Routine Measurement of Natriuretic Peptide to Guide the Diagnosis and Management of Chronic Heart Failure

To the Editor:

We read with interest the viewpoint of Dr Milton Packer in a recent editorial, accompanying a study examining the behavior of B-type natriuretic peptides in outpatients with congestive heart failure (CHF).1

Dr Packer suggested that B-type natriuretic peptides (BNPs) have not been shown to “improve upon the information derived from the patient-physician interaction” (p 2951). We disagree, citing data from the BNP (Breathing Not Properly) Multinational Study,2 in which the results of the BNP testing were superior to clinical judgment for the detection of CHF among patients presenting in an urgent fashion. Similar results are now pending for NT-proBNP.

Dr Packer also asserted that no study has demonstrated that BNPs are superior to standard prognostic assessment in CHF. We would point out a recent study suggesting that N-terminal pro-BNP (NT-proBNP) results were superior to those of all methods for risk stratification among an outpatient heart failure population, even superior to the maximum oxygen uptake, which is the current gold standard for prognosticating outcomes in CHF.3

We also feel that Dr Packer’s characterization of BNP-guided therapy of outpatients with CHF as “an intellectual crutch to remind physicians to practice optimal medicine” (p 2952) is incorrect. We point out that the care of CHF patients is more often in the hands of non-cardiovascular specialists who may find biomarker-guided therapy useful to guide or ensure optimal therapy. Further, even when CHF patients are managed by a cardiovascular specialist, data suggest that there is room for improvement. We point out that Dr Packer’s comments are directly contradicted by the accompanying study,2 wherein only 57% of patients in a specialized CHF clinic were taking a β-blocker, and no mention was made regarding the rates of treatment with spironolactone or biventricular pacing, presumably because of low rates of use. Lastly, we do not suggest that patients with low BNP or NT-proBNP levels should have therapies of proven benefit withheld or used in a suboptimal fashion.

We enthusiastically agree with Dr Packer that we need to be excellent clinicians, we will need to continuously integrate our outstanding clinical skills with emerging tools that offer powerful diagnostic and prognostic information. As we learn more about BNP and NT-proBNP, we suggest that these markers will play an increasingly important role in the care of our patients with heart failure, without eroding the quality of care we deliver to these patients.

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To the Editor:

Many of the points raised by Dr Packer in his focused perspective can be challenged on grounds of logic or fact. We comment here only on his reference to our own work. Dr Packer quoted a target level of amino-terminal BNP (N-BNP) of “200 pg/mL” from our pilot study of N-BNP–guided therapy for heart failure. In fact, the target was 200 pmol/L.2 Based on a molecular weight for N-BNP of 8457, an N-BNP level of 200pmol/L would be equivalent to 1700 pg/mL (conversion factor 8.457). The molecular weight for BNP is 3456. There are currently multiple commercial assays available that measure different parts of the BNP molecule, each with a different reference range.3,4 Additionally, plasma levels of N-BNP tend to be higher than those for BNP, by a factor close to 10. The use of different assays and units in reporting BNP levels is a potential source of confusion in interpreting and applying results from clinical studies. There is a need for greater standardization in reporting BNP levels, and authors and readers should pay careful attention to the molecule assayed (BNP or N-BNP), the assay used, and the units reported. Application of specific threshold BNP or N-BNP levels should take into account the assay used by an institution’s laboratory.

Dr Packer suggests that treatment groups were not balanced in our N-BNP–guided study. In fact, as described, baseline differences were not statistically significant and the effect of the N-BNP–guided strategy was more significant once trends toward baseline differences were accounted for in multivariate analysis.1 Dr Packer suggests that the degree of treatment intensification did not differ meaningfully between our study groups. In fact, we reported a significantly greater increase in angiotensin-converting enzyme inhibitor doses and significantly more patients received spironolactone in the N-BNP group than in the “usual care” group. There was a clinically significant increase in loop diuretic that was greater for the N-BNP group but did not quite achieve statistical significance.2

At present, there is no objective guide to optimal individualized dosing of medication in heart failure. The “one dose fits all” approach of applying trial doses to all individuals will undertreat some and overtreat others while providing no guidance regarding diuretic dosage. Given that BNP levels identify high-risk patients and those who benefit most from heart failure treatments,5 it is a scientifically appealing hypothesis that a BNP-guided strategy may facilitate more optimal dosing for individuals. We agree with Dr Packer, however, that results from larger randomized studies are needed to validate this strategy.

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To the Editor:

We read with great interest the recent article by Dr Packer1 concerning plasma brain natriuretic peptide (BNP) levels in chronic heart failure. He claims that routine measurement of plasma BNP is not useful for the diagnosis and management of heart failure because (1) BNP levels are affected by age;2 (2) BNP levels are influenced by sex, coronary artery disease, chronic pulmonary disease, pulmonary embolism, and renal insufficiency;3,4; and (3) it is consequently difficult to determine the diagnostic threshold of BNP for heart failure. Although Dr Packer’s statements are facts, we do not understand why he has singled out BNP.

We do not know of any laboratory tests that have the same normal range or diagnostic threshold irrespective of factors such as age, sex, body size, or renal function. ECG findings in young subjects, heart size as assessed by chest radiography or echocardiography in young patients with heart failure, and diastolic function as assessed by Doppler examination in young subjects all differ from the respective values in adult or elderly subjects. Even in the same age range, body size affects left ventricular dimension and mass and therefore must be standardized mathematically. Renal function also changes in the elderly. We know that all of the above laboratory examinations are clinically useful only when we standardize them according to the clinical characteristics of patients. Why does Dr Packer have to regard BNP as an almighty laboratory test that should not be affected by demographic factors? It is natural to assume that similar BNP levels in young patients with heart failure and in elderly patients with hypertensive renal impairment most likely result from different pathophysiological mechanisms. Systolic blood pressure (SBP) is another good example. Everyone would agree that a SBP of 170 mm Hg in a 20-year-old patient has different clinical implications from the same SBP in a 70-year-old patient.

Therefore, when we evaluate BNP in individual patients with heart failure, it seems natural to take into consideration patients’ clinical characteristics, as we do for other laboratory examinations. It is inappropriate to focus solely on the specific diagnostic value of BNP. We should allow some latitude when determining the diagnostic implications of BNP, taking into account clinical factors such as age, sex, and renal insufficiency.

Dr Packer stated that the diagnosis and evaluation of heart failure is difficult because it relies on the scholarship, skills, and judgment of the practicing physician. We propose that the interpretation of BNP based on other clinical characteristics should be included in such scholarship; the task of a physician may thus be made slightly easier.

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Response

Drs Nishikimi and Matsuoka suggest that values for BNP need to be interpreted in light of age, gender, body size, and renal function. I agree, having made precisely this point in my editorial.1 Unfortunately, this is not what physicians have been told to do. The companies that market BNP assays and advocates for BNP testing have instructed physicians to use a single diagnostic threshold (100 pg/mL), regardless of demographic or clinical factors. Therefore, the complaint from Drs Nishikimi and Matsuoka about the use of a single threshold value should be directed to the companies and investigators who have proposed it.

My editorial focused on the misuse of the BNP assay in patients with chronic heart failure. Therefore, it is hard to understand why Drs Januzzi and Maisel cite the BNP Multinational Study,2 which did not evaluate chronic heart failure but enrolled patients presenting with acute dyspnea. Even that study, however, fails to support their belief that BNP testing has value as a diagnostic test. According to the nomogram published in that paper,3 a BNP of 100 pg/mL did not meaningfully influence the likelihood of heart failure in patients whose pretest probability was low (10%), intermediate (50%), or high (90%). Drs Januzzi and Maisel also confuse statistical modeling with clinical utility. As I stated in my editorial,1 reports showing that BNP measurements are prognostically powerful do not establish the usefulness of such measurements, because statistical models can be easily manipulated and the proper management of heart failure is similar across a wide range of prognostic groups. Drs Januzzi and Maisel directly imply that BNP testing would increase the likelihood that optimal therapy will be prescribed by physicians. Unfortunately, in doing so, they firmly establish their advocacy of BNP testing as an “intellectual crutch.” In truth, physicians should prescribe the right treatments for patients with heart failure because such treatments have been shown to reduce morbidity and mortality in clinical trials that did not use BNP testing. Drs Januzzi and Maisel agree that these patients need the right treatment whether or not their BNP levels are increased. Why then do physicians need BNP measurements?

Dr Troughton and his colleagues discuss several issues raised by their clinical trial evaluating the utility of BNP guidance in the management of chronic heart failure.3 In that trial, drugs were titrated to achieve a N-BNP level <200 pmol/L, which approximates a BNP level of 200 pg/mL (~1700/10). Unfortunately, their pilot trial suffered from the inevitable imbalances that are known to plague small studies. When compared with the no-BNP guidance group, the patients assigned to BNP guidance had lower BNP levels (217 versus 251 pmol/L) while receiving higher doses of furosemide (123 mg/d versus 87 mg/d), indicating that they were more effectively diuresed before the start of the study. Furthermore, the use of BNP guidance did not result in significant intensification of treatment during the study. At the end of the trial, the doses of diuretics, angiotensin-converting enzyme inhibitors, and β-blockers did not differ between the two groups. Although more BNP-guided patients received spironolactone at the end of the trial, the two groups were similar in the frequency of institution of spironolactone during the study as a result of BNP testing. Therefore, it is difficult for the authors to conclude that BNP testing—even when its use is formally imposed and acted on in the context of a research study—actually led physicians to improve the treatment of heart failure.

In the final analysis, we need to be honest with physicians about the value of BNP testing. If we are going to encourage them to measure BNP to guide the management of heart failure based on current evidence, we need to admit that it is an intellectual crutch and that it may not work.

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Response

Drs Nishikimi and Matsuoka suggest that values for BNP need to be interpreted in light of age, gender, body size, and renal function. I agree, having made precisely this point in my editorial.1 Unfortunately, this is not what physicians have been told to do. The companies that market BNP assays and advocates for BNP testing have instructed physicians to use a single diagnostic threshold (100 pg/mL), regardless of demo-
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doi: 10.1161/01.CIR.0000132585.12965.D6
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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