An International Consensus Statement
Regarding Amino-Terminal Pro-B-Type Natriuretic Peptide Testing: The
International NT-proBNP Consensus Panel

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Over the past several years, the broad clinical utility of testing for natriuretic peptides (NPs) has been increasingly recognized. These valuable biomarkers, including B-type NP (BNP) and the cosecreted amino-terminal pro-fragment proBNP (NT-proBNP), have surpassed the original expectation for use as diagnostic tests for heart failure (HF). NPs are useful as biomarkers of HF. However, they are now regarded as having potential utility in a wide range of diagnostic, prognostic, and possibly therapeutic situations in modern medicine. Although BNP was the first NP assay released, NT-proBNP assays subsequently became commercially available for clinical use, and the use of NT-proBNP has increased significantly worldwide. Furthermore, after publication of hundreds of laboratory and clinical studies supporting the use of NT-proBNP, the marker is now extensively incorporated into several clinical and laboratory consensus statements and position papers, giving it equal footing with BNP.

The field surrounding NP testing has moved rapidly, and, consequently, uncertainty about the understanding of the biology, laboratory aspects, and optimal clinical applications for BNP and NT-proBNP is inevitable. A consensus statement on BNP was recently published. However, given the unique biology of NT-proBNP, many of the statements within the BNP consensus document do not apply to NT-proBNP (a point acknowledged by the authors). The BNP consensus did not address NT-proBNP testing in any formal manner, and many hundreds of studies supporting the use of NT-proBNP have been published since the BNP consensus document was first generated.

With the rapid worldwide increase in testing for NT-proBNP, a formal up-to-date and unbiased consensus statement reviewing the current understanding of the biologic, analytic, and clinical applications of NT-proBNP is necessary. The articles contained within this supplement to The American Journal of Cardiology represent proceedings of a symposium at the American Heart Association Scientific Sessions, November 12–15, 2006, in Chicago Illinois. The lectures and consequent summaries by thought leaders from around the world in the field of cardiac biomarker testing address numerous issues regarding NT-proBNP. At the end of each article, key points are presented, along with recommendations for clinical application, as appropriate.

The members of the International NT-proBNP Consensus Panel thank the sponsors of the symposium whose support made this consensus document possible.

We extend our gratitude to the scientists, clinical researchers, and clinicians worldwide whose efforts generated the abundant data supporting the use of NT-proBNP on which this series of documents is based.
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Biology of the Natriuretic Peptides

Abelardo Martinez-Rumayor, MD, A. Mark Richards, MD, PhD, John C. Burnett, MD, and James L. Januzzi, Jr., MD

The natriuretic peptide (NP) family is believed to have evolved for the common homeostatic purpose of volume, osmosis, and pressure regulation of the circulatory system. More recently, evidence has been found that this family of cardiovascular NPs plays an autocrine and paracrine role in the control of myocardial structure and function.2,3 The known NP system in human and nonhuman vertebrates consists of at least 6 cardiovascular peptides, including A-type (ANP), B-type (BNP), C-type (CNP), D-type (DNP), and V-type (VNP), as well as a renal peptide urodilatin.4–8 In addition, there are at least 3 types of NP receptors, including NP receptor–A and NP receptor–B, the guanylyl cyclase–coupled receptors responsible for biologic effects; and NP receptor–C, the short cytoplasmic domain receptor responsible for peptide clearance and possibly regulation of cell proliferation.9–18

The endocrine component of cardiovascular NP biology includes ANP, BNP, DNP, and VNP. Although all may be found in cells other than cardiomyocytes, most of these NPs in humans are thought to be secreted primarily by the heart. In contrast, CNP, which is secreted by endothelial cells, appears to serve an endocrine and paracrine role in the brain and vasculature.19 Although each member of the NP family appears to exert vasodilator or venodilator effects and may induce diuresis and natriuresis, the relative balance of these effects varies somewhat from peptide to peptide.

The NP system seems to be phylogenetically preserved, and both components (endocrine and paracrine) have been identified in the heart and brain of a wide range of species, including teleost fish, amphibians, reptiles, birds, and selected species of mammals (human, cat, cattle, dog, mouse, rat, sheep, and swine).20–24 In the case of elasmobranchs (cartilaginous fish), only CNP has been identified in the brain and heart, where interestingly the same CNP prohormone (proCNP) appears to function as both a circulating hormone and paracrine factor.25 Across all species, CNP is the most structurally conserved member of the NP family.27 Studies have also found that tetrapods generally have 2 of the 3 cardiac subtypes (ANP, BNP, and CNP). Some teleosts lack BNP, but they are the only group with the unique peptide VNP (isolated from the cardiac ventricle) and CNP, whereas sharks and hagfish have only CNP. The realization that CNP was present in all groups led to efforts to determine whether CNP was the only NP in the more primitive vertebrate group cyclostomes (lamprey and hagfish) in order to elucidate the structural and functional evolution of NPs. It was not until recently that molecular phylogenetic analyses confirmed that the ancestral gene of the NP family is indeed CNP-4, which codes for the 4 types of CNP.28

From early and subsequent studies of NP phylogeny, it was inferred that the NP system evolved from sodium-extruding hormones in fishes into volume-depleting hormones that promote the excretion of sodium and water in tetrapods, both of which are regulated in the same direction.23,30 It is now recognized that the NP family seems to be more important for volume regulation in mammals, whereas in fish its main function is osmoregulation.27

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The B-Type Natriuretic Peptide Gene

The BNP gene has been assigned to chromosome 1 in humans and is organized in tandem with the ANP gene (approximately 8 kilobases upstream)\textsuperscript{31}; it is not known whether this close proximity allows coordinated regulation. The complete nucleotide sequence of BNP was elucidated in 1989,\textsuperscript{35} and the 5' flanking sequence has been found to be in the heart, lungs, kidneys, aorta, and adrenal glands in much smaller amounts compared to the heart.\textsuperscript{36}

All NP receptor types have been cloned in vertebrates, but only the 2 guanylyl cyclase–coupled NP receptors have been identified in mammals: NP receptor–A, which exhibits high affinity to ANP and BNP, and NP receptor–B, which is specific to CNP.\textsuperscript{31,32}

Downstream biologic effects of NPs are well known. In the case of BNP, these include vasodilation, natriuresis, and diuresis. BNP may also downregulate the renin–angiotensin–aldosterone system. In addition, BNP may have an antifibrotic effect on the heart muscle\textsuperscript{12,32,33} because myocardial fibrosis with abnormal remodeling in the setting of ventricular pressure overload is the phenotype of BNP knockout mice.\textsuperscript{32} Lastly, BNP also appears to possess proinflammatory properties.\textsuperscript{34}

Natriuretic Peptide Processing and Secretion

After translation of the BNP gene, an initial gene product is produced, pre-proBNP\textsubscript{1-108}. This peptide undergoes rapid removal of a 26–amino acid signal peptide, which results in the formation of a 108–amino acid prohormone, proBNP\textsubscript{1-108}.\textsuperscript{54} Subsequently, proBNP\textsubscript{108} is cleaved by proteolytic enzymes furin\textsuperscript{55} and corin\textsuperscript{56} to release 2 portions: the biologically inert 76–amino acid amino-terminal portion NT-proBNP\textsubscript{1-76} and the biologically active 32–amino acid molecule BNP\textsubscript{1-32}, which possesses a characteristic 17–amino acid ring formed by disulfide-linked cysteines essential for biologic activity.\textsuperscript{57}

Importantly, this overly simplistic paradigm for NP secretion has undergone a dramatic shift in recent years, with a better understanding of the true complexity of the biology of these important peptides. Indeed, early studies using radioimmunoassays to evaluate BNP in subjects with heart failure (HF) suggested the presence of both high- and low-molecular-weight forms of BNP, with high-molecular-weight BNP being the major component (mean ratio, 1.9:1).\textsuperscript{58} More recent studies have used Western blot analysis techniques to better characterize these immunoreactive BNP species in HF plasma and have confirmed that there are both low-molecular-weight (similar to BNP\textsubscript{1-32}) and higher-molecular-weight forms of BNP, which when deglycosylated,
were similar to recombinant proBNP1-108.59 These results were subsequently further confirmed in population testing, which demonstrated that a great percentage of circulating “NT-proBNP” or “BNP” is, in fact, proBNP1-10860 (Figure 1).

At present, it is hard to know exactly what forms of NP are present in circulation and whether the heterogeneity of forms is associated with variability in biologic effect. This uncertainty particularly focuses on BNP because it represents the biologically active portion of the molecule. Once in circulation, studies suggest that the BNP molecule is rapidly truncated to yield a number of fragments that dominate in proportion relative to mature BNP1-32. Indeed, Hawkridge et al61 suggested a complete absence of BNP 1-32 in patients with HF. Among the more important fragments of BNP that circulate is BNP 3-32, which results from the cleavage of BNP 1-32 by dipeptidyl peptidase–IV. Cleavage by dipeptidyl peptidase–IV does not change the resistance of human BNP to further degradation by human neutral endopeptidase.62 Moreover, a recent study has demonstrated that the peptidase meprin A, which is highly expressed in the kidney, also processes BNP1-32 to BNP7-32.63

There is mounting evidence that these different molecular forms of BNP have differential biologic activity in HF. A recent study sought to evaluate the ability of proBNP1-108, NT-proBNP1-76, and BNP3-32 to activate cyclic guanosine monophosphate (cGMP) in cultured cardiac fibroblasts and cardiomyocytes compared with the biologically active mature BNP3-32. Predictably, NT-proBNP1-76 had no biologic activity, and proBNP1-108 had significantly reduced cGMP activity in vitro: it was 6- to 8-fold less potent than BNP.64 Whereas in vitro BNP3-32 was similar to BNP1-32 in activating cGMP in fibroblasts and cardiomyocytes, studies have demonstrated that in vivo BNP3-32 has significantly reduced renal actions, probably because of the rapid degradation of BNP3-32.65

Because the amino-terminal region of NT-proBNP1-108 contains sequences permitting oligomerization, a trimer of

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**Table 1** Important regulators of the B-type natriuretic peptide (BNP) gene*  

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Potential Effectors</th>
<th>cis Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Adrenergic agonist</td>
<td>cAMP, Src, Rac, GSK3β, CaMKII, PI3K</td>
<td>GATA (−85), MCAT (−97 and −124)</td>
</tr>
<tr>
<td>Interleukin-1β</td>
<td>Ras, Rac, p38 MAPK, PKC</td>
<td>MCAT (−97)</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>Rac, Src</td>
<td>GATA; region between −1818 and −408; TRE at −1000</td>
</tr>
<tr>
<td>Stress</td>
<td>Activators of MKK6 and p38 MAPK</td>
<td>AP-1–like site at −111</td>
</tr>
<tr>
<td>Ischemic injury</td>
<td>Unknown</td>
<td>Region between −408 and +100</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Calcineurin</td>
<td>NF-AT at −927</td>
</tr>
<tr>
<td>Thyroid hormone (T3)</td>
<td>Thyroid receptor</td>
<td>TRE at −1000</td>
</tr>
<tr>
<td>Mechanical stretch</td>
<td>p38 MAPK</td>
<td>SSREs (−652 to −633 and −162)</td>
</tr>
</tbody>
</table>

AP-1 = activating protein–1; cAMP = cyclic adenosine monophosphate; CaMKII = calcium/calmodulin-dependent protein kinase-II; GSK3β = glycogen synthase kinase–3β; MAPK = mitogen activated protein kinase; MCAT = muscle-CAT binding site; MKK6 = mitogen-activated protein kinase kinase 6; NF-AT = nuclear factor of activated T cells; PI3K = phosphatidylinositol 3-kinase; PKC = protein kinase C; SSREs = shear stress response elements; TRE = TPA-response element.  

* The wide variety of factors with significant effects on BNP gene activity is reflected clinically in the broad array of disease states known to affect concentrations of BNP and N-terminal pro-BNP in patients.
NT-proBNP\textsubscript{1-76} has been described.\textsuperscript{66} Also, fragmentation of NT-proBNP\textsubscript{1-76} occurs because proteolysis can exist at both the carboxy- and amino-terminal ends of the molecule.\textsuperscript{67} Therefore, a number of molecules larger and smaller than NT-proBNP\textsubscript{1-76} are present in the circulation. Lastly, NT-proBNP is glycosylated to a variable degree.\textsuperscript{68}

The ramifications of the emerging understanding of novel NP biology are significant. Indeed, it is now known that currently available commercial assays for detection of NT-proBNP\textsubscript{1-76} or BNP\textsubscript{1-32} actually measure a mixture of each peptide; in the case of NT-proBNP, assays likely are detecting NT-proBNP\textsubscript{1-76} plus variable amounts of proBNP\textsubscript{1-108}. For BNP, conventional assays likely detect various degradation products of BNP\textsubscript{1-32}, including BNP\textsubscript{3-32}, in addition to intact proBNP\textsubscript{1-108}.\textsuperscript{59,64} Furthermore, it remains entirely unclear whether degradation or oligomerization of either BNP or NT-proBNP impairs the accuracy of the commercial assays for their detection. A high priority for future studies is the need to apply advanced state-of-the-art techniques to fully elucidate the molecular forms of BNP in the circulation.

It is also important to recognize marked reductions in—or near absence of—biologic activity in proBNP\textsubscript{1-108} relative to bioactive BNP; in a patient with HF, marked elevation measurements for BNP or NT-proBNP may not accurately indicate that the individual actually has a deficiency of the beneficial activity of bioactive BNP.

### Clearance of B-Type Natriuretic Peptides versus Amino-Terminal Pro–B-Type Natriuretic Peptides

After their release, BNP and NT-proBNP have differential modes of clearance. BNP is cleared by receptor-mediated binding and removal by the NP receptor–C, as well as through the activity of neutral endopeptidases in the bloodstream. In addition, it is cleared via passive excretion (or regional degradation through the activity of neutral endopeptidases) by organs with high rates of blood flow, including the kidneys.\textsuperscript{59,70} In contrast, NT-proBNP appears to lack active clearance mechanisms and is cleared by organ beds with large degrees of blood flow (muscle, liver, renal, etc.).

The relative contribution of the kidneys to the removal of NT-proBNP from the bloodstream remains extremely controversial. Although many suggest that NT-proBNP is cleared solely by the kidneys and is thus more dependent than BNP on renal function for its clearance, the results of carefully performed mechanistic studies suggest that the renal extraction ratios of both BNP and NT-proBNP are equivalent and are only about 15%–20%.\textsuperscript{71} A later study confirmed these results by evaluating the renal and peripheral extraction of NT-proBNP and BNP in patients with hypertension and cirrhosis versus control subjects by catheterization of the femoral artery and the femoral and renal veins. The investigators found that the renal extraction ratio of NT-proBNP (0.16) was not different from that of BNP (0.16). In contrast, the NT-proBNP extraction in the lower extremity was lower compared with BNP, suggesting active degradation of BNP in the periphery, explaining in part the higher concentrations of NT-proBNP seen in patients with normal plasma.\textsuperscript{72}

### Conclusions

**Key points—NP biology:**

- The NP system is highly preserved across species and has complex genetic regulation.
- After synthesis of an intracellular precursor proBNP\textsubscript{1-108}, variable amounts of BNP\textsubscript{1-32} and NT-proBNP\textsubscript{1-76} are released. A significant amount of uncleaved proBNP\textsubscript{1-108} is liberated into the bloodstream.
- After secretion, BNP\textsubscript{1-32} rapidly undergoes processing and degradation into several circulating forms, including BNP\textsubscript{3-32}.
- proBNP\textsubscript{1-108} and NT-proBNP\textsubscript{1-76} have absent or nearly absent biologic activity, and BNP\textsubscript{3-32} has less biologic activity than BNP\textsubscript{1-32}.
- Commercial assays detect a mixture of peptides; in the case of assays for NT-proBNP, it is likely that at least NT-proBNP\textsubscript{1-76} and proBNP\textsubscript{1-108} are detected.
- BNP is cleared by numerous mechanisms, including receptor clearance, neutral endopeptidase degradation, and passive removal by multiple organs. Numerous organ systems likely clear NT-proBNP in a passive fashion.
- Mechanistic studies demonstrate the kidneys clear NT-proBNP and BNP equally.

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44. He Q, LaPointe MC. Src and Rac mediate endothelin-1 and lysophosphatic acid stimulation of the human brain natriuretic peptide promoter. Hypertension 2001;37:478–484.


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**Amino-Terminal Pro–B-Type Natriuretic Peptide: Analytic Considerations**

Jordi Ordonez-Llanos, MD, PhD, a Paul O. Collinson, MD, b and Robert H. Christenson, PhD c, *

Amino-terminal pro–B-type natriuretic peptide (NT-proBNP) is a convenient molecule to work with in clinical laboratories, with preanalytic and analytic advantages, such as excellent stability at different temperatures, flexibility in sample type, and strong harmony across all commercially available NT-proBNP assays (including recently released point-of-care methods). Another major advantage of NT-proBNP assays is that they show excellent analytic precision. Reference values for NT-proBNP testing are strongly affected by the population tested. Among nondiseased populations, lower values are expected, whereas in diseased populations, such as in patients with acute dyspnea, higher reference values are more useful. Also, the biologic variability of NT-proBNP should be taken into account to evaluate the significance of any change in its values. When analyzed in patients with stable heart failure, biologic variability was 25%–40%. This article reviews the laboratory aspects of NT-proBNP testing from the perspective of the clinical laboratorian. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:9A–15A)

Natriuretic peptide (NP) measurements are valuable diagnostic and prognostic tools in cardiovascular medicine. For this reason, clinical and analytic guidelines have been developed, and laboratories are increasingly requested to perform B-type NP (BNP) and amino-terminal proBNP (NT-proBNP) measurements. The number of available assays for these markers continues to grow, and the laboratory medicine specialist is faced with a wide variety of options. The challenges are substantial in this setting. NPs and their molecular precursors and products constitute heterogeneous chemical entities in the circulation, and an accepted reference method for their measurement does not exist. Thus, the main goal for clinical laboratories must be to produce results that are independent of methodologies and instruments and are comparable to those produced in other laboratories. In addition, because of the proliferation of methods and instruments for BNP and NT-proBNP measurements, the clinical laboratory community must produce information on all preanalytic, analytic, and postanalytic issues that would facilitate the use of such measurements by the clinical community. The aim of this article is to review the most important factors affecting NT-proBNP measurements and compare NT-proBNP characteristics with those of BNP, when appropriate.

**Preanalytic Issues**

The control of any cause of preanalytic variation in biologic measurements is a matter of major importance because the preanalytic phase of testing is responsible for about 68% of laboratory errors, and preanalytic imprecision is assumed to be 0 (or near to 0).

Accordingly, a good understanding of the potential impact of the preanalytic phase on BNP and NT-proBNP measurement is important. Minimizing the potential for preanalytic variability should be an important consideration when selecting an assay. NT-proBNP appears to have few preanalytic issues—fewer than those seen with BNP.

NT-proBNP can be measured in different specimens. Serum and heparin plasma produce interchangeable results and are the recommended specimen types for measurement of NT-proBNP. Testing from ethylenediaminetetraacetic acid (EDTA) plasma produces predictably lower NT-proBNP values (10%–13%, depending on the method) than those observed in serum or heparin plasma. NT-proBNP fragmentation was described in blood and appears to be more intense in serum than in EDTA plasma. In this regard, the use of EDTA (or antiprotease agents, such as aprotinin) may be advisable if in vitro NT-proBNP fragmentation is described. However, until the in vitro issue is elucidated and the relevance of such fragments to NT-proBNP measurement and its clinical utility is unequivocally demonstrated,
serum or heparin plasma remain the specimens of choice for NT-proBNP measurement. Citrate plasma and oxalate plasma are not recommended for NT-proBNP analysis. Heparinized whole blood can be used in point-of-care systems whose performance for NT-proBNP measurement have recently been reported.5,6

BNP measurement requires EDTA as anticoagulant, and samples must not be collected in nonsiliconized glass tubes because blood kallikreins become activated by glass contact and rapidly degrade BNP. On the other hand, blood for NT-proBNP analysis can be drawn into either glass or plastic tubes, without alteration in the stability.

The conditions advisable in subjects before and during blood sampling for BNP and NT-proBNP measurements to minimize preanalytic variation are not fully established. Physical exercise before sampling for NPs may have an effect on both BNP and NT-proBNP concentrations. However, little is known about the effect of nonprotocolized physical exercise practice as a preanalytic source of variation for measurements both in healthy subjects and patients with heart failure (HF). It is known that exercise done at 50% of the maximal heart rate increases BNP and NT-proBNP concentrations over preexercise levels in patients with HF; no similar increase was observed in reference individuals for the same or an even higher exercise load.7 A different point is the effect of strenuous exercise in endurance-trained subjects; most of these subjects presented with values that were higher than reference values after competitive events,8 although variations of reference values in samples obtained during rest or noncompetitive periods have not been consistently reported.

There is not a significant effect of posture on NT-proBNP values. Samples obtained after sitting, standing, or after walking show differences <7% compared with samples obtained in the supine position.9 Accordingly, posture does not contribute substantially to differences between ambulatory and hospitalized patients. However, when patients were sampled without previous rest or after 30 minutes of standing and walking, BNP levels increased by 15–20%.10 Therefore, it is advisable for an individual to be sampled for NT-proBNP after lying in bed or sitting for ≥10–15 minutes. As for many other biochemical variables, the time of tourniquet use should be as short as possible.

A significant circadian variation is not consistently documented for NT-proBNP, as opposed to variations found in other neuroendocrine hormones and co-metabolites,9,11 although daily concentrations can vary by approximately 20%. A small but significant circadian rhythm was reported for BNP values in patients with HF.11

In terms of effects of storage on NT-proBNP, serum or plasma NT-proBNP concentrations are stable under a variety of storage conditions ranging from 7 days at room temperature, or 10 days at 4°C, to several months at –20°C or a lower temperature9,12; 5 freeze-thaw cycles do not significantly modify NT-proBNP concentrations.9,13 Stability at room temperature facilitates the handling of speci-}{mens for NT-proBNP measurement in usually busy clinical laboratories; in this regard, NT-proBNP is a more convenient molecule to work with than BNP, where stability is dependent on the specific assay.14 In addition, BNP is largely unstable at room temperature and even after freezing (Figure 1).14,15

BNP and NT-proBNP are detectable in urine, and urine measurements have been advocated as a convenient alternative to serum or plasma, mainly when BNP measurements are used for population screening purposes. The correlation of BNP concentrations between plasma and urine is weak in individuals with left ventricular systolic dysfunction (LVSD) and not significant in subjects without LVSD. However, in community screening, NT-proBNP measured in urine has been shown to have higher sensitivity for detecting LVSD than that measured in plasma.16 However, these results should be interpreted with caution because of the possible matrix effects caused by the use of a low protein–containing sample, such as urine in assays designed for serum/plasma.

Analytic Issues

Several currently marketed NT-proBNP assays are fully automated. Total imprecision of automated methods in multicenter studies is <6.5%, and it is even lower when studies are conducted in single laboratories. These values fulfill the imprecision criteria (ie, imprecision <15% for values within the reference interval and under 10% when values are used for monitoring trends of the marker2,17) recommended for NP measurements by guidelines of the Committee on Standardization of Markers of Cardiac Damage (International Federation of Clinical Chemistry).

Given the high biologic variability of NPs, the other recommended criterion for analytic imprecision (ie, half of the biologic variance) is largely satisfied by all available methods. A point of major interest for any biologic measurement is the imprecision of its measurement at values detected in the nondiseased population (ie, at the range of values where cutoff points will be found). Imprecision profile studies have shown that with different instruments and methods, values as low as 10–20 ng/L can be measured with a total analytic imprecision <15%, and that the imprecision is much lower around the cutoff points.12,18 Therefore, analytic imprecision at NT-proBNP values that may be appropriate for HF screening will be compliant with these specifications. Further, values up to 35,000 ng/L can be measured without previous dilution of the sample given the linearity of the methods.

Which molecules among the different BNP molecules found in the circulation are detected by current assays is a point of major interest for laboratory professionals and clinicians alike. The understanding of which NP forms are native to serum or plasma, mainly when BNP measurements are used for population screening purposes. The correlation of BNP concentrations between plasma and urine is weak in individuals with left ventricular systolic dysfunction (LVSD) and not significant in subjects without LVSD. However, in community screening, NT-proBNP measured in urine has been shown to have higher sensitivity for detecting LVSD than that measured in plasma.16 However, these results should be interpreted with caution because of the possible matrix effects caused by the use of a low protein-containing sample, such as urine in assays designed for serum/plasma.

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BNP1-32 may be absent in patients with severe HF, yet commercial assays for "BNP" still detected the presence of BNP1-32 in these subjects. A further proteolyzed form of BNP (BNP 3-32) has also been identified in circulation. Because the amino-terminal region of proBNP1-108 contains sequences permitting oligomerization, a trimer of NT-proBNP has been described. As already mentioned, fragmentation of NT-proBNP occurs because proteolysis can exist at both the carboxy- and amino-terminal ends of the molecule. Therefore, a number of molecules larger and...
smaller than NT-proBNP$_{1-76}$ are present in the circulation; both oligomerization and fragmentation could expose or hide epitopes recognized by the antibodies used in the assays. Finally, intact proBNP$_{1-108}$ has also been found in the circulation.\textsuperscript{22} It is important to note that these metabolic issues do not mitigate the established link between BNP and NT-proBNP measurements and diagnosis and outcomes, using current assays.

Currently available NT-proBNP assays are a family of methods based on the original assay of Roche Diagnostics, Basel, Switzerland. They use the same pair of polyclonal antibodies (ie, a capture antibody directed against the amino-terminal part of the NT-proBNP molecule [amino acids 1–21] and against the central part of the NT-proBNP molecule [amino acids 39–50]). By using these antibodies, the assays should recognize not only NT-proBNP$_{1-76}$ but also proBNP$_{108}$ and possibly fragmented NT-proBNP forms because most of the smaller forms are detected by antibodies recognizing the amino acid sequence 10–29 of the NT-proBNP.\textsuperscript{4,23} Currently, a new version of the NT-proBNP assay using a pair of monoclonal antibodies is under a multicenter evaluation.

There are 3 point-of-care devices for NT-proBNP (Cardiac reader, Roche Diagnostics, Basel, Switzerland; RAMP, Response Biomedical Corporation, Vancouver, British Columbia, Canada; Stratus CS, currently Siemens Medical Solutions, Erlangen, Germany) available in Europe and the United States. The point-of-care devices offer the option of rapid turnaround times and have demonstrated very strong harmony with automated versions of the assays, as these methods are based on the original Roche Diagnostics antisera for NT-proBNP. Independent evaluations of the available assays based on the original Roche Diagnostics assay showed a maximal bias among methods of approximately 20\% (Figure 2)\textsuperscript{18}; bias would be mainly because of the adaptation of the method to different analyzers. On this basis, harmonization of results obtained in different laboratories by different assays but using the same antibodies and calibrator would be easy, and the possibility of a different impact of NT-proBNP heterogeneity on the assays would be minimized.

Unfortunately, this is not the case for BNP because currently marketed assays are based on different licensors using antibodies directed against different parts of the original BNP molecule and also on different calibrators. Heterogeneity of the circulating NP forms might also be a further source of discrepancy among methods.\textsuperscript{24} For this reason, BNP results of the same sample can vary $>$40\% among the different methods.\textsuperscript{24} According to all these data, a more difficult process for standardizing BNP (rather than NT-proBNP) measurements can be anticipated.

Finally, although both peptides are secreted in an equimolecular ratio, they have very different half-lives. For this and other reasons, including the numerous analytic issues described above, the comparison among circulating concentrations of NT-proBNP and BNP are not predictable, and the measurements cannot be used interchangeably.

Postanalytic Issues

References values and healthy patients: When considering the application of cut points, it is always necessary to acknowledge the population to which they apply.\textsuperscript{25} thus, cut points derived for a healthy population might not necessarily apply to an acutely ill population. Accordingly, covariates affecting NT-proBNP concentrations may also differ among various populations. As will be discussed further in this article, important covariates to consider in apparently healthy patients include sex (Table 1)\textsuperscript{26,27}; healthy women typically show NT-proBNP concentrations 1.4 times higher than men.\textsuperscript{26,28} It should be noted that few data are available on healthy subjects in whom cardiac dysfunction was ruled out by echocardiography.\textsuperscript{18} However, in the context of acute dyspnea, it is unnecessary to adjust cut points based on sex.\textsuperscript{29} Age is another powerful predictor of increased NT-proBNP levels in reference subjects. Both in men and women, subjects aged $>65$ years have a median NT-proBNP value 1.5 times higher than those aged $<65$ years.\textsuperscript{26} When NT-proBNP is used as a clinical tool for diagnosis of acute decompensated HF, age adjustment is appropriate, as discussed in the HF diagnosis article in this supplement.\textsuperscript{30} With regard to ethnicity, in a population with suspected acute coronary syndromes, slightly higher NT-proBNP values were described in whites than in blacks;\textsuperscript{31} similar findings were observed in whites and blacks with acute dyspnea.\textsuperscript{29} In both cases, when analyzed by multivariate analysis, differences appear to be more related to demographic or physiologic variables (such as age or renal function) than to ethnicity.\textsuperscript{29}

Biologic variation: Serial biomarker measurements are frequently used for the monitoring of disease presence and severity. Importantly, whether a difference among serial measurements is significant should be interpreted within the context of the total biologic variability (ie, the sum of its analytic and normal physiologic variability).

Individual variation is the highest contributor to biologic variation; it can be measured in reference or diseased individuals from serial measurements of the variable. As mentioned previously, preanalytic variation is also a component of the biologic variability, although given the difficulty in controlling all causes contributing to this variability, it is usually assumed to be 0\% (or near 0\%) for biologic variability calculation. This assumption stresses the need for accurate control of preanalytic sources of variation. Once the biologic variation is known, critical differences (also called reference change values) to be considered as significant among consecutive measurements can be calculated.

Initial data on NT-proBNP in patients with stable HF suggested the biologic variability to be as high as 98\%\textsuperscript{11,52}; the corresponding rates for BNP were 132\% and 113\%, respectively. These rather large changes required to definitively conclude a change in disease severity have been challenged. Although potentially impor-
tant for monitoring nondiseased individuals, serial measurements of NPs are mainly of interest for monitoring patients with HF. To obtain the most accurate estimate of the minimum reference change values indicating significant variation in patient status, biologic variation must be estimated in patients with HF in their most stable condition. In a group of patients with well-controlled HF, much lower 1-week reference change values of 23% for NT-proBNP and 43% for BNP have been reported; again, NT-proBNP emerged with lower individual variation than BNP.

Interestingly, the lowest differences in biologic variability in NT-proBNP concentrations were observed for NT-proBNP values $>1,300$ ng/L. 

Figure 2. Amino-terminal pro–B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) measurement. Percent differences of currently marketed assays versus (A) Roche Elecsys NT-proBNP, Roche Diagnostics, Basel, Switzerland, and (B) Biosite Triage BNP Biosite Inc., San Diego, California USA, methods at cutoff values recommended by clinical trials.
Reference values for amino-terminal pro–B-type natriuretic peptides (NT-proBNP) in healthy subjects aged 40–76 years: effect of age and sex

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<th>Age (yrs)</th>
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<th>95% CI (ng/mL)</th>
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Adapted from Clin Biochem$^{26}$ and Eur Heart J.$^{27}$

Conclusions

Key points—analytic considerations:

- NT-proBNP is a very convenient molecule to work with in clinical laboratories, given its stability at different temperatures and the flexibility in specimen type.
- Many forms of NT-proBNP and related peptides exist in the circulation; however, the potential effect of molecular heterogeneity on NT-proBNP assays is diminished because most assays use the same antibodies against the NT-proBNP molecule.
- Given the equivalence of antibodies and calibrators of most NT-proBNP assays, harmony of results is good, and measurement discrepancies among the different assays are minimal.
- Point-of-care NT-proBNP assays are now available; these are harmonized with values from automated NT-proBNP assay results.
- The analytic imprecision of NT-proBNP automated assays fulfills current recommendations and is adequate for diagnosis of decompensated HF in symptomatic patients.
- Reference NT-proBNP values are typically higher in women, whereas they increase with age in both sexes. Only age, not sex, should be considered when evaluating NT-proBNP concentrations in patients with disease.
- Biologic variability of NT-proBNP should be taken into account to evaluate the significance of any change in its values. When analyzed in patients with stable HF, biologic variability is 25%–40%.

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Amino-Terminal Pro–B-Type Natriuretic Peptides: Testing in General Populations

James A. de Lemos, MD, a,* and Per Hildebrandt, MD b

Screening of general populations with amino-terminal pro–B-type natriuretic peptides (NT-proBNP) holds promise for the detection of significant underlying cardiac structural and functional abnormalities, as well as for the early detection of the propensity to develop future cardiovascular events. In comparative studies to date, NT-proBNP performs at least as well as BNP in the detection of heart disease and prognostication in the general population. In some studies and subgroups, NT-proBNP appears to outperform BNP in population screening. More needs to be learned about noncardiac sources of NT-proBNP variation in “apparently well” populations. Better understanding of these factors may allow optimization of thresholds for screening of apparently well patients and concomitant delineation of patient populations in whom NT-proBNP screening is less appropriate. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:16A–20A)

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. Identification of subjects with asymptomatic cardiac structural and functional abnormalities, including left ventricular systolic dysfunction (LVSD) and left ventricular hypertrophy (LVH), may allow preventive therapies to be initiated in the preclinical phase of disease, delaying or preventing the progression to heart failure (HF).1,2 Moreover, recent data suggest that certain biomarkers, including NT-proBNP, may also identify subjects without evident cardiac abnormalities who are at increased risk for cardiovascular morbidity and mortality.3

Accurate screening for subclinical disease requires clear delineation of the normal range for a bioassay. In addition, important cardiac and noncardiac sources of variation in the population must be defined to maximize the utility of a biomarker for screening.

Normal Range Studies of Amino-Terminal Pro–B-Type Natriuretic Peptides

Galasko and colleagues4 reported data for the expected normal values of NT-proBNP. Of 734 subjects ≥45 years of age in the general population, only those subjects without a history of ischemic heart disease, peripheral arterial disease, stroke, hypertension, diabetes mellitus, HF, or loop diuretic use were included. Other requirements included blood pressure <160/90 mm Hg, estimated glomerular filtration rate (GFR) ≥60 mL/min, and no significant abnormalities on echocardiography.4 The normal range data (n = 397) are shown in Table 1. These data are similar to those from Olmsted County, Minnesota5 and Glostrup, Denmark.6

Major Cardiac and Noncardiac Sources of Variation in the Population

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. Importantly, however, several noncardiac factors have important effects on circulating plasma levels of NT-proBNP including age, sex, body composition, and renal function. In asymptomatic subjects, the contribution of these noncardiac factors to NT-proBNP variation can be as strong as the contribution of the cardiac factors. Some of these factors are interrelated. For example, the well-described increase in NT-proBNP with aging may be, in part, owing to the association between older age and reduced GFR, as well as age-related changes in cardiac diastolic function.

BNP levels are lower in obese than in nonobese subjects,7,8 a paradoxical observation that had previously been explained by the presence of NP clearance receptors on adipocytes. However, several studies recently have reported the same association for NT-proBNP, which does not bind the clearance receptor.9–11 Thus, body composition must influence NP synthesis and release rather than clearance.

Moreover, in the Dallas Heart Study, where body composition was assessed using dual energy x-ray absorptiometry,
the lean component of body mass completely explained the inverse association between body mass and NT-proBNP levels. No association was seen between fat mass and NT-proBNP after accounting for lean mass (Table 2).

Healthy women have significantly higher NT-proBNP levels than healthy men. This difference was thought to be mediated by estrogen, a hypothesis supported by the observation that women taking supplemental estrogens have slightly higher BNP levels than those not taking hormones. However, recent evidence suggests that androgens rather than estrogens may mediate the sex-related differences in NP levels. In a population-based study of relatively young women, no association was observed between estrogen status and NT-proBNP levels, whereas testosterone remained inversely associated with NT-proBNP levels. These findings suggest that androgens may mediate the association between a higher body mass index and lower NT-proBNP and BNP levels.

Renal function has an important influence on circulating concentrations of both NT-proBNP and BNP. Within the normal range of GFR, this effect is similar between NT-proBNP and BNP, but at the lowest levels of GFR (e.g., <30 mL/min per 1.73 m²) the effect appears to be slightly steeper for NT-proBNP. The relation between renal function and NPs is by no means complex, as patients with worsening degrees of renal failure clearly have parallel increases in structural heart disease, likely detected by NPs.

### Screening for Asymptomatic Left Ventricular Systolic Dysfunction and Left Ventricular Hypertrophy

Building on correlations between BNP and LVEF, initial studies evaluating BNP as a screening test in the general population focused on identification of LVSD, and to a lesser extent, LVH. These studies generally reported only modest discriminative ability, as assessed using the area under the curve (AUC).
under the receiver operating characteristic curve.\textsuperscript{15,16} It is not surprising that the operating characteristics were only modest because in asymptomatic subjects, the signal-to-noise ratio for NT-proBNP and BNP is considerably lower than in symptomatic patients. In addition, there is considerable overlap in NP levels between those with asymptomatic LVSD and LVH and those with normal cardiac structure and function.\textsuperscript{5,15–19}

The operating characteristics of NT-proBNP and BNP were directly compared for detecting LVSD in the Olmsted County, Minnesota, population.\textsuperscript{5} Both NPs performed better for identifying severe LVSD (LVEF $\leq 0.40$) than modest LVSD (LVEF $\leq 0.50$). NT-proBNP performed at least as well as BNP in the overall population. Among men, NT-proBNP discriminated better than BNP, but among women, the 2 tests performed similarly.\textsuperscript{5} It should be noted that the operating characteristics for NPs are considerably worse in women than in men, probably because the higher normal range in women overlaps with the low-level elevation typically seen with subclinical cardiac structural and functional abnormalities.

Recently, other investigators expanded the use of NT-proBNP beyond screening for only LVSD, appreciating that NT-proBNP levels may become elevated because of a large array of different pathologic cardiac conditions, including LVSD, LVH with or without diastolic dysfunction, valvular heart disease, atrial fibrillation, and pulmonary hypertension. The concept of using NT-proBNP as a nonspecific tool to screen for significant subclinical heart disease was highlighted in the study by Galasko et al.\textsuperscript{4} When the full spectrum of cardiac abnormalities was included, NT-proBNP levels at the 97.5th percentile value for age and sex provided a 99% negative predictive value and a 56% positive predictive value. Moreover, 95% of the subjects with NT-proBNP levels $>4$ times above the upper limit of normal had $\geq 1$ significant cardiovascular abnormality (Figure 1).\textsuperscript{4}

**Predicting Events in the General Population**

Several studies have moved beyond using NPs as a surrogate for echocardiographic abnormalities and have investigated their value as screening tools for mortality and cardiovascular events in the general population. Wang et al\textsuperscript{20} reported powerful independent associations among BNP and death and cardiovascular events in the Framingham Offspring Study. This finding was of particular interest in light of the previous report of only modest utility of BNP testing to screen for LVSD and LVH in this same cohort.\textsuperscript{15} Recently, data have also begun to emerge with regard to NT-proBNP testing for risk prediction in the population. In a population-based prospective study of individuals aged 50–89 years, NT-proBNP, C-reactive protein, and urinary albumin/creatinine measurements were performed in 626 participants and correlated with events through 5 years of follow-up. After adjustment for cardiovascular risk factors and serum creatinine, NT-proBNP levels $>80$th percentile were associated with an approximate 2-fold increase in the risk for mortality and a 3.24-fold increased risk for first major cardiovascular events. Of particular importance, the association with mortality persisted after further adjustment for LVSD. The prognostic information provided by NT-
proBNP was greater than that provided by high-sensitivity C-reactive protein.\(^3\)

In 2,656 persons from the Glostrup population studied observed for 9.4 years, serum NT-proBNP and urinary albumin/creatinine, but not high-sensitivity C-reactive protein, predicted cardiovascular death in an additive fashion after adjustment for established cardiovascular risk factors.\(^21\)

In the Olmsted County population of 1,991 subjects without HF and with complete clinical and echocardiographic data, NT-proBNP measurements using the Roche NT-proBNP assay (Roche Diagnostics, Indianapolis, IN) were directly compared with measurements of BNP by 2 different assays (Biosite TRIAGE, San Diego, CA; and Shionogi Co. Ltd., Tokyo, Japan). Although all 3 assays predicted mortality through 5.6 years of follow-up, only the NT-proBNP and Biosite assays predicted mortality after adjustment for traditional risk factors and echocardiographic abnormalities. Moreover, NT-proBNP testing improved the prognostic power of multivariable models that included clinical variables and the results of the Shionogi and Biosite BNP assays. However, these BNP assays did not improve the power of similar models that contained NT-proBNP.\(^22\) These results suggest superiority of NT-proBNP over commercially available BNP assays for prediction of death in general populations.

**Conclusions**

NT-proBNP holds promise as a tool to screen the general population both for prevalence of a broad array of significant underlying cardiac structural and functional abnormalities as well as for the future development of cardiovascular events, including death, HF, and possibly stroke and MI. NT-proBNP may prove to be particularly useful in at-risk populations, such as patients with diabetes, who have not yet developed evident heart disease. In comparative studies to date, NT-proBNP performs at least as well as BNP, and in some studies and subgroups, it appears to outperform BNP for population screening.

Much remains to be learned before routine screening of the population can be recommended. First, more needs to be known about noncardiac sources of variation. Better understanding of these factors may allow optimization of thresholds and delineation of patient populations in whom NT-proBNP screening is less appropriate.

**Key points—NT-proBNP in general population-based testing:**

- NT-proBNP holds promise as a tool to screen the general population both for prevalence of a broad array of significant underlying cardiac structural and functional abnormalities as well as for the future development of cardiovascular events, including death, HF, and possibly stroke and MI.
- In comparative studies to date, NT-proBNP performs at least as well as BNP, and in some studies and subgroups, it appears to outperform BNP for population screening.
- More needs to be learned about noncardiac sources of variation. Better understanding of these factors may allow optimization of thresholds and delineation of patient populations in whom NT-proBNP screening is less appropriate.
- There are not enough data to recommend routine measurement of NT-proBNP for evaluation of apparently well patients, but with clarity forming around the actionable information yielded by an elevated NT-proBNP result, routine screening may be in the near future.

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Amino-Terminal Pro–B-Type Natriuretic Peptide Testing in Patients with Diabetes Mellitus and with Systemic Hypertension

Per Hildebrandt, MD, a and A. Mark Richards, MD, PhD b,*

Although the current value of amino-terminal pro–B-type natriuretic peptides (NT-proBNP) to generally screen populations of “apparently well patients” remains promising but still undefined, the use of NT-proBNP to screen patients at high risk for heart disease (such as elderly patients, or patients with diabetes mellitus, hypertension, or known coronary artery disease) appears logical and is supported by data. NT-proBNP has strong prognostic value in such at-risk patients. However, the exact implications for clinical management after detection of an elevated NT-proBNP value should be driven by clinical judgment. At present, data suggest that when an elevated NT-proBNP is detected in an at-risk patient, it is a high-risk finding. In this context, consideration for a more in-depth cardiovascular workup, as well as initiation or intensification of medical therapies with proven benefits might be indicated. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:21A–24A)

As outlined in another article in this supplement, BNP and the co-secreted peptide amino-terminal pro–B-type natriuretic peptide (NT-proBNP) are useful for evaluation of the symptomatic community-based patient. In addition, natriuretic peptides (NPs) are powerful markers for risk of death and cardiovascular complications in the general population and may be useful for detection of asymptomatic left ventricular systolic dysfunction (LVSD) and symptomatic heart failure (HF) in the general population.

Despite the proven value of NPs in this context, consensus on the application of NP testing in the outpatient setting—particularly for those without symptoms referable to HF—is lacking. This is because there are many patients whose pretest probability for detection of significant underlying structural heart disease is lacking, or in whom the pretest risk for adverse cardiovascular events is so low as to influence the likelihood for a “true-positive” result when screened with a diagnostic study.

Illustrating this point are the results from several studies on NP-based screening for asymptomatic LVSD in unselected populations, where the sensitivity of NT-proBNP is balanced by the relatively low prevalence of the condition of interest (ie, a left ventricular ejection fraction [LVEF] <0.40) within such general population samples. Using Framingham substudy data, the cost-effectiveness of peptide-based screening (of men aged 60 years) has been debated when the prevalence of a significantly reduced LVEF exceeds 1% of the population under scrutiny. It is likely that the higher prevalence of LVSD in high-risk patients (eg, elderly patients, or patients with preexisting diabetes mellitus, hypertension, or ischemic heart disease) will increase the cost-effectiveness to a degree that warrants the use of screening in these groups, but further studies evaluating such targeted application of BNP are required.

Indeed, pretest probability is among the most important variables to consider when applying any predictive test in medicine. Accordingly, when using a screening tool (such as NT-proBNP) that may be prognostically valuable, selection of high-risk populations may specifically sharpen the value of the biomarker considerably.

Patients with Diabetes Mellitus

Screening for LVSD: Identification of both frank HF and LVSD is crucial because prognosis without treatment is very severe, whereas modern surveillance coupled with the introduction of proven pharmacologic and mechanical treatments can markedly reduce morbidity and mortality.

Known HF is more prevalent in patients with diabetes, and it typically manifests earlier in these patients as well. Among patients aged <75 years, there is a 3-fold increase in the prevalence of HF in patients with diabetes versus those without diabetes.

Furthermore, asymptomatic LVSD (or LVSD with subtle or unrecognized symptoms) is also substantially more prevalent in patients with diabetes. In population studies, NP levels are generally higher in patients with diabetes versus those without diabetes. Epsteyn et al screened symptomatic and asymptomatic patients with diabetes in an outpa-
tient clinic setting. Patients with abnormal systolic and/or diastolic function on echocardiography had significantly higher BNP levels than those with normal echocardiographic findings. The difference, which is most clear-cut in the presence of symptoms, was also highly significant in asymptomatic patients. This was supported by mortality data.10

Prognostic value: Several studies show a very strong prognostic value of NT-proBNP in patients with type 1 and type 2 diabetes.11,12 Even among patients with diabetes with micro- or macroalbuminuria, the strong prognostic value is preserved and is supplementary to the micro- or macroalbuminuria. For example, in a cohort of patients with diabetes under long-term follow-up study, the 9-year mortality rate in patients with macroalbuminuria and NT-proBNP above the median, macroalbuminuria and NT-proBNP below the median, and patients without albuminuria was 40%, 12%, and 7%, respectively.11 In patients with microalbuminuria, a steeper increase in NT-proBNP is seen over time in parallel with a more adverse prognosis than is seen in patients with albuminuria.12

Patients with Arterial Hypertension

Screening for asymptomatic LVSD and left ventricular hypertrophy in patients with arterial hypertension: In population studies,8 the NP levels are generally higher in patients with hypertension. Levels of NT-proBNP are related to both clinic and 24-hour ambulatory blood pressures.13 Furthermore, NT-proBNP is related to left ventricular mass measured by magnetic resonance imaging,14 although the elevation in NT-proBNP with left ventricular hypertrophy (LVH) is generally less pronounced than in patients with significant LVSD. The value of general community screening with BNP for LVH is modest and cannot be recommended.15 There are no studies of the utility of BNP or NT-proBNP for detection of LVSD conducted solely within hypertensive populations, and although there is a sound rationale behind such an approach, further prospective observational data are required.

Prognostic value of NT-proBNP in patients with arterial hypertension: NT-proBNP is a strong predictor for both mortality and morbidity in patients with hypertension. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study recruited high-risk patients with hypertension and electrocardiographic LVH.16 NT-proBNP testing markedly improved risk stratification when added to the presence or absence of a history of cardiovascular disease (CVD) (Figure 1), implying an incremental usefulness for risk stratification as the medical complexity of the patient increased.

Screening High-Risk Patients

There have been discussions on the use of biochemical markers, especially NPs, for identifying not only established asymptomatic LVSD but also patients at risk for developing HF (ie, pre-HF or American Heart Association [AHA] stage A HF) in the community. The detection of asymptomatic LVSD would have clinical implications because treatment with angiotensin-converting enzyme inhibitors would be indicated.17 More recently, data from the large Heart Outcomes Prevention Evaluation (HOPE) study18 and the Heart Protection Study (HPS)19 involving high-risk patients primarily with established ischemic heart disease have been published. In these, NT-proBNP was predictive of cardiovascular events and highly predictive for the development of HF. The highest NT-proBNP quintile in the HPS had an

Figure 1. Association between amino-terminal pro–B-type natriuretic peptide (NT-proBNP) values, baseline risk, and a composite of cardiovascular (CV) disease, nonfatal stroke, and nonfatal myocardial infarction (light gray), as well as CV deaths (dark gray) in patients with hypertension. *History of ischemic heart disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, or heart failure.
adjusted relative risk for HF hospitalization or death that was 9 times greater than the lowest quintile.

**Screening for pre-HF:** Currently, stage A HF (ie, pre-HF) is appropriately addressed by managing risk factors (eg, hypertension, diabetes, and known coronary artery disease [CAD] or other arterial disease) according to current guidelines. There is no evidence that further adjustment of treatment in such patients based on BNP levels will offer benefit, although data from HOPE and the HPS suggest this approach may warrant prospective trials.

Importantly, at an earlier stage of risk, BNP or NT-proBNP testing may be unhelpful. Olsen et al have reported NT-proBNP levels in patients with metabolic cardiovascular risk factors and the metabolic syndrome. In 2,656 people aged 41, 51, 61, or 71 years who were randomly selected from the general population, a subset of 2,070 patients who had no history of cerebrovascular or other cardiovascular events and who were not under treatment for CVD or diabetes and were not taking lipid-related drugs underwent standardized assessment. As expected, plasma NT-proBNP was significantly, independently, and directly related to sex, age, and pulse pressure. However, levels were also independently, but inversely, related to body mass index, plasma insulin, plasma glucose, and triglycerides. Hence, overall, the metabolic syndrome was associated with lower levels of NT-proBNP for those with versus those without metabolic syndrome (35 ng/L vs 48 ng/L; p <0.001).

**Conclusions**

**Key points—NT-proBNP testing/screening in high-risk populations:**

- Whereas use of NT-proBNP to generally screen populations of apparently well patients is of debatable value, use of NT-proBNP to screen patients at high risk for heart disease (eg, patients aged >60 years, or patients with diabetes, hypertension, or known CAD) holds great promise.

- Although NT-proBNP has strong prognostic value in patients with diabetes, hypertension, and pre-HF, the exact implications for clinical management after detection of an elevated NT-proBNP value remain undefined. If an elevated NT-proBNP is detected in such at-risk populations, a cardiovascular workup, with therapeutic intervention as appropriate for the cause of the NT-proBNP elevation is recommended.

**Author Disclosures**

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**Per Hildebrandt, MD,** reports receiving significant funds in the form of research support, speaker honoraria, and consulting fees from Roche Diagnostics.

**A. Mark Richards, MD, PhD,** reports receiving significant funds in the form of research support, speaker honoraria, and consulting fees from Roche Diagnostics.

5. Galasko GI, Barnes SC, Collinson P, Lahiri A, Senior R. What is the most cost-effective strategy to screen for left ventricular systolic dysfunction: natriuretic peptides, the electrocardiogram, hand-held echocardiography, traditional echocardiography, or their combination? *Eur Heart J* 2006;27:193–200.


Amino-Terminal Pro–B-Type Natriuretic Peptide Testing to Assist the Diagnostic Evaluation of Heart Failure in Symptomatic Primary Care Patients

Per Hildebrandt, MD, a, * and Paul O. Collinson MD b

When used for the evaluation of symptomatic patients in general practice, amino-terminal pro–B-type natriuretic peptide (NT-proBNP) testing is highly sensitive, with an excellent negative predictive value for cost-effective exclusion of the diagnosis of heart failure (HF). Importantly (similar to other NP assays), lower values for NT-proBNP are expected among patients with HF in the primary care setting compared with patients with acute dyspnea. Among primary care patients with dyspnea, a noncardiac source of dyspnea is most likely in patients with findings below the recommended age-stratified NT-proBNP cut points. Conversely, an NT-proBNP result above the age-stratified primary care cut points does not absolutely indicate the presence of HF; a more directed cardiovascular workup is indicated. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:25A–28A)

Because the symptoms of heart failure (HF) are often non-specific, patients may not be properly investigated, resulting in a delay (or failure) of diagnosis and therapy for HF. After comprehensive history and physical examination, the most commonly used diagnostic method for outpatient evaluation of cardiac function is echocardiography, an investigation demanding expensive equipment and trained sonographers. Thus, a marker for HF diagnosis among symptomatic outpatients would be very valuable. The ideal marker for outpatient HF diagnosis should be effective in screening, provide a high sensitivity, have prognostic impact, be stable and simple to use, and be cost-effective. During recent years, natriuretic peptide (NP) testing has been recommended in the European guidelines as part of the screening process for symptomatic outpatients. 1

Natriuretic Peptide Testing in Symptomatic Outpatients

Several studies have examined the value of amino-terminal pro–B-type NP (NT-proBNP) testing for the evaluation of patients with symptoms suggestive of HF. In each of these studies, the value of NT-proBNP for excluding HF was clearly superior to that for diagnosing HF.

Accordingly, the focus for use of NT-proBNP in the symptomatic outpatient is based on its superb negative predictive value. Accordingly, in each of the studies examining the value of NT-proBNP for outpatients, 2–7 the optimal range of values to rule out HF has been suggested to be 100–160 ng/L, yielding a negative predictive value of 92%–100% and retaining a positive predictive value of 15%–76%, dependent on the prevalence of HF in the populations (Table 1).

Gustafsson et al 4 demonstrated a very high sensitivity (97%) using a predefined value of 125 ng/L. The very high sensitivity implies a very low risk of overlooking a patient with HF, a fact essential for a good screening method. A randomized study by Wright et al 8 further supported the potential value of NT-proBNP as an adjunct to clinical judgment. They showed that the use of NT-proBNP in general practice significantly improved the diagnostic accuracy over clinical judgment alone. Other adjunctive testing, such as electrocardiography, added very little to NT-proBNP in the evaluation of patients with dyspnea in the outpatient setting. 9

A substantial proportion of HF patients have nonsystolic HF, including diastolic dysfunction. The value of NPs in HF evaluation in these patients is less well investigated, partly because of the lack of diagnostic “gold standards” for nonsystolic HF. However, published research shows that NT-proBNP appears useful in the evaluation of patients with nonsystolic HF, 10 although generally lower values for NT-proBNP in the context of nonsystolic HF are expected.

Cost–Benefit Analysis: Any discussion of diagnostic evaluation requires some consideration of the strategy associated with the diagnostic tool applied. For outpatient evaluation, the use of a test, such as NT-proBNP, to
exclude the diagnosis of HF is optimal to direct therapy away from potentially costly diagnostic efforts. Accordingly, with negative NT-proBNP results, alternative diagnoses should be pursued. An elevated NT-proBNP value would direct diagnostic focus to the cardiovascular system. This approach was supported by Heidenreich et al., using a decision analytic framework. In addition, prospective evaluation of NT-proBNP as a gatekeeper screening test in the primary care setting has been conclusively demonstrated to be cost-effective. These data were borne out in another healthcare system, lending further support to their validity. Using data from the Copenhagen echocardiography laboratory, the approach was borne out in another healthcare system, lending further support to their validity. Using data from the Copenhagen echocardiography laboratory, the approach was supported by Heidenreich et al., using a decision analytic framework. In addition, prospective evaluation of NT-proBNP as a gatekeeper screening test in the primary care setting has been conclusively demonstrated to be cost-effective.

Prognosis: The very strong prognostic value of NT-proBNP in outpatient HF (discussed elsewhere in this supplement) supports the rational use of NT-proBNP testing in outpatients. An increased value strongly indicates that further investigation might be warranted to find a potential reversible cardiac etiology or to intensify the treatment.

Putative Pitfalls: Age and Sex. A major problem is the increasing concentrations of NPs observed with increasing age, which may be found in those without any clinically overt cardiac disease. The reasons for these findings could be age-related changes in the metabolism of NPs, age-dependent changes in the heart, or the decrease in renal function with age.

The use of the NT-proBNP value of 125 ng/L as a single cut point has been explored for patients with symptoms suggestive of HF, with an excellent negative predictive value. However, for younger patients (aged <50 years), a lower value of ~50 ng/L might be even more useful; for middle-aged patients (50–75 years), ~75–100 ng/L may be superior to 125 ng/L. Because the mean value of NT-proBNP in those aged 80 years is approximately 150 ng/L, and symptoms suggestive of HF are common in older persons, the uncritical use of the value of 125 ng/L to rule out HF could potentially induce further cardiologic evaluation in a larger percentage of older persons. The US Food and Drug Administration (FDA)-approved value of 450 ng/L for those aged ≥75 years may be less useful than values of ~250–300 ng/L (P. Hildebrandt, personal communication, September 2007). More precise age-related cut point values still have to be validated.

### Table 1: Studies of amino-terminal pro-B-type natriuretic peptide (NT-proBNP) cutoff limits for excluding heart failure in primary care settings

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Optimal Cutoff Limits (ng/L)</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaphiriou et al.</td>
<td>306</td>
<td>125</td>
<td>97%</td>
<td>44%</td>
</tr>
<tr>
<td>Nielsen et al.</td>
<td>345</td>
<td>93 and 144*</td>
<td>97%</td>
<td>57%  and 48%</td>
</tr>
<tr>
<td>Gustafsson et al.</td>
<td>367</td>
<td>125</td>
<td>99%</td>
<td>15%</td>
</tr>
<tr>
<td>Fuat et al.</td>
<td>279</td>
<td>150</td>
<td>92%</td>
<td>48%</td>
</tr>
<tr>
<td>Al-Barjas et al.</td>
<td>220</td>
<td>125</td>
<td>97%</td>
<td>76%</td>
</tr>
</tbody>
</table>

NPV = negative predictive value; PPV = positive predictive value.

* Age adjusted.

In contrast to age, sex appears to affect NT-proBNP results, with higher values in women than in men. However, the magnitude of these differences is fairly small and of no importance in outpatient testing; thus the same cutoff value can be used in women and men.

### Comparison Between B-Type Natriuretic Peptides and Amino-Terminal Pro–B-Type Natriuretic Peptides

Several of the aforementioned studies compared the diagnostic accuracy of B-type NP (BNP) and NT-proBNP. In general, NT-proBNP performed at least as well as BNP, with important caveats learned about the influence of symptom acuity on optimal cut points for these markers. In a study by Zaphiriou et al., the use of the manufacturer-recommended cut point of 100 ng/L for BNP gave a disastrously low sensitivity for a screening test, and the use of a substantially lower cut point of 30 ng/L (optimal for BNP in this study) gave the same specificity but a lower sensitivity than NT-proBNP. Accordingly, it is obvious that both NT-proBNP and BNP require lower cut points for evaluation of the outpatient when compared with the substantially higher cut points used in the acute setting.

### Conclusions

Hard evidence now supports the use of NT-proBNP for evaluation of outpatients with suspected HF. A strategy for use of the marker is proposed in Figure 1. If results are negative, HF is exceedingly unlikely; performing further diagnostic cardiovascular tests, such as echocardiography, in patients with negative levels of NT-proBNP is neither likely to be cost-effective nor to yield positive results. Thus, given the sensitivity at selected cut points, if elevated levels are detected, proceeding with a cardiovascular evaluation (including echocardiography) would be supported.

**Key points—NT-proBNP for diagnostic evaluation of symptomatic primary care patients:**

- NT-proBNP is highly sensitive with an excellent negative predictive value for the cost-effective exclusion of the diagnosis of HF in symptomatic outpatients.
Similar to BNP, lower values for NT-proBNP are expected among patients with HF in the community compared with patients with acute dyspnea.

Presently, there is consensus on an age-independent cut point of 125 ng/L for outpatient evaluation, although among the elderly population, a higher cut point is necessary.

A more comprehensive approach that includes cut points of 50–75 ng/L for patients aged <50 years, 75–100 ng/L for middle-aged patients, and 250–300 ng/L for elderly patients may be more useful. The precise cut point values are presently being validated.

Among patients with dyspnea, a noncardiac source of dyspnea is most likely for those below the age-stratified NT-proBNP cut points.

An NT-proBNP value above the age-stratified cut points does not absolutely indicate the presence of HF; a more directed cardiovascular workup is indicated.

**Author Disclosures**

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**Per Hildebrandt, MD**, reports receiving significant funds in the form of research support, speaker honoraria, and consulting fees from Roche Diagnostics.

**Paul Collinson, MD**, has no financial arrangement or affiliation with a corporate organization or manufacturer of a product discussed in this supplement.


10. Tschope C, Kasner M, Westermann D, Gau R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic


Amino-Terminal Pro–B-Type Natriuretic Peptide Testing for the Diagnosis or Exclusion of Heart Failure in Patients with Acute Symptoms

James L. Januzzi, Jr., MD, a,* Annabel A. Chen-Tournoux, MD, a and Gordon Moe, MD b

When used for the evaluation of patients with acute symptoms in the emergency department setting, amino-terminal pro–B-type natriuretic peptide (NT-proBNP) testing is highly sensitive and specific for the diagnosis or exclusion of acute destabilized heart failure (HF), with results comparable to those reported for B-type natriuretic peptide (BNP) testing. When used for the diagnostic evaluation of the patient with possible HF, NT-proBNP testing returns information that may be superior to clinical judgment. However, the optimal application of NT-proBNP is in concert with history and physical examination, adjunctive testing, and with the knowledge of the differential diagnosis of an elevated NT-proBNP level. Studies indicate a dual use for NT-proBNP, both to exclude acute HF (where NT-proBNP concentrations <300 ng/L have a 98% negative predictive value), as well as to identify the diagnosis. To identify acute HF in patients with dyspnea, an age-independent NT-proBNP cut point of 900 ng/L has a similar value as that reported for a BNP value of 100 ng/L. However, age stratification of NT-proBNP using cut points of 450, 900, and 1,800 ng/L (for age groups of <50, 50–75, and >75 years) reduces false-negative findings in younger patients, reduces false-positive findings in older patients, and improves the overall positive predictive value of the marker without a change in overall sensitivity or specificity. Clinically validated, cost-effective algorithms for the use of NT-proBNP testing exist. Therefore, the logical use of NT-proBNP for the evaluation of the patient with suspected acute HF is useful, cost-effective, and may reduce adverse outcomes compared with standard clinical evaluation without natriuretic peptide testing. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]: 29A–38A)

Natriuretic peptide (NP) testing is probably most widely applied to the evaluation of the patient with acute symptoms to correctly exclude or secure a diagnosis of acute destabilized heart failure (HF). Since the value of amino-terminal pro–B-type NP (NT-proBNP) or B-type NP (BNP) for the evaluation of the acutely symptomatic patient was first suggested, abundant data have been generated from several landmark studies supporting the adjunctive use of NP testing for evaluation of the patient with symptoms/signs suggestive of HF. Furthermore, NT-proBNP shares an equal role with BNP in the current guidelines for use of NP testing in the diagnostic evaluation of HF.1–4

This article summarizes the up-to-date understanding of the value of NT-proBNP testing in the patient presenting with acute symptoms. This summary does not consider studies of NT-proBNP using assay methods that are not used commercially (such as the relatively cruder enzyme-linked immunosorbent assays). These studies are not germane to the everyday needs of most clinicians, and inclusion of the occasionally encountered comparisons of these less accurate methods with the more highly refined clinical NP assays5–7 would not be instructive.

Amino-Terminal Pro–B-Type Natriuretic Peptide Testing and the Diagnosis or Exclusion of Acute Heart Failure

After early clinical studies demonstrated that NT-proBNP concentrations were elevated among patients with HF,8 several other studies followed that have allowed a better understanding of the role of this marker in the evaluation of patients with suspected or proven acute destabilized HF. Among the first were studies from Christchurch, New Zealand and Barcelona, Spain.

In the Christchurch study,9 concentrations of NT-proBNP were considerably higher among patients with acute HF compared with those who had dyspnea due to other causes. Importantly, in this and in subsequent trials of patients with acute symptoms, the optimal NT-proBNP cut point for diagnosis of acute HF was found to be consider-
ably higher than cut points observed in studies of outpatient evaluation. In this study, investigators compared the NT-proBNP assay (Roche Diagnostics, Indianapolis, IN) with the Biosite BNP assay (San Diego, CA) and demonstrated identical areas under the receiver operating characteristic (ROC) curve (0.89 for both), arguing for significant comparability of the 2 assays for the evaluation of the patient with acute symptoms.9

The Barcelona analysis10 showed the considerable value of NT-proBNP testing for the correct diagnosis of acute HF in the patient with dyspnea (area under the ROC curve, 0.96). In addition, Bayes-Genis et al10 showed the importance of NT-proBNP for discernment of previously unsuspected HF among those with pulmonary disease—a concept known as HF “masked” by pulmonary disease. The investigators also proposed a novel dual cut point strategy using an NT-proBNP value of 253 ng/L to “rule out” acute HF (ie, a value below which the likelihood for acute HF is extremely low) and a value of 973 ng/L to “rule in” acute HF (ie, a value above which the likelihood for acute HF is higher).10

Subsequent to these 2 earlier studies, Mueller et al11 published a head-to-head comparison of the NT-proBNP assay (Roche Diagnostics) to the automated Abbot BNP assay (Abbott Park, IL) for the diagnostic evaluation of 251 patients with acute dyspnea with and without acute HF. In this study, similar to the Christchurch analysis, areas under the ROC curve for NT-proBNP and BNP were not significantly different; the optimal NT-proBNP cut point for HF

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Median NT-proBNP (ng/L)</th>
<th>25th–75th Percentile (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute CHF (N=209)</td>
<td>4.054</td>
<td>1.675–10.028</td>
</tr>
<tr>
<td>Not Acute CHF (N=390) in patients with prior CHF (N=35)</td>
<td>1.175</td>
<td>462–2,590</td>
</tr>
<tr>
<td>Not Acute CHF (N=390) in patients without prior CHF (N=355)</td>
<td>114</td>
<td>42–340</td>
</tr>
</tbody>
</table>

Figure 1. Concentrations of amino-terminal pro–B-type natriuretic peptides (NT-proBNP) in patients with acute dyspnea as a function of final diagnosis. *p < 0.001 versus not acute congestive heart failure (CHF). (Reprinted with permission from Am J Cardiol.13)

Table 1

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated NT-proBNP</td>
<td>44.0</td>
<td>21.0–91.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Interstitial edema on chest x-ray</td>
<td>11.0</td>
<td>4.5–26.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>9.6</td>
<td>4.0–23.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Loop diuretic use at presentation</td>
<td>3.4</td>
<td>1.8–6.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Rales on pulmonary examination</td>
<td>2.4</td>
<td>1.2–5.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.03</td>
<td>1.01–1.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Cough</td>
<td>0.43</td>
<td>0.23–0.83</td>
<td>0.05</td>
</tr>
<tr>
<td>Fever</td>
<td>0.17</td>
<td>0.05–0.50</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NT-proBNP = amino-terminal pro-B-type natriuretic peptides. Adapted from Am J Cardiol.13
diagnosis in this study (825 ng/L) was strikingly similar to that generated from the Barcelona cohort. Interestingly, in this analysis, the optimal cut point for BNP was considerably higher, at 295 ng/L, than the currently endorsed BNP cut point of 100 ng/L, which may reflect an older patient population in the Mueller group’s analysis, compared with other landmark studies of BNP.12

Definitive support for the value of NT-proBNP for the diagnostic evaluation of the patient with symptoms suggestive of HF in the emergency department setting came from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study,13 an analysis of 599 subjects presenting with acute dyspnea to the emergency department setting. In the PRIDE study, the 209 subjects with acute destabilized HF had considerably higher NT-proBNP values than those without acute HF as the cause of their dyspnea (4,435 ng/L vs 131 ng/L, p <0.001) (Figure 1), and NT-proBNP concentrations directly paralleled the severity of HF symptoms, based on the New York Heart Association (NYHA) classification. In multivariable analyses, an elevated NT-proBNP was the single strongest predictor of a final “gold standard” diagnosis of acute HF in the PRIDE study (Table 1).

In the PRIDE study, NT-proBNP testing was found to be useful for the diagnostic evaluation of several patient subgroups, including those with renal impairment,14 prior obstructive airways disease (where NT-proBNP testing uncovered a significant percentage of patients with obstructive pulmonary disease who had previously unsuspected masked HF),15 and those with diabetes mellitus.

An important component of the PRIDE study analysis was an assessment of the value of NT-proBNP for correctly identifying acute HF compared with clinical judgment. In the PRIDE study, clinicians were asked to provide an estimate of likelihood for acute HF, and this estimate was compared with the results of NT-proBNP testing. When used in isolation, NT-proBNP testing had an area under the ROC curve for diagnosis of acute HF of 0.94 that was superior to clinical judgment, which had an area under the ROC curve of 0.90 (Figure 2). Indeed, in the PRIDE study, NT-proBNP was the strongest predictor of a gold standard diagnosis of acute HF in the patient with dyspnea, was a stronger predictor than other diagnostic evaluations, such as chest radiography, and was a considerably stronger predictor of HF than elements from history or physical examination. However, and very importantly, the combination of NT-proBNP plus standard clinical evaluation increased the area under the ROC curve for diagnosis of HF to 0.96.13 This argues for the necessity of a balanced evaluation in the emergency department, incorporating the results of NT-proBNP testing with that of standard clinical evaluation to most optimally use this important diagnostic advance. Indeed, the results of the recent landmark Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF) study16 lend further support to this concept. IMPROVE-CHF was a randomized trial of unblinded versus blinded NT-proBNP testing for the evaluation of patients with dyspnea in the emergency department setting. It demonstrated that unblinded NT-proBNP testing was associated with 21% shorter stays in the emergency department, a 35% reduction in rehospitalization during 60 days of follow-up, and no excess adverse outcomes associated with these improvements in utilization—undoubtedly the consequence of more confident identification or exclusion of HF.16

With respect to optimal cut points for the evaluation of the patient with acute dyspnea, the PRIDE investigators found that, similar to the earlier data from Barcelona, a dual
cut point approach to rule out or rule in HF was superior to a single cut point approach endorsed by consensus documents for BNP. In the PRIDE study, a cut point of 300 ng/L provided excellent utility for excluding the diagnosis of acute HF, with a considerably higher negative predictive value (99%) than a single BNP cut point of 100 ng/L (89%), whereas a cut point of 900 ng/L was optimal for the diagnosis of acute HF, yielding a similar positive predictive value to a BNP cut point of 10 ng/L (76% vs 79%).

In contrast to data from “apparently well patients,” sex did not affect the optimal cut points for NT-proBNP in the context of acute dyspnea. In addition, whereas black patients had slightly lower NT-proBNP values than non-black patients in the absence of HF, this finding was attenuated in the presence of other variables, such as age, and did not factor in when optimal cut points for diagnosis of HF were considered.

Interestingly, when restricting the analysis to only those patients aged <50 years, the PRIDE investigators found that 450 ng/L might be a superior cut point for the diagnosis of HF in this younger population. Indeed, age and its parallel/associated biologic processes (such as diastolic dysfunction, subclinical heart disease, and loss of renal function) are important when considering diagnostic tools, such as NPs, which are extremely sensitive to such comorbidities. As was demonstrated by the Breathing Not Properly Multinational Study, the most common cause of a BNP value over the diagnostic threshold of 100 ng/L was advancing age, with an increase of 30% per decade in the odds of a false-positive result. With this in mind, the International Collaborative of NT-proBNP (ICON) analysis was performed to examine optimal cut points for NT-proBNP.

In the ICON study of 1,256 subjects with and without HF, the combined area under the ROC curve for the diagnosis of HF using NT-proBNP was significant (0.94), and from the ROC curve, a single NT-proBNP cut point of 1,243 ng/L was optimal for diagnosis. As with the PRIDE analysis (and supported by the results from the Breathing Not Properly Multinational Study), the ICON study showed that the effect of age on optimal cut points was significant, with significant heterogeneity of optimal cut points noted across age ranges. In the ICON study, using multivariable bootstrapping statistical methods, the investigators demonstrated that an age-adjusted cut point strategy was far superior to a single diagnostic cut point. Using cut points of 450 ng/L, 900 ng/L, and 1,800 ng/L, the ICON investigators demonstrated it was possible to improve the overall positive predictive value to 88% (which compares very favorably with a positive predictive value of 79% using a single BNP cut point), without sacrificing overall sensitivity or specificity.

Although slightly more complex than a single cut point strategy, the age-stratified approach for NT-proBNP sharpens sensitivity for the younger patient with acute HF, and it improves specificity for the older patient without HF. Indeed, lending support to this approach in the elderly patient was a recent study of NT-proBNP testing in elderly patients with acute dyspnea (mean age, 81 years), where the optimal NT-proBNP cut point was 2,000 ng/L.

What age adjustment corrects for remains somewhat speculative. However, given the age-related increase in subclinical cardiac abnormalities that may lead to elevations in NT-proBNP as well as parallel decreases in renal function, it is likely that age adjustment of NT-proBNP corrects for >1 physiologic change of aging.

Importantly, chronic kidney disease increases the optimal cut point for NT-proBNP to 1,200 ng/L. However, when using age stratification, no further adjustment is necessary for impaired renal function, except for the unusually young patient with significant chronic kidney disease.

To be clear, no data exist that suggest that NT-proBNP is any more age-dependent than is BNP. Indeed, the preponderance of data from a large number of analyzed patients suggests that NT-proBNP and BNP deliver largely the same diagnostic value when using a single age-independent cut point.
point strategy for the diagnosis of HF. However, when using an age-stratified approach, the NT-proBNP diagnostic value is increased. Optimal age-stratified cut points for BNP are yet to be identified.

Lastly, similar to prior analyses, the ICON investigators confirmed the value of a single age-independent exclusion cut point of 300 ng/L.

The recommended cut point strategy for NT-proBNP testing in the setting of acute dyspnea is depicted in Table 2.

Differential Diagnosis of Elevated Amino-Terminal Pro–B-Type Natriuretic Peptides

Numerous other diagnoses are associated with an elevation in NT-proBNP levels in the absence of acute destabilized HF (the differential diagnosis of elevated NT-proBNP concentrations is amply covered in another article in this supplement). As shown in Table 3, these diagnoses include prior HF; acute coronary syndromes; cardiac structural abnormalities without HF (such as heart muscle or valve disease); arrhythmia; pulmonary hypertension, either acute (such as is seen with acute pulmonary embolism) or chronic; and numerous other situations, including critical illness/sepsis syndrome, or toxic-metabolic insults (such as cancer chemotherapy).

Knowledge of the differential diagnosis of NT-proBNP will assist in minimizing false attribution of HF to a patient with another cause of elevation in NT-proBNP. In addition, in many, if not most of these situations, elevated NT-proBNP is strongly prognostic and thus may be useful for triage decision-making.

Amino-Terminal Pro–B-Type Natriuretic Peptide Testing in Patients with Prior Heart Failure

As shown in the PRIDE study, patients with prior HF who present with acute symptoms from a cause other than HF typically have levels of NT-proBNP that are considerably higher than those without incident or prevalent HF. This situation, which also affects BNP, leads to some degree of difficulty in interpretation of NP results when a patient with prior HF presents for urgent evaluation. To optimally apply NT-proBNP testing in the setting of antecedent heart disease, including HF, it is recommended that the clinician compare the presenting NT-proBNP concentrations with the previous results of NT-proBNP testing, particularly measures of “dry” NT-proBNP. Given that the biologic variation of NT-proBNP in the context of HF is probably ≤ 25%, an increase greater than this value is supportive of a diagnosis of acute-on-chronic HF, and, at the very least, is strongly prognostic as well, particularly if the value exceeds 1,000 ng/L.

Gray Zone Amino-Terminal Pro–B-Type Natriuretic Peptide Results

An NT-proBNP value between the exclusion cut point of 300 ng/L and the age-adjusted inclusion cut point (450
As was demonstrated by the PRIDE 13 investigators and Natriuretic Peptide Testing Optimal Application of Amino-Terminal Pro–B-Type Natriuretic Peptide Testing

Typically associated with a very good prognosis. Relatively short duration; such low NT-proBNP results are acute HF very likely have relatively mild HF, or HF of mild HF, diastolic HF, several cardiac diagnoses other than HF, and increased body-mass index.\(^{45}\)

False-Negative Results

Although the exceptional sensitivity of NT-proBNP makes a false-negative result unlikely, acute HF in the context of an NT-proBNP value \(<300\) ng/L may occur, albeit rarely. Patients with an NT-proBNP value \(<300\) ng/L who have acute HF very likely have relatively mild HF, or HF of relatively short duration; such low NT-proBNP results are typically associated with a very good prognosis.

Optimal Application of Amino-Terminal Pro–B-Type Natriuretic Peptide Testing

As was demonstrated by the PRIDE\(^{13}\) investigators and subsequently supported by the IMPROVE-CHF study,\(^{16}\) the optimal approach for the use of NT-proBNP testing is its use in combination with clinical variables. Methods for combining NT-proBNP testing with standard clinical evaluation to improve the diagnostic value of both approaches have been proposed.

A diagnostic “score” incorporating NT-proBNP results with history and physical examination has been described.\(^{46}\) Also, similar to BNP, algorithms have been recommended for the appropriate application of NT-proBNP testing (Figure 3).\(^{47}\) Although more complex than the recommended 1-step pathways for use of BNP testing, the algorithms for NT-proBNP testing are decidedly more comprehensive, providing considerably more information to the clinician regarding commonly encountered situations, such as how to manage the patient with prior HF. Thus, the recommended algorithm for NT-proBNP testing more appropriately reflects the complexity of everyday medical situations and emphasizes the time-tested importance of history and physical examination as well as differential diagnosis.

After implementation, the above NT-proBNP algorithm was subjected to evaluation using a “before and after” analysis of hospital length of stay and outcomes at a large urban institution.\(^{48}\) As reported, the use of NT-proBNP in the context of the recommended algorithm was associated with a significantly shorter length of stay in the hospital and lower morbidity and mortality.\(^{48}\) Cost-effectiveness was implied and, indeed, a decision-analytic framework analysis examining the algorithm demonstrated significant cost-savings out to 60 days, with nearly $500 saved per patient evaluated and with a parallel decrease in adverse outcomes implied.\(^{49}\)

In a prospective randomized fashion, the IMPROVE-CHF investigators confirmed the cost-effectiveness of NT-proBNP testing for the diagnostic evaluation of the patient with acute dyspnea, with $949 savings observed by 60 days from presentation. These savings were related to previously mentioned reductions in hospital stay or rehospitalization, as well as reduced use of other diagnostic studies, such as echocardiography or radiologic studies.\(^{16}\)

Special Considerations: Amino-Terminal Pro–B-Type Natriuretic Peptide Testing and Other Diagnostic Studies

Radiologic studies: As noted above, NT-proBNP testing was superior to chest radiography for the diagnosis of acute HF in the PRIDE study.\(^{13}\) However, chest radiography is time tested, rapidly available, and frequently depended on by clinicians in the emergency department setting. Furthermore, although inferior to NT-proBNP for the diagnosis of acute HF, chest radiography was nonetheless an independent predictor of the diagnosis of HF in the PRIDE study. Thus, the relative value of the 2 methods of imaging is important to understand.

In the context of an abnormal chest radiograph, NT-proBNP test results may add useful information for the diagnosis or exclusion of HF. Studies have demonstrated that an elevated NT-proBNP level may help to confirm or exclude HF in patients with pleural effusions,\(^{50–52}\) whereas in the PRIDE study, a negative NT-proBNP result was associated with a lower likelihood for acute HF in the context of interstitial edema (47% vs 94% when NT-proBNP results were positive) or alveolar consolidation (5% vs 67% when NT-proBNP results were positive) (unpublished data). Conversely, in the setting of a normal chest radiograph, an elevated NT-proBNP level in the PRIDE study was associated with a much higher rate of acute HF compared with when the NT-proBNP finding was negative (64% vs 8%) (J. L. Januzzi, Jr., personal communication, December 2007).

Thus, this somewhat limited experience shows that NT-proBNP results supersede those from a “normal” chest radiograph, although in the context of radiographic abnormalities, NT-proBNP can still be very useful, particularly in the context of alveolar consolidation.

Although computed tomography (CT) is frequently used in the context of evaluation of acute dyspnea, particularly to exclude the presence of pulmonary thromboembolism (a situation associated with elevated NT-proBNP concentrations caused by stretch of the right ventricle), relatively few data exist on the use of NT-proBNP in this setting. Melanson et al\(^{15}\) demonstrated that the use of NT-proBNP (together with \(\alpha\)-dimer) was incrementally useful for the ex-
clusion of pulmonary thromboembolism in subjects with dyspnea and would have allowed significant reduction in the application of subsequently unnecessary CT angiography.

**Echocardiography:** Perhaps among the most used diagnostic imaging studies for the evaluation of the patient with dyspnea is echocardiography. Accordingly, a good understanding of the interrelation between NT-proBNP testing and echocardiography is important.

Although myocardial stretch is generally considered the main trigger of NP release, NT-proBNP concentrations are, indeed, independently associated with several important echocardiographic indices, including measures of heart muscle structure and function, as well as valvular heart disease.

The relation between NT-proBNP levels and left ventricular systolic dysfunction is well established.\(^\text{19,54}\) Levels of NT-proBNP also appear to correlate with diastolic dysfunction,\(^\text{54–56}\) even in the absence of systolic dysfunction, and may be superior to BNP for the detection of milder stages of diastolic dysfunction, possibly because of the longer half-life of NT-proBNP. Indeed, clinical data from the PRIDE study suggest that among patients with HF and preserved left ventricular systolic function, NT-proBNP testing was superior in sensitivity to the Bayer BNP assay, Tarrytown, NY (91% vs 80%).\(^\text{57}\) These sensitivity results were comparable to those generated from the Breathing Not Properly Multinational Study, where nonsystolic HF was associated with higher rates of a falsely negative BNP.\(^\text{58}\)

In addition to left ventricular size and function, NT-proBNP levels independently correlate with indices of pulmonary artery pressure, right ventricular dysfunction, and valvular regurgitation in patients with acute dyspnea.\(^\text{54}\)

Lastly, among symptomatic patients with significant valvular heart diseases, including mitral stenosis or regurgitation\(^\text{23–26,30,54}\) and aortic stenosis or regurgitation,\(^\text{24,27–29}\) NT-proBNP values may be elevated in parallel with the severity of the valvular lesions.

On a clinical level, the additive value of NT-proBNP to echocardiography was examined by Chen et al\(^\text{54}\) who demonstrated significant interrelations between elevated NT-proBNP and various echocardiographic parameters. Importantly, in the context of an NT-proBNP concentration <300 ng/L, few, if any clinically meaningful echocardiographic abnormalities were noted. Furthermore, NT-proBNP was powerfully prognostic, even in the context of echocardiographic abnormalities. Thus, the investigators concluded that in the presence of an NT-proBNP value <300 ng/L (the recommended exclusion cut point), echocardiography could be deferred or avoided among patients with acute dyspnea. The results of the IMPROVE-CHF study demonstrate real-time verification of the ability of NT-proBNP testing to assist in reducing unnecessary echocardiographic procedures.

**Electrocardiography:** Although data are relatively sparse on the relation between NT-proBNP concentrations and parameters from electrocardiography, Sakhuja et al\(^\text{59}\) showed that the combination of elevated NT-proBNP and a wide QRS complex on resting 12-lead electrocardiography was associated with a higher likelihood of acute HF compared with those with a narrow QRS complex. There is also an association in the absence of HF between elevated NT-proBNP values and atrial arrhythmias, such as atrial fibrillation,\(^\text{32}\) as discussed in the article on the differential diagnosis of an elevated NT-proBNP elsewhere in this supplement.\(^\text{21}\)

**Conclusions**

NT-proBNP testing is a powerful adjunctive tool in the diagnostic armamentarium of the clinician. When appropriately applied and interpreted, NT-proBNP testing represents a major advance in the diagnosis and triage of the patient with acute dyspnea.

**Key points—NT-proBNP and the diagnosis of acute HF:**

- Well-designed clinical studies demonstrate that NT-proBNP testing is highly sensitive and specific for the diagnosis of acute destabilized HF in patients with dyspnea, with results comparable to those in BNP testing.
- When used for the diagnostic evaluation of the patient with possible HF, NT-proBNP testing returns information that may be superior to clinical judgment alone.
- As with any diagnostic modality, the optimal application of NT-proBNP testing is in conjunction with a good history and physical examination and knowledge of the differential diagnosis of an elevated NT-proBNP value.
- To exclude acute destabilized HF in the emergency department, NT-proBNP concentrations <300 pg/mL have a 98% negative predictive value.
- To identify acute destabilized HF in the emergency department, an age-independent NT-proBNP cut point of 900 ng/L has a sensitivity, specificity, and positive predictive value similar to a BNP cut point of 100 ng/L.
- Age stratification of NT-proBNP results using cut points of 450, 900, and 1,800 ng/L (for age groups of <50, 50–75, and >75 years) reduces false-negative results in younger patients, reduces false-positive results in older patients, and improves the overall positive predictive value of the marker without a change in overall sensitivity or specificity. Because of this superiority, an age-stratified approach for NT-proBNP testing is recommended.
- Algorithms for the use of NT-proBNP testing exist and contain abundant valuable information on the complex
clinical scenarios that frequently occur in the setting of an acute patient presentation.

- Logical use of NT-proBNP testing for the evaluation of the patient with suspected acute HF is cost-effective, reduces hospital resource utilization, and may reduce adverse outcomes compared with standard clinical evaluation without NT-proBNP testing.
- When used in the context of the evaluation of acute dyspnea, NT-proBNP testing has an adjunctive value with other diagnostic modalities, such as radiographic or echocardiographic imaging.
- In the setting of an NT-proBNP value <300 ng/L, echocardiography is not likely to be a cost-effective next step for the diagnosis of the patient with acute dyspnea.

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Importance and Interpretation of Intermediate (Gray Zone) Amino-Terminal Pro–B-Type Natriuretic Peptide Concentrations

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Amino-terminal pro–B-type natriuretic peptide (NT-proBNP) values between the cut point of 300 ng/L for “ruling out” acute heart failure (HF) and the consensus-recommended age-adjusted cut points for “ruling in” acute HF are referred to as intermediate or gray zone values, which may be seen in approximately 20% of patients with dyspnea in the emergency department. Knowledge of the differential diagnosis of the causes of a gray zone NT-proBNP finding is useful to ascertain the correct diagnosis. Possible causes include cardiac ischemia, atrial fibrillation, and infectious/inflammatory pulmonary diseases. Importantly, a gray zone NT-proBNP result is not associated with a benign prognosis. Regardless of the cause, it should not be ignored because it is a “negative” result. Patients with a gray zone NT-proBNP value are at higher risk for hazard compared with those with a negative NT-proBNP result. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[ suppl ]: 39A–42A)

Although amino-terminal pro–B-type natriuretic peptide (NT-proBNP) is frequently diagnostic in the context of acute dyspnea, circumstances arise when levels of the marker are above the cut point of 300 ng/L for “ruling out” acute heart failure (HF) but below the age-adjusted diagnosis cut points for “ruling in” acute HF recommended by the International NT-proBNP Consensus Panel elsewhere in this supplement.1 These “intermediate” values for NT-proBNP have been variously referred to as values in the natriuretic peptide (NP) gray zone, and although age-stratified cut points for NT-proBNP in acute dyspnea are less likely to result in a gray zone value than a single cut point,2–4 the phenomenon exists and is necessary to consider in detail.

In general, levels of B-type NP (BNP) and NT-proBNP are directly related to the severity of underlying cardiac abnormalities, and they are best viewed as continuous variables. Thus, as with all binary-model quantitative diagnostic tests that require the determination of a cutoff value to identify patients with and without disease from a range of values, NPs by definition will have values that are above the result yielding a strong negative predictive value but below the result yielding a strong positive predictive value.

In the presence of the diagnosis of acute destabilized heart failure (HF), gray zone values (by definition, lower than the cut point for diagnosis of acute HF) are more likely to be found among those with mild HF symptoms (such as New York Heart Association [NYHA] class II symptoms),2 nonsystolic HF5,6 (a circumstance potentially more likely to render the BNP test result falsely negative), and those with increased body mass index,7,8 similarly less of an issue with NT-proBNP than with BNP.7,8

Perhaps, the most important variable associated with an NP value above the HF cut point in the absence of the diagnosis of HF is age. Indeed, advancing age affects both NT-proBNP and BNP equally with respect to increased values in older patients without clinically overt HF. In the Breathing Not Properly Multinational Study, there was a 30% increase per decade in the likelihood for a BNP concentration >100 ng/L in the absence of HF.4 The utility of age stratification for reducing false attribution of HF to an elevated NT-proBNP value in elderly individuals is discussed elsewhere in this supplement.1 The reason for the age-related increase in BNP or NT-proBNP is much debated but presumably relates to the parallel age-related increase in subclinical structural heart disease, including heart muscle disease, diastolic abnormalities, valve disease, and arrhythmia. Furthermore, an age-related decrease in renal function must be considered as being partially (but by no means largely) responsible.

When considering renal dysfunction as a cause of gray zone NT-proBNP results, it is worthwhile to recognize that many patients with chronic kidney disease have normal NT-proBNP values,9 and among those with elevated values, there exists a strong inverse relation between renal function and heart disease. Indeed, regardless of clinician perception of the presence of structural heart disease in those with
chronic kidney disease, an elevated NT-proBNP value in such a patient is a strong negative prognostic finding and is suggestive of underlying heart disease. However, when attempting to attribute an elevated NT-proBNP value to a diagnosis of acute HF, the clinician should strongly consider the use of age-adjusted NT-proBNP cut points, or for the rare patient with chronic kidney disease aged <50 years, a cut point of 1,200 ng/L.

Other important diagnoses associated with gray zone NT-proBNP values in the absence of HF include ischemic heart disease (discussed elsewhere in this supplement), atrial fibrillation, severe infectious or inflammatory pulmonary diseases, lung cancer, and other cardiac diseases that cause elevated right ventricular pressures, such as pulmonary hypertension or pulmonary embolism (Table 1).

Clinically, to secure a correct diagnosis when NT-proBNP concentrations are in the intermediate range or gray zone, recognition of the differential diagnosis of the gray zone NT-proBNP result along with traditional clinical parameters can help physicians in further differentiating HF from other causes of acute dyspnea. A substudy of the International Collaborative of NT-proBNP (ICON) study showed that among subjects with intermediate NT-proBNP concentrations, the absence of cough, the use of a loop diuretic on presentation, and the presence of paroxysmal nocturnal dyspnea, jugular vein distention, and a previous history of HF are all parameters that are independent predictors of HF in patients with intermediate NT-proBNP concentrations (Table 2).

Although it seems intuitively obvious that a patient with prior HF should not have a “normal” value for a sensitive measure of neurohormonal activation, such as an NP, chronic stable HF is a diagnosis that frequently leads to confusion when interpreting NP test results in the acute setting. Certain assumptions must be made on the interpretation of gray zone NP results in those with chronic HF who are evaluated with acute symptoms. First, given the relation between NT-proBNP concentrations and the severity/cause of HF, a gray zone value for NT-proBNP in a patient with HF of any cause is more likely to be mild in severity or etiologically nonsystolic in origin. Second, because lower values for NT-proBNP are associated with more favorable short- and longer-term outcomes, a patient with acute-on-chronic HF with a gray zone result is more likely to have a better outcome than a result with a “diagnostic” value. These 2 considerations not withstanding, it can be challenging to interpret NP values in the context of chronic HF. Because it has been suggested that the variability around a “dry” or chronic stable NT-proBNP value is ≤25%, a change >25% from a baseline value might help to correctly ascertain the right diagnosis in this setting.

As noted above, patients with NT-proBNP concentrations in the gray zone typically have more favorable outcomes compared with those above the “diagnostic” age-stratified cut point. However, the prognosis in the gray zone is worse than for those who have an NT-proBNP level below the exclusion cut point of 300 ng/L (Figure 1). This underscores the importance of gray zone values from a prognostic perspective. Thus, these results should not be discarded as “negative” because they have very real prognostic import.

### Conclusions

#### Key points—importance and interpretation of intermediate or gray zone NT-proBNP concentrations:

- NT-proBNP values between the cut points that “rule out” and “rule in” an acute HF diagnosis are referred to as intermediate or gray zone values.
- Although age stratification of NT-proBNP cut points for the evaluation of patients with acute dyspnea reduces the likelihood of a gray zone value, this finding was still present in 17% of subjects in the ICON study.
- Knowledge of the differential diagnosis for the causes of a gray zone NT-proBNP result is useful for cor-
directly diagnosing or excluding HF or, conversely, differentiating other pathologies from HF (eg, cardiac ischemia, atrial fibrillation, and infectious/inflammatory pulmonary diseases).

- A gray zone NT-proBNP value is not associated with a benign prognosis, and regardless of the cause, it should not be ignored as being a "negative" result.

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The Differential Diagnosis of an Elevated Amino-Terminal Pro–B-Type Natriuretic Peptide Level

Aaron L. Baggish, MD, a Roland R. J. van Kimmenade, MD, PhD, a, b and James L. Januzzi, Jr., MD a,*

Although amino-terminal pro–B-type natriuretic peptides (NT-proBNP) are useful for the diagnosis or exclusion of heart failure (HF), this marker may identify a wide range of disease processes other than HF. Indeed, elevation of NT-proBNP may occur in a number of heart diseases (including heart muscle disease, valve disease, rhythm abnormalities, pulmonary hypertension, and cytotoxic injury to the heart) and in disease processes other than primary cardiac illnesses, including gram-negative sepsis. Importantly, although NT-proBNP may increase in settings other than HF, the presence and severity of such NT-proBNP release is often significantly associated with risk for adverse outcome. Accordingly, elevation of NT-proBNP in the context of non-HF situations should not be regarded as a “false-positive” finding, and elevated NT-proBNP values should not be discarded without consideration of the serious adverse outcomes associated with the elevation. Future studies will be necessary to further understand the utility of NT-proBNP testing in states other than cardiovascular disease. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008; 101[suppl]:43A–48A)

Natriuretic peptide (NP) release by cardiac myocytes occurs in response to cardiac muscle fiber stretch and strain, as noted elsewhere in this supplement. 1 Many disease processes other than primary left ventricular failure can result in elevated levels of circulating amino-terminal pro–B-type NP (NT-proBNP). The present article reviews this topic, emphasizing the potential utility in these settings.

Myocardial Disease

Concentrations of NT-proBNP may be significantly elevated in a wide array of myocardial diseases, including hypertrophic, restrictive, and inflammatory heart muscle diseases.

Among patients with progressive left ventricular hypertrophy, concentrations of NT-proBNP are typically elevated in proportion to the degree of left ventricular mass increase. The paradigm for this process is hypertrophic cardiomyopathy, where patients may show significant elevations of NT-proBNP, frequently in the range described for acute destabilized heart failure (HF). 2 –8 Elevation of NT-proBNP in hypertrophic cardiomyopathy is more associated with the severity of hypertrophy than the severity of obstruction 3, 4, 6; thus it is not surprising that the marker may be elevated in nonobstructive variants of the disorder. 2, 5

Other myocardial disease states characterized by restrictive myocardial function include infiltrative cardiomyopathies, such as amyloidosis. Although heart muscle is typically replaced by nonmyocyte tissue in this setting, prognostically important concentrations of NT-proBNP may be elevated in these patients 9 and parallel the activity and severity of heart muscle disease. 10

Inflammatory states affecting myocardial structure and function may lead to elevations of NT-proBNP. This includes acute reversible cardiomyopathies, such as apical ballooning syndrome, 11 infectious myocarditis, 12 and toxic metabolic insults to the heart muscle, such as those related to cancer chemotherapy. 13 –19 In these settings, NT-proBNP levels most often parallel the presence and severity of myocardial dysfunction, and in the case of chemotherapeutic agents, they may predict future development of ventricular dysfunction.

Valvular Heart Disease

It is well established that various forms of valvular heart disease may lead to elevations in NT-proBNP concentra-
tions, and that these elevations may have significant diagnostic and prognostic implications.

Several studies now demonstrate an intimate relation between NT-proBNP elevation and symptom onset as well as prognosis in patients with asymptomatic aortic stenosis.20–23 Early data suggested a close relation between the severity of aortic stenosis and concentrations of NT-proBNP.21 In fact, NP values were more strongly associated with eventual symptom onset than aortic valve area. Subsequent data demonstrate that among patients treated with or without aortic valve replacement, NT-proBNP concentrations were consistently related to myocardial performance and survival for those patients treated surgically as well as those patients treated conservatively.23–25 Among a cohort of asymptomatic subjects from New Zealand, NT-proBNP elevation was the earliest harbinger of the onset of symptoms (the traditional crossroad for surgical intervention).23,25,26 Although a limited amount of data exist, there appears to be a similar, albeit less intimate, relation between levels of NPs and aortic valve regurgitation.26–28

In patients with mitral valve stenosis, the left ventricle is theoretically “protected” from volume or pressure load. However, concentrations of NPs still appear to be useful for tracking disease presence and severity. In a study of 29 patients with isolated mitral stenosis, Arat-Ozkan et al29 demonstrated that NT-proBNP values were related to echocardiographic findings and functional classification. The mechanism of the elevation of NPs in these patients likely reflects both left and right atrial distention, as well as right ventricular pressure and volume overload caused by secondary pulmonary hypertension.

The relation between mitral valve regurgitation and NPs is also well established.30–32 Although concentrations of NT-proBNP generally parallel the severity of mitral regurgitation, it is now thought that elevations of these NPs not only reflect volume overload but also the myocardial consequences of such volume load.31,33 Hence, in patients with significant mitral regurgitation, concentrations of NPs parallel the likelihood of death (hazard ratio [HR] per 10 ng/L, 1.23; 95% confidence interval [CI], 1.07–1.48; p = 0.004) or the composite of death and HF (HR per 10 ng/L, 1.09; 95% CI, 1.001–1.19; p = 0.04).34

**Atrial Arrhythmia**

Patients with atrial fibrillation (AF) have increased B-type NP (BNP) messenger RNA expression in atrial tissue and elevated circulating levels of NT-proBNP, even in the absence of HF or significant structural heart disease.35–38 These observations apply even to those with lone AF when in sinus rhythm.39 The relation between AF and NT-proBNP levels appears strongest in patients without acute destabilized HF. In a large study, NT-proBNP levels among 276 patients with persistent AF were higher than levels in 1,045 patients with normal sinus rhythm.36 In multivariable regression analysis, AF was significantly associated with elevated NT-proBNP levels, regardless of whether structural heart disease was present, but AF appeared to contribute more to NT-proBNP levels in the group with structurally normal hearts. A similar pattern was observed among 599 patients presenting with dyspnea to an emergency room setting, of whom 13% were in AF. NT-proBNP levels were significantly associated with AF only in those without acute HF.35 In contrast, among 354 patients with moderate-to-severe HF (New York Heart Association [NYHA] functional class III–IV), no significant relation was found between AF and concentrations of NT-proBNP.40

With the described changes in atrial tissue quality related to AF as well as the upregulation of the BNP gene related to this arrhythmia, it is likely that elevations of NT-proBNP associated with AF likely represent atrial and/or ventricular release in response to the arrhythmia. Nonetheless, given these findings, caution is necessary when interpreting elevations in NT-proBNP in patients with AF.

**Anemia**

For reasons yet to be explained, the presence and severity of anemia is associated with NT-proBNP elevation.41–43 This association may be related to tissue level myocardial ischemia, plasma expansion in response to anemia, or both. Regardless, patients with anemia, including among those with HF,44 stroke,42 and sickle cell disease,45 NT-proBNP demonstrated incremental prognostic value.

**Critical Illness**

Levels of NT-proBNP have been shown to be highly variable and often markedly elevated in critically ill patients with septic and other noncardiac varieties of shock.46–49 These elevations may be comparable to those in patients with acute HF.47,50 Myocardial depression is often seen in sepsis and other critical conditions, but the exact causes of increased NT-proBNP levels in these settings remain uncertain. Possible mechanisms include altered myocardial contractility, increased wall stress, ventricular dilation, and right heart strain caused by acute respiratory distress syndrome. Study findings showed that levels of NT-proBNP appeared to peak 12–24 hours after admission to the intensive care unit (ICU) in most patients with sepsis.49

The increase in NT-proBNP levels is of important prognostic value.47–49,51 Among 57 patients with septic shock, 35% of whom had evidence of an impaired left ventricular ejection fraction by echocardiography, NT-
proBNP levels were predictive of survival. In another study of 39 patients admitted to the ICU with septic shock, NT-proBNP level was an independent predictor of mortality and also correlated with cardiac function as assessed by invasively measured left ventricular stroke work index.49

In a similar study of 49 patients admitted to the ICU with various types of shock, NT-proBNP was the strongest independent predictor of ICU mortality. Although the NT-proBNP level did not correlate with invasively measured filling pressures or cardiac index, it was superior to both BNP testing and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.47

Ischemic Stroke

NT-proBNP levels are frequently elevated in the setting of acute ischemic stroke.52–55 Various mechanisms have been proposed, including increased secretion of NT-proBNP for the vasodilatory modulation of cerebral ischemia or sympathetic nervous system activation resulting in higher arterial pressures and left ventricular wall stress. In a study of 250 patients, NP levels peaked the day after symptom onset and decreased over 5 days, with no significant difference between levels at 5 days and 6 months after the event. High levels at day 2 appeared to correlate with 6-month mortality.54 Finally, NT-proBNP levels increased in patients with traumatic brain injury with increased intracranial pressure.56

Pulmonary Heart Disease Syndromes

Because all myocytes are able to produce NT-proBNP when stimulated, it is not surprising that the right ventricle can produce significant amounts of NT-proBNP when stretched.57 Although concentrations are usually lower with conditions producing primary right ventricular stress than with those primarily affecting the left ventricle, NT-proBNP concentrations are indeed elevated in with patients with increased right ventricular pressures, such as in complex congenital heart disease, pulmonary embolism, and pulmonary arterial hypertension.58,59 In patients with pulmonary embolism, echocardiographic studies have confirmed that NT-proBNP concentrations correlate with both echocardiographic and invasive parameters of right ventricular dysfunction.45,59,60

Furthermore, it has been shown that elevated concentrations of NT-proBNP correlate with adverse clinical outcome in patients with pulmonary embolism.61 As such, NT-proBNP is both a powerful predictor of prognosis and may be a useful therapeutic decision-making tool in the setting of pulmonary embolism.

In addition to acute right ventricular overload, NT-proBNP concentrations are also elevated in situations of chronic right ventricular overload, such as in sleep apnea and primary pulmonary arterial hypertension.62 Fijalkowska et al63 demonstrated that NT-proBNP concentrations were not only increased in pulmonary arterial hypertension but also predicted 3-year death. A high rate of long-term mortality (61%) was observed in patients in whom plasma NT-proBNP levels increased by ≥50% during the follow-up period, whereas the mortality rate was significantly lower among those patients with more stable NP levels. Lastly, pulmonary arterial hypertension is often an important component of systemic diseases, such as systemic sclerosis, mixed connective tissue disease, and rheumatoid arthritis. A small study by Allanore et al64 comprising 40 patients with systemic sclerosis suggests that NT-proBNP can be used as a screening tool for the early stage of pulmonary arterial hypertension when clinical symptoms are not yet present. Further studies in this area are needed.

Conclusions

Because NT-proBNP testing has become a routine standard of care in both the diagnostic and prognostic assessment of patients with dyspnea, it is essential that clinicians familiarize themselves with all of the common disease processes that are associated with elevated levels of NT-proBNP (Table 1) to avoid the misattribution of HF in this setting.

Key points—differential diagnosis of an elevated NT-proBNP level:

- NT-proBNP should not be considered as simply a marker of HF.
• Myocytes in all 4 cardiac chambers are often exposed to processes that result in NT-proBNP release, including stretch, strain, or hypoxia, as well as less common scenarios, such as exposures to cytotoxic agents.

• As a consequence, elevation of NT-proBNP may occur in states of various forms of heart disease, including heart muscle disease, valve disease, rhythm abnormalities, pulmonary disease, and cytotoxic injury to the heart.

• A unifying theme among the various diagnoses that may lead to NT-proBNP release is a profound relation between the presence/severity of NT-proBNP elevation and adverse outcome.

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

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Amino-Terminal Pro–B-Type Natriuretic Peptide Testing and Prognosis in Patients with Acute Dyspnea, Including Those with Acute Heart Failure

Aaron L. Baggish, MD, a Roland R. J. van Kimmenade, MD, PhD, b and James L. Januzzi, Jr., MD a, *

In patients presenting with acute dyspnea of any cause, elevation of amino-terminal pro–B-type natriuretic peptides (NT-proBNP) is powerfully prognostic for adverse outcomes, including death. Among those with acute destabilized heart failure (HF), an NT-proBNP cut point of approximately 5,000 ng/L is powerfully predictive of death by 76 days after presentation. For 1-year risk stratification, an NT-proBNP value of approximately 1,000 ng/L at presentation is optimal. Among those patients with elevated NT-proBNP levels, a posttreatment NT-proBNP value may be of even greater value than the presenting value. Although NT-proBNP is powerfully prognostic in patients with acute dyspnea with and without HF, the addition of clinical variables strengthens the ability to discriminate risk. In addition, multimarker approaches, including NT-proBNP, for the assessment of acute dyspnea or acute HF appear promising. Indeed, when combined with conventional markers, such as measures of renal dysfunction, anemia, myocardial injury, or inflammation, the predictive value of NT-proBNP is considerably strengthened. Given the strong value of NT-proBNP for risk assessment of the patient with acute dyspnea, a baseline measurement for all patients with dyspnea is recommended, with pretreatment and posttreatment measurement of NT-proBNP recommended for patients with an elevated value, especially those with HF. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:49A–55A)

The prognostic evaluation of patients with heart failure (HF) is among the most powerful applications of natriuretic peptide (NP) testing. Recent NP investigations have led to an enhanced understanding of the syndrome of HF, including acute destabilized and chronic compensated disease. Considering the concept of risk stratification for a disease state of HF, the distinction between acute destabilized and chronic HF is a relatively new concept, with most of the early research focused on patients with chronic HF. Data defining the prognostic capacity of amino-terminal pro–B-type NP (NT-proBNP) across a wide spectrum of disease states and severity in HF now demonstrate the utility of the marker to prognosticate for adverse outcomes among acutely symptomatic individuals, including those with decompensated preexisting HF, as well as those with a newly established diagnosis of HF. In addition, data also support the use of NT-proBNP testing to establish a prognosis in patients with acute dyspnea, regardless of the causal diagnosis.

Prognostic Evaluation of Patients with Acute Dyspnea, Including Those with Acute Heart Failure

The utility of NT-proBNP measurement to estimate a prognosis in patients presenting with new-onset dyspnea from acute HF or other causal pathologies has been firmly established. The short- and longer-term follow-up from trials examining the diagnostic role of NT-proBNP has afforded the opportunity to examine the relation between either presentation or posttreatment NT-proBNP concentrations and outcomes in patients with acute breathlessness. Early studies of NT-proBNP testing in patients hospitalized with acute destabilized HF suggested a potential role of NT-proBNP measurement for prognostication, but they largely focused on the posttreatment concentration of NT-proBNP, with a suggestion that the presenting NT-proBNP value might be less powerfully predictive of outcomes. The most common explanation for this observation is that presentation values of NT-proBNP may be driven primarily by the wall stress incurred by volume overload—a process rapidly rectified by diuretic therapy. In contrast, posttreatment NT-proBNP values may be more reflective of the neurohormonal activation related not only to volume retention but also to the other derangements in HF, such as valvular heart disease, rhythm abnormalities, and pulmonary artery pressures. As such, they may be a more accurate index for future adverse events. Although these earlier studies pointed clinicians and
investigators alike toward the potentially important use of NT-proBNP for treatment surveillance in the hospital and in more chronic HF management, the studies were small and underpowered, and, consequently, they were unable to detect with accuracy the prognostic value of the presenting NT-proBNP concentration.

The first definitive data on the utility of NT-proBNP for short-term mortality risk in acute decompensated HF came from the International Collaborative of NT-proBNP Study (ICON). Among ICON subjects with acute destabilized HF (n = 720), median NT-proBNP levels were higher in those patients dying by 76 days of follow-up (10,426 ng/L; interquartile range, 5,611–23,818 ng/L) compared with survivors at the same time interval (4,873 ng/L; interquartile range, 2,204–10,897 ng/L; p <0.001 for the difference). Receiver operating characteristic curve analysis determined an optimal 76-day mortality prediction NT-proBNP value of 5,180 ng/L (odds ratio, 5.2; 95% confidence interval [CI], 2.2–8.1; p <0.001) with a sensitivity of 68%, a specificity of 72% for predicting, and a negative predictive value of 96% for 76-day mortality status (Figure 1).

Data supportive of NT-proBNP–based risk stratification for longer-term survival after presentation with acute dyspnea (either with or without HF) were reported by the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study groups, who examined the utility of NT-proBNP testing in 599 patients presenting with acute dyspnea. NT-proBNP measurements were made at the time of enrollment among this cohort of 209 (35%) patients with acute destabilized HF and 390 (65%) with an alternative cause of dyspnea. The 1-year mortality status was a prespecified end point, and an analysis of the association between patient characteristics at presentation (including NT-proBNP level) and 1-year mortality was performed. Median NT-proBNP concentrations at presentation for patients who died by 1 year were significantly higher than for survivors (3,277 ng/L vs 299 ng/L, p <0.001). With cohort subdivision into NT-proBNP deciles, a threshold effect characterized by a sharp increase in mortality was observed at an NT-proBNP concentration of approximately 972 ng/L. Subsequent receiver operating characteristic curve analysis identified an NT-proBNP concentration of approximately 1,000 ng/L (986 ng/L) as the optimal cut point for 1-year mortality prediction. Cox regression multivariate analysis was performed to determine and to rank independent predictors of mortality in acute dyspnea and demonstrated that a presentation NT-proBNP concentration >986 ng/L was strongly predictive of death at 1 year, with a hazard ratio of 2.88 (95% CI, 1.64–5.06). Interestingly, the value of NT-proBNP for prediction of death by 1 year in patients with acute dyspnea was equally valuable in subjects with and without acute destabilized HF.

Figure 1. Association between presentation amino-terminal pro–B-type natriuretic peptide (NT-proBNP) values and short-term mortality in acute destabilized heart failure. Log rank, p <0.001. (Reprinted with permission from *Eur Heart J*.)
Utility of Amino-Terminal Pro–B-Type Natriuretic Peptide Testing Relative to Clinical Factors Predictive of Risk in Acute Heart Failure

NT-proBNP levels represent a dominant variable in risk prediction models for HF. However, similar to the data pertaining to acute destabilized HF, diagnosis variables other than NT-proBNP retained prognostic value in multivariate analysis for mortality prediction among patients with acute dyspnea. Furthermore, the c-statistic in a mortality prediction strategy improved from 0.76 to 0.82 by adding clinical variables to isolated NT-proBNP concentrations. This improvement in the prognostic accuracy of a multivariable model, including both clinical and NT-proBNP results, serves as the basis for the subsequently developed PRIDE acute dyspnea risk score.7

A time-honored clinical tool for the assessment of risk in patients with HF is the New York Heart Association (NYHA) symptom severity scale. Ranging from class I (no
symptoms) to IV (symptoms at rest), the NYHA classification is valuable for stratifying risk in chronic HF. Although widely applied in patients presenting with acute destabilized symptoms of HF, the use of the NYHA symptom severity tool to evaluate risk in acute destabilized HF remained poorly defined. As demonstrated in the ICON study, NYHA classification was inadequate for 1-year risk stratification of acute HF, whether it was from systolic or nonsystolic causes. Conversely, an NT-proBNP value >5,180 ng/L (the same cut point for predicting short-term risk in acute HF) was powerfully prognostic for hazard out to 1-year follow-up and was consistently superior to NYHA classification. Furthermore, NT-proBNP measurement was equally useful for prognostication in those with either systolic or nonsystolic HF.

Utility of Amino-Terminal Pro–B-Type Natriuretic Peptide Testing Relative to Biochemical Factors Predictive of Risk in Acute Heart Failure

As noted above, NT-proBNP represented the dominant variable in risk models for the prediction of death in patients with acute dyspnea, including those with acute HF. However, other biochemical variables may be useful for risk stratification in this setting. Among these are more characterized biomarkers, such as measures of renal function, anemia, and myonecrosis, although emerging markers, such as measures of inflammation or myocardial strain may also be of use. Indeed, the prospect of a multimarker approach for risk stratification, as has been suggested for acute ischemic syndromes, is intuitively and clinically attractive.

Multimarker Testing: Amino-Terminal Pro–B-Type Natriuretic Peptides and Other Biomarkers

Renal function and NT-proBNP: In the ICON study, serum creatinine measures at presentation were prognostic of hazard by 76 days, whereas in the PRIDE study, blood urea nitrogen represented an independent predictor of mortality in acute HF, similar to the described use of this measure in registries of acute HF. The interaction between NT-proBNP and renal function is a hotly debated area. Thus, examining the conjoined use of renal assessment and NT-proBNP measures for risk stratification can lead to a better understanding of the impact of renal function on NT-proBNP. In other words, if renal function leads to a more passive accumulation of NT-proBNP, then its prognostic value would be lost in those with renal dysfunction. As was shown first by Anwaruddin et al in the PRIDE study, NT-proBNP retained its value for short-term mortality prediction in patients with impaired creatinine clearance. A subsequent landmark analysis from the ICON study demonstrated that outcomes in acute HF might be better predicted when considering NT-proBNP in the context of renal function. However, rather than diluting the prognostic value of NT-proBNP, impaired renal function appeared to accentuate the prognostic ability of NT-proBNP, with most mortality evident among patients with impaired renal function and an elevation of NT-proBNP (Figure 3). Furthermore, when considering NT-proBNP values in the context of dynamic changes in kidney function during treatment for acute HF (cardiorenal syndrome), it was possible to better refine risk stratification for adverse outcomes. Patients with decreasing renal function in the context of elevated NT-proBNP levels demonstrated the highest mortality, whereas those with no change or improvement of renal function in the context of elevated NT-proBNP levels demonstrated intermediate or more favorable outcomes. Conversely, those with low NT-proBNP levels in the context of dynamic changes of renal function demonstrated favorable outcomes (Figure 4).

Hemoglobin: In the ICON study, serum hemoglobin levels were an independent predictor of short-term hazard in acute HF, although an NT-proBNP value of 5,180 ng/L was superior to measures of anemia. Notably, anemia is highly prevalent in HF and has been variably associated with adverse outcomes in this setting. In addition, the deleterious effects of anemia on myocardial function may lead to elevation of NT-proBNP values independent of the presence or severity of HF. Indeed, in the ICON study, hemoglobin levels independently predicted NT-proBNP values, and the additive use of anemia (as defined by the World Health Organization [WHO] criteria) plus NT-proBNP values >5,180 ng/L provided risk stratification that was more refined than either alone.

Troponin: Serum troponin testing has been shown to be of use for mortality prediction in HF. The mechanism of troponin release in HF is thought to be related not only to ischemic heart disease, but also (possibly because of supply demand inequity) to increased transmural pressure in the context of inadequate cardiac output, as well as ongoing myocardial cell death caused by other, still undefined processes. In this context, troponins have been shown to be prognostically useful in both acute and chronic HF. In the ICON study, troponin T was a predictor of 76-day mortality in acute HF, albeit a weaker predictor than NT-proBNP. In the PRIDE study, Sakhju et al demonstrated that the combination of troponin T plus either B-type NP (BNP) or NT-proBNP gave a more refined ability to stratify risk in acute destabilized HF. In this analysis, NT-proBNP was superior to BNP for prediction of short-term hazard, although both markers were equally useful for longer-term mortality prediction.

Other biomarkers: In addition to the markers discussed above, other biomarkers have been shown to be potentially useful for risk assessment in HF. Among these are measures of inflammatory cell function, such as C-reactive protein. Similarly, levels of galectin-3 (a product of activated cardiac macrophages), and ST2 (an interleukin receptor fam-
ily member thought to be secreted by myocytes in response to stretch) have been shown to be powerfully predictive of short-term (galectin) and longer-term (ST2) mortality in acute HF and were incrementally useful when used in a multimarker strategy with NT-proBNP.

Incremental Prognostic Value of Repeated Measurements of Amino-Terminal Pro–B-Type Natriuretic Peptides

Although a presenting NT-proBNP measurement is of value for estimating risk, it is logical to consider the value of both the presenting and the follow-up/posttreatment NT-proBNP values when considering the likelihood for adverse outcome after presentation for acute HF. As shown by Bettencourt et al, an inadequate response in NT-proBNP values after treatment for acute destabilized HF is associated with significant hazard. This likely reflects a combination of inadequate treatment for the index HF event and persistent derangement in the neurohormonal system, despite acute symptom improvement. Given the logical relation between response to therapy (or lack thereof) and change in NT-proBNP in acute HF, a single follow-up measure after perceived adequate treatment for acute HF may be of incremental value for identifying patients in whom intensification of therapy may be needed.

Other Considerations in Acute Dyspnea: Risk Stratification in Acute Pulmonary Embolism

NT-proBNP is prognostic in those with acute dyspnea, regardless of the mechanism. Among the non-HF causes of dyspnea with the elevation of NT-proBNP levels are acute coronary ischemia (discussed elsewhere) as well as acute pulmonary embolism.

The prognostic value of NT-proBNP for patients with acute pulmonary embolism has been demonstrated in an important study by Kucher et al. NT-proBNP levels were assessed within 4 hours of admission in 73 patients with acute pulmonary embolism. The association between NT-proBNP levels and adverse outcomes as defined by inhospital death, cardiopulmonary resuscitation, mechanical ventilation, pressor requirement, thrombolysis, catheter-based clot fragmentation, or surgical embolectomy was as-
Patients who fulfilled this definition of adverse outcome had significantly higher NT-proBNP levels (median, 4,250 ng/L; range, 92–49,607 ng/L) compared with those after a more benign clinical course (median, 121 ng/L; range, 16–34,802 ng/L; \( p < 0.0001 \)). An NT-proBNP level \(<500 \text{ ng/L}\) was shown to have a negative predictive value for the adverse outcome events of 97%. The prognostic utility of NT-proBNP in the setting of acute pulmonary embolism remained robust (odds ratio, 14.6; 95% CI, 1.5–139.0) after adjusting for indices with known prognostic significance, including pulmonary embolus severity, serum troponin T level, age, and a history of prior HF. A risk stratification strategy for acute pulmonary embolism integrating NT-proBNP testing with troponin T measurement and echocardiography has also been developed.  

Conclusions

Key points—NT-proBNP and prognosis in acute dyspnea/acute HF:

- Among patients presenting with acute dyspnea of any cause, elevation of NT-proBNP levels is powerfully prognostic for adverse outcomes, including death. Therefore, regardless of diagnosis, a measurement of NT-proBNP at presentation with acute dyspnea is recommended.
- Among those with acute destabilized HF, an NT-proBNP cut point of approximately 5,000 ng/L is powerfully prognostic for short-term hazard prediction; given the moderating effects of time on optimal NT-proBNP cut points, a longer time horizon results in lower optimal NT-proBNP cut points. Accordingly, for 1-year risk stratification, an NT-proBNP value of approximately 1,000 ng/L is optimal.
- Although the NT-proBNP value in patients presenting with acute HF is powerfully prognostic, it is intuitively logical that a posttreatment NT-proBNP value would be of greater value. Thus, serial measurement of NT-proBNP is recommended with a baseline and posttreatment assessment.
- NT-proBNP is powerfully prognostic in acute HF, and the addition of clinical variables strengthens the risk assessment. However, NT-proBNP is clearly superior to many clinical variables for prediction of risk in acute HF, including the NYHA symptom severity scale.
- The prospect for a multimarker approach for the assessment of acute dyspnea or acute HF appears promising. When combined with conventional markers,
such as measures of renal dysfunction, anemia, myocardial injury, or inflammation, the predictive value of NT-proBNP is strengthened.

- In addition to predicting prognosis in acute HF from left ventricular failure, NT-proBNP is powerfully prognostic in patients with acute HF caused by right ventricular failure, such as those with pulmonary thromboembolism.

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Amino-Terminal Pro–B-Type Natriuretic Peptides and Prognosis in Chronic Heart Failure

Serge Masson, PhD, and Roberto Latini, MD*

In patients with chronic heart failure (HF), amino-terminal pro–B-type natriuretic peptide (NT-proBNP) levels are among the strongest independent predictors of hazard, and their measurement is useful for prognostication across the entire spectrum of HF disease severity. In patients with chronic HF, repeated determinations of NT-proBNP levels appear to convey additional prognostic value for relevant adverse outcomes, including death or HF hospitalization. Although “hard targets” for NT-proBNP values are not entirely defined, morbidity and mortality in chronic HF appear to increase markedly with an NT-proBNP concentration >1,000 ng/L. Confounding factors (such as renal function or obesity) should be kept in mind when prognostically evaluating patients using NT-proBNP measurements; however, the value of NT-proBNP is retained in these patients. Thus, serial assessment of NT-proBNP is valuable for prognostication in chronic HF in outpatients, and, as such, a measurement at each patient visit or the following of changes in clinical stability is recommended. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008; 101[suppl]:56A–60A)

The determination of B-type natriuretic peptides (BNP) provides powerful and independent prognostic information in patients at all stages of the evolution of chronic heart failure (HF), in a variety of clinical settings.

Prognostic Value in Multicenter Controlled Clinical Trials

The best evidence of the prognostic value of amino-terminal pro-BNP (NT-proBNP) in chronic HF comes from statistically robust controlled clinical trials that include a large number of clinically well-characterized patients from different sites. The first data on NT-proBNP from such a trial came from the Australia–New Zealand Heart Failure Group. In approximately 300 patients with well-characterized chronic HF of ischemic etiology (left ventricular ejection fraction [LVEF] <0.45) randomized to receive carvedilol or placebo, levels of NT-proBNP above the median were associated with increased risks for new decompensated HF events (relative risk [RR], 4.7; 95% confidence interval [CI], 2.2–10.3) and all-cause mortality (RR, 4.7; 95% CI, 2.0–10.9) during 18 months of follow-up, independent of age, New York Heart Association (NYHA) functional class, LVEF, previous myocardial infarction, or previous HF admission. Benefit from carvedilol was confined to those patients entering the trial with above-median peptide levels randomized to active treatment.

In the far larger Valsartan Heart Failure (Val-HeFT) trial, 5,010 patients (85% with blood samples collected at study entry) with mild-to-moderate chronic HF receiving recommended medical therapy were randomized to an angiotensin II type 1 receptor blocker or placebo. A progressive risk for mortality and hospitalization for HF, the 2 centrally adjudicated end points, was found, starting from concentrations of NT-proBNP well below the diagnostic value for chronic HF and extending to very high levels. An increment of 500 ng/L above the baseline concentration of NT-proBNP carried an increased adjusted risk of 3.8% for mortality and 3.0% for hospitalization for HF. On multivariate analysis, NT-proBNP ranked as the first prognostic factor in these patients—again, independent of and more powerful than traditional risk factors, such as NYHA class, age, left ventricular dilation, or renal dysfunction.

The value of NT-proBNP for risk stratification can be seen, even at the more advanced stages of HF. In a subgroup of 1,011 patients in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial that enrolled patients with an LVEF <0.25 and severe HF, NT-proBNP was found to be a powerful predictor of 1-year all-cause mortality (RR, 2.7; 95% CI, 1.7–4.3; \( p = 0.0001 \) for above vs below median) and all-cause mortality or hospitalization for HF (RR, 2.4; 95% CI, 1.8–3.4; \( p = 0.0001 \)). A trend toward the same interaction between NT-proBNP and study treatment as observed in the Australia–New Zealand trial did not attain statistical significance. Similarly, in a substudy (181 patients) of the Prospective Randomized Amloidipine Survival Evaluation II (PRAISE II) trial that enrolled...
patients with severe HF (NYHA class III–IV and LVEF <0.30) of a presumed nonischemic etiology, an increased plasma NT-proBNP level was an independent predictor of 1-year mortality. The prognostic value of NT-proBNP in patients with severe HF has also been observed in smaller single-center studies and in patients referred for consideration of or post cardiac transplantation.

Incremental Prognostic Value of Repeated Measurements of Amino-Terminal Pro–B-Type Natriuretic Peptides in Chronic Heart Failure

A single determination of NT-proBNP at any time during the progression of chronic HF provides a clinically useful tool for risk stratification. As with acute HF, the hypothesis that repeated measurements could carry prognostic information beyond that of a single measure has been confirmed in different settings. The value of repeated determinations of NT-proBNP levels is of special interest for monitoring progression of disease and may help in evaluating the clinical effects of medical therapy. For instance, as noted, changes in NT-proBNP levels during hospitalization were independent predictors of 6-month hospital readmission and death of patients hospitalized for decompensated HF.

In another study, patients who experienced a reduction of NT-proBNP levels >50% after cardiac resynchronization therapy had a more favorable outcome than the rest of the population, and this was associated with positive changes in left ventricular remodeling and exercise capacity. Changes in NT-proBNP concentrations across a median value for 4 months predicted survival in patients with advanced HF referred for consideration of cardiac transplantation, whereas in the Val-HeFT study, relative changes in NT-proBNP concentration during a 4-month period were related to all-cause mortality in 3,488 patients with mild-to-moderate stable and chronic HF (Figure 1).

The value of repeated determinations of NT-proBNP level should be assessed after considering the intraindividual variations of BNP, even in patients deemed clinically stable. Whereas the first reports suggested high intraindividual variations for NT-proBNP (reference change values of 98%), recent findings indicate that this is a gross overestimate and that reference range values around 25% are more appropriate. Intraindividual variations of NT-proBNP are usually smaller than those of BNP, maybe because of a smaller analytic variability and a longer plasma half-life that offers greater biologic stability. In addition, NT-proBNP changes below the estimated “significant” biologic variation have clinical relevance.

Comparison with Other Cardiac Biomarkers

The prognostic value of NT-proBNP is generally superior to that of other circulating biomarkers used in chronic HF (endothelin peptides, adrenomedullin, tumor necrosis factor–α, C-reactive protein, norepinephrine, and erythropoie-
In patients with chronic HF (as in patients with acute HF), the combination of NT-proBNP values with markers of cardiac injury, such as cardiac troponin T, troponin I, or imaging techniques (echocardiography), generally provides independent and incremental prognostic information compared with NT-proBNP alone.

**Prognostic Value in Patients with Chronic Heart Failure and Preserved Systolic Function**

Left ventricular systolic function is preserved in 20%–50% of patients with chronic HF. The plasma levels of NT-proBNP correlate with echocardiographic measurements of both ventricular systolic and diastolic functions. Whereas the prognostic value of NT-proBNP in patients with impaired left ventricular systolic function is well documented, there are a scarce data for the population of patients with chronic HF and preserved systolic function. In a prospective study that included 161 patients with HF, the probability of death within 12 months after hospital admission was predicted by plasma levels of NT-proBNP in patients with systolic dysfunction as well as in patients with preserved systolic function. Similarly, NT-proBNP values at discharge or changes in NT-proBNP concentration during hospitalization were strong prognostic predictors of mortality, regardless of systolic function, in 244 patients admitted for decompensated HF and followed for 6 months. Upcoming prospective trials will clarify the utility of NT-proBNP in the prognosis and management of HF with preserved LVEF.

**Influence of Confounding Factors**

The clinical interpretation of NPs may be confounded by factors that influence the plasma levels of NT-proBNP. For instance, an inverse relation between body mass index and both BNP and NT-proBNP has been observed in patients with and without HF, as shown in Table 1. Introduction of metoprolol causes a transient increase in plasma NPs (BNP, NT-proBNP, and NT-pro–A-type NP) that is not related to a deterioration of clinical status. Similarly, renal dysfunction may also influence the plasma levels of NT-proBNP, further complicating the interpretation of NT-proBNP levels, although it is logical to assume that elevated NT-proBNP values in patients with combined chronic HF and chronic kidney disease have a higher risk for adverse outcomes.

**Conclusions**

**Key points—NT-proBNP and prognosis in chronic HF:**

- In chronic HF, measurement of NT-proBNP is among the strongest independent predictors of all relevant clinical outcomes and is useful across the entire spectrum of HF disease severity.
- Among patients with chronic HF, repeated determinations of NT-proBNP levels appear to convey additional prognostic value for relevant adverse outcomes, including death or destabilization of HF requiring hospitalization, and are thus recommended at each patient evaluation.
- Target values for outpatient prognostication remain relatively undefined. However, the risk for morbidity and mortality in HF appears to increase markedly with an NT-proBNP concentration >1,000 ng/L.
- With serial measurements of NT-proBNP in the chronic outpatient setting, patterns of NT-proBNP levels may be identified, such that increasing levels of NT-proBNP might identify patients at higher risk for impending complications.
- Confounding factors (including obesity and renal dysfunction) may complicate the clinical interpretation of circulating NT-proBNP levels in patients with chronic and stable HF and should be considered when evaluating patients using NT-proBNP measurements.

**Author Disclosures**

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Amino-Terminal Pro–B-Type Natriuretic Peptides in Stable and Unstable Ischemic Heart Disease
Torbjørn Omland, MD, PhD, MPH, and James A. de Lemos, MD

Across the entire spectrum of ischemic heart disease, amino-terminal pro–B-type natriuretic peptides (NT-proBNP) are a strong and independent prognostic indicator, representing a particularly strong predictor of heart failure or death. This risk is independent of all other variables, including renal function or troponin, and is proportional to the magnitude of NT-proBNP release, with higher risk observed among those with a more marked elevation of the marker. Although prospective studies on the effect of NT-proBNP measurement in guiding therapy in ischemic heart disease are lacking, among patients presenting with acute coronary syndromes, it is recommended to measure NT-proBNP on (or near) the time of admission. An elevated initial NT-proBNP concentration should prompt consideration of an early invasive management approach. Consideration should be given to repeating the NT-proBNP measurement after 24–72 hours and again at 3–6 months because these follow-up measurements provide more long-term prognostic information than single measures at presentation. In acute ischemic heart disease, an NT-proBNP value >250 ng/L is associated with an adverse prognosis. In patients with stable coronary artery disease, measurement may be performed for prognostication purposes at 6- to 18-month intervals. In the case of clinical suspicion of disease progression, a new sample may be warranted. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:61A–66A)

The cardiac natriuretic peptide (NP) system is rapidly activated after acute ischemic injury. Increased production of amino-terminal pro–B-type NPs (NT-proBNP) after episodes of acute ischemia may be caused by a variety of factors. Increased myocardial stretch secondary to ischemia-induced left ventricular systolic and/or diastolic dysfunction may be quantitatively the most important stimulus. However, ischemia and cellular hypoxia can also stimulate production of BNP and NT-proBNP in the absence of demonstrable hemodynamic changes. Other factors, including increased heart rate and a variety of proinflammatory cytokines and neurohormones with vasoconstrictive, antidiuretic, hypertrophic, and cytoproliferative effects may also stimulate NP synthesis during ischemia. Expression of NPs in human coronary atherosclerotic plaques has been reported, raising the possibility that the atherosclerotic lesions may represent an additional source of circulating NT-proBNP, a finding supported by recent observational data showing an association between the burden of atherosclerosis and NT-proBNP levels after accounting for left ventricular structural and functional abnormalities.

On a clinical level, studies clearly demonstrate that NT-proBNP levels are increased after episodes of ischemia. Elevated NT-proBNP levels have been observed in patients with unstable angina and during and after percutaneous coronary intervention (PCI). In patients with angiographically documented coronary artery disease (CAD), the increase in NT-proBNP concentration is in proportion to the size of the reversible perfusion defect as assessed by nuclear imaging methods.

Amino-Terminal Pro–B-Type Natriuretic Peptides in Acute Coronary Syndromes

Plasma profile and determinants of NT-proBNP elevation: The magnitude and duration of the increase in plasma concentrations of NT-proBNP after acute coronary syndromes (ACS) are proportional to myocardial infarct size and the degree of left ventricular dysfunction. Circulating concentrations are higher in anterior than in inferior myocardial infarction (MI), and a variably observed biphasic pattern of BNP and NT-proBNP secretion (with a second peak on days 2–5) may be more common in patients with anterior MI than with inferior MI.

Diagnostic value of NT-proBNP: Although NT-proBNP may increase during ischemic episodes, use of NT-proBNP as a marker of coronary ischemia lacks both sensitivity and specificity for diagnostic purposes in suspected ACS. In contrast to the narrow range of normal values for cardiac-specific troponins, circulating NT-proBNP levels are determined by a variety of cardiac and noncardiac factors (eg, age, sex, renal function) and therefore display a relatively wide range of values. In addition, the magnitude of increase in NT-proBNP observed in patients with ACS is typically considerably lower than is observed in patients with acute destabilization of heart failure (HF). Accordingly, the signal-to-noise ratio is relatively
low and unfavorable for diagnostic purposes, particularly if the individual’s “normal” value is unknown.

**Prognostic value of NT-proBNP:** The first study showing an association between NT-proBNP levels and outcome after ACS, published in 1998, mainly comprised patients with ST-segment elevation MI. Based on studies showing that BNP and NT-proBNP were elevated in unstable angina and could be normalized after successful PCI, it was subsequently postulated that NT-proBNP would be predictive of outcome across the spectrum of ACS.

Beginning in 2002, a series of large observational studies (with >12,000 patients) has convincingly shown that NT-proBNP levels obtained acutely or in the subacute phase after non-ST-segment elevation ACS are strongly associated with both short-term and long-term cardiovascular and total mortality, independent of conventional risk factors, including troponin concentrations, presence of clinically overt HF, or left ventricular systolic dysfunction. The relation between NT-proBNP concentrations and hazard in ACS is directly proportional; that is, with higher values of NT-proBNP, a higher risk for mortality is observed (Figure 1). Indeed, NT-proBNP has consistently been found to be among the strongest, if not the strongest, predictor of mortality compared with standard risk stratification variables.

To date, we are not aware of any negative study relating NT-proBNP with mortality and HF outcomes after ACS. In contrast, a weak or nonexistent association has been observed between NT-proBNP and recurrent MI after adjusting for confounding variables. This finding is surprising, given the strong associations seen between NT-proBNP and the extent of CAD and ischemia, raising the suggestion that either NT-proBNP is unable to predict recurrent MI or that any recurrent MI in a patient with elevated NT-proBNP is much more likely to result in mortality, thus obscuring the clinical event of ischemia. Although both hypotheses are plausible, the fact that NT-proBNP has been found to be strongly associated with risk for HF after ACS suggests that the ability of NT-proBNP to predict death in ACS may be in large part explained by its ability to predict subsequent pump failure, rather than another ischemic event.

**Serial measurements of NT-proBNP:** Studies evaluating the additional value of serial measurements of NT-proBNP in patients with ACS are still relatively sparse. Data from the Fragmin and Fast Revascularization During Instability in Coronary Artery Disease–II (FRISC-II) study show that NT-proBNP levels are highest on admission, decrease markedly in the first 24 hours, and then decrease more gradually over the following 6 months. In a substudy of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study, the addition of a second NT-proBNP value 72 hours after admission appeared to improve risk prediction of the end point of death or recurrent MI at 30 days. In the PRISM study, regardless of the NT-proBNP value on admission, an NT-proBNP concentration >250 ng/L indicated a markedly increased risk (Figure 2). However, the clinical relevance of the findings is somewhat unclear because most patients presenting with ACS will be referred to coronary angiography within 72 hours of presentation, a strategy not espoused in the PRISM study, and the effects of early revascularization on
both NT-proBNP values and the prognostic impact of the level of NT-proBNP remains less clear.

**Prediction of the effect of therapeutic intervention in ACS:** A crucial question concerning the use of NT-proBNP in ACS is whether the test result will predict the effect of specific therapeutic interventions and thus could be used to guide subsequent management. Currently, the evidence for such a relation is relatively limited, partly because few contemporary clinical trials document a significant effect of intervention on mortality in ACS. In an analysis based on the FRISC-II trial, a trend toward greater mortality reduction in the early invasive arm was observed in the highest NT-proBNP tertile. In contrast, no beneficial effect of the early invasive strategy was observed in those in the lower 2 NT-proBNP tertiles, suggesting that NT-proBNP may be useful for identifying patients who will benefit from an early invasive strategy. These findings were confirmed and extended by recently published data based on the Global Utilization of Strategies to Open Occluded Arteries–IV (GUSTO-IV) trial, which suggested that patients with higher NT-proBNP levels may have a survival benefit from coronary revascularization. In contrast, no beneficial effect of the early invasive strategy was observed in those in the lower 2 NT-proBNP tertiles, suggesting that NT-proBNP may be useful for identifying patients who will benefit from an early invasive strategy. These findings were confirmed and extended by recently published data based on the Global Utilization of Strategies to Open Occluded Arteries–IV (GUSTO-IV) trial, which suggested that patients with higher NT-proBNP levels may have a survival benefit from coronary revascularization.

**Amino-Terminal Pro–B-Type Natriuretic Peptides in Stable Coronary Artery Disease**

As mentioned above, myocardial ischemia can induce a reversible increase in regional wall stress that may lead to augmented NT-proBNP production. Accordingly, NT-proBNP levels are increased in patients with stable CAD after episodes of ischemia. Several studies have reported a relation between circulating levels of NT-proBNP and long-term, all-cause mortality in patients with stable CAD, independent of left ventricular systolic dysfunction and other conventional risk factors. Extending these novel data, an association between NT-proBNP levels and cardiovascular end points (death, MI, stroke, HF) in patients with stable CAD and without symptoms or signs of HF at presentation was reported recently. Importantly, NT-proBNP provided prognostic information above and beyond that obtained from echocardiog-
raphy and nuclear stress tests for detection of myocardial ischemia. Furthermore, the addition of NT-proBNP to standard clinical assessment and echocardiographic indices improved the area under the receiver operating characteristics curve for prediction of adverse cardiovascular events compared with clinical risk factors and echocardiographic indices alone. NT-proBNP also provides important prognostic information in patients undergoing nonurgent PCI.

Prediction of the effect of therapeutic intervention:
The effect of therapeutic interventions is commonly associated with the patient’s baseline risk. Accordingly, angiotensin-converting enzyme (ACE) inhibitors have proved to be effective in reducing mortality and morbidity in patients at high risk, but they failed to reduce cardiovascular death, MI, and coronary revascularization in low-risk patients with stable CAD. Given the prognostic value of NT-proBNP in stable CAD, measurement of this marker could potentially represent an effective strategy to identify patients who benefit from ACE inhibition.

However, in a post hoc analysis of 3,761 subjects participating in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial, which randomized patients with stable CAD and preserved left ventricular ejection fraction to the ACE inhibitor trandolapril or to placebo, no interaction was observed with treatment strategy. In other words, the ACE inhibitor treatment was ineffective, regardless of NT-proBNP concentration at baseline. A contributing factor to the failure of NT-proBNP to identify patients who benefit from ACE inhibition may be related to its inability to predict ischemic events.

Relative Prognostic Value of B-Type Natriuretic Peptides and Amino-Terminal Pro–B-Type Natriuretic Peptides

Data on the relative prognostic value of BNP and NT-proBNP in patients with unstable and stable CAD are relatively limited. Most available data in high-risk patients suggest that the prognostic merit of BNP and NT-proBNP are relatively similar. Recent data, however, indicate that NT-proBNP may have prognostic advantages over BNP in low-risk populations with stable CAD and preserved left ventricular systolic function (Table 1). A possible explanation may be that NT-proBNP, because of its longer half-life, is less prone to rapid fluctuations in plasma levels and thus provides a more accurate reflection of cardiorenal status.

![Figure 3. Amino-terminal pro–B-type natriuretic peptides (NT-proBNP), troponin T, and the effect of coronary revascularization in acute coronary syndromes. (Reprinted with permission from J Am Coll Cardiol.17)](image)
Conclusions

Key points—NT-proBNP and prognosis in ischemic heart disease:

- NT-proBNP is a strong and independent prognostic indicator in unstable and stable CAD, and is a particularly strong predictor of subsequent HF or death.
- The risk associated with NT-proBNP elevation in unstable and stable CAD is independent of all other variables, including renal function or troponins.
- The risk associated with NT-proBNP elevation in both unstable and stable CAD is proportional to the magnitude of NT-proBNP release, with higher risk observed among those with a more marked elevation of the marker.
- Although prospective studies on the effect of NT-proBNP measurement in guiding therapy in ischemic heart disease are lacking, among patients presenting with ACS, it is recommended to measure NT-proBNP on (or near) the time of admission. An initial NT-proBNP concentration that is elevated should prompt consideration of an early invasive management approach, particularly if troponin concentrations are also elevated.
- Repeat NT-proBNP measurement should be considered after 24–72 hours and again at 3–6 months be-

![Figure 4. Relation between amino-terminal pro–B-type natriuretic peptide (NT-proBNP) concentrations in stable coronary artery disease and long-term outcome.](image)

Across quartiles of NT-proBNP, a significant and continuous risk was detectable out to 10 years from enrollment. First quartile, $<64$ ng/L; second quartile, 64–169 ng/L; third quartile, 170–455 ng/L; and fourth quartile, $>455$ ng/L. (Reprinted with permission from *N Engl J Med.* 19)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BNP HR (95% CI)* † p Value</th>
<th>NT-proBNP HR (95% CI)* † p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular mortality</td>
<td>1.06 (0.87–1.38) 0.47</td>
<td>1.69 (1.38–2.07) &lt;0.001</td>
</tr>
<tr>
<td>Fatal/nonfatal MI</td>
<td>0.91 (0.77–1.07) 0.24</td>
<td>1.02 (0.87–1.19) 0.84</td>
</tr>
<tr>
<td>Fatal/nonfatal HF</td>
<td>1.62 (1.32–1.97) &lt;0.001</td>
<td>2.35 (1.86–2.98) &lt;0.001</td>
</tr>
<tr>
<td>Fatal/nonfatal stroke</td>
<td>1.15 (0.91–1.45) 0.24</td>
<td>1.63 (1.26–2.12) &lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; HF = heart failure; HR = hazard ratio; MI = myocardial infarction.

* Adjusted for randomization status; age; sex; body mass index; left ventricular ejection fraction <0.50; estimated glomerular filtration rate; current smoking; history of hypertension or measured hypertension or history of MI; diabetes mellitus; stroke; percutaneous coronary intervention; coronary artery bypass graft surgery; total cholesterol; C-reactive protein; and use of a β-blocker; lipid-lowering drug; aspirin or antiplatelet medication; and a diuretic.

† HR and 95% CI per 1 SD pg/mL in log BNP and log NT-proBNP.
cause these follow-up measurements provide more long-term prognostic information than single measures at presentation. In ischemic heart disease, a persistently elevated NT-proBNP value >250 ng/L is associated with an adverse prognosis.

- In patients with stable CAD, measurement may be performed for prognostication purposes at 6- to 18-month intervals. In the case of clinical suspicion of disease progression, a new sample may be warranted.

Author Disclosures

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Amino-Terminal Pro–B-Type Natriuretic Peptide Testing for Inpatient Monitoring and Treatment Guidance of Acute Destabilized Heart Failure

Paulo Bettencourt, MD,a and James L. Januzzi, Jr., MDb,∗

Although typically elevated at presentation in the context of destabilized heart failure (HF), amino-terminal pro–B-type natriuretic peptide (NT-proBNP) values typically decrease rapidly among patients who have a favorable response to therapy. Given this, it is natural to examine the relation between NT-proBNP and therapeutic interventions for acute HF. Both presentation and posttreatment NT-proBNP concentrations have some value for prognostication of recurrent HF hospitalization or death. However, the percent change in NT-proBNP after treatment for acute HF may be a more powerful method for risk stratification. Although prospective studies on the effect of NT-proBNP measurement in guiding therapy in acute destabilized HF are lacking, observational data suggest that a 30% decrease in NT-proBNP values during hospitalization is a reasonable goal. If a baseline measure of NT-proBNP is not available, an NT-proBNP level <4,000 ng/L after acute treatment is an alternative goal. Because the criteria for determining restabilization from destabilized HF prominently include clinical and routine laboratory testing rather than NP measures, the frequency of NT-proBNP measurement should not be excessive in patients with acute HF, with measures at baseline/presentation and after perceived recompensation to evaluate for the desired decrease in NT-proBNP concentrations. A remeasurement of NT-proBNP may also be useful for evaluation of new or worsened symptoms. In those patients without a decrease in NT-proBNP despite perceived recompensation from HF, a review of adequacy of treatment, goals of therapy, and consideration of prognosis is recommended. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:67A–71A)

At present, the recommended standard approach for therapy monitoring of patients with acute heart failure (HF) is based on clinical assessment (including history and physical examination, vital signs, and daily weights) as well as simple laboratory evaluations, including assessment of renal function.1,2 Unfortunately, given the relative insensitivity and poor specificity of these recommended approaches, a very high short-, medium-, and longer-term mortality and readmission rate is noted among patients after hospitalization for acute HF. Accordingly, improvements in the methods by which patients are assessed for adequacy of therapy are needed. In this, there is increasing interest in the use of natriuretic peptides (NPs) to monitor adequacy of therapy for acute HF, from presentation to outpatient follow-up.3–9 Several studies have shown a robust prognostic value of NPs across the entire HF severity spectrum.5,6,10–15 Also, several therapies with known benefit for HF are accepted to decrease concentrations of NPs after their initiation. Among these agents are diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, spironolactone, and nesiritide.7,16–20 Thus, it is natural to speculate on the potential application of NP measurement during recompensation of acute destabilized HF to monitor and guide HF therapy.

With respect to the use of amino-terminal pro–B-type NP (NT-proBNP) as a guide to prognosis, it is accepted that a baseline/presenting NT-proBNP value offers significant prognostic information; a subsequent follow-up measure after treatment for acute HF may offer even more value. Indeed, given the inadequacy of subjective assessment for HF severity in decompensation (and likely, consequent concomitant inadequacy of subjective assessment of HF recompensation),21 the relation between more favorable outcomes in patients with a significant decrease in NT-proBNP concentration during acute HF therapy argues for a relation between adequacy of therapy for HF and NT-proBNP values. Knebel et al8 demonstrated that among patients treated for acute decompensated HF, those who had a significant response in pulmonary capillary wedge pressure or cardiac hemodynamics had a significant and sustained decrease in NT-proBNP values, with an evident decrease in values as early as 16 hours from presentation. In contrast, those pa-
tients who did not have a significant recompensation in filling pressures or hemodynamics did not have a significant decrease in NT-proBNP values (Figure 1). Similar results were reported by Cioffi et al,7 who noted that a lack of NT-proBNP response after treatment was not always paralleled by a decrease in filling pressures, but it was associated with adverse outcome.

The importance of the response of NT-proBNP to therapeutic intervention in terms of clinical events has been demonstrated. Bayes-Genis et al5 showed that changes in NT-proBNP values from admission to discharge among hospitalized patients who had acute destabilized HF with complications were more likely to be much smaller (a decrease typically ≥15%) than those who survived (who typically showed a decrease ≥50%). In this study, the NT-proBNP reduction percentage during admission for acute HF had an area under the receiver operating characteristic curve of 0.78 (p = 0.002), superior to the presenting NT-proBNP concentration for this purpose. Similar results were subsequently demonstrated by Di Somma and colleagues,16 who found a 58% reduction in NT-proBNP concentrations over a 7-day period after successful treatment for acute destabilized HF.

Subsequently, more definitive data on the importance of NT-proBNP concentrations at hospital admission and discharge for predicting outcomes were demonstrated by Bettencourt and colleagues.6 In this landmark analysis, the admission and discharge NT-proBNP concentrations were compared for their ability to predict subsequent hazard. In this analysis, an NT-proBNP level >6,779 ng/L at presentation predicted a trend toward hazard for readmission or death. However, the posttreatment NT-proBNP value of 4,137 ng/L was a much stronger predictor of hazard, with a 8% increase in the likelihood of death or readmission over 6 months per 1,000 ng/L of NT-proBNP over this threshold (p <0.0001). These data are compelling and supportive of monitoring the discharge NT-proBNP concentration to gauge adequacy of HF therapy and to predict hazard. However, the difference between selecting an NT-proBNP target for discharge or the relative change in NT-proBNP over hospital treatment must be considered.

To best consider the ramifications of a target NT-proBNP value or a percent change goal, it is necessary to consider the mechanism that underlies the NT-proBNP elevation and resolution among patients with acute destabilized HF. Given the relation between NT-proBNP elevation and the presence of HF, even when compensated, it is reasonable to expect that even when stable, a patient with chronic stable HF will usually have some degree of derangement in the NP system, frequently with marked elevations in NT-proBNP; these elevations are strongly correlated with adverse outcome. However, when such patients develop destabilized HF, a significant elevation of the NT-proBNP concentration is usually observed, frequently dramatically above that of an already elevated baseline.

Accordingly, the basis of NT-proBNP elevation in acute destabilized HF might be considered as being related to 2 general pathologies. First, there is probably a chronic baseline level of NT-proBNP which, although not likely to be entirely immutable, probably reflects the sum total of the various cardiac abnormalities that may lead to the elevation of NT-proBNP in the heart, including left ventricular systolic dysfunction, left ventricular diastolic dysfunction, valvular heart disease, pulmonary artery hypertension, and right ventricular size and function, as well as heart rhythm abnormalities.10,22,23 It is on this baseline level of NT-proBNP that a second pathology, namely acute destabilization may occur—typically related to volume retention—with consequent acute elevation of NT-proBNP, reflective of this secondary component of myocardial wall stress, namely fluid overload. Given the significant variability from patient to patient with respect to the various components of pathologies that will lead to NT-proBNP elevation in acute destabilized HF,24 as well as the significant intrapatient biologic variability of the peptide,25,26 rather than selecting a “hard target” NT-proBNP concentration for determining treatment success (as has been suggested for B-type NP9), a more logical approach might be to examine the relation between the relative change in NT-proBNP and outcomes. In doing so, similar to Bayes-Genis and colleagues,5 Bettencourt et al6 demonstrated that in fact, the percent change in NT-proBNP from hospital admission to discharge was more important for predicting hospitalization-free survival from HF than the absolute value at discharge. Among those with acute destabilized HF, regardless of the NT-proBNP value at discharge, a decrease by >30% in NT-proBNP concentration from presentation to discharge was associated with very favorable outcomes (Figure 2). In contrast, among those patients with a <30% decrease in NT-proBNP concentrations (but no increase), intermediate outcomes were observed, whereas in those in whom an increase in NT-proBNP concentrations was observed, an extremely poor prognosis was demonstrated.

These results suggest that the magnitude of the decreasing slope of NT-proBNP during hospitalization is superior, as a marker of prognosis, to a particular threshold value of NT-proBNP. In particular, patients who have both subjective and objective clinical improvement, but who do not achieve an NT-proBNP reduction, may be candidates for more intensified medical approaches and perhaps more intensive outpatient monitoring and follow-up.

No data exist to support daily or even more than daily measurement of NT-proBNP in the context of acute HF monitoring. Rather, because clinical recompensation from acute destabilized HF is considered to be a clinical as well as a biochemical event, monitoring of symptoms/signs, daily weights, and recommended laboratory tests, such as renal function, is obviously still necessary. Only when other measures argue for clinical recompensation is the application of NT-proBNP testing likely to be effective. Thus, a suggested algorithm for NT-proBNP–based management of the inpatient with acute destabilized HF is to obtain a
Figure 1. Relation between successful treatment for acute destabilized heart failure (HF) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP) values. In patients with successful treatment for acute HF, a significant decrease in NT-proBNP concentrations (frequently >50%) were observed. CV = cardiovascular; ED = emergency department. (Reprinted with permission from *Eur J Heart Fail*.)

Figure 2. Association between in-hospital change in amino-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations and subsequent outcomes in patients treated for acute heart failure. In those with an inadequate decrease (or increase) in NT-proBNP concentrations, a significant risk for death or rehospitalization is noted. *p* < 0.0001. (Reprinted with permission from *Circulation*.)
baseline measurement for diagnosis, triage, and in-hospital prognostication; treat the patient per usual guidelines for HF; and then, when the patient is deemed to be successfully recompensated on clinical grounds, obtain an NT-proBNP level to evaluate for successful resolution. Whenever possible, a decrease of ≥30% of the NT-proBNP concentration after treatment for acute destabilized HF is desirable.

Conclusions

Key points—NT-proBNP and therapy monitoring for acute destabilized HF:

- NT-proBNP is a strong and independent prognostic indicator in acute destabilized HF.
- NT-proBNP values typically decrease rapidly among patients with acute destabilized HF who have a favorable response to therapy.
- Although NT-proBNP presentation values or the absolute values after treatment of acute destabilized HF each have some value for prognostication of recurrent HF hospitalization or death, the percent change in NT-proBNP after acute HF treatment may be a more powerful method for risk stratification.
- Although prospective studies on the effect of NT-proBNP measurement in guiding therapy in acute destabilized HF are lacking, observational data suggest that a 30% decrease in NT-proBNP values during hospitalization for acute destabilized HF is a reasonable goal. If a baseline measure of NT-proBNP is not available, an NT-proBNP level <4,000 ng/L after acute treatment is desirable.
- Because criteria for determining restabilization from destabilized HF include clinical factors as well as biochemical measures, the frequency of NT-proBNP measurement should be optimally applied at 2 time points: baseline/presentation (for diagnosis, triage, and a “starting point” for therapy) and after perceived recompensation has occurred, to determine eligibility for discharge or intensification of therapy.
- In patients with an increase in NT-proBNP during perceived recompensation from acute destabilized HF, a review of adequacy of treatment, goals of HF therapy, and consideration of HF prognosis is recommended.

Author Disclosures

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- **James L. Januzzi, Jr., MD**, reports receiving significant funds in the form of research support, speaker honoraria, and consulting fees from Dade-Behring, Inverness Medical Innovations, and Roche Diagnostics; modest fees for consulting from Ortho Clinical Diagnostics and Response Biomedical; and modest fees for speaking and consulting from Biosite.


Amino-terminal pro–B-type natriuretic peptide (NT-proBNP) is a strong and independent prognostic marker in patients across the spectrum of heart failure (HF) stages, including patients managed in the outpatient setting. Serial measures of NT-proBNP are more valuable than single measures for prognosis, and biologic variation of the marker should allow serial monitoring. Furthermore, given that NT-proBNP levels decrease in response to the addition of therapies with proven benefit for HF (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, spironolactone, exercise therapy, and biventricular pacing), it is logical to expect that targeting therapy to decrease NT-proBNP levels may facilitate more optimal use of proven HF therapies and may reduce adverse clinical outcomes. The optimal strategy for NT-proBNP monitoring with regard to frequency of testing or whether to use standard or individualized targets is still being determined. Preliminary results are promising for targeting an outpatient NT-proBNP concentration of approximately <1,000 ng/L. Current data suggest that when NT-proBNP levels are not at goal or increase from prior measurements, the risk for hazard is increased. Adjustments in treatment and serial clinical follow-up with NT-proBNP retesting should be considered at frequent intervals until biochemical stabilization or achievement of a maximally tolerated medical program. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:72A–75A)

Plasma amino-terminal pro–B-type natriuretic peptides (NT-proBNP) are accurate and powerful markers of heart failure (HF) symptom status, severity of cardiac dysfunction, and prognosis. Therefore, serial testing could potentially be used to monitor clinical status and to guide treatment in chronic HF.

Serial Prognostic Assessment

Across the spectrum of HF stages, assessment of NT-proBNP levels at a single time point in stable outpatient settings provides a powerful independent prediction of mortality and new HF events. Serial testing provides incremental prognostic information: a decrease in levels at follow-up predicts fewer HF hospitalizations or deaths, and an increase in levels predicts a greater likelihood of these adverse outcomes.1–3

Variability in Amino-Terminal Pro–B-Type Natriuretic Peptide Levels

In clinically stable individuals, plasma NT-proBNP levels vary among serial tests, reflecting analytic accuracy and altered secretion and clearance.4 Multiple factors contribute to variability, including myocardial ischemia, renal dysfunction, and neurohormonal activation. Clinically undetected elevation of cardiac filling pressures has been demonstrated with new implantable devices and may be an important determinant of NP variability.5,6 Alternative splicing of NT-proBNP may also contribute to variability in circulating levels.7 Recent studies suggest that in stable patients, long-term intraindividual variation in NT-proBNP levels is approximately 30%, with a change >23% likely to indicate a clinically significant change beyond background variation.8,9 Variability is lower at higher peptide levels in the range associated with greater adverse outcome and above target levels in intervention studies.10 NT-proBNP secretion is nonlinear, and when log-transformed peptide levels are assessed in stable patients, peptide levels appear constant with a variability <10%.8,9

Response to Treatment

NT-proBNP levels change after treatment with proven HF medications.11–14 NT-proBNP levels decrease after institution of diuretic and vasodilator therapy,12,15 whereas with-
drawal of diuretics is associated with an increase in peptide levels. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers cause a decrease in peptide levels, as does initiation of spironolactone. The response to β-blockers is more complex. Introduction of metoprolol in stable mild HF is associated with an initial increase in NT-proBNP levels that reflects changes in secretion and clearance but is not caused by clinical decompensation. Longer-term NT-proBNP levels decrease, paralleling changes in left ventricular remodeling. The response of NT-proBNP to carvedilol (and other vasodilator β-blockers) may be different from metoprolol, with an initial decrease in natriuretic peptide (NP) levels. Because there were significant differences in the stages of HF in the studies comparing the effects of β-blockers, these findings may be more attributable to different responses in NT-proBNP at different stages of HF, rather than heterogeneity in response to different agents.

Exercise therapy has beneficial effects in chronic HF, and adequate cardiopulmonary training has been shown to decrease levels of NPs in a clinically relevant manner. Changes in NT-proBNP levels with cardiac resynchronization therapy (CRT) were assessed in the Cardiac Resynchronization in Heart Failure (CARE-HF) study. Median peptide levels were similar at baseline in CRT and medical groups, but they were significantly lower in the CRT group at 3 and 19 months. These changes were associated with improvements in left ventricular volumes and systolic function. Importantly, although NT-proBNP values may be affected by therapeutic intervention, NT-proBNP levels may also identify subjects who benefit most from therapy. In the Australia–New Zealand trial of carvedilol in HF caused by ischemic cardiomyopathy and also in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study of carvedilol in advanced HF, subjects with the highest NT-proBNP levels appeared to gain the greatest benefit from treatment with carvedilol.

Figure 1. Kaplan-Meier event curves for time to first heart failure event or death show a significant reduction in the events in the group whose treatment was adjusted according to serial measurements of plasma amino-terminal pro–B-type natriuretic peptide (solid curve) compared with standard clinical evaluation (dashed curve). p = 0.049. (Reprinted with permission from Lancet.)

Guiding Heart Failure Therapy

Because lower levels of NT-proBNP are associated with better clinical outcome, titration of treatment to achieve lower NT-proBNP levels may be advantageous compared with standard empiric therapy. Vasodilator therapy can be titrated to achieve lower NP levels. In a small pilot study, treatment targeted to achieve NT-proBNP levels <200 pmol/L resulted in fewer combined events of HF decompensation, hospitalization, and mortality (Figure 1). Compared with clinically guided treatment, patients randomized to the NT-proBNP–guided arm of this study received higher doses of diuretic and ACE inhibitor therapy. Plasma NT-proBNP levels decreased in the hormone-guided group but not in the clinically guided group. Similar findings were demonstrated in the recently published Systolic Heart Failure Treatment Supported by BNP Multicenter Randomized Trial (STARS-BNP), where treatment was targeted to the B-type NP (BNP) level.

More recently, the Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide versus the Clinical Congestion Score (STARBRITE) study assessed the impact of targeting treatment to achieve an individualized BNP target during shorter-term follow-up. Although this strategy did not significantly reduce the number of days alive and out of the hospital, it may improve quality of life and other outcomes.
hospital, it did result in more optimal use of ACE inhibitor and β-blocker therapy, whereas diuretics were less likely to be increased.

The effect of guiding treatment to achieve targeted levels of NT-proBNP is currently being tested in several larger randomized trials. The BNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) study\(^{36}\) and the Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF)\(^{37}\) have been published as methods studies, and many other studies are ongoing to examine the role of NT-proBNP guidance for HF therapy. These studies will assess the effect of this strategy in large cohorts that are representative of real-life HF populations receiving modern therapy.

### Conclusions

**Key points—NT-proBNP and therapy monitoring for chronic stable HF:**

- NT-proBNP is a strong and independent prognostic marker across the spectrum of HF stages.
- Serial NT-proBNP levels provide incremental risk stratification.
- Variation in NT-proBNP levels between serial measurements in stable individuals is approximately 30% and is at a level that should allow serial monitoring.
- NT-proBNP levels decrease in response to the addition of therapies with proven benefit for HF, including ACE inhibitors, angiotensin receptor blockers, diuretics, spironolactone, exercise therapy, and biventricular pacing.
- There is a short-term increase in NT-proBNP levels after initiation of β-blocker therapy that does not reflect clinical decompensation. Levels decrease with longer-term β-blocker therapy.
- Targeting therapy to decrease NT-proBNP levels may facilitate more optimal use of proven HF therapies and may reduce adverse clinical outcomes.
- The optimal strategy for NT-proBNP monitoring with regard to frequency of testing and whether to use a standard or individualized targets is still being determined. Current data suggest that when clinical signs and/or NT-proBNP levels indicate decompensation (increase >30%), adjustments to treatment, and serial clinical follow-up and NT-proBNP retesting should be considered at 1- to 2-week intervals.

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15. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoter-


Amino-Terminal Pro–B-Type Natriuretic Peptide Testing
in Neonatal and Pediatric Patients

Martin Christopher Johns, MD,* and Carol Stephenson, MT(ASCP)SBB

Concentrations of amino-terminal pro–B-type natriuretic peptides (NT-proBNP) are often markedly elevated immediately after birth and typically decrease to normal concentrations after the first week of life. Despite these early life elevations (which likely reflect activity of the natriuretic peptide system to assist in mobilization of fluid in the neonatal period), NT-proBNP has been shown to be useful for the diagnosis or exclusion of heart failure (HF) in the neonate, infant, adolescent, and older child. After the resolution of the normative early-life elevations of NT-proBNP, it is reasonable to use age-adjusted cut points suggested for younger adults (<50 years), namely levels <300 ng/L to “rule out” HF, and >450 ng/L to “rule in” HF. In children with congenital heart disease with or without symptoms of HF, NT-proBNP concentrations are typically elevated and may be prognostically useful. Furthermore, NT-proBNP may be useful for the identification of patients treated with cardiotoxic chemotherapy at risk for the subsequent development of cardiomyopathy. Knowledge of expected concentrations of NT-proBNP at varying stages of life is important to optimally utilize this assay in the pediatrics setting. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008; 101[suppl];76A–81A)

Natriuretic peptide (NP) assays have been used extensively in adults for a number of cardiovascular indications. However, publications in neonatal and pediatric medicine are, to date, relatively limited with respect to applications of testing for either B-type NP (BNP) or its amino-terminal cleavage pro-fragment, NT-proBNP. Multiple factors account for this fact, including the complexity of physiology in the developing and perinatal heart, the complexity of congenital and acquired cardiac disease in children, and the difficulty inherent in pediatric research in acquiring large sample sizes. Gradually, however, centers across the world are beginning to use NPs for neonatal and pediatric indications.

Establishing Pediatric Reference Ranges

For the evaluation of newborn and pediatric patients, it is important to be familiar with expected ranges for the marker in each patient type, taking into account the age-related differences that are illustrated in Tables 1, 2, and 3.1–9

NT-proBNP concentrations in the perinatal period: BNP has been shown to play a key role in cardiac organogenesis, blood pressure regulation in fetal development, and natriuretic and diuretic changes related to birth and transition to life outside the womb.10 Although theoretically small enough to pass from mother to child, NPs, including NT-proBNP, derive from the fetus itself and do not reflect transplacental exchange of maternal NT-proBNP.1,2,11 NT-proBNP concentrations in newborn cord blood average approximately 12 times higher than NT-proBNP concentrations in their mothers.11 No differences were reported in arterial or venous cord blood concentrations related to mode of delivery (cesarean section versus vaginal) or sex. Cord blood reference ranges taken from 3 studies are shown in Table 1.

Several studies have shown a dramatic increase in levels of NT-proBNP in the period immediately after birth.3–5,12,13 In the first few days of life, it has been postulated that significant elevation of the NPs in this period is necessary for diuresis and natriuresis after delivery.14,15 Water loss accounts for an expected 10%–15% decrease in weight in the first week of life. Redistribution of blood from the placenta to the lungs as the infant emerges from the womb increases ventricular volume and pressure, which also may stimulate release of BNP and NT-proBNP.15,16 Study findings showed a disparity of NT-proBNP in the umbilical artery versus the umbilical vein, which led to the suggestion that an increase in NPs in the immediate newborn period may be related to cessation of peptide clearance by the placenta.17 A subsequent study showed no significant difference between umbilical artery and umbilical vein NT-proBNP values, making placental clearance of the peptide less likely to be related to concentration increases.1

In the first few days of life, there is a dramatic release of NT-proBNP, suggesting the active hormone BNP assists in alleviating ventricular load after birth and also serves to

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support the heart by decreasing preload post delivery. The levels of NPs decrease accordingly, as the newborn kidneys mature, the systemic vascular resistance decreases, and the pulmonary pressures diminish. The newborn heart also has an increased water concentration and a higher percentage of collagen, resulting in a noncompliant ventricle, which makes left ventricular functioning critical to assure systemic perfusion.

Assessing a neonate for pathology using NT-proBNP values requires awareness of the reference ranges for the first week of life. Variances between values are dependent on the timing of the test (hours of life) and the laboratory assay chosen (Table 2). It should also be noted that the most significant changes in amplitude of NT-proBNP occur in the first 48 hours of life and diminish toward normal values within 1 week post delivery. The increase and decrease of NP values correlate with the expected 10%–15% perinatal weight loss in the first week of life. No studies to date have shown a significant difference in NT-proBNP levels between boys and girls in the neonatal period.

Pediatric and adolescent normal ranges: Several studies have determined NT-proBNP normal values to be constant in children approximately 4 months to 15 years of age. The level of NT-proBNP may approach stability as early as 5–10 days of life. Sex-specific differences between adolescent boys and girls are apparent but are not significant until age 13, with lower NT-proBNP values in boys. This could be related to estrogen levels, which might stimulate the gene expression of NPs via sex hormones, or the effects of androgens, which suppress NP concentrations.

Clinical Applications of Amino-Terminal Pro–B-Type Natriuretic Peptide Testing in Pediatric Patients

Heart failure: The causes of heart failure (HF) in the pediatric population are considerably different than in adults (primarily including congenital malformations as well as infectious/inflammatory causes in children, as opposed to ischemia and cardiomyopathy in adults). However, similar to adult medicine, the evaluation of the pediatric patient with dyspnea and suspected HF may be challenging. Indeed, given the wide range of diseases that may lead to dyspnea in the pediatric patient, a biomarker with sensitivity correlated to cardiovascular disease is welcome. In this regard, NT-proBNP has been shown to identify and quantify the presence and severity of HF in young patients – children with HF have marked elevations in NT-proBNP, and there are close relations between the magnitude of NT-proBNP release and worsening clinical score and decreasing left ventricular ejection fraction. Comparison of BNP and NT-proBNP to establish cardiac functional capacity showed that both assays were similarly correlated in terms of their ability to indicate a decreased exercise capacity, increased volume overload, and worse overall prognosis.

The diagnostic value of NT-proBNP for determination or exclusion of acute HF in children is quite similar to that in adults. As shown by Cohen et al., values for NT-proBNP in children with acute HF are often dramatically higher (median, 18,452 ng/L [1 ng/L = 0.118 pmol/L]) than in children with dyspnea and lung disease (median, 311 ng/L) or in healthy subjects (median, 89

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Table 1

Umbilical cord blood reference ranges for amino-terminal pro–B-type natriuretic peptides (NT-proBNP)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>NT-proBNP Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mir et al</td>
<td>37</td>
<td>200 fmol/mL</td>
</tr>
<tr>
<td>Schwachtgen et al</td>
<td>62</td>
<td>819 ng/L</td>
</tr>
<tr>
<td>Hammerer-Lercher et al</td>
<td>42</td>
<td>553 ng/L</td>
</tr>
<tr>
<td>Bar-Oz et al</td>
<td>122</td>
<td>579 ng/L</td>
</tr>
</tbody>
</table>

Table 2

Neonatal and infant reference ranges for amino-terminal pro–B-type natriuretic peptides (NT-proBNP)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Sex</th>
<th>Age</th>
<th>NT-proBNP Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwachtgen et al</td>
<td>8</td>
<td>All</td>
<td>Day 0–1</td>
<td>6,072 ng/L</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>All</td>
<td>Day 2–3</td>
<td>2,972 ng/L</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>All</td>
<td>Day 4–8</td>
<td>1,731 ng/L</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td>All</td>
<td>Day 9–365</td>
<td>215 ng/L</td>
</tr>
<tr>
<td>Mir et al</td>
<td>109</td>
<td>All</td>
<td>10 days–17 yr</td>
<td>311 fmol/mL</td>
</tr>
<tr>
<td>Albers et al</td>
<td>13</td>
<td>All</td>
<td>0–3 yr</td>
<td>129 ng/L</td>
</tr>
<tr>
<td>Bar-Oz et al</td>
<td>33</td>
<td>All</td>
<td>Day 1</td>
<td>3,042 ng/L</td>
</tr>
<tr>
<td>Soldin et al</td>
<td>40</td>
<td>Male</td>
<td>&lt;1 mo</td>
<td>97.5th percentile:</td>
</tr>
<tr>
<td>Nir et al</td>
<td>20</td>
<td>All</td>
<td>1–5 days</td>
<td>1,937 ng/L</td>
</tr>
</tbody>
</table>

Table 3

Childhood/adolescent reference ranges for amino-terminal pro–B-type natriuretic peptides (NT-proBNP)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Sex</th>
<th>Age</th>
<th>NT-proBNP Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwachtgen et al</td>
<td>55</td>
<td>All</td>
<td>1–10 yr</td>
<td>107 ng/L</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>F</td>
<td>10–13 yr</td>
<td>50 ng/L</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>M</td>
<td>10–13 yr</td>
<td>54 ng/L</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>F</td>
<td>13–18 yr</td>
<td>69 ng/L</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>M</td>
<td>13–18 yr</td>
<td>42 ng/L</td>
</tr>
<tr>
<td>Mir et al</td>
<td>109</td>
<td>All</td>
<td>10 days–17 yr</td>
<td>311 fmol/mL</td>
</tr>
<tr>
<td>Nir et al</td>
<td>58</td>
<td>All</td>
<td>4 mo–15 yr</td>
<td>90 ng/L</td>
</tr>
<tr>
<td>Albers et al</td>
<td>292</td>
<td>All</td>
<td>1–18 yr</td>
<td>79 ng/L</td>
</tr>
<tr>
<td>Soldin et al</td>
<td>160</td>
<td>All</td>
<td>1–3 yr</td>
<td>97.5th percentile:</td>
</tr>
<tr>
<td>578</td>
<td></td>
<td>All</td>
<td>3–18 yr</td>
<td>97.5th percentile:</td>
</tr>
</tbody>
</table>

F = female; M = male.
ng/L) (Figure 1). Furthermore, in children with acute HF, posttreatment concentrations of NT-proBNP typically decrease down to a more normal range (Figure 2). Such posttreatment changes are likely to have clinical relevance from a prognostic perspective. For example, persistent elevation of NT-proBNP may identify persistent ventricular abnormalities in children recovering from acute myocarditis.

The diagnostic value of NT-proBNP in children with HF is preserved, even in those with other reasons for NT-proBNP elevation. As shown by Fried et al., NT-proBNP is significantly elevated in acute ventricular dysfunction compared with other states, such as sepsis or more chronic stable ventricular abnormalities. Indeed, in the former case, although NT-proBNP is elevated in children with sepsis (similar to adults), it is not to the degree of increase observed in ventricular dysfunction.

To use NT-proBNP for evaluation of the pediatric patient with suspected HF, it is worthwhile to once again review expected concentrations of NT-proBNP across age groups. Among children in their first days to weeks of life, NT-proBNP values will be higher, even in those without acute HF, and clinical correlation will be necessary to optimally interpret values of NT-proBNP. After the resolution of the normative early-life NT-proBNP elevations, it is most reasonable to apply cut points optimized from younger adult (aged <50 years) populations.

**Figure 1.** Concentrations of amino-terminal pro–B-type natriuretic peptides (NT-proBNP) in healthy children and children with dyspnea as a function of final diagnosis. Compared with those without heart failure (HF), pediatric patients with acute destabilized HF had markedly higher concentrations of NT-proBNP. (Reprinted with permission from Pediatrics.)

**Figure 2.** Changes in amino-terminal pro–B-type natriuretic peptides (NT-proBNP) among pediatric patients with treated heart failure (HF). After treatment for acute destabilized HF, concentrations of NT-proBNP decrease significantly. (Reprinted with permission from Pediatrics.)
for the diagnosis or exclusion of HF, specifically values <300 ng/L to “rule out” HF and >450 ng/L to identify it.

Specific congenital heart diseases: Although large cohorts of specific syndromes are not available in the literature for either BNP or NT-proBNP, among mixed cohorts of HF patients with various forms of congenital heart diseases, including valvular heart diseases, atrioventricular canal defects, ventricular septal defects, hypertrophic or dilated cardiomyopathy, tetralogy of Fallot, hypoplastic left heart syndrome, ventricular septal defect, truncus arteriosus, or anomalous venous return, NT-proBNP is elevated more often than not and demonstrates useful diagnostic value.19–22,26 Among groups of patients with stable clinical status, concentrations of NT-proBNP in those with the congenital heart diseases listed above typically are more often elevated compared with stable children without congenital heart diseases (Figure 3).4

Among the better-studied congenital heart conditions with respect to the utility of NT-proBNP for structural, functional, and prognostic value is tetralogy of Fallot, a complex cyanotic congenital heart lesion that may be associated with HF, particularly involving the right ventricle. Among those patients with tetralogy of Fallot, concentrations of NT-proBNP are frequently elevated, with correlations between the marker and the presence/magnitude of pulmonary regurgitation and/or right ventricular dilation.27–29 Indeed, NT-proBNP concentrations may be useful for the diagnosis of right ventricular dysfunction in patients with tetralogy of Fallot, even in presymptomatic patients.30 Importantly, concentrations of NT-proBNP may decrease in parallel with improvement in right ventricular size and function after the repair of tetralogy of Fallot, suggesting a potential role for the marker as a noninvasive monitoring tool for improvement after surgery.

In addition to being useful for the diagnostic evaluation of patients with suspected congenital heart lesions, NT-proBNP measurements may be useful to stratify risk for complications after correction of these congenital heart lesions31–33; in the adolescent or adult patient with congenital heart disease, it may serve as an indicator of functional status and may be useful to identify early HF,34 potentially pointing to a role for the use of NT-proBNP to direct the timing of intervention.
Other applications—detection of anthracycline toxicity: After cancer treatment with anthracyclines (a class of chemotherapeutic agents widely used in pediatric cancer therapy), development of cardiomyopathy may occur in up to 10%–15% of all survivors. Although this most often occurs in patients treated with larger doses of anthracycline, this grave complication may be difficult to predict, particularly because those who develop cardiomyopathy do not have acute symptoms or signs of HF. Accordingly, the use of NPs might offer a window into the potentially significant adverse cardiovascular effects from treatment with these cardiotoxic agents.

After first exposure to anthracyclines during cancer chemotherapy, NT-proBNP concentrations may increase significantly, even in the absence of echocardiographic abnormalities. Furthermore, elevated NT-proBNP concentrations in patients treated with the anthracycline doxorubicin identified those with reduced left ventricular mass after treatment, raising the question as to whether such elevations of NT-proBNP would be predictive of development of cardiomyopathy. Similar findings have been shown in adults after chemotherapy.

Conclusions

Key points—NT-proBNP testing in neonatal and pediatric patients:

- Knowledge of expected concentrations of NT-proBNP at varying stages of life is important to optimally use this assay in pediatrics.
- Concentrations of NT-proBNP are markedly elevated during the first hours of life, typically decreasing to normal concentrations after the first week of life.
- After the resolution of the normative early-life elevations of NT-proBNP, it is reasonable to use age-adjusted cut points suggested for adults aged <50 years, namely <300 ng/L to rule out HF, and >450 ng/L to rule in HF.
- In children with dyspnea, NT-proBNP may be useful to diagnose or exclude HF as the cause of dyspnea.
- In children with congenital heart disease with or without symptoms of HF, NT-proBNP concentrations are typically elevated relative to those without structural heart disease.
- NT-proBNP may be useful to identify those patients treated with anthracyclines at risk for subsequent development of cardiomyopathy.

Author Disclosures

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Martin Christopher Johns, MD, has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this article.

Carol Stephenson, MT(ASCP)SBB, has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this article.

References


Concentrations of amino-terminal pro–B-type natriuretic peptides (NT-proBNP) are typically higher in patients with chronic kidney disease (CKD) than in those without CKD. These elevated levels of NT-proBNP in patients with CKD do not simply reflect the reduced clearance of the peptide; rather, they largely reflect a true-positive finding, identifying the presence of heart disease in these patients, while similarly indicating prognosis as well. Although modestly stronger inverse correlations exist between renal function and NT-proBNP compared with B-type natriuretic peptide (BNP), the dependence of both peptides on renal clearance is similar. Across the range of CKD, correlations between BNP and NT-proBNP remain strong, and the prognostic impact of NT-proBNP in patients with CKD is preserved. When evaluating the patient with acute dyspnea and CKD, both BNP and NT-proBNP are affected similarly, with higher decision limits necessary compared with patients with preserved renal function. Importantly, when using NT-proBNP to evaluate a patient with dyspnea and impaired renal function, the recommended cut points of 450, 900, and 1,800 ng/L for those aged <50, 50–75, and >75 years, respectively, do not require further adjustment for renal function. Thus, NT-proBNP testing remains useful for the diagnostic and prognostic evaluation of patients with CKD. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:82A–88A)

Chronic kidney disease (CKD) and heart failure (HF) are common conditions. An estimated 8.3 million individuals in the United States have stage III CKD or higher (ie, estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m²). Compared with age-matched subjects in the general population, there is a higher prevalence of both coronary disease and left ventricular hypertrophy among patients with impaired renal function. Therefore, it is not unexpected that 33%–56% of patients with HF have impaired renal function. The interpretation of natriuretic peptide (NP) results in either symptomatic or asymptomatic patients with CKD has been a source of confusion and controversy since the introduction of these assays into clinical practice. However, in the past 2–3 years, numerous studies have provided considerable insight into the interpretation of these tests in the setting of impaired renal function. This article reviews aspects of B-type NP (BNP) and amino-terminal pro-BNP (NT-proBNP) measurement in patients with renal disease.

Renal Clearance and the Association of Natriuretic Peptide Levels with Glomerular Filtration Rate

During the early clinical experience with NPs, an assumption developed that BNP clearance was independent of renal clearance based on the findings that BNP, but not NT-proBNP, was cleared by NP receptor–C and degraded by neutral endopeptidases. This incorrect assumption was further fueled by studies that detected NT-proBNP in the urine. Early work from the 1990s identified an inverse univariable relation between urinary BNP and creatinine clearance (r = −0.43, p <0.01), although—as with NT-proBNP—these inverse relations do not argue for causality. Notably, elevated urine levels of NT-proBNP were associated with a higher probability of both a diagnosis of HF and a depressed left ventricular ejection fraction (LVEF), which immediately implies that the levels of NP in the context of renal dysfunction may reflect a true signal of the highly prevalent cardiac disease in these populations.

To further elucidate the relative role of renal clearance for both NP markers, the fractional renal excretion of NT-proBNP and BNP were compared head-to-head by measurement of arterial and renal vein NP levels in several populations, including young male volunteers, medically
Figure 1. Scatter plot of log-transformed estimated glomerular filtration rate (eGFR) and B-type natriuretic peptide (BNP) values obtained at baseline in patients with congestive heart failure (n = 715). Many patients had values exceeding the upper limit of the BNP assay, leading to underestimation of the correlation with eGFR. $r = -0.20$; $p < 0.0001$. (Adapted from *Am J Kidney Dis*.)

Figure 2. Creatinine clearance (CrCl) plotted against B-type natriuretic peptides (BNP) (closed symbols) and amino-terminal pro–B-type NPs (NT-proBNP) (open symbols) in 1,049 patients with stable ischemic heart disease. $n = 1,049$, $r = -0.51$, $r^2 = 0.26$, $p < 0.001$. (Adapted from *J Am Coll Cardiol*.)
Correlation of natriuretic peptides with estimated glomerular filtration rate

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>NT-proBNP</th>
<th>BNP</th>
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<tbody>
<tr>
<td>Mark et al</td>
<td>296</td>
<td>Amb CKD</td>
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<td>207</td>
<td>Amb CKD</td>
<td>—</td>
<td>—</td>
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<td>54</td>
<td>Amb CKD</td>
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<tr>
<td>Vickery et al</td>
<td>213</td>
<td>Amb CKD</td>
<td>—0.36</td>
<td>—</td>
</tr>
<tr>
<td>Austin et al</td>
<td>171</td>
<td>Amb CKD</td>
<td>—0.36</td>
<td>—</td>
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<tr>
<td>Richards et al</td>
<td>1,049</td>
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<td>Luchner et al</td>
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<td>Amb CAD</td>
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<td>van Kimmenade et al</td>
<td>178</td>
<td>Amb HTN</td>
<td>—0.32</td>
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<tr>
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<td>van Kimmenade et al</td>
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<tr>
<td>Bruch et al</td>
<td>142</td>
<td>HF</td>
<td>—0.29</td>
<td>—</td>
</tr>
</tbody>
</table>

Amb = ambulatory; BNP = B-type natriuretic peptide; CAD = coronary artery disease; CKD = chronic kidney disease; CM = cardiomyopathy; ED = emergency department; HF = heart failure; HTN = hypertension; NT-proBNP = amino-terminal pro–B-type natriuretic peptide.

Significance of Elevated Amino-Terminal Pro–B-Type Natriuretic Peptide Levels in Patients with Asymptomatic Chronic Kidney Disease

Levels of NT-proBNP are frequently elevated in ambulatory patients with CKD who do not require renal replacement therapy. In a study of 207 ambulatory patients, the median NT-proBNP level was 490 ng/L. In another similarly sized study of 213 patients, the median NT-proBNP level was 753 ng/L. The differences in NT-proBNP levels can be explained by a much larger proportion of stage V (eGFR <15 mL/min per 1.73 m²) patients in the latter study. Despite typically elevated levels in this population, NT-proBNP values remain predictive of depressed LVEF, increased left ventricular mass, and vascular disease, including a history of coronary disease. The association with increased left ventricular mass and coronary disease remains independent of eGFR and traditional cardiovascular risk factors. BNP and NT-proBNP both appear to have a similarly strong association with known “arteriopathic” diseases (peripheral and coronary vascular disease) and similar predictive accuracy for the presence of left ventricular hypertrophy, depressed LVEF, and known coronary disease. Few data are available with respect to prognosis and NPs in this population, but preliminary evidence suggests BNP and NT-proBNP can predict death and hospitalization. This question should be answered definitively in the National Institutes of Health (NIH) ongoing Chronic Renal Insufficiency Cohort (CRIC) study, which is prospectively measuring NT-proBNP.

Impact of renal disease on the diagnosis of acute decompensated heart failure in patients presenting with dyspnea

Table 2

<table>
<thead>
<tr>
<th>BNP (mL/min per 173 m²)</th>
<th>Area Under the Curve</th>
<th>Cut Point (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>0.91</td>
<td>70.7</td>
</tr>
<tr>
<td>60–90</td>
<td>0.90</td>
<td>104.3</td>
</tr>
<tr>
<td>30–59</td>
<td>0.81</td>
<td>201.2</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0.86</td>
<td>225</td>
</tr>
<tr>
<td>NT-proBNP ≥60</td>
<td>0.95</td>
<td>900/450</td>
</tr>
<tr>
<td>&lt;60</td>
<td>0.88</td>
<td>1,200</td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide; GFR = glomerular filtration rate; NT-proBNP = amino-terminal pro–B-type natriuretic peptide.
Diagnosing Acute Decompensated Heart Failure in Patients with Dyspnea and Chronic Kidney Disease

Measurement of NT-proBNP and BNP is an established methodology for diagnosing decompensated HF in patients with dyspnea. However, until recently, studies examining the role of NPs examined only a small minority of patients with an eGFR $\leq 60$ mL/min per 1.73 m². Based on analyses from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study and the Breathing Not Properly study, the accuracy of NT-proBNP and BNP, respectively, to diagnosis decompensated HF in patients with an eGFR $\leq 60$ mL/min per 1.73 m² was modestly diminished compared with patients with an eGFR $\geq 60$ mL/min per 1.73 m², with an upward shift in the optimal cutoff value (Table 2). In fact, using the age-adjusted cut points recommended in the International Collaborative of NT-proBNP (ICON) study, there is no further adjustment required for NT-proBNP based on impaired renal function (Table 2). These cut points for NT-proBNP and BNP appear durable. In a study of clinician-selected patients with dyspnea, including 393 with an eGFR $<60$ mL/min per 1.73 m², simultaneously measured NT-proBNP and BNP had a similar accuracy. The optimal cut points were as reported in the PRIDE and BNP studies.

Predicting Outcomes in Patients with Dyspnea and Chronic Kidney Disease

In a subanalysis of 720 patients presenting with acute decompensated HF from the ICON study, NT-proBNP level was predictive of 60-day outcome in the setting of impaired renal function. Both an eGFR $<60$ mL/min per 1.73 m² and an NT-proBNP level above the median (4,647 ng/L) predicted a poor outcome. Intriguingly, these investigators identified that it was the combination of both that carried the greatest risk. Furthermore, the absence of either feature resulted in a 60-day outcome similar to that of patients with an eGFR $\geq 60$ mL/min per 1.73 m² and a NT-proBNP level below the median (Figure 3). An additional study has also compared BNP and NT-proBNP for all-cause mortality in emergency department patients presenting with dyspnea and an eGFR $<60$ mL/min per 1.73 m². NT-proBNP levels were superior predictors of 1-year mortality after adjustment for comorbidities, renal function, and diagnosis of decompensated HF. The superior prognostic impact of NT-proBNP in patients with impaired renal function further supports the importance of this marker in those with CKD and contradicts the incorrect notion that NT-proBNP cannot be applied in those with renal failure.
Predicting Outcomes in Patients with Acute Coronary Syndromes

Similar to findings in BNP studies, multiple studies have demonstrated that elevated levels of NT-proBNP on entry into an acute coronary syndromes study or on presentation is associated with an increased risk of death, independent of traditional cardiovascular risk factors, electrocardiographic changes, and other biochemical markers. Generally, multicenter therapeutic clinical trials of acute coronary syndromes, from which most of these prognostic NP data are derived, excluded patients with more than mildly impaired renal function. Nevertheless, in a recent analysis of approximately 6,800 patients whose renal function ranged from normal to mild-to-moderate impairment, there was a synergistic effect between NT-proBNP level on enrollment and creatinine clearance when predicting 1-year mortality.

Predicting Outcomes in Patients on Dialysis

Elevated levels of NT-proBNP and BNP are ubiquitous in patients on chronic dialysis therapy. Levels of both NPs remain, in part, dependent on the presence and severity of structural heart disease as well as on factors such as the type of dialysis membrane used. In a recent study of 109 hemodialysis patients, NT-proBNP was associated with left ventricular mass, LVEF, and Kt/V (extent of dialysis), but it may eventually be used as a prognosticator in patients on dialysis in conjunction with a strategy that incorporates NT-proBNP into an acute coronary syndromes study or on presentation.

Conclusions

Key points—NT-proBNP in chronic kidney 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 and are not necessarily reflective of reduced clearance of NT-proBNP.
- Although modestly stronger inverse correlations exist between renal function and NT-proBNP compared with BNP, across the range of CKD, correlations between BNP and NT-proBNP remain strong and the prognostic impact of NT-proBNP in CKD patients is preserved.
- Mechanistic studies of BNP and NT-proBNP argue for similar dependence on renal function for clearance.
- Given the preponderance of data outlined above, no clear differences between BNP and NT-proBNP in CKD can be asserted.
- When evaluating the patient with acute dyspnea and CKD, both BNP and NT-proBNP are affected similarly, and higher decision limits are necessary compared with patients with preserved renal function.
- Importantly, when using NT-proBNP to evaluate patients with impaired renal function, the recommended cut points of 450, 900, and 1,800 ng/L for those aged <50, 50–75, and >75 years do not require further adjustment for renal function.
- For the unusual patient aged <50 years with severe CKD, a cut point of 1,200 ng/L for NT-proBNP would be indicated.

Author Disclosures

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Christopher DeFilippi, MD, reports receiving significant research support from Dade Behring and Roche Diagnostics; significant speaker honoraria from Dade-Behring; and modest consulting fees from Roche Diagnostics.

Roland R. J. van Kimmenade, MD, PhD, reports receiving modest speaker honoraria from Roche Diagnostics.

Yigal M. Pinto, MD, PhD, reports receiving modest speaker honoraria and consulting fees from Roche Diagnostics.


Understanding Amino-Terminal Pro–B-Type Natriuretic Peptide in Obesity

Antoni Bayes-Genis, MD, a Christopher DeFilippi, MD, b and James L. Januzzi, Jr., MD c,*

Concentrations of both B-type natriuretic peptide (BNP) and its amino-terminal cleavage fragment (NT-proBNP) are relatively lower among patients with a higher body mass index (BMI). Based on data at hand, this is probably related to reduced synthesis or secretion of the peptides, rather than increased clearance (which may play only a minor role in this context). Despite this fact, age-adjusted NT-proBNP cut points to “rule in” heart failure (HF) and age-independent cut points to “rule out” HF in patients with acute dyspnea are equally useful for obese and lean patients, and no adjustment of NT-proBNP thresholds for BMI is recommended. Furthermore, the consensus-recommended NT-proBNP cut point of 1,000 ng/L for prognostication in acute dyspnea is equally useful across all BMI categories, without the need for further adjustment for weight. Thus, despite the BMI-related NP handicap observed in overweight and obese patients, NT-proBNP remains powerfully useful for diagnostic and prognostic evaluation across the entire range of BMI values. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:89A–94A)

Obesity is a problem that is reaching unprecedented proportions both in wealthy and developing countries. The use of the body mass index (BMI) to classify patients as underweight (BMI <18.5), normal (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥30) as per World Health Organization (WHO) guidelines1 reveals numbers that are staggering: nearly 70% of adults in the United States are classified as overweight or obese,2 with data suggesting that this growing problem will lead to higher rates of cardiovascular disease with the passage of time. The Renfrew-Paisley study, a 20-year follow-up population-based study of >15,000 individuals, demonstrated that obesity is associated with an increase in a broad range of fatal and nonfatal cardiovascular events. This study found a clear association between obesity and increased risk for heart failure (HF) events, including hospital admission for HF.3

The Obesity Paradox in Heart Failure

Obesity is a well-known risk factor for the development of HF. Surprisingly, for reasons that remain unclear, obese patients with HF have a better prognosis than patients whose weight is normal, giving rise to the so-called obesity paradox (Figure 1).4 Indeed, although obesity is clearly associated with more cardiovascular disease, and several studies indicate a progressive increase in all-cause mortality and years of life lost associated with obesity,5,6 recent studies have focused on an apparent paradox regarding the relation between obesity and subsequent cardiovascular prognosis.7 It appears that the presence of obesity is associated with improved survival in patients with HF. It may be that patients with a high BMI have HF symptoms at an earlier and less severe stage of HF. Conversely, patients with a low BMI, specifically those with cachexia and wasting, may experience more advanced and severe HF and have higher mortality.8,9

In patients with acute dyspnea, including those with acute destabilized HF, the data for the obesity paradox again appear to be present and even extend to those without HF. In a study of patients presenting to the emergency room with acute dyspnea, a higher BMI was associated with lower rates of death in those with and without acute HF.10 Although BMI was significantly and inversely associated with survival in univariate analysis, this association was attenuated with the addition of age to the model. Thus, these data support the contention of Lavie and Milani11 that the apparent obesity paradox in HF represents an association that is unlikely to be causal.

Low Levels of Natriuretic Peptides in Obesity

In parallel with the improved prognosis of overweight and obese patients who have cardiovascular disease, circulating levels of both B-type natriuretic peptides (BNP) and amino-terminal proBNP (NT-proBNP) are significantly lower in overweight and obese patients compared with lean patients.
with HF.\textsuperscript{12,13} Horwich et al\textsuperscript{12} found that obesity was associated with an increase >6-fold in the odds of having low BNP values. Similarly, Krauser and colleagues\textsuperscript{13} showed a nearly identical suppression of both BNP and NT-proBNP with increasing BMI. Furthermore, Taylor and colleagues\textsuperscript{14} demonstrated that this reduction in NT-proBNP levels in obesity occurred despite heavier patients having higher filling pressures than those at lower weights.

There are several potential mechanisms responsible for the inverse association between NPs and BMI (Table 1). First, the NP clearance receptor NPR-C has been isolated in adipose tissue in humans,\textsuperscript{15} and both elevated NPR-C expression and increased secretion of neutral endopeptidases have been demonstrated in patients with obesity.\textsuperscript{16} These findings suggest that the clearance of NPs may be increased in obese patients with HF, which could explain, in part, the impact of BMI on plasma levels of BNP. However, the peripheral elimination of NT-proBNP is not based on NPR-C activity or neutral endopeptidase degradation. Consequently, impaired synthesis and release of NT-proBNP from the myocytes in obese subjects must play a part in the mechanisms underlying the reduced circulating levels of this peptide in persons with higher BMI values. Lending further support to this fact are data from the Framingham Heart Study that show NT-pro–A-type NP values are also inversely proportional to BMI (importantly, NT-pro–A-type NP is not cleared by NPR-C or neutral endopeptidase degradation).\textsuperscript{17,18} In addition, in a series of patients undergoing bariatric surgery, van Kimmenade et al\textsuperscript{19} found a parallel increase of BNP and NT-proBNP after weight loss. Moreover, Das et al\textsuperscript{17} demonstrated that the inverse relation between higher BMI values and lower NT-proBNP levels was mediated by lean mass rather than fat mass. These investigators postulate that a substance produced in the lean mass and possibly mediated by sex steroid hormones (possibly androgens) suppresses either synthesis or release of NPs from cardiomyocytes.

Thus, available data generally refute the hypothesis that the negative correlation between NPs and BMI is owing to increased clearance of the peptide. Whether increased clearance plays a role at all remains speculative. However, it might explain the slightly lower impact of BMI on concentrations of NT-proBNP relative to BNP.\textsuperscript{13}

### Obesity, Amino-Terminal Pro–B-Type Natriuretic Peptides, and Diagnosis/Prognosis

The clinical diagnosis of HF is often a challenge, which is accentuated in the obese patient, in whom history and physical examination may be limited in sensitivity and specificity. Indeed, dyspnea is a common symptom in HF as well as in obesity, making the early diagnosis of cardiac impairment difficult in patients with obesity. In patients with HF, obesity is common, and, thus, further elucidation of the relation between NPs and BMI is relevant.

**Obesity**

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{obesity_paradox.png}
\caption{Schematic depiction of the obesity paradox in heart failure.}
\end{figure}

**Mortality**

\begin{table}[h]
\centering
\caption{Proposed mechanisms to explain low levels of natriuretic peptides in obesity}
\begin{tabular}{|l|}
\hline
\hline
- Increased degradation \\
  - BNP is cleared by NPR-C, abundantly expressed in human adipocytes \\
  - BNP is degraded by neutral endopeptidases, abundantly secreted by human adipocytes \\
  - NT-proBNP is not cleared by NPR-C or neutral endopeptidases \\
- Reduced cardiomyocyte synthesis \\
  - Altered neurohormonal interactions \\
  - Sex steroid hormones (estrogens, androgens) \\
\hline
\end{tabular}
\end{table}

BNP = B-type natriuretic peptide; NPR–C = natriuretic peptide receptor–C; NT-proBNP = amino-terminal pro–B-type natriuretic peptide.

NPs are useful in establishing or excluding the diagnosis of HF in patients who present to the emergency department with acute dyspnea.\textsuperscript{20} Although obese patients have lower NP levels, less is known about how to interpret BNP and NT-proBNP values in this population.

Krauser et al\textsuperscript{13} analyzed 209 patients with acute HF as the cause of their dyspnea. The investigators found that obesity was associated with a 2- to 3-fold increase in the odds of having an NP value below the diagnostic cut points for both NT-proBNP and BNP. This study demonstrated that BMI should be taken into consideration when interpreting NP results, and that these diagnostic cut points need to be validated for overweight and particularly obese individuals.

The analysis of the usefulness of the proposed cut points for diagnosis of acute HF in overweight and obese patients was
performed in a subgroup of patients in the International Collaborative of NT-proBNP (ICON) study (Figure 2).10 NT-proBNP levels were lower in overweight and obese patients with dyspnea without acute HF, although in patients without HF, median NT-proBNP levels were typically below the established cut point of 300 ng/L20 used to rule out HF in all BMI categories, emphasizing the utility of this cut point in patients of all weights.

More importantly, this study confirmed the usefulness of the proposed age-specific cut points for NT-proBNP for diagnosing HF in patients with acute breathlessness. The previously recommended optimal cut points for identifying acute HF of 450, 900, and 1,800 ng/L in patients aged <50, 50–75, and >75 years, respectively,20 performed with strong diagnostic accuracy and specificity in this population of subjects with a wide range of BMI values (Table 2). Despite slightly lower sensitivity at a higher BMI, these cut points demonstrated a very similar positive predictive value across all BMI strata, including the subjects who were most obese.10

The Breathing Not Properly Multinational Study, which examined how obesity affects cut points for BNP in acute HF, concluded that the selection of cut points for BNP in diagnosing acute HF needed to be adjusted to BMI. The investigators proposed a lower BNP cut point of ≥54 pg/mL for patients with the highest BMI to preserve sensitivity and a higher BNP cut point of ≥170 pg/mL for lean patients to increase specificity.21

### Table 2

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>% Sensitivity* (95% CI)</th>
<th>% Specificity* (95% CI)</th>
<th>Accuracy* (%)</th>
<th>PPV* (%)</th>
<th>NPV† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>84 (78–88)</td>
<td>84 (78–89)</td>
<td>84</td>
<td>88</td>
<td>99</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>80 (74–85)</td>
<td>94 (89–97)</td>
<td>87</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>≥30</td>
<td>75 (67–82)</td>
<td>90 (84–94)</td>
<td>83</td>
<td>86</td>
<td>94</td>
</tr>
</tbody>
</table>

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

* Using age-specific cut points: <50 years, 450 ng/L; 50–75 years, 900 ng/L; and >75 years, 1,800 ng/L.

† Using the age-independent cut point of 300 ng/L.

### Obesity, Amino-Terminal Pro–B-Type Natriuretic Peptide, and Prognosis

A study recently addressed whether the presence of obesity affects the prognostic value of NPs in HF. As mentioned before, BMI is associated with mortality in some series, and part of this relation might be mediated by NT-proBNP.22

Horwich et al12 examined whether elevated BMI is associated with lower circulating levels of BNP both in the general
population and in patients with HF. This is the first study to show that BNP retains its prognostic capacity despite relatively less circulating BNP in overweight and obese patients with HF. In this study, BNP not only predicted ventricular filling pressures and functional class, but it also correlated with mortality at each level of BMI. The receiver operating curves for prediction of death or urgent transplantation at 1-year follow-up identified different cut points according to the BMI of the patients: 590 pg/mL was the optimum cut point for lean patients; 491 pg/mL, for overweight patients; and 343 pg/mL, for obese patients (Figure 3).

Bayes-Genis et al. assessed whether the association between plasma NT-proBNP and long-term prognosis was preserved across the different weight categories in patients presenting to the emergency department with acute breathlessness. A previously published NT-proBNP prognostic cut point of 986 pg/mL was applied to this population to validate its utility. In a Cox analysis adjusted for age, sex, and BMI, an NT-proBNP level >986 pg/mL remained strongly prognostic across all 3 BMI categories (Figure 4).

Moreover, the hazard associated with elevated NT-proBNP remained largely the same across BMI strata when examined as a function of the presence or absence of a diagnosis of acute HF. The Kaplan-Meier curves showed that the risk associated with elevated NT-proBNP levels in patients with or without acute HF was present early and was sustained in all 3 BMI categories for a full year from presentation.

Conclusions

Key points—understanding NT-proBNP in obesity:

- Levels of both BNP and NT-proBNP are relatively lower in patients with a higher BMI than in those with a lower BMI. Based on available data, this is more likely related to reduced synthesis or secretion of the peptides rather than increased clearance (which may play only a minor role in this context).
- Unlike BNP cut points, the consensus-recommended age-adjusted NT-proBNP cut points to rule in HF and age-independent cut points to rule out HF in patients with acute dyspnea are equally useful for obese and lean patients. Thus, no adjustment of NT-proBNP thresholds for BMI is recommended.
- Unlike BNP cut points, the consensus-recommended NT-proBNP cut point for prognostication in acute dyspnea (approximately 1,000 ng/L) is equally useful across all BMI categories, without the need for further adjustment for weight.
Author Disclosures

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