. Similar results (not shown) were seen when splitting rather than stratifying by sex, as well as when BMI and eGFR were included separately as covariates. Serum creatinine was also analyzed in place of eGFR (not shown) with no reduction in the predictive value of NT-proBNP.

DISCUSSION

The major finding of our study is the close association of elevated serum NT-proBNP levels with mortality in a population applying for life insurance. The effect was greatest at very high (>1000 pg/mL) NT-proBNP levels, but could be demonstrated in a graded manner down to values in the 101–300 pg/mL range. Our study confirms initial reports on the value of NT-proBNP for both general[25–30] and insurance[31] populations as an independent marker of mortality risk.

Viewed from another perspective, for those screened, approximately 7% of all deaths among insurance applicants age 50 to 89 who denied a history of heart disease were associated with NT-proBNP values >1,000 pg/mL while only 0.5% of such applicants had values that high. While only applicants denying heart disease were included in our mortality analysis, other findings or history would likely have identified some of these 7% who died as higher risk individuals. However, relative to other potential screening tests, NT-proBNP may identify a higher proportion that might benefit from identification and medical intervention.

Using NT-proBNP as a screening tool for a pool of lower risk individuals requires attention to the different distributions by age and sex (as shown in Table 2) as well as relative mortality (as shown in Table 3 and Figure 1). Equivalent distribution and relative mortality across sex can be accomplished by setting a cut-off for further evaluation approximately 100 pg/mL higher for women.

Cut-off values of 300 pg/mL for women and of 200 pg/mL for men identify roughly 5% of insurance applicants age 50+ denying heart disease. Those applicants have all-cause mortality risks at least doubled relative to those with values <101 pg/mL. Adjustment for age when setting a screening cut-off value may not be required because relative risk for increasing values is higher at younger ages but the distribution of NT-proBNP values is lower. Those same cut-offs (ie, 300 and 200 pg/mL) may prove most effective across all ages where such testing may be considered.

For NT-proBNP values less than 300 pg/mL for women and 200 for men, there is limited risk discrimination based on level, especially for women. At values <100 pg/mL (Table 4), there is almost none. Because it is a marker for a disease (congestive heart failure and perhaps other forms of cardiac stress) rather than a traditional risk factor such as hypertension, this is not surprising.

In this study, the ability of NT-proBNP to predict adverse mortality was largely independent of traditional risk factors, build and renal function as noted in Tables 5 and 6. The lack of impact by traditional CVD risk factors on the prediction of mortality by NT-proBNP has been found by McKie et al as well.[32] The Malmõ Diet and Cancer study[33,34] reported only modest impact when adding biomarkers, but Rogers et al[14] found that clinical covariables (including age, body mass, serum creatinine, and history of atrial fibrillation) did improve the clinical utility of B-type natriuretic peptides in an older population. Conversely, adding NT-proBNP to traditional risk factors has limited impact on the hazard ratios associated with them in a multivariate analysis.[35] Traditional cardiovascular risk factors and this marker of ventricular dysfunction may be additive in a risk analysis but appear largely independent of one another.

A number of limitations to our study should be acknowledged. First, the analysis was retrospective and the population self selected (individual life insurance applicants) and non-randomized. This may limit its applicability to general population screening, although the individuals applying for insurance are also representative of those (based on age, health and socio-economic status) receiving health maintenance evaluations in private medical clinics.

Second, our data on medical history is self-reported and may not fully represent the prevalence of disease in this population. However, the insurance-buying population is generally healthy, with a lower prevalence of medical and cardiac impairments than the general population.

Finally, our study is limited to single NT-proBNP determinations for each participant; part of the value of the B-type natriuretic peptides may be related to serial measurements over time.[36]

CONCLUSION

At age 50 and older, NT-proBNP, performed as a screening test, is a potent independent risk predictor of all-cause mortality in life insurance applicants but results must be used with sex-specific cut-off values to be effective. It remains equally predictive across typical ranges of eGFR and BMI values when traditional cardiovascular risk factors are considered.

REFERENCES

1. Maisel AS, Clopton P, Krishnaswamy P, et al. Impact of age, race and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. *Am Heart J*. 2004;147:1078–1084.
2. deFilippi CR, Christenson RH, Kop WJ, et al. Left ventricular ejection fraction assessment in older adults: an adjunct to natriuretic peptide testing to identify risk of new-onset heart failure and cardiovascular death? *J Am Coll Cardiol*. 2011;58:1497–1506.
3. Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. *Arch Intern Med*. 2010;170:507–514.

4. Grewal J, McKelvie RS, Persson H, et al. Usefulness of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide to predict cardiovascular outcomes in patients with heart failure and preserved left ventricular ejection fraction. *Am J Cardiol*. 2008;102:733–737.
5. Karthikeyan G, Moncur RA, Levine O, et al. Is a pre-operative brain natriuretic peptide or N-terminal pro B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery?: a systematic review and meta-analysis of observational studies. *J Am Coll Cardiol*. 2009;54:1599–1606.
6. Binder J, Ommen SR, Chen HH, et al. Usefulness of brain natriuretic peptide level in the clinical evaluation of patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2007;100:712–714.
7. Pizarro R, Bazzino OO, Oberti PF, et al. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. *J Am Coll Cardiol*. 2009;54:1099–1106.
8. Patton KK, Ellinor PT, Heckbert SR, et al. N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study. *Circulation*. 2009;120:1768–1774.
9. Ndrepepa G, Braun S, Schömig A, Kastrati A. Accuracy of N-terminal pro-brain natriuretic peptide to predict mortality in various subsets of patients with coronary artery disease. *Am J Cardiol*. 2007;100:575–578.
10. Omland T, Sabatine MS, Jablonski KA, et al. Prognostic value of B-type natriuretic peptides in patients with stable coronary artery disease: the PEACE trial. *J Am Coll Cardiol*. 2007;50:205–214.
11. Singh HS, Bibbins-Domingo K, Ali S, et al. N-terminal pro-B-type natriuretic peptide and inducible ischemia in the Heart and Soul Study. *Clin Cardiol*. 2009;32:447–453.
12. Linssen GC, Bakker SJ, Voors AA, et al. N-terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population. *Eur Heart J*. 2010;31:120–127.
13. Frankenstein L, Remppis A, Frankenstein J, et al. Variability of N-terminal probrain natriuretic peptide in stable chronic heart failure and its relation to changes in clinical variables. *Clin Chem*. 2009;55:923–929.
14. 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.
15. Rogers RK, Stoddard GJ, Greene T, et al. Usefulness of adjusting for clinical covariates to improve the ability of B-type natriuretic peptide to distinguish cardiac from noncardiac dyspnea. *Am J Cardiol*. 2009;104:689–694.
16. Ordonez-Llanos J, Collinson PO, Christenson RH. Amino-terminal pro-B-type natriuretic peptide: analytic considerations. *Am J Cardiol*. 2008; 101[suppl]:9A–15A.
17. Galasko GI, Lahiri A, Barnes SC, Collinson P, Senior R. What is the normal range for N-terminal pro-BNP? How well does this normal range screen for cardiovascular disease? *Eur Heart J*. 2005;26:2269–2276.
18. 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.
19. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Eng J Med*. 2004; 350:655–663.
20. 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.
21. Laukkanen JA, Kurl S, Ala-Kopsala M, et al. Plasma N-terminal fragments of natriuretic propeptides predict the risk of cardiovascular events and mortality in middle-aged men. *Eur Heart J*. 2006;27:1230–1237.
22. Olsen MH, Hansen TW, Christensen MK, et al. N-terminal pro-brain natriuretic peptide, but not high sensitivity C-reactive protein, improves cardiovascular risk prediction in the general population. *Eur Heart J*. 2007;28:1374–1381.
23. Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol*. 2008;52:450–459.
24. D'Agostino RBSr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
25. Kistorp C, Raymond I, Pedersen F, et al. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA*. 2005;293:1609–1616.
26. de Lemos JA, Hildebrandt P. Amino-terminal pro-B-type natriuretic peptides: testing in general populations. *Am J Cardiol*. 2008;101(suppl): 16A–20A.

27. Goetze JP, Mogelvang R, Maage L, et al. Plasma pro-B-type natriuretic peptide in the general population: screening for left ventricular hypertrophy and systolic dysfunction. *Eur Heart J*. 2006;27:3004–3010.
28. März W, Tiran B, Seelhorst U, et al. N-terminal pro-B-type natriuretic peptide predicts total and cardiovascular mortality in individuals with or without stable coronary artery disease: the Ludwigshafen Risk and Cardiovascular Health Study. *Clin Chem*. 2007;53:1075–1083.
29. McKie PM, Cataliotti A, Lahr BD, et al. The prognostic value of N-terminal pro-B-type natriuretic peptide for death and cardiovascular events in healthy normal and stage A/B heart failure subjects. *J Am Coll Cardiol*. 2010;55:2140–2147.
30. Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham Heart Study. *JAMA*. 2002; 288:1252–1259.
31. Illango RK. Utilizing NT-proBNP in the selection of risks for life insurance. *J Insur Med*. 2007;39:182–191.
32. McKie PM, Cataliotti A, Sangaralignham J, et al. Predictive utility of atrial, N-terminal Pro-atrial, and N-terminal pro-B-type natriuretic peptides for mortality and cardiovascular events in the general community: a 9-year follow-up study. *Mayo Clin Proc*. 2011;86:1154–60.
33. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular deaths in the community. *JAMA*. 2009;302:49–57.
34. Smith JG, Newton-Cheh C, Almgren P, et al. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. *J Am Coll Cardiol*. 2010;56:1712–1719.
35. Rutten JH, Mattace-Raso FU, Steyerberg EW, et al. Amino-terminal pro-B- type natriuretic peptide improves cardiovascular and cerebrovascular risk prediction in the population. The Rotterdam study. *Hypertension*. 2010;55:785–791.
36. Goei D, van Kuijk JP, Flu WJ, et al. Usefulness of repeated N-terminal pro-B-type natriuretic peptide measurements as incremental predictor for long-term cardiovascular outcome after vascular surgery. *Am J Cardiol*. 2011;107:609–614.