

NT-proBNP: Implications for Life and Morbidity Risk Underwriting

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Preface

This paper is the third comprehensive literature review on the cardiac marker NT-proBNP.

The first and second review papers are posted at www.insureintell.com and may be accessed directly at the following links, respectively: <http://insureintell.com/content/underwriting-perspective-nt-probnp-novel-marker-cardiovascular-disease> and <http://insureintell.com/content/nt-probnp-4>.

This new paper is based on 577 studies, reviews and commentaries published in the global medical literature between mid-2009 and March 2014.

It documents the length and breadth of the burgeoning evidence of NT-proBNP's value as a screening and reflexive test in life insurance underwriting.

Together with the NT-proBNP mortality study by Clark et al, this paper should put to rest any lingering questions or reservations in this regard.

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Unless otherwise specifically cited, the opinions expressed herein are solely those of the author.

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Background and Overview

NT-proBNP is one of a complex family of hormones called natriuretic peptides. The following observations put this cardiac marker in perspective in terms of when it is detected in the blood.

“N-terminal pro-B-type natriuretic peptide (NT-proBNP), known as the inactive fragment of prohormone of brain natriuretic peptide (BNP), is primarily secreted by cardiac myocytes in response to abnormal ventricular wall stress and loading conditions.”

Jannet A. Eindhoven, MD
Erasmus Medical Center, Rotterdam
Journal of the American College of Cardiology
62(2013):1203

“...atherosclerosis itself, even in the absence of ischemia, may contribute to higher circulating levels of BNP and NT-proBNP...”

Direct NP expression within the human coronary arterial wall has been reported, with greater expression in atherosclerotic regions compared with normal segments.”

James A. de Lemos, MD, FACC
University of Texas Southwest Medical Center
Reviews in Cardiovascular Medicine
11, Supplement 2(2010):S24

“...even in asymptomatic individuals without overt heart or renal failure, elevated levels of BNP and NT-proBNP are independently associated with subclinical and functional abnormalities...”

Sachin Gupta, MD, et al
University of Texas Southwest Medical Center
American Heart Journal
159(2010):817

In the past, it was thought that myocardial stretch consistent with systolic and/or diastolic

dysfunction was the primary, if not the sole, mechanism accounting for NT-proBNP elevations.

We now know that NT-proBNP is also released from the myocardium in response to ischemia/hypoxia, inflammation, ventricular hypertrophy/fibrosis and, potentially, other neuro-endocrine stimuli. [Clerico-1, Rodseth, van der Zee]

Further evidence, albeit indirect, of NT-proBNP being an indicator of cardiac dysfunction is reflected in the fact that long term supplementation with coenzyme Q10 and selenium significantly lowers NT-proBNP levels and cardiovascular mortality. [Johansson-1]

NT-proBNP is now recognized as a valued marker in a clinical context:

“...minimal elevation of NT-proBNP is due to other factors besides myocardial stretch and thus it may serve as a biomarker for preclinical cardiovascular disease and may aid in identifying disease progression and patients who may benefit from preemptive therapies.”

Hector O. Ventura, MD, and Marc A. Silver, MD
Mayo Clinic Proceedings
86(2011):1143[editorial]

The normal range for NT-proBNP, based on the Roche Diagnostics assay used by all three U.S. insurance laboratories, depends on the subject's age:

Age	Normal Range
Up to Age 75	1-125 pg/mL
≥ Age 75	1-450 pg/mL

In some studies, results are reported in picomoles per liter (pmol/L), and these results are converted to picograms per milliliter (pg/mL) by multiplying pmol/L by 8.457. [Jouni]

All NT-proBNP values cited in this paper will be in picograms per milliliter, and thus we will not redundantly cite readings as being in pg/mL.

For comparative purposes, Olivieri et al reported mean NT-proBNP levels in healthy elders as ± 180 pg/mL at ages 75-95 and ± 606 over age 95.

Additional Considerations

NT-proBNP is more than adequately stable in serum for use in blood specimens collected on a mobile paramedical basis. [Ala-Kopsala]

NT-proBNP measurement is not impacted by either hemolysis or lipemia in laboratory specimens. [Daves, Radiometer Medical/Denmark accessed online 12/13/13]

It does not correlate significantly with levels of alcohol intake. [Doi]

The only medications that interfere with NT-proBNP measurement are acetylcysteine, furosemide and cyclosporine, and they only do so at high dose levels. [Radiometer Medical/Denmark accessed online 12/13/13]

There will soon be a second-generation proBNP test, likely the proBNP 1-108 to proBNP 1-76 ratio. The current NT-proBNP assay is equivalent to proBNP 1-76. [Macheret]

This new test will probably be cost prohibitive for insurance screening. [Goetze]

NT-proBNP and Various Forms of Exercise

It is well established that NT-proBNP occasionally exceeds normal levels in individuals who engage in (at least) the following activities:

- Marathon running [Legaz-Arrese, Scherr]

- Indoor soccer matches [Carranza-Garcia]
- Endurance/competitive long-distance cycling [Chan-Dewar, Corsetti]
- Intensive aerobic exercise [Serrano-Ostariz]
- Non-specific forms of maximal exercise [Romagnoli]

However, baseline NT-proBNP elevations measured prior to endurance sport activity may reflect unsuspected heart problems at older ages.

In a study of 185 subjects, mean age 61, who participated in a 30-kilometer cross-country race, 15 had baseline elevated NT-proBNP, and 4 of these individuals were found to have “*serious cardiovascular disease.*” [Sahlen-2]

NT-proBNP does not elevate due to walking or recreational running. [Li-2, Mingels]

These studies confirm that NT-proBNP elevations after rigorous athletic activity may exceed twice the normal limit on a transient basis, almost always normalize within 72 hours, and the cardiac mechanisms involved are nearly always benign in this setting.

NT-proBNP was shown to be inverse to a lifestyle-based Physical Activity (PA) score in 2,933 subjects age 65 and older who were free of known heart failure and followed for 3 years: [de Filippi-2]

Physical Activity Score	Median NT-proBNP
Low	180
Moderate	135
High	109

This PA score correlated significantly with heart failure risk.

NT-proBNP and Other Risk Factors

Note: Diabetes and hypertension will be reviewed separately further on in this paper.

Age: Children, Young Adults and General Population

“Our suspicion is that in healthy young to middle-aged populations, BNP/NT-proBNP levels will not prove to be clinically useful or cost-effective as a marker of further cardiovascular disease or overall mortality.”

Richard W. Troughton, MD, et al
Department of Medicine
University of Otago; Christchurch, NZ
Annals of Medicine
43(2011):188

While NT-proBNP does not appear to be useful in screening in young and middle-aged applicants, it likely has an important role as a reflexive test for suspected cardiac disease in a wide range of circumstances in this age group. [Lee-2, Welisch]

“BNP and NT-proBNP have shown very strong prognostic value in the general population. Data indicate that [their] use in risk evaluation could result in improved risk classification.”

Per Hildebrandt
Section of Cardiology
Glostrup University Hospital, Denmark
Disease Markers
26(2009):227

Age: Elderly

In the Leiden 85-Plus Study, subjects with NT-proBNP in the 3rd tertile had significantly increased risks of adverse echocardiographic findings, including greater LV mass index and

volume, presence of pulmonary hypertension, moderate aortic regurgitation and moderate mitral regurgitation, as well as the total number of unfavorable echo findings. [Vaes-2]

In the same study, median NT-proBNP was over 3 times higher in those with significant cardiac dysfunction (445) as compared to subjects free of cardiac compromise (137). The investigators concluded that NT-proBNP was a “good first line triage test” in this setting. [Vaes-1]

In a Swedish investigation of 452 persons, mean age 75 at baseline, NT-proBNP > 300 was significantly linked to increased vascular disease and mortality risks. Cystatin C was also independently predictive of vascular disease risk. [Nilsson-1]

In another report on this study, NT-proBNP correlated significantly with increased probabilities of MI, heart failure, atrial fibrillation, stroke/TIA and incidence of adverse CT scan findings. [Nilsson-2]

Gender

NT-proBNP is generally higher in females, sometimes significantly so. However, the impact here will rarely, if ever, affect underwriting outcomes based on prevailing NT-proBNP underwriting practices. [Fradley, Leosdotter]

Obesity

Mangge et al found no significant effect from obesity and called NT-proBNP “...a useful cardiac marker irrespective of age and obesity.”

There are a number of theories as to why NT-proBNP is generally inverse to BMI, but the reason has not yet been established. [Neeland-2]

Five additional studies clearly show that the

impact of obesity, like that of gender, will rarely, if ever, impact underwriting. [Choi-2, Dadu, Haaf, Jarai, Linssen]

Cigarette Smoking

In an investigation of 5,397 patients free of CV disease at baseline, NT-proBNP was largely inverse to smoking. [Choi-2]

NT-proBNP Quartile	% Current Smokers	
	Males	Females
1	17%	16%
2	15%	11%
3	12%	10%
4	14%	8%

Haaf et al reported a more substantial inverse relationship:

NT-proBNP Quartile	% Current Smokers
1	35%
2	28%
3	19%
4	15%

In a 16-study metaanalysis, mean NT-proBNP was lower (54.4) in smokers than in non-smokers (89.4). [Garcia-Berrocso]

In 10 of 11 additional reports, there was no significant correlation between cigarette smoking or pack-years of consumption and NT-proBNP. [Dadu, Doi, Harutyunyan-1, Hijazi-1, Kim-1, Lee-2, Linssen, Otsuka, Plitt, Ruff, Scheven]

In 796 cigarette smokers followed for 562 days, NT-proBNP ≥ 49 had an independently significant hazard ratio (2.19) for all-cause mortality after full adjustment. [Stamm]

Bottom line: NT-proBNP levels are lower

in current cigarette smokers. Smoking and NT-proBNP are independent morbidity and mortality risk predictors.

C-Reactive Protein (CRP, hs-CRP)

NT-proBNP correlates closely with CRP levels. [Aujollet, Che-2, Weishammer-2]

Aujollet and colleagues reported the following relationship between CRP and NT-proBNP:

CRP	Odds Ratio for NT-proBNP ≥ 125
≤ 4 mg/mL	1.0
5-6	2.2
≥ 7	4.9

These findings are consistent with the evidence supporting inflammation as a mechanism accounting for excess NT-proBNP secretion.

Troponin

The troponins are markers for myocardial injury/infarction and are a key part of the criteria for diagnosing acute coronary syndrome (ACS) events.

In the Atherosclerosis Risk in Communities (ARIC) Study, Saunders et al compare high-sensitivity troponin T (hs-cTnT) and mean NT-proBNP levels in 9,698 subjects:

hs-cTnT	Median NT-proBNP
$< .003$	70.1
$.003 - \leq .005$	92.4
$.006 - \leq .008$	112.4
$.009 - \leq .013$	149.9
≥ 0.14	530.7

Leistner-1 et al made a similar comparison in 5,388 subjects enrolled in the DETECT Study:

hs-cTnT	Median NT-proBNP
None detected	89
1 st Tertile	180
2 nd Tertile	173
3 rd Tertile	452

More or less equivalent results were reported in the Dallas Heart Study [de Lemos-1], the Cardiovascular Health Study [Hussein] and a large cohort of elderly individuals. [deFilippi-4]

In the Heart and Soul Study, baseline troponin T (cTnT) tertiles in subjects with stable coronary artery disease (CAD) were compared to median NT-proBNP levels: [Beatty]

cTnT Tertile	Median NT-proBNP
1 (Low)	86
2 (Intermediate)	174
3 (high)	473

These cTnT tertiles correlated significantly with LV mass, LV ejection fraction (LVEF), and both ischemia and METS on treadmill stress testing.

Ruyi et al found that the level of hs-cTnT was an independent predictor of elevated NT-proBNP after adjustment for 17 risk factors, including age and gender.

NT-proBNP and troponin T are largely independent of one another and are synergistic in risk prediction. [Everett-2]

Growth Differentiation Factor-15 (GDF-15)

GDF-15 is part of the transforming growth

factor cytokine family. It responds to oxidative stress and inflammation in cardiac and neoplastic cells. [Breit]

Roche Diagnostics has a non-commercial ELCIA GDF-15 assay that has not yet been FDA approved. [Lorda, personal communication]

A growing inventory of studies, mainly published over the last several years, has linked GDF-15 to a wide range of major insurability risks.

Schopfer et al found a significant association between GDF-15 and various outcomes in a cohort of patients with stable CAD and reported the following hazard ratios comparing 3rd versus 1st tertile subjects:

	Hazard Ratio
All-Cause Mortality	2.73
MI, Stroke or CV Death	1.59
Heart Failure	2.39

NT-proBNP was independent of GDF-15 in this study, suggesting both markers could be used together in risk assessment.

Wallentin-1 et al (Sweden) followed 940 71-year-old subjects for 10 years.

They compared GDF-15 tertiles to mean NT-proBNP levels:

GDF-15 Tertile	Median NT-proBNP
1	128.5
2	189.9
3	319.9

NT-proBNP and GDF-15 were independent of one another.

It is noteworthy that while both NT-proBNP and GDF-15 were significant markers for CV

disease, only the latter was also a robust cancer mortality marker:

- Adjusted for conventional risk factors, cancer mortality was 46% increased per SD of log GDF-15.
- After further adjustment for NT-proBNP, CRP, cystatin C and cTnT, high GDF-15 remained a significant cancer mortality predictor (32% greater risk).
- None of these other markers independently correlated with the risk of cancer.

This study – and many others not addressed here – strongly suggests GDF-15 has the potential for use in screening older age insurance applicants. The author intends to review the GDF-15 literature in the near future and publish the findings for the benefit of our industry.

Other Risk Markers

Kavousi et al compared 12 risk markers for predicting heart disease risk in 5,933 subjects, mean age 69, who participated in the Rotterdam Study.

NT-proBNP was 2nd to coronary artery calcium (CAC) score in this regard and was substantially more significant than leukocyte count, homocysteine, carotid intima-media thickness, CRP and 6 other variables.

It should be noted that CAC scoring is not an acceptable insurance screening option due to its high cost and the inappropriateness of exposing applicants to ionizing radiation to complete a financial services transaction.

NT-proBNP and Heart Failure

When emergency department physicians and other clinicians began using natriuretic peptides, they did so in the context of patients presenting with acute dyspnea and other symptoms/findings potentially incited by heart failure (HF). Most of the early studies examining the efficacy of NT-proBNP were based on the assessment of these cases.

“Among cardiovascular diseases, HF is projected to have the largest increases in incidence over the coming decades.”

Vijay Nambi, MD, et al
Baylor University College of Medicine
Clinical Chemistry
59(2013):1802

It is likely underwriters will see an increasing number of applicants with suspected heart failure in the years ahead. Therefore, it is important they understand how NT-proBNP is relevant in this setting.

In the British Regional Heart Study, 3,870 males, ages 60-79, were followed for 11 years to assess the risk of developing heart failure. The hazard ratio in those with baseline NT-proBNP ≥ 152 had a 9-fold greater risk compared to subjects with readings < 42 .

The authors concluded that NT-proBNP *“markedly improved prediction of HF beyond the established Health ABC heart failure score and beyond routine clinical parameters.”* [Wannamethee-2]

In the Cardiovascular Health Study involving 3,752 subjects, mean age 73 and free of heart failure at baseline, NT-proBNP correlated significantly with projected heart failure risk:

Projected HF Risk	% NT-proBNP > 190
< 5%	18.4%
5-10 %	34.1%
10-20%	51.9%
> 20%	72.9%

Echocardiographic findings were insignificant after adjusting for NT-proBNP. [Kalogeropoulos]

In 5,597 individuals, mean age 62, those with NT-proBNP in the 4th quartile (> 112.5) were 9 times more likely to develop cardiac failure over the ensuing 5.5 years. NT-proBNP was independent of and additive to LV mass index in predicting this outcome. [Choi-2]

In 11,779 German subjects, ages 45-83, NT-proBNP > 220 correlated with a significantly increased risk of heart failure with preserved LVEF. [Tiller]

Oudejans et al showed that NT-proBNP ≥ 440 had the same sensitivity, but twice the specificity, as a resting ECG in pinpointing subjects with heart failure.

In the ARIC study, NT-proBNP *“markedly improves the prediction of 10-year risk of HF in middle-aged adults.”* [Agarwal-1]

Campbell et al concluded that NT-proBNP should be considered an appropriate screening tool for suspected HF based on presenting symptoms and at all levels of perceived risk.

Many additional studies over the past 5 years robustly support the above findings. [Brouwers, Kelder, Luers, Meluzin, Nambi, Olofsson, Smith]

Diastolic Dysfunction (DD)

In 1,452 persons ages 65 to 84, NT-proBNP was the best predictor of the onset of

moderate-to-severe DD, and an ECG added nothing significant to DD risk assessment. [Mureddu-2]

Four additional investigations confirm that NT-proBNP is an independent marker for onset of DD. [Barutcuoglu, Huang, Qiong-Wen, Sonoda]

NT-proBNP – but not echocardiography – predicted all-cause mortality and HF-related hospitalization in 375 patients with diastolic dysfunction: [Cleland]

NT-proBNP Quartile	Hazard Ratio
1	1.00
2	1.38
3	2.84
4	4.47

Systolic Dysfunction (SD)

In a review of 10 studies involving 5,508 older individuals, 18% had an LVEF \leq 40. When NT-proBNP was $>$ 75, it was 80% sensitive and 71% specific for this degree of systolic dysfunction.

The authors advised that screened patients be referred to cardiologists if NT was $>$ 50, $>$ 75 and $>$ 250 at ages less than 50, 50-75 and over 75, respectively. [Hildebrandt]

In 2,001 subjects ages 65-84, NT-proBNP was 3 times higher in the presence of heart failure and 7 times greater if systolic dysfunction was detected. [Meruddu-1]

Additional Studies

Eight recent studies demonstrated significant relationships between NT-proBNP and various echo, Doppler and cardiopulmonary exercise testing abnormalities. [Frederiksen, Gupta,

Luchner-1, Kasner, Krakowiak, McGrady, Uraizee, Zacharopoulou]

Manzano et al recommend that an echocardiogram not be done routinely when NT-proBNP is $<$ 400 because of the low risk of heart failure.

NT-proBNP significantly correlated with heart failure stage in 1,939 residents of Olmsted County, Minnesota: [Macheret]

Heart Failure Stage	Median NT-proBNP
No HF	39.4
A	72.1
B	138.5
C	778.8

NT-proBNP predicts for heart failure as the cause of acute dyspnea in patients presenting for emergent care, as well as 1-year survival in those with acute dyspnea despite preserved LV function. [Robaei, Shah]

Heart Failure Mortality

In the last 4 years, 7 new studies have reaffirmed findings in dozens of pre-2010 investigations that showed NT-proBNP to be a major predictor of all-cause and cardiac mortality in patients with various degrees of heart failure. [Alehagen-1, Alehagen-2, Gruson, Lupon, Al-Najjar, Tentzeris, Velibey]

Many cardiologists now recommend that NT-proBNP be used to monitor the effectiveness of treatment of patients with heart failure. [Berger, Kelly, Januzzi, Richards]

NT-proBNP in Chest Pain and Suspected CAD

Chest pain history and suspected coronary artery disease (CAD) are two of the leading reasons underwriters pursue medical records.

In 658 consecutive chest pain cases seen in an emergency department, there was a direct and powerful correlation between higher NT-proBNP readings and the likelihood of myocardial infarction (MI): [Haaf]

NT-proBNP Quartile	% Diagnosed with MI
1	2%
2	11%
3	16%
4	42%

NT-proBNP was also an independent predictor of 2-year mortality in this cohort. Median readings were 1,368 in those who died and 147 in survivors.

There were no deaths in patients with NT-proBNP < 163, and the cut-off with the best combination of sensitivity and specificity was said to be 271. Additionally, NT-proBNP was superior to troponin T in this context.

Among 550 ED patients with “ischemic-like” chest discomfort, median NT-proBNP readings were 2,114 in those who were diagnosed with MI or had died, compared to 319 in other patients. [McCann]

Three additional studies support these findings. [Melki, Olivieri, Tziakas]

In 453 subjects presenting with chest pain, mean age 66 and followed for 5.8 years, baseline NT-proBNP was 1,128 in those who died over this interval vs. 140 in survivors. The adjusted hazard ratio for long-term mortality based on NT-proBNP was 2.0. [Eggers-1]

Tests for CAD/Ischemia

Doi et al looked at the relationship between NT-proBNP and abnormal resting ECGs performed on 3,140 community-dwelling adults, ages 40 and older, and free of known CVD.

Mean NT-proBNP	% Abnormal ECG
< 56	10%
56-124	15%
125-399	30%
≥ 400	55%

Among 382 chest pain patients free of acute coronary syndrome (ACS) events, there was a highly significant correlation between median NT-proBNP and CAD risk based on stress testing:

CAD Risk Based on Stress Test	Median NT-proBNP
Low	35.1
Intermediate	184.6

This comment by the authors is highly relevant to us, given the discredited, yet lingering, view that stress ECGs should be retained in risk appraisal:

“Although stress tests have long been established as an effective method of refining clinical risk stratification, using biomarkers as a substitute may provide a less expensive and speedier alternative.”

Shin Mathewkutty, MD, et al
Mt. Sinai School of Medicine, New York
American Journal of Cardiology
111(2013):493

In the summary of their findings in a study of 320 patients, average age 64 and presenting with chest pain, Spanish cardiologists concluded:

“The present study shows that a strategy combining clinical history and NT-proBNP, without exercise testing, reduced initial emergency hospitalizations in patients with chest pain of uncertain origin in comparison with the usual strategy involving exercise testing.”

Juan Sanchis, MD, et al
Cardiology Department
University of Valencia, Spain
American Heart Journal
159(2010):176

In a cohort of patients with stable angina, NT-proBNP closely correlated with treadmill stress test (TST) results, and the authors attributed elevated NT-proBNP to *“repetitive ischemic episodes in daily life.”* [Surdacki]

After assessing 44 patients with a TST and angiography, it was shown that NT-proBNP had markedly greater sensitivity for coronary disease than a TST (88% vs. 52%). [Zhu-1]

Two additional studies revealed similar results in terms of the link between elevated NT-proBNP and ischemia in patients with chest pain or known stable angina. [Bhardwaj, Kokowicz]

Nadir et al undertook a 16-study metaanalysis, encompassing 2,784 subjects, assessing the role of natriuretic peptides in identifying ischemia. They concluded:

“Our results suggest that a BNP or NT-proBNP measurement can identify inducible myocardial ischemia as detected by myocardial perfusion imaging or stress echocardiography.”

M. Adnan Nadir, MMBS, et al
University of Dundee Medical School, Scotland
American Journal of Cardiology
107(2011):662

In 901 outpatients with stable CAD evaluated

with a TST and stress echocardiography, subjects in the highest NT-proBNP quartile (> 410) had 7-fold greater odds of inducible ischemia compared to those in the 1st quartile (P < .0001).

After full adjustment for CV risk factors, LVEF, evidence of diastolic dysfunction and other variables, the risk associated with high NT-proBNP was increased 3.6-fold. [Singh]

Rathcke and associates performed myocardial perfusion scintigraphy (MPS) on subjects judged to be at intermediate risk for CAD. They reported these findings:

CAD Risk Based on Stress Test	Median NT-proBNP	
	Males	Females
Normal	44	83
Abnormal	279	236

An NT-proBNP of 25 or lower had a negative predictive value of > 95%, regardless of existing angiographic CAD.

Three more studies reported similar findings in patients undergoing myocardial imaging stress tests. [Haapio, Ping, Schulz]

Lastly, NT-proBNP was found to be significantly associated with shorter 6-minute walking distance and significantly lower LVEF in patients with severe stable angina. [Sahlen-1]

Angiography

In an analysis of 1,316 patients with known/suspected CAD, there was a correlation between the number of obstructed vessels and NT-proBNP:

Number of Obstructed Arteries	Median NT-proBNP
None	143.4
1	170.5
2	246.2
3	285.2

These cardiologists found that NT-proBNP and high-sensitivity troponin T (hs-cTnT) had equivalent and independent impacts in this setting. [Ndrepepa-1]

In another assessment, patients with symptoms suggesting coronary disease had angiography:

Extent of Stenosis	Median NT-proBNP
None	315
1 Vessel	348
2 Vessels	484
3 Vessels	568
Left Main Artery	513

These investigators note that their findings are consistent with those of others, and that there is *“a meaningful and direct relationship between the severity of angiographic lesions and the serum levels of NT-proBNP.”* [Rajabiani]

Three further studies reveal similar findings. [Ikeda, Krecki-1, Kablak-Ziembicka-1, Naqiong]

Lastly, Kadi et al found that NT-proBNP was predictive of poor collateral circulation in patients with at least one occluded coronary artery.

Interventional Procedures in CAD

In a study following 372 elective percutaneous coronary intervention (PCI) patients for 1,000 days, preprocedural NT-proBNP ≥ 105 was linked to a 4.5-fold greater incidence of cardiac

events, whereas hs-cTnT was insignificant.

NT-proBNP also closely correlated with increased mean platelet volume (MPV), a proven mortality risk factor in this setting. [Ki]

In another study involving CAD patients having elective stenting, NT-proBNP was an independent predictor of MACE (mortality and acute coronary events). [Masaki]

Holm et al followed patients who had had elective coronary artery bypass grafting (CABG) for 4 years. Those with baseline NT-proBNP $\geq 1,028$ had nearly 11-fold higher mortality risk, after adjustment for other CAD risk factors.

Two additional studies in this setting also revealed substantially higher mortality associated with preprocedural NT-proBNP after 18 months and 3.3 years, respectively. [Schachner, Sung]

Bottom Line: The studies involving patients with chest pain and/or stable CAD show us the powerful risk implications attributable to higher levels of NT-proBNP and make a compelling case for use of this test in these contexts.

NT-proBNP and Acute Coronary Syndrome (ACS)

“Accurate markers of risk, such as BNP and NT-proBNP, are valuable for the assessment and monitoring of ACS patients in the emergency department, during the hospital stay and at the time of outpatient follow-up.”

Peter A. McCullough, MD, et al
Division of Cardiology
William Beaumont Hospital, Michigan
Reviews in cardiovascular Medicine
11, Supplement 2(2010):S51

NT-proBNP rises continuously during the first 75 minutes of an acute MI, then decreases below baseline after 8 hours. [Liebetau]

Truong et al showed that mean NT-proBNP is 2 times higher in emergency department patients with an acute coronary event, with a negative predictive value of 97%.

In 110 patients with unstable angina ACS, NT-proBNP was a predictor of positive angiography, as well as abnormal fractional flow reserve (FFR), a novel cardiac marker. [Xu]

Post-ACS MRI and Angiography

Haeck et al showed that NT-proBNP ≥ 260 correlated with all 7 abnormal MRI parameters. In patients with completely normal MRIs, mean NT-proBNP was 71, compared to 1,406 in those with abnormal MRIs.

Two further studies reveal similar results on MRI analysis. [Kleczynski, Mistry]

In an investigation of patients whose MRI detected a scar from an unrecognized prior heart attack, NT-proBNP correlated with the findings: [Themudo]

	Median NT-proBNP
MRI Negative for Scar	94.9
MRI Positive for Scar	140.2

Gravning assessed 458 post-STEMI patients admitted for angiography. NT-proBNP was linked to significantly obstructive lesions and, unlike troponin T, was predictive of cardiac death.

In a study of 133 patients with unstable angina ACS, those with $> 50\%$ left main or $> 75\%$ LAD/LP obstructions had a median NT-proBNP of 367.5, compared to 112 when angiography was negative. These cardiologists considered NT-proBNP to be a bona fide marker for angiographic results. [Wei-1]

Other studies have shown NT-proBNP to be:

1. An independent marker for vulnerable plaque lesions based on virtual histology intravascular ultrasound [Hong]
2. A significant predictor of 1-year post-ACS heart failure [Raposeiras-Roubin]
3. An independent predictor of adverse post-MI remodeling in 9 of 11 studies in a metaanalysis [Fertin]

MACE components Post-ACS

In a 30-month follow-up of 849 ACS patients, log NT-proBNP had a hazard ratio of 4.4 for death or repeat cardiac hospitalization based on blood drawn within 36 hours of ACS admission. [Ersboll]

Lorgis and coworkers followed 2,217 French MI patients for 1 year and found that log NT-proBNP conferred an odds ratio of 2.37 for mortality, which was more significant than conventional risk scoring methods.

In a metaanalysis of 13 studies, the relative risks associated with elevated NT-proBNP for

mortality and new MI were 4.89 and 1.66, respectively, over internals ranging from 1 to 48 months after the baseline ACS event. [Zeng]

After a 6-month follow-up of 1,146 non-ST-segment elevation MI (NSTEMI), the odds ratio for death or non-fatal new MI was increased 2.4-fold per 1 standard deviation of NT-proBNP. The area under the curve (AUC) was greater than that for hs-cTnT. [Widera]

Scirica et al followed 4,352 ST-segment elevation MI (STEMI) patients for 343 days and reported the following data:

NT-proBNP	% New Event		
	Heart Attack	Heart Failure	CV Death
< 400	6.0%	1.4%	1.8%
≥ 400	11.4%	8.7%	9.2%

MI risk was not significant after full adjustment. However, the adjusted hazard ratios at ≥ 400 for heart failure (3.36) and CV death (1.45) were both highly significant.

In 706 patients with prior ACS events followed for 2.2 years, NT-proBNP was a major marker for adverse outcomes. It was almost 3 times higher (477) in those with a new MI, stroke/TIA, onset of heart failure or death.

Despite adjusting for medical history, CV risk factors, medication, hs-CRP, number of diseased vessels, use of stents and several novel markers, including galactin-3 and MCP-1, the risk conferred by NT-proBNP remained notably higher. [Tunon]

More or less similar results related to MACE risk were also reported in 10 other studies between 2009 and 2014. [Buchner, Dhillon, Jarai, Kim-2, Leong, Narayan, Rhew, Squire, van Drepen, Wallentin-2]

Post-ACS PCI

In a cohort of ACS patients undergoing PCI and followed for an average of 600 days, log NT-proBNP had increased hazard ratios for all-cause (2.36) and CV-related (4.09) mortality. Only NT-proBNP and LVEF were significant in this study. [Jaberg]

In terms of adverse 6-month outcomes, Damman et al found high-risk patients had a 6-fold greater median NT-proBNP compared to those with no unfavorable consequences (417 and 64, respectively).

Polish cardiologists reported that NT-proBNP was a predictor of poor post-PCI perfusion (no reflow phenomenon), as well as 6-month risks of death and new events. [Ayhan]

Lastly, NT-proBNP > 80 correlated with a 5.3-fold greater incidence of high-grade microvascular obstructions (MVO). [Kim-1] Research has demonstrated MVOs are caused by micro-thromboemboli incited by the PCI procedure. [Taylor]

Bottom Line: All of these findings show us that NT-proBNP is the ideal reflexive test in potentially insurable cases of acute coronary events.

NT-proBNP and Other Circulatory Disorders

There is increasing evidence that the implications of elevated NT-proBNP extend beyond heart failure and coronary disease to encompass other cardiac and non-cardiac circulatory impairments.

Heart Valve Disease

NT-proBNP correlates significantly with E/E' ratio (marker for diastolic dysfunction), as well as impaired cardiac flow reserve in aortic stenosis (AS). [Banovic, Boer, Piestrzeniewicz]

Farre et al found that an NT-proBNP of 490 was the optimum cutoff for predicting increased mortality in degenerative moderate/severe AS. NT-proBNP is also a significant 2-year mortality marker in low-flow, low-gradient AS. [Bartko]

NT-proBNP is an independent predictor of mortality in both surgically and medically managed cases of severe AS. [Katz]

In calcific aortic valve disease, NT-proBNP is significantly elevated only when frank valve stenosis is present. [Sainger]

In severe mitral regurgitation with normal LV function, NT-proBNP independently predicts progression to symptoms and LV dysfunction. [Klaar]

After heart valve replacement, NT-proBNP is an effective marker for assessing cardiac function and prognosis. [Cai]

Hypertrophic Cardiomyopathy (HCM)

When screening 1st degree relatives of patients with HCM, NT-proBNP could not distinguish gene carriers from controls. However, it was

significantly higher in those relatives with undiagnosed HCM. In one study of 106 subjects, NT-proBNP ≥ 70 correlated closely with abnormal echocardiographic findings. [Fernandes, Silva]

In a cohort of patients, average age 50 and with stable baseline HCM, NT-proBNP > 310 predicted for 3 major consequences:

	Increased Risk
Peak LVOT gradient ≥ 30 mmHg	1.8-fold
Hospitalization for heart failure	4-fold
Progression to end stage disease	5-fold

After 4 years, NT-proBNP and a restrictive LV filling pattern were the only independent markers of CV death, as well as the need for ICD, resuscitation and transplantation. The authors recommended NT-proBNP cutoff to be 810 for these risks. [D'Amato]

Elevated NT-proBNP is linked to increases in left atrial volume, wall thickness and LV mass in HCM. [Park-2]

In 847 HCM patients, mean age 53, NT-proBNP was a “*strong predictor of overall prognosis,*” including transplantation and death, even in cases with normal baseline LVEF. [Coats]

Congenital Heart Disease (CHD)

After assessing a cohort of children with cyanotic or noncyanotic congenital cardiac conditions matched to healthy controls, Uner et al found that NT-proBNP was significantly higher in cyanotic patients, in patients with vs. without symptoms and – most importantly – in subjects with all types of congenital heart defects vs. controls.

Four studies looked at congenital heart disease in adults:

In 394 patients, mean age 35, median NT-proBNP was 211, as compared to 42 in controls; 25th to 75th percentile range was 110-466 in those with congenital defects vs. 24-69 in controls. [Popelova]

In a similar group of patients, NT-proBNP correlated significantly with echocardiographic findings, diastolic dysfunction, exercise capacity and the risk of atrial arrhythmias. These authors concluded that NT-proBNP holds “...promise as a marker of cardiac dysfunction in adults with CHD.” [Eindhoven]

Lemmer et al reported that after 16 years of post-surgical follow-up, NT-proBNP linked significantly to adverse echocardiographic parameters, decreased exercise capacity and abnormal MRI findings.

Tutarel and coworkers found that NT-proBNP was a significant marker for severely limited cardiopulmonary exercise capacity.

Two additional studies focused on atrial septal defect (ASD) in adults. Both demonstrated that NT-proBNP correlated closely with RV pressure, pulmonary artery pressure and degree of blood shunting. [Elsheikh, Li-1]

Risk of Atrial Fibrillation (AF)

Plitt and associates found that NT-proBNP levels are directly linked to the burden of AF based on continuous ambulatory monitoring of subjects in the SMART Study:

AF Burden (%)	Median NT-proBNP
0%	166
1%-25%	252
26%-99%	639
100%	731

In the Multi-Ethnic Study of Atherosclerosis

(MESA) study, 5,518 healthy subjects were followed for 7.6 years. The adjusted hazard ratio for AF in the 4th vs. 1st NT-proBNP quartile was 11.4. [Patton-2]

Two additional studies affirm the significantly increased risk of developing AF. [Nadrowski, Smith]

Post-Treatment for AF

Den et al discovered that NT-proBNP was an important indicator of the risk of recurrent AF after ablative therapy. For every 100-unit increase, the odds of recurring AF increased 35%.

After post-ablation follow-up, Fiala reported that a substantial decrease in NT-proBNP correlated with successful ablation and no recurring AF.

Four additional studies showed a significant association between NT-proBNP and outcomes following cardioversion, ablation or pulmonary vein isolation. [Fan-1, Kallergis, Nilsson-3, Solheim]

AF and Cerebrovascular Events

In the ARISTOTLE Trial involving 18,201 subjects followed for 1.9 years, the hazard ratio for ischemic stroke in AF patients correlated significantly with NT-proBNP quartiles: [Hijazi-2]

NT-proBNP Quartile	Hazard Ratio
1	1.00
2	1.66
3	2.06
4	2.43

Purroy and colleagues showed that baseline NT-proBNP \geq 313 predicted for AF within 90 days following a transient ischemic attack (TIA).

Two studies found AF to be significantly associated with NT-proBNP in cryptogenic stroke. [Fonseca, Rodriguez-Yanez]

In a 16-study metaanalysis, there was a dramatic link between NT-proBNP and the risk of post-stroke AF: [Garcia-Berrocso]

Mean NT-proBNP	
Atrial Fibrillation	1865
No Atrial Fibrillation	165

NT-proBNP has been shown to be a marker in additional atrial fibrillation contexts:

- AF recurrence in patients with sinus rhythm and prior AF [Latini]
- AF in patients with diastolic dysfunction and preserved systolic function at a threshold of > 433 [Kim-3]
- Increased left atrial volume [Psychari]
- Increased right atrial diameter [Bai]
- Risks of CAD and heart failure [Hijazi-1]
- New onset AF in patients hospitalized with MI [Parashar]
- New onset AF following coronary bypass surgery [Iskesen]
- New onset AF after cardiopulmonary bypass in cardiac surgery [Samy]

In addition, NT-proBNP > 310 raises the risk of AF 3-fold in middle-aged patients with hypertrophic cardiomyopathy (HCM). [D'Amato]

In 6,189 subjects with AF, mean age 72 and followed for 2.2 years, ARISTOTLE Trial investigators compared NT-proBNP and troponin T (cTnT) as risk factors for vascular death: [Hijazi-1]

Quartile	Hazard Ratio for Vascular Death	
	NT-proBNP	cTnT
1	1.00	1.00
2	2.44	1.94
3	3.71	2.31
4	6.73	4.38

Cerebrovascular Disease

In patients with asymptomatic internal carotid artery stenosis, NT-proBNP significantly correlated with increased all-cause mortality and was embraced as a triage tool at age 75 and over in terms of surgical vs. medical management. [Duschek]

In the ARIC study, NT-proBNP was significantly linked to both white matter lesion grade and risk of silent infarction based on MRI: [Dadu]

NT-proBNP Quartile	% Infarct on MRI
1	5.8%
2	7.5%
3	10.7%
4	18.7%

The investigators suggested a cutoff of > 50 as a basis for further assessment of subjects.

Peripheral Arterial Disease (PAD)

Kollerits et al found that NT-proBNP was the best marker for PAD among the tests they considered:

Mean NT-proBNP	
PAD Present	179
No PAD	78

In a 2,443-patient cohort, mean age 58,

NT-proBNP was independently associated with an ankle-brachial index (ABI) at the threshold for a diagnosis of PAD (≤ 0.9). [Ye]

Elevated (> 1.04) ABI is a recognized marker for poorly compressible arteries due to medial artery calcification. It is associated with diabetes and increased risks of both adverse CV events and lower extremity amputation.

Jouni et al looked at the link between NT-proBNP in both low and elevated ABI vs. controls with ABI between 1.0 and 1.4:

ABI	% NT-proBNP > 300	% Coronary Disease
1.0-1.4	4%	22%
< 1.0	33%	56%
> 1.4	56%	59%

Mean NT-proBNP was substantially higher in elevated (417) vs. low (174) ABI.

NT-proBNP also predicts for reduced functional capacity based on walking distance in patients with known PAD. [Fan-2]

After following 98 PAD patients for 71 months, Skoglund et al showed NT-proBNP was an independent predictor for CV events.

In 487 patients with symptomatic PAD followed for 5 years, NT-proBNP was an independent marker for mortality in both diabetics and nondiabetics, and in patients $<$ age 75, as well as older subjects. [Mueller]

Deep Venous Thrombosis (DVT)/ Pulmonary Embolism (PE)

In DVT patients followed for 6 months, NT-proBNP ≥ 435 was linked to a 9.4-fold increased mortality risk. [Calero-Paniqua]

Hogg et al showed that it is also an independent

predictor of 3-month post-DVT mortality.

In acute PE, NT-proBNP correlates with RV dysfunction on transthoracic echocardiography, as well as both increased LV end diastolic pressure and decreased RVEF. [Latho, Pasha]

Adverse outcomes in PE were linked to a median NT-proBNP of 605, compared to 109 in those free of serious consequences. [Verschuren]

Other Circulatory Disorders

Two investigations demonstrate that NT-proBNP is a major mortality marker in pulmonary hypertension. [Mauritz, Soon]

NT-proBNP is a predictor of supraventricular tachycardia in emergency department patients presenting with palpitations. [Ocak]

It is also an independent predictor of ventricular fibrillation in Marfan syndrome. [Aydin]

NT-proBNP distinguishes between tachycardia-mediated cardiomyopathy and major structural heart disease in patients with tachycardia and reduced LVEF. [Nia]

When it is 548 or higher, NT-proBNP is a marker for progression in pericardial effusion. [Hwang]

NT-proBNP is a robust predictor of CAD in patients with Kawasaki disease and is a sensitive marker of for heart involvement in subjects with the carcinoid syndrome. [Dobson, Kaneko]

Bottom Line: NT-proBNP is a powerful resource for identifying high-risk cases in a wide range of cardiac and other circulatory disorders.

NT-proBNP and Diabetes

“This biomarker [NT-proBNP] can be considered an integral of the most important cardiac risk markers in diabetes mellitus, as this marker not only mirrors the presence but also the severity of the burden on the cardiovascular system.”

Marin Huelsmann, MD, et al
University of Vienna Medical School
Journal of the American College of Cardiology
62(2013):1365

NT-proBNP is inverse to the risk of developing T2 diabetes and is not a significant marker for future onset of diabetes. [Lazo]

NT-proBNP Quartile	Hazard Ratio for DM Diagnosis
1	1.0
2	0.8
3	0.8
4	0.75

Coronary Disease

In a study of diabetic Chinese subjects, researchers found that *“NT-proBNP is a stronger predictor of CHD than other biomarkers such as troponin T.”* [Fang-1]

Wiersma and coworkers showed that NT-proBNP ≥ 180 in diabetics is an independent predictor of inducible ischemia on myocardial perfusion scans (OR 2.36).

Two studies reveal that NT-proBNP is a highly significant marker for angiographic CAD in diabetic subjects. [Reinhard-2, Rodriguez]

For example:

Significant CAD	Median NT-proBNP
Yes	76.7
No	30.1

In the presence of known CAD in diabetics, NT-proBNP is an independent predictor of hospitalization and death. [Ponikowska]

Hamano et al described NT-proBNP as an *“out-standing”* marker for silent myocardial ischemia in diabetics. The odds ratio between the 3rd vs. 1st tertile was 26.7, with a recommended cutoff of 52.

Ventricular Dysfunction

Four studies showed a significant relationship between NT-proBNP and diastolic dysfunction in diabetics, and one team of investigators called it a *“simple screening tool”* for DD in this setting. [Ciftel, Dencker, Gormus, Poulsen]

In one study [Ciftel], the following association was found between mean NT-proBNP and DD based on Doppler imaging:

	Mean NT-proBNP
Controls – No DM or DD	134.5
DM without DD	166.3
DM with DD	566.7

Giorda et al evaluated 61 type 2 diabetics and found that NT-proBNP did not significantly demarcate early systolic dysfunction. However, only 2.8% of these subjects had an LVEF $\leq 50\%$, and no echocardiographic data other than LVEF were cited.

Type 1 Diabetes

Yazici et al revealed that NT-proBNP was not a marker for generalized atherosclerosis or diastolic dysfunction in T1 DM. However, the

mean age of his patients was only 30, and these complications are far less common in T1 (compared to T2) diabetics in the younger age population.

In another study of major complications in T1 diabetics, when NT-proBNP was > 84, the following odds ratios were cited after adjustment for all major CV risk factors: [Gruden]

	Adjusted OR
All Major Complications	2.56
Cardiovascular Disease	2.57
Albuminuria	2.98
Polyneuropathy	2.86
Retinopathy	2.16

Other Diabetic Contexts

There is an association between NT-proBNP and albuminuria in diabetics. [Danis]

	Mean NT-proBNP
Healthy Controls	42
Diabetes with no albuminuria	32
Diabetes and microalbuminuria	91
Diabetes and macroalbuminuria	331

Somarathne et al discovered that NT-proBNP had 68% sensitivity for echocardiographic LVH in diabetics (which was far better than either of two sets of ECG criteria). However, NT-proBNP was deemed inadequate to screen for LVH in this context due to low specificity (58%).

NT-proBNP is independently linked to a low ankle-brachial index (ABI) in T2 diabetics. [Senmaru]

In the Edinburgh Type 2 Diabetes Study, NT-proBNP was an independent predictor of cognitive decline and considered by these researchers to be a suitable biomarker for this outcome. [Feinkohl]

Elevated NT-proBNP is significantly associated with white matter lesions (hyperdensities) in diabetics. [Reinhard-3]

NT-proBNP increases over the first 6 months after bariatric surgery in diabetics, but this rise is usually well within the normal range. There may be cases of minimally elevated NT-proBNP during rapid weight loss intervals in these patients. [Chen-Tournoux]

Diabetic Outcomes

“Studies in patients with diabetes and diabetic nephropathy have shown that NT-proBNP is an important prognostic marker for CV events and all-cause mortality.”

Yan Miao, MD, et al
University Medical Center
Groningen, Netherlands
Clinical Chemistry
57(2011):186

In 1,071 diabetics, mean age 61 and followed for 33 months, NT-proBNP and albuminuria were independent and complementary as markers for CV events: [Clodi]

- When NT-proBNP was < 125, ACR > 30 did not increase the low risk.
- When it was > 125, the risk of CV events increased sharply and was twice as great as when ACR was > 30.
- NT-proBNP was the primary driver of CV event risk.

In the Casale Monferrato Study, 1,825 diabetics, mean age 68, were followed for 5.5 years. There was a significant relationship between albumin excretion ratio (AER) and all-cause mortality: [Bruno]

NT-proBNP	Albumin Excretion Ratio (AER)	
	< 20 µg/min	≥ 20 µg/min
< 91	1.00	1.55
≥ 91	1.97	3.94

In 3,862 diabetics, age 55 and older and with CV disease or at least one major CV risk factor, NT-proBNP was associated with a 2-fold increased risk of both CV events and death over a 5-year follow-up interval. While hs-cTnT was also a significant marker, most discriminative information was “...contributed by NT-proBNP alone”. [Hillis]

In a cohort of diabetics followed for 8.8 years, the hazard ratios for mortality increased progressively across NT-proBNP tertiles: [Reinhard-1]

NT-proBNP Tertile	Mortality Risk HR	
	All-Cause	Cardiovascular
1	1.00	1.00
2	1.62	1.39
3	2.44	2.28

Two other studies also demonstrated the significant impact of NT-proBNP on diabetic mortality. [Neuhold, Resl]

Huelsmann et al showed a normal NT-proBNP had the same impact on CV event risk and mortality as intensification of diabetic treatment with ACE inhibitors, angiotensin receptor blockers and beta-blockers.

Bottom Line: NT-proBNP appears to be an excellent reflexive test in a range of contexts associated with diabetes mellitus.

NT-proBNP and Hypertension

NT-proBNP is not elevated outside the normal range by high blood pressure and is therefore not a screening test for hypertension. [Tebbe, Toda]

In some hypertension patients, blood pressure does not decrease by at least 10% during sleep. These cases are referred to as “non-dippers,” and they are linked to a greater risk of complications. NT-proBNP is an independent predictor of “non-dipper” hypertension. [Cayli]

Di Stasio et al found there is a “*strong relationship between its [NT-proBNP] concentration and the establishment of irreversible cardiac hypertrophy*” in hypertension.

This usually excludes one subset of patients: middle-aged, never treated and (apparently) otherwise healthy hypertensives. [Partanen]

However, in a study of healthy middle-aged subjects with mean ambulatory BP of 144/89 and LVEF > 50%, NT-proBNP > 421 was as effective in pinpointing MRI-detected LVH as typical ECG criteria. [Courand]

Elbasan et al showed that NT-proBNP was a predictor of increased LV mass index and LV remodeling; both are precursors to LVH.

In the PREVEND Study involving 8,383 hypertension patients, mean age 49, NT-proBNP had a significant association with the presence of LVH: [Linssen]

NT-proBNP Quintile	Mean NT-proBNP	% LVH
1	7.4	3.4%
2	20.7	3.5%
3	37.8	4.1%
4	65.1	4.1%
5	336.5	9.9%

Masson et al showed that NT-proBNP in the 4th quartile (> 185) was an independent marker for LVH in 1,973 patients, mean age 73.

It is also a significant predictor in patients having hypertension with chronic renal disease. [Mishra]

Scheven and associates discovered that NT-proBNP ≥ 125 correlated with Cornell LVH criteria.

Three additional studies revealed that NT-proBNP is as good (two studies) or better (one study) in demarcating LVH than widely used ECG criteria. Two studies recommended using ECG criteria and NT-proBNP together to optimize detection of LVH. [Andrade, Limkakeng, Neeland-1]

Diastolic Dysfunction (DD) in Hypertension

Comparing NT-proBNP to echocardiographic evidence of both LVH and DD, Zile et al found that NT-proBNP effectively distinguishes LVH accompanied by DD in asymptomatic patients:

	Mean NT-proBNP
No LVH or DD	87.5
LVH without DD	109.5
LVH and DD	214.3

In another echo-based study of 236 newly diagnosed hypertensive patients, mean age 53, NT-proBNP > 113 was associated with impaired myocardial performance index despite normal LVEF. [Sahin]

Four more studies affirm the link between elevated NT-proBNP and DD in persons with hypertension. [Pejovic, Vasiuk, Wang-3, Yang]

Secondary Hypertension

NT-proBNP is a biomarker for significant renal artery stenosis in Rx-refractory hypertension. [Nowakowska-Fortuna, Wongpraparut]

In one study, NT-proBNP ≥ 450 was associated with a 5.1-fold greater incidence of CV events in elders with renal artery stenosis. [Zhu-3]

In another study, elevated NT-proBNP was an excellent marker for mortality in patients with atheromatous renovascular disease. [Chrysochou]

It is also elevated in primary aldosteronism in patients with suspected secondary hypertension. [Pizzolo]

reflexive test in late-middle-aged and older applicants with secondary, long-standing, inadequately controlled and/or refractory hypertension, as well as those satisfying ECG criteria for LVH.

Hypertension Outcomes

In a 5.5-year follow-up of 6,549 hypertensive patients on Rx and free of CAD at baseline, NT-proBNP predicted CV event risk independent of blood pressure variations. Odds ratio per SD increase in log NT-proBNP was 1.24. [Welsh-2]

In 648 hypertensives, mean age 52 and followed for 5.7 years, NT-proBNP correlated significantly with mortality:

NT-proBNP Tertile	Relative Mortality Risk
1	1.00
2	1.99
3	3.30

These authors concluded that NT-proBNP *“...was the most powerful predictor of mortality without any significant modifying effect of ECG markers. Consequently, NT-proBNP kept its prognostic value after exclusion of patients with ECG LVH.”* [Paget]

Bottom Line: NT-proBNP is an excellent

NT-proBNP and COPD

Colice et al stated that NT-proBNP identifies a “...subset of COPD patients with a particularly poor prognosis.”

In a cohort of patients with stable COPD, NT-proBNP significantly correlated with: [Chi]

- Gold III/IV vs. I/II stage
- FEV-1 < 50%
- Increased systemic pulmonary arterial pressure
- Abnormal blood gases

In patients with normal LV function undergoing vascular surgery, NT-proBNP ≥ 500 was independently linked to both mild and severe comorbid COPD. When NT-proBNP was ≥ 450 , it was associated with 2-fold greater mortality in those patients with COPD.

The authors considered NT-proBNP to be a “subtle marker” for identifying undiagnosed COPD and risk stratification in surgical patients. [van Gestel]

NT-proBNP is a marker for endothelial dysfunction, decreased LV function, biventricular dysfunction and LV failure during exacerbation in COPD patients. [Gale, Lee-1, Macchia, Ouanes, Wang-2]

NT-proBNP is highly sensitive to COPD-associated pulmonary hypertension (PH); when < 95, it rules out PH based on echo criteria. [Agoston-Coldea, Anderson]

Acute exacerbations are associated with worsening of COPD and high mortality. In a study of 99 patients followed for 1.9 years post-exacerbation, NT-proBNP was a multivariate predictor of mortality, independent of heart failure, troponin T, pulmonary function tests, and clinical and radiological findings: [Hoiseth]

NT-proBNP		
Tertile	Range	Mortality Hazard Ratio
1	< 264	1.0
2	264-909	2.4
3	> 909	3.2

Other studies further document the links between NT-proBNP and COPD exacerbations:

- Elevated NT-proBNP increases 6-month post-exacerbation mortality 4.2-fold. [Marcun]
- Following either COPD or asthma exacerbations in elders, NT-proBNP > 588 was linked to a 4-fold greater 1-year mortality, after multivariate adjustment. [Medina]
- NT-proBNP > 220 was associated with a 9-fold increased 30-day mortality following acute exacerbations; this was independent of all risk factors, including troponin T. [Chang-1]
- Sanchez-Marteles and colleagues also found that NT-proBNP was a post-exacerbation mortality indicator.

Bottom Line: Emerging evidence suggests NT-proBNP has an important role as a reflexive test in potentially insurable cases of COPD.

NT-proBNP in Other Non-Circulatory Contexts

In their review of NT-proBNP, Thygesen and his fellow cardiologists emphasized that NT-proBNP is neither heart failure nor cardiac disease-specific, and that it is also elevated in other disorders and contexts related to excess mortality.

Kidney Function

NT-proBNP correlates inversely with eGFR at all stages of renal function, increasing markedly when eGFR is < 60. [Horii, Jafri, Takase]

Nevertheless, eGFR and NT-proBNP are independent of one another in terms of CV disease risk. [Luchner-2]

Scheven and colleagues looked at NT-proBNP ≥ 125 and the risk of CV events in 1,505 subjects, mean age 49. On the basis of eGFR as the indicator of chronic kidney disease (CKD), they found the significance of NT-proBNP is not impacted by comorbid CKD:

CKD Present	HR for CV events
Yes	1.55
No	1.45

They concluded that “*NT-proBNP in a subject with lower eGFR should be taken seriously as a prognostic marker for a worse cardiovascular outcome and not be discarded as merely the result of decreased renal clearance.*”

NT-proBNP is also independently associated with a higher probability of significant albuminuria as demonstrated in the same study:

NT-proBNP	% ACR > 30
< 125	12.6%
≥ 125	30.7%

Metabolic Syndrome

Overall, NT-proBNP tends to be lower in patients with this syndrome. [Bao, Fang-2]

In one study, NT-proBNP was increased with higher BMI, but was not influenced significantly by waist circumference (the superior marker for abdominal obesity in this syndrome). [Li-3]

In another investigation, NT-proBNP was inversely associated with the presence of metabolic syndrome in elderly community-dwelling subjects. [Wang-4]

Sleep-Disordered Breathing (Sleep Apnea)

Two investigations reported no association between apnea/hypopnea index (AHI) and NT-proBNP. [Johansson-2, Roca, Zhao]

In 83 patients undergoing angiography and PCI for stable CAD, NT-proBNP was significantly higher if AHI was ≥ 15 , and it also correlated with LVEF.

The authors felt that NT-proBNP was reflective of subclinical cardiac stress in sleep-disordered breathing. [Inami]

Thyroid and Parathyroid Dysfunction

In patients with suspected Graves disease, NT-proBNP was significantly linked to elevated T3 and T4 levels, and considered a marker for endothelial dysfunction and vascular stiffness in these cases. [Gu]

NT-proBNP is an important risk consideration in hyperparathyroidism:

- It is increased as much as 80-fold in symptomatic patients and is

associated with increased ventricular wall thickness, greater LV mass and diastolic dysfunction. [Agarwal-2, van Ballegooijen]

- It correlates closely with 3 major markers for inflammation: CRP, ESR and interleukin 16 (IL-16). [Almqvist]

Connective Tissue Disease

NT-proBNP has multiple significant links to rheumatoid arthritis (RA), making it an important marker in assessing these risks:

- It correlates with CRP, ESR, troponin T, handgrip strength, carotid intima/media thickness (cIMT) and the presence of anemia. [Avouac, Targonska-Stepniak]
- It is significantly higher in active vs. latent disease. [Kotby, Provan-3]
- It is an independent marker for CV events and 10-year all-cause mortality. [Finckh, Provan-1]

In 6,273 patients with either RA or osteoarthritis (OA) who were taking NSAIDs, 2-year cardiovascular outcomes were independently affected by NT-proBNP: [Ruff]

NT-proBNP Quartile	CV Death	CV Events
1	1.00	1.00
2	1.53	0.85
3	3.46	2.17
4	5.62	3.53

NT-proBNP is associated with elevated hs-CRP and incidence of LV diastolic dysfunction in patients with various acute autoimmune conditions. [Giannoni]

Six studies affirm it is a capable marker for impaired ventricular function and pulmonary hypertension in scleroderma and systemic lupus erythematosus. [Allanore, Chighizola, Gladue, Goldenberg, Gunnarsson, Thakkar]

Liver Disease

Two studies revealed that NT-proBNP relates to the risk of hepatitis C at a median level of 125 or higher and should be of value in distinguishing those with positive HCV antibodies that are actively infected. [Antonelli, Okada]

In another investigation, NT-proBNP was strongly associated with hs-CRP levels in HCV, making it a surrogate marker for chronic inflammation. [Che-3]

It also correlates with increased LV diastolic diameter, LV posterior wall thickness and other echocardiographic parameters for diastolic dysfunction in chronic HCV cases. [Che-1]

Wang-1 et al looked at the relationship between NT-proBNP and the presence of chronic disease, cirrhosis and hepatocellular carcinoma in subjects with hepatitis B or hepatitis C:

	Mean NT-proBNP
Controls free of both	21.8
Hepatitis B:	
Chronic Disease	87.2
Cirrhosis	517.2
HCC	134.0
Hepatitis C:	
Chronic Disease	66.5
Cirrhosis	561.7
HCC	268.6

Bottom Line: NT-proBNP appears to be a valuable reflexive test in potentially insurable applicants with chronic HBV and HCV.

Cancer

Comparatively few studies have been done regarding the association between NT-proBNP and cancer risks, except as NT-proBNP relates

to late outcomes in childhood cancer survivors.

In 493 patients presenting for elective noncardiac surgery, NT-proBNP ≥ 125 conferred an odds ratio of 7.0 for undiagnosed lung cancer. [Aujollet]

NT-proBNP closely correlates with multiple adverse risk variables in non-Hodgkin lymphoma. Among patients treated with chemotherapy, NT-proBNP ≥ 900 was a significant predictor of a fatal outcome. [Gimeno]

It also elevates in elderly cancer survivors who have comorbid heart disease. In 374 cases, mean NT-proBNP was 791 in these individuals vs. 96 when heart disease was absent. [Wieshammer-1]

Adult Survivors of Childhood Cancer

There are over 350,000 long-term survivors of childhood cancer in the U.S. alone. Many are at greatly increased heart disease risk due to chest-area radiotherapy and/or treatment with anthracyclines such as doxorubicin.

These individuals are disproportionately disposed to purchase life insurance and often have inadequate post-oncology follow-up in primary care. [Suh]

Early investigations of the links between NT-proBNP and the delayed effects of childhood cancer therapy were covered in the first and second NT-proBNP literature reviews. Now, we have additional evidence affirming and expanding these associations.

In 217 survivors, mean age 28, matched to 130 healthy siblings, NT-proBNP was a strong indicator of subclinical systolic dysfunction based on wall motion score index in those treated with anthracyclines and mediastinal irradiation. [Brouwer]

A study of leukemia survivors found that NT-proBNP was the “*best available marker for late anthracycline cardiotoxicity*” based on echocardiographic evidence of subclinical heart damage. [Mladosevicova]

Three additional studies corroborate these findings in survivors of leukemia and other childhood cancers treated with anthracyclines. [Krawczuk-Rybak, Urbanova, Yildirim]

D’Errico et al discovered that NT-proBNP ≥ 125 independently correlated with increased risk of echocardiographic abnormalities in women receiving left breast irradiation in breast cancer.

Bottom Line: NT-proBNP, not an ECG, is the reflexive test of choice in all at-risk childhood/adolescent cancer survivors, many of whom might otherwise be insured at standard rates despite asymptomatic (or undisclosed) cardiac issues.

Alzheimer Dementia (AD)

Marksteiner and fellow gerontologists regard NT-proBNP to be a potential screening test for “*both diagnosis and AD progression.*”

In another investigation, NT-proBNP improved specificity for differentiating AD from control subjects based on cerebrospinal fluid analysis. [Soares]

Psychiatric Disorders

Van den Broek et al looked at 5,270 subjects, mean age 72 and free of heart failure at baseline, and followed them for 11 years to determine the prognostic implications of NT-proBNP and comorbid major depression:

NT-proBNP	Depression	CV Events	
		Heart Failure	CV Mortality
< 190	No	1.0	1.0
< 190	Yes	1.3	2.3
≥ 190	No	2.8	3.0
≥ 190	Yes	2.9	6.0

NT-proBNP and major depression (MD) work synergistically to increase the risk of CV mortality.

At admission, 52% of alcoholics had elevated NT-proBNP; this improved dramatically if the patient remained abstinent.

The authors concluded that this was evidence for the value of NT-proBNP predicting for sub-clinical cardiac dysfunction in alcohol-dependent patients, and they advised that NT-proBNP be routinely used in this context. [Hofer]

Sarcoidosis

Elevated NT-proBNP is a marker for cardiac involvement in patients not previously diagnosed with sarcoid heart disease. [Handa]

However, NT-proBNP has no value in assessing pulmonary function status in sarcoidosis patients. [Magri]

Syncope

Pfister et al showed that NT-proBNP is highly predictive of cardiac origin in patients admitted for diagnostic assessment of syncopal episodes. They argued that NT-proBNP should be used to reduce the need for typical cardiac testing in this context.

Costantino and coworkers found that the extent of change in NT-proBNP 6 hours post-syncope

distinguishes episodes due to ventricular arrhythmia vs. vasovagal syncope.

Beta-Thalassemia

NT-proBNP predicts for subclinical LA and LV dysfunction not detected on echocardiography. [Kostopoulou, Marci]

Community-Acquired Pneumonia (CAP)

CAP is often cited in the medical history of older life insurance applicants.

In 341 patients treated for CAP, NT-proBNP was a “powerful” predictor of mortality 942 days post-hospitalization. At discharge, those who survived had an average NT-proBNP of 103, vs. 318 in patients who died over this interval. [Nowak]

NT-proBNP is a powerful indicator of risk of inpatient and 30-day post-discharge survival in CAP. [Chang-2, Goritsas, Jeong, Xiao]

NT-proBNP also rises markedly in patients with sepsis. [Li-4]

Bottom Line: These studies demonstrate the impact of NT-proBNP in a broad range of non-circulatory disorders.

NT-proBNP in Hospitalization and Surgery

“Screening a primary care population with hypertension, diabetes and CAD using NT-proBNP has an excellent predictive value to rule out patients at risk for hospitalization or death.”

Christopher Adlbrect, MD, et al
 Medical University of Vienna
European Journal of Preventive Cardiology
 19(2011):55

In the Adlbrect study, investigators assessed the 1-year risks of hospitalization in 1,203 primary care patients, mean age 66. The subjects had a high prevalence of hypertension, diabetes and/or CAD:

NT-proBNP	% Hospitalized within 12 Months	
	All Reasons	Cardiac Only
< 125	14%	2%
> 125	33%	6%

In the Copenhagen Heart Study, there was a strong link between baseline NT-proBNP and all-cause mortality in subjects with acute symptoms who were admitted to a hospital: [Lauridsen]

NT-proBNP Quartile	All-Cause Mortality	
	1-Year	11-Years
1	1.00	1.00
2	1.02	1.02
3	1.72	1.22
4	3.15	1.97

In a German study of 1,086 patients age 65 and older screened in the emergency department, NT-proBNP positively correlated with in-hospital death, 6-month readmission and 6-month mortality.

[Luchner-3]

In 481 consecutive patients admitted to a tertiary care Swedish intensive care unit (ICU), NT-proBNP significantly distinguished those at risk for excess 30-day mortality.

Patients with NT-proBNP in the 4th quartile had a 3-fold greater risk of death (36.1%) compared to those in the 1st quartile (12.8%). [DeGeer]

Cardiovascular Surgery

Cuthbertson et al followed 1,010 patients, mean age 66, following heart surgery:

- 3-year mortality hazard ratio was 3.5 when admission NT-proBNP was ≥ 289 , as compared to 2.7 with an abnormal preoperative ECG.
- Mortality in the 10th NT-proBNP decile was 19%, as compared to just 2% in the 1st decile.

In 1,458 consecutive subjects undergoing heart surgery, preoperative NT-proBNP was 2,215 in those who did not survive 30 days, compared to 488 in those who lived at least 1 month.

[Heringlake]

Ternacle and associates reported that NT-proBNP was a marker for subclinical myocardial dysfunction in patients undergoing aortic valve and mitral valve surgery, as well as CABG when LVEF was normal.

After 2 years following major elective vascular surgery patients in Scotland, preoperative NT-proBNP ≥ 359 was associated with 68% survival, as compared to 93% survival when it was < 359 . The adjusted odds ratio was 3.6.

[Rajagopalan]

Median NT-proBNP was significantly higher (391 vs. 179) in patients developing a new arrhythmia within 72 hours following general

vascular surgery. The hazard ratio for 2-year mortality was 2.2 in those who developed an arrhythmia within this interval. [Winkel]

Scrutino et al looked at 411 vascular surgery patients to determine the association between NT-proBNP and the primary outcomes of death, acute coronary syndrome, pulmonary edema within 30 days of surgery and post-operative cTnI readings. NT-proBNP > 221 was a multivariate outcome predictor (odds ratio 4.1) and was independent of both hs-CRP and fibrinogen.

Non-Vascular Surgery

In a metaanalysis of 18 studies encompassing 2,179 patients undergoing various nonvascular surgeries, NT-proBNP was a powerful independent marker for death or nonfatal MI over the ensuing 6 months.

Preoperative NT-proBNP	% Dead or Nonfatal MI
< 300	5.2%
300-900	16.1%
901-3000	26.0%
> 3000	39.5%

Adjusted odds ratios for preoperative and postoperative NT-proBNP were 2.2 and 1.9, respectively.

This team of 27 cardiologists from 11 countries concluded that:

“...a preoperative NP [natriuretic peptide] measurement was the strongest predictor of mortality or nonfatal MI after noncardiac surgery, and the addition of a postoperative NP measurement augmented the identification of at-risk patients.”

Reitze N. Rodseth, MBChB, PhD, et al
Journal of the American College of Cardiology

63(2014):170

In 1,923 noncardiac surgery patients, mean age 68, Korean cardiologists performed preoperative transthoracic echocardiograms (TTE) and measured NT-proBNP. They reported the following 30-day outcomes: [Park-1]

	Relative Risk		
	MI	CHF	CV Death
Any TTE Abnormality	1.6	1.8	1.1
NT-proBNP ≥ 30	3.0	4.7	5.4

In 979 elderly subjects post-hospitalization for noncardiac surgery, NT-proBNP ≥ 300 was linked to 4.8% mortality, vs. 1.4% when NT-proBNP was < 300. Median NT-proBNP was 166 in those who survived vs. 576 in patients who died. [Weber]

Two additional studies affirm the powerful association between NT-proBNP and MACE after noncardiac surgical procedures. [Borges, Novo]

NT-proBNP is also a marker for perioperative MI and CV death. In 2,054 patients, average age 68 and having elective major procedures, NT-proBNP in the 4th quartile conferred relative risks of 1.55 for MI and 2.30 for CV death compared to those with readings in the 1st quartile. [Choi-1]

These authors stated that NT-proBNP *“...could be a marker for myocardial ischemia or generalized cardiac impairment in perioperative situations as well as nonsurgical situations.”*

In 89 patients having emergent lower limb orthopedic surgery, NT-proBNP ≥ 842 conferred a mortality hazard ratio of 19.3 over the ensuing 24 months. [Chong-1]

Another report on 187 emergent lower limb orthopedic surgery cases by the same authors

revealed that NT-proBNP was the #1 predictor of survival, superior to histories of MI, CHF and renal failure, and elevated troponin readings. [Chong-2]

European experts have now recommended NT-proBNP be added to future guidelines for CV risk assessment in patients undergoing major noncardiac surgical procedures. [Clerico-2]

Bottom Line: NT-proBNP is clearly a major indicator of mortality and other adverse outcomes in patients undergoing both cardiac and other surgical procedures.

NT-proBNP, CV Events and CV-Related Mortality

“The fully-adjusted association between BNP and NT-proBNP with incident CV events is strong across a range of baseline risks.”

Brenden M. Everett, MD
Harvard Medical School
Clinical Chemistry
56(2010):883[editorial]

In a 2009 metaanalysis of 40 prospective studies involving 87,474 subjects, the adjusted relative risk for CV events in the 3rd NT-proBNP tertile was 2.82 compared to those in the 1st tertile. [Di Angelantonio]

Among 4,801 men in the Scottish WOSCOPS Study of middle-aged subjects with elevated cholesterol and intermediate CAD risk, 15-year adverse events were strongly associated with a 1-SD increase in log NT-proBNP: [Welsh-1]

Outcome	Hazard Ratio
CV Death	1.47
ALL CV Events	1.22

This study was adjusted for social deprivation index and other significant risk variables we cannot assess in underwriting. The authors maintained their findings *“...provide further support to consider the wider use of NT-proBNP in CVD risk prediction.”*

In the British Regional Heart Study of 3,649 males, ages 60-79 and followed for 9 years, investigators reported the following relationship between NT-proBNP quartiles in several risk contexts:

NT-proBNP Quartile	No CVD at Baseline		CVD at Baseline
	CV Death	CV Events	CV Death
1	1.00	1.00	1.00
2	1.14	1.12	2.76
3	1.29	1.24	2.84
4 (≤ 151)	2.64	1.77	6.79

This study was fully adjusted for all CV risk factors, plus anemia, physical activity and alcohol intake. The authors ended with this statement: [Wannamethee-1]

“These results suggest a genuine potential for NT-proBNP to offer potential prognostic value beyond clinically applicable markers.”

In 2,975 community-dwelling elders, a 25% rise in NT-proBNP over 2-3 years significantly correlated with increases in CV mortality even when baseline NT-proBNP was normal. [deFilippi-3]

Three more studies support these findings. Their findings led researchers to make statements such as NT-proBNP is a *“...novel and universal marker for various types of CVD”* and rising NT-proBNP over 24-36 months represents *“a preclinical HF phenotype.”* [Doi, Glick, Rutten]

In another investigation, deFilippi and his coworkers looked at 4,137 subjects, mean age 73, who were free of heart failure and followed for over a decade. They compared LVEF and NT-proBNP as markers for adjusted risk of CV mortality and new onset heart failure: [deFilippi-1]

LVEF	NT-proBNP	CV Mortality	New Onset HF
≥ 55%	< 190	1.00	1.00
< 55%	< 190	1.68	1.26
≥ 55%	≥ 190	1.92	2.05
< 55%	≥ 190	2.95	2.67

The authors concluded that the addition of LVEF to NT-proBNP adds little in the assessment of new onset HF or CV mortality.

NT-proBNP and Echocardiography

In 433 patients with known CV disease and normal echocardiograms, Toggweiler et al assessed the impact of NT-proBNP on CV risk. They found that CAD was twice as prevalent in those with elevated versus normal NT-proBNP, and those with elevated levels were 3 times more likely to have previously sustained an MI (25% vs. 8%):

NT-proBNP	Echo	2-Year Cardiovascular Events
Normal	Normal	1.5%
Normal	Abnormal	0.0%
Elevated	Normal	8.9%
Elevated	Abnormal	20.2%

These cardiologists argued that NT-proBNP is “a surrogate of hemodynamics and of cardiac stress... [and] the strongest independent predictor of prognosis in cardiac outpatients.”

They further advocated using NT-proBNP when assessing the clinical relevance of echocardiographic findings.

Stable Coronary Artery Disease

This subject has been addressed in many investigations since the 2nd NT-proBNP literature review paper.

In a 2013 metaanalysis of all-cause mortality and new CV events in patients with known stable CAD, Wei-2 and coworkers reported the following aggregate findings:

NT-proBNP Quartile	Risk of Combined Outcomes
1	1.00
2	1.33
3	1.85
4	2.74

They observed that a “poor prognosis was significantly increased with the elevation of NT-proBNP.”

Giannitsis et al followed 1,469 stable CAD patients, mean age 65, for 7.5 years. Median NT-proBNP was 208 in survivors vs. 757 in those who died over this interval.

Only patient age had a greater impact than NT-proBNP as a predictor of long-term mortality.

Another study documented the relationship between high-sensitivity troponin T (hs-cTnT) and NT-proBNP as 4-year all-cause and CV mortality markers in 869 stable CAD patients undergoing non-emergent PCI: [Ndrepepa-2]

NT-proBNP	hs-cTnT	All-Cause	Cardiovascular
Low	Low	2.5%	1.4%
High	Low	5.9%	4.4%
Low	High	7.4%	4.7%
High	High	18.1%	12.6%

These cardiologists concluded that hs-cTnT and NT-proBNP are “...integrative indexes of increased cardiovascular risk.”

Nine additional recent studies underscore and affirm the major mortality risk implications of NT-proBNP in stable CAD. [Ahluwalia, Bode, Harutyunyan, Ivandic, Kablak-Ziembicka-1, Kavsak, Krecki-2, Ruwald, Schnabel]

In a 12.5-year assessment of 5,447 patients related to the risk of sudden cardiac death, the hazard ratio was 1.8-fold and 2.5-fold greater in the 4th and 5th quintiles, respectively, as

compared to the 1st and 2nd quintiles [Patton-1]

In 2,975 community-dwelling healthy elders followed for nearly 12 years, there was a significant correlation between NT-proBNP quintiles and risks of incident heart failure and CV mortality: [deFilippi-3]

NT-proBNP Quartile	Hazard Ratio	
	Incident HF	CV Mortality
1	1.00	1.00
2	1.10	1.05
3	1.30	1.40
4	1.81	1.91
5 (> 267.5)	3.05	3.02

These findings were fully adjusted for CV risk factors, as well as both ECG and echocardiographic findings.

In a cohort of octogenarians with CAD and normal kidney function, NT-proBNP > 369.5 was associated with an independently increased mortality hazard ratio of 1.69. [Fu]

Bottom Line: NT-proBNP is a powerful marker for cardiovascular events and CV mortality.

NT-proBNP and All-Cause Mortality

“NT-proBNP has been accepted to be one of the most useful markers of mortality in various populations.”

Shih-Hsien Sung, MD, et al
 Department of Medical Research and Education
 Taipei Veterans General Hospital, Taiwan
Heart
 97(2011):648

In a 9.9-year study of 11,913 subjects, ages 54-74 and free of CV disease at baseline, Oluleye et al reported the following relationships between NT-proBNP quintiles and both all-cause and CV mortality:

NT-proBNP Quintile	Mortality Hazard Ratio	
	All-Cause	Cardiovascular
1	1.00	1.00
2	1.33	1.99
3	1.78	3.03
4	1.92	2.77
5 (≥ 159)	3.05	7.48

McKie et al looked at NT-proBNP and echocardiography in the assessment of 9.1-year prospective outcomes in the Rochester Epidemiology Project.

After full adjustment, including abnormal echo findings, NT-proBNP beyond the 80th percentile had hazard ratios of 1.80 and 2.37 for all-cause mortality and new-onset heart failure, respectively. They stated that NT-proBNP is “...independently predictive of mortality and cardiovascular morbidity beyond conventional clinical risk factors and structural abnormalities of the heart.”

In a 5-year study involving 4,775 German subjects, mean age 56 and free of known CAD, cardiologists reported that using an NT-proBNP

threshold of > 85.8 correlated with a 2.5-fold greater all-cause mortality risk. [Leistner-2]

For MACE, a cutoff of > 121.9 linked to a 3-fold higher risk. This was after full adjustment for CV risk factors, including depression. The authors advocated use of NT-proBNP in primary prevention.

In the PREVEND study in the Netherlands, involving 7,819 subjects ages 25-75, all-cause mortality was increased by 1.28 per log increase in NT-proBNP. This was also after full adjustment for CV history and risk factors. [van Hateren]

In 8,503 postmenopausal females followed for 9 years, adjusted mean NT-proBNP was 83 in those who survived, as compared to 138 in subjects who died over this interval. [Cramer]

Dieplinger et al followed 1,345 patients referred for angiography for 9.8 years. Baseline median NT-proBNP was 201 in survivors vs. 751 in those who died during follow-up. There were linear increases in both all-cause and cardiovascular mortality across quartiles of NT-proBNP.

Clark (Swiss Re), Kaufman (Mass Mutual) and a team of researchers from Clinical Reference Laboratory (CRL) studied mortality associated with NT-proBNP in 144,027 applicants, ages 50 to 89, matched to the Social Security Master File. Follow-up was for 2.6 years. [Coens, personal communication]

At this writing, their paper – **NT-proBNP as a Predictor of All-Cause Mortality in a Population of Insurance Applicants** – is pending publication in the *Journal of Insurance Medicine*.

Applicants were excluded if they answered “yes” to heart disease questions on the application.

These are the key findings in this study:

- Male mortality doubled when NT-proBNP was 101-300, and it was 2.5-fold increased at levels exceeding 300 in all age/sex bands.
- NT-proBNP > 1,000 showed mortality in excess of 10 times expected.
- NT-proBNP predicted excess mortality independent of CV risk factors, creatinine, BMI and eGFR.
- The authors cited significant mortality cutoff thresholds of 300 for males and 200 for females at all screening ages.
- Further separation of subjects into CVD risk factor tertiles had no impact on the predictive value of NT-proBNP.

The authors made the following statement regarding their findings:

“...relative to other potential screening tests, NT-proBNP may identify a higher proportion of who might benefit from identification and medical intervention.”

All-Cause Mortality in the Elderly

In 970 community-dwelling subjects, ages 65 and older, free of CV disease and followed for 6.7 years, Muscari et al reported these findings:

- Mean NT-proBNP in those who died over this interval was 222, as compared to 119 in survivors.
- All-cause mortality hazard ratio in the top quartile, as compared to the 1st quartile, was 2.34.
- CV mortality hazard ratio was 5.41 and non-cardiovascular mortality was nearly 2-fold greater in the 4th vs. 1st NT-proBNP quartile.

These investigators labeled NT-proBNP the “strongest predictor” of mortality outcomes in their study.

In the Japanese Tsurugaya Study, Howaza and

coworkers followed 512 subjects age 70 and over for 6 years. They reported the following adjusted hazard ratios for death or disability ($p < .05$):

NT-proBNP Quintiles	Adjusted Hazard Ratio
1	1.00
2	1.40
3	1.34
4	1.32
5	1.90

Among 331 community-dwelling individuals, ages 71-87 at baseline and followed for 4.5 years, NT-proBNP had a 4th vs. 1st quartile odds ratio for all-cause mortality of 3.6, which was superior to the impact of diabetes, cigarette smoking or LVEF < 50%. [Johansson-1]

In the Leiden 85-Plus Study, NT-proBNP was the #1 predictor of mortality in very elderly subjects with known CVD. Mortality was 1.8-fold increased after adjustment for conventional risk factors, plus CRP and homocysteine. [van Peet]

Eggers et al followed 1,016 participants in the PIVUS Study. NT-proBNP was measured at age 70 and again at age 75. [Eggers-2]

The significant threshold for all-cause mortality was NT-proBNP > 200. For those whose baseline NT-proBNP was 200 or lower, an increase in NT-proBNP after 5 years doubled mortality thereafter.

Horii et al discovered that 52-month all-cause mortality was significantly greater in elderly subjects with CAD whose baseline NT-proBNP was > 258.6.

Bottom Line: NT-proBNP is one of the finest markers for excess all-cause mortality in the history of life underwriting.

NT-proBNP: Underwriting Considerations

Three primary mandates from life insurer top management are now universally recognized regarding all aspects of the new business process:

1. Do it cheaper by controlling new business acquisition costs.
2. Do it faster by reducing application-to-issue cycle time.
3. Do it in a way that enhances the customer's insurance purchase experience, consistent with the notion that life insurance is a financial services product.

NT-proBNP robustly satisfies all of these mandates and does so to a far greater extent than other cardiac screening tests still retained by most insurers.

At the end of the proverbial day, these mandates will drive the future of how we assess risk, regardless of objections from any quarter by those resistant to wider use of NT-proBNP.

In 2007, just 5% of U.S. life insurers were using NT-proBNP, based on the 2007 Life Underwriting Requirements Survey in which over 100 companies participated.

Four years later (2011 Life Underwriting Requirements Survey), 45% were using NT-proBNP, and half of nonusers stated they were actively considering the deployment of this test.

Among those in the top 25 (based on lives underwritten), 62% were using NT-proBNP, and 66% of all survey respondents expressed the opinion that use of this test would continue to increase.

At our August 2013 underwriting study group meeting, 2/3rd of member companies

acknowledged using NT-proBNP on some basis.

Moreover, anecdotal reports from both insurers and industry laboratories reveal that many companies using NT-proBNP are expanding their use for both screening and reflexive purposes.

Bottom Line: NT-proBNP is the most rapidly embraced new underwriting tool since the introduction of HIV-1 testing nearly 30 years ago!

NT-proBNP and Exercise ECGs

“Although stress tests have long been established as an effective method of refining risk stratification, using biomarkers as a substitute may provide a less expensive and speedier alternative.”

Shiny Mathewkutty, MD, et al
Mt. Sinai School of Medicine, New York
American Journal of Cardiology
111(2013):493

The majority of respondents to the 2011 Life Underwriting Requirements Survey agreed that exercise ECG screening by life insurers would be discontinued over the next 5 years.

Nearly 75% concurred that insurers should completely abandon this test as a routine age/amount requirement at ages 70 and over.

The argument for replacing exercise ECGs with NT-proBNP has already been fully outlined in the life underwriting literature. [George]

NT-proBNP and Resting ECGs

“ECGs certainly still have their place in the current system of cardiac evaluation and medical screening in underwriting...”

Robert Goldstone, MD

This statement is vulnerable to challenge, considering the major drawbacks to screening with resting ECGs (independent of whether they confer protective value akin to that of NT-proBNP):

- **Cost** – The NT-proBNP test has a significantly lower out-of-pocket cost than a resting ECG in our industry.
- **Analysis/Delay** – NT-proBNP is entirely objective, whereas the interpretation of many abnormal ECG findings is highly subjective and dependent on review by medical directors. This often delays the underwriting process.
- **Customer Perception** – NT-proBNP is tested for on blood samples routinely collected for screening blood profiles. Doing an ECG is a cumbersome and highly inconvenient undertaking on a mobile paramedical basis and therefore wholly inconsistent with the notion of completing a financial services transaction.
- **Quality** – There is growing concern, as acknowledged by producers, underwriters and even executives of paramedical providers, regarding the poor quality of many ECGs performed on a mobile paramedical basis.
- **Challenges from Attending Physicians** – It is a tedious and time-consuming process to respond to challenges regarding ECG interpretations and their implications. Fill-ins on a form letter suffice for challenges to the use of NT-proBNP.

Bottom Line: Given the myriad advantages conferred by NT-proBNP, it is

illogical to insist upon continued routine CV risk screening with resting ECGs.

Recently, we invited reinsurers doing business in the U.S. market to take a 10-question survey regarding their perceptions of NT-proBNP.

Eight of 10 accepted this invitation.

These are some of the salient insights gained from this survey:

- 75% of respondents agreed that NT-proBNP had “great/significant” value as an older age screening test.
- 75% felt that NT-proBNP was “roughly equal” to a resting ECG in terms of protective value at older ages.
- 75% concurred that NT-proBNP had “great/significant” value as a reflexive test.
- 75% said they would extend favorable pricing consideration to automatic clients screening with NT-proBNP at older ages.
- All but one respondent would allow insurers to substitute NT-proBNP for resting ECGs if the client had “*favorable mortality and satisfactory audits.*”

Lastly, chief reinsurance underwriting officers were asked if – in the role of chief underwriting for a direct insurer – they would use NT-proBNP as a screening test.

100% said “yes.”

Both teleinterviews and pharmacy records gained enthusiastic acceptance by reinsurers, and, in many cases, their use culminated in more favorable reinsurance pricing.

NT-proBNP will inexorably realize the same outcomes in the near-term future.

Maximizing the Pay-Off from NT-proBNP in Life Underwriting

In their state-of-the-art paper published in the *Journal of the American College of Cardiology*, Maisal and his coworkers cited all of the perceived scenarios where they deemed NT-proBNP to be “useful” or “potentially useful” based on evidence in the literature prior to publication of their paper in 2012.

These are the scenarios they cited:

- Ruling out heart failure in primary care
- Risk prediction in heart failure and both stable and unstable coronary artery disease
- Risk prediction in the community
- Pre-operative risk assessment
- Risk prediction with cardiotoxic chemotherapy
- Risk prediction in valvular heart disease

They concluded by stating: *“as the wealth of NP [natriuretic peptide] data continue to accumulate, we expect to see progressively more clinical applications for NPs as well as increased acceptance by practicing clinicians.”*

The main concern with wider use of NT-proBNP in clinical medicine is the need for identifying therapies targeting elevated NP levels. [de Lemos-2, Everett-1] This concern has no implications for us.

There will always be pushback by some attending physicians when we use any new test, based upon their personal knowledge – or, more to the point, lack thereof – regarding that test and its implications.

Indeed, we continue to be challenged when we rate or decline applicants for elevated GGT!

Concern for such pushback should no longer influence our decision to embrace NT-proBNP as both a screening and reflexive test.

In addition to age/amount screening at ages 55 and older, it is clearly appropriate for underwriters to use NT-proBNP in all of the following reflexive contexts:

- Known or suspected circulatory disease at all adult ages
- Longstanding, inadequately controlled or complicated cases of hypertension, diabetes and hyperlipidemia
- Heart murmurs described as or consistent with cardiac pathology, with or without a clinical diagnosis
- Potentially insurable cases of congenital heart disease at all adult ages
- Significant abnormalities on ECGs, echocardiograms and other cardiac-related tests
- Stage 3a chronic kidney disease (defined as eGFR between 45 and 59) and other contexts consistent with early and potentially insurable CKD
- Ankle-brachial index (ABI) < 0.9 or > 1.3, whether or not a clinical diagnosis has been made
- Hepatitis C, rheumatoid arthritis and other disorders associated with an increased risk of premature CV disease or cardiac complications
- Potentially insurable cases of COPD
- Childhood cancer survivors managed with mediastinal radiation and/or cardiotoxic chemotherapy
- Breast cancer survivors treated with left breast irradiation

No doubt, additional appropriate contexts for NT-proBNP reflexive testing will be recognized based on clinical and epidemiological studies in the years ahead.

“Circulating levels of BNP/NT-proBNP are normally very low in healthy individuals.”

Han-Na Kim, MD, MPH, et al
Massachusetts General Hospital, Boston
Circulation
123(2011):2015

Life insurance applicants with low screening NT-proBNP should be seen in a favorable light and given credits to offset debits for at least some other CV risk factors.

Bottom Line: The evidence reviewed in this paper, together with that reported in two previous papers, as well as our industry experience to date, leads us to four conclusions:

- 1. NT-proBNP is the most efficient cardiovascular screening and reflexive test in the history of life insurance underwriting.**
- 2. NT-proBNP screening should be done at age 55 and over.**
- 3. NT-proBNP must inevitably replace screening with both resting and exercise electrocardiography.**
- 4. NT-proBNP should be widely used as a reflexive test in a growing range of circulatory and other contexts.**

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Hank has organized over 40 seminars for the Society of Actuaries. He has presented at both insurance medicine meetings and national conferences on clinical chemistry and forensic toxicology. He was also a panelist in a National Institutes of Health Consensus Conference on precursors to malignant melanoma.

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Persons interested in subscribing to **Hot Notes** or becoming a registered member of InsureIntell.com are invited to visit www.hankgeorgeinc.com for details.

Hank is a scheduled contributor to NAILBA

Perspectives magazine and *Best's Review*. His work has also appeared in many industry publications including *On the Risk*, *ALUCA Risk-e-Business*, *National Underwriter*, *Broker World*, *Journal of Insurance Medicine*, *LOMA Resource*, *LIMRA MarketFacts*, and *Contingencies*.

As an underwriting educator, Hank has written over 200 continuing education courses. Over 3,500 underwriters on 4 continents have participated in this program since its inception in 2003.

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