

New Results Regarding NTproBNP: Implications for Underwriting

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N-terminal pro B-type natriuretic peptide (NTproBNP) is actually a cardiac function test and a consistent predictor of cardiovascular disease severity in applicants. The resting EKG, at least the assessment of abnormal Q-waves, is an anatomic test, providing information about the amount of damaged myocardium, but not really assessing LV function. Analysis of rhythm disturbance is a functional result, as are conduction abnormalities, but these are present in very small proportions of applicants. In that regard, NTproBNP may be a better predictor of mortality than the resting EKG.

NTproBNP can classify the severity for a variety of cardiovascular diseases. NTproBNP may prove to be equal in prognostic value to the information offered by a stress EKG test, even assuming the stress EKG is scored properly and not considered as a positive/negative result based on ST segment analysis. (The aspersions being cast around the industry against the stress EKG regarding its low value are in part due to an inadequate appreciation of exercise capacity as the most critical component of ETT results.) The aspects of NTproBNP which should allow it to dominate the stress EKG in cost-effectiveness include the substantial differences in cost and ease of ascertainment in the insurance setting, rather than differences in the prognostic value of the two tests.

Hank George has been very persistent in promoting NTproBNP as a replacement for the stress EKG. You can see his perspective as well as a large number of literature citations at his website <http://insureintell.com>. Is his charge that the reinsurers are unfairly holding back progress in this area a fair description of the current state of affairs? I don't think the evidence is iron-clad, but it may soon be sufficient to support the shift to a lab-test strategy for older or high-face-amount cases.

Growing Evidence Supports Testing Shift

My approach is to assemble studies of similar composition and endpoints, assess their level of agreement and then determine a summary level of confidence. In essence, I am attempting to do an informal "meta-analysis." When reviewing this topic a year ago, I found relatively few studies of the use of NTproBNP in true screening studies. The number of identified events in those studies was insufficient to draw conclusions of satisfactory credibility to make good estimates of mortality risk. In contrast, the for-cause use of NTproBNP as a cardiovascular disease severity marker was well supported in a variety of conditions: coronary artery disease (CAD), aortic and mitral valvular diseases, hypertrophic heart disease, comorbid diabetes with hypertension or renal disease. Even the conditions for which NTproBNP might provide false positives in a clinical setting, such as pulmonary hypertension or renal disease, are still important, and not at all "false" from a life insurance perspective.

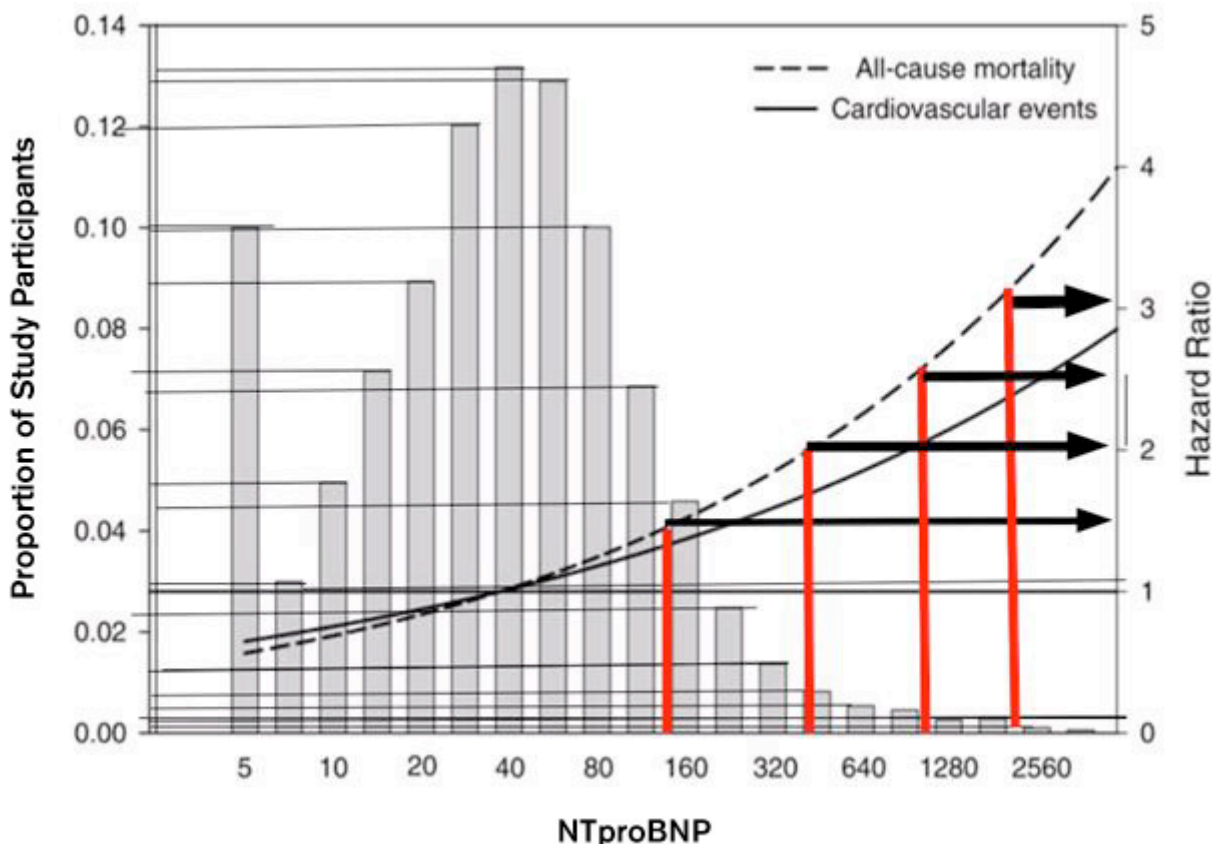
To review my advice from last year (eEnvoy, January 2009): NTproBNP is useful in cases of CAD where the mean values of NTproBNP are generally around 140 to 200 pg/mL. Because these values are significantly elevated compared to healthy populations., values substantially below or above the 140 to 200 pg/mL range deserve appropriately better or worse ratings. NTproBNP is also helpful in assessing aortic stenosis and mitral regurgitation, two conditions for which echocardiograms are often not available or up to date. In addition,

NTproBNP will be very helpful in resolving contradictory implications from current echo reports (Review Table 4 for CAD cases at the end of this article).

Putting NTproBNP to Use

I was pleasantly surprised to find two large prospective studies which reported outcomes for NTproBNP-associated cardiovascular and all-cause mortality. Both studies are from towns on opposite sides of the Netherlands: Groningen and Rotterdam. I marked up and measured **Figure 1** from an article by Linssen, et al, which appeared in the *European Heart Journal*, January 2010. The PREVEND study is a large, population-based, longitudinal assessment of outcomes with a primary purpose of determining the natural history

FIGURE 1



The multivariable model was adjusted for all confounders: age, gender, smoking, medical history, waist-hip ratio, BMI, systolic and diastolic blood pressure, serum cholesterol, serum HDL-cholesterol, serum glucose, eGFR, mean 24 h UAE, C-reactive protein, and LVH. Source: *Eur Heart J* (2010) 31(1): 120-127

of albuminuria. Linssen, et al, reported that both cardiovascular and all-cause mortality were strongly associated with rising levels of NTproBNP among a group whose composition makes it particularly applicable for comparisons to an insurance seeking population. The group includes a mixture of almost 2500 randomly selected individuals combined with 6000 persons who were found to have mild-or-greater micro-albuminuria. After a follow-up of over seven years, there were 437 deaths, of which over half were persons with values above 87.5 pg/mL, the highest 20 percent of NTproBNP values. The researchers found that NTproBNP in the highest 20 percent had more severe albuminuria, more left ventricular hypertrophy (LVH), higher proportions of myocardial infarction and hypertension, and lower estimated glomerular filtration rate (eGFR). What's more, when the independent predictive capacity of NTproBNP was analyzed—after controlling for the potentially confounding effects of all of these features—researchers still found each doubling of NTproBNP is associated

with an increase of risk by a factor of 1.46. This is equivalent to considering cases that have already been underwritten and then further adjusting up or down in your assessment of risk based on the NTproBNP results. The same type of results were seen for cardiovascular events (CVE) although the association of NTproBNP was not quite as strong for CVE.

To access the article, N-terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population, click on <http://eurheartj.oxfordjournals.org/content/31/1/120.full/>.

By adding up the heights at each level and dividing by the total measurements in Figure 1, I found that 11 percent of cases had values at or above 160 pg/mL. Above that value the age-sex-smoking-and-medical-conditions adjusted risk exceeded 150 percent. When I showed it to Doug Ingle, now at Hannover Life Reassurance Company, he calculated the prevalence-weighted average mortality as 190 percent for those 11% of persons with NTproBNP values above 160 pg/mL.

TABLE 1 (From Figure 1)

NTproBNP Values pg/mL	160	226	320	453	640	905	1280	1810	2560
Proportion	4.7%	2.6%	1.4%	0.9%	0.5%	0.3%	0.4%	0.1%	0.1%
Mortality ratio	150%	175%	175%	200%	200%	225%	250%	275%	300%

The Rotterdam study was slightly smaller, but analyzed the independent contribution from NTproBNP from a "differential" perspective in 5063 persons without evident cardiac disease or history. It measured how much extra information about cardiac risk is received by adding NTproBNP to the "classic" (Framingham) test predictions. Joost H.W. Rutten, et al, "Cerebrovascular Risk Prediction in the Population: The Rotterdam Study Amino-Terminal ProB-Type Natriuretic Peptide Improves Cardiovascular and Cerebrovascular Risk Prediction in the Population: The Rotterdam Study", *Hypertension*, 2010;55;785-791.

<http://hyper.ahajournals.org/cgi/content/full/55/3/785>

TABLE 2
Change in Risk Stratification by Adding NTproBNP

Classic Model Predicted 10 yr Risk	MEN Model + NTproBNP			WOMEN Model + NTproBNP		
	<10%	10 – 20%	20+%	<10%	10 – 20%	20+%
Participants who DO experience a CVD event						
<10%	3	3	0	19	11	2
10 – 20%	4	33	17	11	33	21
20+%	0	11	153	0	7	92
Participants who DO NOT experience a CVD event						
<10%	118	46	0	1179	172	10
10 – 20%	104	566	113	298	433	136
20+%	0	181	680	9	158	440

In Table 2, from the Rotterdam study, the outcomes for men and women show that NTproBNP is a powerful addition to the "classical" risk predictors. This is especially apparent in the predicted 10% – 20% "classic-model" category where 104 men and 298 women are reclassified to the low side. Another large proportion of each gender, 113 men and 136 women, are reclassified to the high side. The underwriting take-away from this...using NTproBNP as a screening tool helps to better classify risk, both favorably and unfavorably, even when traditional risk predictors have already been factored in.

Conclusions:

Clinicians have one perspective; underwriters have another. Clinicians need to have an available course of treatment to pursue before they decide to request a test. Underwriters *always* have an available course: pricing the risk. Therefore, they should always be asking themselves, "Does this test give me sufficient differential pricing information to pay for itself? How many high-risk persons will it identify?" The "underwriting treatment" is simply the assignment of the appropriate risk class. It may seem a bit detached to take this perspective, but we need to remember that our job is not treatment nor deciding ratings on the basis of availability of treatments for the issues identified in the course of medical underwriting.

The new NTproBNP study results add to the evidence from the Mayo Clinic study of Olmstead County residents and from the Framingham study, which show that natriuretic peptides are an effective and powerful risk measure in general populations. This expands the range of NTproBNP's value from simply that of assessing applicants with CVD history. Companies may want to consider including its use as a screening tool and/or a replacement for EKGs on apparently asymptomatic, healthy individuals. If this test were used as a substitute for a requirement EKG, the starting point would be different from underwriting a CAD case. The presumption should be that the applicant is healthy, so there can be no credits for a value in the middle of the normal range. Furthermore, the level at which a result exceeds the expected average should be significantly lowered. I would advise that for persons 50-65 years of age, values above 80 would carry added risk; preferred offers would be unwise; and values above 125 would be inconsistent with standard pricing for most companies.

In summary, we see three distinct applications for using NTproBNP in daily underwriting: Preferred Classification; Age and Amount screening; and Applicants with history of CAD. In each category though, NTproBNP will contribute differently to the case and should be treated differently in underwriting. In Figure 4 we outline our recommendations for use of NTproBNP in preferred underwriting and age and amount screening and in Figure 5 for applicants with a history of CVD.

For companies that are currently using NTproBNP, you may wish to re-evaluate your requirements based on this new information. For companies that are not currently using NTproBNP, we would suggest implementing it with the following rules for underwriting:

- Any time History of CVD is marked YES on the lab ID slip
- Age 65 and above
- A substitute or complement to any EKG
- With any admitted history of CVD or history discovered in APS
- With the combination of diabetes and hypertension

TABLE 3

NTproBNP in Preferred Underwriting / Age and Amount Screening

NTproBNP			Decisions regarding Preferred/Standard	Percentiles targeted
Age <65	Age 65 – 74	Age 75+		
<30 pg/ml	<50 pg/ml	<75 pg/ml	0 (perhaps -25)	Lowest 30th
30 – 80	50 – 125	75 – 150	OK preferred	31st to 70th
81 – 125	126 – 175	151 – 250	OK standard	70th to 90th
125 – 160	175 – 250	250 – 400	25 debits	90th to 95th
			Rating with APS	Rating w/o APS information
161 – 225	250 – 350	400 – 550	50 debits	75-100 debits
226 – 320	351 – 500	551 – 800	75 debits	125 debits
321 – 450	501 – 700	801 – 1100	100 debits	150 debits
450 – 640	701 – 1000	1101 – 1500	125 debits	200 debits
>640	>1000	>1501	Postpone	Postpone

When considering ratings for NTproBNP results, please take into account whether there is an actual APS and other objective measures of health. Also note that women have higher NTproBNP results than men, so a reasonable adjustment to a woman's value would be to multiply her values by 0.80 before rating. The hazard ratios calculated in Linssen, et al, were derived after adjustment for medical history, blood pressure measurements and treatment. Without such information, the safer course would be to assume something worse.

TABLE 4

NTproBNP for applicants with CVD history but where extensive credits have not been applied for exercise capacity or demonstrated fitness

NTproBNP			Adjustment to CAD rating
Age < 60	Age 61-74	Age 75+	
<50 pg/ml	<75 pg/ml	<100 pg/ml	-50
50-100	75-150	100-150	-25
101-200	150-250	151-300	0
201-400	251-500	301-600	50 debits
401-600	501-750	601-1000	100 debits
>600	>750	>1000	Postpone; reconsider with full evaluation.