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MORTALITY

NT-proBNP Predicts All-Cause Mortality in a Population of Insurance Applicants, Follow-up Analysis and Further Observations

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Objective. – Further refine the independent value of NT-proBNP, accounting for the impact of other test results, in predicting all-cause mortality for individual life insurance applicants with and without heart disease.
Method. – Using the Social Security Death Master File and multivariate analysis, relative mortality was determined for 245,322 life insurance applicants ages 50 to 89 tested for NT-proBNP (almost all based on age and policy amount) along with other laboratory tests and measurement of blood pressure and BMI.
Results. – NT-proBNP values ≤75 pg/mL included the majority of applicants denying heart disease and had the lowest risk, while values >500 pg/mL for females and >300 pg/mL for males had very high relative risk. Those admitting to heart disease had a higher mortality risk for each band of NT-proBNP relative to those denying heart disease but had a similar and equally predictive risk curve.
Conclusion. – NT-proBNP is a strong independent predictor of all-cause mortality in the absence or presence of known heart disease but the range of values associated with increased risk varies by sex.

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INTRODUCTION

NT-proBNP is a well-established marker for congestive heart failure and left ventricular strain associated with a variety of heart diseases including stable coronary artery disease, hypertrophic cardiomyopathy, congenital heart disease, diastolic dysfunction and dilated cardiomyopathy.[1–5] In our 2014 *Journal of Insurance Medicine* report, we reviewed the predictive ability of this test as an age-based screening tool for all-cause mortality in insurance applicants as well as the available literature.[6] That review, limited to those not admitting to heart disease, included relative mortality based on Social Security Death Master File follow-up, distribution of values and predictive value independent of a clinically-derived cardiovascular risk score. Though it was one of the larger studies of NT-proBNP screening at the time, granularity and relative risk by duration were still constrained by cohort size and follow-up duration. We now have almost twice the number of tested applicants and reported deaths as we did for 2014 as well as more subjects at longer durations of

follow-up allowing for a more granular picture as to what value NT-proBNP might offer as a screening tool in a relatively healthy (individual life insurance applicant) pool.

In addition, although we previously had demonstrated the predictive value of NT-proBNP independent of a cardiovascular risk score, the relationship between NT-proBNP and the entire broad panel of laboratory tests, blood pressure, and build measurements routinely obtained from life insurance applicants remained unexplored.

Finally, as information on left ventricular function is often limited at the time of underwriting (risk evaluation), we wanted to examine the predictive value of the NT-proBNP level in those insurance applicants who admitted to heart disease, as well as those who denied it.

METHODS

We included all life and disability insurance applicants, ages 50 to 89, tested at Clinical Reference Laboratory (CRL) for NT-proBNP levels from 2004 through 2015, who also answered the testing authorization question regarding "any history of heart disease" (97.8% of applicants responded with 6.3% of those responding answering "yes"). NT-proBNP screening parameters are set by each insurer based on age (usually age 50+, 60+ or 70+) and policy amount applied for (higher) and are almost always accompanied by other routine applicant laboratory testing as well as measurement of blood pressure and build, although some for-cause testing may have occurred.

Vital status was determined by use of the May 2016 Social Security Death Master File (DMF) including all state-reported deaths reported up to October 2011 when that information was removed from the DMF. This resulted in 245,322 tested applicants (including 144,027 from our prior report) with 2079 reported deaths. Median follow-up was 2.7 years with a mean of 3.5 years. Mortality reporting by DMF is not complete and more incomplete at younger ages, made worse by the removal of state-reported deaths, impacting mostly younger ages, in 2011. However, only risk relative to those in the same pool with different levels of NT-proBNP (or combinations of testing) is reported here and we are unaware of any reason to think DMF death reporting would vary by laboratory value or presence of pre-existing disease.

Various combinations of NT-proBNP value bands were investigated to find the combination that resulted in meaningful distributions and best identified changes in relative mortality risk across both sexes and all ages. The final ranges chosen were $\leq$75 pg/mL, 76-175 pg/mL, 176-300 pg/mL, 301-500 pg/mL, 501-1,000 pg/mL and >1,000 pg/mL. Selected analysis is shown for those having values <50 pg/mL and 51-75 pg/mL as well. These bands are more granular and have different cut-points than those used in our earlier report.[6] Smoker status was determined by the presence of $\geq$200 ng/ml of cotinine in the urine. Details of NT-proBNP and other laboratory testing methodology and additional information on our subjects can be found in our prior report.[6]

The Cox regression and other statistical analyses were performed using IBM SPSS version 24. Prior to calculating relative risk by use of the Cox algorithm (which assumes that relative risk is similar by duration of follow-up), Kaplan Meier plots (same software package) were created separately for males age 60-79 and for females age 60-79 denying heart disease to evaluate the consistency of relative risk by duration. Those age-sex groups were chosen to provide sufficient data by duration while limiting mortality rate variation. An assumption was made that if these bands showed no variation in relative risk by duration then it was highly unlikely that variation by duration would be present for any age-sex groupings shown. Neither Kaplan Meier plot (not shown) revealed any progressive variation in relative risk by year for the first year through eighth year (durations where sufficient data was available) for the

Table 1. Cumulative Distribution of NT-proBNP Values (pg/mL) by Age and Sex for Applicants DENYING Heart Disease

	Age	≤50	51-75	76-175	176-300	301-500	501-1000	1001 +
Female	*50-59*	55.0%	74.4%	96.6%	99.3%	99.8%	100.0%	100.0%
	60-69	37.5%	57.5%	89.1%	97.0%	99.0%	99.7%	100.0%
	70-79	19.3%	34.8%	72.6%	88.7%	95.5%	98.7%	100.0%
	80-89	8.8%	17.5%	50.1%	72.5%	87.4%	95.6%	100.0%
Male	*50-59*	80.1%	90.8%	98.5%	99.4%	99.8%	99.9%	100.0%
	60-69	59.9%	76.2%	94.3%	97.6%	98.8%	99.6%	100.0%
	70-79	34.7%	52.2%	82.4%	91.8%	95.9%	98.5%	100.0%
	80-89	16.0%	27.6%	59.6%	77.1%	86.6%	94.2%	100.0%

NT-proBNP value bands shown in the Results section.

RESULTS

Distribution of NT-proBNP values varies substantially by sex and by age as shown in Table 1 for those denying heart disease and in Table 2 for those admitting to heart disease. Women and older ages have higher values, and this must be appreciated when reviewing relative mortality risk by value band. The extent to which the higher values shown with older ages represent more heart disease is uncertain but the differences by sex (higher in age-matched females) appears to be physiologic as the prevalence of heart disease in females is lower.

For those denying heart disease (mean age 65 years), the mean NT-proBNP value was 81 pg/mL for males and 128 pg/mL for females. For those admitting to heart disease (mean age 68 years), the mean NT-proBNP value was 251 pg/mL for males and 376 pg/mL for females.

The relative all-cause mortality risk increases with increasing levels of NT-proBNP, although the value at which risk begins to increase varies by age and sex. The relative risk including age and smoking status as covariates, as compared to those having values ≤75 pg/mL, is shown divided by age and sex for applicants denying heart disease in Table 3 and is plotted in Figure 1.

Before establishing NT-proBNP ≤75 pg/mL as our reference pool, we utilized the

Table 2. Cumulative Distribution of NT-proBNP Values (pg/mL) by Age and Sex for Applicants ADMITTING to Heart Disease

	Age	≤50	51-75	76-175	176-300	301-500	501-1000	1001 +
Female	*50-59*	36.5%	50.9%	79.2%	87.6%	95.0%	98.5%	100.0%
	60-69	24.6%	38.0%	66.2%	82.1%	89.7%	96.7%	100.0%
	70-79	8.4%	17.2%	44.2%	63.8%	78.0%	91.2%	100.0%
	80-89	3.4%	7.6%	26.8%	44.3%	58.4%	78.0%	100.0%
Male	*50-59*	51.4%	66.8%	86.9%	93.0%	96.2%	98.4%	100.0%
	60-69	32.3%	48.1%	75.9%	86.7%	92.3%	97.0%	100.0%
	70-79	14.0%	24.9%	55.6%	72.1%	82.9%	93.6%	100.0%
	80-89	3.5%	7.0%	29.8%	50.2%	64.0%	78.9%	100.0%

Table 3. Relative Risk for All-cause Mortality by NT-proBNP Level with ≤75 pg/mL as Reference Range with 95% Confidence Intervals

	≤75 (ref)	76-175	176-300	301-500	501-1,000	>1,000
Male age 50-69	1	1.85	2.54	6.55	6.63	16.15
		1.51-2.26	*1.77-3.64*	*4.47-9.60*	*4.16-10.5*	*10.4-25.0*
Male age 70-89	1	1.72	2.84	3.23	5.07	7.17
		1.38-2.15	*2.20-3.67*	*2.37-4.39*	*3.72-6.91*	*5.20-9.90*
Female age 50-69	1	0.88	1.58	2.65	4.11	8.24
		0.59-1.31	*0.91-2.72*	*1.22-5.80*	*1.75-9.64*	*2.58-26.3*
Female age 70-89	1	1.49	1.96	2.29	4.14	7.7
		1.10-2.01	*1.41-2.72*	*1.57-3.35*	*2.79-6.15*	*5.10-11.6*

distributions shown and explored relative risk using alternative cut-offs. In Table 4, results are shown when NT-proBNP ≤50 pg/mL is used as a reference instead and compared to 51-75, 76-100 and >100 pg/mL with age and smoking status as covariates. These results show flattening or even increasing relative risk for values ≤50 pg/mL except for young males where risk continues to decline consistent with the different distribution ranges by age and sex. A small increase in relative risk is also seen for older females for the NT-proBNP 51-75 pg/mL band but the 95% CI (not shown in table) is 0.73 to 1.91, the increased risk for next higher NT-proBNP band of 76-100 pg/mL is only 1.33 and no increase is seen for older males or younger women for the NT-proBNP 51-75 pg/mL band so the validity of that 1.18 ratio in the lower band is uncertain.

The relative risk for the same NT-proBNP bands was also determined for those admitting heart disease for all age-sex combined including age, sex and smoking as covariates in the Cox algorithm. The relative risk in the NT-proBNP ≤75 reference pools for those admitting to and denying heart disease was then compared and that relative risk (1.264) was multiplied times the relative risk already identified in those admitting to heart disease for each successively higher NT band >75 pg/mL. This creates two curves shown in Figure 2 for those admitting or denying heart disease all relative to a reference pool of those denying heart disease with NT-proBNP levels ≤75 pg/mL. As shown in Tables 1 and 2, most applicants with heart disease are actually in higher NT-proBNP bands as compared to those denying heart disease.

How much of the increase in risk related to increasing NT-proBNP values could be explained by other laboratory findings, blood pressure and build was evaluated by adding the CRL age- and sex-neutral Smart Score®

Table 4. Relative Risk for All-cause Mortality by NT-proBNP Level with ≤50 pg/mL as Reference Range

	≤50	51-75	76-100	>100
Male 50-69	1	1.38	1.78	3.32
Male 70-89	1	0.91	1.38	2.7
Fem. 50-69	1	0.89	0.87	1.41
Fem. 70-89	1	1.18	1.33	2.36

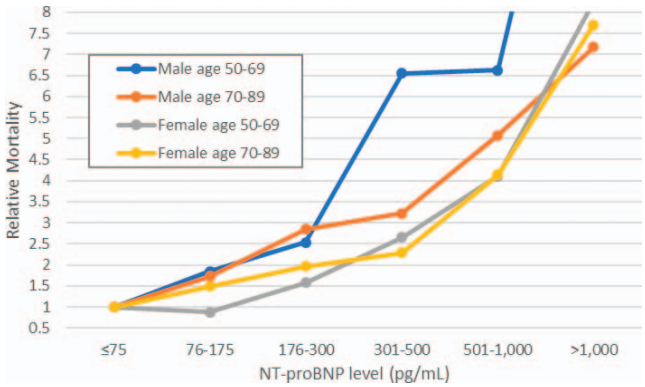

Figure 1. *Relative risk for all-cause mortality by NT-proBNP level with ≤75 pg/mL as reference range.*

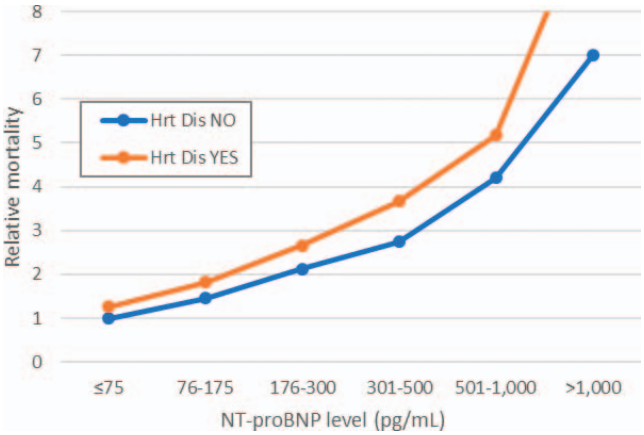

Figure 2. *Relative risk for all-cause mortality by NT-proBNP level for those admitting to and denying heart disease (age, sex and smoking as covariates).*

(a single risk score which combines the contribution of all those findings in a multivariate manner) minus any potential NT-proBNP contribution, as a covariate. Smart Score bands utilized were scores ≤40 (consistent with typical favorable insurance offers), scores 41-130 (consistent with typical "standard" insurance offers) and scores >130 (potentially needing further review). The results shown in Table 5 including age and cotinine status as covariates demonstrate that some of the total risk allocated to NT-proBNP might also be explained by other laboratory, blood pressure or build findings.

Higher Smart Scores (excluding any contribution from NT-proBNP) associated with higher NT-proBNP values would potentially have led to a reclassification of some insurance applicants to less favorable risk classes even without the NT-proBNP test. For males, that percentage potentially achieving the most favorable insurance classes based on a Smart Score ≤40 dropped from 73% to 43% when NT-proBNP moved from ≤75 to ≥175 and for females from 70% to 44% when NT-proBNP values increased from ≤175 to ≥300 (these are comparable NT-proBNP cut-offs by sex based on distribution and relative risk).

Further evaluation using Pearson correlations separately by males and females showed that for the Smart Score component scores significantly associated with increasing NT-proBNP levels, urine protein-creatinine ratio, serum albumin and eGFR had by far the highest correlations for both sexes. However, the actual mean difference in each of the other test values for those low and high NT-proBNP values noted above was quite limited. Men had differences in urine protein-creatinine ratio +0.13 mg/mg, albumin of -0.2 g/dL, and eGFR of -14 mL/min. For women those differences were urine protein-creatinine ratio +0.12 mg/mg, albumin of -0.2 g/dL, and eGFR of -16 mL/min.

DISCUSSION

With the additional data available since our prior report, we can provide better granularity. For adults denying heart disease, those with NT-proBNP values ≤75 pg/mL represent an optimal risk pool except for men age <70 where that limit may be lower at ≤50 pg/mL. If one were to accept risk levels up to 130% of reference mortality (NT-proBNP ≤75 pg/mL) as favorable, then values ≤175 pg/mL in women up to age 70 and ≤75 pg/mL for all males and for females age 70 or greater are included. This represents the

Table 5. Relative Risk for All-cause Mortality by NT-proBNP Level With and Without Using Smart Score (SmSc) as a Covariate in Addition to Age, Sex and Smoking

	≤75	76-175	176-300	301-500	501-1,000	>1,000
Male, no SmSc	1	1.82	2.88	4.12	5.7	9.2
Male, with SmSc	1	1.26	1.81	2.17	3.86	6.97
Female, no SmSc	1	1.68	2.34	3.1	3.89	5.69
Female, with SmSc	1	1.27	1.74	1.85	2.99	4.67

large majority of insurance applicants at ages less than 70 and a majority at ages 70 to 79. Risk likely needing review (≥200% of reference) begins at NT-proBNP levels of >300 pg/mL in women and >175 pg/mL in men. Very high risk (≥500%) is always present at NT-proBNP values >1,000 pg/mL in women and >500 pg/mL in men representing a fraction of 1% at ages less than 70 and approximately 1% at ages 70-79.

As an alternate approach, if NT-proBNP cut-off values of >300 pg/mL for men and >500 pg/mL for women denying heart disease were used to indicate the need for further clinical evaluation, then 4.7% of male applicants age 50-89 would be referred accounting for 24.5% of the deaths in that group and 3.3% of female applicants age 50-89 would be referred accounting for 19.7% of deaths (number of applicants and deaths by age-sex not otherwise shown).

In contrast to the minimal association between a clinically-derived cardiovascular risk score and NT-proBNP level noted in our prior report (for those not admitting to heart disease), urine protein-creatinine ratio, serum albumin and eGFR (and to a lesser degree, other tests) do appear to be associated with NT-proBNP level and might explain or identify some of the added risk shown for elevated NT-proBNP values when not accounting for these other variables. However, actual risk category reclassification based these other test results without performing NT-proBNP testing would likely be limited during traditional laboratory underwriting because the differences in actual test value means are small and many values would not be identified as either being associated with increased risk or with ventricular strain.

As compared to those denying heart disease, those admitting to it have a substantially higher mean NT-proBNP while being only about 3 years older as a group. However, their risk associated with increasing bands of NT-proBNP levels appears to have a progression very similar to those denying heart disease. Progressively higher levels are equally predictive of increasing all-cause mortality risk, and the relative mortality risk between applicants with and without such history at various NT-proBNP levels can be directly compared as shown in Figure 2.

Presumably, most heart disease history in our series of insurance applicants would be classified as stable coronary disease. Information on extent of disease and risk factor control (lipids, blood pressure) is commonly available but information on the third leg of the risk evaluation, left ventricular function, is often absent. We were able to incorporate risk factors including lipids and BP as covariates (Table 5) to identify the additional contribution of NT-proBNP (ventricular function) but could not include the extent of coronary disease as such information was unavailable to us.

One limitation is the improved but still limited granularity at higher NT-proBNP levels, such as 301 to 500 pg/mL and 501-1,000 pg/mL. As shown in Table 1, the percentage of insurance applicants falling into these bands is small so that potential narrowing of those bands would require several more years of data acquisition.

On a cautionary note, although our findings demonstrate the utility of NT-proBNP in mortality risk screening, it must be recognized there is variability of NT-proBNP levels over a period of several weeks in both healthy adults and in those with heart failure.[7] Small differences in values between two time points do not imply a change in cardiac status and single point screening may result in a value higher or lower than the average for that individual. When used for screening, one must accept that not all "elevations" will prove to be associated with disease on further review and that, conversely, milder ventricular dysfunction may occasionally not be associated with identifiable elevations. However, substantial increases in NT-proBNP (as reflected in the bands of values we utilized) are highly associated with increasing risk most likely from the presence of common (at older

age) and often unappreciated ventricular dysfunction and strain (regardless of cause).

Variability of test results for the potential alternative test, serum BNP, which must be drawn into a plastic tube and immediately frozen for transport to avoid degradation, is even higher than for NT-proBNP testing, which does not require any special handling.[8] Much of this additional variability likely reflects BNP's much shorter half-life and possibly its handling requirements. How to interpret and how much weight should be placed on a single BNP result in refuting an earlier unfavorable NT-proBNP result is uncertain especially if drawn in a typical outpatient setting.

REFERENCES

1. Mishra RK, Beatty AL, Jaganath R, Regan M, Wu AH, Whooley MA. B-type natriuretic peptides for prediction of cardiovascular events in patients with stable coronary heart disease: the heart and soul study. *J Am Heart Assoc*. 2014 doi:10.116/JAHA.114.000907.
2. D'amato RD, Tomberli B, Castelli G, et al. Prognostic value of N-terminal pro-brain natriuretic peptide in outpatients with hypertrophic cardiomyopathy. *Am J Cardiol.* 2013;112:1190-1196.
3. Popelová RJ, Kotaška K, Tomková M, Tomek J. Usefulness of N-terminal pro-brain natriuretic peptide to predict mortality in adults with congenital heart disease. *Am J Cardiol.* 2015;116:1425-1430.
4. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction. *Circulation.* 2002;105:595-601.
5. Kim G, Ok J, Kang I, Song J, Huh, J. Clinical implications of serial serum N-terminal prohormone brain natriuretic peptide levels in prediction of outcome in children with dilated cardiomyopathy. *Am J Cardiol.* 2013;112:1455-1460.
6. Clark M, Kaufman V, Fulks M, Dolan V, Stout R. NT-proBNP as a predictor of all-cause mortality in a population of insurance applicants. *J Insur Med.* 2014;44:7-16.
7. Meijers WC, van der Vedle AR, Muller Kobold A, et al. Variability of biomarkers in patients with chronic heart failure and healthy controls. *European Journal of Heart Failure.* 2016 doi:10.1002/ejhf.669.
8. Prontera c, Zaninotto M, Giovannini S, et al. Proficiency testing project for brain natriuretic peptide and N-terminal part of propeptide of BNP immunoassays: the CardioOrmocheck study. *Clin Chem Lab Med.* 2009;47:762-768.