HHS Public Access

Author manuscript

Curr Heart Fail Rep. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Curr Heart Fail Rep. 2019 December ; 16(6): 250–256. doi:10.1007/s11897-019-00441-2.

Targeting Natriuretic Peptide Levels in Heart Failure with Therapy: Does "X" Really Mark the Spot?

Juliette K. Logan, MD[*], **Robert J. Mentz, MD**[*,†]

[*]Department of Medicine, Duke University School of Medicine, Durham, NC,

[†]Duke Clinical Research Institute, Durham, NC, USA

Abstract

Purpose of review: Explore controversial biomarker-guided management of patients with heart failure (HF) with reduced ejection fraction.

Recent findings: Natriuretic peptides (e.g., BNP, NT-proBNP) are elevated in HF as a result of end-diastolic stress and are used in the diagnosis and prognosis of heart failure. Natriuretic peptide levels decrease with guideline directed medical therapy (GDMT). Multiple small studies examined whether the use of biomarker-guided therapy would be beneficial to guide HF care and potentially improve outcomes. Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT), the largest randomized control study seeking to answer that question, did not find biomarker guided therapy to be more effective than usual care in improving the primary endpoints of HF hospitalization or cardiovascular mortality in HF patients.

Summary: Natriuretic peptides are important for diagnosis and prognosis in HF. GUIDE-IT showed than patients with HF and reduced ejection did not benefit from biomarker-guided strategy in terms of clinical outcomes. Future studies could focus on additional routine clinical care settings and take into account other HF phenotypes including preserved ejection fraction.

Keywords

Heart failure; biomarker; natriuretic peptides; guidelines; heart failure therapy; clinical trials

Reprinted from the *Journal of the American College of Cardiology*, **Volume 70, Issue 6**, Yancy CW et al, 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, Pages 776-803, 8 August 2017, with permission from Elsevier.

Corresponding Author: Robert J. Mentz, MD, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715; telephone: 919-668-7121; fax: 919-668-7063; robert.mentz@duke.edu; Twitter: @robmentz.

Conflicts of Interest

Dr. Mentz reports grants and personal fees from Novartis, grants and personal fees from Amgen, grants and personal fees from AstraZeneca, grants and personal fees from Merck, grants and personal fees from Bayer, personal fees from Sanofi, grants from American Regent, grants from Medtronic, personal fees from Abbott, personal fees from Boehringer Ingelheim, during the conduct of the study.

Dr. Logan has nothing to disclose.

Human and Animal rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors

Introduction

Heart failure morbidity and mortality has been substantially reduced with the advent of medical therapies such as angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, angiotensin receptor neprilysin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists as well as device-based therapies. Current guidelines recommend that the guideline-directed medical therapies (GDMT) be uptitrated to reach target dosing, however not all heart failure (HF) patients are on appropriate therapy nor have they achieved target dosing [1–4].

Biomarkers, specifically natriuretic peptides (NPs): brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) represent one potentially appealing strategy to personalize the approach. NPs are powerful predictors of adverse outcomes in HF patients whose concentrations decline is response to guideline-directed medical therapy[5–7].

Given this data, it has been suggested that NP guided therapy may be a useful was to guide medication titration and improve HF outcomes[8]. In this review article, we summarize contemporary literature and give clinical recommendations regarding the use of BNP-guided therapy.

Background of Natriuretic Peptides

BNP is a product of pro-BNP (pro brain natriuretic peptide) which is continuously produced by the heart under normal demands. When pro-BNP is cleaved enzymatically, it releases BNP and NT-proBNP, its active and inactive forms, respectively (Figure 1). These NP levels vary with age, gender, obesity status, other cardiac, and noncardiac causes. [8, 9].

In heart failure, BNP and NT-proBNP are released into circulation from the myocardium as a result of end-diastolic stress from increases in volume or pressure. Significant evidence supports the use of NP biomarkers to assist in the diagnosis of heart failure in both chronic and decompensated HF especially when the cause of dyspnea is unknown[1]. These molecules have significant predictive value in assessing the risk of incident heart failure. In fact, BNP accurately diagnoses HF in patients and supports the clinical diagnosis of acute decompensated or chronic ambulatory HF.

Kelder et al estimated the quantitative diagnostic contribution of elements of history and physical exam in the diagnosis of heart failure in primary care outpatients and found that the largest additional quantitative diagnostic contribution was provided by measurement of NT-proBNP [5]. The utility of NPs in an urgent care setting found that BNP measurements added significant, independent explanatory power to other clinical variables in models predicting which patients had HF [10]. When evaluating patients presenting to urgent care or emergency rooms, BNP was found to be elevated in dyspneic patients with HF but not in dyspneic patients with a primary lung disorder thus making it an important way to distinguish between lung disease and HF [6, 11].

In patients with acutely decompensated HF, measurement of BNP or NT-proBNP (in addition to cardiac troponins) can help establish disease severity. Predischarge BNP and NT-proBNP values are stronger markers of post-discharge outcomes than either baseline or percent change in BNP during hospitalization[8].

While BNP and NT-proBNP are useful clinical tools in the diagnosis and identification of HF, biomarker guided therapy in the outpatient setting is more controversial and not advised per current HF guidelines [8]. Additionally, serial measurement of BNP or NT-proBNP to guide management in order to reduce HF hospitalization or mortality is not well established.

Guideline-directed therapy for HF including angiotensin-converting enzyme inhibitors (ACEi), beta-blockers, aldosterone antagonists, and cardiac resynchronization therapy (CRT) has been shown to favorably decrease NP levels after initiation and uptitration [12]. Concentrations of NPs decline in response to use of guidelines-recommended therapies for HF and rising levels portend poor patient outcomes which have led to the hypothesis that serial measurements of natriuretic peptides may be used to guide titration of chronic medical therapy in patients with HF [13]. Multiple studies have sought to test this hypothesis, with pivotal studies discussed below.

Trials data and key secondary analyses

RCTs

Early studies of natriuretic peptide guided therapy were mixed with respect to clinical outcome benefits (Table 1). The first of these studies to compare whether NP guided care was superior to usual care was performed by Troughton et al in 69 patients with heart failure with reduced ejection fraction (HFrEF) with primary endpoints being death, cardiovascular hospitalization, or worsening HF. During the follow-up period, there were fewer total CV events in the BNP group than in the usual care group (19 vs 54, p=0.002). At 6 months follow-up, 27% of patients in the BNP group and 53% in the clinical group had experienced their first cardiovascular (CV) event (p=0.034)[14].

Over the past two decades multiple studies have further investigated whether the use of NP guided therapy improves outcomes (Table 1). The primary outcome in the majority of these studies included HF mortality and HF admission. However, there was significant variability in design of these studies. As demonstrated in Table 1, there was lack of consistency on NP level goals and participant selection, and study size tended to be modest. The study by Berger et al and STARS-BNP, demonstrate the widely variable BNP and NT-proBNP goals, with levels varying from as low as 100pg/ml up to 2,200 pg/ml [15, 16]. Studies such as PRIMA, STARBRITE, SIGNAL-HF did not have a set NP goals, and instead based goal levels off of the patient's study admission or hospitalization discharge values[17–19]. Additionally, heterogeneity in participants has also caused issues. Both BATTLESCARRED and TIME-CHF had different BNP goals based on participant age and ended up recruiting older patients (average age 76 and 77 years, respectively) than other studies[20, 21]. BATTLESCARRED and PRIMA included patients with heart failure with preserved ejection fraction (EF≥45%) in addition to those with reduced ejection fraction[20, 19]. Troughton et al contained the smallest sample size of 69 participants while others recruited up to 499

patients[14, 21]. For the most part, these studies sought to examine the same overall strategy and end points—how do serial NP measurements and medication titration affect CV death or hospitalization? Overall, studies with results that favored biomarker therapy tended to have smaller sample sizes without consistent NP goals. The lack of definitive results due to varied NP goals, heterogeneity in inclusion criteria, and differing treatment strategies makes it difficult to truly garner the potential benefit of NP guided therapy [9].

Systematic Review

A Cochrane Review on BNP guided treatment for heart failure published in 2016 had similar overall conclusions as noted above[22]. This review included 3660 participants using NP-guided treatment with the evidence for all-cause mortality or heart failure showing "uncertainty". Notably heart failure admission was reduced, but evidence for all-cause admission showed uncertainty.

Recent RCTs and meta-analysis

Given this lack of definitive results in the aforementioned studies, a large prospective randomized control trial was designed to further investigate this question. GUIDE IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) was a randomized multicenter clinical trial conducted between 2013–2016 in the US and Canada which planned to randomize 1100 patients with HFrEF, elevated natriuretic peptide levels within the prior 30 days, and history of a prior HF event (HF hospitalization or equivalent) to either an NT-proBNP-guided strategy or usual care [13]. Those in the NT-proBNP strategy arm underwent HF therapy titrated with the goal of achieving a target NT-proBNP less than 1000pg/ml with primary end point being time-to-first HF hospitalization or cardiovascular mortality. GUIDE-IT enrolled 894 patients with chronic HFrEF and did not find NP-guided therapy to be more effective than the usual care group. The primary endpoint occurred in 164 patients (37%) in the biomarker guided group and 164 patients (37%) in the usual care group (adjusted hazard ratio [HR], 0.98; 95% CI, 0.79–1.22; $P = .88$). Cardiovascular mortality was 12% (n = 53) in the biomarker-guided group and 13% (n = 57) in the usual care group (HR, 0.94; 95% CI; 0.65–1.37; P = .75)[23]. None of the secondary end points nor the decreases in the NT-proBNP levels differed significantly between groups. The study was stopped early for futility per the data safety monitor board recommendations as there was no difference in primary or secondary end points.

A recent meta-analysis from Pufulete et al (which included GUIDE IT and additional international trials) showed that BNP guided therapy did not reduce all-cause or cardiovascular mortality[24]. Notably, BNP-guided therapy was found to reduce HF hospital admission. Additionally, subgroup analyses showed more benefit for NP guided therapy in patients <75 years old and in HFrEF.

Key secondary analyses

Secondary analyses of GUIDE-IT assessed treatment-related quality-of-life (QOL) and economic outcomes of the study[25]. QOL measures were collected for usual care and biomarker guided therapy groups using two multiple questionnaires [Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score and the Duke Activity

Status Index (DASI)], measured at 3, 6, 12, and 24 months post-randomization. Both of the questionnaires demonstrated improvement in QOL at 6 months but no evidence was found for a strategy-related difference (mean difference [biomarker-guided - usual care] at 24 months of follow-up 2.0 for DASI [95% confidence interval (CI): −1.3 to 5.3] and 1.1 for KCCQ [95% CI: −3.7 to 5.9]). Total costs averaged $5,919 higher in the biomarker-guided strategy (95% CI: - $1,795, +$13,602) over 15-month median follow-up. Based on these analyses, it was found that natriuretic guided therapy had high total costs and was not more effective than usual care in improved QOL outcomes for HF patients.

Guidelines

Current 2017 HF Guidelines regarding the use to NP have been updated to emphasize that admission NP levels are useful to establish prognosis in acute decompensated HF[1]. These guidelines along with updated recommendations are presented in Table 2.

Clinical Application

- BNP measures are useful in the diagnosis or exclusion of heart failure in patients who *present with dyspnea*.
- NP levels in chronic heart failure patients is a good way to establish *severity or disease prognosis*.
- *Admission levels of NP* can be useful is establishing the severity of a heart failure exacerbation.
- For patients with chronic HF, measuring NPs and troponins may be using in *risk stratifying patients*.

The two cases below demonstrate the application of these guidelines.

Case 1:

A 60 year old Caucasian female with HTN, COPD, and DM2 presents to a local Emergency Department complaining of new dyspnea. She is found to have a new oxygen requirement with crackles heard in bilateral lung bases and 2+ lower extremity edema on exam. A BNP is drawn which is found to be elevated >1000pg/ml.

In this case, checking a natriuretic peptide level would be a class I indication given his new dyspnea. His BNP is found to be elevated which suggests the diagnosis of new heart failure. As discussed above, studies have shown BNP elevation in HF patients but not found to be elevated in patients with a primary lung disorder. Thus, BNP becomes an important way to differentiate if the cause of dyspnea is related to HF versus lung pathology.

Case 2:

A 69 year old African American male with heart failure with reduced ejection fraction, CAD s/p CABG, HTN, and hyperlipidemia presents to a local Emergency Department complaining of dyspnea. He is found to have a new oxygen requirement with crackles heard in bilateral lung bases and 2+ lower extremity edema on exam. His weight is up 10lbs since

last being seen by his primary care physician one month ago. A BNP is drawn which is found to be elevated >1000mg/dL whereas his baseline has been 200–300pg/ml. He is admitted to the hospital and undergoes diuresis back to dry weight. Upon discharge, another BNP is drawn which is found to be 300pg/ml.

In this case, checking a natriuretic peptide level on admission is a class I indication as it is useful in establishing acutely decompensated heart failure. The elevated BNP from his prior baseline suggests that this presentation is consistent with an acute exacerbation. The BNP level drawn on discharge is a class II recommendation, as this can help suggest post discharge prognosis. He has returned to his dry weight with BNP found to be elevated above his baseline which may suggest worsening heart failure.

Future Directions

While GUIDE-IT sought to investigate the utility of BNP guided therapy in a large trial given the significant variability within earlier, smaller biomarker studies, it had several limitations. The care in GUIDE-IT was commonly performed by more specialized heart failure cardiologists and may be considered more intensive than routine practice. These specialists have more experience with this subset of complex patients. Both patient groups (biomarker guided and usual care) were followed at two week intervals after medications changes until the target of maximum tolerated doses was achieved. A discrepancy exists between how frequently patients were seen in the biomarker guided arm vs patients in the usual care arm, with the latter being seen on a month basis on average and the former being seen even more frequently.

Results from GUIDE IT suggest that aggressively managed, frequently seen patients may not necessarily benefit from incremental data from a biomarker-guided strategy to drive better care. The study design of GUIDE IT may be less generalizable to routine clinical care settings including primary care clinics. Future studies could be performed in a more real world settings compared to routine non-biomarker based care.

Unaccounted for in prior HF biomarker-guided therapy studies, recent investigations have suggested that there is a high degree of disease heterogeneity that exists within chronic HF patients even within those with reduced ejection fraction[26]. A cluster analysis was performed to explore clinical phenotypes in chronic HF patients using 1,619 participants in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study. Four clusters were identified (ranging from 248 to 773 patients in each), in which patients varied considerably among measures of age, sex, race, symptoms, comorbidities, HF etiology, socioeconomic status, quality of life, cardiopulmonary exercise testing parameters, and biomarker levels. Taking into account different HF phenotypes could also be another consideration in future biomarker studies as well as the consideration of a multi-marker approach.

Conclusion

Natriuretic peptides remain the gold standard biomarker for the diagnosis, prognosis, and risk assessment in HF. Multiple studies sought to utilize natriuretic peptides in attempts to

guide personalized GDMT. GUIDE IT, designed as the largest RCT designed to answer this question, showed that there was no difference between usual care and biomarker guided therapy.

However, the study design of GUIDE-IT was not “usual care” as commonly applied in clinical practice. Future studies could focus on testing biomarker therapy in different settings compared to more routine non-biomarker based clinical practice. Studies centering around phenotypes and multimarker approaches to HF prognosis suggest that further exploration is needed and biomarkers are one piece of the approach to optimize clinical outcomes in patients with heart failure.

Disclosures:

JKL reports no relevant disclosures. RJM receives research support from the National Institutes of Health (U01HL125511-01A1 and R01AG045551-01A1), Akros, Amgen, AstraZeneca, Bayer, GlaxoSmithKline, Gilead, InnoLife, Luitpold/American Regent, Medtronic, Merck, Novartis and Sanofi; honoraria from Abbott, Amgen, AstraZeneca, Bayer, Boston Scientific, Janssen, Luitpold Pharmaceuticals, Medtronic, Merck, Novartis, and Sanofi; and has served on an advisory board for Amgen, AstraZeneca, Luitpold, Merck, Novartis and Boehringer Ingelheim.

References

Recently published papers of particular interest have been highlighted as:

• Of importance

•• Of major importance

••1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., Colvin MM et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70(6):776–803. doi:10.1016/j.jacc.2017.04.025. [PubMed: 28461007] (Most recent update to heart failure guidelines)

2. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. J Am Coll Cardiol. 2018;72(4):351–66. doi:10.1016/j.jacc.2018.04.070. [PubMed: 30025570]

3. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM et al. Titration of Medical Therapy for Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol. 2019;73(19):2365–83. doi:10.1016/j.jacc.2019.02.015. [PubMed: 30844480]

4. Fonarow GC, Yancy CW, Albert NM, Curtis AB, Stough WG, Gheorghiade M et al. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Circ Heart Fail. 2008;1(2):98–106. doi:10.1161/circheartfailure.108.772228. [PubMed: 19808279]

5. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation. 2011;124(25):2865–73. doi:10.1161/circulationaha.111.019216. [PubMed: 22104551]

6. Davis M, Espiner E, Richards G, Billings J, Town I, Neill A et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet. 1994;343(8895):440–4. doi:10.1016/s0140-6736(94)92690-5. [PubMed: 7905953]

7. Moe GW. BNP in the diagnosis and risk stratification of heart failure. Heart Fail Monit. 2005;4(4):116–22. [PubMed: 16234898]

8. Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM et al. Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the

American Heart Association. Circulation. 2017;135(22):e1054–e91. doi:10.1161/cir.0000000000000490. [PubMed: 28446515]

9. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. Am Heart J. 2009;158(3):422–30. doi:10.1016/j.ahj.2009.06.018. [PubMed: 19699866]
10. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol. 2001;37(2):379–85. doi:10.1016/s0735-1097(00)01156-6. [PubMed: 11216950]
11. Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation. 2007;115(24):3103–10. doi:10.1161/circulationaha.106.666255. [PubMed: 17548729]
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004. doi:10.1056/NEJMoa1409077. [PubMed: 25176015]
••13. Felker GM, Ahmad T, Anstrom KJ, Adams KF, Cooper LS, Ezekowitz JA et al. Rationale and design of the GUIDE-IT study: Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure. JACC Heart failure. 2014;2(5):457–65. doi:10.1016/j.jchf.2014.05.007. [PubMed: 25194287] (Design of GUIDE IT: largest RCT investigating BNP guided therapy)
•14. 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(9210):1126–30. [PubMed: 10791374] (Initial trial exploring biomarket guided therapy)
15. Berger R, Moertl D, Peter S, Ahmadi R, Huelsmann M, Yamuti S et al. N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure a 3-arm, prospective, randomized pilot study. J Am Coll Cardiol. 2010;55(7):645–53. doi:10.1016/j.jacc.2009.08.078. [PubMed: 20170790]
16. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol. 2007;49(16):1733–9. doi:10.1016/j.jacc.2006.10.081. [PubMed: 17448376]
17. Shah MR, Califf RM, Nohria A, Bhapkar M, Bowers M, Mancini DM et al. The STARBRITE trial: a randomized, pilot study of B-type natriuretic peptide-guided therapy in patients with advanced heart failure. J Card Fail. 2011;17(8):613–21. doi:10.1016/j.cardfail.2011.04.012. [PubMed: 21807321]
18. Persson H, Erntell H, Eriksson B, Johansson G, Swedberg K, Dahlstrom U. Improved pharmacological therapy of chronic heart failure in primary care: a randomized Study of NT-proBNP Guided Management of Heart Failure--SIGNAL-HF (Swedish Intervention study--Guidelines and NT-proBNP AnaLysis in Heart Failure). Eur J Heart Fail. 2010;12(12):1300–8. doi:10.1093/eurjhf/hfq169. [PubMed: 20876734]
19. Eurlings LW, van Pol PE, Kok WE, van Wijk S, Lodewijks-van der Bolt C, Balk AH et al. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study. J Am Coll Cardiol. 2010;56(25):2090–100. doi:10.1016/j.jacc.2010.07.030. [PubMed: 21144969]
20. Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. J Am Coll Cardiol. 2009;55(1):53–60. doi:10.1016/j.jacc.2009.02.095. [PubMed: 20117364]
21. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA. 2009;301(4):383–92. doi:10.1001/jama.2009.2. [PubMed: 19176440]

22. McLellan J, Heneghan CJ, Perera R, Clements AM, Glasziou PP, Kearley KE et al. B-type natriuretic peptide-guided treatment for heart failure. Cochrane Database Syst Rev. 2016;12:Cd008966. doi:10.1002/14651858.CD008966.pub2. [PubMed: 28102899]

••23. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N et al. Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA. 2017;318(8):713–20. doi:10.1001/jama.2017.10565. [PubMed: 28829876] (GUIDE IT results: largest RCT investigating BNP guided therapy)

24. Pufulete M, Maishman R, Dabner L, Higgins JPT, Rogers CA, Dayer M et al. B-type natriuretic peptide-guided therapy for heart failure (HF): a systematic review and meta-analysis of individual participant data (IPD) and aggregate data. Systematic reviews. 2018;7(1):112. doi:10.1186/s13643-018-0776-8. [PubMed: 30064502]

•25. Mark DB, Cowper PA, Anstrom KJ, Sheng S, Daniels MR, Knight JD et al. Economic and Quality-of-Life Outcomes of Natriuretic Peptide-Guided Therapy for Heart Failure. J Am Coll Cardiol. 2018;72(21):2551–62. doi:10.1016/j.jacc.2018.08.2184. [PubMed: 30466512] (Key secondary analysis exploring economic and quality of life outcomes in BNP guided therapy)

26. Ahmad T, Pencina MJ, Schulte PJ, O'Brien E, Whellan DJ, Pina IL et al. Clinical implications of chronic heart failure phenotypes defined by cluster analysis. J Am Coll Cardiol. 2014;64(17):1765–74. doi:10.1016/j.jacc.2014.07.979. [PubMed: 25443696]

27. Januzzi JL Jr. The role of natriuretic peptide testing in guiding chronic heart failure management: review of available data and recommendations for use. Arch Cardiovasc Dis. 2012;105(1):40–50. doi:10.1016/j.acvd.2011.10.007. [PubMed: 22369917]

28. Karlstrom P, Johansson P, Dahlstrom U, Boman K, Alehagen U. Can BNP-guided therapy improve health-related quality of life, and do responders to BNP-guided heart failure treatment have improved health-related quality of life? Results from the UPSTEP study. BMC Cardiovasc Disord. 2016;16:39. doi:10.1186/s12872-016-0221-7. [PubMed: 26905220]

29. Schou M, Gustafsson F, Videbaek L, Andersen H, Toft J, Nyvad O et al. Adding serial N-terminal pro brain natriuretic peptide measurements to optimal clinical management in outpatients with systolic heart failure: a multicentre randomized clinical trial (NorthStar monitoring study). Eur J Heart Fail. 2013;15(7):818–27. doi:10.1093/eurjhf/hft037. [PubMed: 23507787]

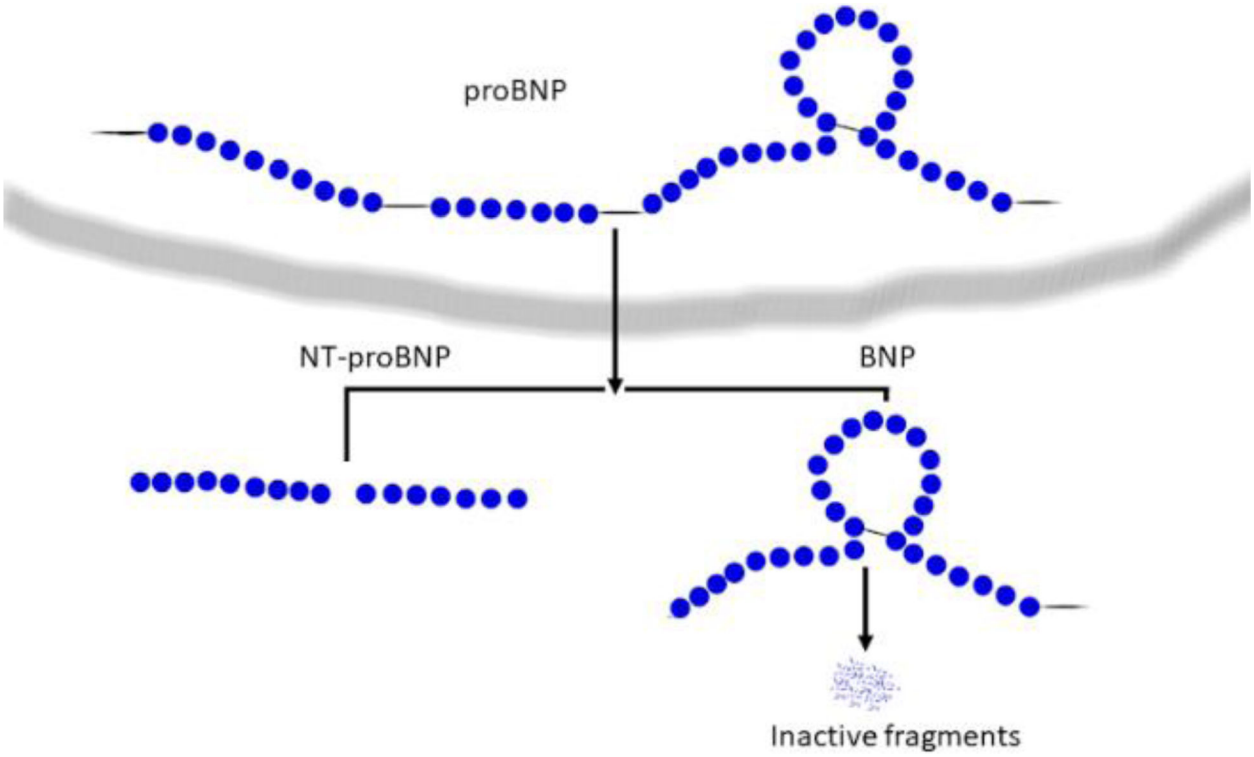

Figure 1.
Cleavage of proBNP to NT-proBNP and BNP

Table 1.

Summary of RCTs of Biomarker-Guided Therapy in HF.

Study (ref.#)	GUIDE-IT [13••, 14••]	Troughton et al. [15•]	BATTLESCARRED [16]	Berger et al. [17]	UPSTEP [18]	Northstar [19]	STARS-BNP [20]
Years	2013–2016		2001–2006	2003–2004	2006–2009	2005–2009	
Sample size	894	69	364	278	279	407	220
Marker	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP	BNP	NT-proBNP	BNP
Target	1000 pg/ml	1692 pg/ml	1270 pg/ml	2200 pg/ml	< 75 years BNP < 150, > 75 years < 300		100 pg/ml
Length of follow-up (months)	15	9.6	12	12	12	30	15
HF-preserved EF included	No	No	Yes	No	No	No	No
Primary endpoint	CV death or hospitalization for HF	Death + CV hospitalization or worsening HF	All-cause mortality	Days alive and out of hospital	Death, hospitalization, worsening HF	Death + CV hospitalization	Death + hospitalization for HF + time to endpoint
Favors biomarker-guided therapy	No	Yes	No	Yes	No	No	Yes

Study (ref.#)	PROTECT [21]	STARBRITE [22]	TIME-CHF [23]	PRIMA [12]	SIGNAL-HF [11]
Years	2006–2009	2003–2005	2003–2006	2004–2007	2006–2009
Sample size	151	137	499	345	252
Marker	NT-proBNP	BNP	NT-proBNP	NT-proBNP	NT-proBNP
Target	1000 pg/ml	1/2 × discharge level	400 pg/ml if < 75 years. of age, 800 pg/ml if > 75 years. of age	Discharge level	50% decrease from entry
Length of follow-up (months)	10	3	18	12	9
HF-preserved EF included	No	No	No	Yes	No
Primary endpoint	Total CV events	Days alive and out of hospital	All-cause death or hospital	Days alive and out of hospital	Days alive and out of hospital
Favors biomarker-guided therapy	Yes	No	No	No	No

Table 2.

ACC 2017 BNP Guidelines

	COR, LOE	Recommendation	Updates from 2017
Recommendation for Prevention of HF	IIa, B-R	**For patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF**	**NEW:** New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF.
Recommendation for Diagnosis	I,A	**In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF**	**MODIFIED:** 2013 acute and chronic recommendations have been combined into a diagnosis section.
Recommendation for prognosis	I, A	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF	
	I,A	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF	MODIFIED: Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful
	IIa, B-NR	**During a HF hospitalization, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis**	**NEW:** Current recommendation reflects new observational studies.
	IIb, B-NR	**In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification**	**MODIFIED:** 2013 recommendations have been combined into prognosis section, resulting in LOE change from A to B-NR.