Review Article

Treatment of Heart Failure Based on Natriuretic Peptide Levels: A Question That Has Yet to be Solved?

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Heart failure (HF) is one of the leading causes of death, hospitalization, and rehospitalization worldwide. In spite of advances in treatment with new medications, devices, and heart transplantation, the condition is still associated with significant morbidity and mortality.[1] One factor that likely contributes to this fact is the difficulty in titrating doses of drugs targeted at treating HF.[2]

Many professionals who deal with this disease have difficulties in recognizing early stages of deterioration and are reluctant to increase medications due to concerns regarding possible side effects, such as hypotension or renal failure.[3] There is also an endless search for a more objective parameter that can guide titration of medications.

In recent years, especially after the revolution set in motion by the neurohumoral theory of HF, biomarkers such as natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) have been used as more objective measures to diagnose and define prognosis of patients with HF.[3]

BNP is a neurohormone predominantly secreted by the cardiac ventricle in response to pressure[4] and/or volume overload.[5] The precursor of BNP is proBNP, a biologically inactive prohormone of 108 amino acids, stored in secretory granules in the myocytes. ProBNP is cleaved by protease into BNP, which is a physiologically active peptide of 32 amino acids, and NT-proBNP, which is a biologically inert peptide of 76 amino acids. Compared with BNP, NT-proBNP has a longer peptide sequence (76 versus 32 amino acids) and a longer half-life (60 to 120 minutes versus 15 to 20 minutes) (Figure 1).[6] BNP and NT-proBNP are biomarkers used for diagnosis, prognosis, risk stratification, and management of patients with HF.[7] BNP is not only a gold standard biomarker in HF; it also plays a key role in maintaining circulatory homeostasis, and, as its name indicates, it has natriuretic properties.[7]

Keywords

Heart Failure; Natriuretic Peptides; Natriuretic Peptide, Brain

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Multiple randomized clinical trials[3,9-15] have evaluated whether serial use of BNP could be useful to guide titration of medical therapy for HF, improving clinical outcomes in comparison to therapy guided only by symptoms. The trials were designed in a rather heterogeneous manner, and the results, especially those related to reduction of hospitalization and mortality, are controversial, depending on the BNP reduction strategy and the study population.

We emphasize that, in relation to use of BNP/NT-proBNP for diagnosis or prognostic definition of HF, there is no doubt as to their usefulness; in the most current guidelines and even in the recently published Universal Definition of Heart Failure, natriuretic peptides have been included as part of the diagnostic flowchart for HF, regardless of presentation phenotype (Figure 2).[16-18]

The following brief review attempts to summarize information about studies that have attempted to guide medical treatment of HF based on natriuretic peptide levels, as well as the clinical results presented to date.

Trials in chronic HF

Several studies have addressed the hypothesis that therapy guided by BNP or NT-proBNP would improve clinical outcomes in chronic HF.[1-12] Even though some of these studies demonstrated a reduction in clinical events, none of them, taken alone, was adequately powered to test the effect of this strategy on all-cause mortality.

One of the first published studies addressing this issue, published in 2000, was promising, suggesting a benefit in terms of mortality and hospitalization due to HF. Troughton et al.[19] demonstrated a reduction in total cardiovascular events (death, hospital admission, or decompensation of HF) (19 versus 54, p = 0.02), but their study had a small number of patients (69 patients) and a short-term follow-up.

Larger randomized trials were published later, including the 2009 TIME-CHF,[20] a multicenter study of patients over 60 years of age, with a number of patients about 7 times greater than the study by Troughton et al.[19] (499 patients). This trial showed no difference in BNP-guided versus symptom-guided therapy in relation to all-cause hospitalization-free survival (41% versus 40%, hazard ratio [HR] 0.91 [95% CI: 0.72 to 1.14]; p = 0.39) or quality of life of the patients included. There was only a reduction in all-cause hospitalization-free survival in the subgroup analysis of patients between 60 the ages of and 74 years and in hospitalization for HF (secondary outcome).

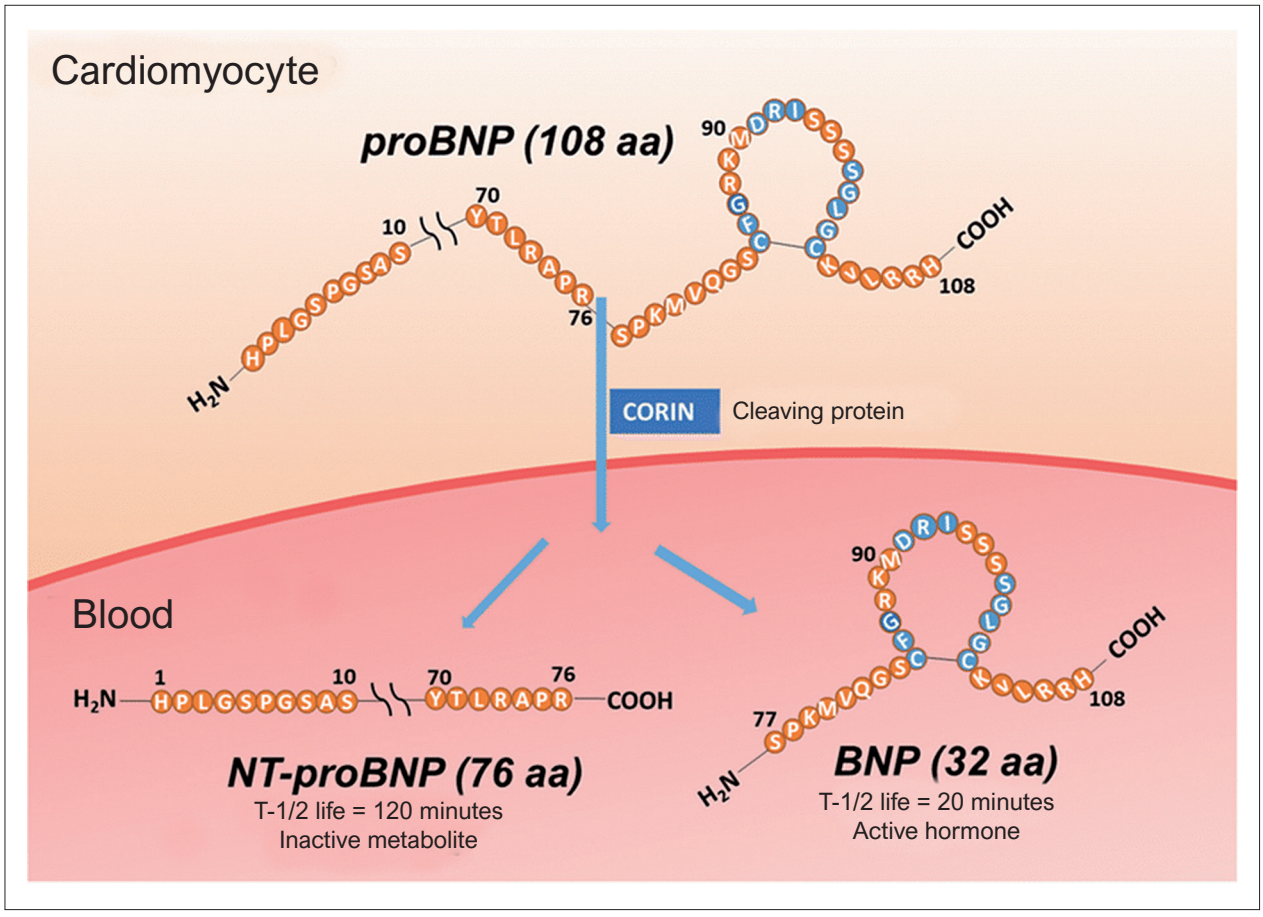

Figure 1 – *NT-proBNP and BNP synthesis pathways from proBNP. Adapted from Kim et al.[8]*

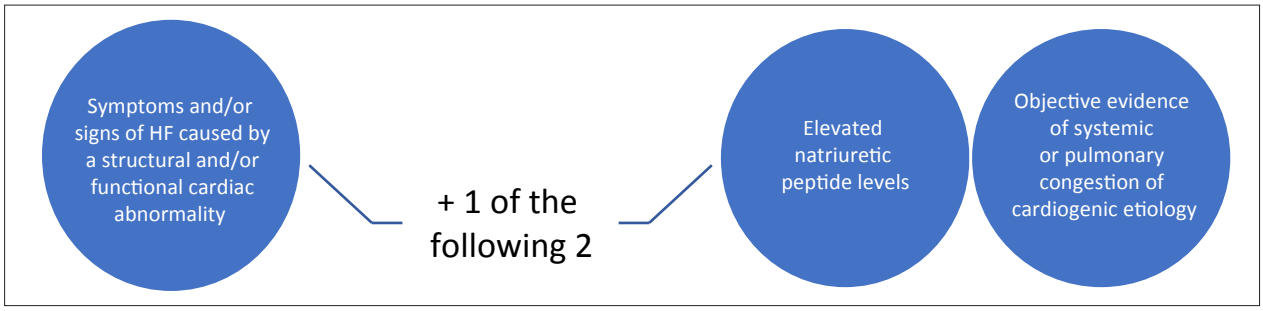

Figure 2 – *Universal definition of heart failure, 2021. Adapted from Bozkurt et al.[17]*

In 2013, Schou et al.[21] published another randomized clinical trial, with a total of 407 outpatients with HF, who were allocated to clinical management or clinical management and NT-proBNP monitoring, with 2.5 years of follow-up. In the event that NT-proBNP increased by more than 30%, a clinical checklist was performed, and treatment was modified. Patients had average age of 73 years and ejection fraction of 30%, and 85% of them were in NYHA functional class I or II. NT-proBNP monitoring did not improve the primary composite outcome (death or cardiovascular hospital admission) (HR 0.96, 95% CI: 0.71 to 1.29, p = 0.766), and it did not lead to a significant change in the pharmacological strategy.

A meta-analysis published in 2014 by Troughton et al.[15] compiled the majority of articles on the topic (11 randomized clinical trials), published between 2000 and 2012, and its primary outcome was analysis of all-cause mortality. In this meta-analysis, a reduction was observed in the primary outcome in the group whose treatment was guided by natriuretic peptide levels (HR 0.62 [0.45 – 0.86]; p = 0.004), but a survival benefit was only observed in younger patients (up to 75 years) (HR 0.62 [0.45 – 0.85]; p = 0.004)

and not in older patients (≥ 75 years) (0.98 [0.75 – 1.27]; p = 0.96). Secondary outcomes, such as hospitalization due to HF (0.80 [0.67 – 0.94]; p = 0.009) or cardiovascular disease (0.82 [0.67 – 0.99]; p = 0.048) were significantly lower in BNP-guided patients.

In contrast, the Cochrane database, in 2016, also published a systematic review with meta-analysis[7] on the topic, including 18 randomized controlled trials with 3660 participants (mean age range: 57 to 80 years). However, unlike the meta-analysis cited above, this one did not demonstrate any evidence for a decrease in all-cause mortality (HR 0.87, 95% CI: 0.76 to 1.01; patients = 3169; studies = 15), even when examining subgroups under or over 75 years of age, or for mortality due to HF (HR 0.84, 95% CI: 0.54 to 1.30; patients = 853; studies = 6) using natriuretic peptide-guided treatment. There was only a reduction in HF admission in the BNP-guided treatment group (38% versus 26%, HR 0.70, 95% CI: 0.61 to 0.80; patients = 1928; studies = 10), but there was no evidence for reduced all-cause hospital admission (57% versus 53%, HR 0.93, 95% CI: 0.84 to 1.03; patients = 1142; studies = 6).

In addition to those mentioned, at least 11 reviews were performed on the effects of treatment guided by natriuretic peptides: three narrative reviews (De Vecchis et al.,[22] DeBeradinis et al.,[23] Richards et al.[24]), one systematic review without meta-analysis (Balion et al.[25]) and 6 reviews that included meta-analyses (Felker et al.,[9] Porapakkham et al.,[10] Savarese et al.,[11] Li et al.,[12] De Vecchis et al.,[14] Li et al.,[26] Xin et al.[13]). Of these meta-analyses, 4 reported that peptide-guided therapy reduced all-cause mortality in patients with HF, and the other 2 reported no effects on all-cause mortality. All-cause hospital admission was analyzed in 2 of the reviews, and no effects were reported. Four reviews reported a decrease in HF admissions favoring natriuretic peptide-guided treatment. Moreover, 2 reviews examined adverse events and reported no significant difference between groups.

The meta-analysis by De Vecchis[14] cited above included 6 randomized controlled trials (n = 1775 patients), comparing BNP-guided therapy versus symptom-guided therapy in outpatients with chronic HF. This review reported that guided therapy decreased a composite outcome of mortality and HF hospitalizations during the follow-up period (odds ratio [OR] 0.64; 95% CI: 0.43 to 0.95; p = 0.028); however, when analyzing all-cause mortality alone, without including it in a composite outcome, there was no significant difference.

In the review with meta-analysis by Li et al.[12] also cited above, which included 11 randomized clinical trials (2414 patients), there was a lower risk of all-cause mortality (HR 0.83; 95% CI: 0.69 to 0.99; p = 0.035) and readmission due to HF (HR 0.75; 95% CI: 0.62 to 0.91; p = 0.004) in the BNP-guided therapy group. In subgroup analysis, readmissions due to HF were found to be lower, mainly in patients under 70 years of age (HR 0.45; 95% CI: 0.33 to 0.61; p = 0.000) or patients with higher baseline BNP (≥ 2114 pg/mL) (HR 0.53; 95% CI: 0.39 to 0.72). Moreover, in 2014, Li et al.[26] concluded sensitivity analyses and showed that the reduction in all-cause mortality and admission due to HF was observed especially in patients with reduced ejection fraction.

In 2017, the largest randomized and multicenter clinical trial to date was published, the GUIDE-IT,[27] which explored the same strategy as the previous ones but showed no difference between the groups in the primary outcome (time to first HF hospitalization or cardiovascular mortality) (32% versus 37%; HR 0.98; 95% CI: 0.79 to 1.22; p = 0.88), and the study was stopped early for futility, when 894 of 1100 patients were enrolled with a mean follow-up of 15 months. There was also no difference in the analysis of secondary outcomes (all-cause mortality, total HF hospitalizations, the individual components of the primary outcome, and adverse events) or NT-proBNP levels.

Finally, another meta-analysis, published by Pufulete et al.[3] in 2018, with 14 randomized clinical trials, studied the topic and found no significant difference in all-cause mortality (13 studies; HR 0.87, 95% CI: 0.75 to 1.01) or cardiovascular mortality (5 studies; OR 0.88, 95% CI: 0.67 to 1.16). For all-cause mortality, there was a significant interaction in the peptide-guided therapy group only when subgroups were evaluated. When analyzing the treatment strategy by age, there was a difference in the group under 75 years of age (p = 0.034, 11 studies, HR 0.70, 95% CI: 0.53 to 0.92 for patients < 75 years; and HR 1.07, 95% CI: 0.84 to 1.37, for patients ≥ 75 years), and when the groups were analyzed by ejection fraction, the group with HF with reduced ejection fraction had a significant result (p = 0.026, 11 studies, HR 0.84, 95% CI: 0.71 to 0.99 for patients with HF with reduced ejection fraction; and HR 1.33, 95% CI: 0.83 to 2.11 for patients with HF with preserved ejection fraction). When evaluating adverse events, there was evidence that they were significantly more frequent with BNP-guided therapy versus symptom-guided therapy, mainly at the expense of renal failure and hypotension (5 studies; OR 1.29; 95% CI: 1.04 to 1.60).

Trials in acute or acute decompensated heart failure

Seeing the importance of natriuretic peptides for diagnosis and prognosis in patients with acute HF, it was expected that other studies would attempt to establish treatment strategies guided by natriuretic peptides.[28-30] Carubelli et al. evaluated the strategy of using NT-proBNP (> 3000 ng/L before discharge) in 280 patients in order to intensify drug therapy for acute HF.[31] One of the groups had intensified drug therapy, mainly based on increased dose of diuretics (without a pre-specified NT-proBNP target), versus another group of patients who were discharged without any adjustments in therapy. The study was unable to demonstrate a difference in the results, and, when compared with only clinical evaluation, there was no evidence of improved prognosis.[31]

Within this same context, Stienen et al.[32] conducted a prospective randomized controlled study with the intention of evaluating the impact of hospital treatment following the pre-defined NT-proBNP reduction guideline (> 30% reduction from admission to discharge) versus conventional treatment.[31] The study population had NT-proBNP levels > 1700 ng/L. The primary composite outcome comprised all-cause mortality, HF readmissions within 180 days, and

death within 180 days of discharge. Secondary endpoints comprised all-cause mortality at 180 days, HF readmissions at 180 days, and a composite of all-cause mortality and HF readmissions at 90 days.

This study's Kaplan-Meier curve (Figure 3) demonstrates that all-cause mortality or HF readmission at 180 days after randomization occurred in 72 patients (36%) in the NT-proBNP-guided group and in 73 patients (36%) in the conventional therapy group (HR for NT-proBNP-guided therapy 0.96; 95% CI: 0.72 to 1.37; p = 0.99). In relation to secondary outcomes, there was also no statistical significance between the groups, in this context, demonstrating that guided therapy did not improve prognosis. It is worth highlighting that patients with NT-proBNP reduction of 30% had more cardiovascular events than patients in the control group, where treatment was not guided by the NT-proBNP value.[32]

In relation to adequate control of congestion in acute HF, several studies have demonstrated the relationship between residual congestion and increased morbidity and mortality.[33] O'Neill et al.[34] evaluated the correlation between hemodynamic measurements (through pulmonary artery catheter) and BNP levels in patients with severe acute HF, in measurements upon admission, with 12 and 36 hours of follow-up.[34] Serum BNP concentrations were not able to predict hemodynamic changes in these patients.

In contrast, retrospective analysis of the DOSE-AHF study, which involved hospitalized patients with diagnosis of acute HF, evaluated the relationship between 3 markers of decongestion in 72 hours: weight loss, fluid loss, and percentage reduction in serum NT-proBNP levels, in addition to symptomatic clinical improvement of dyspnea.[35] They also determined the relationship between each marker of decongestion and clinical outcomes at 60 days, such as death, first rehospitalization, and emergency department visit. The mean age of the patients was 66 years; mean ejection fraction was 35%, and 27% of the participants had ejection fraction ≥ 50%. Of the 3 measures of congestion improvement assessed, only reduced NT-proBNP was associated with dyspnea relief (r = 0.13; p = 0.04). However, reductions in the 3 measures were associated with improvement in time to death, first rehospitalization, and emergency department visit at 60 days (4 lbs of weight loss [HR 0.91; 95% CI: 0.85 to 0.97], 1000 mL of fluid loss [HR 0.94; 95% CI: 0.90 to 0.99], and 10% reduction in NT-proBNP [HR 0.95; 95% CI: 0.91 to 0.99]).[35]

Conclusions

Summarizing the data presented herein, the authors' impression is that this is a question that can be answered in several ways. The highly controversial data regarding HF therapy guided by natriuretic peptide levels in patients with chronic HF allow us to speculate that there is some applicability for their use in clinical practice, perhaps not routinely, but in a more specific niche of patients (bedridden patients, for example, where clinical assessment may be more impaired) and perhaps not taken alone, but in association with other markers of congestion, such as weight loss, urinary output, or even some that have been less tested, such as pulmonary ultrasound or bioimpedance. Trials in acute HF are already more uniform in not recommending this strategy for these patients. In conclusion, our impression is that the HF treatment strategy guided by BNP/NT-proBNP levels should not be used as a single strategy to guide HF treatment, based on the data that are currently available, but we cannot assert that this is a question that has already been solved, and new evidence may lead us to reevaluate our impression.

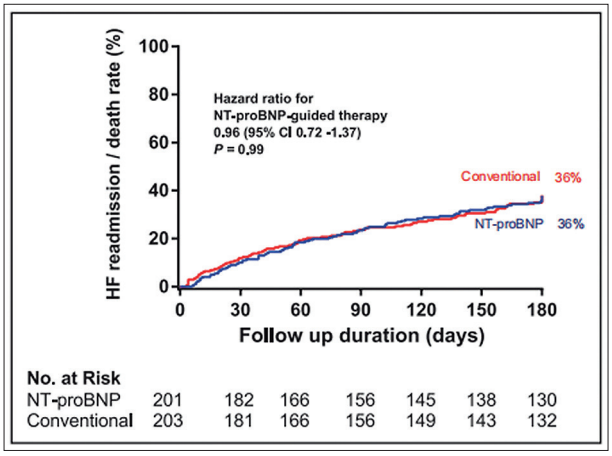

Figure 3 – *Kaplan-Meier cumulative survival curve for the study group.*

Author Contributions

Conception and design of the research: Montenegro CEL, Dias LA; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Montenegro CEL, Gomes TQM, Lyra ACAS, Nascimento JS, Dias LA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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