

## USING NT PROBNP TO IMPROVE RISK ASSESSMENT FOR APPLICANTS WITH HEART DISEASE



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#### Introduction

Coronary artery disease (CAD) comprises the bulk of heart disease seen for life insurance applicants age 50+. Deaths from CAD result from a new event such as a dysrhythmia or an acute coronary obstruction (usually at the site of a previously NON-obstructive plaque), or from progressive congestive heart failure (CHF). The occurrence of life-threatening dysrhythmias, the lethality of any new coronary event and the development of congestive heart failure are all highly associated with existing, symptomatically silent, ventricular dysfunction. Underwriting CAD requires knowledge of: (1) the extent or severity of the disease process and (2) the degree of improvement in risk factor control and (3) the condition of the ventricles (primarily the left). Numbers 1 and 2 are available from history, laboratory studies and physical measurements, but number 3, current ventricular status, may be absent or out of date at initial underwriting, leading to delays or suboptimal risk decisions.

The gold standard for measuring ventricular status has been a high-quality echocardiogram including left ventricular (LV) ejection fraction (EF), wall motion and wall thickness. Other imaging techniques may also be used. Unfortunately, none can be done as part of underwriting requirements and a high-quality study in the recent past is often not available, making assessment of current LV status problematic.

Fortunately, new data on NT-proBNP, part of the prohormone produced by the ventricles of the heart (mostly LV, as its walls are usually far thicker than the right ventricle) in response to strain, allows it

**Executive Summary** *NT-proBNP, part of a prohormone released by the ventricles of the heart, is a sensitive indicator of ventricular strain, information that is critical but may be limited or outdated at underwriting. We studied NT-proBNP levels for applicants age 50+ admitting to heart disease (most of which would be stable coronary artery disease) and found that mortality risk (split by sex and accounting for age) increased in a graded manner. Those having the highest 10% of NT-proBNP values had a risk over 6 times higher than those with the lowest 40% of values. Use of NT-proBNP could improve risk decisions for applicants with heart disease and obviate the need for additional records.*

to be used to assess ventricular status of applicants with heart disease. The test is widely used in the urgent clinical setting to differentiate shortness of breath or other non-specific symptoms and signs potentially caused by cardiovascular disease vs. pulmonary or other causes. We (and other authors for non-insurance populations) have also demonstrated the effectiveness of NT-proBNP in screening older, apparently well applicants. Unappreciated LV dysfunction is common in this cohort and associated with substantially increased mortality risk.<sup>1</sup> However, the value of NT-proBNP in discriminating risk in a pool of applicants with known heart disease was less clear. Because stable CAD is by far the most common heart disease in life insurance applicants age 50+, it will be our focus.

### How the Study Was Done

All 15,284 insurance applicants (300 recorded deaths) ages 50-89 tested for NT-proBNP from 2004 through 2015 at CRL, who also answered the testing authorization question “YES” for “any history of heart disease,” were included in the study. Vital status was determined in May 2016 by use of the Social Security Death Master File (DMF). All state reported deaths in the DMF (up until removal of this information in October 2011) were included as well. All statistical analysis was conducted using IBM SPSS 24 software.

NT-proBNP bands were chosen to provide sufficient numbers of deaths as well as meaningful distributions and mortality differences. Because distribution varies by sex, bands with higher ranges of values (but reasonably comparable distribution and relative mortality risk) were used for females. Mortality was assessed by Cox regression including tobacco use (cotinine  $\geq 200$  ng/mL) and age as covariates. A Kaplan Meier plot (not shown) of relative risk for males age 60-79 for each year after testing from year 1 to 6 had no consistent or progressive variance in annual relative risk between the NT-proBNP bands shown, allowing use of Cox methodology to determine relative risk in a multivariate manner.

### What the Study Found

The median age of the cohort admitting to heart disease was 68 years with 82% being male and 6.7% being tobacco users. Median NT-proBNP values were 99 pg/mL for males and 159 pg/mL for females (females have physiologically higher values than males). These values are much higher than the median seen for comparable applicants denying heart disease tested at CRL (39 pg/mL and 74 pg/mL, respectively) indicating some degree of LV strain is present for most applicants with a heart disease history.

Table 1 shows the distribution of NT-proBNP values split by sex. Also shown is the risk for each band of NT-proBNP relative to the reference pool (NT-proBNP  $\leq 75$  pg/mL for males and  $\leq 100$  pg/mL for females) accounting for both age and tobacco status. Mortality risk increased in a graded manner as NT-proBNP values increased. As compared to the reference band, male applicants who have NT-proBNP values  $>150$  pg/mL and female applicants  $>200$  pg/mL comprise roughly 40% of those with a heart disease history, and have at least doubled all-cause mortality with a  $>6$ -fold mortality increase in the top band including 9.8% of males and 11% of females.

If the upper limits of the reference (lowest) band were reduced below  $\leq 75$  pg/mL for males or  $\leq 100$  pg/mL for females, little further risk reduction occurred for males and none for females (data not shown).

### What Do the Study Results Contribute to Risk Assessment?

NT-proBNP allows objective risk assessment of applicants with CAD in a graded manner at the time of initial underwriting. Roughly 10% of applicants admitting to heart disease have a very high risk with an additional 30% at substantially increased risk.

Whether values in our lowest band of NT-proBNP (40% of males and 34% of females) might actually be associated with slightly lower risk than otherwise suggested by an insurer’s current CAD underwriting guidelines is beyond our data, but those guidelines are based on mortality experience that would have included individuals with unrecognized LV dysfunction, even when the extent of the disease and risk factor control appeared favorable.

**Table 1. Distribution and relative risk by NT-proBNP level (pg/mL) for applicants with a heart disease history**

Male	NT-proBNP range	$\leq 75$	76-150	151-300	301-600	601+
	% in each band	40.9%	22.7%	17.2%	9.5%	9.8%
	Relative Mortality	1 (ref.)	1.5	2.1	2.9	6.2
Female	NT-proBNP range	$\leq 100$	101-200	201-400	401-800	801+
	% in each band	34.2%	23.1%	19.1%	12.6%	11.0%
	Relative Mortality	1 (ref.)	1.5	2.8	4.8	9.2

A limitation in the applicability of our data to CAD is that our tested cohort includes all applicants admitting to heart disease, a few of whom would have had other heart conditions. Supporting our results are the PEACE trial, limited to stable CAD patients dividing applicants by sex and then into quartiles by NT-proBNP level using cardiovascular mortality as the outcome measure, and the Heart and Soul trial in stable CAD patients, based on quartiles of both sexes combined using cardiovascular events as a measure.<sup>2,3</sup> Our analysis of applicants included only age and smoking as covariates (splitting by sex), but both the PEACE and Heart and Soul trials had more history data and attempted to account for history and multiple other findings in their multivariate Cox analysis. The PEACE trial first quartile NT-proBNP cut-off values were 66 pg/mL (males) and 105 pg/mL (females), while the Heart and Soul trial had a combined first quartile cut-off of 74 pg/mL. Both trials showed increases in cardiovascular mortality/events comparable to what we found for all-cause mortality associated with similar elevations of NT-proBNP.<sup>2,3</sup>



The level of risk discrimination demonstrated by NT-proBNP in our study and referenced clinical literature

could improve the underwriting of many applicants presenting with a CAD history and largely eliminate the need for additional records regarding LV status. Some risk associated with LV dysfunction would already be identifiable at underwriting by prior history of CHF, low EF or large infarcts and a few by ECG, but many would not be identified because LV strain is often silent. Nor can the lowest risk applicants with CAD be identified without a measure of current LV status. NT-proBNP testing requires no special handling and could be reflexed off a heart disease question on a laboratory authorization or performed on saved blood when such history became apparent if within laboratory sample retention.

#### Notes

1. 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. Reprinted in *ON THE RISK*. 2014;30 n.2:64-72.
2. 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:10.1161/JAHA.114.000907.
3. 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;50:205-14.

#### About the Authors

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**Robert L. Stout, PhD**, is Chief Science Officer, Laboratory Director and board member of Clinical Reference Laboratory, based in Lenexa, KS. He completed undergraduate studies at California State University at Fullerton and obtained a PhD in Biological Chemistry from UCLA School of Medicine. Since 1978, he has been directly responsible for introducing many of the new tests and procedures used in risk assessment such as urine and saliva HIV. Dr. Stout has nine US patents and numerous papers on the relationship between laboratory testing and insurance applicant mortality.