Naysayers abounded; not everyone initially grasped the unmet need for a test to diagnose heart failure. B-type natriuretic peptide (BNP) was first described by Japanese researchers in 1988 (1), and when an early study, published in 1994, showed that this biomarker could help distinguish between cardiac and noncardiac causes of dyspnea, a seed was planted (2). It was not until the publication of the prospective, multinational Breathing Not Properly study in 2002, which convincingly showed the usefulness of BNP in establishing or excluding a diagnosis of congestive heart failure in patients presenting to emergency departments with dyspnea, that BNP began to take off clinically (3). Now, 10 years later, a PubMed search for “natriuretic peptide” yields more than 25,000 results, and one would be hard pressed to find an emergency department without access to natriuretic peptide (NP) testing.

Since the initial studies showing the usefulness of NPs for aiding in heart failure diagnosis, a vast number of other clinical applications for these neurohormones have emerged. In addition to refining our capabilities to diagnose and prognosticate in acute heart failure, natriuretic peptides are now being used in outpatient heart failure clinics, in screening programs, and in risk prediction algorithms in various settings. In just 10 years, B-type natriuretic peptide has gone from being an unknown biomarker to being one of the most useful in cardiology and beyond. In this perspective piece, we review what we have learned about using natriuretic peptides over the past 10 years and the advances we anticipate in their use over the next decade.

Acute Heart Failure

Diagnosis of acute heart failure. There is little dispute about the usefulness of NPs in clarifying the differential diagnosis of patients presenting with dyspnea. The physical findings of AHF are not always present, and other tests such as chest x-ray and echocardiography are insensitive measures of acute elevations of filling pressures (4). Mistakes in diagnosis can be costly, so rapid and accurate diagnostic tests are important. NP testing is highly accurate in this setting, with sensitivity being its major strength. A BNP level $\leq 100$ pg/ml or an N-terminal pro-BNP (NT-proBNP) level $\leq 300$ pg/ml can rule out AHF in 9 of 10 cases (3). Additionally, levels higher than 400 pg/ml are highly specific for AHF, especially if this is a new diagnosis in an untreated patient. The PRIDE (N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department) study demonstrated equal value of NT-proBNP with cut points related to patient age (5).

Valuable information continues to accumulate since Breathing Not Properly. For instance, even if a physician were to forgo an NP level to help with diagnosis because of a high probability of AHF, NP levels still provide important prognostic information. In ADHERE (Acute Decompensated Heart Failure National Registry), the later the NP level was drawn in the emergency department and the higher that level was, the higher the risk for hospital mortality (6). Indeed, NP levels perform better than physicians’ assessments of heart failure severity (7). Many treat-
Caveats. Along with the value of NPs in patients with dyspnea, we have also learned much about their limitations. The major caveats of NPs are decreased levels in obese patients, mild increases in those with renal impairment, and midrange, nondiagnostic “gray-zone” levels (10–12). Van Kimmenade et al. (13) reported that patients with gray-zone NT-proBNP results were at higher risk for future events compared with those with negative results.

The issue of renal dysfunction is of particular importance, because patients often present with acute cardiorenal syndromes. In most cases, even in the setting of reduced glomerular filtration rates, NP levels are higher in patients with heart failure than in those without heart failure. A patient’s baseline level may be especially important for interpretation in these settings (14,15).

To the intelligent physician, these caveats are easily understood in the context of the rest of the illness. Nevertheless, we are reminded that NPs should not be used as stand-alone tests but as adjuncts to the doctor’s armamentarium.

Tracking inpatients and discharge monitoring. Although there have been no randomized trials of an NP-lowering strategy in patients hospitalized with AHF, data and common sense suggest the potential usefulness of this paradigm. Acute elevations of NP levels over baseline levels are considered “wet NP levels.” With a relatively short half-life, the hypervolemic “wet BNP” decreases rapidly as cardiac filling pressures are reduced. The closer one gets to true euvoemia, the lower the BNP approaches its “optovolemic” level. Patients discharged with BNP levels under 300 to 400 pg/ml, whether it takes 2 days or >5 days, have a better prognosis than those with higher levels (16,17). Although there is no consensus as to the best ways to lower NP levels in the hospital, consensus statements have suggested that 2 or 3 levels should be drawn during hospitalization: 1 at admission, 1 at discharge, and in some cases 1 during treatment to ensure a downward trend (12,17,18). The discharge NP level may in fact be the most important level of all (19). Not only do low levels predict less death and readmission at 30 days, but this level can be compared with the level obtained if a patient returns to the emergency department or clinic with symptoms of possible decompensation. Before routine hospital monitoring of NP levels can be added to guidelines, research much show clinical benefit as well as effective algorithms.

Outpatient Heart Failure

Preventing readmission. The problems with high 30-day readmission rates cannot be overemphasized in the era of diminished health care dollars. Preventative strategies include adequate discharge preparation (appropriate medication and dietary teaching, along with education about when to report symptoms), early follow-up in the clinic, and accurate assessment of volume overload, the chief culprit for early readmissions. Studies have clearly demonstrated that congestion may precede symptoms by 7 to 10 days (20). Because NP release parallels increases in end-diastolic wall stress, NPs are attractive targets for monitoring. A recent trial demonstrated that discharged patients whose 30-day BNP levels are greater than their discharge levels are at highest risk for decompensation (19). With the advent of home monitoring of BNP with finger-stick technology (Alere Inc., San Diego, California), future studies will focus on the feasibility of early intervention on the basis of a combination of weight gain and frequent home BNP testing. Home testing also has the potential to favorably tilt the cost-benefit ratio, though this too will need to be evaluated.

NP-guided therapy. NP-guided therapy for treatment of chronic heart failure has had its vocal share of advocates as well as detractors, depending on whether they interpret the cup as half full or half empty. Clearly, because heart failure is one disease for which “personalized medicine” is lacking (e.g., for most drugs, the same dose is prescribed for most patients), the prospect of combining biomarker-guided therapy with “biomonitoring” of disease is appealing (21). Although many of the studies on biomarker-guided therapy have yielded equivocal and often controversial results, it is generally accepted that there is some benefit, especially in those under 75 years of age (22). However, a weakness of many studies is that either NP levels were infrequently measured, or, more important, little was done after they were measured. One recent study that did show a significant benefit to biomarker-guided therapy was the PROTECT (Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting) study (23). Although this was a single-center study, the investigators paid rigorous attention to lowering NT-proBNP levels. Indeed, the 50% drop in levels was associated with a near 50% drop in event rates. Future studies in this area should certainly attempt to achieve a vigorous lowering of NP levels, not by a percent drop but to a pre-specified low level.

Screening

Screening for heart disease. NP levels cannot absolutely determine who has or does not have subclinical cardiovascular disease (CVD), but as time goes by, we are learning ways to successfully incorporate NPs into various screening
algorithms (Table 1). In the past 5 years, NPs have been recognized by the European Society of Cardiology guidelines as useful agents for ruling out heart failure in a primary care setting (24). The American College of Cardiology and American Heart Association guidelines also have recognized that elevated NP levels are associated with left ventricular hypertrophy, reduced left ventricular systolic function, left ventricular diastolic dysfunction, and elevated filling pressures (25). Because NPs are sensitive to factors such as age, sex, body mass index, renal function, and other clinical factors, the use of a one-size-fits-all cut point for ruling in or excluding heart disease may not be the best use of the test. Recently, a multinational study of more than 5,000 primary care patients suggested that age-based cut points for NT-proBNP considerably improved performance compared with a single cut point, with a high negative predictive value for ruling out decreased left ventricular systolic function (26). Another way to improve screening performance of NPs, as recently reported from the Dallas Heart Study in an analysis of identifying stage B heart failure, is to use them in conjunction with traditional risk scores, rather than in isolation (27).

Clearly, the successful implementation of NPs to screen for heart disease will hinge on targeting the appropriate population. Screening tools are rarely indicated for everyone regardless of age, sex, or other risk factors, even when the aim is primary prevention. A more effective strategy is to target patients with certain risk factors who are at somewhat higher risk (28). Although studies have demonstrated that NPs are not ideal for identifying patients with left ventricular systolic dysfunction overall, performance among high-risk men (age ≥50 years or with hypertension) was comparable with the performance of other commonly used screening tests, such as prostate-specific antigen screening for prostate cancer, Papanicolaou smears for cervical cancer, and mammography for breast cancer (29). A strategy targeting moderate-risk or higher risk groups has a much higher likelihood of success than does a shotgun approach whereby every patient is evaluated.

### Cardiovascular risk prediction

Since BNP became accepted in clinical practice 10 years ago, additional studies have informed us of its utility in cardiovascular risk prediction across a variety of clinical scenarios. Early on, it was established that BNP is useful for risk prediction in patients with pre-existing cardiac disease, including stable (30,31) and unstable coronary heart disease (32) and heart failure (11). Simultaneously, large community-based studies have documented that NPs can improve CVD risk prediction above and beyond traditional CVD risk factors, even in patients without heart failure or coronary disease at baseline. Wang et al. (33) initially reported this in the Framingham Offspring cohort, in which BNP levels were associated with an increased risk for death and first cardiovascular event over a mean 5.2 years of follow-up. The results have been bolstered by similar findings in a number of other cohorts. More recently, a study of Olmstead County, Minnesota, residents suggested that the prognostic utility of NPs in the general community may be limited to patients with risk factors for CVD and may not provide a significant level of prognostic information in completely healthy subjects, even when levels are greater than the 80th percentile (34). This is consistent with the previously demonstrated concept that screening may be most cost effective when targeted to higher risk populations (28).

Areas that are evolving rapidly in the use of NPs to predict CVD risk include pre-operative evaluations. Including an NP in risk assessment algorithms is improving predictive performance for the risk for mortality and cardiovascular complications after vascular and other procedures (35–37).

The potential for NPs to help identify chemotherapy patients at risk for drug-induced cardiotoxicity is another area of active exploration. Persistently elevated levels of NPs are associated with the development of early and late myocardial dysfunction after chemotherapy with anthracyclines and other cardiotoxic agents, though there seems to be a good deal of overlap in NP levels between those who develop cardiotoxicity and those who do not (38–41). Clinical trials are needed to determine whether early identification and treatment of these patients can improve outcomes.

NP levels are also being increasingly used to assist with risk prediction and assessment of patients with valvular heart disease. In the setting of severe organic mitral regurgitation, a normal NP level has a very high negative predictive value for the development of symptoms or deterioration of left ventricular function over the following 6 months (42), whereas elevated levels are associated with increased risk for heart failure, left ventricular dysfunction, or death (43). In patients with aortic stenosis, NP levels are consistently related to the severity of the disease and symptom status (44). In those with severe, asymptomatic aortic stenosis, an elevated or rising NP level is predictive of short-term need for valve replacement and of worse outcomes (45) and may therefore help with the timing of surgery in patients with equivocal symptoms. In addition,

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**Table 1**

<table>
<thead>
<tr>
<th>Application</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for stage A HF</td>
<td>Not currently recommended</td>
</tr>
<tr>
<td>Screening for stage B HF</td>
<td>Recognized as useful; depends on population</td>
</tr>
<tr>
<td>Ruling out HF in primary care setting (stage C)</td>
<td>In guidelines</td>
</tr>
<tr>
<td>Risk prediction in stable coronary heart disease</td>
<td>Useful</td>
</tr>
<tr>
<td>Risk prediction in unstable coronary heart disease</td>
<td>Useful</td>
</tr>
<tr>
<td>Risk prediction in HF</td>
<td>Useful</td>
</tr>
<tr>
<td>Risk prediction in the community</td>
<td>Potentially useful; depends on population</td>
</tr>
<tr>
<td>Pre-operative risk assessment</td>
<td>Potentially useful</td>
</tr>
<tr>
<td>Risk prediction with cardiotoxic chemotherapy</td>
<td>Potentially useful</td>
</tr>
<tr>
<td>Risk prediction in valvular heart disease</td>
<td>Potentially useful</td>
</tr>
</tbody>
</table>

HF = heart failure.
elevated NP levels independently predict perioperative complications of aortic valve replacement surgery, as well as major adverse cardiac and cerebrovascular events within 36 months after aortic valve replacement (46). A BNP level is also helpful in low-flow, low-gradient aortic stenosis, in which levels >550 pg/ml predict poor outcomes independent of contractile reserve (47). Similarly, in chronic, severe aortic regurgitation, an elevated BNP level (≥130 pg/ml) predicts poor outcomes even when patients have normal left ventricular function and are asymptomatic (48). Thus, NPs are becoming an invaluable aid to clinicians caring for patients with challenging presentations of a variety of valvular heart diseases.

In summary, one of the most rapid and successful areas of expansion in the use of NP levels over the past 10 years has been in risk prediction in a multitude of clinical settings beyond the one originally targeted, AHF. We anticipate that this application will continue to evolve and grow.

**Outpatient risk profiling with multimarker panels.** Individual biomarkers, including NPs, have certain shortcomings that have limited or slowed their clinical uptake as risk predictors in outpatient settings. Variability in day-to-day values and poor predictive values at the level of the individual patient have been difficult obstacles to overcome in lower risk outpatient populations. Creating a risk profile by combining NP levels with other biomarkers from distinct pathophysiologic pathways has the potential to overcome some of this and to improve risk stratification. However, results using this approach have been mixed.

Several studies have evaluated multimarker panels for predicting CVD in the community. Some found statistically significant though clinically modest improvements in prediction by using multiple biomarkers compared with using traditional risk factors alone (49–51), while a few reported substantial improvements in risk prediction with a multimarker approach (52–55). NP levels have been the cornerstone of the multimarker approach; nearly all of the successful multimarker panels have included NP measurements.

A similar pattern has emerged in secondary prevention populations. A subanalysis from the HOPE (Heart Outcomes Prevention Evaluation) study evaluated 11 biomarkers (including 9 inflammatory markers plus NT-proBNP and microalbuminuria) in 3,199 patients with histories of coronary artery disease, peripheral vascular disease, diabetes, or stroke (56). After a mean 4.5 years of follow-up, only NT-proBNP provided incremental prognostic information for the prediction of cardiovascular events compared with a traditional risk factor model. Although several inflammatory markers were significantly related to future cardiovascular events compared with the traditional risk factor model, most currently published studies were performed before the introduction of high-sensitivity cardiac troponin assays, and it remains to be seen whether this latest comer will integrate with NPs to improve risk stratification.

Table 2 highlights potential components of a multimarker panel. A consistent theme in multimarker panels for outpatient risk profiling, in both primary and secondary heart disease prevention populations, is the central role that NPs play. In the past 10 years, NPs have evolved from their initial role in the diagnosis of acute patients to a more ubiquitous role as a prognostic aid in both inpatients and outpatients. In the next 10 years, new biomarkers are likely to emerge and share the spotlight, but NP levels are unlikely to be cast aside by any of them.

**Conclusion: The Next 5 Years**

Figure 1 conceptually predicts where we will be in NP testing 5 years from now, compared with present times. As the wealth of NP data continue to accumulate, we expect to see progressively more clinical applications for NPs, as well as increased acceptance by practicing clinicians.
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Reprint requests and correspondence: Dr. Lori B. Daniels, University of California, San Diego, Department of Medicine, Division of Cardiology, 9444 Medical Center Drive, La Jolla, California 92037-7411. E-mail: lbdaniels@ucsd.edu.

Figure 1 Prediction of NP Uptake in the Next 5 Years

The investigators’ assessment of current and future acceptance of natriuretic peptide (NP) testing for various clinical applications. BNP = B-type natriuretic peptide; Dx = diagnosis; Dyfx = dysfunction; HF = heart failure; HFPEF = heart failure with preserved ejection fraction; LV = left ventricular; Rx = therapy.
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Key Words: acute heart failure • BNP • natriuretic peptide • screening.