Critical Review Form
Diagnostic Test

Pfister R, Hagemeister J, Esser S, Hellmich M, Erdmann E, Schneider CA. NT-pro-BNP for diagnostic and prognostic evaluation in patients hospitalized for syncope. Int J Cardiol. 2012 Mar 8;155(2):268-72.

Objectives: "to evaluate the diagnostic and prognostic application of NT-pro-BNP in patients with syncope and to compare with conventional parameters of history and examinations." (p. 268)

Methods: This prospective, observational study was conducted at the University Hospital of Cologne, Germany between May 2007 and December 2008. Consecutive patients with a diagnosis of syncope admitted to the cardiological unit were enrolled. All patients had a natriuretic peptide NT-pro-BNP measured. Additional testing was at the discretion of treating physicians. Patients were then followed up at six months by phone call with the patient, the patient's relatives, or the patient's general practitioner.

For the purposes of the study, patients with either an identified arrhythmia or structural cardiac/cardiopulmonary abnormality were considered to have had cardiac syncope. The authors also evaluated the combined clinical endpoint of an adverse event during the index hospitalization consisting of all-cause mortality, coronary revascularization, interventional therapy for left-ventricular outflow obstruction, urgent administration of antiarrhythmic drugs or electrical cardioversion, and placement of a pacemaker or AICD.

A total of 161 patients were enrolled, with a median age of 69 years; 57.8% were male. A cardiac cause of syncope was identified in 78 patients (53 with an arrhythmia and 25 with a structural cardiac/cardiopulmonary abnormality). The remaining 83 patients were felt to have a non-cardiac etiology (neurally-mediated in 24, non-syncopal in 15, and unknown etiology in 18).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Likely yes. These were patients admitted to the cardiological service for syncope, though it is unclear if the etiology had been determined prior to admission or was determined during hospitalization. Typically such patients would have undergone some form of evaluation prior to admission (ECG, basic labs, chest x-ray) and an etiology would already have been determined in at least some of these patients. The fact this study only included patient admitted to the

		hospital (and specifically admitted to a cardiac unit) suggests that this cohort was at higher risk of having a cardiac etiology for their syncope than all patients seen in the ED; this would introduce spectrum bias when trying to generalize the results to all emergency department patients, which would affect the reported measures of diagnostic accuracy.
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 patients in this study did not all undergo the same testing; tilt table testing was performed in 40.4% of patients, Holter-ECG in 62.7%, telemetry monitoring in only 24.8%, stress testing in 32.9%, echocardiography in 65.8%, coronary angiography in 46.6%, and an electrophysiological examination in only 12.4% (differential verification bias and partial verification bias).
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	Uncertain. Again, there is no true gold standard test. It is unlikely that the results of the BNP influenced the decision to perform additional testing, but the authors do not specifically mention blinding of clinicians to BNP results.
II.	**What are the results?**	
A.	**What likelihood ratios were associated with the range of possible test results?**	• For the receiver operator characteristic (ROC) curve, the area under the curve was 0.80 (95% CI 0.73-0.86). • Using a cutoff of 156 pg/mL, NT-pro-BNP had a sensitivity of 89.7%, specificity of 51.8%, positive predictive value of 63.6%, and negative predictive value of 84.3%. The LR+ was 1.86 (95% CI 1.47-2.36) and the LR- was 0.20 (95% CI 0.10-0.39), calculated using http://araw.mede.uic.edu/cgi-bin/testcalc.pl. • The combined end-point of death or need for cardiac intervention occurred in 58 total patients; additionally, 6 patients died and 5 cardiovascular hospitalizations occurred during the 6-month follow-up. A total of 63 patients (39.1%) had an adverse event from admission to 6 months of follow-up. NT-pro-BNP was associated with the risk of developing an adverse outcome, with an odds ratio of 2.08 per standard deviation increase (95% CI 1.44-3.01).
III.	**How can I apply the results to patient care?**	
A.	**Will the reproducibility of the test result and its**	Yes. This is a standard blood test offered in most (if not all) hospitals and emergency departments across

	interpretation be satisfactory in my clinical setting?	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?**	No. The cohort of patients in the study was admitted to a cardiac unit for evaluation of syncope. There would likely be a much higher prevalence of cardiac disease in this population than I would see among all patients presenting to the ED for syncope. Additionally, this would likely be a sicker patient population with a more severe spectrum of disease (spectrum bias), affecting the specificity, sensitivity, and likelihood ratios of the test.
C.	**Will the results change my management strategy?**	No. This study would need to be reproduced in an emergency department of cohort of patients and would need to show some kind of impact on admission rates and testing to change my management. The primary question among ED patients with syncope is whether or not they should be admitted to the hospital. By only including patients already admitted, this study does not address how the use of BNP testing would influence that decision.
D.	**Will patients be better off as a result of the test?**	Uncertain. Again, this study did not address the primary question of whether BNP testing will help aid in the decision to admit or discharge patients presenting to the ED with syncope. Additionally, while there does appear to be an association between the BNP level and the existence of a cardiac cause for syncope, it remains unclear how this test will alter decision-making, even for admitted patients (i.e. how the BNP result would guide further testing).

Limitations:

1. **This study enrolled only patients admitted to a cardiac floor for syncope, rather than all patients seen in the emergency department. This would likely introduce spectrum bias, and the results may not be applicable to our patient population.**
2. **Not 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 do not provide 95% confidence intervals for the measures of diagnostic accuracy (sensitivity/specificity/negative predictive value/positive**

predictive value). Such measures of precision provide an important context for understanding the results of a study.

4. **Where there appears to be some association between BNP and arrhythmia or structural cardiac/cardiopulmonary abnormality as the cause of syncope, the study demonstrates a very poor positive likelihood ratio and modestly helpful negative likelihood ratio. It remains unclear how this test would impact care and disposition for patients presenting with undifferentiated syncope.**

Bottom Line:

This prospective, observational cohort study conducted on patients with syncope admitted to the cardiological ward of a single hospital in Germany demonstrated a significant correlation between the BNP level and the eventual identification of a cardiac cause for syncope. Unfortunately, the associated likelihood ratios are poor (LR+ 1.86) to moderate (LR- 0.20) and it remains unclear how this test could be used to guide evaluation of patients with undifferentiated syncope. Additionally, these results may not apply to a more heterogeneous group of patients seen in the ED due to potential spectrum bias.