Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP), have emerged as powerful markers of cardiovascular risk in patients with heart failure. Circulating natriuretic peptide (NP) levels add incremental prognostic value to standard clinical risk stratification algorithms for both ambulatory and hospitalized heart failure patients, with a steady increase in the risk of mortality and recurrent heart failure hospitalization as NT-proBNP levels rise above 1000 pg/mL. A systematic review of 19 studies of patients with heart failure demonstrated that for every 100-pg/mL rise in BNP concentration, there was a corresponding 35% increase in the relative risk of death.

Beyond the prognostic value of a single NP measurement, changes in NP concentrations over time may help to further stratify risk. Reductions in NP levels, whether achieved spontaneously or through application of appropriate medical therapy, appear to be associated with improvement in clinical outcomes. In the Valsartan Heart Failure Trial, subjects with the largest proportional reductions in BNP levels at 4 months after randomization experienced the best outcomes, whereas those with the greatest increase in BNP levels experienced the highest event rates. Among patients hospitalized with decompensated heart failure, both predischarge NP levels and the relative change in NP levels during hospital treatment are strong predictors of the risk for death or hospital readmission at 6 months.

In addition to their association with risk for adverse cardiovascular outcomes, circulating levels of NP appear to vary in relationship to the biology of heart failure progression. NP levels tend to rise during acute heart failure decompensation and to fall with successful treatment in a pattern that mirrors reductions in filling pressure, improvements in left ventricular structure and function, and improvements in functional capacity. Therapies with proven benefit in heart failure patients with reduced ejection fraction, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, spironolactone, β-blockers, and cardiac resynchronization therapy, appear to reduce NP levels in parallel with improvements in cardiac remodeling and clinical outcomes.

The prognostic importance of NP levels and their potential for modulation with treatment have fueled interest in the use of serial NP measurements to guide heart failure therapy. The fundamental premise is an alluring one: that patients with high biomarker levels (and therefore high risk for adverse outcomes) should receive more intensive disease-modifying therapy and those with low or normal biomarker levels (low risk) should receive less intensive treatment. Advocates of this approach highlight the substantial residual risk for heart failure hospitalization and death in even well-managed populations, the lack of adherence to guidelines recommending titration...
of neurohormonal antagonists to maximally tolerated doses, the inability of many practitioners to reliably estimate filling pressures or to recognize the signs/symptoms of clinical decompensation, and the limited sensitivity of weights and vital signs for monitoring heart failure progression. The hope is that by providing an objective and responsive measure of heart failure severity, NP levels will prompt providers to titrate disease-modifying heart failure therapies more appropriately and to improve clinical outcomes.

**Risk Marker or Therapeutic Target?**

Implementation of an effective biomarker-guided strategy depends on fulfillment of 4 basic assumptions. First, a clinically relevant biomarker target must be easily defined for each patient. Second, a therapeutic strategy to adjust biomarker levels to reach the target should be available. Third, the additional treatments triggered by serial biomarker assessments should improve clinical outcomes. Finally, to be truly valuable, a biomarker-driven treatment strategy must provide different content and superior benefits compared with routine heart failure management guided by the clinical assessment.

Even the most potent markers of cardiovascular risk are not necessarily suitable targets for therapy. The serum sodium concentration varies in parallel with heart failure severity and the degree of neurohormonal activation and is an accurate predictor of short- and long-term outcomes in heart failure patients. Treatments directed at normalization of serum sodium levels, however, have not been associated with improvements in clinical outcomes among hospitalized heart failure patients. Moreover, even for parameters that show a graded association with risk such as blood pressure, lower may not always be better. For example, in the Action to Control Cardiovascular Risk in Diabetes—Blood Pressure (ACCORD-BP) trial, a strategy of intensive treatment to aggressive blood pressure targets among diabetic patients was associated with no benefit and a higher rate of adverse events.

Uncertainty about the incremental value of serial BNP assessment in routine heart failure management has spawned a number of randomized, controlled trials of NP-guided treatment with a wide range of study designs and treatment targets (see Tables 1 and 2). The overall results are mixed, with the largest studies showing no clear evidence of benefit but recent positive trials resurrecting enthusiasm for this approach. Although some have leveraged meta-analytic techniques to infer mortality benefit from the biomarker-guided approach, the considerable between-trial heterogeneity makes it difficult to interpret the results of a pooled analysis. In the discussion that follows, the evidence supporting the efficacy of an NP-targeted strategy against the 4 assumptions outlined above is reviewed.

**Can We Define an Optimal NP Target?**

The core premise of a biomarker-guided approach is that heart failure patients can be efficiently risk stratified for treatment by comparing measured biomarker values with a reference benchmark. The success of an NP-driven strategy turns heavily, therefore, on identification of the appropriate BNP or NT-proBNP target. Clinical trials of NP-guided therapy have generally tested 1 of 2 general approaches: a uniform strategy in which treatment for all patients is adjusted to target a single absolute level of BNP or NT-proBNP or an individualized strategy in which different targets are defined for different patients based on a measured baseline value.

Identification of a single NP target for all heart failure patients is challenging. Levels of BNP and NT-proBNP vary in relation to heart failure severity but may also be influenced by several other factors. Age, sex, body mass index, and genetic factors are important confounders, as are concomitant conditions such as atrial fibrillation, pulmonary hypertension, myocardial ischemia, pulmonary embolism, and chronic kidney disease. Patients with heart failure and preserved EF tend to have lower NP levels than those with heart failure and reduced EF, even when the severity of heart failure is similar. Furthermore, NP levels correlate imperfectly with measured filling pressures and may remain elevated in those with more advanced or end-stage disease even in the absence of significant congestion. The marked interpatient and intrapatient variability of NP levels has substantially limited the utility of these assays for heart failure diagnosis and has similarly challenged the design of trials of NP-guided treatment. Six trials testing the value of an absolute NP target (Table 1) all used a different threshold NP value, with NT-proBNP targets ranging widely from 400 to 2200 ng/L. Paradoxically, the trials that have demonstrated benefit for NP-guided therapy have not been those with the most stringent NP targets, arguing against the notion that more aggressive efforts to reduce NP levels are necessarily better.

In the face of these limitations of uniform NP targets, some have advocated instead for individualizing NP targets. The reference point for this approach is typically set as the BNP or NT-proBNP nadir at or shortly after hospital discharge, with treatment targeted at maintaining NP levels at or near this value. Although this approach has the virtue of acknowledging the inherent between-patient variability in NP levels, the challenge is the need to define both an appropriate reference baseline and the amount of deviation from this baseline that should trigger intervention. Because the long-term within-patient variability in BNP levels exceeds 30% even in stable heart failure patients, the amount of change in NP levels that is clinically relevant is particularly difficult to discern. In the Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality? (PRIMA) study, the NT-proBNP target was based on the lowest plasma level within 2 weeks of hospital discharge, resulting in a median target value of 2491 pg/mL, well above the absolute threshold used in any of the trials using uniform BNP targets. Uptitration of therapy was recommended for patients in the biomarker-guided arm when
NT-proBNP levels exceeded the reference by >850 pg/mL. No difference was noted between an NP-guided strategy using these parameters and routine care with regard to the primary end point of days alive and out of hospital. Although some have argued that the PRIMA BNP targets were not aggressive enough, patients in the NT-proBNP group received more intensive medical treatment with both renin-angiotensin-system inhibitors and diuretics as in other trials. In addition, both of the other randomized trials of NP-guided therapy that have been conducted using individualized targets have returned similar negative results (Table 2).

**Are NP Targets Reachable?**
The typical approach to NP-guided treatment involves serial assessment of NP levels and ongoing modification of treatment until the set target is achieved or a therapeutic limit is reached. Even if an optimal NP target can be defined, therefore, it must be possible to adjust NP levels successfully to

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**Table 1. Trials of Natriuretic Peptide–Guided Management Using a Fixed Natriuretic Peptide Target**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Inclusion Criteria</th>
<th>Mean Age, y</th>
<th>Target for NP-Guided Arm</th>
<th>Comparator Group(s)</th>
<th>Follow-up Duration</th>
<th>Primary End Point(s)</th>
<th>Favors NP-Guided Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troughton et al(^{25})</td>
<td>69</td>
<td>HF hospitalization, LVEF &lt;40%, NYHA III-IV</td>
<td>70</td>
<td>NT-proBNP &lt;200 pmol/L (≈1700 pg/mL)</td>
<td>Standardized HF score</td>
<td>9.5 mo (median)</td>
<td>Cardiovascular death or HF hospitalization</td>
<td>Yes</td>
</tr>
<tr>
<td>STARS-BNP(^{26})</td>
<td>220</td>
<td>Stable outpatient, optimal background therapy, LVEF &lt;45%, NYHA II-III</td>
<td>65</td>
<td>BNP &lt;100 pg/mL</td>
<td>Usual care</td>
<td>15 mo (median)</td>
<td>Unplanned HF hospitalization or death</td>
<td>Yes</td>
</tr>
<tr>
<td>TIME-CHF(^{24})</td>
<td>499</td>
<td>Age ≥60 y, LVEF ≤45%, NYHA II-IV, HF hospitalization within last year, NT-proBNP &gt;2× upper limit of normal</td>
<td>76</td>
<td>NT-proBNP &lt;400 pg/mL, if &lt;75 y of age or &lt;800 pg/mL if ≥75 y of age</td>
<td>Symptom-guided treatment (target NYHA class II or less)</td>
<td>18 mo</td>
<td>Hospitalization-free survival and quality of life</td>
<td>No</td>
</tr>
<tr>
<td>BATTLESCARRED(^{29})</td>
<td>364</td>
<td>Symptomatic HF with preserved or reduced LVEF, HF hospitalization within 2 wk, NT-proBNP &gt;400 pg/mL</td>
<td>76</td>
<td>NT-proBNP &lt;150 pmol/L (≈1300 pg/mL)</td>
<td>Standardized HF score, standard care (3 arms)</td>
<td>2.8 y</td>
<td>Total mortality and death or HF hospitalization</td>
<td>No</td>
</tr>
<tr>
<td>PROTECT(^{31})</td>
<td>151</td>
<td>Hospital admission, emergency room visit, or outpatient therapy for HF within 6 mo, LVEF &lt;40%, NYHA II-IV</td>
<td>63</td>
<td>NT-proBNP ≤1000 pg/mL</td>
<td>Standard HF care</td>
<td>10 mo (mean)</td>
<td>Total cardiovascular events</td>
<td>Yes</td>
</tr>
<tr>
<td>Berger et al(^{32})</td>
<td>278</td>
<td>HF hospitalization, NYHA III-IV on admission, LVEF &lt;40% or CTR &gt;0.5</td>
<td>71</td>
<td>NT-proBNP &lt; 2200 pg/mL</td>
<td>Multidisciplinary care, usual care (3 arms)</td>
<td>15 mo (median)</td>
<td>Days of HF hospitalization, time to death or HF hospitalization</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BATTLESCARRED indicates NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death; BNP, B-type natriuretic peptide; CTR, cardiothoracic ratio; HF, heart failure; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; PROTECT, Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting; STARS-BNP, Systolic Heart Failure Treatment Supported by BNP; and TIME-CHF, Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure.

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**Table 2. Trials of Natriuretic Peptide–Guided Management Using an Individualized Natriuretic Peptide Target**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Inclusion Criteria</th>
<th>Mean Age, y</th>
<th>Target for NP-Guided Arm</th>
<th>Comparator Group(s)</th>
<th>Follow-up Duration</th>
<th>Primary End Point(s)</th>
<th>Favors NP-Guided Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARBRITY(^{27})</td>
<td>130</td>
<td>HF hospitalization, LVEF ≤35%, NYHA III-IV</td>
<td>59</td>
<td>BNP &lt;2× hospital discharge</td>
<td>Standardized congestion score</td>
<td>90 d</td>
<td>Hospitalization-free survival</td>
<td>No</td>
</tr>
<tr>
<td>PRIMA(^{30})</td>
<td>345</td>
<td>HF hospitalization, NT-proBNP ≥1700 on admission, NT-proBNP drop &gt;10% (&gt;850 pg/mL) before discharge</td>
<td>72</td>
<td>Lowest NT-proBNP at discharge and subsequent 2-wk follow-up</td>
<td>Standard HF care</td>
<td>1.9 y (median)</td>
<td>No. of days alive outside hospital</td>
<td>No</td>
</tr>
<tr>
<td>SIGNAL-HF(^{33})</td>
<td>252</td>
<td>LVEF &lt;50%, NYHA II-IV, elevated NT-proBNP (men &gt;800 pg/mL, women &gt;1000 pg/mL)</td>
<td>77</td>
<td>50% Reduction from baseline NT-proBNP</td>
<td>Usual care (trained primary care physicians)</td>
<td>9 mo</td>
<td>Days alive, days out of hospital, and quality of life (KCCQ)</td>
<td>No</td>
</tr>
</tbody>
</table>

BNP indicates B-type natriuretic peptide; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; PRIMA, Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Mortality and Mortality?; SIGNAL-HF, Swedish Intervention Study–Guidelines and NT-ProBNP Analysis in Heart Failure; and STARBRITY, Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score.
reach the target. Although many therapies with proven benefit in heart failure patients reduce circulating NP concentrations, it is not clear that “ideal” NP levels are achievable in every patient. High circulating NP levels may become harder to modulate with conventional treatment for the elderly or those with more advanced heart failure.

In general, patients randomized to treatment guided by serial NP levels tend to achieve lower NP levels with time than those treated according to the clinical assessment alone. However, the absolute reduction in NP levels from baseline is modest in most studies, leaving many patients well above the established targets at the end of follow-up (Table 3). The lower the set targets are, the more aggressive NT-proBNP targets (NT-proBNP <400 pg/mL if <1000 pg/mL. The proportion of PROTECT subjects successfully reaching the more liberal targets was similar to that reported in other studies (Table 4).

If NP-targeted therapy is effective even in populations in which the set target is not achievable, it is unclear that the biomarker itself is of much incremental value to the determination of therapy. A constantly “abnormal” biomarker has little discriminative power and simply forces routine titration of therapy. A constantly “abnormal” biomarker has little discriminative power and simply forces routine titration of therapy until an alternative therapeutic limit is reached. In a sense, the same outcomes might be achieved by substituting a physiologically irrelevant but similarly immovable parameter for NP measurements in the treatment strategy (eg, instruct clinicians to intensify therapy if the patient’s body mass index or height does not change with time). Among patients allocated to NP-guided treatment in the Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score; STARS-BNP, Systolic Heart Failure Treatment Supported by BNP; and TIME-CHF, Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure.

In the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF),28 which set the most aggressive NT-proBNP targets (NT-proBNP <400 pg/mL if <75 years of age or <800 pg/mL if ≥75 years of age), fewer than one fourth of patients appear to have reached their goals in both arms, and there was no statistically significant difference in the achieved NT-proBNP reduction in both groups. Older patients (>75 years of age) appeared to be particularly resistant to NT-proBNP reduction, with an even smaller proportion achieving target values. Trials applying more liberal thresholds (particularly those using individualized NP targets) tend to report greater success in achieving the set goals but have failed to show relative benefits to the NP-guided approach. Even in the Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting (PROTECT) study,23 which achieved dramatic NT-proBNP reductions (>50%, from 2344 to 1125 pg/mL in the NP-guided group versus 1946 to 1844 pg/mL in the placebo arm) with associated reductions in cardiovascular events, 56% of patients in the NP-guided arm and 64% of those in the standard care arm failed to reach the target NT-proBNP of <1000 pg/mL. The proportion of PROTECT subjects successfully reaching the more liberal targets was similar to that reported in other studies (Table 4).

Table 3. Absolute Reductions in Natriuretic Peptide Levels and Percent Achieving Set Targets in Trials of Natriuretic Peptide–Guided Heart Failure Therapy

<table>
<thead>
<tr>
<th>Trials with uniform NP Targets</th>
<th>Absolute Reduction in NP* Levels, NP-Guided Group, pg/mL</th>
<th>Absolute Reduction in NP* Levels, Control Group, pg/mL</th>
<th>Achieving Target, NP-Guided Group, %</th>
<th>Achieving Target, Control Group, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troughton et al25</td>
<td>668</td>
<td>25</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>STARS-BNP26</td>
<td>68 (BNP)</td>
<td>...</td>
<td>33</td>
<td>Minority</td>
</tr>
<tr>
<td>TIME-CHF28</td>
<td>...</td>
<td>...</td>
<td>Minority</td>
<td>Minority</td>
</tr>
<tr>
<td>BATTLESCARRLED29</td>
<td>463</td>
<td>399</td>
<td>49</td>
<td>32</td>
</tr>
<tr>
<td>PROTECT31</td>
<td>1219</td>
<td>102</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td>Berger et al32</td>
<td>...</td>
<td>...</td>
<td>Majority</td>
<td>Majority</td>
</tr>
<tr>
<td>Trials with individualized NP targets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAR-BRITE27</td>
<td>40 (BNP)</td>
<td>−31 (BNP)</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>PRIMA30</td>
<td>432</td>
<td>572</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>SIGNAL-HF33</td>
<td>301</td>
<td>362</td>
<td>19</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 4. Proportion of Patients Achieving Different N-Terminal B-Type Natriuretic Peptide Targets in the PROTECT31 Trial

<table>
<thead>
<tr>
<th>NT-proBNP, pg/mL</th>
<th>NP-Guided Arm, %</th>
<th>Standard Care Arm, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>44.3</td>
<td>35.6</td>
</tr>
<tr>
<td>&lt;2000</td>
<td>68.6</td>
<td>57.5</td>
</tr>
<tr>
<td>&lt;3000</td>
<td>80.0</td>
<td>69.9</td>
</tr>
</tbody>
</table>

NP indicates natriuretic peptide; NT-proBNP, N-terminal B-type natriuretic peptide; and PROTECT, Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting.
Score (STARBRITE) trial, discordance between BNP measurements and the clinical assessment of congestion was infrequent, suggesting that NP levels often do not add information to what clinicians already know.

In most trials, persistently high NP levels obligated more frequent follow-up visits. Superior outcomes with NP-guided therapy in selected trials could therefore be attributable in large measure to the more intensive clinical support provided to patients with persistently elevated NP levels rather than success in reducing NP levels to target. In the Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) trial, patients in the BNP-guided arm had twice the number of physician visits and more frequent medication changes than those in the standard care arm, even though only 33% reached the target BNP of <100 pg/mL. In the 3-arm study by Berger et al., which also favored NP-guided therapy, patients with NT-proBNP levels >2200 pg/mL were deliberately triaged to a heart failure specialist for more intensive management, and the remainder of patients were managed either by primary care physicians or a nurse-led multidisciplinary team. The NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) trial specifically tested the incremental value of the NP-guided approach relative to both a positive control of intensive, standardized clinical care that directed medication titration based on a clinical score and a usual-care arm that received routine primary care follow-up. Relative to usual care, both treatment groups experienced similar reductions in NP levels, intensification of medical therapy, and reductions in the composite of death or heart failure hospitalization. No overall difference in survival was seen between the NP-guided strategy and intensive clinical follow-up.

Should Patients With Elevated NP Levels Be Treated Differently?

Most trials of NP-guided therapy have not defined a specific algorithm to address elevated NP levels but have encouraged clinicians to respond to elevated NP levels by further titrating drugs with established benefit in heart failure to recommended targets. Acknowledging the association among loop diuretics, neurohormonal activation, and adverse outcomes in heart failure, more recent trials have in addition discouraged titration of loop diuretics in patients with high NP levels and have even recommended dose reduction in stable patients. Because high NP levels frequently direct intensification of therapy even in patients who may be clinically asymptomatic, the NP-guided therapy is typically associated with a relative increase in the use of angiotensin-converting enzyme inhibitors, β-blockers, angiotensin receptor blockers, and spironolactone over standard, symptom-guided care.

Guideline-based recommendations for heart failure management emphasize titration of neurohormonal antagonists to maximally tolerated doses and minimization of diuretic dosing in all heart failure patients with reduced ejection fraction. There is little evidence that the benefit of heart failure therapies varies according to heart failure severity or NP levels. In fact, trials of β-blockers, renin-angiotensin system antagonists, and cardiac resynchronization therapy have shown benefits that are largely independent of baseline NP concentrations. Accordingly, the vast majority of those with chronic heart failure who do not have markedly elevated NP levels should still derive benefit from uptitration of proven therapies. In addition, for the nearly 50% of patients with heart failure and preserved ejection fraction for whom there is little evidenced-based treatment, it is unclear how elevated NP levels should influence clinicians to adapt their approach.

Advocates of the NP-guided approach point out that adherence to published guidelines is suboptimal in clinical practice and note that serial NP measurement may be an important lever to remind clinicians of the ongoing need to titrate therapy. As one critic has noted, however, this formulation reduces the “guidance” provided by serial NP measurement to little more than an “intellectual crutch” to practice evidence-based medicine. Moreover, if NP levels truly facilitate more appropriate medication titration, the greatest opportunity for NP-guided treatment would be expected in the hands of inexperienced clinicians who are less aware of guidelines and for whom the assessment of volume status or heart failure stability is especially difficult. However, the 1 trial examining the benefits of such a strategy in a primary care population (Swedish Intervention Study–Guidelines and NT-ProBNP Analysis in Heart Failure [SIGNAL-HF]) suggested no significant difference in drug titration or clinical outcomes between routine care and an NP-guided approach.

Ultimately, serial NP measurements are an inadequate surrogate for good clinical judgment. Routine titration of neurohormonal antagonists or other heart failure therapies in some patients with persistently elevated NP levels may be harmful. Excessive reliance on NP levels to assess volume status might prompt inappropriate dose escalation of loop diuretics among patients without significant congestion and increase the rate of hypotension, renal dysfunction, and other adverse events. Low NP levels may provide false reassurance that treatment is adequate, even as other clinical parameters suggest otherwise. Aggressive medication titration to manage high NP values may also be poorly tolerated in the elderly or those with significant renal dysfunction (who were systematically excluded from most trials). In the TIME-CHF trial, which overall showed no incremental benefit from NP-guided drug titration, a strong interaction with age was noted in secondary analyses. Although patients <75 years of age experienced a reduction in recurrent heart failure hospitalization and survival, those >75 years of age derived no benefit and experienced a higher rate of adverse events from NP-guided drug titration. Similar variation in the benefits of NP-guided treatment according to age noted in other trials suggests that this is not a spurious result. This signal of potential harm among older patients within the context of a well-managed clinical trial raises serious concerns for the generalization of the NP-guided approach to unselected patients in real-life practice, in which an increasing...
proportion of heart failure patients are elderly with substantial comorbid medical illness. Indeed, the most compelling study favoring NP-guided treatment to date also has the distinction of enrolling a much younger population of patients (median age, 63 years) than other trials.

**Conclusion: Serial NP Levels Are Not Useful for Most Heart Failure Patients**

In an era of increasing concern about both the clinical and economic consequences of the growing heart failure burden, there is an imperative to design new approaches to longitudinal heart failure management that are both scalable and effective in improving outcomes. Early recognition of patients with early instability or impending decompensation is a key step to effective intervention but is challenging when based on clinical assessment alone. Given that NPs rise with hemodynamic stress in a pattern that correlates with risk for short- and long-term clinical outcomes, it is appealing to look to serial NP measurements to help direct the necessary intensity of heart failure treatment.

Exactly how clinicians should leverage NP levels to improve heart failure outcomes, however, remains unclear. Although some trials have suggested benefits for a strategy focused on reducing NP levels below a fixed target level, no 2 trials have tested the same target, and trials with similar targets have returned discrepant results. The substantial between-patient variability in NP levels makes individualized NP targets more appealing than fixed targets, but none of the trials of this approach has shown significant impacts on morbidity or mortality. Even if appropriate targets can be established, values that are set too low are generally unachievable and those that are set too high likely do not materially alter clinical management. Furthermore, the core assumption of NP-guided therapy, the notion that heart failure therapy should vary on the basis of measured NP levels (or indeed any other risk marker), is not well supported by clinical evidence. Guidelines recommend titration of evidence-based therapies to maximally tolerated doses in all patients regardless of background risk. If the problem is lack of adherence to these guidelines, strategies should focus on educating clinicians about the clinical assessment and optimal management of heart failure patients rather than on the use of serial laboratory testing that does not clearly influence the selection of appropriate treatment. Sadly, there are no shortcuts.

This is not to say that NP levels have no place in heart failure management. Risk stratification by NP levels may be important to identify a subset of patients who benefit from more intensive subspecialty care, as highlighted in the study by Berger et al. Additionally, the age interaction suggested in TIME-HF and BATTLESCARRED and the positive results of the PROTECT trial reserve the possibility that there may be a role for NP-targeted treatment in younger patients with reduced ejection fraction, particularly those being treated by clinicians who require the objective prompt to titrate treatment that a laboratory measure provides. However, patients with normal NP levels and those with advanced age, preserved ejection fraction, and significant medical comorbidities, who make up the growing majority of the heart failure burden, will continue to rely on the best clinical judgment of physicians skilled in the art of medicine.

**Disclosures**

Dr Desai reports having been a paid consultant to Novartis, Reata, Boston Scientific, and Intel.

**References**


Response to Desai

James L. Januzzi, Jr, MD; Richard Troughton, MD, PhD

We appreciate the elegant comments of Dr Desai; unfortunately, he did not make a strong case against biomarker-guided therapy (BGT) and was factually incorrect on several important points, only the most important of which we highlight because of space constraints. Raising concern about potential harm from BGT is a tired and incorrect argument, as is suggesting the risk of undertreatment in those with low natriuretic peptide (NP) values. Not 1 trial has demonstrated safety concerns of BGT, and no trial withheld treatment for those with low NPs: in fact, achieved doses of therapies in BGT studies are more often equivalent to those in landmark trials. Is this not important? The assertion that benefit from BGT has not come from stringent NP targets is totally incorrect. In addition, the argument that the inability to always achieve NP targets limits the value of the approach is flawed: Outcomes are significantly associated with the lowest achieved NP value; some lowering is better than none; and higher-risk patients may thus be better identified to correctly receive precious resources in this cost-conscious healthcare environment. The laughable argument of using an immovable/irrelevant parameter such as height to guide HF therapy ignores the prognostic value of NPs and the value of their lowering. These are only a few of the incorrect statements made in Dr Desai’s commentary. However, there is a common reassuring theme in both of our arguments: Best care is needed for our patients with HF. Routinely combining biomarkers with clinical judgment helps achieve this goal.
Are Serial BNP Measurements Useful in Heart Failure Management?: Serial Natriuretic Peptide Measurements Are Not Useful in Heart Failure Management: The Art of Medicine Remains Long
Akshay S. Desai

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