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Can natriuretic peptides be used to guide therapy?

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ABSTRACT

Over the last 15 years, the hypothesis that intensified treatment directed at reducing natriuretic peptide (NP) concentrations may improve the outcomes of patients with heart failure (HF) has been scrutinized in several prospective clinical trials, with conflicting results. Collectively, however, the data suggest that NP concentrations may be useful in guiding HF management and improving HF-related morbidity and mortality. In this review, we summarize the existing data investigating the use of NPs as targets for outpatient HF therapy. We focus on the information gathered in randomized clinical trials and comprehensive meta-analyses, and also on the recommendations of international guidelines (primarily guidelines from the European Society of Cardiology and the American College of Cardiology/American Heart Association). Although the results for this approach are promising overall, additional well-designed prospective randomized controlled trials (e.g., the GUIDE-IT trial) are necessary to confirm or refute the utility of NP-guided outpatient HF management.

CAN NATRIURETIC PEPTIDES VALUES BE USED TO GUIDE HEART FAILURE THERAPY?

Clinicians have been asking this question for 15 years now, and the answer is still unclear. Richard Troughton and Mark Richards published a seminal paper in *The Lancet* in 2000, in which they launched the hypothesis of guiding heart failure (HF) treatment with objective measurement of natriuretic peptides (NPs). This prospective pilot study was conducted in Christchurch, New Zealand and included 69 patients with a history of decompensated HF and systolic dysfunction. The participants were randomized to management by a standardized clinical algorithm or to clinical management with NP-guided drug uptitration (1). The goal in the NP-guided arm was to drive plasma concentrations of NTproBNP to <200 pmol/L (approximately 1700 pg/mL). During 9 months of follow-up, patients who received NP-guided treatment had significantly fewer deaths or hospitalizations for HF. This study recruited relatively young patients with reduced left ventricular ejection fraction (LVEF); however, due to patient enrollment in the late 1990s, very few of the patients were on beta blockers or mineralocorticoid receptor antagonists (MRAs). This initial study has provided the nucleus for a multitude of prospective studies launched in the forthcoming years. Nevertheless, as of 2015, the results from the clinical trials published to date are in most cases conflicting, in part due to disparities in their design. Thus, the multiple meta-analyses that have been performed to clarify the situation have been less definitive.

WHAT DO THE CLINICAL TRIALS SAY?

Because NPs are reflective of hemodynamic state and disease severity in HF, their role in therapeutic guidance has been investigated in several clinical trials. Three potential strategies for using cardiac peptides in the management of HF patients may be considered.

The first approach consists of targeting pharmacologic therapy to prespecified NP concentrations to optimize the effects of drugs. This approach has received much interest and has been tested in several prospective randomized trials that yielded conflicting results. Some studies demonstrated mortality or morbidity benefits from NP-guided therapy: Troughton, STARS-BNP, Berger, PROTECT (1,3-5); others reported benefits only in younger patients: TIME-CHF, BATTLESCARRED (6,7); or only in responder patients: UPSTEP (8); and other studies showed no advantages for NP-guided compared to clinically guided therapy: Beck-da-Silva, SIGNAL-HF, PRIMA, Anguita, STARBRITE (9-13).

The second strategy, reported in the recent NorthStar trial (2), assessed whether high-risk but stable chronic HF patients, identified as those with NTproBNP levels >1000 pg/mL, would benefit from prolonged specialized HF clinical assistance (pre-PARADIGM clinical treatment) compared to referral back to general practitioners. The results demonstrated no differences in the composite score for mortality and hospitalization for cardiac causes, suggesting that baseline NP had limited value in the selection of out-of-hospital management strategy in HF patients.

The problems with these trials are multiple but in many ways understandable as clinicians struggle to find the right metrics to use to guide therapy. Although some trials have had targets for titration of the natriuretic peptides, in many instances, these goals have not been achieved in a majority of the patients. If only 30% of the cohort reaches the goal suggested, one might ask “has the hypothesis really been tested?” In addition, should the goals of therapy be a fixed level of natriuretic peptide regardless of the starting point or should it be some percentage change in the baseline value or is there a need

for both types of criteria. This is of particular importance because of the marked biological variation of natriuretic peptides (14). In some studies, very large changes are necessary to be sure that the changes observed are due to treatment and not conjoint biological and clinical variability (15). Finally, the types of patients included may make a huge difference. Those with heart failure with preserved ejection fractions (HFPEF) tend to have different natriuretic peptide levels than those with heart failure with reduced ejection fractions (HFREF). Those with valvular heart disease may or may not be similar to either of those groups.

A third strategy may emerge with availability of LCZ696 in the market (post-PARADIGM clinical treatment). Although the mechanisms involved are complex, it appears that BNP levels are increased by LCZ696. On the other hand, NTproBNP values are reduced although we do not know if they are reduced commensurate with the levels that would be necessary to make outcomes with agents that do not include Neprilysin inhibition. Thus, it could be that NTproBNP will become the preferred peptide biomarker for therapy guidance (16).

In addition, given its markedly improved efficacy, it may be that natriuretic peptides elevations will help to identify those who may benefit from Neprilysin inhibition. An analogy between acute coronary syndrome (ACS) and chronic HF relative to the use of biomarkers and their impact on therapy is clear. In ACS, the presence of chest pain, ST segment ups and downs in the ECG and cardiac troponin rise and fall is indicative of a high-risk patient that requires urgent-preferred catheterization to open the culprit artery in order to relief symptoms and improve prognosis. In chronic HF, the presence of dyspnea, a reduced ejection fraction in the echocardiogram and a very high level of circulating natriuretic peptides may identify a high-risk patient who is a candidate to switch to LCZ696 in order to improve symptoms, reduce mortality (both sudden and pump failure death), and reduce HF-hospitalizations (Figure 1). This is not strictly NP guided therapy, as it was firstly hypothesized by Troughton and Richards, but rather using NPs to prescribe a new treatment option which has shown a dramatic beneficial effect compared with conventional treatment. This new strategy is supported by the data from the PARADIGM Trial, the first trial in incorporating an objective measure of severity using NPs into the inclusion criteria (17).

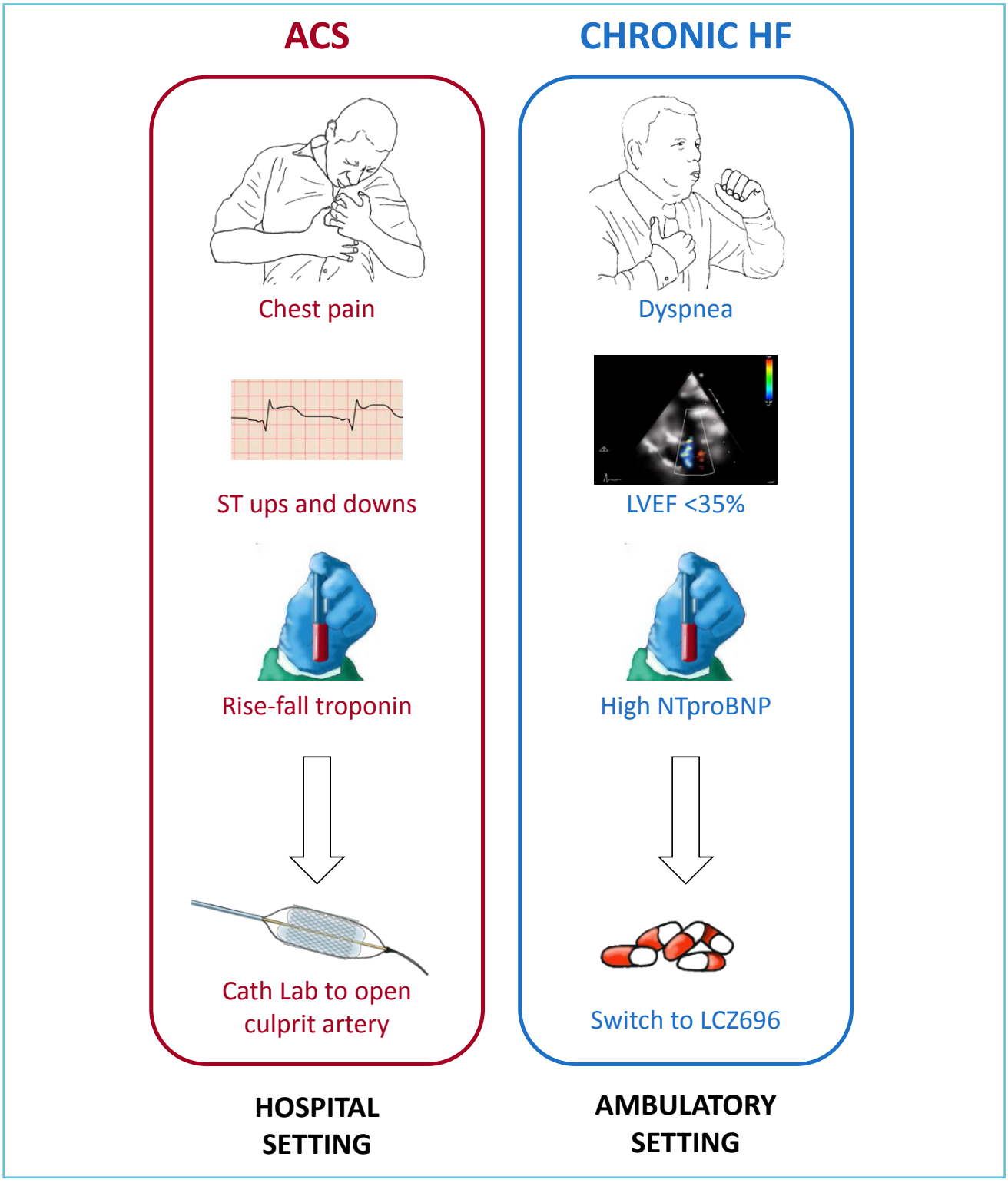
WHAT DO THE META-ANALYSES SAY?

To overcome the uncertainty produced by the conflicting results of single studies of the first strategy described above, three meta-analyses investigated the utility of NP-guided therapy in patients with chronic HF (18-20). These meta-analyses comprised data from six, eight, or 12 randomized clinical trials.

In the meta-analysis by Felker et al. (18), only six studies were collected, which reported on 1,627 patients. Although a significant benefit for all-cause mortality in patients assigned to NP-guided therapy was reported, the analysis was limited by the inclusion of three still unpublished studies, which prevented detailed collection of patient population characteristics.

The meta-analysis by Porapakkham et al. (19) included 1,726 patients in eight studies. In this analysis, the favorable effect on all-cause mortality in patients assigned to NP-guided therapy was mostly driven by the TIME-CHF trial (6) in the sensitivity analysis section of the meta-analysis. The statistical significance of the effect was lost when the TIME-CHF trial, but not any other trial included in the meta-analysis, was removed from the analysis. Notably, no difference was observed for all-cause or HF-related hospitalization.

Figure 1 **Scheme of the analogy between ACS and chronic HF (with the advent of LCZ696), and the value of biomarkers to guide decisions***

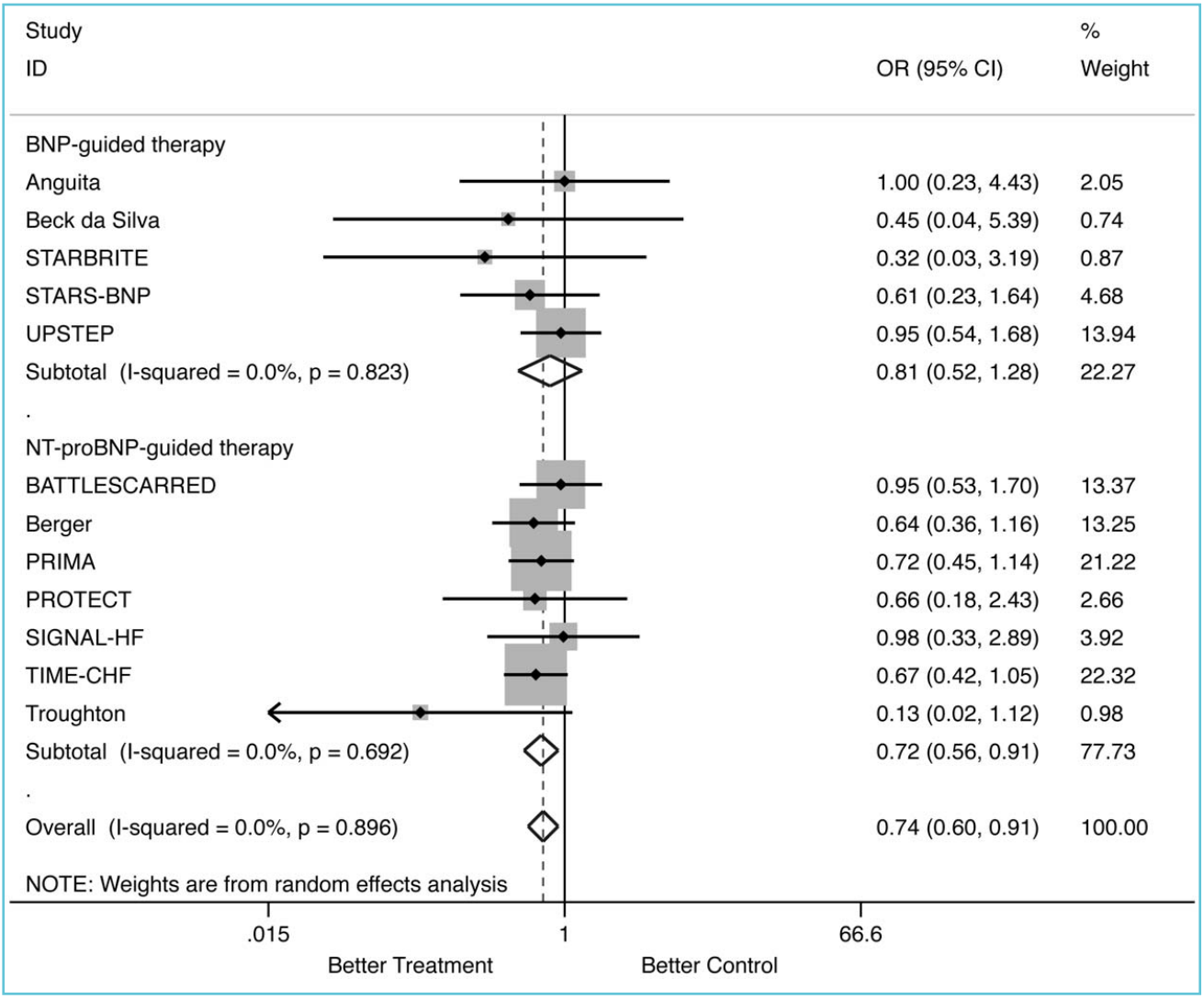


** Created by Carolina Gálvez-Montón*

The most recent and largest meta-analysis by Savarese et al. (20) included 2,686 patients included in 12 studies (Figures 2,3). This meta-analysis for the first time reports a benefit for HF-related hospitalization; moreover, the mortality benefit observed was more consistent and not influenced in the sensitivity analysis by any single study or by any potential confounders. This meta-analysis was the only one to investigate separately the effects of BNP- and NTproBNP-guided therapy, suggesting that NTproBNP- but not BNP-guided therapy was significantly associated with improved survival as well reduced hospitalization. A word of caution is necessary here, since no single trial has been designed specifically to compare head-to-head BNP- vs. NTproBNP-guided therapy.

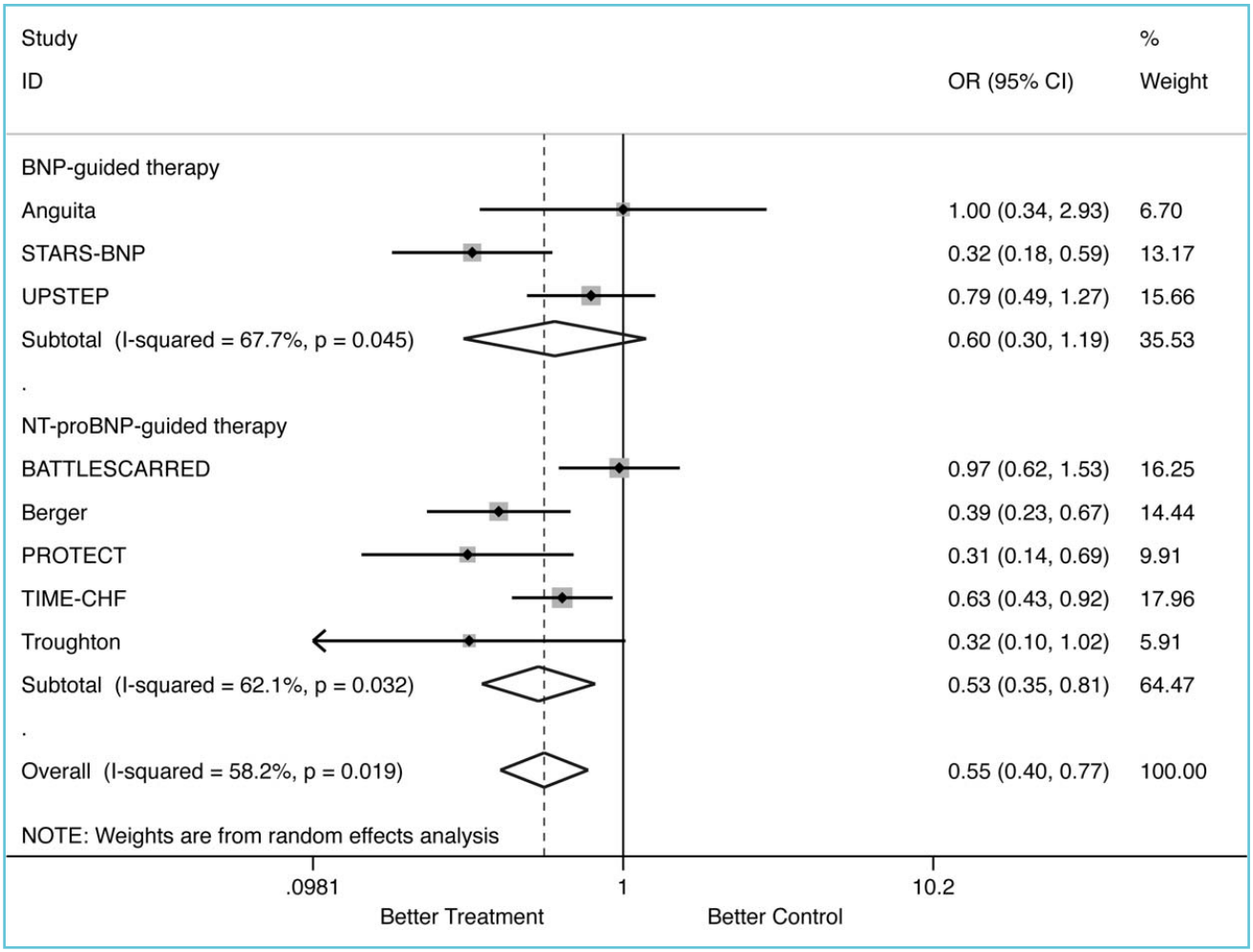
Meta-analysis data did not find a significant benefit for elderly patients when, elderly subgroups from three trials were analyzed: TIME-CHF, BATTLESCARRED, and UPSTEP Trials (6-8). It is conceivable that the more frequent presence of comorbidities may prevent or even promote potentially harmful up titration of HF drugs in elderly patients; however, this speculation requires further confirmation.

Figure 2 **Odds ratios of all-cause mortality***



** Taken from (20).*

Figure 3 Odds ratios of heart failure–related hospitalization*



** Taken from (20).*

WHAT DO THE GUIDELINES SAY?

The dense and comprehensive guidelines on HF from both the European Society of Cardiology (ESC) (65 pages) (21) and the American College of Cardiology/American Heart Association (ACC/AHA) (92 pages)(22) devote just a few lines to the issue of NP-guided therapy.

The ESC guidelines for the diagnosis and treatment of HF published in 2012 state that "High NP concentrations are associated with a poor prognosis, and a fall in peptide levels correlates with a better prognosis. However, several randomized clinical trials that evaluated NP-guided treatment (intensifying treatment in order to lower peptide levels) have given conflicting results. It is uncertain whether outcome is better using this approach than by simply optimizing treatment (combinations and doses of drugs, devices) according to guidelines" (21). No indications on Class of Recommendation or Level of Evidence are provided in the ESC guidelines.

The 2013 ACC/AHA guidelines for the management of HF state that NP-guided HF therapy can be useful in achieving optimal dosing of guideline-directed medical treatment in select clinically euvolemic patients who are followed

in a well-structured HF disease management program with a Class of Recommendation IIa and a Level of Evidence B (22). This statement is followed by the explanatory text: "NP levels improve with treatment of chronic HF, with lowering of levels over time in general, correlating with improved clinical outcomes. Thus, NP "guided" therapy has been studied against standard care without NP measurement to determine whether guided therapy renders superior achievement of guideline-directed medical treatment in patients with HF. However, randomized clinical trials have yielded inconsistent results. The positive and negative NP-guided therapy trials differ primarily in their study populations, with successful trials enrolling younger patients and only those with HFrEF. In addition, a lower NP goal and/or a substantial reduction in NPs during treatment are consistently present in the positive "guided" therapy trials. Although most trials examining the strategy of biomarker "guided" HF management were small and underpowered, two comprehensive meta-analyses concluded that NP-guided therapy reduces all-cause mortality in patients with chronic HF compared with usual clinical care, especially in patients <75 years of age. This survival benefit may be attributed to increased achievement of guideline-directed medical treatment. In some cases, NP levels may not be easily modifiable. If the NP value does not fall after aggressive HF care, risk for death or hospitalization for HF is significant" (22). In sum, both guidelines solicit additional information.

WHAT IS THE FUTURE?

Where to next for the biomarker-guided management of HF? There is no doubt that further trials are required to provide conclusive evidence. Such a confirmation study is currently under way: the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) study is designed to definitively assess the effects of an NP-guided strategy in high-risk patients with systolic HF on clinically relevant endpoints of mortality, hospitalization, quality of life, and medical resource use. GUIDE-IT is a prospective, randomized, controlled, unblinded, multicenter clinical trial designed to randomize approximately 1,100 high-risk subjects with systolic HF (LVEF ≤ 40%) to either usual care (optimized guideline-recommended therapy) or a strategy of adjusting therapy with the goal of achieving and maintaining a target NT-proBNP level of <1,000 pg/ml (23). The estimated study completion date is December 2017.

In addition to revisiting the strategy in the event of new effective drugs, such as the groundbreaking LCZ696 (17), which has been approved for use in the United States, further studies should examine the potential utility of other markers, such as ST2, either alone or in combination with NPs (24). ST2 manifests much less variability than do natriuretic peptides which may be ideal for following changes with treatment (25). However, the targets that need to be achieved are still unclear.

Despite the uncertainties, the consistently strong and independent relationship of NPs with prognosis should encourage physicians to measure NPs early after diagnosis and periodically thereafter for risk stratification. This will allow appropriate surveillance and fully informed counselling of both patients and their families.

CONCLUSIONS

In spite of the fact that the trials conducted to date have had different designs and pursued different NP targets in varied populations of patients with HF, the use of NPs to guide pharmacologic therapy in patients with chronic HF seems to be associated with a reductions in mortality and HF-related hospitalization, especially in younger patients (<75 years) with reduced

LVEF. There remains a need for definitive trials with sufficient power to confirm the efficacy of this strategy (e.g., GUIDE-IT), yet the existing evidence suggests that serial NP measurement as an audit and/or adjunct to decision making for dose titration in HF is rational and likely to improve outcomes.

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