Critical Review Form
Diagnostic Test

Isbitan A, Hawatmeh A, Elnahar Y, et al. Utility of brain natriuretic peptide assay as a predictor of short term outcomes in patients presenting with syncope to the emergency department. Cardiovasc Diagn Ther. 2016 Jun;6(3):234-40.

Objectives: **"to assess the use of BNP value to predict short term (one month) serious outcomes for patients presenting to ED with syncope..." and "to determine if adding BNP to the standard evaluation of syncope in ED will help in risk stratification of patients and avoid unnecessary admissions without increasing adverse outcomes." (p. 235)**

Methods: **This prospective cohort study was conducted at two tertiary medical center EDs in New Jersey between August 2012 and August 2013. Patients aged 18 years or older presenting to the ED for syncope were eligible. Exclusion criteria were inability to give consent, persistent neurologic deficits concerning for stroke, collapse related to alcohol consumption, hypoglycemia, trauma, seizure activity, or if the treating clinician was already ordering a BNP. BNP levels were checked on all patients enrolled and the treating physicians were blinded to the results. All treatment and disposition decisions were at clinician discretion. A cutoff of 250 units was chosen for the BNP level.**

Patients were followed through the hospital electronic medical record or by telephone call 30 days after presentation. The primary endpoint was any "serious outcome" thirty days after ED presentation, which included all-cause death, acute myocardial infarction, life-threatening arrhythmia, implantation of a pacemaker or defibrillator, cerebrovascular accident, hemorrhage requiring a blood transfusion of at > 2 units, or need for acute surgical procedure or endoscopic intervention.

Out of 159 patients presenting to the ED with syncope during the study period, 113 were eligible for enrollment. There were 86 patients with a BNP ≤ 250 and 27 with a BNP > 250. The median age in these two groups was 64 and 75 years, respectively, with nearly 50% split between men and women in both groups.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes. This study enrolled consecutive patients presenting to the ED with undifferentiated syncope whose etiology was not yet clear.
B.	**Was there a blind comparison with an independent gold standard applied similarly to all patients? (Confirmation Bias)**	No. There is no single gold standard test in the evaluation of syncope and no single test to determine if a patient's syncope was of cardiac etiology. The authors report patient outcomes rather than final diagnoses, and do not report

		what testing each patient underwent. It is quite likely that testing varied from patient to patient, with not all patients undergoing cardiac monitoring, cardiac ECHO, coronary artery cathterization, etc., which could potentially lead to differential verification bias and partial verification bias. In addition, clinicians were specifically NOT blinded to BNP results, and it is possible that these values affected the decision to perform additional testing (i.e. patients with elevated BNP levels would be more likely to undergo cardiac ECHO).
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	No. Again, there is no true gold standard test, but clinicians were blinded to results of BNP testing and hence additional testing would not have been influenced by the results.
II.	**What are the results?**	
A.	**What likelihood ratios were associated with the range of possible test results?**	For a cutoff of 250, BNP had a sensitivity of 48.8% and specificity of 90.3% with a positive likelihood ratio of 5.02 (95% CI 2.32-11) and a negative likelihood ratio of 0.57 (95% CI 0.42-0.77).
III.	**How can I apply the results to patient care?**	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Yes. This is a standard blood test offered in most (if not all) hospitals and emergency departments across the United States. While different assays exist and different forms of natriuretic peptide are checked, it would be easy to adjust the cutoff for these various forms of the test.
B.	**Are the results applicable to the patients in my practice?**	Yes. This study enrolled a group of patients presenting to the ED of two US hospitals with undifferentiated syncope. The patients in this study had a high prevalence of significant comorbidities such as diabetes and hypertension, but the authors do not report the prevalence of heart failure, coronary artery disease, or other important risk factors. It is likely that these patients were similar, as a group, to those seen in our ED for syncope (external validity).
C.	**Will the results change my management strategy?**	No. This was a very small study conducted in a limited practice setting. In addition, the authors report measures of association between BNP elevation and serious outcomes rather than measures of diagnostic test accuracy, which would be more relevant. When calculated, the associated likelihood ratios (5.02 and 0.57) are

		rather poor and would not likely have much effect on the probability of a serious outcome. This study does nothing to address the potential impact of BNP testing on the disposition or management of such patients.
D.	**Will patients be better off as a result of the test?**	No. See above.

Limitations:

1. **While it would appear that a consecutive sample of patients was enrolled, patients already getting a BNP value checked were excluded. This would potentially exclude a large number of patients in whom BNP would be most valuable, such as those with a history of heart failure (spectrum bias).**

2. **It is unlikely that all patients underwent the same evaluation in this study, with a variety of tests (ECHOcardiography, telemetry monitoring, stress testing, etc.) performed only certain patients. Given this fact, some patients may have had dysrhythmias or structural lesions that were not identified (due to lack of testing), which would result in inaccurate measures of diagnostic accuracy (differential verification bias and partial verification bias).**

3. **The authors report results as relative risks and odds ratios, which are more applicable to studies evaluating the effects of a therapy on outcomes. The authors should have reported diagnostic test characteristics (i.e. sensitivity, specificity, likelihood ratios) instead, as these would be more applicable to the study type.**

4. **When calculated, the resulting diagnostic test characteristics were rather poor; specifically, the likelihood ratios associated with a BNP > 100 pg/mL demonstrate that the test results would have very little impact on post-test probability.**

Bottom Line:

This small, prospective study of ED patients with undifferentiated syncope demonstrated a positive association BNP levels > 250 and "serious outcomes," but also demonstrated rather poor diagnostic accuracy (LR+ 5.02, LR- 0.57). Despite the apparent association, it is unlikely based on this data that BNP would be helpful in determining disposition or further management for patients with undifferentiated syncope.