The natriuretic peptides are important tools to establish diagnosis and prognosis in heart failure (HF). With application of therapies for HF, changes in both B-type natriuretic peptide (BNP) and its amino terminal cleavage fragment (NT-proBNP) parallel the benefits of the HF therapy applied. This dynamic nature of BNP and NT-proBNP relative to therapeutic intervention in HF has led to the concept of using the biomarkers as a 'guide' for intensification of HF care with a goal of not only achieving guideline-directed medical therapy goals accompanied by targeted natriuretic peptide suppression below prognostic thresholds. In studies achieving this combination of therapy optimization and BNP/NT-proBNP suppression, superior outcomes have been observed, and the approach was well tolerated. Natriuretic peptide-guided HF therapy has recently been given a recommendation in US HF guidelines to achieve guideline-directed medical therapy (Class IIa) and possibly improve outcome (Class IIb), while other clinical practice guidelines (including those from the European Society of Cardiology) await results from emerging clinical trial data. We will review lessons learned in the past regarding this novel concept of biomarker guided HF care, and discuss future directions for the approach.

Keywords
Heart failure • Natriuretic peptides • Management • Outcomes

Introduction

The concept of treatment of heart failure (HF) using natriuretic peptide (NP) guidance has been proposed, studied, and debated for more than a decade. We review the rationale for this approach, summarize the available studies evaluating this strategy, discuss limitations and unanswered questions, and consider future directions for the application of this approach.

Rationale for biomarker guided treatment of heart failure

The burden of HF is forecast to grow significantly into the middle part of this century\(^1\),\(^2\) in terms of prevalence, costs, and healthcare utilization. Although treatment for HF, especially in the setting of LV systolic dysfunction, has advanced significantly in the last three decades, optimal uptake and dosing with proven medications is rarely achieved, while mortality and hospitalization rates for those affected remain high.\(^3\),\(^4\)

The reasons for suboptimal medical therapy in HF are multiple, but the ramifications are clear: despite the fact that clinical practice guidelines emphasize the importance of achieving maximally tolerated doses of available therapies,\(^5\) considerable gaps exist in adherence to this approach. Additionally, the highest risk patients are often the most undertreated, the so-called ‘risk-treatment’ mismatch. There are multiple reasons for discrepancies including intolerance of medications in high-risk patients—such as due to hypotension and azotaemia, the challenge of physical assessment in HF as well as the lack of reliable objective markers to guide the titration of proven therapies. In this regard, availability of a biological measure providing objective data for judging HF severity and response to therapy would be welcome; the widely-studied NP assays [B-type natriuretic peptide (BNP) and NT-proBNP] are objective markers that could be used in this manner to ‘guide’ optimal HF care.\(^5\) Both BNP and NT-proBNP are proven diagnostic and prognostic markers in HF, and their clinical use is now endorsed in clinical practice guidelines for these indications.\(^6\)

B-type natriuretic peptides

The B-type NPs are secreted primarily from cardiac myocytes. Secretion is constitutive in response to changes in LV loading, but is...
modified by local factors including neurohormonal activation—including the sympathetic system and endothelin—and ischaemia. Increasing ventricular wall stress causing myocyte stretch is the primary stimulus for secretion and activates synthesis of the BNP propeptide, which is cleaved into two major molecules—an inactive marker molecule (NT-proBNP) and the bioactive BNP molecule. Both peptides are released into the circulation and are readily measured using commercially available assays. Concentrations of NPs are slightly higher in women, increase with age and also with declining renal function. NP levels also fall with increasing body-mass index.\textsuperscript{9} The correlation of these peptides with measures of LV filling pressure is modest, meaning that neither peptide can be used as an accurate estimate of filling pressure,\textsuperscript{9} and indeed NP concentrations are also determined by a wide array of cardiac structure and functional correlates, including LV size, function, diastolic parameters, and right ventricular filling pressures.\textsuperscript{9}

When measured sequentially, day-to-day variation in plasma NPs levels are evident, but only a small portion is due to measurement variability, with most of the variation reflecting pathophysiological factors. In clinically stable patients with HF, a change in peptide of more than 20–30\% between clinic visits months apart indicates a clinically important change greater than would be expected from background variation.\textsuperscript{10,11} Recent data suggest that there may be more significant day to day variability in BNP levels that is not associated with changes in symptoms, weight, or obvious change clinical status.\textsuperscript{12} Whether the summation of these more frequent measures of BNP would provide a more integrated view of clinical trajectory remains unclear; as well, it is not yet known if daily measurement of BNP would provide a more integrated view of clinical trajectory.\textsuperscript{10,11}

![Figure 1](image)

When measured serially, persistently elevated or increasing levels of NPs are consistently associated with an increased risk of hospitalization or death. The value of NPs as prognostic markers may in part reflect their correlation with other risk markers including age, renal dysfunction, and severity of LV dysfunction. It is important to note that the NPs offer risk prediction that is independent to these other factors.\textsuperscript{13} For subjects with stable chronic HF, increased risk is evident from a BNP level of 100 pg/mL with each further 100 pg/mL rise associated with a 35\% increase in risk.\textsuperscript{14,15} For NT-proBNP, risk is evident from 200 pg/mL and rises almost exponentially with increasing levels, especially above 1000 pg/mL.\textsuperscript{16}

As noted above, beyond merely reflecting elevated filling pressures, NP concentrations reflect a number of relevant targets for standard HF care; importantly, whether in the acute or chronic HF setting, NP concentrations have been shown to fall in response to commonly used therapies for the condition. This includes loop diuretics, but also angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), or mineralocorticoid receptor antagonists (MRA).\textsuperscript{17} The response to \textbeta\-blocker (BB) therapy is more complex, with an occasional initial rise in peptide levels in the first 8–12 weeks followed by a later fall.\textsuperscript{18} Levels of both peptides also fall with initiation or optimization of cardiac resynchronization therapy (CRT)\textsuperscript{19,20}, as well as exercise therapy.\textsuperscript{21} Treatment with newer agents such as the direct renin inhibitor aliskiren is associated with a significant fall in NT-proBNP levels.\textsuperscript{22} However, falls in NT-proBNP levels with aliskiren were not associated with a reduction in clinical events in one study.\textsuperscript{23}

Importantly, the change in NP levels is an important independent predictor of clinical outcome, with the most recent value providing the most accurate estimate of risk. This was most clearly demonstrated in the ValSartan Heart Failure (VAL-HeFT) study, where the lowest risk was seen in subjects whose BNP levels fell <100 pg/mL or NT-proBNP fell <1000 pg/mL during the follow-up.\textsuperscript{24} In contrast, failure of NP concentrations to fall in response to HF therapy suggests that risk is not reduced. These data suggest that serial monitoring with NP levels can provide powerful objective information about the response to therapy and remaining risk.

### Natriuretic peptides for guiding heart failure management

The concept of utilizing a biomarker target for therapy was first examined more than a decade ago by Murdoch et al.,\textsuperscript{25} who demonstrated that BNP levels could be used successfully to guide the up-titration of ACEi. Troughton et al. followed with a seminal study\textsuperscript{26} where HF care ‘guided’ by NT-proBNP was superior to clinical care guided by a congestion score. Notable in this study was significant up-titration of therapy in order to meet a low NT-proBNP goal. From these early studies, the approach for NP-guided HF care has evolved (Figure 1); additionally, through experience gained, hypotheses may be made why several subsequent studies demonstrated benefit from biomarker guided therapy.\textsuperscript{27–29} while some have had encouraging trends [such as reduced event rates in younger subjects or in those with reduced left ventricular ejection fraction (LVEF)]\textsuperscript{30–32} and still others have been neutral\textsuperscript{33–36} (Table 1).

### Importance of the natriuretic peptide target

Risk in HF is directly proportional to NP concentrations, and as articulated above, lower concentrations of either BNP or NT-proBNP following treatment intervention are associated with improved outcome. Accordingly, many of the guided therapy trials that did not meet their primary outcome may have chosen NP targets that were too high to reduce risk in the intervention group.

Part of the evolution of this concept relates to the fact that the choice of target NP values has evolved over time. For example, some studies have evaluated the concept of using the ‘individualized’ value of BNP or NT-proBNP at the time of hospital discharge after an acute decompensation as the ‘stable’ or ‘dry’ NP value; lessons learned from this approach are that immediate post-discharge values are often higher than can be achieved with further therapy titration and considerably higher than the targets mentioned above. In the Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting (STARBRITE) study,\textsuperscript{36} the goal BNP value was near 450 pg/mL, with a change by the end of the trial that was no different than the biological variability of the peptide, and quite similar to that at hospital discharge; given the threshold of risk for BNP is more than half this value, it is unsurprising that adverse event rates were high in the BNP-guided arm, and no different than usual care. In
another study, the Can PRo-brain-natriuretic peptide-guided therapy of chronic heart failure IMprove heart Failure morbidity and mortality (PRIMA) study, the individualized choice of an NT-proBNP value at the end of hospitalization was accompanied by a high event rate.

In addition to high NP targets in the biomarker guided arm, many neutral studies had no significant difference between NP concentrations between the guided therapy and standard care arms, potentially related to inadequate suppression of NP in the guided arm, patient characteristics, or other unmeasured factors. Studies that achieved improved outcomes with guided therapy, such as the Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) or ProBNP Outpatient Tailored Chronic HF Therapy (PROTECT) trial have generally targeted a very low NP level in the intervention group, with considerable difference between the NP arm and the usual care arm.

The approach to natriuretic peptide lowering

No common approach to medication adjustments was taken across the various completed NP-guided HF therapy studies. Across most studies, however, NP-guided therapy was accompanied by numerically (and often statistically) greater addition or up-titration of HF therapies (Table 2)—itself a desirable finding, given gaps in care that are well documented in modern HF care. In those studies with positive results, the difference in therapy additions or up-titrations between natriuretic peptide-guided patients and those treated by usual care was often significant. For example in the PROTECT study, while both arms received more aggressive care than at baseline, NT-proBNP-guided patients received more intensified MRA and BB therapy compared with usual care.

To this point, generally, studies that successfully lowered BNP or NT-proBNP concentrations did not solely titrate loop diuretics, and focused on titration of medications proven to reduce adverse clinical outcomes, such as ACEI, ARB, MRA, and BBs. Indeed in most successful studies, the average doses of therapies compared very well with achieved dose in the landmark studies for each of these agents. In addition to up-titration of proven neurohormonal antagonists, medication adherence, improvement of heart rhythm control for those with atrial fibrillation, and optimization of CRT may improve NP levels. If implementing the approach, clinicians should therefore avoid simply manipulating loop diuretic doses, and regard the under-lying reason(s) for elevated BNP or NT-proBNP when making therapy adjustments; this personalized approach to HF care is one attractive aspect of NP-guided management.

In most of the neutral trials, there was no difference in office visits between guided vs. control arms, whereas increased out-patient visits generally occurred in the intervention arm of successful studies. While low NP target values may seem unreachable in many patients, the successful trials of guided therapy suggest that it takes gradual drug titration and more office visits to achieve these goals.

Understanding natriuretic peptide ‘non-response’

Some patients do not show a significant improvement in these NP levels in response to intensified HF therapy (so-called ‘non-response’). Many other patients have decrease in NP concentrations with therapy but do not reach the goal value regardless of how aggressively they are treated. Aggregate experience would suggest that some NP lowering is better than no lowering at all; for example, in two neutral trials, subjects that had a robust reduction

Figure 1 Conceptual approach for natriuretic peptide-guided heart failure care.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year published</th>
<th>N</th>
<th>Target NP</th>
<th>Primary endpoint</th>
<th>Follow-up</th>
<th>More aggressive care in NP guided arm?</th>
<th>Significant NP lowering?</th>
<th>Result (NP arm vs. usual care)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARBRITE36</td>
<td>2011</td>
<td>130</td>
<td>BNP at hospital discharge</td>
<td>Days alive and not hospitalized</td>
<td>3 months</td>
<td>Yes</td>
<td>No</td>
<td>HR = 0.72, 95% CI = 0.41–1.25 (P = 0.25)</td>
</tr>
<tr>
<td>PRIMA33</td>
<td>2010</td>
<td>345</td>
<td>NT-proBNP at hospital discharge</td>
<td>Days alive and not hospitalized</td>
<td>1.9 years</td>
<td>Yes</td>
<td>No</td>
<td>685 vs. 664 days (P = 0.49)</td>
</tr>
<tr>
<td>SIGNAL-HF35</td>
<td>2010</td>
<td>252</td>
<td>NT-proBNP 50% below entry to the trial</td>
<td>Days alive and not hospitalized, quality of life</td>
<td>9 months</td>
<td>No</td>
<td>No</td>
<td>HR = 0.98, 95% CI = 0.33–2.89 (P = 0.28)</td>
</tr>
<tr>
<td>UPSTEP34</td>
<td>2011</td>
<td>279</td>
<td>BNP &lt;150 pg/mL for age &lt;75; &lt;300 pg/mL for age ≥75</td>
<td>Time to all-cause death, all-cause hospitalization, worsening HF</td>
<td>12 months</td>
<td>No</td>
<td>Not reported</td>
<td>HR = 0.82, 95% CI = 0.6–1.1 (P = 0.18)</td>
</tr>
<tr>
<td>TIME-CHF31</td>
<td>2009</td>
<td>499</td>
<td>NT-proBNP &lt;400 pg/mL for age &lt;75 and 800 pg/mL for age ≥75</td>
<td>All-cause death, all-cause hospitalization</td>
<td>18 months</td>
<td>Yes</td>
<td>No</td>
<td>HR = 0.91, 95% CI = 0.72–1.14 (P = 0.39)</td>
</tr>
<tr>
<td>BATTLESCARRED30</td>
<td>2010</td>
<td>364</td>
<td>NT-proBNP 1270 pg/mL</td>
<td>All-cause mortality</td>
<td>2.8 years</td>
<td>Yes</td>
<td>No</td>
<td>9.1% vs. 18.9% (P = 0.03)</td>
</tr>
<tr>
<td>Troughton et al.26</td>
<td>2000</td>
<td>69</td>
<td>NT-proBNP 1735 pg/mL</td>
<td>Total cardiovascular events</td>
<td>9.5 months</td>
<td>Yes</td>
<td>Yes</td>
<td>19 vs. 54 events (P = 0.02)</td>
</tr>
<tr>
<td>STARS-BNP28</td>
<td>2007</td>
<td>220</td>
<td>BNP 100 pg/mL</td>
<td>HF death, HF hospitalization</td>
<td>15 months</td>
<td>Yes</td>
<td>Unknown</td>
<td>Event rate of 24 vs. 52% (P &lt; 0.001)</td>
</tr>
<tr>
<td>Berger et al.27</td>
<td>2010</td>
<td>278</td>
<td>NT-proBNP 2200 pg/mL</td>
<td>All-cause mortality, HF hospitalization</td>
<td>12 months</td>
<td>Yes</td>
<td>Yes</td>
<td>488 vs. 1588 days (P &lt; 0.001)</td>
</tr>
<tr>
<td>PROTECT29</td>
<td>2011</td>
<td>151</td>
<td>NT-proBNP 1000 pg/mL</td>
<td>Total cardiovascular events</td>
<td>10 months</td>
<td>Yes</td>
<td>Yes</td>
<td>58 vs. 100 events (P = 0.009)</td>
</tr>
</tbody>
</table>

Table I Comparison of B-type natriuretic peptide (BNP) or NT-proBNP guided heart failure therapy trials
<table>
<thead>
<tr>
<th>Trial</th>
<th>Loop diuretics</th>
<th>ACEi</th>
<th>ARB</th>
<th>BB</th>
<th>MRA</th>
<th>Reported as % of target doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIGNAL-HF</td>
<td>N/R</td>
<td>N/R</td>
<td>51% of target</td>
<td>14.7% of target*</td>
<td>43.5% of target*</td>
<td>43.8% of target*</td>
</tr>
<tr>
<td>Berger et al.</td>
<td>47 mg</td>
<td>76 mg</td>
<td>100% of target (ACEi/ARB)</td>
<td>54% of target (ACEi/ARB)</td>
<td>100% of target (ACEi/ARB)</td>
<td>54% of target (ACEi/ARB)</td>
</tr>
<tr>
<td>TIME-CHEF</td>
<td>N/R</td>
<td>N/R</td>
<td>Age &lt;75 years: 29% of target</td>
<td>Age &gt;75 years: 16% of target</td>
<td>Age &lt;75 years: 29% of target</td>
<td>Age &gt;75 years: 16% of target</td>
</tr>
<tr>
<td>Troughton et al.</td>
<td>197 mg</td>
<td>141 mg</td>
<td>20.1 mg</td>
<td>19 mg***</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>UPSTEP</td>
<td>74 mg</td>
<td>82 mg</td>
<td>21 mg</td>
<td>20 mg</td>
<td>25 mg</td>
<td>16 mg</td>
</tr>
<tr>
<td>BATTLESCARRED*</td>
<td>200 mg</td>
<td>140 mg*</td>
<td>12.4 mg</td>
<td>16 mg</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>STARS-BNP</td>
<td>55%</td>
<td>26%****</td>
<td>21%</td>
<td>17%****</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>STARBRITRE</td>
<td>120 mg</td>
<td>120 mg</td>
<td>75 mg</td>
<td>68.3%</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>PRIMA</td>
<td>91%</td>
<td>92%</td>
<td>87% (ACEi/ARB)</td>
<td>78%**** (ACEi/ARB)</td>
<td>87% (ACEi/ARB)</td>
<td>78%**** (ACEi/ARB)</td>
</tr>
<tr>
<td>PROTECT</td>
<td>85.3%</td>
<td>96.1%***</td>
<td>74.7%</td>
<td>60.5%</td>
<td>12.0%</td>
<td>22.4%***</td>
</tr>
</tbody>
</table>

P-values refer to NP guided vs. usual care, and are displayed as reported. N/R denotes: not reported; mg denotes: milligrams. Abbreviations are otherwise as defined in the text. ACEi/ARB identifies studies that reported the combination of either/or agent, rather than individually. *P < 0.001; **P = 0.03; ***P = 0.05; ****P = 0.06; *****P < 0.05; ******P = 0.001.
in their NT-proBNP had improvement in outcome, despite the neutral overall trial results. In the PROTECT study, a clear gradient of risk was present relative to achieved NT-proBNP values and the amount of time spent at or below the target was a better predictor of outcomes than the absolute value achieved.

Subgroup analyses of the larger studies of NP-guided therapy have suggested that this older patients are more likely to have BNP or NT-proBNP values that are difficult to lower, and NP-guided HF care may be less useful in this population. This observation underscores the challenge of HF therapy in the elderly: intolerances to therapies are greater in older patients, and goal doses of drugs are less likely to be achieved.

Regardless of the heterogeneity of published results, three meta-analyses of published studies indicate significant reduction in mortality associated with biomarker guided care on top of standard management (Figure 2). More recently, a pooled analysis of primary data from all studies confirms this finding, and in fact indicates a 41% reduction in all cause mortality in those <75 years of age; the benefits of biomarker guided care in the pooled analysis were less obvious in elderly subjects, however.

**Unanswered questions about biomarker guided heart failure management**

As reviewed above, the accumulated data to date have both provided intriguing signals regarding the efficacy of biomarker guided HF therapy. However, the accumulated evidence still represents less than 3000 patients randomized overall, a modest sample size when comparing two ‘active’ strategies, which pales in comparison with typical drug development programs. Given this still limited experience and the heterogeneity of methodology and results across trials, biomarker guided management has not been given a Class I recommendation in any of the major clinical practice guidelines. The new guidelines from the American College of Cardiology/American Heart Association take a somewhat more nuanced stance on the utility of this approach; in these recently published clinical practice guidelines, a class IIa recommendation (i.e. ‘is reasonable to consider’) was stated for use of NP guidance to achieve optimal dosing of guideline-directed medical therapy. However, the guidelines note that the usefulness of this approach to reduce hospitalization or mortality is not well established (class IIb). Still, the overall balance of current guideline recommendations suggests persistent equipoise about the efficacy and safety of biomarker guided therapy based on the current evidence base, but none of the other major clinical practice guidelines from the USA, Europe, or Australia/New Zealand have taken a stance on this matter to the pro or con. In addition to this fundamental uncertainty, additional questions remain to be fully answered.

**Can both B-type natriuretic peptide and NT-pro-B-type natriuretic peptide be used for out-patient biomarker guided heart failure care?**

Although it would seem intuitively obvious that BNP and NT-proBNP might be both useful for guiding HF care, substantial...
differences between these biomarkers exist. For example, BNP and NT-proBNP have considerably different half lives, which may lead to different behaviour of concentrations during the course of HF care. Indeed, meta-analytic data suggest that BNP-guided HF care may be less useful than that with NT-proBNP.\(^{40,41}\) In the meta-analysis by Savarese et al.,\(^{41}\) NT-proBNP-guided therapy reduced death by 28% (\(P = 0.007\)) and HF hospitalization by 47% (\(P = 0.003\)), whereas BNP-guided therapy reduced these outcomes by 19% (\(P = 0.37\)) and 40% (\(P = 0.14\)). The aggregate number of subjects studied with BNP was smaller in this meta-analysis; thus, more information is needed regarding the comparative merits of the two markers for guided therapy.

**What is the best timing or location for biomarker guided heart failure care?**

As noted above, considerable heterogeneity exists with respect to the various trials that have examined natriuretic peptide-guided HF care. One of the biggest differences among the studies was the timing of patient enrolment; some trials enrolled subjects close to hospital discharge,\(^{27,33,36}\) while others studied ambulatory patients with chronic HF. Presumably, patients close to hospital discharge are at higher risk for recurrent events and thus might benefit from earlier biomarker guided care. Additionally, an open question is who might deliver biomarker guided HF care, and in what venue: in most trials, NP-guided care was administered by experienced cardiologists; whether this strategy can be adopted by non-cardiovascular specialists remains unclear.

**How truly safe is this strategy?**

One important uncertainty about biomarker guided HF therapy is whether more aggressive titration of HF therapy in order to achieve specific NP targets will be safe, particularly with regard to therapy-related side effects such as hypotension, hyperkalemia, and worsening renal function. As noted, while none of the prior studies published to date has reported an important increase in adverse events associated with biomarker guided therapy, in general previous trials have potentially been too small to exclude important safety signals. The most robust analysis of safety to date has been a recent publication from the TIME-CHF study, which showed no difference in dropout rate, adverse events, or serious adverse events between those randomized to biomarker guided therapy vs. those randomized to usual care.\(^{45}\) Interestingly, while more aggressive care typically follows NP-guided HF care, these same investigators reported worse worsening renal function or hyperkalemia (common concerns in those treated with more aggressive means, such as biomarker guided care) was no more common in those treated with NT-proBNP-guided care.\(^{46,47}\)

**Is there an interaction with age?**

As noted above, most (but not all) studies that have examined the relative efficacy by age have suggested that benefits are primarily limited to younger patients; this finding is confirmed in a meta-analysis of three trials\(^{41}\) and a pooled analysis of all available trial data. In both BATTLESCARRED and TIME-CHF, randomization was stratified by age; these analyses were pre-specified in the protocol, and the outcomes were notably better in younger subjects.\(^{30,31}\) In contrast, in the PROTECT trial, which suggested a substantial benefit of biomarker guided therapy in the elderly, the results came from a post hoc analysis.\(^{43}\) Whether this is a true subgroup effect or whether the apparent lack of efficacy in older patients is related to trial design factors or limited sample size remains unknown. This question is important given that HF is substantially a disease of the elderly.

**Could other factors confound the use of biomarkers to guide therapy?**

Gender, renal function, body mass, and the presence of atrial fibrillation all influence BNP/NT-proBNP levels. Whether these factors impact on the efficacy of NP-guided HF care is uncertain and requires further analysis, especially to determine whether alternative targets may be more appropriate in some settings. By comparison, the accurate diagnosis of acute HF using BNP/NT-proBNP is modified only slightly by age, gender, body-mass index, presence of renal dysfunction, or atrial fibrillation, allowing standard peptide cut-points to be used to rule out HF in each of these settings.

The impact of LVEF on NP-guided care is also uncertain—only 10% of patients involved in studies of BNP or NT-proBNP-guided therapy had preserved LVEF. Heart failure with preserved EF differs in pathophysiology, patterns of neurohormonal activation, natural history, and treatment efficacy when compared with HF with reduced LVEF.\(^{49,50}\) Recent reports suggest that treatment efficacy may be attenuated in subjects with HF with preserved EF and very high NT-proBNP levels, a finding that could limit utility for NF-guided care in this context\(^{32,51}\); that said the role of biomarker guided care of any kind in HF with preserved EF may only be defined once proven therapies that reduce improve clinical outcomes in such patients are established.

**Is there a benefit on quality of life?**

Although improving morbidity and mortality remain the critical focus for HF therapies, improvements in health-related reported quality of life is also highly desirable given the high symptom burden of affected patients. The TIME-CHF study examined several quality of life instruments, finding similar improvement in biomarker-guided and control patients.\(^{35}\) Alternatively, the PROTECT study showed significant improvements in Minnesota Living with HF Quality of Life questionnaires in patients assigned to a biomarker guided strategy.\(^{52}\)

**Does natriuretic peptide-guided therapy lead to improvements in cardiac function?**

Recent data suggest that over the long term, NP concentrations may be predictive of deleterious LV remodelling\(^ {53} \); accordingly, a strategy that results in durably significant lowering of BNP or NT-proBNP (which indirectly reflect a risk for progressive LV dilation or reduction in LVEF) may hypothetically be associated with favourable reverse LV remodelling. Recent data suggest this to be possibly the case.\(^ {54}\)

**Is biomarker guided therapy cost-effective?**

A critical question for any therapeutic strategy in the current era of cost containment relates to cost and cost effectiveness. A biomarker-guided strategy is likely to be somewhat more expensive than usual
care initially due to the higher intensity of care provided. Importantly however, much of this care is provided in an ambulatory setting and thus may be less expensive compared with the cost of hospitalization. Depending on the balance of these issues, biomarker guided HF therapy could be cost effective or potentially even ‘dominant’ (i.e. more efficacious yet cheaper), as suggested by recent European analyses. An analysis of data from TIME-CHF suggested that a biomarker guided strategy saved approximately $3000 US dollars per patient (Figure 3). Despite the consistency of data across these several analyses, given the heterogeneity between trials, caution is required when considering the cost effectiveness of NP at this stage. Whether larger studies in more diverse populations

**Figure 3** Cost effectiveness of NT-pro-B-type natriuretic peptide-guided HF care in the TIME-CHF study. Biomarker guided care was more likely to be cost effective than standard management in multiple study groups with most patients in the ‘southeast’ quadrant of less expensive (y-axis) and greater survival (x-axis). Reproduced with permission from Ref.57
will bear out this finding remain a critical unanswered question that requires considerable examination.

Future directions

In light of the persistent uncertainties about the role of biomarker-guided management in HF, the US National Heart Lung Blood Institute has funded the GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) study (NCT01685840, clinicaltrials.gov). GUIDE-IT is a prospective, multicentre, randomized trial that will randomize 1100 patients with HF and LVEF ≤ 40% at the time of discharge from a HF hospitalization to either a strategy of biomarker guided care (targeting NT-proBNP levels ≤ 1000 pg/mL) or usual care. The primary endpoint is time to cardiovascular death or first HF hospitalization. Important secondary endpoints will include all-cause mortality, cumulative morbidity, health-related quality of life, cost and cost effectiveness, and safety. Enrolment into the GUIDE-IT study began in January 2013. GUIDE-IT will represent the largest and most generalizable study of biomarker guided therapy performed to date, and will enrol patients at over 40 sites in the USA and Canada. In association with prior data reviewed above, the GUIDE-IT study should be adequately powered to provide more definitive answers about the safety and efficacy of natriuretic peptide HF guided therapy.

Although this review has focused on the use of natriuretic peptide-guided titration of therapies in the management of patients with chronic HF, the underlying principles are potentially generalizable beyond just chronic HF and beyond just the natriuretic peptides. The use of natriuretic peptides in guiding treatment for patients hospitalized with acute HF, or in targeting patients at the risk of HF for prevention strategies are both attractive avenues for future research. Prevention of HF, in particular, is a major public health goal; both BNP and NT-proBNP are well-established markers of future risk of the diagnosis in the general population. Emerging data from completed and ongoing studies suggest that a strategy of targeting prevention strategies based on NP levels may be safe and efficacious. Further studies will be needed to provide evidence of whether this approach is generalizable to broader populations.

At present, biomarker guided therapy for HF has focused almost exclusively on the use of the NPs, which are by far the most well characterized HF biomarkers. A variety of other biomarkers to guide or select HF therapy have been proposed, although to date none of these has been tested prospectively. In particular, two biomarkers, soluble (s)ST2 and galectin-3, have been proposed to have utility for selecting patients most likely to benefit from specific interventions. A study of the relationship between sST2 and the effect of eplerenone in post-MI patients with LV dysfunction showed that elevations of sST2 at baseline were associated with greater adverse post MI remodelling, and that this effect could be attenuated in patient randomized to MRA therapy. Similarly, a post hoc analysis suggested that high galectin-3 levels could predict lack of treatment response with statins. Although these observations would need to be replicated prospectively in randomized trials before they could incorporated into clinical practice, they suggest a way forward in developing targeted therapies for HF based on knowledge of specific pathophysiological processes measured in vivo, using specific biomarkers.

Conclusions

During the last decade or more, the concept of biomarker-guided management for HF based on NP targets has been an intriguing and controversial topic. While individual studies have had inadequate power to test hard clinical endpoints, recent pooled analyses suggest that this strategy may reduce mortality and hospitalization, particularly for younger patients with HF due to LVSD. The recent launch of the largest randomized trial of this approach to date, the GUIDE-IT study, promises to provide more data to inform decision making about the efficacy and safety of this approach. Moving forward, the continued discovery and validation of new biomarkers that characterize specific pathophysiological processes may allow for more precise targeting of specific therapies at specific populations of patients with the greatest likelihood of benefit.

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