

Testing for B-type natriuretic peptide in the diagnosis and assessment of heart failure: What are the nuances?

■ NATRIURETIC PEPTIDES: DECADES OF INQUIRY BEGIN TO PAY OFF

Dr. James Young—I'd like to start with a few words on the physiology of natriuretic peptides. Gary, would you speak to that?

Dr. Gary Francis—The natriuretic peptides are hormones produced in the heart and vasculature that improve loading conditions of the failing heart through their diuretic, natriuretic, and vasodilating properties (**Figure 1**). They were first observed in the heart in the late 1950s and early 1960s, but their significance wasn't appreciated until the mid-1970s, when Adolfo de Bold published a study suggesting that these peptides caused substantial diuresis and natriuresis. Soon thereafter, Japanese researchers identified the amino acid sequences involved, and A-type (atrial), B-type (initially called "brain"), and C-type natriuretic peptides (ANP, BNP, and CNP) have all since been identified, along with adrenomedullin. There undoubtedly are more, as this is a family of peptides.

Initially, ANP was the subject of the most intense investigation, but BNP emerged as a much better marker. In the early 1990s, once researchers learned what the BNP molecule looked like and they could identify it in the blood, it became clear that there was a whole host of cardiovascular disorders in which BNP levels were increased (**Table 1**).

During the mid-1990s Biosite developed the first assay for BNP, a point-of-care assay, and it received US regulatory approval in 2000. Additional BNP assays have since been introduced, and data show that a large number of hospitals now can measure BNP in their patients.

BNP is a diuretic, albeit a relatively weak one, a natriuretic, and a vasodilator. It circulates in the blood and acts on a host of receptors. Its vasodilatory response is modulated by cyclic GMP. BNP also has activity against neurohormones—it tends to mitigate or diminish the activity of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and probably other neurohormones as well. BNP is, then, a very attractive autoregulatory peptide that is not only a marker but now also a form of therapy, with the 2001 marketing approval of the drug nesiritide, which is the human BNP molecule manufactured using recombinant DNA technology.

As will be discussed, when BNP is used as a biomarker, levels determined by the point-of-care Biosite assay to be below 100 pg/mL are not usually associated with congestive heart failure.

■ WHY FOCUS ON BNP?

Dr. Young—Alan, why measure BNP, rather than ANP, as a marker of cardiac decompensation and heart failure?

Dr. Alan Maisel—In a way, the stimulus for release of ANP and BNP is the same in that increased wall stretch, increased fluid overload, and decreased clearance can all lead to increasing levels of both peptides.

The problem with ANP is that it's released very quickly, and almost always in response to atrial stretch—that is, from the atrial stretch granules. In contrast, BNP, for the most part, does not sit preformed in the granules; it is controlled at the ventricular myocyte and transcriptional levels, where the stimulus



BNP is an attractive autoregulatory peptide that is both a marker and a form of therapy for heart failure
—Dr. Gary Francis

How BNP and other natriuretic peptides are released and act on the failing heart

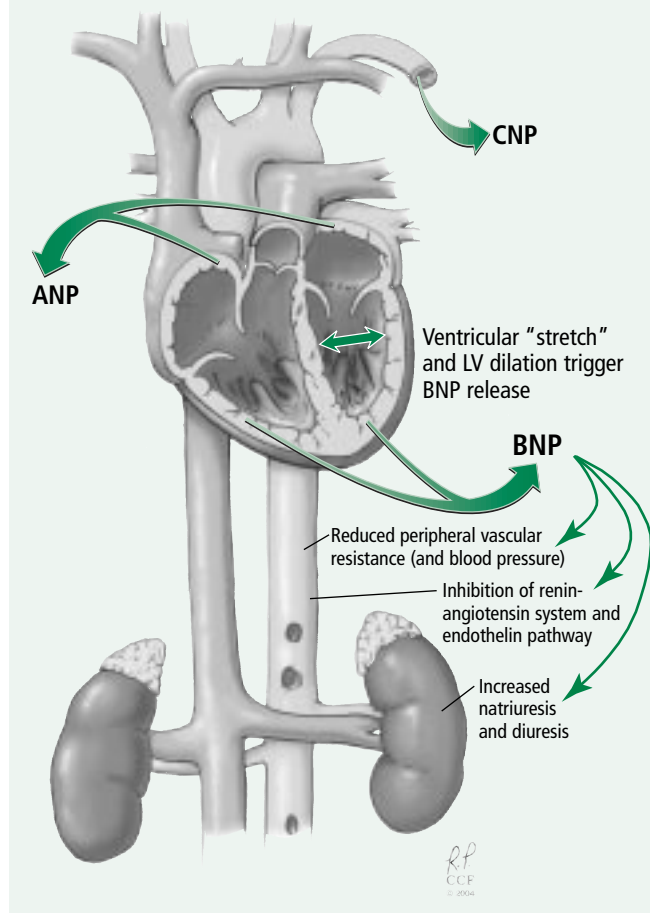


FIGURE 1. B-type natriuretic peptide (BNP) is secreted predominantly by the ventricles in response to wall stretch, left ventricular (LV) dilation, and increased end-diastolic pressure and volume. A-type natriuretic peptide (ANP) is released primarily by the atria in response to dilation. C-type natriuretic peptide (CNP) is secreted by endothelial cells in response to shear stress. BNP and the other natriuretic peptides induce diuresis, natriuresis, and vasodilation, along with inhibiting secretion of aldosterone and endothelin. Together, these actions improve the loading conditions of the failing heart.

takes a bit longer. Since the major stimuli of BNP release include wall tension, which would probably include increased afterload and increased wall stretch, but also wall thickness, these are good stimuli for a very rapid RNA turnover and production of the precursor molecule, which is then cleaved into the 32-amino acid active compound BNP and the N-terminal inactive compound, N-terminal pro-BNP. BNP is, then, probably a more

accurate and stable indicator of left ventricular decompensation.

Dr. Young—What are your thoughts on measuring N-terminal pro-BNP vs BNP?

Dr. Maisel—There's a lot of debate about which of these molecules is best for the diagnosis or monitoring of heart failure today, and both may have a significant role. The chief differences between them are half-life and renal clearance.

BNP is excreted partly via clearance receptors in the kidney and partly via a neutral endopeptidase-mediated breakdown of the BNP molecule. As renal failure develops in a patient, he or she will start retaining a bit of BNP rather than quickly excreting it. In fact, a recent analysis from the Breathing Not Properly trial shows that as the creatinine goes up to about 2 mg/dL, the optimal BNP cut point for the diagnosis of congestive heart failure may go from 100 pg/mL to about 200 pg/mL.¹

N-terminal pro-BNP, on the other hand, is excreted almost exclusively through the kidney. This could cause problems in interpreting N-terminal pro-BNP levels in patients with renal failure and even in the general elderly population, since older people tend to have worse renal function. Studies are under way to ascertain the significance of this.

The second area of difference is half-life, which is about 20 minutes for BNP compared with about 2 hours for N-terminal pro-BNP, although the latter value is based on only one study. What might be the significance of this difference? A longer half-life may give a broader snapshot of how the patient is doing. On the other hand, a longer half-life might preclude seeing rapid changes with treatment, which we can appreciate with BNP. So, in the hospital, if we have a Swan-Ganz catheter in a patient, or if we are looking at changes over a day or so, we may see those changes reflected more quickly in BNP than in N-terminal pro-BNP. Again, studies are currently exploring this.

Ultimately, both molecules should prove to be effective in the evaluation and management of heart failure. So far there have been a lot more studies done, and a lot more clinical

cal algorithms developed (Figure 2), on the use of BNP than of N-terminal pro-BNP.

■ BNP TESTING AS AN OUTPATIENT DIAGNOSTIC TOOL: WHEN CAN IT HELP?

Dr. Young—Frank and Natalie, from your perspective as internists, what characterizes the need for a BNP test in somebody with heart failure in the outpatient setting? Where might this tool be useful among the patients who pass through a busy afternoon clinic?

Dr. Natalie Correia—It seems to be most useful in two areas. First is when the diagnosis of heart failure is really not clear—for example, in the patient who comes in a little short of breath, with a little bit of ankle swelling, and without a good sense of whether he or she has gained weight. In that situation, the BNP level can be the deciding factor and push the diagnosis in one direction or the other.

I think that the assay's other most useful aspect is its negative predictive value (Figure 3). This can be very helpful in the patient who needs to be reassured that he or she is not actively in congestive heart failure. Or, to a lesser extent, in the patient with chronic obstructive pulmonary disease (COPD), since COPD can be a confounder in the diagnosis of heart failure.

Dr. Young—So you see the assay being most valuable as a tool to help with the differential diagnosis, either in a new patient you have never seen before or in a patient you have been following who comes in with new physical findings or complaints.

Dr. Correia—Correct, and generally this would be a patient with diabetes and hypertension who comes in short of breath, or a smoker who also has COPD that has recently become a little more troublesome.

Dr. Frank Michota—Medicine in the United States is moving from a model of treating after the fact to trying to keep people healthy. I see BNP measurement fitting nicely into that transition. You know, some automobiles now have sensors that indicate how the car is functioning as it moves along. Wouldn't it be great

TABLE 1

Conditions associated with increased BNP levels

Heart failure
Left ventricular hypertrophy
Cardiac inflammation (eg, myocarditis, cardiac allograft rejection)
Arrhythmogenic right ventricle with reduced ejection fraction
Kawasaki disease
Primary pulmonary hypertension
Pulmonary embolism
Renal failure
Ascitic cirrhosis
Endocrine disease (primary hyperaldosteronism, Cushing syndrome)
Geriatric age

Adapted, with permission, from: Peacock WF IV. The B-type natriuretic peptide assay: a rapid test for heart failure. *Cleve Clin J Med* 2002; 69:243–251.

if the human body had similar sensors so that we could keep track of our internal processes? Actually, BNP serves that function to some extent because it is one of the first autoregulatory components of a patient who is experiencing some volume overload or increased pressure in the ventricles.

In the outpatient setting, where we are trying to keep people healthy, a noninvasive tool that could give a window into how the heart is functioning, even before the patient shows symptoms, would be very powerful, particularly for people who are at elevated risk of heart failure because of comorbidities. So, yes, at the point where patients are having symptoms, the BNP assay and other such tests become very helpful in the differential diagnosis. In patients for whom I am monitoring blood pressure and monitoring lipid status, perhaps adding BNP monitoring could help me predict where they are and how their heart is functioning. With that kind of longitudinal tracking, even a small increase in BNP may give me an idea of whether the patient is progressing toward something that will become clinically manifest later.

Dr. Young—You raise the issue of whether BNP testing is as much a prognostic as a diagnostic tool. I'd like to come back to that in a



The BNP test's negative predictive value can help move you in a different direction in a patient with confusing symptoms

—Dr. Frank Michota

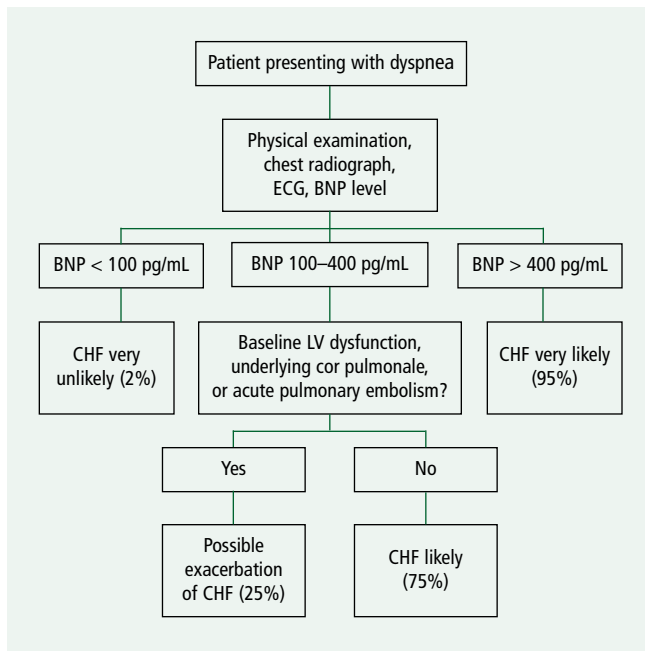


FIGURE 2. Algorithm for using BNP testing in the diagnosis of congestive heart failure (CHF). (ECG = electrocardiogram; LV = left ventricular)

© MedReviews, LLC. Reprinted with permission of MedReviews, LLC, from: Maisel A. B-Type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. *Rev Cardiovasc Med* 2002; 3(suppl 4):S10–S17. *Reviews in Cardiovascular Medicine* is a copyrighted publication of MedReviews, LLC. All rights reserved.

moment, but Natalie focused on the challenge of diagnosis in certain types of patients, and she characterized at least one cohort that makes up a large group: hypertensive diabetics who may be cardiovascularly deconditioned and have a substrate of coronary heart disease to begin with. This type of patient comes in feeling weak and fatigued, with a little bit of peripheral edema. Nothing on physical examination really points toward congestion, but you measure the BNP and it comes back at 300 or 400 pg/mL. Right away you raise your eyebrows and conclude that perhaps there is some ventricular dysfunction.

Natalie also alluded to another group of patients in whom I find BNP testing particularly helpful—those with COPD. In the patient with COPD, who perhaps also has diabetes, a past myocardial infarction, and so forth, the BNP test is extraordinarily useful in helping me differentiate between left ventricular dysfunction and elevation of end-diastolic pressure that perhaps requires concomitant bronchodilators and diuretics. At

the same time, we probably haven't done enough work in COPD patients to determine what right ventricular failure and cor pulmonale may also do to the BNP level. We'll explore these and other confounding factors for BNP elevation in a moment. First, though, are there other areas in differential diagnosis where you think BNP measurement can be helpful?

Dr. Michota—Since BNP is a marker of wall stress, you can imagine situations where it could play a role in the processes that lead to ventricular wall stiffening. That certainly includes myocardial ischemia, where we are searching for the perfect marker for unstable angina or even for angina that precedes infarction. Although we now have cobalt albumin testing, which has some benefits over troponin testing, perhaps BNP may play a role there as well since it could potentially be an early marker of wall stiffness. That's one area that I think about, although I'm not sure how much it plays into office-based practice.

Dr. Correia—I think it does. We often see the diabetic patient who comes in with an atypical presentation of angina or an acute coronary syndrome in the form of complaints of shortness of breath. Since BNP rises in the first 2 to 5 hours of an acute event, what you initially see may only be shortness of breath, but that may be a “chest pain equivalent.”

Dr. Young—Natalie earlier touched on something else that I think is important. When a patient comes to your clinic with a number of cryptogenic issues and complaints that are difficult to sort through, how much stock do you put in a BNP that is very low—say, 10 pg/mL? Is that a clear reassurance that at least there's nothing terribly wrong with the cardiovascular system?

Dr. Correia—Not necessarily. It's helpful, but as an adjunct to the clinical examination and not as a substitute for it.

Dr. Michota—I agree. Very few findings in medicine are pure, and so your eyes will tell you that one thing is going on but then your data points don't concur. Ultimately, the negative predictive value of the BNP test, at least

as it relates to wall stiffening, is quite reassuring and can help move you in a different direction in a patient who has confusing symptoms.

COMORBIDITIES BRING FURTHER DIAGNOSTIC CHALLENGES

Dr. Young—We know that comorbidities will affect BNP levels (Table 1), and I alluded to one group that do—cor pulmonale, pulmonary hypertension, and right ventricular failure. At least one other group of comorbidities is also associated with BNP elevation—myocardial infarction and acute ischemic syndromes—and that has been plumbed more from the prognostic standpoint in large clinical trials.

A few observations have been published that link BNP elevation and pulmonary embolism to the pathophysiology of right ventricular failure and pulmonary hypertension. In a general internal medicine practice, do you ever use BNP measurement to screen for pulmonary embolism?

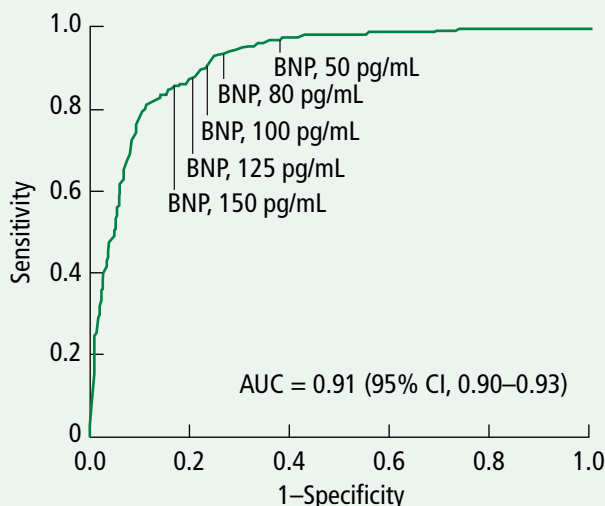
Dr. Correia—I haven't, because there are so many other screening tools and because it is not really going to make the diagnosis absolute one way or the other.

Dr. Young—Would you perhaps throw it in with a D-dimer assay?

Dr. Correia—Again, its usefulness would probably lie in its negative predictive value, as with the D-dimer assay. If the BNP level were low, I would be more reassured, but if the clinical situation were still suspicious, I wouldn't rest my diagnosis on it.

Dr. Michota—I see this as an issue that deserves further study. Although it would be difficult to interpret BNP vis-à-vis pulmonary embolism in the typical hospitalized population or the chronically ill patient, I can imagine it having a role in patients who don't have so many comorbidities as those populations do. Take a patient undergoing minor surgery, for instance, who has risk factors for a venothromboembolic event. If the patient has symptoms that are not quite clear and doesn't have any confounding issues,

Accuracy of BNP levels in determining whether dyspnea is due to heart failure



BNP (pg/mL)	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	ACCURACY
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

All values are percentages. Values in parentheses are 95% confidence intervals.

FIGURE 3. Receiver-operating-characteristic (ROC) curves for accuracy of various BNP levels in differentiating between dyspnea due to congestive heart failure and dyspnea due to other causes in a clinical trial among 1,586 emergency department patients. As the table shows, the BNP level is particularly useful in terms of its negative predictive value. (AUC = area under the ROC curve)

Reprinted, with permission, from: Maisel AS, Krishnaswamy P, Novak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347:161–167. Copyright © 2002 Massachusetts Medical Society. All rights reserved.

then BNP measurement could be helpful in relation to the diagnosis.

Dr. Maisel—I think that the combination of a D-dimer assay with a BNP assay could be powerful. A very high D-dimer level with a high BNP level might suggest pulmonary embolism, whereas a very low D-dimer level with a high BNP level might point more toward heart failure. The real usefulness of BNP measurement in this area may be when

you know the patient has a pulmonary embolism, because the BNP level is very prognostic in this setting. If you are deciding whether to intervene with a catheter, for instance, and the patient's BNP level is rising, which suggests right ventricular dysfunction, these findings will help guide the decision.

Dr. Young—Alan, would you speak a bit more about the comorbidities that affect BNP? I'm thinking specifically of comorbidities as opposed to demographic factors that might modulate BNP, such as age, race, sex, and body habitus.

Dr. Maisel—I'm glad you call these comorbidities rather than false positives because BNP that comes from the right ventricle isn't a false positive. It's simply that the right ventricle makes BNP, albeit not as much as the left ventricle does.

Early studies from Japan have looked at primary pulmonary hypertension and BNP. A high level of BNP, and particularly a further increase in BNP during follow-up, had a strong independent association with increased mortality in patients with primary pulmonary hypertension.² Additionally, the degree of BNP elevation in patients with pulmonary hypertension correlates well with the extent of right ventricular dysfunction, and right ventricular pressure overload gives rise to much higher concentrations of BNP than does volume overload.³

For a clinician skilled in managing cor pulmonale, BNP testing can be very helpful, as illustrated by a recent case managed by one of our residents. The patient had a baseline BNP level of about 300 pg/mL and some cor pulmonale, but was fairly stable. He came in with an upper respiratory infection that triggered a cascade of events that probably led to pulmonary vasoconstriction, a little more cor pulmonale, and left-sided heart failure. The BNP level went from about 400 to 800 pg/mL, and this helped guide management of the patient. He was given steroids and his nebulization treatments, and then he was diuresed back to his baseline BNP level. As a result, the patient wasn't made hypotensive and there was no renal dysfunction. A good clinician can use BNP measurements to his or

her advantage in this way.

Among the other comorbidities are acute coronary syndromes. BNP does rise in this setting, although not nearly to the levels that we see in decompensated heart failure. The Thrombolysis in Myocardial Infarction (TIMI) trials showed BNP levels of 100 or 200 pg/mL to be typical in patients with acute coronary syndromes,⁴ as opposed to the levels of 1,000 pg/mL or so that are often seen in patients with severe, decompensated congestive heart failure.

As for renal dysfunction, there have been several studies showing that if you know the baseline BNP level in a patient with renal dysfunction, you can differentiate how much elevation is from left ventricular dysfunction and how much is from not clearing BNP.¹

Dr. Young—What about those situations that can produce falsely low BNP levels despite the presence of heart failure?

Dr. Maisel—We also need to keep those situations in mind, and in my experience they fall into three categories.

First is flash pulmonary edema, which we don't see very often. It probably takes at least an hour for any BNP to be released when a patient goes into flash pulmonary edema. And part of that is probably pre-release of BNP that is in the atrium. Then the signal for BNP release gets turned on to such a high degree that even after the patient is treated and is feeling better, his or her BNP may still be climbing, at least in our limited experience. It may take a little longer for the signal to be turned off.

A second instance is when there is heart failure but it is upstream from the left ventricle, as with an acute papillary muscle rupture, and the left ventricle hasn't had time to really get ill yet.

The third instance, and probably the most important for the outpatient setting, is obesity. Though we're not yet sure why, it appears that obese people (those whose body mass index is greater than 30 to 35) with heart failure have lower BNP levels than do thinner people in the same New York Heart Association (NYHA) functional class. It's highly likely that this is due to some kind of clear-



BNP levels seem to be lower in obese patients with heart failure than in thinner patients, but we're not sure why

—Dr. Alan Maisel

ance effect, as limited experience has shown that when obese patients are given exogenous BNP in the form of the drug nesiritide, their levels come right down after the bolus infusion and don't go very high thereafter. So there may be some clearance issues.

Among patients diagnosed with heart failure in the emergency room in the Breathing Not Properly trial,⁵ the BNP level was greater than 1,000 pg/mL in half of the nonobese patients compared with only about 10% to 20% of patients whose body mass index was above 35. So we have to be careful in this setting. I have seen obese patients with mild degrees of heart failure who had BNP levels below 100 pg/mL when nonobese patients with similar degrees of heart failure have levels of 300 to 400 pg/mL. Unfortunately, the gold standard for heart failure diagnosis in obese patients is hard to precisely define in any situation. The relation between obesity and BNP level is under ongoing study, so we hope to know more about this soon.

■ BEYOND COMORBIDITIES: OTHER FACTORS THAT MODULATE BNP

Dr. Young—Let's consider a patient with stable NYHA class II heart failure who comes to you in the outpatient setting. Gary, how might you modulate your interpretation of a given BNP level in such a patient, vis-à-vis the patient's stability, with respect to age, race, sex, renal function, and body habitus?

Dr. Francis—Well, it can cut both ways. Perhaps I can discuss it best with a real-life example. I have a patient who is 94 years old and has diastolic heart failure. So she is elderly, and she is also very thin and has a normal ejection fraction, but she does have heart failure. We have been unable to get her BNP level below 1,000 pg/mL: it's always 1,200 or 1,300 or 1,800. When we try to induce more diuresis, she actually gets worse, so that is a strong signal that her prognosis is not very good.

We know that age alone can raise BNP levels to some extent. We also know that women tend to have somewhat higher BNP levels than men. We've just heard the very interesting obesity story from Alan, which is

still unfolding. So what all of this suggests to me is that this lady doesn't have a very good prognosis. This is one of the reasons why I oppose the notion that if the BNP level is above 1,000 pg/mL, the patient automatically needs more treatment—more diuretic therapy, more ACE inhibitor therapy, more beta-blocker therapy. After all, this patient is doing pretty well. She lives in a nursing home, but she is ambulatory, she comes to clinic, and she is about as good as we can get her, even though her prognosis is poor.

■ BNP AS PROGNOSTIC SCALAR: HOW HELPFUL CAN IT BE?

Dr. Young—I'd like to turn back and get our internists' thoughts about using BNP measurements in the outpatient setting to determine a patient's prognosis. Do we have enough information about that, or are there other areas for prognostication that might be more important?

Dr. Correia—Based on the data, serial BNP measurement is clearly a good prognostic indicator. Persistently elevated BNP levels in spite of well-compensated heart failure is clearly a negative prognostic indicator, so following BNP levels serially offers a lot of advantages, including the ability to identify acute exacerbations of heart failure.

Dr. Young—Imagine a patient with known left ventricular systolic dysfunction who is doing fine but suddenly has a BNP reading of 950 pg/mL. Frank, would you change anything in your management of this patient, or would you just tell yourself that you better follow him or her more closely?

Dr. Michota—It would definitely change how I approach the patient. I'd either have a specialist make sure I hadn't missed anything, or I would reevaluate the patient and perhaps bring him or her back in a little sooner and have a more comprehensive visit. My response to a significantly elevated BNP level in a patient who is being followed and is doing well would be similar to my response to an elevated prostate-specific antigen level or elevated lipid levels. It calls for doing something different.



Following BNP levels serially offers advantages, including the ability to identify acute exacerbations of heart failure

—Dr. Natalie Correia

Dr. Maisel—In our heart failure clinic, we usually follow patients on a 3- to 6-month basis. Resource-utilization data show that when I have patients who are clinically stable and have very low BNP levels, I order echocardiograms less frequently and I tend not to send those patients for biventricular pacing.

What we don't yet know is exactly what to do with patients who seem to be stable but have higher BNP levels, although the recent study by Wang and colleagues from the Framingham Heart Study cohort speaks to this somewhat.⁶ It suggests that even a BNP level only 10% above the normal median distributed value might be a marker for heart disease 4 to 5 years down the road in patients without overt disease. That's helpful to those of us who see patients with higher than expected BNP levels (75 to 125 pg/mL, for example) in whom we cannot uncover any specific findings. It reinforces the notion that this might be a marker that needs watching.

An editorial⁷ that accompanied that study in the *New England Journal of Medicine* suggested that BNP and C-reactive protein (CRP) have become two chief biomarkers for cardiology. I don't know how often the rest of you use CRP, but I take care of veterans who often have so many risk factors for atherosclerotic cardiovascular disease that it obviates the need for CRP measurement. I do, however, still find a great need to check BNP levels in many of those patients.

Dr. Young—Let me raise a tangential question here: the hospitalized patient with an acute coronary syndrome. Gary, since you are the director of our coronary care unit, do you think every patient with acute myocardial infarction or unstable angina should have BNP measured as part of the diagnostic panel on admission?

Dr. Francis—We almost never measure BNP in patients with acute coronary syndromes. Maybe we should, but the only data out there are the TIMI data.⁴ I think we can profile these patients without measuring their BNP levels, so it certainly isn't routine for us, but I would be open to discussing it.

Dr. Maisel—I agree, although conceptually

BNP might be important in acute coronary syndromes. We have been doing serial sampling of BNP levels for a study we're conducting, and we see patients come in with clear-cut acute coronary syndromes with electrocardiographic changes but no troponin elevation, yet we see their BNP levels climb during their admission. They don't climb to 1,000 pg/mL, but rather from about 50 to 100 to maybe 200 pg/mL. These patients seem to have a lot of myocardium "at risk"; on angiography, they tend to have left anterior descending artery disease or three-vessel disease. While this has not yet proven the importance of BNP as a biomarker in this setting, there are some interesting suppositions that require further testing.

Dr. Young—Well, the Wang study⁶ that was referred to earlier used outpatient measurement in a community-based sample, and what disturbed me was that even in the tertile of patients with the lowest BNP levels, which were normal, there was increased risk of adverse events, particularly if the patient had a stratum of ischemic heart disease underneath.

Dr. Francis—Yes, any level over approximately 20 pg/mL was associated with a poor prognosis. That's a startling observation, and one that is very, very interesting.

Dr. Young—Well, it led Dan Mark to comment in his editorial that BNP could be a "biomarker for all seasons."⁷

Dr. Maisel—Some BNP levels that we thought were elevated because of advanced age (50 to 70 pg/mL) may, in fact, represent early cardiac abnormalities. I believe that, in the future, other specialists are going to get quite involved with BNP measurement, including pediatricians, who are already finding BNP to be remarkable in children with acute shortness of breath because their baseline levels are so low.

■ BNP LEVELS IN SPECIAL CIRCUMSTANCES: FODDER FOR NAYSAYERS OR FUEL FOR FUTURE RESEARCH?

Dr. Young—I'd like to turn to some challenging situations that are important to explore, especially for internists. Some physi-



Physicians should realize that they may encounter heart failure patients with low BNP levels
—Dr. Gary Francis

cians have not enthusiastically embraced the use of BNP to help with diagnosis and prognosis in heart failure, pointing to these challenging situations in a naysaying sense and arguing that BNP testing isn't needed, especially if we know how to use our stethoscopes and our eyes when we examine patients. One of these challenging situations is the patient with bad congestive heart failure with low BNP levels—for example, a hospitalized patient with overt congestion, an ejection fraction of 10%, a pulmonary capillary wedge pressure of 30% to 35%, a cardiac index well below 2, but BNP readings of 25 or 50 pg/mL. Gary, would you like to comment?

Dr. Francis—This type of patient has come as a surprise to us. The issue first arose when we obtained a very high BNP level in a patient on the ward who was quite ill. The patient was sent to our acute heart failure unit, where the BNP was measured again and had come down, despite nothing else having been changed.

This made us wonder about the trustworthiness of the test, so several of us have studied a small number of patients who fit this profile of obvious heart failure with low BNP levels. These patients tend to be well compensated and their filling pressures can be high, but they also may have low wedge pressures. They tend to have relatively normal cardiac indices despite having the syndrome of dilated cardiomyopathy and low ejection fraction.

Others have made the same observation, including John Burnett at the Mayo Clinic, who has found in the MIRACLE trial database some very low BNP levels in a subset of patients who are very sick—after all, they met the entry criteria for the MIRACLE study. He wonders if there might come a point in heart failure where the heart stops synthesizing BNP. We know that happens with other peptides. The idea is that, for whatever reason, the stretch of the ventricle that normally turns on the gene to make BNP may become dysfunctional. It's a very interesting hypothesis. The important message is that you may, in fact, encounter patients with heart failure who have low BNP levels.

Dr. Young—Natalie and Frank, have you

seen this from time to time?

Dr. Correia—I haven't, but I have read about it and I wonder if, in addition to the question of synthesis, the ventricle might eventually become so dilated that there isn't enough stretch to trigger BNP production.

Dr. Young—Or if the pressure is high you can say, "Well, the ventricle is big and it may be failing, but the pressure is still up and the wall tension is still high." However, in a pathophysiologic sense, this could be the absolute worst finding because what may have happened is total molecular biodynamic failure to produce one of the few identified beneficial counterregulatory hormones that is secreted in heart failure. I am anxious to follow up the cohort that we have identified because I think they are the worst of the worst heart failure patients. Frank?

Dr. Michota—Yes, that's why it would be interesting if there were serial measurements over time. You would perhaps see a patient progress to compensated failure with BNP levels in the range of 800 to 900 pg/mL, which would be a poor prognostic factor, and then see the BNP start to drop, after which something really bad would happen. You would see that as the "terminal phase."

Also, remember that although medicine is full of studies with representative patient populations, we always find subsets that are different. So whether these cases are receptor-related or occur along genetic lines from some point mutation that alters the receptor mechanisms, we will always find people who fall outside the curve. The question is whether we will be able to predict who those people are. I would again emphasize the importance of everyone having his or her own individual set point for BNP that can be followed and tracked so that if there is a delta change for any individual it would turn into a prognostic factor, regardless of what the maximum value necessarily was.

Dr. Young—Alan, do you have anything to add?

Dr. Maisel—I have seen a handful of cases of this type, but most are fairly well compensat-



The hottest question about BNP is whether it can be used to drive outpatient therapy for heart failure

—Dr. Alan Maisel

ed. As to what's going on in these cases, another theory is that the patients who are very ill might form antibodies that sit on the receptor, causing the pro-BNP to gear up even more until the cleavage products become abnormal and BNP is no longer recognized in the assay. Scientists at Scios, which makes exogenous BNP, and other companies are looking at this possibility because if that were indeed the case, an antibody to an antibody might be the next treatment for congestive heart failure.

Dr. Young—That's an interesting hypothesis.

Dr. Maisel—It's an area that clearly needs more work. To me it's somewhat enjoyable that not everything makes sense because it gives us room to try to figure things out and advance. But it's certainly no reason to turn our backs on BNP testing.

Dr. Francis—Something else that puzzles me is the relationship between left ventricular hypertrophy, wall tension, and the release of BNP. It's understandable that if wall tension is high, BNP is released. But if there is a lot of hypertrophy, it tends to normalize wall stress, and presumably that would shut off the trigger for BNP release. Yet there are data that suggest that hypertrophy in and of itself is associated with somewhat higher BNP levels. Some data have been all over the place on this question: some patients have normal BNP levels, while others have high levels. So what is the role of hypertrophy in the generation of BNP?

Dr. Maisel—If I knew the answer to that one I'd be collecting a prize in Stockholm. The one exception I would take to what you said, especially after the recent Wang study,⁶ is that there are very few patients with hypertrophic cardiomyopathy who have truly normal BNP levels. We have seen a whole spectrum of BNP levels in these patients, from about 40 pg/mL up to the thousands. Barry Maron and his team just published an article⁸ showing this same variability in BNP levels in patients with hypertrophic cardiomyopathy. They found that when these patients get symptoms their BNP levels go way up.

Even in the setting of left ventricular

hypertrophy alone, without wall tension, there is probably some baseline synthesis of BNP by the myocytes. As wall stress increases (ie, diastolic dysfunction) or systolic function deteriorates, BNP levels will rise further.

Dr. Francis—Maybe it's the size of the myocytes. If they are larger, maybe more BNP is released.

Dr. Maisel—I don't know, but that is a hypothesis worth looking at.

Dr. Young—I'd also point you to a recent article⁹ and companion editorial¹⁰ about ANP—granted, not BNP—suggesting that natriuretic peptides in general play a significant role in inhibiting this hypertrophic response to the ventricle. A very elegant mouse knockout model demonstrated that.

Getting back to the beneficial counterregulatory hormonal aspect of BNP, this could explain some of the nuances of the rising and falling of natriuretic peptides when we measure them as a marker in the outpatient or inpatient setting. It may be that the turning on and off of BNP production is a vastly more complicated molecular biodynamic phenomenon. That could be why, if you are serially tracking BNP levels of someone with bad heart failure in the outpatient setting, as the BNP starts to drop, the patient may not look terribly different, but the drop in BNP could raise your eyebrows and, as Frank said, make you think that deterioration is about to occur. I don't know.

Dr. Francis—Pretty robust data from John Burnett's lab at the Mayo Clinic suggest that BNP has definite antifibrotic and antiremodeling activity, at least in animals. Years ago Dr. Chien from your institution, Alan, was one of the first to point out that these peptide concentrations go up when the fetal program is turned on. So maybe it is not the hypertrophy per se but rather the genetic switch that is thrown in early heart failure. Maybe it is the regulation of the release that becomes abnormal—I'm not sure.

Dr. Maisel—I agree, and that line of thinking will form the basis of many research studies in the near future.



The RABBIT trial aims to learn whether driving the BNP level down will reduce morbidity and mortality

—Dr. James Young

■ CAN WE USE BNP LEVELS TO DRIVE OUTPATIENT THERAPY?

How BNP is already affecting management

Dr. Young—Let's turn to using BNP to guide therapy in the outpatient setting, specifically in patients who come in with a bit of decompensation—increased edema, more symptoms in general. Take, for example, a patient who has been receiving 40 mg of furosemide a day. He has gained 8 pounds since you last saw him, and his BNP level has risen from 300 pg/mL at his last visit 6 or 12 months ago to 900 pg/mL now. You boost his diuretic dose a bit and have him come back in a week or 10 days. At that point he has lost 5 or 6 pounds and is feeling better, but his BNP level is still 800 or 900 pg/mL.

What would you do at this point, Natalie and Frank? Would you push harder with the medications? Would you repeat the BNP measures every week or two and then adjust therapy solely on the basis of the BNP response?

Dr. Correia—It depends in part on patient education and what the patient has been doing at home. I'd try to probe further to find out what caused the decompensation. Was the initial weight gain traceable to something that changed intrinsically or extrinsically? Are we looking at a worsening clinical picture in terms of left ventricular function or diastolic dysfunction? Or has the patient been having a lot of pepperoni pizza and beer, and is that the driver?

Dr. Michota—I would probably push a bit harder with my therapy. Outside of understanding the modulating effect of the patient's age and weight on his BNP level, if I knew what his baseline level was, a level that was still elevated at this point would make me concerned that he was in a high state of potential decompensation, even though he may look great. Natalie's comments are very well taken in the sense that it's a time to reassess what he is doing at home, but I would place a lot more emphasis on the BNP than on his weight, especially since we may be near the margin of error of his weight in the first place.

Dr. Maisel—It's important to separate using BNP to monitor acute decompensation fol-

lowing hospital discharge from using BNP to guide therapy in a stable patient.

At our institution, we try to establish the patient's euvolemic, or "dry-weight," BNP level as best we can prior to discharge. Dry-weight BNP is associated with NYHA functional class if it is all from the left ventricle. A patient could have end-stage heart failure and a dry-weight BNP of 2,000 pg/mL, but if you try to induce diuresis, the patient will go into renal failure, so you don't want to give diuretics. Of course, there can be variability in that dry-weight BNP from time to time, usually of about 10% to 40%.

When a recently discharged patient returns to our clinic or calls up a nurse describing symptoms that sound like decompensation, we will send him or her to the emergency room or schedule a visit if it sounds particularly bad. Otherwise, we sometimes will have the patient get a BNP measurement and see how it compares with the baseline dry-weight BNP level. Given the variability of the test, we feel that an elevation of 50% or more over baseline should trigger a visit or some sort of change in diuretic therapy.

Still, decompensation can sometimes be very hard to determine, even for experienced cardiologists. A colleague and I laugh about having often sent patients to the units for Swan-Ganz catheters because we thought in the clinic that they were decompensated, only to find out that their wedge pressure was normal, they were given fluids, and then pneumonia sprouted the next day or their blood cultures turned positive. But we have not really had that happen since BNP testing has been available. If the BNP level isn't changed from the dry-weight baseline, the patient's symptoms are usually due to something else.

I would emphasize that BNP is not a stand-alone test in this area. We have to use other things. But in a clinic setting where patients come in with symptoms referable to decompensation and you know their baseline level, BNP testing can certainly be a helpful adjunct.

A bevy of trials and what they may tell us

Dr. Young—Alan, why don't you tell us about the ongoing clinical trials that are using serial BNP measurements in the outpa-



Getting BNP test results quickly is key as our face time with patients continues to shrink
—Dr. Natalie Correia

Can BNP testing drive more effective outpatient therapy? Several trials aim to find out

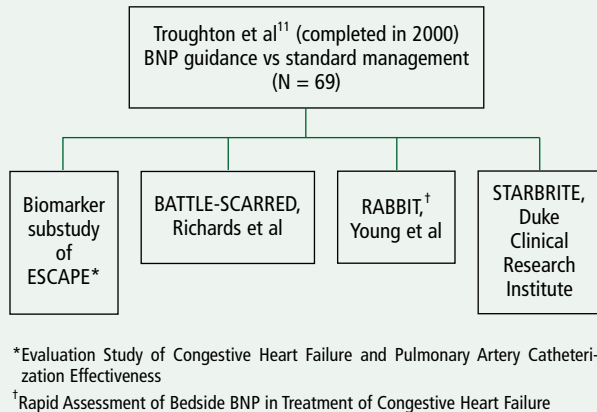


FIGURE 4. Studies assessing whether and how BNP measurement can be used to guide outpatient therapy in patients with heart failure. The study by Troughton et al¹¹ suggested that BNP-guided therapy may be beneficial, but it was limited by its small sample size. The other four trials, all of which are ongoing, are much larger.

tient setting in patients with known heart failure?

Dr. Maisel—Let me start with a little context. I think the hottest question that physicians have today about BNP testing in heart failure is whether it can be used to drive changes in outpatient therapy. Say you have two patients, each of whom is receiving an ACE inhibitor, a beta-blocker, and a diuretic. One has a BNP level of 200 pg/mL and the other has a level of 600 pg/mL. Should the patient with the level of 600 be given an angiotensin receptor blocker? Should he be given spironolactone? Nobody really knows yet what to do with that kind of patient.

There are pretty good data that if you keep a patient's BNP at discharge below about 400 pg/mL and keep it from going higher, the patient is likely to do well over the short haul. But we don't know the answer over the long term, leaving us to wonder where the angiotensin receptor blockers might fit in, or spironolactone, or the endothelin antagonists, if they get approved for treatment of heart failure.

There are a number of studies under way that are trying to get at this (**Figure 4**). Mark

Richards and his group from New Zealand are probably the farthest along. They conducted the first study¹¹ comparing BNP-guided therapy with standard management, and though it seemed to show benefit with BNP-guided therapy, it was a very small study, with just 69 patients. So they have a larger study under way called BATTLE-SCARRED. Additionally, researchers at Duke University are conducting the STARBRITE study, and the ESCAPE trial has a BNP substudy that is related to this. There is also the RABBIT trial, which I will let Jim describe since he is the lead investigator.

Dr. Young—The RABBIT trial may be key for internists like Frank and Natalie because we're hoping it will give insight into whether or not serial BNP measurements can help direct therapy with "enlightened" interventions. One of the aims is pretty much what Alan alluded to—how to use BNP measurement to optimize therapy, not necessarily through diuresis but perhaps by adding an angiotensin receptor blocker, getting the patient up to the target ACE inhibitor dose, getting the patient on the target dose of a beta blocker, or adding an aldosterone antagonist if the BNP levels remain high.

We also expect to gain a lot of information on whether morbidity and mortality are affected by trying to aggressively lower the BNP level. It's analogous to using biochemical markers for prostate cancer, where the intensity of therapy often is focused on where the prostate-specific antigen level is. If we do the same thing with heart failure, aiming to drive BNP down irrespective of signs of congestion or how the patient feels, perhaps that will translate to decreased morbidity and mortality.

The design of the RABBIT trial is interesting but difficult because it is randomizing centers rather than patients, with some centers having BNP testing available to help guide treatment and other centers not having it.

So what do you think, Frank and Natalie, about that approach to BNP testing? How helpful would serial BNP readings be to you?

Dr. Michota—We look at many things that don't really help us understand the physiolo-

gy beneath a clinical problem, such as symptoms, which vary from person to person. So a marker like BNP that helps us understand what is happening inside the patient could be quite valuable. After all, most nephrologists live and die by their ability to serially follow creatinine, which gives some idea of what the end organ is doing. The value of this kind of marker is particularly clear in heart failure, given the resources that we spend on this disease and are projected to spend in the future. It's basically common sense to take advantage of a test that tells you what's happening to a patient on the inside so that you can intervene before the patient suffers consequences, which would almost certainly lead to increased morbidity and resource use.

So I think this is an incredibly valuable question to study. It would be helpful to measure BNP in certain patients as we see them in the clinic once a year, or however often, to allow us to develop a strategy and perhaps bring them back sooner or trigger a second round of evaluation, as appropriate. Of course, predicting who would benefit from this type of resource utilization will be very important.

Dr. Correia—The other piece from the outpatient perspective is having the BNP data available as the patient comes in. That means being able to do the test and get the results quickly—having the patient come to the appointment early to get his or her BNP measured and having that information before the physician actually sees the patient. This is important as our face time with patients continues to shrink in primary care.

Dr. Michota—Also, although we still cling to the idea of longitudinal care, that may just be a myth in the future, at least in most urban settings. We are facing the fragmentation of care in the United States, and people will be bringing their portfolios with them, bar-coded or otherwise, to various facilities when they are not feeling well. As patients continue to move around the country and among different facilities, having this type of information in a serial, longitudinal fashion will give some idea of what is happening inside them.

Dr. Maisel—I'm not sure that "driving the BNP level down," as we have been discussing it, is necessarily what will be good for the patient. I think it's probably the other way around—if you find treatments that make the patient better, that might be reflected in reverse remodeling, which then might yield a lower BNP level.

It's also worth noting that if serial BNP measurement proves to be effective in monitoring patients, it may mean that the physician sees the patient more often because of the need for serial measurement. And that might be the key to the overall benefit—more frequent and more attentive care in general rather than the BNP level in and of itself. But that is not necessarily bad. If it takes a serial test to trigger more office visits that result in better overall management, so be it.

Dr. Francis—I measure BNP frequently and pretty much serially in patients. Having said that, I am aware that there is currently not a shred of data to show that doing so is associated with better outcomes. That is what Jim is trying to prove with his study.

But I don't believe you need a randomized controlled trial for every conceivable outcome. As I see it, we measure the blood pressure, we measure the pulse rate, and maybe we measure BNP, and we integrate all that information into our gestalt of how we think the patient is responding to treatment. You may or may not make a change, and you're certainly not going to hospitalize a patient on the basis of the BNP level alone, but you might alter something or perhaps it will just reassure you that the patient is responding to what you think is your great care. Something positive usually comes out of it, and it is not a terribly expensive test.

The issue is that the Centers for Medicare and Medicaid Services (CMS) and the Food and Drug Administration want outcomes data. As the payer, CMS will say, "If you can't show us the patient is better, why should we pay for this test?" I think this will be tough to show. I hope it comes out positive because I want to continue to order it, I want payers to pay for it, and I don't want the patient to bear the cost. But remember, we are not talking about an exotic hormone that costs \$600 to



Serial BNP testing may mean we see patients more often, which might be the key to the overall benefit

—Dr. Alan Maisel

measure. I understand that the suggested list price of BNP assays is around \$35, and of course hospitals can obtain volume discounts beyond that.

Dr. Maisel—Yes, and the Medicare reimbursement fee limit for BNP testing is now approximately \$47.

■ BNP QUANTIFICATION: POINT-OF-CARE TESTING VS CORE LABORATORY TESTING

Dr. Young—There seem to be important differences between platform BNP testing that would be done in a clinical pathology laboratory and point-of-care BNP testing done at the patient's bedside. Alan, what do you see as the pros and cons of each?

Dr. Maisel—We discussed this issue of laboratory vs point-of-care testing at the Versailles panel 2 years ago, which was a gathering of experts on BNP from around the world in which both Gary and I took part.¹² There was a consensus that BNP measurement in the central laboratory offers tight quality control and may be the preferred way to go if very precise measurements are desired. We also do have a number of laboratory assays now—one from Bayer, one from Abbott, and recently one from Biosite using the Beckman Coulter automated assay platform.

But the expert panel also concluded that, for emergency care, the BNP test result should be available within 1 hour of blood collection, and we viewed point-of-care testing as justifiable when the central laboratory cannot provide a result that quickly. Many laboratories say they can do it in an hour, but when you actually send them the blood, they're out to lunch, or they batch-run them and therefore can't do it right away. It was a consensus that the 1-hour time limit should direct which type of test to use.

Personally, I am fortunate in my office-based setting. My heart failure clinic starts at 1:00 in the afternoon, and we have it set up so that patients come in early for their appointments, starting at noon, to have their blood drawn and to get other testing, and their blood samples are sent immediately to our point-of-care laboratory so that I have

the BNP results when I see each patient. It's great to be able to have that, whether it's to help decide if the patient is heading toward decompensation or perhaps to help guide therapy. Point-of-care testing certainly can facilitate the use of BNP measurement right there in the outpatient setting.

Dr. Francis—I agree that point-of-care testing works very well in the emergency department, but it's been a little more difficult for us to implement in our clinic. Alan said he actually has a point-of-care laboratory in his clinic, which would facilitate it, but practicing physicians should be aware that this is an imposition on people. You need to have a nurse draw the blood, and then the nurse is away doing the test, so unless you have the manpower and the time to do it, point-of-care testing is not quite so easy to implement.

Dr. Young—The emergency department is perhaps the place where the BNP assay can be used best and most efficiently as a point-of-care test. My own use of BNP measurement, both with the point-of-care test and with the platform test, has been more ad hoc—I use it in patients for whom I'm having trouble deciding what to do. It certainly does require a nurse to draw the blood and then run it on the machine there in clinic. However, schemes can be set up, as at Alan's clinic, where patients come in early and then an hour or two is spent just doing batched samples.

The other place where I use the assay more as a point-of-care test is in the intensive care unit, where sometimes we really want to know what the BNP is right away and don't have the luxury of waiting until the next morning. I think that it's reasonable to have both quantification techniques available. The one problem with that approach is that you need to know the comparability or incomparability of one technique to the other, because there will be some variability in results.

Dr. Maisel—Physicians in community offices tell me, "When I have a patient come in with shortness of breath, I have to send out the BNP assay and can't get it back until 2 days later." In those situations, especially outside of suburbia, if you see a patient with shortness



Screening for heart failure in high-risk patients is the most controversial potential use of BNP testing

—Dr. James Young

of breath and you have the ability to get the BNP results right there in the office, you are then in a position to decide whether to send the patient to an emergency room or to get a cardiology consult.

■ RECOMMENDATIONS FOR THE USE OF BNP TESTING: WHAT WE BELIEVE TODAY

Dr. Young—Table 2 lays out some specific recommendations on using BNP measurement that have arisen out of our discussion so far. Would anyone like to elaborate on or amend any of these?

Dr. Michota—I agree very much with the third application, about its use in directing therapeutic interventions, and I think this goes beyond just medication interventions to apply to behavior modification as well. An elevated BNP level gives you a good opening to say to the patient, “You know, this objective test shows that your heart is working harder to compensate for that beer, that pepperoni, that extra weight. What can we do about that?”

Dr. Correia—This educational piece certainly is undervalued. Sharing the BNP test result presents an opportunity to establish a dialogue with the patient about a number of things: Is this a question of dietary indiscretion? Is medication noncompliance an issue? It can be a way to find out that the patient is not taking her diuretic on days when she goes out because she doesn’t want to have to stop three times to go to the bathroom. So it may help open up that dialogue.

Dr. Young—The fourth application listed in Table 2, for screening in high-risk patients, is probably the most controversial. What are your thoughts on it?

Dr. Maisel—Well, it’s consistent with the report from the Versailles panel.¹² That paper was developed before the recent Wang study in the Framingham cohort,⁶ so it was a speculation among experts who had seen elevated BNP levels in people in whom they might not be expected, and we wondered whether these people were at some risk down the road.

TABLE 2

Current recommendations on the use of BNP testing

- 1) Helpful in the differential diagnosis of patients with suspected heart failure due to either systolic or diastolic dysfunction
- 2) May be helpful as a prognostic tool in patients with known heart failure who are being followed serially
- 3) *May* be helpful in directing therapeutic interventions in patients with known heart failure, depending on the degree of elevation
- 4) Possibly of value in screening for heart failure, prior to echocardiographic screening, in high-risk populations, such as post-myocardial infarction patients, patients with diabetes, and patients with poorly controlled hypertension

Dr. Francis—Practicing office physicians in the UK don’t have easy access to echocardiography, so they use BNP in lieu of an echocardiogram. From what I understand, that works fine for them, although I’m not sure we are ready to throw away the echo machines here.

Dr. Maisel—There’s a study coming out in *American Heart Journal*¹³ from our VA Medical Center in which we tried to identify the BNP level below which you would not find much on echocardiography. Interestingly, the level we found was 20 pg/mL, after doing receiver-operating-characteristic (ROC) curves. Granted, since I don’t know of many veterans with BNP levels under 20 pg/mL, that will lead to a lot of false positives. But you just don’t find much on echocardiography in patients with those really low levels, unless the patient is obese. We’ll have to see whether that holds true for the general population as well.

Dr. Michota—I think the key for applying the fourth recommendation from Table 2 to the real-world setting is having some fairly concrete recommendations for what to do in response to specific BNP findings in specific high-risk populations. We sometimes suffer in the United States from being able to test for things whose implications we don’t adequately understand. Genetic thrombophilia is one



Screening for heart failure too widely could lead to situations where we don’t know what to do with the BNP data
—Dr. Frank Michota

example that I see on a regular basis. People test positive for it in the absence of a clinical event and we're left wondering, "What do we do now?" So if BNP screening can be targeted to specific high-risk populations for which there is fairly concrete information on what to do about BNP elevations, it could be very helpful. But I would caution against screening that is too widespread, to avoid situations where we don't know what to do with the information.

Dr. Young—Diastolic dysfunction is an example. We know that BNP can be perturbed in a patient with a normal ejection fraction and diastolic dysfunction. What to do about it is a bit more controversial. Alan, how have you used BNP testing to try to pick up diastolic dysfunction?

Dr. Maisel—It can be a double-edged sword. First, probably half of the new cases of heart failure seen in the office setting involve diastolic dysfunction—and the proportion will be even higher if you see established cases. I think a general statement can be made that, when a patient has symptoms that are referable to heart failure—substantial shortness of breath, especially on presentation—and a normal ejection fraction, a high BNP level rules in diastolic dysfunction, unless there is another reason for the high BNP value. In those patients from the Breathing Not Properly trial⁵ who came to the emergency room with shortness of breath and were found to have heart failure with preserved left ventricular function, the median BNP level was about 400 pg/mL. That was half as high as in patients with systolic dysfunction. So that's the good news.

The bad news is for patients who are less symptomatic. When you try to pick up the people with impaired relaxation and mild degrees of diastolic dysfunction, you get down to those BNP levels that could easily be confused with age-related changes in BNP. That's not to say that an 80-year-old with a BNP level of 90 pg/mL doesn't have a stiff ventricle, but because the level is somewhat lower, it's a little harder to make that claim. But we've had patients with BNP levels of 80 or 90 pg/mL and just mild impaired relaxation on echocardiography who then had ischemia or an

episode of atrial fibrillation, and their BNP level was up from a baseline dry-weight level of 80 or 90 pg/mL to a wet level of 1,500 pg/mL. When we get rid of the atrial fibrillation or the ischemia in these patients, the BNP level falls back to baseline.

So it is a double-edged sword. In symptomatic patients who have preserved left ventricular function and BNP elevation, I think the BNP level is a good tool. In the less symptomatic patients, it's not ready to be a gold standard yet.

■ FINAL REFLECTIONS ON THE ROLE AND PROSPECTS OF BNP TESTING

Dr. Young—I am going to summarize my thoughts and ask you all to do the same.

I think the BNP assay is an exciting tool for the outpatient management of heart failure, in both the internal medicine setting and the general cardiology setting as well as in the heart failure subspecialty setting. There is a wide spectrum of patients for whom this diagnostic test can help us. I personally believe that using it to screen some high-risk patients is important. I find BNP measurement to be extremely helpful in the differential diagnosis of heart failure, and I disagree with those who think they can do as well with simply a stethoscope and history-taking.

I also believe it is an important prognostic tool, with higher BNP levels indicating a worse prognosis, up to a certain point at which the levels then begin to fall, which also is perhaps associated with an adverse prognosis.

I find BNP measurement of use in helping me decide about the presence of pulmonary emboli and pulmonary hypertension. I am also inclined to order it as a routine in patients with acute ischemic syndromes. In this I am on the opposite side of the fence from Alan and Gary. Given the TIMI data,⁴ I think the BNP level is another piece of information of interest in such patients and it may help me decide whether or not a given patient is in real trouble.

It is important to put in perspective the factors that modulate BNP, particularly:

- Age (advanced age increases levels slightly)
- Sex (levels are slightly higher in females)



This is not a stand-alone test for diagnosing heart failure, but it can facilitate the diagnosis

—Dr. Gary Francis

- Renal function (elevated levels of blood urea nitrogen and creatinine can increase BNP levels slightly)
- Obesity (body mass index is negatively correlated with BNP, so BNP levels are slightly lower in obese persons).

Whether or not to use these factors to dictate therapy is a question I am less comfortable answering now. I will wait for the data from the clinical trials. In sum, I would get BNP measurements more often than not in patients with known heart failure.

Dr. Michota—For me, what's exciting about the BNP assay is the window it gives into the patient. Any good clinician can use that information to help guide decision-making, and it will be nice if that guidance is proven to clearly improve outcomes. Overall, the ability to longitudinally track patients' BNP levels in outpatient clinics, perhaps leading to interventions that may delay heart failure progression, is very valuable. And I look forward to the further information that will ultimately emerge to help modulate specific BNP values.

Dr. Correia—I see the assay as a valuable tool in terms of prognostication, diagnosis, and, again, the opportunity to intervene with the

patient, particularly for the office-based physician. It offers a good opportunity to make the patient a participant in his or her own care rather than a recipient thereof.

Dr. Francis—There are zealots at either end of the spectrum—those who think everybody should have their BNP measured all the time, and others who absolutely would never order the test. Most of us fall somewhere in between. For me, it's important to get house staff to recognize that this is not a stand-alone test. It is not a blood test for the diagnosis of heart failure. But it certainly can facilitate the diagnosis, and even so-called experts like us use it to help make the diagnosis.

Dr. Maisel—It's now well established that the assay is a useful tool in the emergency room. Our discussion today suggests that the prospects for using it in the outpatient setting are exciting, not only to predict or diagnose decompensation but also, hopefully, to help track patients over time. I would echo Gary's point, however, that we must remember that this is an adjunct to what physicians would otherwise use in this setting and not a stand-alone test. If we remember that, it will play a valuable and exciting role in the care of our patients.

REFERENCES

1. McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003; 41:571–579.
2. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; 102:865–870.
3. Nagaya N, Nishikimi T, Okano Y, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. *J Am Coll Cardiol* 1998; 31:202–208.
4. de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001; 345:1014–1021.
5. Maisel AS, Krishnaswamy P, Nowak RM, et al, for the Breathing Not Properly Multinational Study investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347: 161–167.
6. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; 350:655–663.
7. Mark DB, Felker GM. B-Type natriuretic peptide—a biomarker for all seasons? *N Engl J Med* 2004; 350:718–720.
8. Maron BJ, Tholakanahalli VN, Zenovich AG, et al. Usefulness of B-type natriuretic peptide assay in the assessment of symptomatic state in hypertrophic cardiomyopathy. *Circulation* 2004; 109:984–989.
9. Holtwick R, van Eickels M, Skryabin BV, et al. Pressure-independent cardiac hypertrophy in mice with cardiomyocyte-restricted inactivation of the atrial natriuretic peptide receptor guanylyl cyclase-A. *J Clin Invest* 2003; 111:1399–1407.
10. Molkentin JD. A friend within the heart: natriuretic peptide receptor signaling. *J Clin Invest* 2003; 111:1275–1277.
11. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000; 355:1126–1130.
12. Cowie MR, Jourdain P, Maisel A, et al. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003; 24:1710–1718.
13. Atisha D, Bhalla M, Morrison LK, et al. A prospective study in search of an optimum BNP level to screen patients for cardiac dysfunction. *Am Heart J* 2004. In press.