We have been asked to take the position that serial natriuretic peptide (NP) testing is useful for heart failure (HF) management. To do so, we primarily draw on our experience as physicians with active clinical practices replete with patients suffering from the diagnosis but also from our in-depth knowledge of NP testing and its strengths and weaknesses.

Response by Desai on p 508

To best consider the value of B-type natriuretic peptide (BNP) or its amino-terminal congener (N-terminal-proBNP [NT-proBNP]) for managing HF patients, it is worthwhile to first consider the need: Why would a biomarker be necessary beyond clinical means to assess and manage patients? Beyond this, we then identify the background science that led to the use of serial measurement of BNP or NT-proBNP, and then we finally review the aggregate data supporting their use in this capacity.

The HF Crisis: Why Do We Need to Consider Alternative Means to Manage Our Patients?

HF is reaching epidemic proportions, with millions of affected patients in the United States alone and more than half a million new cases yearly. With a lifetime risk for HF of >20% beyond middle age, the crisis is only expected to worsen as the population grows and ages. Furthermore, although prognosis in HF has improved over the past 50 years, it remains among the most lethal diagnoses in modern medicine, with a mortality rate that equals or exceeds many malignancies. Moreover, HF patients are frequently hospitalized, causing a financial burden on the healthcare system that will not abate soon. For all these reasons, a substantial focus now exists on improving the care of patients affected by HF.

Landmark randomized, controlled trials (RCTs) have identified a wide range of pharmacological- and device-based therapies that improve HF symptoms, reduce the risk for HF progression, prevent HF hospitalization, and lower mortality rates related to the diagnosis. Unfortunately, however, contemporary studies consistently demonstrate inadequacies not only in the uptake and achieved dosing of proven pharmacological therapies (such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenergic blockers, and mineralocorticoid receptor antagonists) but also in the use of cardiac resynchronization therapy and implantable cardioverter-defibrillators. These gaps in care leave the real-world HF patient at high risk for adverse outcomes.

The reasons for inadequate HF management are numerous and extend beyond this discussion but in part include the way HF therapy is delivered. The standard therapeutic approach to chronic HF, as articulated in clinical practice guidelines, is predicated on the strategies used in well-designed RCTs to uptitrate therapies to target doses or, short of that, to maximally tolerated doses. Compounding the issue is the fact the pharmacopoeia for patients with chronic HF has become very complex. Even in patients with left ventricular systolic dysfunction, for whom these therapies have proven benefit, the sequence of addition and uptitration is largely left to
Clinical judgment. Furthermore, to achieve goals of therapy as outlined in guidelines, frequent office visits for evaluation and management are often necessary. Considerable skill is required to recognize opportunities to titrate therapies, and acumen is needed to implement such changes.

Thus, as a result of the complexity of HF therapy, adherence to the well-articulated goals of HF guidelines is widely recognized as suboptimal, and as a result, higher-risk patients are frequently unrecognized and thus undertreated.6

There is reason for optimism. Quality-improvement efforts may lead to more assiduous care for the patient with chronic HF. For example, in the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF), substantial improvement in the application of guideline-derived medical therapy goals was observed after initial gaps in care were identified,6 with a favorable effect on outcome.7 On the other hand, the same investigators reported that doses of agents achieved after quality improvement were significantly below those applied in RCTs, suggesting that room for improvement remained.8

Thus, it is hard to assert that the status quo in HF is acceptable, and despite repeated calls for improvement, gaps in the quality of care remain, leaving a huge number of patients at risk, including many who would be very likely to benefit greatly from individualized intervention to improve their care. This individualized focus is lacking in the current HF treatment approach.

Recent position statements call for novel means for diagnosis, risk assessment, and particularly therapy for patients affected by high-prevalence, high-morbidity, high-cost conditions such as HF.5 Such novel tools should be designed to supplement clinical acumen and to afford improved care to those patients at highest risk for adverse outcomes while improving the care for all patients with HF. In short, whatever approach is taken should not only identify inadequate adherence to guideline-derived medical therapy targets but also allow longitudinal monitoring of optimally managed patients to proactively identify a change in their risk.

A concept that would allow an optimized yet individualized approach to HF care is to leverage the results of biomarker tests. This approach is attractive, given the wide availability, low cost, and easy assessment of HF biomarkers, coupled with their noninvasive nature. Because of their ability to reflect processes behind the presence, exacerbation, and complication of HF, biomarkers provide important prognostic value beyond that already available at the bedside and, as we will argue, also provide an easily acquired, actionable therapeutic target for therapy.

Although numerous biomarker candidates now exist, we focus our discussion on BNP and NT-proBNP, which are by far the best-characterized biomarkers for use in guiding HF management. The biology of BNP and NT-proBNP has been widely studied and forms the foundation for the clinical trials that have tested the utility of BNP and NT-proBNP in guiding HF therapy.

Concentrations of NPs in HF Provide an Integrated Assessment of Cardiac Structure, Function, and Loading

Indeed, rather than specifically reflecting volume status in HF, values for both BNP or NT-proBNP reflect a wide array of important cardiac pathophysiology, including left and right ventricular size and function, diastolic function, valvular heart disease, filling pressures, heart rhythm, and even coronary ischemia. This provides the clinician with a tool that reflects the extent of each patient’s individual cardiac dysfunction and hence may allow a more personalized approach to therapy.

NP Concentrations Are Prognostically Among the Most Powerful Objective Tools Available in HF Care and Offer Dynamic Risk Stratification

Beyond their guideline-supported use to identify patients with decompensated HF in both inpatient and outpatient venues, BNP and NT-proBNP provide powerful risk stratification across the entire range of HF stages. In this regard, NPs are additive to clinical judgment for prognostication and supplement or supersede other means of assessment for predicting adverse HF outcomes such as cardiopulmonary exercise testing.10 Indeed, it is now widely accepted that NPs are among the gold standards for prognosis in HF, affording easily obtainable, reproducible, and interpretable information of all sorts for clinicians.

The use of BNP or NT-proBNP to assist in therapy decision making requires knowledge of a concentration at which the biomarker identifies a clear increase in risk. Although there is a relatively continuous relationship between NP levels and risk of adverse outcome, values for BNP of 125 pg/mL and for NT-proBNP of 1000 pg/mL have been shown to clearly dichotomize between low and high risk.11 Whereas a single measurement for BNP or NT-proBNP provides prognostic value, the serial measurement of either provides incremental risk stratification. For example, Masson and colleagues12 measured BNP and NT-proBNP in the Valsartan Heart Failure Therapy trial and showed that information from temporal trends in either peptide superseded the prognostic value of a single assessment (Figure 1).12 This dynamic nature of BNP or NT-proBNP thus unlocks their use for sequential monitoring, allowing therapy guidance, identifying a changing risk, and tending to identify those patients undergoing deleterious myocardial remodeling.13,14

The Biological Variability for BNP and NT-proBNP Is Established

Biological variability is the amount of change that a biomarker rises or falls in a stable physiological state. Simply put, biological variability is how much the marker must change before one can confidently state that a disease is worsening (marker rising) or improving (marker falling). Knowledge of the biological variability (expressed as relative change value) of a biomarker is a prerequisite if it is to be used as a

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monitor for disease stability or as a target for therapy. Present analyses suggest that the relative change values are 40% for BNP and 25% for NT-proBNP. Thus, a rise or fall in BNP or NT-proBNP greater than these amounts—relative to the previous value at each measurement—allows the clinician to identify a significant change has occurred.15

Methods for Lowering BNP and NT-proBNP Are Established
Therapies for HF directly affect the processes that contribute to the rise of BNP or NT-proBNP, and it is well established that many HF therapies lower the concentrations of both BNP and NT-proBNP after introduction or intensification (Table 1). These include loop diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenergic blockers, mineralocorticoid receptor antagonists, exercise therapy, and cardiac resynchronization therapy.

In aggregate, using the knowledge of each individual patient’s underlying structural heart disease and their NP signature, the clinician has a broad range of therapeutic options to select from to more directly target the individual HF pathophysiology within each patient. For example, if faced with an elevated BNP or NT-proBNP in a patient with marked bradycardia, knowledge of underlying significant valvular disease might lead the clinician to preferentially adjust a vasodilator, whereas a similar patient with room in their heart rate but less valve disease might get cautious adjustment in his or her β-adrenergic blockers. Therapy gaps also exist in those patients with relative contraindications for therapy changes such as those with impaired renal function or the elderly. In this setting, adverse drug reactions are a reasonable concern and often lead to withholding of care. Given a markedly elevated NP value, a clinician might cautiously introduce a therapy such as a mineralocorticoid receptor antagonist, recognizing that the benefits of the drug might outweigh the risk. On the other hand, if a patient is on an optimal medical program but shows a rising BNP or NT-proBNP, an assessment of filling status, drug therapy/lifestyle adherence, or need for therapy intensification would also be indicated.

After a Therapy Change, the Appropriate Moment for NP Resampling Is Known
Although biological data are limited with regard to the time at which steady state is reached for the salutary effects of chronic HF therapies on BNP or NT-proBNP release, data from studies of serial NP monitoring suggest that concentrations of NT-proBNP 2 to 4 weeks after a therapy change are most prognostic, identifying this time window as the appropriate time for NP resampling and consideration of retitration of medication.16

NP HF Management: What Has Been Learned?
Based on a strong rationale for using BNP or NT-proBNP to guide HF therapy, a number of RCTs have explored this strategy (Table 2).

In their seminal study of biomarker-guided HF care,17 investigators from the Christchurch Cardioendocrine Group demonstrated that therapy with a goal to suppress NT-proBNP values was associated with superior event-free survival compared with therapy guided by a congestion score. Subsequent RCTs have explored the concept, some with clear benefit demonstrated from guided therapy, others with benefits in subgroups,20,21 and others without clear benefit compared with standard HF care.22–25

From the aggregate experience of the range of RCTs that have explored the approach, several important generalizations can be made.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Typical Effect on BNP/NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis (loop or thiazide)</td>
<td>↓</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>↓</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>↓</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Some transiently ↑, most ↓</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td>↓</td>
</tr>
<tr>
<td>Exercise</td>
<td>↓</td>
</tr>
<tr>
<td>Rate control of atrial arrhythmia</td>
<td>↓</td>
</tr>
</tbody>
</table>

BNP indicates B-type natriuretic peptide; and NT-proBNP, N-terminal B-type natriuretic peptide.

Table 1. Therapies for Heart Failure That May Lower Natriuretic Peptide Values
of their HF medications and that biomarker guidance added to clinical judgment. The finding of more optimal care triggered by biomarker guidance across most studies should be a reassuring observation to those who decry the approach. Rather than replacing clinical judgment, BNP/NT-proBNP–guided management is an effective adjunctive strategy.

Examples of the improvements of care for patients in biomarker-guided trials are abundant. Among patients in the multicenter Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) trial, although 99% of patients received an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker at 94% of the recommended dosage and 94% of patients received a β-adrenergic blocker at 58% of the recommended dosage, changes in treatment occurred more frequently in the BNP group compared with the clinical group: 134 versus 66 occasions (P<0.05), with all classes of drug titrated more frequently and more patients achieving guideline-derived medical therapy goals in the biomarker arm. In a similar manner, in the ProBNP Outpatient Tailored Chronic HF Therapy (PROTECT) study, patients were well managed at baseline (and both arms of the study had up titration), but NT-proBNP–guided patients had more frequent drug changes, had greater dose increases of therapies with mortality benefits (including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, β-adrenergic blockers, and mineralocorticoid receptor antagonists), and were more likely to have their loop diuretic therapy removed, and NT-proBNP guidance resulted in a greater likelihood of achieving guideline-derived goals. Notably, even in studies neutral for their primary outcome measures such as the Trial of Intensified versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) and NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) study, therapy was more aggressively applied in the NT-proBNP–guided arms, which likely explains encouraging improvement in secondary outcome measures in both studies.

Among the 3 published trials with no difference in medical management between the 2 study arms, all were neutral for their primary end point, and perhaps

### Table 2. Summary of Published Biomarker-Guided Heart Failure Therapy Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Age, y</th>
<th>NP Target</th>
<th>Lower NP Level Achieved in Active Arm?</th>
<th>Biomarker-Guided Treatment Different From Standard Management?</th>
<th>Excess Adverse Events?</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STARBRITE</td>
<td>60</td>
<td>High</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Goal BNP based on value at hospital discharge</td>
</tr>
<tr>
<td>PRIMA</td>
<td>72</td>
<td>High</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Responders to NT-proBNP–guided care had better outcomes</td>
</tr>
<tr>
<td>SIGNAL-HF</td>
<td>78</td>
<td>High</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No substantial change in management and no significant lowering of NT-proBNP</td>
</tr>
<tr>
<td>UPSTEP</td>
<td>71</td>
<td>Intermediate</td>
<td>Not reported</td>
<td>No</td>
<td>Not reported</td>
<td>Medications in both study arms aggressively uptitrated</td>
</tr>
<tr>
<td>Neutral studies with positive trends</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIME-CHF</td>
<td>77</td>
<td>Low</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Significant reduction in HF hospitalization–free survival and nearly significant reduction in mortality</td>
</tr>
<tr>
<td>BATTLESCARRED</td>
<td>76</td>
<td>Low</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Significant reduction in mortality among younger subjects at 3 y of follow-up</td>
</tr>
<tr>
<td>Positive studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troughton et al</td>
<td>70</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Performed in the pre-β-blocker era</td>
</tr>
<tr>
<td>STARS-BNP</td>
<td>65</td>
<td>Low</td>
<td>Not reported</td>
<td>Yes</td>
<td>No</td>
<td>Multicenter trial, significant benefit of NT-proBNP guided care</td>
</tr>
<tr>
<td>Berger et al</td>
<td>71</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Benefit in elderly subjects</td>
</tr>
<tr>
<td>PROTECT</td>
<td>63</td>
<td>Low</td>
<td>Yes</td>
<td>Not reported</td>
<td>No</td>
<td>NT-proBNP–guided therapy superior to multidisciplinary HF care</td>
</tr>
</tbody>
</table>

BATTLESCARRED indicates NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death; BNP, B-type natriuretic peptide; NP, natriuretic peptide; NT-proBNP, N-terminal B-type natriuretic peptide; PRIMA, Can Pre-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?; PROTECT, Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting; SIGNAL-HF, Swedish Intervention Study–Guidelines and NT-proBNP Analysis in Heart Failure; STARBRITE, 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; TIME-CHF, Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure; and UPSTEP, Use of Peptides in Tailoring Heart Failure Project.
unsurprisingly, no encouraging trends between study arms were found; however, in 1 study, the lack of difference between the BNP and standard-of-care arms reflected aggressive uptitration of therapies in both study arms, with consequent equal reduction in BNP and parallel improvement in outcome. This demonstrates the value of optimal medical management. In the other 2 studies, medication titration was generally suboptimal in both arms, without any change in NT-proBNP values, thus leaving the concept of biomarker-guided HF care untested.

Thus, when correctly applied, biomarker-guided management appears to improve both the thoroughness of care and the choice of agents used. Additionally, given that an elevated BNP or NT-proBNP identifies those at highest risk for adverse outcomes, including ventricular remodeling, HF progression, hospitalization, and death, use of the biomarker as a target also allows closure of the well-recognized gap in management that exists in these highest-risk patients.

When correctly applied, biomarker-guided care results in lower rates of adverse cardiovascular events, better quality of life, and reverse ventricular remodeling and may be associated with reduced rates of death: As with any strategy, correct application is crucial to success. One important lesson learned is that optimal BNP- or NT-proBNP–guided HF care involves a goal to lower the markers to a low target value, which prompts more frequent visits to achieve the medical therapy goals and lower NP values on which better outcomes are dependent. Thus, a common limitation in neutral biomarker-guided trials was that unacceptably high BNP or NT-proBNP targets did not prompt ongoing uptitration of therapy. In contrast, studies that achieved improved outcomes more often sought (and achieved) lower BNP or NT-proBNP targets. Notably, in 2 neutral trials, responders to biomarker-guided care (those with robust reductions in their NT-proBNP values) had substantially better outcomes than nonresponders, confirming the importance of biomarker suppression.

In the PROTECT study, the substantial reduction in NT-proBNP was accompanied by a significant reduction in a composite outcome, including worsening HF, hospitalization for HF, and cardiovascular death (Figure 2).13 These results are quite reminiscent of the results of STARS-BNP19 and the data from Berger et al18 and closely approximate the significance of improvements in HF hospitalization–free survival seen in TIME-CHF (a secondary outcome measure in this last trial).21 In the PROTECT study, improved outcomes were accompanied by significantly better patient-reported quality of life, and interestingly, NT-proBNP–guided HF treatment was associated with greater reverse ventricular remodeling, presumably reflecting increased personalized application of antiremodeling therapies (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenergic blockers, mineralocorticoid receptor antagonists) in those patients most vulnerable to this deleterious process.13 These data not only suggest that biomarker-guided HF management improves outcomes but also support the contention that NT-proBNP monitoring may be used as a surrogate for echocardiography for the serial assessment of ventricular remodeling.14

Although the largest biomarker-guided HF trial to date (the TIME-CHF study) had a neutral primary outcome, important nuances of the results from this study exist. First, although in TIME-CHF (which examined an elderly patient population) the primary outcome measure of hospitalization-free survival was not significantly improved (hazard ratio, 0.92; 95% confidence interval, 0.73–1.15), the secondary outcome measure of HF hospitalization–free survival was, in fact, improved (hazard ratio, 0.66; 95% confidence interval, 0.49–0.90; P=0.008). Furthermore, mortality was also improved in the biomarker-guided arm by 32% (95% confidence interval, 0.46–1.01; P=0.06). Moreover, improvements in both HF hospitalization–free survival and overall survival were particularly robust in younger subjects with 62% (P=0.01) and 59% (P=0.002) reductions, respectively. Recent cost-effectiveness data from TIME-CHF indicate that NT-proBNP–guided HF care was a dominant strategy across all levels of HF severity and age, suggesting that although the primary outcome of the trial was negative, there was nonetheless considerable benefit related to the biomarker-guided approach. These data are in agreement with those from the study by Berger et al, in which days spent in the hospital for HF were substantially reduced (1588 versus 488 days; P≤0.001), and from PROTECT, in which HF hospitalization was reduced by >50%. Thus, when we consider the current healthcare crisis posed by HF, it is impossible to ignore the fact that biomarker-guided HF care results in improved outcomes in a cost-effective manner.

Of course, the gold standard in HF therapeutic trials has traditionally been improvement in mortality, and some have raised the general lack of survival improvement in biomarker-guided HF studies as a concern. First, it is worth noting that to date the total number of patients in the published BNP- and NT-proBNP–guided therapy trials is just over 2300; thus,
the strategy has been examined in generally underpowered studies and in collectively fewer patients than are typically in a single drug trial in HF. This has therefore led to difficulty in detecting an effect on mortality. Nonetheless, the largest studies to date, TIME-CHF and BATTLESCARRED, have both indicated reductions in mortality with biomarker-guided HF care. A nearly statistically significant reduction in death was seen in the former study, and in the latter, as shown in Figure 3, among patients <75 years of age, significantly lower rates of death were seen in the NT-proBNP-guided arm (15.5%) compared with patients managed with clinical scoring (30.9%; \( P=0.05 \)) or via usual care (31.3%; \( P=0.02 \)). Thus, encouraging signs would indicate that favorable effects on mortality may follow biomarker-guided HF care in larger trials. To this point, meta-analyses of all studies in the area (positive and negative) indicate a 20% to 25% adjusted reduction in mortality associated with biomarker-guided care on top of standard management (Figure 4),26,27 and preliminary data from a patient data–level pooled analysis of all trials suggest that the reduction in death associated with biomarker-guided care may be even greater (R.T., manuscript in preparation).

Critics of the biomarker-guided HF approach point out that the strategy has gained a reputation for being less effective in elderly patients, but we would argue that this says less about biomarker-guided HF per se and more about the effects of age on HF care and the method of care delivered in the specific trials in question.

First, the elderly are an underrepresented group in RCTs of drug therapies in HF, and some studies suggest that HF therapeutics may have less impact in the elderly. Furthermore, the active clinician is well aware that elderly patients have more medical comorbidities, more advanced HF, and often worse laboratory status compared with younger HF patients. The elderly are also at an increased risk of drug-drug interactions and drug-related side effects, thereby limiting the application of standard HF care in this high-risk population. Thus, biomarker-guided care in the elderly comes with considerable challenges that primarily reflect the difficulties of HF management in this population.

Second, given that biomarker-guided HF care is a strategy, not a simple drug randomization, how the trial clinicians managed the elderly patients and whether substantial NP lowering was achieved in each trial may help to explain why older patients did not show an improvement in outcome in some studies. It is unclear from the TIME-CHF experience whether elderly patients were managed differently than younger patients; however, the degree of NT-proBNP lowering in the aged population was relatively modest. In contrast, although elderly patients in the PROTECT study were nearly twice as likely to suffer adverse cardiovascular events compared with younger subjects, through aggressive management, a 47% reduction in NT-proBNP concentrations was achieved in the elderly subjects treated with biomarker guidance (compared with 45% in younger subjects); this was accompanied by significant lowering of cardiovascular events.28

One possibility is that the successful management of the elderly in PROTECT was achieved by different management strategies: Older patients were seen in the office more frequently than younger patients (7.5 versus 5.0 visits; \( P<0.001 \)), and the aged had more gradual therapy titration.
By the end of the trial, however, the elderly in PROTECT had no significant difference in their medication programs. Another possibility is that patients with HF and preserved ejection fraction (more common in older patients) were not represented in PROTECT as they were in TIME-CMF and BATTLESCARRED. Although NPs are prognostic in patients with HF with preserved ejection fraction and tend to rise and fall in the context of its decompensation, the care of HF with preserved ejection fraction suffers from a lack of guideline-derived medical therapies to improve its outcome. Thus, until more genuinely effective therapies for this form of HF are available, it will not be possible to definitively examine the value of a strategy for its management guided by biomarkers.

**NP-guided care is very well tolerated:** Regardless of overall trial outcome, biomarker-guided care did not lead to an excess of treatment-related adverse events in any trial that has examined the approach. This confirms the ability of clinical judgment to maintain safety if this strategy is used: Clinicians will not keep uptitrating medications in the face of an obvious clinical reason to stop doing so.

**Summary**

To deny the fact that standard HF care has substantial opportunity for improvement is at the peril of even worse outcomes in our patients affected by the disorder. We have presented a strong rationale for the value of BNP- and NT-proBNP–guided HF management. Experience gained in biomarker-guided HF trials suggests that the approach results in improvement in the quality of care without an excess of adverse events related to more aggressive management. This alone is difficult to ignore given the gaps in care that exist between RCTs and real-world practice. Beyond this fact, studies examining the strategy of biomarker-guided HF care have shown substantial improvement in outcome compared with well-managed control arms, benefits that are confirmed in meta-analysis and pooled data analyses, and justifies the imminent launch of the pivotal RCT that will lead to more widespread adoption of the approach.

Compared with standard management, biomarker-guided care appears cost effective, may improve patient quality of life, and may promote reverse ventricular remodeling. Although certain subgroups such as the elderly may respond in a less favorable manner, the care of HF with preserved ejection fraction suffers from a lack of guideline-driven medical therapies to improve its outcome. Thus, until more genuinely effective therapies for this form of HF are available, it will not be possible to definitively examine the value of a strategy for its management guided by biomarkers.

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**References**


Although natriuretic peptides (NPs) are powerful markers of cardiovascular risk in heart failure patients, there is little evidence that heart failure therapy should vary according to measured NP levels. Titration of neurohormonal antagonists to effective or maximally tolerated doses is recommended for all patients regardless of background risk, including the vast majority without markedly elevated NP levels. Although it is intuitively appealing to view NP levels as an objective measure of the adequacy of heart failure therapy, “optimal” NP targets are frequently unachievable in practice. When levels are persistently high, the “guidance” provided by serial NP measurements amounts to little more than a simple prompt to routinely intensify treatment, even when clinical judgment might direct caution. The low rate of serious adverse events with this approach in carefully selected clinical trial populations of younger patients with reduced ejection fraction does not guarantee safety during broader application in real-world practice, in which heart failure patients are often older with complex medical comorbidities and preserved ejection fraction. Drs Januzzi and Troughton correctly highlight the substantial opportunity for improvement in the quality of heart failure care through more consistent application and adjustment of guideline-recommended therapies; however, performance gaps are perhaps better addressed by educating clinicians to make evidence-based decisions rather than by encouraging them to substitute judgment with laboratory testing that has little bearing on the selection of appropriate treatment.
Are Serial BNP Measurements Useful in Heart Failure Management?: Serial Natriuretic Peptide Measurements Are Useful in Heart Failure Management
James L. Januzzi and Richard Troughton

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