Diagnostic Accuracy and Prognostic Relevance of the Measurement of Cardiac Natriuretic Peptides: A Review

ALDO CLERICO[*] and MICHELE EMDIN

Background: The pathophysiologic and clinical relevance of cardiac natriuretic hormone (CNH) assays has been investigated in numerous experimental and clinical studies. Authors have sought to evaluate the diagnostic accuracy and prognostic relevance of the measurement of CNHs according to evidence-based laboratory medicine principles.

Methods: In June 2003, we ran a computerized literature search on National Library of Medicine using keywords "ANP" and "BNP" and found more than 12 300 and 1200 articles, respectively. A more refined search with keywords "ANP or BNP assay" extracted ~7000 and 800 articles, respectively. Only studies specifically designed to evaluate the diagnostic accuracy and prognostic relevance of CNH measurements were selected from this huge mass of articles to be discussed in this review.

Content: Several studies suggested that CNH assays may be clinically useful for the screening and classification of patients with heart failure, as a prognostic marker in cardiovascular disease, in the follow-up of patients with heart failure, and because they may reduce the need for further cardiac investigation. However, it is difficult to compare even the best-designed studies because not only did the authors evaluate different populations, they also used different gold standards.

Conclusions: CNH assays and conventional diagnostic work-ups provide complementary information for evaluation of the presence and severity of cardiac dysfunction and clinical disease. Several aspects of CNH assays are still to be elucidated, and further work is needed to carefully assess their diagnostic accuracy and prognostic value in cardiac disease.
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Cardiomyocytes produce and secrete a family of related peptide hormones, named cardiac natriuretic hormones (CNHs),[1] that have potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects and also carry out complex interactions with the neurohormonal system, as reviewed recently (1–7).

Although the role of CNHs in the identification and management of individuals with asymptomatic ventricular dysfunction remains to be fully clarified (8), the potential clinical usefulness of assays for CNHs [especially B-type natriuretic peptide (BNP) or the NH₂-terminal fragment of proBNP (NT-proBNP)] for screening of heart disease (9), for stratification of patients with congestive heart failure (HF) (10), for detection of left ventricular systolic and/or diastolic dysfunction (11), and for differential diagnosis of dyspnea (12, 13) has been confirmed more recently. Furthermore, the Task Force of the European Society of Cardiology for the Diagnosis and Treatment of Chronic HF recommended that a CNH assay should be included in the first step of the algorithm for the diagnosis of HF along with electrocardiography (ECG) and chest x-rays (14).

Although several reviews have recently been published on the biochemical characteristics and pathophysiologic relevance of CNHs (1–7), a review specifically

CNR Institute of Clinical Physiology, Laboratory of Cardiovascular Endocrinology, Pisa, Italy.

*Address correspondence to this author at: Laboratory of Cardiovascular Endocrinology and Cell Biology, CNR Institute of Clinical Physiology, Via Trieste 41, 56126 Pisa, Italy. Fax 39-0585-493601; e-mail clerico@ifc.cnr.it.

[1] Nonstandard abbreviations: CNH, cardiac natriuretic hormone; BNP, brain (or B-type) natriuretic peptide, COOH-terminal fragment of proBNP; NT-proBNP, NH₂-terminal fragment of proBNP; HF, heart failure; ECG, electrocardiography; ANP, atrial natriuretic peptide, COOH-terminal fragment of proANP; ACE, angiotensin-converting hormone; NT-proANP, NH₂-terminal fragment of proANP; AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; EF, ejection fraction; AMI, acute myocardial infarction; ECLIA, electrochemiluminescent assay; ACS, acute coronary syndromes; CI, confidence interval; POCT, point-of-care testing (method); NYHA, New York Heart Association; FP, false positive; and FN, false negative.

dedicated to evaluate in detail the diagnostic accuracy and prognostic relevance of the assay of CNHs is not available in the literature.

In June 2003, we performed a computerized literature search on National Library of Medicine (i.e., PubMed access to MEDLINE citations, at http://www3.ncbi.nlm.nih.gov/PubMed/), using as the keywords "ANP" and "BNP", and found more than 12 300 and 1200 articles, respectively. A more refined search with the keywords "ANP or BNP assay" extracted ~7000 and 800 articles, respectively. Only studies specifically designed to evaluate the diagnostic accuracy and prognostic relevance of CNH measurements were selected from this huge mass of articles to be discussed in this review.

Contrary to other recent reviews (1–7), we will analyze in detail and critically compare the relevance of interrelationships among the analytical performances of CNH immunoassays, the population selection protocol, and the "gold standard" used in the different studies. Moreover, the diagnostic accuracy and prognostic relevance of assays of different CNHs in the entire spectrum of cardiovascular disease will be evaluated, whereas other reviews have focused the discussion on one peptide only (mainly BNP) and/or on one clinical condition only (mainly HF) (2, 3, 5, 6). Finally, we will evaluate the clinical relevance and cost-effectiveness of different CNH assays in all clinical settings, including their use as screening methods in asymptomatic individuals as well as their use as diagnostic tests in primary care, emergency department, coronary care unit, and cardiologic ambulatory and hospital care settings.

Pathophysiologic Relevance of the CNH System

The CNHs include atrial natriuretic peptide (ANP), BNP, and their related peptides, whereas C-type natriuretic peptide and urodilatin, structurally related to the ANP/BNP peptide family, are predominantly secreted by noncardiac tissues (endothelium and kidney, respectively) (1–4, 6, 7). Recently, another peptide, called dendroaspis natriuretic peptide, with a structure and biological activities similar to those of the CNH family, was identified, but it is still uncertain whether dendroaspis natriuretic peptide is an endogenous entity in humans (15).

CNHs have several physiologic actions, the most important being (a) vasodilation and a hypotensive effect; (b) promotion of natriuresis and diuresis; (c) inhibition of the sympathetic nervous system and of the activities of several hormone systems, including the renin-angiotensin-aldosterone system, endothelins, cytokines, and vasopressin; (d) inhibition of the pathophysiologic mechanisms responsible for ventricular and vascular hypertrophy and remodeling; and (e) beneficial effects on endothelial dysfunction secondary to the atherosclerotic process, including blunting of shear stress and regulation of coagulation and fibrinolysis, as well as inhibition of platelet activation (1–4, 6, 7).

CNHs are greatly increased in diseases characterized by an expanded fluid volume, including renal failure, liver cirrhosis, and HF (1). Table 1 lists the different common clinical conditions affecting the circulating concentrations of CNHs.

An important pathophysiologic mechanism in cardiovascular disease is the imbalance between the vasoconstrictive/antinatriuretic action of some neuroendocrine factors, including the renin-angiotensin-aldosterone system, vasopressin, endothelins, and sympathetic nervous system, and the counterregulatory vasodilatory/natriuretic response, mainly represented by CNHs (6, 16). As cardiac performance decreases, all neurohormonal systems are progressively stimulated in an attempt to sustain cardiac output and circulatory homeostasis. However, the activation of neurohumoral mechanisms may worsen the hemodynamics, have direct adverse effects on myocardial function, and stimulate the CNH system (16). According to this hypothesis, the large increases in circulating concentrations of CNHs in HF could even be related to activation of the neuroendocrine system and thus be considered an adaptive and potentially protective response mechanism in cardiovascular disease.

Concentrations of Circulating CNHs: Physiologic Considerations and Clinical Interpretation

INFLUENCE OF AGE AND GENDER

The circulating concentrations of CNHs are regulated or modified by several physiologic factors, such as circadian variations, age, gender, exercise, body posture, and water immersion; eating habits, especially sodium intake; clinical conditions (Table 1); and drugs, including corticosteroids, sex steroid hormones, thyroid hormones, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and adrenergic agonists and antagonists (1, 6).

Table 1. Diseases characterized by altered plasma cardiac natriuretic peptides compared with healthy individuals.

Diseases	CNH concentrations
Cardiac diseases	
Heart failure	Greatly increased
AMI (first 2–5 days)	Greatly increased
Essential hypertension with LVH[a]	Increased
Pulmonary diseases	
Acute dyspnea	Increased
Pulmonary embolism	Increased
Obstructive pulmonary disease	Increased
Endocrine and metabolic diseases	
Hyperthyroidism	Increased
Hypothyroidism	Decreased
Cushing syndrome	Increased
Primary hyperaldosteronism	Increased
Diabetes mellitus	Normal or increased
Liver cirrhosis with ascites	Increased
Renal failure (acute or chronic)	Greatly increased
Paraneoplastic syndrome	Normal or increased
Subarachnoid hemorrhage	Increased

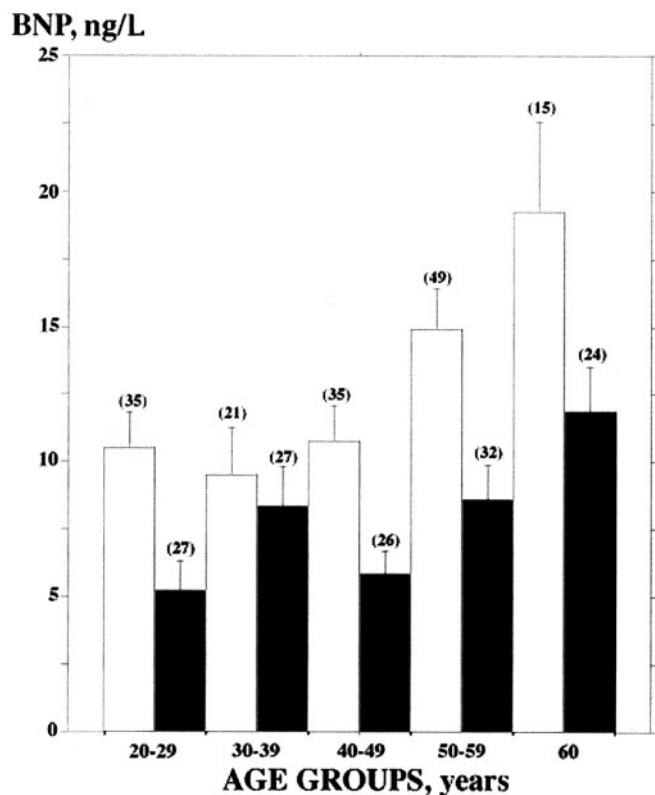[a] LVH, left ventricular hypertrophy.

Fig. 1. Mean (SE) circulating concentrations of BNP measured in 292 healthy individuals according to gender and five age groups.

The number of individuals included in each age group is indicated in *parentheses*. The characteristics of the population studied were reported in detail elsewhere *(17)*. (□, women; ■, men.)

The wide variations in circulating concentrations of CNHs in healthy adults in relation to aging and gender could have particular clinical relevance *(8, 17–19)* (Fig. 1 and Table 2). Indeed, Vasan et al. *(8)* recently demonstrated that the diagnostic accuracy of CNH assays for community screening is gender dependent.

To explain these variations, the possible influence of sex steroid hormones on the CNH system, as well as the modification of the cardiovascular system with aging,

should be taken into account *(20–23)*. According to these mechanisms, the higher CNH values in women during the fertile adult period could be explained by the physiologic stimulation of female sex steroid hormones. In particular, the BNP concentration is, on average, 36% higher in women than in men at age <50 years (Fig. 1 and Table 2). The increases in CNHs with aging may be attributable to the paraphysiologic decrease in myocardial function and other organs, including the kidney, that is typical of senescence *(24)*. In this case, CNH assays may be considered as biochemical markers of increased risk of cardiac morbidity in old age *(25)*. Moreover, the increase in CNHs with aging may be attributable to a decrease in their clearance rate. Indeed, an age modulation of maximum binding capacity of clearance (C-type) receptors for CNHs was reported in platelets of elderly persons *(26)*.

COMPARISON BETWEEN CNH ASSAYS AND ASSAYS FOR CNH-RELATED PROHORMONE PEPTIDES

All CNHs derive from preprohormones (i.e., preproANP and preproBNP) containing a signal peptide sequence at the NH_2-terminal end. The prohormones (i.e., proANP and proBNP) are produced by cleavage of signal peptide and then are further split into inactive longer NH_2-terminal fragments (i.e., NT-proANP or NT-proBNP) and a biologically active shorter COOH-terminal peptide (i.e., ANP or BNP), which are secreted in the blood in equimolar amounts. However, ANP and BNP have shorter plasma half-lives and, consequently, lower plasma concentrations than NT-proANP and NT-proBNP (Table 3) *(1, 6, 21)*.

Table 2. Mean (SD) plasma BNP concentrations in 292 healthy individuals divided into groups according to gender and age.[a]

Age	Men	Women	P[b]
20–50 years	5.9 (6.0) ng/L (n = 79)	10.0 (8.3) ng/L (n = 91)	<0.0001
≥50 years	10.1 (7.8) ng/L (n = 53)	15.6 (11.8) ng/L (n = 68)	0.0033
P[b]	0.0009	0.0020	

[a] Individuals are the same reported in Fig. 1. The age cutoff of 50 years was chosen because it corresponds to the mean age of menopause in Western European countries. The number of individuals included in each subset is indicated in parentheses. The characteristics of the population studied are reported in detail elsewhere *(17)*.

[b] Unpaired *t*-test using the logarithmic transformation of the original set of data.

Table 3. Mean analytical sensitivity, mean (SD) values, and ranges (minimum and maximum) of some commercial competitive (EIA) and noncompetitive (IRMA, ELISA, and ECLIA) immunoassays for CNH, used in our laboratory.[a]

Method[b]	Analytical sensitivity, pmol/L	Mean (SD), pmol/L	Range, pmol/L
IRMA ANP	0.73	5.6 (3.6)	0.2–16.6
IRMA BNP	0.75	2.9 (2.7)	0.1–12.4
TRIAGE BNP	1.44	2.9 (3.8)	0–14.2
ELISA proANP	76.9	731 (628)	43–1502
IRMA proANP	40.5	228 (99)	63–422
EIA proANP$_{1-30}$	9.5	708 (251)	44–1289
EIA proANP$_{31-67}$	38.4	1422 (790)	193–3339
EIA NT-proBNP$_{8-29}$	13.6	246.8 (120.1)	64–488
EIA NT-proBNP$_{32-57}$	4.0	117.5 (100.3)	0.2–368
ECLIA NT-proBNP	0.6	6.1 (4.1)	1.7–21.1

[a] The characteristics of the "normal" population studied have been reported in detail elsewhere *(17)*.

[b] IRMA ANP (SHIONOGI & Co., Ltd,.); IRMA BNP (SHIONOGI & Co., Ltd.); TRIAGE BNP (BIOSITE); ELISA proANP (BIOMEDICA GRUPPE); IRMA proANP (SHIONOGI & Co., Ltd.); EIA proANP 1–30 (BIOMEDICA GRUPPE); EIA proANP 31–67 (BIOMEDICA GRUPPE); EIA NT-proBNP$_{8-29}$ (code BI-20852; BIOMEDICA GRUPPE), uses an antiserum against the NH_2-terminal proBNP$_{8-29}$ peptide fragment; EIA NT-proBNP$_{32-57}$ (code BI-20862; BIOMEDICA GRUPPE), uses an antiserum against the NH_2-terminal proBNP$_{32-57}$ peptide fragment; ECLIA NT-proBNP (proBNP Elecsys System 2010; Roche Diagnostics).

Studies on structure–activity relationships have shown the importance of the central ring structure of CNHs, formed by a disulfide bridge between the two cysteine residues, for the binding to the specific receptors. For this reason, only ANP and BNP, which present the disulfide bridge in the peptide chain, share the typical hormonal activity of CNHs, whereas NT-proANP and NT-proBNP do not (1, 6, 21).

Theoretically, setting up an immunoassay for NT-proANP and NT-proBNP should be easier because their plasma concentrations are higher than those of ANP and BNP (Table 3) (27). On the other hand, NT-proANP and NT-proBNP immunoassays may be affected by several analytical problems, mainly concerning different assay specificities; consequently, very different results are produced by different methods (Table 3) (27). The different analytical performances might affect the diagnostic accuracy of the assays for differentiating between individuals with or without cardiac disease (27–29).

The respective advantages of assaying for the biologically active peptide hormones (ANP and BNP) and assaying for NT-proANP and NT-proBNP are summarized in Table 4. The inactive propeptides better fit the definition of a disease marker than do circulating concentrations of ANP or BNP, which on the other hand may be considered a more reliable index of the activation (hormone) status of the CNH system.

Taking into account the biochemical and physiologic characteristics of the different peptides, it is conceivable that ANP is a better marker of acute overload and/or rapid cardiovascular hemodynamic changes than BNP or, especially, than NT-proANP or NT-proBNP (1, 6, 27). For example, circulating concentrations of ANP are known to be more affected by body position and decreased to a higher extent by a hemodialysis session in patients with chronic renal failure than those of BNP, whereas plasma NT-proANP is unchanged (1, 6, 27). Furthermore, ANP increases more than NT-proANP during rapid ventricular pacing (30).

Clinical Relevance of CNH Assays

The pathophysiologic and clinical relevance of CNH assays has undergone a great deal of experimental and clinical study, as reviewed recently (1–7, 31–34). In particular, it has been suggested that CNH assays may be clinically useful (1–7, 31–38) for the screening and classification of patients with HF, as prognostic markers in cardiac disease, for the follow-up of patients with HF, and to avoid or reduce the need for expensive and/or unnecessary investigations. In the following paragraphs, we will discuss in detail the use of CNH assays in these four settings, taking into account both the pathophysiologic considerations reported above and the findings of some recent large observational studies or clinical trials, according to evidence-based laboratory medicine principles (39–42).

USE OF CNH ASSAYS IN THE SCREENING AND
CLASSIFICATION OF PATIENTS WITH CARDIAC
DYSFUNCTION

The diagnosis of HF can often be difficult, mainly in primary care settings, where patients may present with nonspecific symptoms and signs, such as dyspnea, fatigue, and ankle swelling (5, 7, 14, 33, 43). In several population-based studies, <40% of patients with a suspected diagnosis of HF in primary care had this diagnosis confirmed by more specific and accurate clinical investigations, which are often expensive, time-consuming, and demanding for the patient (33, 43–45). As a result, a relatively simple and inexpensive biochemical test (such as a CNH assay) may be very useful to confirm the clinical suspicion of HF in this clinical setting (5, 14).

DIAGNOSTIC ACCURACY OF CNH ASSAYS IN
ASYMPTOMATIC, MILD VENTRICULAR SYSTOLIC
DYSFUNCTION

Patients with asymptomatic left ventricular systolic dysfunction are likely to have lower plasma BNP than patients with overt HF (1–7, 33, 46–50), as shown in Fig. 2.

Two recent studies (8, 9) evaluated the diagnostic accuracy of the CNH assay as a screening method in a general population. The first study analyzed the Framingham Heart Study cohort (3177 individuals), using BNP and NT-proANP in the evaluation of left ventricular hypertrophy and systolic dysfunction in a community population (8). Disease presence was evaluated by echocardiographic findings (the prevalence of left ventricular systolic dysfunction was 9.3% in the 1470 men and 2.5% in 1707 women tested, respectively). The area under the ROC curve (AUC) for the ability of the CNH assay to identify both left ventricular hypertrophy and systolic dysfunction was, on average, ~0.75, with a good specificity (i.e., mean of 95% both in men and women) and negative predictive value (NPV; mean of 92% and 93% in men; 91% and 98% in women), but a poor sensitivity (mean of 27% and 28% in men; 13% and 14% in women) and positive predictive value (PPV; mean of 38% in men; 32% and 30% in women), based on use of gender-related BNP cutoff values (8).

The aim of the second study was to examine the validity of plasma BNP measurements (with the same IRMA method as the other study) for detection of various cardiac abnormalities in a rural Japanese population (1098 individuals; 693 men and 405 women) with a low preva-

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Table 4. Relative advantages of ANP/BNP and NT-proANP/BNP assays.

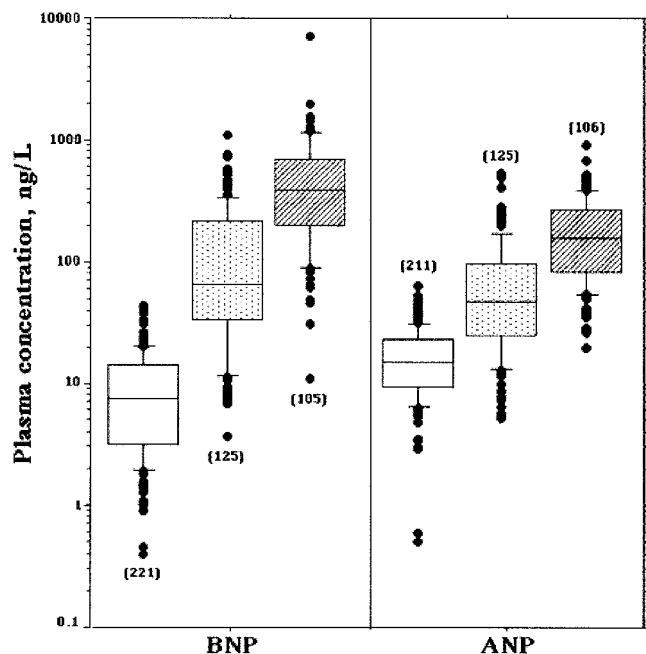| ANP/BNP	NT-proANP/BNP
Close correlation between hormonal and immunologic activities	Higher and more stable circulating concentrations
Better correlation with physiologic or clinical conditions after acute changes of hemodynamics	Less degradation in vivo and in vitro

Fig. 2. Circulating concentrations of ANP and BNP measured in healthy individuals and in patients with HF, divided according to severity of disease.

□, controls; ▨, mild HF (patients in NYHA classes I and II); ▨, severe HF (patients in NYHA classes III and IV). The number of individuals included in each group is indicated in *parentheses*. The results are expressed as box-and-whisker plots with the *lines inside* the *boxes* indicating the median (50th percentile), the *limits* of the *boxes* indicating the 25th and 75th percentiles, and the *whiskers* indicating the 10th and 90th percentiles. All values above the 90th percentile and below the 10th percentile (outliers) are plotted separately (as ●). Data are from Refs. *(48–50)*.

lence of coronary heart disease and left ventricular systolic dysfunction [i.e., only 37 participants (3.0%), showed an ejection fraction (EF) <30%] *(9)*. The diagnosis was made by two independent cardiologists based on a medical questionnaire, chest radiogram, ECG, and echocardiographic report. The optimal threshold for identification of disease was a BNP of 50 ng/L (14.4 pmol/L),[2] with an AUC for the ROC curve of 0.970, a sensitivity of 89.7%, a specificity of 95.7%, a PPV of 44.3%, and a NPV of 99.6%.

The conclusions of these two studies, although similar in aim as well as in clinical and experimental protocols, were strongly conflicting. The Japanese study suggested that the BNP assay is a very efficient and cost-effective mass screening technique for identifying patients with various cardiac abnormalities regardless of etiology and degree of left ventricular systolic dysfunction *(9)*, whereas the Framingham study suggested only limited usefulness

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[2] Conversion factors: In this review, both conventional (ng/L) and SI (pmol/L) units have been reported. The text first reports the units as originally used in a cited article (in ng/L or pmol/L) and then gives the corresponding calculated units after conversion. It is important to note that the conversion from the conventional to SI units (or vice versa) for NT-proANP and NT-proBNP may present some drawbacks because the immunoassays use different materials as calibrators to generate the calibration curves.

of CNH assays as mass screening tools for this clinical condition, especially in women *(8)*.

These two studies, taken as a whole, indicate that CNH assays may have only limited usefulness as screening methods for HF in a general population because of the poor sensitivity and PPV. However, both studies also found good specificity and NPV, thus suggesting that CNH assays may be used to rule out HF in an asymptomatic (or paucisymptomatic) individual.

DIAGNOSTIC ACCURACY OF CNH ASSAYS IN PATIENTS WITH SUSPECTED HF

Some recent studies *(33, 37, 38, 51–60)* reported that CNH assays could be useful as screening methods and/or for the differential diagnosis of patients suspected of HF in the following clinical settings: (*a*) randomly selected general (low-risk) and/or high-risk community populations *(37, 51, 54)*; (*b*) patients with a primary care new diagnosis of HF *(52)*; (*c*) patients with acute dyspnea in the emergency department *(55, 57)*; (*d*) consecutive unselected hospital inpatients *(53, 56, 58)*; and (*e*) patients admitted to the intensive care unit *(59, 60)*. The main characteristics of study protocols and the diagnostic accuracy of the best designed studies are reported in Table 5.

Abnormalities of diastolic function may play a major role in determining signs and symptoms of congestive HF *(33, 61, 62)*. Although Doppler echocardiography is currently used to examine left ventricular diastolic filling dynamics, the limitations of this technique suggest the need for other objective measures *(63)*. Some studies suggest that CNH assays, in particular a BNP assay, may be useful for the diagnosis of left ventricular diastolic dysfunction *(11, 64, 65)*, although the authors of a small study (34 patients) found no significant correlation between a CNH assay and decreased diastolic function attributable to doxorubicin-induced cardiotoxicity in children with cancer *(66)*. The reason for some conflicting results may be the different causes and/or mechanisms responsible of cardiac dysfunction *(67)*.

DIAGNOSTIC ACCURACY OF CNH ASSAYS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Circulating concentrations of CNHs increase after acute myocardial infarction (AMI); the extent of the increase is related to the size of the infarct *(68–71)*. Patients with smaller infarcts tend to have a monophasic increase in plasma BNP, peaking at 20 h after the onset of symptoms; on the other hand, those with larger infarcts, lower EF, and clinical signs of HF may present an additional peak at 5 days after admission *(69)*.

Some studies are less convincing regarding the ability of CNH assays to identify patients with significant ventricular damage after AMI *(72, 73)*. These conflicting results could be attributable to the differences in sample collection time, type of CNH (ANP, BNP, or NT-proBNP) measured, type of assay (competitive vs noncompetitive), and inclusion criteria adopted. In summary, CNH assays

Table 5. Study protocols and diagnostic accuracy of CNH assay in patients with HF.

Authors, year (Ref.)	Study protocol	CNH, cutoff value (assay)	ROC (95% CI)	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Omland et al., 1996 (51)	Consecutive series of 254 patients undergoing left cardiac catheterization were enrolled in the study; 128 with a history of previous AMI	ANP (RIA) NT-proANP (RIA) BNP (RIA)	0.665 0.610 0.789				
Cowie et al., 1997 (52)	122 consecutive patients referred to a rapid-access HF clinic with a new primary care diagnosis of HF	ANP (RIA) NT-proANP (RIA) BNP (RIA)	0.93 0.89 0.96	97 97 97	72 66 84	55 54 70	98 98 98
Richards et al., 1998 (60)	Consecutive series of 121 patients admitted to the coronary care unit with AMI	NT-proBNP, 160 pmol/L (1353 ng/L; RIA)		91	72	39	97
Hobbs et al., 2002 (54)	591 patients were enrolled, stratified for age and socioeconomic status, and divided into four cohorts (general population, patients with an existing clinical label of HF, patients on diuretics, and patients deemed at risk of HF)	NT-proBNP, 36 pmol/L (304 ng/L; ELISA)	0.92 (0.82–1.0)[a] 0.8 (0.72–0.88)[b]	100[a] 100[b]	70[a] 18[b]	7[a] 3[b]	100[a] 100[b]
Maisel et al., 2002 (55)	1586 patients who came to the emergency departments of seven different sites with acute dyspnea	BNP, 100 ng/L (28.9 pmol/L; ILMA[c] POCT)	0.91 (0.90–0.93)	90	76		
Apple et al., 2003 (56)	334 patients ruled in or out for congestive HF or being monitored for HF therapy decision for a period of 8 months in two urban teaching hospitals	BNP, 100 ng/L (28.9 pmol/L; ILMA POCT)	0.915	94.8	77.1	85.3	91.4
Bay et al., 2003 (58)	During a 10-month period, 2193 patients admitted to a city general hospital (80% of targeted patients) were enrolled	NT-proBNP, 357 pmol/L (3019 ng/L; ELISA)	0.85	73	82	24	98
Maisel et al., 2003 (57)	452 patients with a final adjudicated diagnosis of congestive HF who underwent echocardiography within 30 days of their visit to the emergency department	BNP, 100 ng/L (28.9 pmol/L; ILMA POCT)	0.90 (0.88–0.91)	90	73	75	90
Nielsen et al., 2003 (37)	A random sample of 1257 community members was examined as a pre-echocardiographic screening test for left ventricular systolic dysfunction	BNP, 8 ng/L (0.9 pmol/L; RIA)	0.86	92	53	7	99.4

[a] General population >45 years of age (n = 307).
[b] Patients with existing diagnosis of HF (n = 133).
[c] ILMA, immunoluminometric assay.

seem to be only moderately useful in assessing left ventricular dysfunction after AMI. However, persisting increases in CNHs at 1 or 2 months after AMI would suggest a high risk of adverse remodeling and subsequent HF, although this finding should be confirmed by additional well-designed studies.

DIAGNOSTIC ACCURACY OF CNH ASSAYS IN THE ELDERLY

HF is primarily a disease of old age. The authors of some recent studies have reported that BNP assays could be clinically useful in elderly people suspected to have HF (25, 36). In particular, a prospective cohort study specifically evaluated the diagnostic accuracy for HF of BNP assays in 299 consecutive patients (mean age, 79 years; 65% women) attending a day-hospital over a period of 13 months (36). This study suggested that both BNP assays and ECG were sensitive in detecting left ventricular systolic dysfunction but lacked specificity (the combination of the two tests improved diagnostic accuracy) and that BNP concentrations increased progressively as the number of different cardiac abnormalities increased (36).

DIAGNOSTIC ACCURACY OF CNH ASSAYS IN OTHER CLINICAL CONDITIONS

CNH assays could be clinically useful in other clinical conditions. For example, a very recent study (74) reported that NT-proBNP [measured by an electrochemiluminescent assay (ECLIA)] was the most sensitive index of myocardial dysfunction and the most powerful prognostic determinant in primary systemic amyloidosis. Furthermore, this assay can add prognostic information for newly diagnosed patients more effectively than echocardiography and can be useful in designing therapeutic strategies and monitoring response (74).

Another example is the possibility, mainly by BNP assay, of identifying HF related to anthracycline cardiotoxicity (66, 75–78).

COMPARISON OF CNH ASSAYS WITH OTHER MARKERS OF HF

Signs and symptoms correlate poorly with the presence of HF (5, 33, 79). Davie et al. (80) found that left ventricular systolic dysfunction was virtually never present if the ECG was normal (sensitivity, 94%; NPV, 98%), and a screening ECG reduced the need of echocardiograms by 50%.

However, CNH measurements may exclude a normal heart with high probability, reducing the echocardiographic diagnostic burden (31, 33, 37, 79). Choy et al. (81) showed that in post-AMI patients, plasma BNP is superior to all clinical indices of left ventricular systolic dysfunction (EF <40%), including signs and symptoms and a clinical score (Peel Index). Talwar et al. (82) examined the value of NT-proBNP (measured by a competitive immunoluminometric assay), abnormal ECG, and other baseline clinical and laboratory variables in identifying patients with left ventricular systolic dysfunction in a high-risk population (243 patients; 129 men; median age, 73 years; range, 20–94 years). NT-proBNP alone was a better predictor of left ventricular dysfunction than any other single or combination of factors, whereas the ECG had a poor predictive value for left ventricular systolic dysfunction (82). Cowie et al. (52) (Table 5) reported that ROC curves for BNP (AUC, 0.96), ANP (0.93), and NT-proANP (0.89) were better than that of cardiothoracic ratio on chest radiogram (0.79) in screening for patients likely to have HF and requiring further clinical assessment. Nielsen et al. (37) (Table 5) found that BNP assay, at a cutoff >8 ng/L (0.9 pmol/L), showed a diagnostic accuracy better than that of ECG (sensitivity, 57%; specificity, 85%; PPV, 13%; NPV, 98%) in a random sample of 1257 individuals in a community.

It may well be that a combination of tests is the optimal approach for screening patients with suspected HF (60). Indeed, Richards et al. (60) showed that a combination of NT-proBNP RIA and echocardiographic evaluation of left ventricular function better defined the risk of mortality and/or HF in patients with AMI than either test alone. In particular, for prediction of death over 24 months of follow-up, an early postinfarction NT-proBNP concentration ≥160 pmol/L (1353 ng/L) had a prognostic accuracy superior to any other neurohormone measured and to assessment of left ventricular EF by echocardiography (Table 5). By multivariate analysis, NT-proBNP provided predictive information for left ventricular failure and death, independently from age, gender, left ventricular EF, concentrations of other hormones, previous history of HF, myocardial infarction, hypertension, or diabetes (60).

Use of CNHs as Prognostic Markers

The authors of several well-designed and conducted studies suggested that CNHs may be useful as prognostic markers mainly in two clinical conditions: HF and acute coronary artery syndromes (ACS), as reviewed recently (1–7, 33, 38, 79, 83–86).

PROGNOSIS IN HF

The main protocol characteristics and results of some studies (87–91) that evaluated the prognostic value of CNH assays in patients with HF are reported in Table 6. In all of these studies, BNP and NT-proBNP (but not ANP and NT-proANP) were always found to be independent risk markers for morbidity and/or mortality (87–89).

Two studies specifically investigated whether CNH assays can predict mortality in elderly persons (25, 92). Wallen et al. (92) studied the relationship of BNP concentrations with aging and whether BNP could reflect current disease states in the general elderly population (545 individuals >85 years of age). In multivariate analysis, BNP concentrations were predictive of ischemic heart disease, atrial fibrillation, renal dysfunction, congestive HF, and treatment with β-adrenergic blockers (92).

Table 6. CNH assays as prognostic risk markers in patients with HF.

Authors, year (Ref.)	Study protocol	CNH assay (method)	Main results
Benedict et al., 1996 (87)	A subset of 241 patients with asymptomatic left ventricular dysfunction were enrolled in the SOLVD Prevention Trial	ANP (RIA)	Risk ratio, 0.8 (0.38–1.65) for all clinical events ($P = 0.54$)
Tsutamoto et al., 1999 (88)	290 consecutive patients with asymptomatic or minimally and newly symptomatic left ventricular dysfunction (functional classes I–II; mean left ventricular EF, 37%) were studied	ANP (IRMA) BNP (IRMA)	BNP risk ratio, 1.004 (1.003–1.006) for 2-year mortality ($P < 0.0001$); ANP, $P > 0.05$.
Stanek et al., 2001 (89)	91 patients with HF (left ventricular EF <25%) receiving 40 mg/day enalapril and double-blind atenolol (50–100 mg/day) or placebo were enrolled	NT-proANP (ELISA) NT-proBNP (ELISA) BNP (RIA)	BNP ($P = 0.0001$) and NT-proBNP ($P = 0.0027$) independently related to 4-year mortality by multivariate Cox regression analysis
Anand et al., 2003 (90)	Plasma BNP was measured before randomization and during follow-up in ~4300 patients (the Valsartan HF Trial).	BNP (IRMA)	Risk ratio, 2.1 (1.79–2.42) for mortality; 2.2 (1.98–2.52) for morbidity ($P < 0.0001$)
Koseki et al., 2003 (91)	Multicenter (21 hospitals) prospective observational approach: 721 patients were recruited with chronic HF (the CHART study).	BNP (unspecified)	Risk ratio, 1.90 (1.04–3.47) for DC,[a] 2.02 (1.01–4.04) for AMI; 1.70 (1.02–2.84) for VHD; 2.68 (1.03–6.96) for LVH for 1-year incidence of all events, including all deaths and HF hospitalization

[a] DC, dilated cardiomyopathy; VHD, valvular heart disease; LVH, left ventricular hypertrophy.

Ueda et al. (25) investigated the prognostic implications and potential causes of the increased concentrations of BNP (measured by IRMA) in 111 individuals (age ≥80 years) who had no history of hospitalization for cardiac disease. During a 24-month follow-up, 8 individuals (7%) were hospitalized with cardiac disorders and 21 (19%) died. Each 50-ng/L (14.4 pmol/L) increase in the plasma BNP concentration was associated with a 1.6-fold [95% confidence interval (CI), 1.2- to 2.1-fold] increase in the risk of cardiac events and a 1.4-fold (95% CI, 1.2- to 1.6-fold) increase in total mortality.

PROGNOSIS IN ACS

ACS encompasses a continuum of cardiac ischemic events ranging from unstable angina pectoris with no biochemical evidence of myocardial necrosis to ST-elevation AMI (93, 94). The prognosis for patients with ACS varies widely, and several clinical, ECG, and biochemical markers have been used to identify high-risk individuals in need of aggressive intervention (93–95).

Recently, CNH assays (in particular for BNP and NT-proBNP) have been shown to provide valuable prognostic information for patients with ACS (33–35, 60, 72, 86, 95–107). A summary of study protocol characteristics and mean results of the best-designed studies are reported in Table 7.

PROGNOSTIC RELEVANCE OF CNH ASSAYS IN THE GENERAL POPULATION

Some studies have evaluated the prognostic relevance of CNH assays in the general population, especially the elderly (25, 92, 99, 108–110). The studies by Ueda et al. (25) and McDonagh et al. (99) (Table 7) have been discussed previously.

Davis et al. (108) studied 331 elderly volunteers free of acute illness at study entry [mean (SD) age, 88 (7) years; 23% men] in a 1-year prospective blinded cohort study. The risk of overt HF increased progressively with increasing ANP. In multivariate analysis, only two independent variables significantly predicted acute congestive HF during the 1-year follow-up period: ANP >200 pmol/L (615 ng/L; adjusted odds ratio, 7.9; 95% CI, 3.2–19.2] and a history of HF in the previous year (adjusted odds ratio, 7.0; 95% CI, 2.9–17).

Wallen et al. (92, 109) studied whether prospective measurements of circulating concentrations of ANP, NT-proANP, and BNP could predict mortality in a cohort of 85-year-old individuals from the general population (n = 541), who were followed up prospectively for 5 years. Plasma BNP predicted 5-year mortality better than ANP and NT-proANP in the total population as well as in individuals without a defined cardiovascular disorder (92, 109).

It can be hypothesized that hypertension-prone individuals may have increased CNH concentrations as a result of increased ventricular wall stress or vascular stiffness early in the course of the disease. If this hypothesis is true, CNH assays could serve as markers of future hypertension risk in the general population. Freitag et al. (110) evaluated the relationship of plasma BNP (measured by IRMA) with longitudinal blood pressure tracking and incidence of hypertension in 1801 nonhypertensive Framingham Heart Study participants (mean age, 56 years; 57% women). In multivariate models adjusting for known risk factors, increased plasma BNP was associated with increased risk of blood pressure progression in men (odds ratio of 1.15 for trend across categories; $P = 0.046$) but not in women ($P = 0.82$).

Table 7. CNH assay as prognostic risk marker in patients with ACS

Authors, year (Ref.)	Study protocol	CNH assay (method)	Mean results
Arakawa et al., 1996 (96)	A cohort of 70 patients with AMI were enrolled. Measurements were obtained on admission (mean 6 h after onset) and on day 2 after onset. Mean follow-up period was 18 months	ANP (RIA) BNP (RIA)	BNP related to survival after AMI by Cox proportional hazards model analysis ($P=0.0001$)
Darbar et al., 1996 (97)	CNHs were measured in a cohort of 75 patients after AMI, followed for on average 19.7 months	ANP (RIA) BNP (RIA)	ANP identified patients at risk of symptomatic HF ($P=0.002$) and hospitalization ($P=0.019$). BNP was the only significant independent predictor of cardiovascular mortality ($P=0.0001$)
Omland et al., 1996 (72)	Venous blood samples for CNH assay were obtained on day 3 after symptom onset from a cohort of 131 patients with documented AMI, followed for a median period of 1293 days	ANP (RIA) NT-proANP (RIA) BNP (IRMA)	BNP was an independent predictor of cardiovascular mortality by multivariate Cox regression analysis ($P=0.021$), but not ANP and NT-proANP
Crilley and Farrer, 2001 (98)	133 initial survivors of a first AMI who received thrombolytic treatment were studied for a follow-up period of 1 year	BNP (RIA)	Baseline BNP was associated with 1-year mortality by multiple linear regression analysis ($P=0.003$)
Richards et al., 2001 (100)	NT-proBNP was assessed for prediction of adverse outcome in a cohort of 297 patients with ischemic left ventricular dysfunction who were randomly assigned to receive carvedilol or placebo	NT-proBNP (RIA)	Risk ratio for mortality: 4.67 (2–10.9; $P<0.001$) Risk ratio for hospital admission with HF: 4.7 (2.2–10.3; $P<0.001$)
De Lemos et al., 2001 (35)	BNP in plasma specimens obtained a mean (SD) of 40 (20) h after the onset of ischemic symptoms in 2525 patients from TIMI 16 study. Baseline BNP values were correlated with the risk of death, HF, and AMI at 30 days and 10 months	BNP (unspecified)	Odds ratios for death at 10 months in the second, third, and fourth quartiles of BNP were 3.8 (1.1–13.3), 4.0 (1.2–13.7), and 5.8 (7–19.7). BNP was associated with the risk of new or recurrent AMI and new or worsening HF at 10 months
McDonagh et al., 2001 (99)	A random sample of a cohort of 1640 men and women 25–74 years of age, from a geographic urban population, followed for 4 years was enrolled	BNP (RIA) NT-proBNP (RIA)	BNP ($\geq$17.9 ng/L; 5.2 pmol/L) was an independent predictor of 4-year all-cause mortality by multivariate analysis ($P=0.006$)
Omland et al., 2002 (95)	Blood samples for CNH assay were obtained in the subacute phase in 204 patients with ST-elevation AMI: 220 with non-ST segment elevation AMI and 185 with unstable angina in the subacute phase, followed for a median follow-up of 51 months	NT-proBNP (ILMA)	NT-proBNP was independent predictor of mortality with a mean risk ratio of 2.4 (1.1–5.4)
Jernberg et al., 2002 (104)	A cohort of 755 patients admitted because of chest pain and no ST-segment elevation was studied. Patients were followed concerning death for 40 months (median)	NT-proBNP (ECLIA)	Compared with the lowest quartile, patients in the second, third, and fourth quartiles had a relative risk of subsequent death of 4.2 (1.6–11.1), 10.7 (4.2–26.8), and 26.6 (10.8–65.5), respectively. NT-proBNP was independently associated with prognosis by a Cox regression model
Morrow et al., 2003 (106)	A cohort of 1676 patients, with non-ST-elevation ACSs, and randomized to early invasive versus conservative management (TIMI study) was studied	BNP (ILMA POCT)	BNP was independent predictor of mortality at 6 months with a mean odds ratio of 3.3 (1.7–6.3). BNP >80 ng/L (23.1 pmol/L) increased by fivefold the risk of developing new congestive HF by 30 days (5.9% vs 1.0%; $P<0.0001$)
Richards et al., 2003 (107)	A cohort of 666 patients with AMI were studied followed for 3 years	BNP (RIA) NT-proBNP (RIA)	NT-proBNP was an independent predictor of death 6.63 (3.72–11.79) by stepwise Cox proportional hazrads regression analysis. NT-proBNP and BNP were equivalent prognostic markers for clinical outcomes ($P<0.01$)

PROGNOSTIC RELEVANCE OF CNH ASSAYS IN
PULMONARY DISEASES

The prognostic relevance of CNHs has been evaluated in acute and/or chronic pulmonary diseases because it is well known that circulating concentrations of CNHs increase in these clinical conditions with the degree of hypoxia and right heart overload (111–116).

Ishii et al. (113) evaluated whether plasma BNP and ANP (measured by IRMA) were useful markers of right ventricular overload and whether they had prognostic value as predictors of death in 31 consecutive patients with chronic respiratory disease who underwent right-heart catheterization. During a follow-up period >12 months, BNP (P <0.05) was an independent

predictor of end-stage chronic respiratory disease death (113).

Nagaya et al. (114) sought to assess the prognostic significance of plasma BNP (measured by IRMA) in 60 patients with primary pulmonary hypertension at diagnostic catheterization. Measurements were repeated in 53 patients after a mean follow-up period of 3 months. During a mean follow-up period of 24 months, 18 patients died of cardiopulmonary causes. According to multivariate analysis, baseline plasma BNP was an independent predictor of mortality. Survival was strikingly worse for patients with a supramedian value of follow-up BNP [≥180 ng/L (52 pmol/L)] than for those with an inframedian value (P <0.0001). In addition, ROC analysis indicated that the prognostic power of BNP was comparable or even superior to that of hemodynamic evaluation (114).

Another study (115), in which 110 consecutive patients were evaluated, examined whether plasma BNP (measured by IRMA) is a predictor of fatal pulmonary embolism. The relationship between BNP concentration measured at presentation and clinical outcome was assessed by comparing the proportion of outcome events among tertiles. The risk of death related to pulmonary embolism if BNP was >21.7 pmol/L (75 ng/L) was 17% (95% CI, 6–33%). The NPV for uneventful outcome in individuals with a BNP value <21.7 pmol/L (75 ng/L) was 99% (95% CI, 93–100%) (115).

Kucher et al. (116) measured plasma BNP with a point-of-care testing (POCT) method to determine its prognostic value in 73 consecutive patients with acute pulmonary embolism. A BNP cutoff of 90 ng/L (26 pmol/L) was used for the prediction of a major adverse cardiovascular event. The sensitivity, specificity, NPV, and PPV were 85% (95% CI, 64–95%), 75% (62–85%), 93% (81–98%), and 57% (39–73%), respectively. Moreover, low BNP [<50 ng/L (14.4 pmol/L)] identified 95% of patients with a benign clinical course of acute pulmonary embolism (116).

DIAGNOSTIC ACCURACY AND PROGNOSTIC RELEVANCE OF CNH ASSAYS IN KIDNEY DISEASES

It is well known that cardiovascular events are the major prognostic determinants in patients with chronic hemodialysis (cardiovascular deaths representing >50% of total mortality). In these patients, creatinine concentrations are associated with increased risk of mortality, cardiovascular disease, and chronic HF (117, 118). Circulating concentrations of CNHs are greatly increased in renal failure, and several studies tested their diagnostic accuracy and prognostic relevance (119–128).

Ishii et al. (124) prospectively compared the predictive value of myocardial necrosis markers (cardiac troponin T and I) and CNHs (ANP and BNP, both measured by IRMA methods) in 100 consecutive outpatients on chronic dialysis without ACS. In a stepwise multivariate Cox regression analysis, only cardiac troponin T (P <0.05 and

P <0.01) and a history of HF requiring hospitalization (P <0.05 and P <0.005) were independent predictors of both all-cause and cardiac mortality after a 2-year follow-up (124). Cataliotti et al. (125) examined the relationship of CNHs with cardiac mortality in 112 dialysis patients without clinical evidence of congestive HF. BNP concentrations were significantly associated with greater risk of cardiovascular death in a Cox regression analysis (P <0.001), as was the ANP concentration (P = 0.002) (125). Goto et al. (126) investigated whether increased plasma concentrations of ANP or BNP predicted future cardiac events in 53 patients undergoing chronic hemodialysis without clinical symptoms suggestive of cardiac disorders and followed for 11.3 (0.2) months. Using the Kaplan–Meier method, Goto et al. (126) found that the incidence of cardiac events was significantly greater in patients with higher concentrations of ANP (50.0% vs 0.0%) or BNP (72.7% vs 11.9%). Naganuma et al. (127) monitored cardiac mortality for 36 months in 164 hemodialysis patients and 14 healthy volunteers. By stepwise multivariate Cox proportional hazards analysis, they found that BNP (relative risk ratios, 1.002; 95% CI, 1.001–1.002), left ventricular mass index (1.027; 95% CI, 1.013–1.042) and C-reactive protein (2.192; 95% CI, 1.532–3.135) were independent predictors of cardiac death compared with other biochemical and clinical markers (127).

The clinical relevance of CNH assay in the stratification risk for cardiac or total mortality in patients with renal failure is uncertain, as suggested by the conflicting results reported above (119–128). The usefulness of CNH assays as diagnostic markers of cardiac function in patients with end-stage renal disease is also doubtful, especially when taking into account the different behavior of CNHs and their N-terminal propeptides and when comparing it with other biomarkers and/or hemodynamic indices (6, 27, 124, 128). Whereas only few data are available on NT-proBNP assays, BNP assays seem to show better diagnostic accuracy and clinical performance as prognostic markers than ANP assays.

These conflicting results could be attributable to the relatively small number of patients studied compared with the larger number of patients in studies concerning HF or ACS. Moreover, only studies with long follow-up periods in a large population allow accurate determination of a sound number of clinically significant events (40, 41). Furthermore, renal failure can be considered to be the end-stage of all renal diseases, so that patients with chronic renal failure studied by different groups could have very different clinical histories and characteristics, pharmacologic treatments, and cardiovascular risk backgrounds. Whereas glomerulonephritis was the leading cause of chronic renal failure in the past, diabetic and hypertensive nephropathies are now more frequent (129). Patients with diabetes mellitus and systemic arterial hypertension are also at high risk for major cardiovascular events; consequently, the prevalence of hypertension and/or diabetes can greatly influence evaluations of the

diagnostic accuracy and risk power for a CNH assay in patients with renal failure.

CNH Assays in the Follow-Up of Patients with HF

Medical therapy for HF is based on improving the symptoms and signs of fluid retention (change in dyspnea, edemas, and body weight are the usual markers of response to treatment) and titrating the dosage of drugs (such as diuretics, ACE inhibitors, β-blockers, and spironolactone), according to the evidence from randomized clinical trials *(14, 33, 43)*. Currently, there is no specific surrogate endpoint for treating patients with HF that can be used to fine tune therapy *(14, 33, 34, 43)*.

Several authors have suggested that CNH assays may be useful in monitoring and tailoring the medical therapy in patients with HF *(5, 33, 34, 84, 90, 100, 130–135)*. To provide a practical objective indicator of optimal anti-HF therapy, CNHs should respond to drug treatment. Indeed, ACE inhibitors, valsartan, diuretics, and nitrates have been shown to reduce plasma CNH concentrations in parallel with hemodynamic and clinical improvement *(34, 84, 130, 136–144)*. More variable effects on plasma CNH concentrations have been reported after β-blockade and are at least in part attributable to their differing specificities or to ancillary properties *(34, 84, 90, 132, 137, 145–148)*. Acute administration of β-blockers may provide an early increase in plasma CNHs, whereas sustained treatment with associated improvement in cardiac function and reduction in filling pressure and cardiac volumes should be associated with a decrease in hormone concentrations *(34)*.

At present, only two published studies *(130, 131)* were designed to specifically evaluate the clinical use of CNH assays in monitoring and tailoring the medical therapy in patients with HF.

Murdoch et al. *(130)* sought to determine whether titration of vasodilator therapy according to plasma BNP may be of value in the individual optimization of vasodilator therapy in chronic HF. Twenty patients with mild to moderate chronic HF and receiving stable conventional therapy were randomly assigned to titration of the ACE inhibitor dosage according to serial measurements of plasma BNP or to optimal empiric ACE inhibitor therapy for 8 weeks. Only the BNP-driven approach was associated with significant reductions in plasma BNP concentrations throughout the duration of the study and a significantly greater suppression compared with empiric therapy after 4 weeks [−42.1% (95% CI, −58.2% to −19.7%) vs −12.0% (−31.8% to 13.8%), $P = 0.03$]. This study suggests that plasma BNP may be chronically reduced by tailored vasodilator therapy in patients with chronic HF. Furthermore, titration of vasodilator therapy according to plasma BNP was associated with more profound inhibition of the renin-angiotensin-aldosterone system and a significant decrease in heart rate compared with empiric therapy *(130)*.

Troughton et al. *(131)* hypothesized that pharmaco-therapy guided by plasma concentrations of the NT-proBNP would produce a superior outcome to empirical trial-based treatment dictated by clinical acumen. In this study, 69 patients with impaired systolic function (EF <40%) and symptomatic HF [New York Heart Association (NYHA) class II–IV] were randomized to receive treatment guided by either plasma NT-proBNP concentration or standardized clinical assessment. During the follow-up (minimum of 6 months; median, 9.5 months), there were fewer total cardiovascular events (death, hospital admission, or HF decompensation) in the NT-proBNP-guided group than in the clinical group (19 vs 54; $P = 0.02$). At 6 months, 27% of patients in the NT-proBNP-guided group and 53% in the clinical group had experienced a first cardiovascular event ($P = 0.034$). Changes in left ventricular function, quality of life, renal function, and adverse events were similar in both groups. This study indicates that NT-proBNP-guided treatment of HF reduced total cardiovascular events and delayed time to first event compared with intensive clinically guided treatment *(131)*.

Can CNH Assays Reduce the Need for Cardiac Investigations?

It has been suggested that CNH assays could reduce the need for cardiac investigations *(14, 31, 33)*. Indeed, ruling out HF by use of CNH assays would make unnecessary other investigations, which are often time-consuming, expensive, invasive, and sometimes, potentially harmful for the patient *(14)*. However, at the present time, only one published study was designed to test this possibility. Nielsen et al. *(37)* sought to assess the cost-effectiveness of using plasma BNP (measured by RIA) as a pre-echocardiographic screening test for left ventricular systolic dysfunction in the general population (Table 5). These authors hypothesized that plasma BNP together with simple clinical indices would reduce the number of echocardiograms and, therefore, the cost of population screening for left ventricular systolic dysfunction in the general population. Screening high-risk individuals by BNP before echocardiography could reduce the cost per detected case of left ventricular systolic dysfunction by 26%, for a cost ratio of 1:20 (BNP/echocardiogram). More reduced costs (up to 50%) can be predicted for the group of low-risk individuals *(37)*.

The results of a cost-effectiveness analysis, however, strongly depend on the relative cost of the CNH test compared with that of echocardiograms, as well as on the prevalence of HF in the population screened. Unfortunately, these factors can vary considerably among departments, countries, and healthcare systems; it therefore is probably necessary that each laboratory/clinical department analyzes the cost-effectiveness in its own economic framework. Furthermore, cost-effectiveness analysis is also dependent on the sensitivity of the CNH assay for detecting HF. Cost-effectiveness will improve if more specific assays are used: this would decrease the number

of individuals with false-positive (FP) results and, consequently, the number of additional useless investigations.

General Discussion

As reviewed in detail in the previous sections, the authors of several studies hypothesized that CNH assays may be clinically useful for the screening and classification of patients with HF, as prognostic markers in cardiac disease, for follow-up of patients with HF, and to avoid unnecessary diagnostic procedures. A critical review should test whether sufficient experimental data support these hypotheses. We believe that at present it is very difficult to answer these questions positively, mainly because of the problems discussed below.

The first problem is that there is a general lack of good, primary studies of test evaluations for CNH assays (42). In particular, even some high-quality studies were not designed with the primary goal of evaluating the diagnostic accuracy of CNH assays. Indeed, this aim was considered only at a post hoc analysis and was assessed retrospectively in blood samples collected for different original purposes, even some years before the actual evaluation of diagnostic accuracy. This may introduce a significant bias, although its true clinical relevance is difficult to assess.

A second problem is that a simple and objective definition of chronic HF is currently impossible because there are no defined cutoffs for valvular or myocardial dysfunction or for changes in cardiac output or cardiovascular pressures, dimensions, or volumes that can be used to reliably identify patients with HF (14). Instead, HF is a clinical syndrome characterized by specific symptoms (dyspnea and fatigue) and signs (edemas) (14, 43). Furthermore, it should be emphasized that HF is not equivalent to cardiomyopathy or to left ventricular dysfunction; these latter terms describe possible structural reasons for the development of HF (43).

Because there is no a objective rule to identify and/or clinically stratify patients suspected to have HF, the different groups of investigators used different gold standards to evaluate the diagnostic accuracy of CNH assays, including clinical scores. In this case, the patients studied were stratified and grouped according to clinical severity, as described by functional classification (usually NYHA classification; Fig. 2). In other studies, only echocardiographic measurements were used as the gold standard to determine the accuracy of CNH assays for the diagnosis of left ventricular dysfunction (and not for the clinical diagnosis of HF).

It is important to underscore that both mechanical and neuroendocrine functions contribute to overall cardiovascular function and that, although separate, they represent interdependent functions mutually affected by many and complex feed-back mechanisms (4). A corollary of this assumption is that assays of the neuroendocrine system and clinical investigations of cardiac pump function offer different, but complementary, information about cardiac function (4). Both mechanical and neuroendocrine functions should always be tested separately by suitable methods to achieve more complete knowledge of the role played by the heart in all physiologic and clinical conditions. Therefore, we believe that echocardiographic results should not be used as the only gold standard for the evaluation of diagnostic accuracy of CNH assays in patients with HF.

Comparison of the studies concerning the diagnostic accuracy of CNH assay was also difficult because different populations were enrolled and different immunoassays were used. Indeed, diagnostic accuracy (especially predictive values) is strictly dependent on disease prevalence (pretest probability), which evidently varies greatly according to the clinical setting considered (i.e., screening for general population, outpatients seen by a general practitioner, or in primary care, emergency department, coronary care unit, and other settings). Another factor, often underestimated, is that the gold standard (which is not an objective rule, but a clinical synthesis or another diagnostic test) could vary with disease prevalence, sometimes in a different manner than CNH assays.

In an asymptomatic or low-risk population, the diagnostic sensitivity in detecting left ventricular systolic dysfunction could be suboptimal, especially in women (8). A large number of FP results obtained with CNH assays in a general asymptomatic population can be related to the diseases reported in Table 1. Because it is well known that patients suffering from some endocrinologic, metabolic, or renal diseases are at higher risk for cardiac disease, abnormal CNH assay results could predict an increased risk for cardiac disease more accurately and earlier than a standard echocardiographic examination in some clinical settings.

On the other hand, false-negative (FN) results could be found in patients on antihypertensive treatment with antiadrenergic agents or ACE inhibitors, which both reduce CNH concentrations. It is well known that these patients have an overall reduced rate of major cardiac events or mortality compared with untreated hypertensive patients, who could have similar echocardiographic abnormalities.

On the contrary, in populations with higher disease prevalences, the diagnostic sensitivity improves up to 90% or more by selecting appropriate cutoff values in some clinical settings (Table 5). In this case, a strategy, called "SnNout", which maximizes test sensitivity, could be used to rule out the disease (41). Furthermore, CNH assays generally also have high NPV values (Table 5), which can also help in excluding the presence of the disease (i.e., HF) in individual patients. These findings represent the rationale for choosing CNH assays as part of the first step for an algorithm for the diagnosis of HF (14). On the other hand, test specificity ranged between 53% to 84% and PPV between 3% and 85% in some studies (Table 5). These data indicate that CNH assays can produce relatively large numbers of FP results. Consequently,

many individuals who do not have HF (~15–60% of those with positive test results) may undergo expensive and/or harmful investigations to rule out the disease or even be inappropriately labeled as cardiac patients.

Moreover, some data reported in the literature suggested that diagnostic accuracy may significantly vary in relation to the specific cardiac peptide measured and/or immunoassay used (29, 52). At present, the different CNH immunoassays also show greatly different imprecision (27). Consequently, it is not clear whether the observed significant variation in diagnostic accuracy is attributable to a difference in the pathophysiologic behavior of measured peptides and/or in assay performance (27–29, 51–53, 72). Unfortunately, the authors of some studies do not clearly indicate the type of immunoassay used to measure CNHs, and the majority do not report the assay performance (often not even the reference values) evaluated in their own laboratories.

It is important to note that the diagnostic accuracies of conventional clinical investigations could be very similar to those of CNH assays in particular clinical settings. For example, Nielsen et al. (37) reported that a self-reported questionnaire (including blood pressure measurement) together with a standard 12-lead ECG (but without echocardiographic examination) had diagnostic accuracy very similar to that of a BNP assay (sensitivity, 90%; specificity, 56%; PPV, 7%; NPV, 99.3%; Table 5). In another study (149), clinical judgment had a sensitivity of 49% and specificity of 96%, whereas a BNP assay (by a POCT method) had a sensitivity of 90% and specificity of 73% in determining the diagnosis of HF in patients presenting with acute dyspnea in an emergency department. Moreover, the AUCs for ROC curves were 0.86 (95% CI, 0.84–0.88), 0.90 (0.88–0.91), and 0.93 (0.92–0.94) for clinical judgment, for BNP at a cutoff of 100 ng/L (28.9 pmol/L), and for the two diagnostic approaches in combination, respectively. These data (37, 149) suggest that the cost-effectiveness of using CNH assays for the screening of patients suspected to have HF must be accurately evaluated before this test can be used routinely in a particular clinical setting.

Because of these problems, a metaanalysis of all data available for the evaluation of the diagnostic accuracies of CNH assays is difficult or even impossible (this type of analysis is not available in the literature). Moreover, the review of the overall data reported in the previous sections of this article indicates that several aspects are still unsolved; a working list could include:

- There is no nomenclature for CNHs and their related peptides that is universally accepted and used in the literature;
- Standardization of CNH immunoassays is lacking, including use of the same peptide preparation for dose–response curve calibration, as well as use of the same units, references, and cutoff values. Furthermore, the

analytical performance of some immunoassay methods is not yet well established;

- There are insufficient results concerning which hormone (ANP or BNP) or N-terminal propeptide (NT-proANP or NT-proBNP) should be assayed. In particular, the diagnostic accuracies of different immunoassay methods are uncertain, as are the clinical settings (i.e., with low or high prevalence of disease) in which these different assays perform better;
- There are conflicting data concerning the use of CNH assays as risk markers in patients with cardiovascular disease, mainly regarding optimal decision limits and their use in combination with other biochemical markers, clinical findings, or hemodynamic indices. Moreover, additional work is needed to identify therapies that may reduce the risk associated with increased CNH concentrations. Finally, it is not clear whether patients with increased CNH concentrations should be treated more aggressively.
- Additional studies are also needed to analyze the clinical relevance of CNH assays in the follow-up of patients with cardiovascular disease, as well as their cost-effectiveness in different clinical settings.

Conclusions and Future Perspectives

Much work is still needed to carefully assess the diagnostic accuracies and prognostic values of CNH assays in cardiac disease. It is important to highlight that these future studies should be designed to determine what each CNH assay can provide according to its analytical characteristics. CNH assays cannot replace cardiac imaging, but both provide independent and complementary information for the evaluation of cardiac function and clinical patient status.

However, taking into account the limitations discussed above, several well-designed studies have indicated that CNH assays could be clinically useful for the diagnosis and characterization of patients with suspected HF. In particular, increased CNH concentrations in patients with suspicion of HF are highly suggestive of a correct diagnosis. On the other hand, in patients with low CNH concentrations this diagnosis is unlikely (14).

Furthermore, over recent years, several well-designed studies demonstrated the prognostic relevance of CNH assays in patients with both HF (25, 33, 87–92) and ACS (33–35, 38, 60, 72, 86, 94–107). Currently, use as prognostic markers seems to be the main indication for CNH assays. However, additional evidence regarding the optimal decision limits and their use in combination with other prognostic and/or risk markers is needed before they can be accepted in clinical use. Additional work is also needed to identify therapies that may reduce the risk associated with increased CNH concentrations.

Generally speaking, BNP and NT-proBNP assays show better diagnostic accuracy and clinical performance as prognostic markers than ANP and NT-proANP assays;

this finding is probably attributable to the prevalent ventricular production of BNP.

It is important to highlight that the use of CNH assays as both prognostic markers and guides for tailoring pharmacologic therapy is in accordance with the pathophysiologic role played by the CNH system in HF. Increased CNH concentrations indicate that the neuroendocrine system is activated. Several studies have indicated that activation of the neuroendocrine system is the most important pathophysiologic mechanism for the progression of HF (16, 150, 151). CNH assays could be used as a faster, less expensive, and easier way to monitor activation of the neuroendocrine system than assays for catecholamines, angiotensin II, endothelins, and cytokines.

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