NT-proBNP
The Finest Cardiovascular Screening and Reflexive Test In the History of Life Underwriting

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EXECUTIVE SUMMARY

It is incumbent upon those who set underwriting practices for life insurers to do so in a manner which best accommodates the broad mandates of senior management as they relate to risk appraisal.

This paper, building upon the evidence presented in its 2007 predecessor, makes an overwhelming argument for using NT-proBNP as both a screening and reflexive test. It is also clearly shown that NT-proBNP should replace routine screening with resting electrocardiograms and treadmill tests.

The functional characteristics of NT-proBNP make it ideally suited for use within the constraints imposed by the underwriting process. It can be measured in blood specimens currently required universally in insurance screening. It is relatively inexpensive and not encumbered by the subjective aspect of analysis conferred by ECGs and TSTs.

NT-proBNP is a dynamic marker for excess morbidity and mortality in all domains of circulatory disease. In this context, it consistently adds significant value to traditional risk factors for the purpose of establishing insurability.

NT-proBNP is also a "red flag" for occult (asymptomatic, undiagnosed) circulatory disease in a wide range of circumstances. By setting appropriate risk assessment thresholds for NT-proBNP readings, insurers will be able to identify these cases as well as those where known circulatory is not disclosed by the applicant.

We now have sufficient clinical evidence of the impact of NT-proBNP to establish credible, evidence-based underwriting practices optimizing the protective value and mortality gains inherent in NT-proBNP screening and reflexive testing. Therefore, objections to immediate deployment of this test in lieu of ECGs and TSTs by reinsurers and others can no longer be realistically sustained.

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INTRODUCTORY COMMENTS

In March, 2007 this underwriter published a comprehensive research paper titled "An Underwriting Perspective on NT-proBNP, a Novel Marker for Cardiovascular Disease".

This paper was based on 294 sources which constituted the world literature on NT-proBNP at that time. It is posted at www.insureintell.com.

In the intervening 30 months, the volume of research and clinical studies on NT-proBNP has increased all but exponentially. Over the same interval, this test has come to be embraced by a growing number of U.S. life insurers. For these reasons, I undertook a second in-depth review of the medical literature. I have also included broad theoretical guidelines for the use of NT-proBNP as both a screening and reflexive test in risk appraisal.

To complete this project, I reviewed over 400 research papers, clinical studies, meta-analyses, reviews, editorials and study abstracts mainly published between January, 2007 and November, 2009.

The core text of this second NT-proBNP paper, like that of its predecessor, is laid out in a question-answer format. I use this format in my continuing education program for underwriters because it has been shown to enhance comprehension and retention when reading highly technical content.

The content of this paper is solely the work of this author. As with the first NT-proBNP paper, it was understood that there would be no editorial oversight on any aspect of this paper. I have reported my findings objectively, whether favorable or otherwise, as regards the underwriting implications of this test.

I am indebted to Hans-Juergen Loyda, Ph.D., MBA; Director, Clinical Development and Education at Roche Diagnostics for his expert scientific review of this paper. I also extent my sincere gratitude to Sinead Gregory at Roche for her unflagging support which made this paper possible.

THE CURRENT STATE OF CARDIOVASCULAR RISK UNDERWRITING

In the last few years, the need to implement significant changes in how we underwriting risks has become more acute than ever before in our history.

The mandates from senior management compelling radical change are well known to most chief underwriters:

- Reduce new business acquisition costs
- Shorten new business processing (application-to-issue) time
- Lessen our dependence on patient medical records
- Make the insurance acquisition experience more akin to other financial services transactions

To strive to accomplish these objectives, many changes have been put in place affecting every aspect of 21st century risk appraisal.

"Currently, life insurance company risk assessment protocols include cardiovascular tests that are expensive, time-consuming and inconvenient for applicants."

Ross McKenzie, MD, FRCP(C), FACC
Editor-in-Chief
Journal of Insurance Medicine
39(2007):153[editorial]

The tests in question here are resting electrocardiograms, treadmill stress tests and chest x-rays (for heart size). These tools have been with us for decades and their many conspicuous drawbacks have been tolerated only because superior alternatives have not – that is, until now – been available.

Because of the implications of CV disease in mortality and morbidity as well as the above-mentioned goals of senior insurance company management, it is

clearly incumbent upon those accountable for setting underwriting practices to give priority consideration to viable alternatives to the ways of the last millennium.

Hopefully, the findings reported in this paper together with those reviewed in the first NT-proBNP research paper will encourage these individuals to replace obsolete screening tests and adopt NT-proBNP as both a screening and reflexive test. As you will see here, it is no exaggeration to conclude that NT-proBNP is indeed the finest CV test in this history of mortality and morbidity risk underwriting.

"In general, levels of N-type NP (BNP) and NT-proBNP are directly related to the severity of underlying cardiac abnormalities, and they are best viewed as continuous variables"

Roland R. J. van Kimmenade, MD, PhD, et al
Maastricht, Netherlands
The American Journal of Cardiology
101, Supplement (2008):39A

"Circulating B-type natriuretic peptides (BNP and N-terminal part of the pro-B-type natriuretic peptide [NT-proBNP]) increase in proportion to cardiac dysfunction and. . . are powerful independent predictors of outcome across the spectrum of cardiovascular disease."

A. Mark Richards, MD, PhD, DSc, FRCP, FRACP
Christchurch, New Zealand
Journal of the American College of Cardiology
52(2008):1004[editorial]

"Independent of age, traditional cardiovascular risk factors, ECG and echocardiographic abnormalities, an elevated NT-proBNP is a long-term predictor of new onset heart failure and cardiovascular death in community-dwelling individuals aged 65 and older. Furthermore, NT-proBNP levels frequently are dynamic over time, conferring a change in risk for subsequent cardiac events concordant with the direction of change of the biomarker. NT-proBNP measurement may be particularly well suited to an elderly population with highly prevalent cardiovascular risk factors."

Christopher R. deFilippi, MD, et al
Division of Cardiology, University of Maryland School of Medicine
Journal of the American College of Cardiology 55(2010):441

". . . the use of NT-proBNP has increased significantly world-wide."

James L. Jannuzi, Jr. MD et al
International NT-proBNP Consensus Panel
The American Journal of Cardiology
101, 3A(2008):1A

BACKGROUND ON NT-PROBNP

NOTE: *the first research paper covered most of the essential background on NT-proBNP and this paper will focus only on certain key aspects. Readers are referred to the first paper for more details.*

What is NT-proBNP?

A peptide hormone secreted primarily by the cardiac ventricles. Its precursor molecule proBNP is cleaved into two peptides: BNP and NT-proBNP. [Martinez-Rumayor]

What causes cardiac release of NT-proBNP?

"It is now clear that the heart is also an endocrine gland which releases NPs from hemodynamically-stressed myocardium by increased atrial and ventricular myocardial stretch or strain [wall tension]."

Johannes Mair
Innsbruck Medical University
Clinical Chemistry and Laboratory Medicine
46(2008):1507

Contributing factors to increased release of NT-proBNP appear to include ischemia-induced left ventricular (LV) systolic and diastolic dysfunction, the presence of significant atherosclerotic plaque, hypoxia, increased heart rate and various proinflammatory agents (cytokines, etc.). [Omland, Omland and de Lemos]

Why is NT-proBNP a better choice for underwriting purposes than BNP?

It has a longer half-life, is more stable at room temperature and can be stored without significant deterioration for a longer period. [Frankenstein, Ordonez-Llanos, Pu]

Can BNP and NT-proBNP measurements be used interchangeably?

No. [Ordonez-Llanos]

In what units is NT-proBNP reported?

Primarily in picograms per milliliter (pg/mL) and, less often, in picomoles per liter (pmol/L).

The conversion factors are:
pg/mL x 0.118 = pmol/L
pmol/L x 8.457 = pg/mL

Because all NT-proBNP values included in this paper are reported in pg/mL "pg/mL" will not be included when citing them.

What are the upper limits of normal currently recommended for NT-proBNP?

In general patient care:

Under age 75	125 pg/mL
Age 75 and over	450 pg/mL

What are typical NT-proBNP readings in middle aged and older persons? [Ordonez-Llanos]

	MEN		WOMEN	
Ages	**Median**	**97.5th Percentile***	**Median**	**97.5th Percentile***
45-59	**20**	**100**	**49**	**164**
⩾ 60	**40**	**172**	**76**	**225**

** Top 2.5% of subjects tested*

What are the insurability implications of a normal NT-proBNP when screening asymptomatic insurance applicants?

"...peptide values below the 97.5th percentile for the normal population have a high negative predictive value, essentially ruling out cardio-renal abnormalities in asymptomatic subjects."

Richard W. Troughton, MB, PhD, et al
Journal of Cardiovascular Imaging
2(2009):216

Are NT-proBNP gender differences significant from our perspective?

No. [Ordonez-Llanos]

How does weight relate to NT-proBNP?

As BMI increases, NT-proBNP readings increase.

However, this does not affect NT-proBNP's use in underwriting or its impact on CV disease prognostic assessment in any way [Daniels and Maisel, Kragelund]

How does exercise affect NT-proBNP?

It depends on the level of exercise.

- Typical levels of minimal to moderate exertion have no significant effects and will not elevate NT-proBNP. [Daniels and Allison, d'Eril, Mair]
- Participation in marathons has been shown to induce mild-to-moderate transient elevations in some [Knebel, Sahlén, Scott] but not all [Faviou, Lippi] studies.

We need not be concerned in this regard unless the proposed insured has engaged in highly strenuous exercise within 2-3 days of blood specimen collection...and by practice we already caution applicants in this regard because of the implications for aminotransferase (ALT, AST) readings.

Does cigarette smoking elevate NT-proBNP?

Ayalan et al found that smokers had a mean NT-proBNP twice as high (70 ± 16) as nonsmokers (36 ± 20) in one small study. Although this difference was statistically significant ($p < 0.001$) not one of his 75 smoking subjects had a reading greater than the upper limit of normal.

In three large clinical studies, there was no significant difference in mean NT-proBNP between smokers and nonsmokers. [Corteville, Kragelund, Omland and Sabatine]

NT-PROBNP IN PERSONS FREE OF KNOWN CIRCULATORY DISEASE

Why is this topic a key consideration from an underwriting perspective?

The vast majority of insurance applicants are free of known or suspected cardiac and other circulatory diseases. In order for NT-proBNP to have a role in routine screening, there needs to be evidence that it has significant risk implications in this context.

How effective is NT-proBNP as a risk marker in the general population?

Copenhagen-based researchers followed 537 community-dwelling subjects, ages 50-89, free of known CV disease for 5 years prospectively. Those with NT proBNP above the 80th percentile had 2-fold higher all-cause mortality after adjustment for traditional risk factors. Even after further adjustment for LVEF and LVH, excess mortality was still 1.8 times greater.

In this same cohort, NT-proBNP > 80th percentile was linked to a 3.2-fold raised risk of a 1st CV event, again after adjustment for conventional CV risk factors. [Kistorp]

A new study just reported at the 2009 American Heart Association annual meeting looked at 4794 persons, ages 18-45 and free of known or suspected CVD. After 5 years, NT-proBNP levels strongly predicted first CV events and all-cause mortality. [Leistner]

Another investigation from that meeting related 11-year mortality in 2042 individuals, ages 45 and over at baseline. Subjects in the top NT-proBNP quartile had 7-fold increased mortality, independent of all other risk factors. [Macheret]

A third recent investigation assessed 5067 similar subjects, mean age 58, for almost 13 years prospectively. The authors lumped together NT-proBNP with 5 other putative risk markers and this combination showed only minimal added value above that obtained with conventional risk factors.

However, when NT-proBNP was examined as a solitary variable, it was a highly significant independent indicator of the risk of 1st CV and 1st coronary events ($p < 0.001$). [Melander]

At one of my 2009 underwriting study groups, this study was misrepresented by a reinsurer attendee as "evidence" of the limited value of NT-proBNP. I mention this lest this study be miscast in a similar manner by others!

Does NT-proBNP perform equally robustly at older ages?

Absolutely.

Takahashi et al evaluated 13,297 subjects, mean age 63, for 3 years prospectively. They found powerful links between high NT-proBNP levels and increased risk of onset of cardiovascular events:

Gender	NT-proBNP Decile	Relative Increased Risk
Male	9th	2.2
Male	10th	3.5
Female	10th	2.8

Zethelius and his coworkers followed 1135 patients free of CV disorders (mean age 71) for 10 years prospectively. Using a cutpoint of only ≥ 309, NT-proBNP was associated with 4.1-fold greater CV-mortality and 2.6 x greater all-cause death ($p > 0.001$).

In the Rancho Bernardo Study consisting of 957 persons, mean age 77, followed nearly 7 years, NT-proBNP turned out to be a superior mortality marker than troponin T, smoking, diabetes, fasting blood sugar and all lipid parameters. In the cohort subset free of known CV disease, mortality in those with elevated NT-proBNP was 3.5-fold increased. [Daniels and Laughlin]

Even in nonagenarians (age 90 and over), elevated NT-proBNP in the absence of known CV disease linked to the same high degree of excess mortality (3.5-fold), as in the Rancho Bernardo investigation. [Vaes]

How does NT-proBNP fare in elderly subjects with multiple comorbidities?

Barents et al looked at nursing home residents. NT-proBNP significantly predicted 1-year mortality after adjustment for 6 prevalent chronic diseases as well as physical immobilization.

OVERVIEW: NT-PROBNP IN CARDIAC DISEASE

"Natriuretic peptides are well-established risk markers in a broad range of acute and chronic cardiac diseases. In addition, they are the basis of important diagnostic and therapeutic decisions."

Daniel Bollinger, MD, et al
Basel, Switzerland
Journal of the American College of Cardiology
54(2009):1607[editorial]

Is elevated NT-proBNP associated with all cardiac diseases?

Yes. In an analysis of 21 studies, Balion and her Canadian colleagues found that NT-proBNP was associated with all cardiac diseases.

Does NT-proBNP to distinguish between specific cardiac pathologies?

No…which is not an issue for us because differential diagnosis is not one of the functions of underwriting. [Mady and Fernandes]

Is NT-proBNP ever false-positive or false-negative in the presence of cardiac disease?

All immunoassays have the potential for both false-positives and false-negatives. In one new study, 25% of 176 patients with heart disease had NT-proBNP levels below the cut-off. [Wieshammer].

It is important to remember that nearly all studies involving NT-proBNP focus on one specific disorder and the fact that it is deemed false-positive or false-negative in these contexts has no direct bearing on its value as a general marker for CV disease of all types.

"Elevation of NT-proBNP in the context of non-HF [heart failure] situations should not be regarded as a false-positive result, and elevated NT-proBNP values should not be discarded without further consideration of the serious adverse outcomes associated with their elevation."

Aaron L. Baggish, MD, et al
The American Journal of Cardiology
101, Supplement (2008):43A

Do cardiologists recommend additional testing when NT-proBNP is elevated?

"We think it useful to perform echocardiography when plasma BNP/NT-proBNP is increased because it is important to find out what is wrong with the heart".

Richard Isnard
Department of Cardiology, Pierre and Marie Curie University; Paris
Archives of Cardiovascular Disease
101(2008):295

Is NT-proBNP a marker for CV damage which may not be discernible with echocardiograms?

Yes, based on a study of 2656 subjects, ages 41 to 71, followed over 9 years. [Olsen]

What is the incidence of coronary artery disease (CAD) – based on NT-proBNP quintiles – in older subjects free of heart failure?

deFilippi and his coworkers reported the following incidence rates for CAD in 2975 community-dwelling subjects, ages 65 and over, free of HF at baseline (p 0.001):

NT-proBNP Quintile	% with CAD
1	10.0%
2	12.1%
3	15.2%
4	19.4%
5	31.5%

Does NT-proBNP correlate with the severity of CV disease?

Yes, robustly.

Kotaska and his Prague coworkers looked at 280 patients with CV disease and reported the following NT-proBNP levels based on New York Heart Association (NYHA) disease severity status:

NYHA Class	NT-proBNP
1	224 ± 56
2	629 ± 148
3	1642 ± 459
4	5653 ± 5213

Do any circulatory disease medications cause NT-proBNP elevations?

No. [Balion]

Does NT-proBNP correlate with the extent of angiographic CAD?

Yes.

In the Ludwigshafen Risk and CV Health Study, mean NT-proBNP was 338 in subjects with proven CAD vs. 156 in those with angiograms showing no significant disease. [Winkler]

Kragelund and associates assessed 1034 patients referred for angiography because of signs and symptoms of CAD. They reported that NT-proBNP correlated significantly with the presence of 3-vessel and left main disease and was not helpful with lesser degree of obstructive plaque.

Are NT-proBNP elevations influenced by unstable plaque?

Yes.

Korean researchers evaluating CAD patients with vascular ultrasound showed that NT-proBNP readings were linked to both greater unstable plaque and more proximal vulnerable lesions. [Hong]

It must be noted in this context that treadmill stress testing only reflects total plaque burden and is not influenced by unstable (vs. well-calcified) atheromatous lesions.

Is NT-proBNP reflective of myocardial ischemia?

An autopsy study of 96 subjects who either experienced acute and chronic ischemic events or succumbed to other causes revealed the following: [Michaud]

Cause of Death	Mean Serum NT-proBNP
Non-ischemic	68
Acute ischemia	108
Chronic ischemia	310
Acute and chronic ischemia	688

The lower mean NT-proBNP value with acute ischemia only reflects the fact that there was not sufficient time for substantial natriuretic peptide release prior to death.

Findings in patients differ between studies:

- In the Heart and Soul Study of 815 patients with known CAD but free of HF, there was a strong correlation between NT-proBNP and the incidence of inducible ischemia. Nearly 40% of subjects with readings > 500 manifested ischemia vs. only 11% with NT-proBNP < 100. [Corteville]
- Staub et al found that NT-proBNP did not reliably detect inducible ischemia on SPECT perfusion imaging.
- van der Zee et al showed that while NT-proBNP did not directly reflect ischemia on stress testing, the absolute increase at peak treadmill exercise was indicative of ischemia: 64 (32-172) vs. 34 (19-85)
- Omland and de Lemos revealed that NT-proBNP added incrementally-significant prognostic value beyond that obtained from both stress echocardiography and radionuclide stress testing for detection of ischemia.
- Palazzuoli found that NT-proBNP reflects the severity of ischemic insult in acute coronary syndrome even in the absence of myocardial necrosis.

Is NT-proBNP related to the presence and extent of LV dysfunction?

Absolutely; this is one of the areas where NT-proBNP is most helpful.

"In population based studies, NT-proBNP is inversely associated with the left ventricular ejection fraction (LVEF) and directly associated with left ventricular mass. These associations are robust and consistent and appear to be linear."

James A. de Lemos, MD and Per Hildebrandt, MD
University of Texas Medical School
The American Journal of Cardiology
101, Supplement (2008):16A

"NT-proBNP [was] highly accurate in differentiating between patients with less or more severe myocardial dysfunction, either in a resting state as well as during exercise."

M. Heringlake, MD, et al
University of Lubeck, Germany
European Journal of Medical Research
14(2009):106

In a literature review, Troughton and his New Zealand coworkers found that NT-proBNP correlated "…positively with LV dimensions, volumes and mass in a variety of settings and populations". It was reflective of LVEF and the presence of left ventricular hypertrophy (LVH) and also significantly associated with equivalent pathology affecting the right ventricle.

What is diastolic dysfunction?

"There is no universally accepted measurement to determine the presence or absence of diastolic dysfunction. This has led many investigators to term this syndrome heart failure with preserved left ventricular function."

Da-Rong Pu, et al
Heart Failure Review
e-published 4/10/09

Assessment of left ventricular filling dynamics by echocardiography is the most common method of characterizing diastolic dysfunction.

Even asymptomatic diastolic dysfunction is highly significant in underwriting because it is a precursor of systolic dysfunction, one of the most potent predictors of CV mortality.

Does NT-proBNP correlate with diastolic dysfunction?

Tretjak et al showed that it was associated with early evidence of diastolic dysfunction and reduced exercise capacity in asymptomatic and ostensibly health elders.

Other studies have demonstrated that elevated NT-proBNP is a marker for diastolic dysfunction [Barragán, Hettwer] and in the Candesartan in Heart Failure study it was said to be "...the most powerful predictor of significant diastolic dysfunction". [Grewal and McKelvie]

How does NT-proBNP relate to systolic dysfunction?

In a 5393 patient cohort involving subjects from 18 centers, it was shown to be a strong indicator of systolic dysfunction. [Collinson]

Assessment of 2975 community-dwelling subjects ages 65+ showed a markedly increased risk of both borderline and overtly abnormal systolic dysfunction in the highest NT-proBNP quintile: [deFilippi]

Systolic Dysfunction

NT-proBNP Quintile	Borderline Abnormal	Overtly Abnormal
1	4.4%	0.2%
2	2.7%	0.7%
3	4.5%	0.8%
4	5.0%	2.0%
5	9.3%	9.7%

How does NT-proBNP associate with left ventricular ejection fraction, the #1 marker for systolic dysfunction?

Linzbach et al evaluated 880 consecutive patients with stable HF. At a threshold of 379, NT-proBNP was reflective of EF < 50% and mean EF became progressively lower with rising NT-proBNP readings beyond this threshold.

Similar findings were reported in a Korean assessment of 256 patients with chronic kidney disease who did not require dialysis. [Lee, JE]

NT-PROBNP IN KNOWN/SUSPECTED CORONARY ARTERY DISEASE (CAD)

"NT-proBNP levels add prognostic information in patients with stable CAD beyond that provided by conventional risk factors, including patient's age, sex, family history of ischemic heart disease, history of MI, angina, hypertension, diabetes or chronic heart failure, creatinine clearance rate, body mass index, smoking status, plasma lipid levels, LVEF and the presence or absence of clinically significant CAD on angiography"

Vanita Arora, MD and Suman Bhandari, MD
Escorts Heart Institute and Research Centre
New Delhi, India
Indian Heart Journal
58(2006):90[editorial]

Is NT-proBNP independently predictive of CV events in patients with suspected CAD?

Yes.

In a recent study of 205 patients referred for angiography on this basis, the incidence of CV events was 29% in those with NT-proBNP < 472.6 vs. 71% where readings were higher. [Huang]

In an earlier study, subjects with suspected CAD and an NT-proBNP ≥ 456 had a 3-fold increased risk of mortality as compared to those with readings between 64 and 169 and almost twice the risk of those whose NT-proBNP was between 170 and 455. [Kragelund]

Does the same hold true for those with stable CAD?

It does.

- In the 3-country PEACE Trial involving 3761 patients with stable disease, NT-proBNP as a continuous variable was associated with 1.7 x greater CV mortality independent of all risk factors including prior CV history. [Omland and Sabatine]
- In the Heart and Soul Study, NT-proBNP was the #1 predictor of recurrent CV events and readings; > 459 increased this risk more than 2-fold. [Shlipak]
- In the LIPID Study, subjects mean age 63 followed for 2.5 years, NT-proBNP was independently associated with adverse outcomes in subjects. At a threshold of 389, virtually all subjects free of events were distinguished from those who went on to experience serious cardiac consequences. [West]
- Vanzetto et al performed exercise thallium-201 gated myocardial perfusion imaging on 102 subjects with stable CAD. They reported a powerful association between adverse findings and NT-proBNP in the top tertile (> 200):

Moderate-to-Severe Adverse Finding	Increased Risk in Top NT-proBNP Tertile
Resting Defect	12-fold
Exercise Ischemia	5-fold
Scar (prior MI)	14-fold

Does NT-proBNP correlate with the extent of angiographic disease in patients with stable CAD and positive/equivocal treadmill stress tests?

Very efficiently.

European investigators looked at 194 patients with normal LV function undergoing coronary arteriography because of abnormal TSTs. They discovered that NT-proBNP was significantly elevated only in those with significant stenotic disease. There was a clear separation between patients with normal and borderline angiograms (maximum NT-proBNP reading 170) as compared to those whose disease would result in adverse underwriting action (minimum reading 191). [Barbato]

What is the relationship between NT-proBNP and ventricular dysfunction in persons with CAD?

In the Heart and Soul Study, 815 CAD patients without a history of HF were evaluated for LV dysfunction. At a cutoff of >500, LV dysfunction – defined as LVEF ≤ 50 and/or diastolic dysfunction – was 4 times more common than at lower NT-proBNP levels with a specificity of 89%. [Corteville]

Similar findings have also been cited by Peer, et al.

Does NT-proBNP correlate with mortality in subjects with proven CAD?

As expected, very powerfully.

In a cohort of 1135 individuals, those with angiographically-confirmed disease whose NT-proBNP was ≥ 400 had over 6-fold greater all-cause mortality over 7 years than those with readings < 100 and nearly twice the risk of death as subjects with levels between 100 and 399. These results were independent of all risk factors including extent of angiographic disease.

Even in those subjects where CAD had been ruled out, there was a notable trend (HR 1.9) toward increased all-cause mortality after adjustment for all risk factors and use of 7 cardiac drugs [März]

Another useful study involved 573 patients, mean age 66, with CAD or various other types of CV disease. After 1117 days of follow-up, those who NT-proBNP was > 300 had a 7.5-fold increased risk of death, heart failure hospitalization or stroke. [Pfister and Tan]

Is NT-proBNP a helpful marker to predict the need for angioplasty or bypass surgery?

No [Peer]

Does NT-proBNP have any risk implications following either PCI (percutaneous coronary intervention) or CABG (coronary artery bypass grafting)?

Yes:

- In 345 patients with stable CAD post-PCI, elevated NT-proBNP correlated with 5.2-fold greater risk of subsequent adverse CV events over 36 months of follow-up. NT-proBNP also predicted restenosis (p 0.001). [Dai]
- In a Korean study, repeat revascularization was highly unlikely if NT-proBNP was < 122.9 in 445 consecutive patients, mean age 62.5. In the subset with new symptoms, NT-proBNP > 87.5 was a strong independent predictor of further surgery (OR = 12.3). [Sir]
- NT-proBNP was independently predictive of adverse CV outcomes in 813 post-MI patients treated with PCI (p 0.001). [Sinnaeve]
- In a Polish study, NT-proBNP above the median in post-MI PCI patients was directly linked to LV dysfunction, mitral regurgitation, elevated troponin and low eGFR. [Szadkowska]

Do experts advocate serial NT-proBNP screening of patients with CAD for prognostic purposes?

Yes, at intervals of 6 to 18 months. [Omland and de Lemos]

Is NT-proBNP helpful in assessing risk in persons presenting in the ER with acute chest pain not diagnosed as an acute cardiac event?

Yes.

Eggers and associates followed 452 patients, median age 65, for 6 months. If NT-proBNP was 550 or higher, the risk of MI or death was 5-fold higher, independent of both ECG findings and troponin levels.

In another cohort, patients with suspicious chest pain who had normal troponin levels were followed 250 days. Mean baseline NT-proBNP readings were 637 in those with an adverse outcome vs.117 in survivors free of interim MI.

Mortality was 1.5% in those with NT-proBNP < 474 as compared to 8.5% where readings were 474 or higher. [Weber]

NT-PROBNP AND ACUTE CORONARY SYNDROME (ACS)

"The relation between NT-proBNP concentrations and hazard in ACS is directly proportional; that is, with higher values for NT-proBNP, a higher risk of mortality is observed. Indeed, NT-proBNP was been consistently found to be among the strongest, if not the strongest, predictor of mortality compared with standard risk stratification variables."

Torbjørn Omland, MD, PhD, MPH and James A. de Lemos, MD
Akerhus University Medical School; Oslo, Norway
The American Journal of Cardiology.
101, Supplement (2008):61A

What is acute coronary syndrome (ACS)?

A general term of reference encompassing unstable angina and myocardial infarction.

It is important to review the relationship between NT-proBNP and post-ACS outcomes because many life insurers now make aggressive offers of coverage in "best cases" in this context.

How does NT-proBNP correlate with post-ACS outcomes?

To answer this question thoroughly, we will look at outcomes at specific post-ACS intervals ranging from 6 months to 8 years.

Six months:

In a follow-up of 1033 patients, mean age 67, NT-proBNP was more predictive of mortality than any variable considered, including histories of HF and prior MI as well as elevated cardiac enzymes. The test "improved upon the accuracy of mortality prediction of the GRACE score" (GRACE score is a multifactorial prognostic score used in ACS/MI). [Khan and Narayan]

One year:

Windhausen followed 1141 subjects, reporting that NT-proBNP ≥ 1170 in males (top quartile) was associated with nearly 7-fold greater mortality than readings in the lowest quartile. In addition, significantly-impaired systolic function (LVEF < 40%) was 3 times more common in the 4th quartile as compared to even the 3rd quartile.

Six years:

In this study, 385 ACS or coronary revascularization patients mean age 59 and free of heart failure were assessed for mortality. Subjects with NT-proBNP of 862 or greater (top quintile) had nearly 3 times greater 12-month mortality than those in the 4th quintile (readings between 671.1 and 861.9). Mean NT-proBNP levels were 640 in survivors vs. 958 in decedents. [Mayer]

Eight years:

Protracted follow-up of 216 ACS patients found that baseline NT-proBNP readings <184 were associated with > 75% event-free survival, whereas 3 out of 4 whose NT-proBNP was 184 or higher either died or had a second CV event. [Kavsak]

Does NT-proBNP reflect the risk of residual ischemia post-ACS?

Yes.

Sarullo et al tested 130 survivors 30-days post-event with SPECT myocardial perfusion scintigraphy. Patients with NT-proBNP in the top tertile were 8 times more likely to manifest reversible perfusions defects, consistent with new ischemia, as compared to those in the lowest tertile. These individuals also had an increased risk of future anterior MI (41% vs. 25%).

How does NT-proBNP relate to outcomes in patients surviving an MI?

Once again, we will look at studies over various intervals of follow-up.

One year:

Lorgis et al in the RICO Survey Working Group reported that NT-proBNP was significantly predictive of CV mortality in the top 3 quartiles, independent of LVEF.

Eighteen months:

Dhillon et al followed 1024 patients and discovered that elevated NT-proBNP was powerful predictor of all-cause death. It had a significantly greater hazard

ratio risk (2.9) than troponin level (1.2), low LVEF (1.4), prior MI history (1.7) or diabetes (1.2).

Two years:

In the LAMP Study of 983 consecutive MI patients, mean age 65, those in the top NT-proBNP quartile had approximately 8-fold higher mortality than those in the bottom 3 quartiles. [Khan]

Nine years:

New Zealand physicians looked at the relationship between NT-proBNP and survival. Those with readings of 1000 or higher had < 60% 9-year survival as compared to 85% in subjects with lower readings. NT-proBNP was superior to prior stroke or HF, diabetes or in-patient PTCA as a mortality marker. [Palmer]

Is NT-proBNP associated with fatal vs. nonfatal MI?

Yes.

Olsen et al evaluated 2656 individuals, ages 41-71, with echocardiography. The interim risk of an MI being fatal was 43% in those with high NT-proBNP vs. just 3.7% at low levels. [Olsen]

Is there any link between suspected prior heart attack and NT-proBNP?

Yes, as demonstrated in 616 individuals, median age 75, who were thought to have had a prior MI based on medical history and currently abnormal imaging studies. At a cutpoint of > 235, NT-proBNP was highly predictive (23% vs. 8%) of an earlier MI, even if the current LVEF was normal. [Schelbert]

Is post-MI NT-proBNP associated with persistent LV dysfunction?

It is, in terms of both ejection fraction and LV volume.

Six months after sustaining heart attack, mean NT proBNP was 821 with worsening LV function parameters vs. 413 where function was improving. [Giallauria]

How do experts view the clinical implications of elevated NT-proBNP in ACS/MI patients?

Elevated NT-proBNP "...should prompt consideration of early catheterization to complete risk stratification and assess candidacy for revascularization. Even when troponin levels are normal, such patients are at high risk for death and HF and have a higher probability of underlying severe CAD and/or LV systolic dysfunction."

James A. de Lemos, MD and
David A. Morrow, MD, MPH
American Heart Journal
153(2007):450[editorial]

NT-PROBNP AND HEART FAILURE (HF)

In which domain of CV medicine was the diagnostic and prognostic value of natriuretic peptides first discovered?

Heart failure.

Unlike CAD and most other prevalent circulatory diseases, heart failure is most often deemed uninsurable. Nevertheless, we see many cases with findings associated with early heart failure as well as "best cases" of milder heart failure which are eligible for insurance on some basis.

These considerations mandate addressing relationships between NT-proBNP and risk in HF.

"Across the spectrum of heart failure stages, assessment of proBNP levels at a single point in stable outpatient settings provides a powerful independent prediction of mortality and new events."

Koichi Node, et al
Cardiovascular Diabetology
8(2009):5

"Natriuretic peptides also appear to be useful in screening asymptomatic subjects at risk of developing heart failure, such as the elderly and those with hypertension, diabetes, or asymptomatic coronary artery disease."

Eugene Braunwald, MD
Harvard University School of Medicine
The New England Journal of Medicine
358(2008):2148

Does NT-proBNP efficiently correlate with the risk of future heart failure?

Yes.

In the Cardiovascular Health Study of 2975 subjects free of heart failure at baseline, NT-proBNP in the 5th quintile was shown to confer a 3-fold increased risk. Readings became significant at a cutpoint of ≥ 190 (70th percentile). [deFilippi]

Betti and her colleagues in the PROBE-HF Study screened 1012 patients for evidence of heart failure using echocardiography. Their subjects had hypertension and/or diabetes.

Their patients with either no dysfunction or mild diastolic abnormalities only had a mean NT-proBNP of 74, as compared to 258 in those with moderate-to-severe diastolic changes and/or systolic dysfunction. They advised using at cutoff of 125 for NT-proBNP in this context.

In a Swiss study of 384 persons suspected of having HF, NT-proBNP < 125 was a false-negative in only 10% of cases. In other words, 9 out of 10 persons below this level were free of heart failure. [Zuber]

What if the patient already has overt signs and symptoms suggestive – but not diagnostic – of HF?

A recent study found that subjects presenting with acute dyspnea or peripheral edema could be distinguished on the basis of NT-proBNP. Readings < 300 essentially excluded a diagnosis of HF (sensitivity 96%; negative predictive value 96%). In this context, NT-proBNP proved to be superior to physical examination and other diagnostic test findings. [Behnes]

Is NT-proBNP an accurate diagnostic test for both acute and chronic HF?

Yes – so much so that a meta-analysis suggested it should in the first steps of a HF diagnostic algorithm [Clerico]

Do echocardiographic findings correlate with NT-proBNP in HF?

Yes.

In a transthoracic echocardiography study of 137 patients with indications for HF risk assessment matched to healthy controls, mean NT-proBNP readings were 69 in controls vs. 1583 in those with impaired systolic function. [Knebel and Eddicks]

Several other recent studies confirm the value of NT-proBNP in identifying HF subjects with impaired systolic function (defined as low LVEF). [Dini, Koç and Bozkurt, Messer, Moertl]

What is the status of NT-proBNP as a prognostic marker in suspected and proven HF?

It is the most powerful marker we have access to in this context.

- In the placebo arm of the Valsartan Heart Failure Trial (1742 patients, mean age 63, followed for 24.5 months), the NT-proBNP cutoff for significant excess mortality was 1210 (3rd quartile; p <0.001). [Masson]
- Grewal et al followed 181 HF patients, ages 53-80, for 524 days. Using endpoints of death, CV events or HF hospitalization, NT-proBNP > 300 increased the risk of these adversities 5.8-fold. This risk became 8-fold using a cutoff of > 600. At both levels, NT-proBNP was superior to NYHA class, comorbid CAD and prior hospitalization.
- Bruch et al evaluated 341 stable systolic HF patients over 620 days. At a threshold of > 1474, NT-proBNP distinguished those at risk of a cardiac event.
- In the CORONA Study, researchers built models for 9 different fatal and nonfatal outcomes in HF patients. NT-proBNP was the #1 predictor of adversity among the 14 independently predictive variables. [Wedel]

- Danish cardiologists looked at NT-proBNP and suspected heart failure in 5875 primary care patients, mean age 73. Readings in the 4th decile (83-118) were linked to a 90% increased risk of CV hospitalization. By the 7th decile (229-363), mortality was increased 80%. [Rosenberg]
- Swedish investigators followed 474 HF patients for 10 years. Individuals in the top NT-proBNP quartile had 4-fold increased mortality. [Alehagen and Dahlström]

Many other studies corroborate these impressive findings in a variety of HF-related settings [Arnaldo, Berger, Frankenstein and Clark, Hinderliter, Kallistratos, Koç, Li, Schou and Gustafsson, Shah]

NT-PROBNP AND HYPERTENSION (HTN)

"I was just diagnosed with mild essential hypertension and the first thing I did, - before getting an electrocardiogram – was to measure my serum NT-proBNP level. It was 28, so I am going to live forever."

James L. Januzzi, MD
Associate Professor of Medicine
Harvard University Medical School
"The Editor's Roundtable: B-type Natriuretic Peptide"
2008; www.AJConline.org

Underwriters should note that Dr. Januzzi chose NT-proBNP over an ECG in this context!

Is NT-proBNP associated with hypertension per se?

No – not in the absence of cardiac complications. [Wieshammer and many other studies]

It has, however, been shown to correlate with arterial stiffness as shown by high pulse pressure (PP = SBP - DBP). [Sung]

Is NT-proBNP linked to left ventricular hypertrophy (LVH) in hypertensive subjects?

Yes.

Morillas et al assessed LVH in hypertensive patients using magnetic resonance imaging (MRI). Those with this insidious complication had a mean NT-proBNP level of 189 as compared to 47 in those deemed LVH-free. Negative predictive value was 100%, making NT-proBNP our best test to exclude this complication.

Cortés et al reported similar findings.

Which other HTN complications are demarcated with NT-proBNP?

- Furumoto discovered that NT-proBNP pinpointed increased left ventricular end diastolic pressure (LVEDP) – a marker for subclinical diastolic dysfunction – in asymptomatic hypertensive subjects.
- Ceyhan evaluated 40 subjects with controlled HTN and found that LVEDP was significantly higher at a mean NT-proBNP of 203 (± 75) as compared to 39 (± 20) in hypertensives free of early diastolic dysfunction.
- Tekten matched NT-proBNP with echo-proven diastolic dysfunction. A cut-of only 62 conferred a sensitivity of 83% and specificity of 67%, which would facilitate underwriting triage of hypertension risks under consideration of preferred risk status.

Cardiologists now use NT-proBNP to screen for subclinical diastolic failure in hypertensive patients. [Lantelme]

Is NT-proBNP an outcome predictor in HTN?

Absolutely [Garcia, Hildebrandt, Pedersen]

Moreover, a reduction in NT-proBNP has been linked to a lower risk of CV events in treated blood pressure cases. [Campbell and Woodward]

NT-PROBNP AND ATRIAL FIBRILLATION (AF)

Is NT-proBNP a predictor of increased risk of AF?

Yes.

In a Norwegian study of 916 subjects, mean age 75, NT-pro-BNP readings showed the following relationship to AF risk:

Atrial Fibrillation	Mean NT-proBNP
None	95
Paroxysmal	257
Persistent	1119

NT-proBNP was independent of CAD, heart failure and hypertension as a predictor of AF ($p < 0.001$) [Ulimoen]

Nearly identical results were reported in a Greek study [Letsas]

- In the Cardiovascular Health Study involving 5445 persons, ages 65 and older and followed for 10 years, subjects in the top NT-proBNP quintile (> 290) had a 4-fold greater risk of interval onset of AF as compared to those in the lowest quintile. The excess risk of AF was statistically significant in all quartiles, from 2 to 5. [Patton]
- In the PREVEND study of 6494 patients, mean age 49, followed 4 years, subjects with both hypertension and LVH had a 12-fold increased risk of AF when NT-proBNP was elevated. [Asselbergs]
- Following lung surgery, patients developing AF had a mean NT-proBNP of 506 (±108) vs. 198 (±55) in those free of AF. [Gurgo]

Does NT-proBNP influence the degree of atrioventricular asynchrony in AF?

Yes – NT-proBNP levels are directly associated with an increased degree of asynchrony. [Pan]

Does NT-proBNP correlate with the likelihood of AF conversion in emergency care?

Yes – as well as the odds of maintaining sinus rhythm post-conversion. [Magioncalda, Möllmann, Thejus]

Is there any association between NT-proBNP and recurrence of AF?

Yes – elevated levels increase the risk almost 8-fold [Hwang]

NT-PROBNP AND HEART VALVE DISEASE

"[NT-proBNP] levels increase with greater severity of aortic or mitral regurgitation, reflecting regurgitant volume, LV size and function, and symptomatic status. [They] identify higher risk for adverse events in subjects with severe aortic regurgitation and preserved LV function, suggesting that NT-proBNP in combination with echocardiography could refine prognostic assessment and decision-making about timing for intervention."

Richard W. Troughton
op. cit.

Is NT-proBNP associated with an increased risk of an organic heart murmur?

It is, as reflected in a Danish study of 2061 patients admitted to hospital for any reason. NT-proBNP was elevated in 53% with murmurs vs. 28% without. It was also associated with a 2.2-fold increased mortality across all types of murmurs. These researchers advised using NT-proBNP as a supplement to echocardiography in assessment of potentially significant murmurs. [Iversen]

It is important to note that NT-proBNP does not elevate in mild valvular disease. [Wieshammer]

How does NT-proBNP relate to the significance of mitral regurgitation?

In 144 cases of echocardiographic moderate-to-severe MR, NT-proBNP averaged 582 in patients with symptoms vs. 157 in those who were asymptomatic. It was superior to all echo variables and significantly associated with LV end-diastolic dimension. [Potocki]

Several other studies document a direct correlation between severity of MR and NT-proBNP readings [Behnes and Lang, Hellgren]

Does this also apply to aortic regurgitation?

Yes.

In 60 patients with isolated AR, Weber, Hausen and coworkers reported that severe AR patients had 6-fold higher readings (1268) than those with moderate AR (226) and 8-fold greater readings than in patients whose regurgitation was mild (161). An NT-proBNP cutoff of 602 distinguished clearly between those who did vs. did not survive over the ensuing 824 days.

How does NT-proBNP relate to aortic stenosis?

"[Elevated NT-proBNP] in a questionably asymptomatic patients or a symptomatic patient with unclear symptoms appears to point to underlying progression of disease and these patients should be monitored closely for development of symptoms, deterioration of LV function and raised systolic pulmonary artery pressure."

Jutta Bergler-Klein, MD
Current Cardiology Reports
11(2009):85

Cemri found that all patients with a moderately-increased AS gradient (25-40 mmHg) had NT-proBNP levels of 490 or higher. It also correlated directly with increased LV mass. Other authors report similar findings [Poh, Wagner]

It is clear from these studies and those reported in the 2007 paper that NT-proBNP is the test of choice when underwriting known or suspected heart valve disease (including "aortic sclerosis" which we frequently see in elderly applicants).

NT-PROBNP AND OTHER CIRCULATORY DISORDERS

What is the significance of NT-proBNP in insurable "best cases" of hypertrophic cardiomyopathy (HC)?

"[BNP and NT-proBNP] have been demonstrated to correlate with LV outflow tract gradient, symptoms of heart failure, low ejection fraction, maximal LV wall thickness, and diastolic dysfunction in patients with HC. Plasma levels of NT-proBNP have also been shown to predict functional impairment and clinical course in patients with HC."

Jarkko Magga, MD et al
Kuopio University, Finland
The American Journal of Cardiology
101(2008):1185

Is NT-proBNP a marker for the presence of HC?

Yes.

Portuguese investigators compared NT-proBNP levels in patients, healthy relatives and healthy controls: [Brito]

	Mean NT-proBNP
Patients with HC	**910**
Healthy Relatives	**41**
Healthy Controls	**39**

Brazilian cardiologists reported that NT-proBNP was significantly elevated in 5 cardiomyopathic states. In HCM, mean level was 848 vs. 28 in healthy controls. [Mady]

Are there other positive associations between NT-proBNP and HC?

Yes, many:

- Maximum wall thickness and subaortic gradient ≥ 30 mmHg [Efthimiadis]
- LVH and diastolic dysfunction in patients with normal LVEF [Kim, S]
- Left atrial dimension and maximum LV wall thickness [Kahveci]
- Microvascular dysfunction [Knaapen]
- Sudden death [Payá]

Why should underwriters be concerned with anthracycline cardiotoxicity?

Many insurance seekers with a history of cured childhood and adult cancers will have been treated with anthracyclines, especially doxorubicin. These drugs are cardiotoxic on a dose-dependent basis and those who develop chronic, progressive heart damage do so many years after completion of treatment.

Does late anthracycline-mediated cardiac damage manifest with elevated NT-proBNP?

Yes – and for this reason NT-proBNP should be routinely used to screen all applicants with a history of anthracycline therapy as well as any other chemotherapeutic drugs known to induce late cardiac problems. [Mavinkurve-Groothuis]

Is NT-proBNP of any value in underwriting peripheral arterial disease (PAD)?

Absolutely.

- In a Swedish investigation, mean NT-proBNP was 167 in patients with known PAD vs. 68 in controls. Not one control subject had an NT-proBNP reading as high as the mean reading in those with disease. [Arpegård]
- In patients with symptomatic PAD, a median NT-proBNP of 213 was associated with a 2.4 x greater risk of dying over 5-years, as compared to patients with lower readings. This was independent of all other risk factors. [Mueller]
- Shadman et al divided NT-proBNP in PAD patients into tertiles only. Nevertheless, even on this basis, those in the top 1/3rd had a clear trend toward higher all-cause and ischemic heart disease mortality.
- Rajagopalan et al reported a 3.4-fold risk of post-operative myocardial injury at an NT-proBNP cut-off of 308 in patients having surgery for PAD.

How does NT-proBNP relate to stroke mortality?

Jensen et al followed 216 ischemic stroke patients for 6 months. At a cut-off of 194, NT-proBNP was associated with a significantly increased risk of death, as well as the risks of developing ischemic ST-T wave changes, renal failure and heart failure.

Two additional studies showed a direct and significant correlation between NT-proBNP and post-stroke mortality at 120 days [Sharma] and 44 months [Makikallio], respectively.

Does NT-proBNP relate to the risk of sudden death (SD) in the general population?

It does.

In the Nurses Health Study, 99 subjects who succumbed to SD were contrasted to 294 healthy controls.

Considering all SD victims together, NT-proBNP > 389 related to a 5.7-fold increased SD risk. When only those SDs deemed certain to be of cardiac disease origin where considered, this level of elevated NT-proBNP demarcated a 19.9 x greater risk of sudden death. [Korngold]

Does NT-proBNP confer any value in underwriting pulmonary embolism survivors?

Yes.

In one study, NT-proBNP was the only significant marker for unfavorable outcomes in non-massive PE treated on an outpatient basis. A reading of 300+ correlated with a nearly 16-fold higher risk of death 60 days after diagnosis. This was twice the predictive impact of D-dimer. [Vuilleumier]

In a meta-analysis of 23 studies, NT-proBNP elevations correlated with greater than 6-fold increases in both serious events and all-cause mortality following PE. [Lega]

For the record, NT-proBNP is also a significant predictor of adverse findings and/or outcomes in pulmonary hypertension [Andreassen, Bernal], Kawasaki disease [Dahdah] and atrial septal defects [Schoen]

NT-PROBNP AND SURGERY

Is NT-proBNP a marker for significant consequences following both circulatory and other surgeries?

Yes.

- In a Korean study of 2054 patients undergoing non-cardiac surgery, a single preop NT-proBNP of 194 or higher was an independent marker for adverse CV events within 30 days, significantly strengthening the risk impact of an unfavorable CV profile. [Choi, J]
- A Dutch study found that NT-proBNP ≥ 350 identified patients undergoing elective non-cardiac surgery who would have one of three serious endpoints within 30-days: troponin release, Q-wave MI or cardiac death. [Goei]
- When 83 Americans were followed 30 days post-non cardiac surgery, NT-proBNP ≥ 457 increased the risk of interval CV events 10-fold. [Schutt]
- A Scottish study of 1010 non-emergent cardiac surgeries revealed that the mean preoperative NT-proBNP in those who died in the ensuing days was 624, as compared to 279 in survivors. High readings were also independent predictors of prolonged CCU care and hospital stays > 1 week. [Cuthbertson]
- In 400 consecutive patients undergoing elective vascular surgery, readings ≥ 350 preoperatively increased the risk of perioperative CV events 4.7-fold and also correlated with a nearly 2 x greater risk of death in the ensuing 29 months. Only patients with NT-proBNP at this level experienced troponin release after surgery. [Schouten]

Clearly, we need to be alert to any significant degree of NT-proBNP elevation in applicants likely to undergo surgery in the future, whether or not that surgery is elective and/or involves the circulatory system.

DIABETES MELLITUS, METABOLIC SYNDROME AND NT-PROBNP

Is elevated NT-proBNP a marker for the presence of diabetes mellitus (DM)?

No. [Bailon, Corteville, Magnusson, Omland and Sabatine, Schouten]

Are NT-proBNP and diabetes independent markers of excess mortality with at least additive insurability implications?

Yes – as reported in the studies cited above.

Is NT-proBNP an independent predictor of heart disease and its consequences in diabetics?

Yes, robustly.

- In a Spanish study, DM patients with demonstrated cardiac disease had a mean NT-proBNP of 720 (± 278) as compared to 350 (± 197) in those free of evidence of heart impairment. At a threshold of > 490, NT-proBNP demonstrated 84% sensitivity and 75% specificity of ischemic heart disease in these subjects. [Castaño Rodríguez]
- In 107 patients with a 10.6-year mean duration of diagnosed diabetes, NT-proBNP was a marker for LV dysfunction as well as non-cardiac complications, independent of a history of prior heart disease. [Kumaga]
- In another study of diabetics assessed echocardiographically for diastolic dysfunction, the mean reading in those with DD was 1491 vs. 232 in those who did not satisfy DD criteria. [Kim, J]
- Huelsmann and his coworkers showed that NT-proBNP was the only variable among 17 examined which predicted for CV-event hospitalizations as well as mortality in 631 diabetic patients followed for 12 months.
- Pfister et al all followed 156 type 2 diabetics hospitalized with CV disease for 1183 days prospectively. At a cut-off of > 518, NT-proBNP correlated with a 5.5-fold increased mortality risk. It was superior to all other variables including a prior history of CV events.

Does NT-proBNP elevate in the presence of uncomplicated metabolic syndrome?

No – as with diabetes, the risks conferred for circulatory disease are independent and at least additive [Sezen]

Is NT-proBNP predictive of CV events and mortality in patients with metabolic syndrome?

Yes.

But its greatest contribution is its negative predictive value of 92%...which means that older age applicants meeting the criteria for metabolic syndrome may be eligible for a credit against the risks conferred by metabolic syndrome when their NT-proBNP is well within normal limits. [Olsen, Hansen and Christensen]

NT-PROBNP AND RENAL DISEASE

"In patients with chronic kidney disease (CKD), concentrations of NT-proBNP are typically higher than in those without CKD; levels of NT-proBNP in patients with CKD parallel the presence and severity of heart disease in these patients."

Christopher deFilippi, MD, et al
University of Maryland School of Medicine
The American Journal of Cardiology
101, Supplement (2008):82A

Is NT-proBNP of value in assessing risk of progression of renal disease in non-diabetics with mild-to-moderate kidney dysfunction?

Yes.

Spanaus and her associates followed 177 patients, ages 18 to 65, for 7 years and found that NT-proBNP was a significant independent marker of progression to severe renal disease.

In what other ways does NT-proBNP contribute to risk assessment in patients with CKD?

- It predicts for diastolic dysfunction. [Tagore]
- It is associated with reduced LVEF and increased LV mass [Collinson and Gaze]
- It is an independent marker for mortality in non-dialysis, dialysis and transplant cases [Oterdoom, Vickery, Wang]

Is there any association between NT-proBNP and estimated glomerular filtration rate (eGFR) in healthy subjects?

No [Daniels and Maisel]

Is this also true when eGFR is < 60?

No.

In a 9.3-year follow-up study of 1063 community-referral patients, mean age 62, who sustained an MI, the combination of eGFR < 60 and NT-proBNP ≥1000 was a powerful predictor of excess mortality as well as hospitalization for subsequent heart failure. [Palmer]

NT-PROBNP AND SLEEP APNEA

Is NT-proBNP a useful marker for excess mortality in obstructive sleep apnea (OSA)?

Two recent studies found no independent value [Hübner, Maeder] whereas a third study reported added value in conjunction with echocardiographic findings. [Fernández Fabrellas]

Bitter et al discovered that elevated NT-proBNP is associated with central sleep apnea and Cheyne-Stokes respiration but not OSA.

Ybarra et al evaluated 110 morbidity-obese females and showed that NT-proBNP was an independent predictor for sleep-disordered breathing as well as significant increases in IV wall thickness, left atrial enlargement and LV mass, plus increased LV filling pressure.

NT-PROBNP AND CONNECTIVE TISSUE DISEASE

Does NT-proBNP provide value in assessing insurability in rheumatoid arthritis?

Yes.

At a cut-off of 200, it appears NT-proBNP is a worthwhile screening test for subclinical cardiac disease. It correlates well with three major inflammation markers (TNF, IL-6 and CRP). Chronic inflammation is felt to be the driver of premature atherosclerotic disease in RA. [Solus]

Provan also found that NT-proBNP parallels CRP after following 238 rheumatoid arthritics for 10 years. Thus, NT-proBNP may be an effective surrogate for CRP.

Is NT-proBNP a risk marker in any other connective tissue disease?

Three studies demonstrate significant value in patients with scleroderma [Allanore, Choi, H; Chung].

Given its association with the above-mentioned inflammatory markers, it is likely that NT-proBNP is also a predictor of circulatory disease in systemic lupus, ankylosing spondylitis and other chronic rheumatic/connective tissue disorders as well.

It is also interesting to find that NT-proBNP ≥100 is predictive of 7.4-fold increased CV risk in patients using "-coxib" antiinflammatory drugs for osteoarthritis. [Brune]

NT-PROBNP AND LIVER DISEASE

What is the association between NT-proBNP and liver disease severity?

- It has been shown that mean NT-proBNP readings are significantly higher in liver disease patients with severe fibrosis/cirrhosis (407) as compared to patients with mild (61) and moderate (55) fibrotic changes. [Raedle-Hurst]
- In the presence of cirrhosis, NT-proBNP is substantial higher in those with severe (Child class C) disease. [Woo]
- NT-proBNP also elevated with clinically-significant diastolic dysfunction in patients with high stage liver disease, with a cut-off level of 290 being highly predictive. [Raedle-Hurst]
- NT-proBNP is often elevated in hepatocellular carcinoma and has a significantly negative correlation with serum albumin [Montagnana]

Are NT-proBNP elevations in CV disorders confounded by comorbid liver disease?

This subject was carefully investigated. The answer is no. [Zethelius and Venge]

NT-PROBNP, THYROID DYSFUNCTION AND OTHER DISORDERS

Does NT-proBNP elevate significantly in hyperthyroidism?

It can.

In a small study consisting of 45 subjects with either hypo- or hyperthyroidism matched to controls, mean NT-proBNP was 239 in those with excess thyroid hormone output as compared to readings well within the normal range in all other study participants. No CV-related studies were done here. [Özmen]

When hyperthyroidism was acutely-induced in healthy females, NT-proBNP increased but not outside the normal range. [Schultz]. In other investigations, significant CV findings were present in hyperthyroid subjects with high NT-proBNP [Arikan, Bodlaj]

Is there any association between NT-proBNP and thyroid hypofunction?

Yes…in the so-called "low T-3" syndrome. [Pinelli]

Why is this significant?

Low T-3 syndrome has been convincingly linked to high mortality in patients with heart disease. [Iervasi]

Are there any other non-CV disorders associated with NT-proBNP?

Yes, a fair number…and in all cases, NT-proBNP elevations are thought to be due to either clinically-evident or occult cardiac disease.

Syncope

In a new German investigation, NT-proBNP was highly predictive of a cardiac mechanism accounting for fainting episodes. A cut-off of 164 was recommended in the differential diagnosis of syncope etiology. [Pfister and Diedrichs]

Pulmonologists have urged that NT-proBNP be used to rule out cardiac syncope. [Wieshammer]

Polycystic Ovary Syndrome

PCOS has a powerful association with diabetes, metabolic syndrome and premature onset of CV disease.

Celik et al reported that elevated NT-proBNP is a marker for occult heart disease in asymptomatic PCOS patients.

Serious Infections

In a small study of 42 individuals with community-acquired infectious diseases, NT-proBNP was the #1 predictor of adverse prognoses. [Goritsas] Vila et al found that NT-proBNP elevates in systemic infections marked by high degrees of inflammation in healthy persons with normal hearts.

Beta-Thalassemia Major

While this disorder is rarely insurable, it is worth noting that subjects with elevated NT-proBNP are highly likely to have abnormal echocardiographic findings consistent with consequences of their severe anemic state. [Akpinar]

Prostate Cancer

Dockery and his UK colleagues found minimally-elevated NT-proBNP in some patients receiving androgen therapy for prostatic carcinoma.

Cognitive Function

In the Rancho Bernardo study, subjects with low MMSE scores were 2.8 times more likely to have elevated NT-proBNP. There was also a significant adverse association with findings on the Trail-Making B test. [Daniels and Chen]

Pregnancy

NT-proBNP rises early in pregnancy but not outside the normal range [Franz] On the other hand, as one would expect it is strongly linked to both eclampsia and peripartum cardiomyopathy [Forster, Moghbeli]

NT-PROBNP AND OTHER LABORATORY TESTS

Is there any association between NT-proBNP and troponin in healthy persons?

Yes.

- In their study of the utility of the latest cTnT (troponin T) assay, Japanese researchers found that mean NT-proBNP levels were nearly twice as high in subjects with minimally-elevated cTnT as they were in those who had an acceptable troponin T level. NT-proBNP correlated more significantly with cTnT than any other marker, including eGFR, hsCRP, systolic blood pressure and Framingham Risk Score. [Ishii]
- An analysis of 98 post-MI showed that mean NT-proBNP after 6 months was 1355 in subjects above the 99th troponin T percentile as compared to just 255 in those with insignificant cTnT readings. [Neizel]
- In the Heart and Soul study, investigators followed 987 patients with stable CAD for 4.3 years. Mean subject age was 66 years old. [Hsieh]

	Baseline cTnT	
	Positive	Negative
Mean NT-proBNP	1098	161
Adverse CV Events	59%	23%
All-Cause Mortality	55%	18%

What is most telling here is that after adjusting for NT-proBNP, troponin T was no longer a significant prognostic marker.

Is there any advantage in using NT-proBNP and cystatin C together in older-age screening?

Very much so.

Alehagen and his Swedish coworkers followed 464 primary care patients with heart failure, men age 73, for 10 years. If both NT-proBNP and cystatin C were in the top quartile, mortality was 16-fold greater after 5 years and 13 times higher at the end of their study, as compared to readings in the 1st quartile.

They summed up their findings as follows:

"Both cystatin C and NT-proBNP provided significant, independent prognostic information concerning the risk of CV mortality when analyzed as continuous variables in a multivariate analysis and when they were adjusted for each other as well as for other background variables."

A similar correlation between NT-proBNP and cystatin C was reported in two other studies of HF patients. [Kuno, Manzano-Fernández]

Is there an association between anemia and NT-proBNP?

Yes.

In a cohort of 809 ambulatory subjects with CAD, NT-proBNP and anemia were significantly correlated. The mean level was 189 in those with hemoglobin < 13 g/L. With each 1 g/L decrease in Hb, the odds of NT-proBNP being in the highest quartile increased 20%. [Desai]

Schou et al followed HF patients who were anemic. They found that the combination of anemia plus NT-proBNP > 1381 was associated with 4.8-fold greater mortality.

In another investigation, NT-proBNP also added significant predictive value in anemic heart failure victims. [Baggish]

Is NT-proBNP related to Hb A1-c?

No – they are independent risk markers and suitable for use in tandem. [Balion]

Is hs-CRP a better marker for CV events and mortality than NT-proBNP?

No…just the opposite [Campbell]

What do underwriters need in order to improve, speed up and lower the cost of cardiovascular disease risk assessment?

"The 'Holy Grail' for cardiovascular testing would be a simple blood test that provides useful screening information for the many disparate components of overall cardiovascular health and opens the door for earlier identification of applicants at risk for adverse cardiovascular outcomes"

Ross McKenzie, MD, FRCP(C), FACC
Editor-in-Chief
Journal of Insurance Medicine
Op. cit.

Does NT-proBNP have screening potential in a clinical context?

"Measurement of amino-terminal pro-B-type natriuretic peptides (NT-proBNP), performed either alone or in combination with other biomarkers, holds promise as an inexpensive tool for population screening."

James A. de Lemos, MD and
Per Hildebrandt, MD
Op. cit.

What are its implications for life underwriting?

"In the long run NT-proBNP, if utilized properly, has the potential to simplify the underwriting process, reduce costs and improve cardiovascular mortality for insurance companies."

Ramanathan K. Illango, MBBS, MBA
Chief U.S. Medical Director
SCOR Global Life Re
Journal of Insurance Medicine.
39(2007):182

"Overall, the message is that NT-proBNP often adds relevant, actionable information to a case"

David Winsemius, MD, MPH
Heritage Laboratories' *ENVOY*
Spring, 2007

Are there any issues with NT-proBNP which have been raised by industry experts?

In a 2007 article in Broker World magazine, Bob Goldstone, MD and Chief Medical Director of Pacific Life asked three questions about the use of NT-proBNP when it is elevated in applicants thought to be in "reasonable health". The answers to his questions are central to our consideration of the role of NT-proBNP in risk appraisal:

QUESTION #1

"Can they [insurance applicants] be refused insurance because a test that is not part of normal clinical practice may indicate a statistical probability of a condition developing?"

ANSWER

This statement does not apply to NT-proBNP because it is now very much a part of clinical practice.

Treadmill stress testing is no longer recommended by cardiologists to routinely screen healthy persons and yet the majority of American life insurers continue to use it routinely in this capacity.

Underwriting has nothing to do with the diagnosis of disease. Our only concern is identifying individuals at risk for premature mortality and morbidity. Any test which is affordable, readily done within the restraints imposed by our circumstances and associated with a statistically-significant probability of these end points is an excellent candidate for deployment in risk appraisal.

NT-proBNP – more than any other CV test in the history of mortality/morbidity risk assessment – satisfies all of these criteria, while lowering cost, expediting action and replacing the subjectivity of ECGs and TSTs with straightforward objective analysis.

Therefore, NT-proBNP should be used to routinely screen applicants at cost-effective age and amount thresholds. Evidence suggests the age threshold is in the range of ages 55 to 60. Of course, cost-effective thresholds are best determined individually by carriers.

QUESTION #2

"Does it [NT-proBNP] add doubt in a case in which an underlying problem (such as heart disease) is already being priced for through the use of a doctor's notes and clinical exams?"

ANSWER:

Absolutely, as anyone who had read this paper to this point will appreciate.

This bounty of evidence proves that NT-proBNP consistently adds independent predictive value across the entire range of circulatory disorders.

NT-proBNP should be used reflexively in all cases of known or suspected circulatory disease because its results clearly impact mortality and morbidity outcomes.

In addition, NT-proBNP should be a routine component of preferred risk criteria at older ages. Readings well within the normal range should lead to credits against at least some other adverse findings. Conversely, significant elevations should result in debits or refusal of insurance, depending upon their magnitude and context.

QUESTION #3

"Is it [high NT-proBNP] a reason not to issue?"

ANSWER:

The profound implications of substantially elevated NT-proBNP – in all settings and risk contexts – make it at least as appropriate if not more so as a basis for postponing/declining coverage than any other CV-related test we use.

In ostensibly healthy applicants as well as those with suspected and/or clinically-documented mild-to-moderate cardiovascular impairments, it is appropriate to defer coverage when NT-proBNP is substantially elevated. This would presumably be done on the condition that the proposed insured seeks out adequate clinical evaluation and then make this information available to the insurer

In most other cases, significantly elevated NT-proBNP is an absolute indication for outright declination of the risk.

In what ways will NT-proBNP provide outstanding value for insurers?

A. Routine screening, starting at age 55/60 and over at a carefully-considered face amount threshold

B. Reflexive testing of applicants at most or all adult ages using lower face amount thresholds when any of the following are present:
   1. Known or suspected circulatory diseases of any kind
   2. Longstanding, inadequately controlled and/or complicated hypertension
   3. Diabetes, especially if longstanding and/or with evidence of microvascular complications
   4. Heart murmurs thought to be potentially organic (pathological) or where the etiology is not known
   5. eGFR < 60
   6. History of cancer chemotherapy with cardiotoxic drugs
   7. Significantly abnormal CV risk profile consistent with denying coverage "as applied for"

Is NT-proBNP sufficiently independent of traditional CV risk factors to justify its use in modifying debits for these risk factors?

Yes.

"The main potential role for BNP and NT-proBNP in CVD prevention lies in more accurate calculation of cardiovascular risk."

Duncan J. Campbell
University of Melbourne, Australia
Clinical and Experimental Pharmacology and Physiology
35(2008):442

Olsen, Hansen and coworkers sorted 2460 subjects, ages 31 to 61, into 3 subsets based on their HeartScore (a CV risk classification model similar to the Framingham Risk Score). NT-proBNP was significantly predictive of a high score:

	HEARTSCORE		
	Low Risk	Medium Risk	High Risk
Mean NT-proBNP	**60**	**102**	**249**

The Uppsala Longitudinal Study of Adult Men followed 1135 subjects, mean age 71, for 10 years. After adjusting for all traditional risk factors, NT-proBNP ≥ 386 was linked to a 5-fold increase in CV deaths and 2.6 x greater risk of all-cause mortality (p. <0.01). [Zethelius]

Clearly, NT-proBNP adds substantial additional protective value to the CV risk factors routinely used in preferred risk underwriting criteria.

Therefore:

- Highly favorable readings should be considered suitable criteria for assigning credits against debits for these traditional factors, much the same as we currently do for normal treadmill tests, etc.
- Significantly elevated NT-proBNP readings, on the other hand, justify added debits or postponement/declination depending on their magnitude.

Is there an unequivocal threshold at which elevated NT-proBNP should be considered significant?

No.

"...available data suggest that the risk associated with increasing BNP and NT-proBNP concentrations is largely monotonic and does now allow definition of a specific threshold value"

Torbjørn Omland
Op. cit.

Gustafsson et al hold that values below 34 best represent a "normal" level in the general population.

In underwriting we must establish our own insurability-related thresholds.

What credit should be considered, against other CV-related debits, for highly favorable NT-proBNP readings?

Winsemius suggests -50 for readings ≤ 65 in men and ≤104 in women.

I would be a tad more conservative until we gain more experience with NT-proBNP testing:

	Maximum NT-proBNP Reading	
Credit	**Men**	**Women**
- 50	**40**	**55**
- 25	**65**	**90**

I would also be selective, applying greater credits against debits for obesity, hypertension and lipids but lesser credits where diabetes or a strongly positive family history of premature CV disease are present.

In diabetics, Tarnow et al found that NT-proBNP levels > 62 were linked to increased risk of cardiovascular death, even in the absence of microalbuminuria.

The importance of this with family history is highlighted by a study which showed an inverse relationship between quartiles of NT-proBNP and adverse family histories. [Kragelund]

What is the appropriate debit for elevated screening NT-proBNP in cases free of other evidence of circulatory disease?

Galasko et al found that the prevalence of CV disease increased from 18% in subjects with normal NT-proBNP to 42% at 1-2 x normal and 80% at levels greater than twice the normal limit.

The following data reported in 1552 patients who underwent coronary revascularization and were followed for 3.6 years post-operatively are also instructive: [Ndrepepa]

% Dead After 3.6 Years

Patient Characteristic	NT-proBNP ≤ 721	NT-proBNP > 721
Age 66 or under	4.6%	13.2%
Age 67 or over	9.1%	37.4%
Diabetic	12.8%	40.9%
Stable CAD	7.3%	32.6%
LVEF > 55%	5.9%	27.0%
1-vessel CAD	4.2%	32.1%
eGFR > 60	6.3%	22.2%
BMI > 30	8.2%	22.9%
Nonsmoker	6.6%	30.0%
Smoker	6.5%	28.5%
No prior MI	6.0%	27.1%

The significance on NT-proBNP may be best described as a continuous variable but these findings do make an interesting case for the significance of a cut-point of 721!

Winsemius recommends a range of +75-150 for readings between 254-999 in men and 373-999 in women.

These ranges are realistic and I agree with his well-thought out suggestions.

What debits should be considered for NT-proBNP in applicants with known but otherwise insurable CAD?

Once again, Winsemius has done an excellent job in suggesting rating adjustments and all readers are referred to his article on this in the January, 2009 issue of *ENVOY*.

He recommends postponing at these age-related thresholds:

	AGE RANGE ≤ 60	AGE RANGE 61-74	AGE RANGE ≥ 75
NT-proBNP	> 600	> 750	> 1000

I concur that these are appropriate cut-points and will virtually never result in deferring coverage in applicants who do not have significant undiagnosed – or perhaps undisclosed – circulatory disease.

Throughout this paper, cut-off levels associated with substantial risk significance have been cited in studies involving a broad range of circulatory disease and other impairments. I encourage underwriters to consider these findings in the context of specific cases.

Does interval change in NT-proBNP have any insurability implications?

Yes.

In a recent study, interval increases as low as 25% were associated with significant increases in CV mortality. In subjects with high initial readings, a decrease of 25% or more lowered the risk by over 40%. [deFilippi]

Is NT-proBNP a satisfactory replacement for resting ECGs?

Yes.

- In a cohort of 848 subjects, mean age 65, referred for angiography, NT-proBNP was independently associated with pathologic resting ECGs. [Peer]
- In a study of 2975 seniors, ages 65+ and free of heart failure, nearly 54% in the 5th NT-proBNP quartile had major resting ECG abnormalities. [de Filippi]
- A systematic review of by Mant et al found that NT-proBNP was superior to ECGs in heart failure diagnosis.
- A French investigation involving hypertensive females found that NT-proBNP was far superior to ECGs in ruling out LVH. [Mouly-Bertin]

These reports along with the demonstrated protective value conferred by NT-proBNP argue for substituting NT-proBNP for resting ECGs as a screening test for CV disease risk. This argument is further enhanced when one considers that resting ECGs are:

- At least 3 times more costly
- Inconvenient for clients
- Sometimes improperly done in conjunction with mobile paramedicals
- Highly subjective in their interpretation

Should NT-proBNP replace treadmill stress testing as a screening requirement?

In addition to significant protective value, there are at least 5 characteristics inherent in defining a desirable insurance screening test:

1. Acceptable to the applicant
2. Easy to perform
3. Easy to interpret
4. Low cost
5. Free of potentially-significant consequences

NT-proBNP is vastly superior to the TST in each case.

One of the major drawbacks to treadmill testing is its predilection for identifying anatomical CAD as opposed to specifically vulnerable plaque.

This is shown in a study of ER chest pain patients by Sanchis et al. After 60 weeks of follow-up, stress testing only predicted for the need for interim revascularization whereas NT-proBNP was significantly linked to increased risks of death or MI.

The length and breadth of the evidence presented in this paper demonstrates beyond any doubt that NT-proBNP has far broader risk implications than TSTs.

If a legitimate – defined as considering all relevant variables – cost/benefit (protective value) study is done comparing NT-proBNP and treadmill testing in a risk appraisal context, NT-proBNP will prove to be the superior choice as a screening test.

How could NT-proBNP screening be optimized?

By combining it with several other readily-available, insurance-feasible tests

In an editorial on CV biomarkers in a recent issue of the Journal of the American College of Cardiology, deFilippi and Selinger identified an optimal older age screening profile addressing 5 parameters of circulatory disease risk:

Risk Domain	Biomarkers of Choice
Myocardial Stress and Mortality	**NT-proBNP**
Vascular Damage	**Cystatin C and Microalbumin**
Accelerated Atherosclerosis	**HbA1-c**
Inflammation	**hsCRP**
Myocardial Damage	**Troponin**

In additional to NT-proBNP we currently have affordable access to cystatin C, microalbumin and HbA1-c…and in the opinion of this underwriter, there has yet to be convincing evidence that C-reactive protein (CRP) cannot be used in risk screening.

Given the evidence favoring use of NT-proBNP in lieu of ECGs and treadmill, why are some reinsurers unwilling to recognize this logical change in underwriting practices and reflect its merits in their pricing?

1. Reinsurers are concerned only with mortality. If decades of screening with ECGs and treadmills have given them a "comfort zone", they may have little incentive to "rock the boat".
2. The high adverse-action thresholds used for NT-proBNP by the insurers which first introduced the test may be seen as far too generous, allowing genuinely impaired risks to be approved on an inappropriately favorable basis.
3. Pressing concerns affecting direct companies – business acquisition cost, turnaround time and client-friendly practices – have no implications for reinsurers.
4. Reinsurers have a history of early opposition to significant changes in underwriting screening practices as we have seen with both teleunderwriting and Rx profiles. In both of these cases, their attitudes changed to the extent that carriers using these innovations may be accorded significant advantages in terms of the cost of securing reinsurance.

Hopefully, the evidence reported in this paper coupled with the successes already realized by proactive carriers using NT-proBNP will motivate life and morbidity risk insurers to move forward with NT-proBNP as a fundamental part of the ongoing metamorphosis in underwriting.

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