

Rapid measurement of B-type natriuretic peptides reduced time to discharge and treatment costs in patients with acute dyspnea

I would like to remark on a recent commentary (1) about B-type natriuretic peptide (BNP) as a test for heart failure and on the B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study (2). Schünemann and Akl cite the BNP Multinational Study (3, 4) as demonstrating that BNP has good test characteristics for the diagnosis of heart failure. However, their stated positive likelihood ratios (LRs) of 2.5 to 5.0 (for the 50 pg/mL cutpoint) only result in small-to-moderate changes in test probability. Moreover, this study was flawed by its practice of enrolling undifferentiated patients with dyspnea, including a substantial number with clinically obvious diagnoses. When the sensitivity and specificity of a test are calculated from a population that contains large numbers of patients at the extremes of the disease spectrum, the test performance is inappropriately inflated when subsequently applied to less obvious patient presentations (5).

The calculation of interval LRs (6) for the Multinational Study data reveals that the authors' suggested binary cutpoint of 100 pg/mL is untenable (Table) (7). Values between 80 and 400 pg/mL produce LRs of little to no diagnostic significance. On the positive side, a lower cutpoint of 80 pg/mL makes heart failure unlikely and a lower cutpoint of 50 pg/mL virtually rules it out. Conversely, an upper cutpoint of 400 pg/mL produces a moderate likelihood of heart failure, and levels over 1000 pg/mL seem to virtually rule it in. However, even these cutpoints must be taken with a large grain of salt because of spectrum bias, as described above.

Unfortunately, the gray zone between 50 and 400 pg/mL is substantial, for it contains 40% of the Multinational Study patient population as well as roughly 50% of their patients with heart failure. Thus, BNP testing is far from a major diagnostic advance. At least 40% of the time, it produces no useful information, in perhaps 10% of patients it adds nothing to what are clinically obvious diagnoses, and much of the rest of the time it must be closely combined with good clinical judgment.

Even such extremely high BNP values as 1000 pg/mL and higher can have causes other than heart failure, including pulmonary embolism (8) and sepsis (9), so if the pretest probabilities of either of these diseases are even moderate, any BNP result must be viewed with caution. A further pitfall can occur when the patient with chronic symptomatic heart failure develops worsening dyspnea from a pulmonary embolism, a far-from-uncommon occurrence. Would a high BNP value be diagnostically helpful or harmful in this situation?

Given these limitations, I wonder how BNP testing could have had such a major positive effect on treatment time and costs in the BASEL study. I find the "black box" nature of this report disconcerting. Did the treating clinicians ever disregard the BNP results and if so, how often? What were the final diagnoses and what were their respective BNP values? Could it be that the study protocol, with its encouragement of further diagnostic testing, *increased* the time to discharge and treatment costs for the control group rather than *decreased* the time and cost for the BNP group?

Likelihood ratios (LRs) from the Multinational Study (3)*

BNP range (pg/mL)	LR (95% CI)
< 50	0.048 (0.03 to 0.07)
50 to 79	0.33 (0.23 to 0.50)
80 to 99	1.5 (0.78 to 2.74)
100 to 124	1.0 (0.60 to 1.82)
125 to 150	0.50 (0.27 to 0.91)
151 to 400	3.1 (2.5 to 3.8)
401 to 1000	5.0 (3.3 to 7.9)
> 1000	16 (10 to 26)

*CI defined in Glossary.

Eric Schwam, MD
Sturdy Memorial Hospital
Attleboro, Massachusetts, USA

References

- Schünemann HJ, Akl E. Rapid measurement of B-type natriuretic peptides reduced time to discharge and treatment costs in patients with acute dyspnea. *ACP J Club*. 2004 Sep-Oct;141:35.
- Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004;350:647-54.
- Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161-7.
- McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation*. 2002;106:416-22.
- Hohl CM, Mitelman BY, Weyer P, Lang E. Should emergency physicians use B-type natriuretic peptide testing in patients with unexplained dyspnea? *Canadian Journal of Emergency Medicine*. 2003;5:162-5.
- Brown MD, Reeves MJ. Evidence-based emergency medicine/skills for evidence-based emergency care. Interval likelihood ratios: another advantage for the evidence-based diagnostician. *Ann Emerg Med*. 2003;42:292-7.
- Schwam E. B-type natriuretic peptide for diagnosis of heart failure in emergency department patients: a critical appraisal. *Acad Emerg Med*. 2004;11:686-91.
- Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. *Circulation*. 2003;107:2545-7.
- Jones AE, Kline JA. Elevated brain natriuretic peptide in septic patients without heart failure. *Ann Emerg Med*. 2003;42:714-5.

Author response

I agree with some of Dr. Schwam's detailed critique. The sensitivity and specificity of BNP for the diagnosis of CHF in patients with acute dyspnea are not 100%. Our knowledge and understanding of BNP testing has substantially improved within the past 2 years. The effect of renal dysfunction (1, 2) and obesity (3) as major confounders has been disclosed. Even with the use of the most appropriate cutpoint values, there will always remain patients incorrectly classified by this marker alone. Beyond doubt, further studies are necessary to improve our use of BNP testing.

However, these limitations should not distract us from accepting 3 evidence-based findings: First, BNP performs better than our other tools in the diagnosis of patients with acute dyspnea in the emergency department (ED) (4–8). Second, BNP is most useful in patients with diagnostic uncertainty after standard evaluation in the ED. In fact, due to the extensive comorbid conditions in patients presenting with acute dyspnea to the ED, considerable diagnostic uncertainty remains in nearly half of all patients with acute dyspnea (7, 8). Third, used in conjunction with other clinical information, BNP improves diagnostic accuracy (5, 7, 8) and patient management (9).

*C. Mueller, MD
University of Basel
Basel, Switzerland*

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;41:571-9.
2. Mueller C, Laule Kilian K, Scholer A, et al. B-type natriuretic peptide for acute dyspnea in patients with kidney disease: insights from a randomized comparison. *Kidney Int.* 2004; in press.
3. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation.* 2004;109:594-600.
4. Cowie MR, Struthers AD, Wood DA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet.* 1997;350:1349-53.
5. Wright SP, Doughty RN, Pearl A, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol.* 2003;42:1793-800.
6. Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet.* 1994;343:440-4.
7. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med.* 2002;347:161-7.
8. McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation.* 2002;106:416-22.
9. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med.* 2004;350:647-54.

Commentators' response

We understand Dr. Schwam's letter as support for our commentary in which we cautioned readers on issues not described in the original report by Mueller and colleagues, regarding implications for practice and generalizability of the findings (1, 2). Contrary to Dr. Schwam, however, we commend the authors for their outstanding efforts in performing a randomized controlled trial (RCT) of a diagnostic and management strategy; these studies are few and far between in the medical literature and are important to understanding the clinical value of tests. We will return to this issue.

Dr. Schwam is unhappy with our statement about the good test characteristics of BNP. In fact, we provided a brief summary of LRs for BNP diagnostic thresholds over 50 pg/L. This threshold finds support in a recent systematic review by Doust and colleagues (3). In our short commentary, we did not provide a complete listing of LRs for

all threshold values of BNP, and several of these articles were previously summarized in *ACP Journal Club*. Although it is not clear where the best threshold lies, it is well known that for many tests, higher levels come with higher LRs.

Dr. Schwam suggests that a binary threshold value is untenable. Mueller and colleagues did not use a binary cutpoint, and Dr. Schwam's review as well as his table are not based on a systematic review that would pass critical appraisal criteria as easily as other reviews on the topic (3, 4). What Dr. Schwam ignores is that LRs of 2 to 5 generate small but sometimes important changes in disease probability. For example, given an LR of 5 for a positive test, a pretest probability of 50% turns into a posttest probability of over 80%, a large change in disease probability that can cause a shift across the treatment threshold, particularly if the outcomes prevented are severe and the downsides of treatment are minor.

Most important, we remind Dr. Schwam that Mueller and colleagues performed an RCT. That is, the use of BNP with the cutpoints given in the article was associated with improved patient-important outcomes in the group labeled as having congestive heart failure. In the absence of contrary evidence, we would assume that randomization had balanced all unknown confounders and that patients were cared for equally in the 2 groups. If this is not the diagnostic contribution of BNP values, what else is it? How many intervention groups should the authors have used if we consider that there are perhaps unlimited pretest and posttest probabilities?

The restricted length for commentaries precluded us from including all possible hypotheses that would explain differences in the BASEL study groups and from reviewing basic methodological issues of diagnostic tests. Neither did the authors of the BASEL study have unrestricted space to describe all details of their study protocol. The difference between what actually happens in a study and what is reported does indeed sometimes remain a "black box" due to many reasons, including article length. Nevertheless, the conclusion that patients were better off in this study as a result of BNP testing is the most credible explanation of the findings.

*Holger J. Schünemann, MD, PhD
Elie Akl, MD, MPH
University at Buffalo, State University of New York
Buffalo, New York, USA*

References

1. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med.* 2004;350:647-54.
2. Schünemann HJ, Akl E. Rapid measurement of B-type natriuretic peptides reduced time to discharge and treatment costs in patients with acute dyspnea. *ACP J Club.* 2004 Sep-Oct;141:35.
3. Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. *Arch Intern Med.* 2004;164:1978-84.
4. Schwam E. B-type natriuretic peptide for diagnosis of heart failure in emergency department patients: a critical appraisal. *Acad Emerg Med.* 2004;11:686-91.