Natriuretic Peptide-Guided Therapy for Heart Failure

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Chronic heart failure (HF) remains a major medical problem in the developed world, with rapidly rising prevalence, substantial morbidity, and high costs. The concept of titrating chronic HF therapies using physiologic markers, so called “biomarker guided therapy (BGT)”, has become an area of substantial interest in HF given the underutilization of evidence-based medications and suboptimal outcomes with current management strategies. Several recent trials of BGT have had mixed results, with some demonstrating improved outcomes and others showing no benefit. The heterogeneity of patient populations compounded by the lack of standardized BGT algorithms and trial endpoints has complicated interpretation of these results. This article reviews the rationale, accumulated data, and unanswered questions for BGT in chronic HF. (Circ J 2011; 75: 2031–2037)

Key Words: Biomarker-guided therapy; Heart failure; Natriuretic peptides

Heart failure (HF) is a major and growing public health problem worldwide, and there is a pressing need to improve outcomes and decrease costs.1 Although a variety of medical treatments have been shown to improve outcome in chronic HF, proven treatments are frequently underutilized or prescribed an inadequate doses.2 Current guidelines recommend titrating evidence-based medications to doses attained in clinical trials or to the maximally tolerated dose.1,3 but therapy in clinical practice frequently fails to approach these target doses. Physicians are often reluctant to aggressively titrate therapies in apparently stable patients, and the perceived side effects of medications overlaps with symptoms of HF. This therapeutic inertia leads to a “quality gap” between guideline recommendations and clinical practice.

A variety of methods have been evaluated to improve quality of care and long-term outcomes of ambulatory HF patients. These have included disease management strategies such as nursing-based interventions, daily weight algorithms, remote HF-status monitoring systems, and implantable hemodynamic monitoring.4 The benefits of these strategies have been mixed and their high cost and difficult implementation limit their universal application. The use of biomarkers as a target for titration of therapy, so called “biomarker guided therapy (BGT)”, has been investigated as a novel approach to guiding HF management. This review will provide an overview of the rationale, accumulated data, and unanswered questions for BGT in chronic HF.

Defining Biomarkers

A “biomarker” can be defined as “a characteristic that is objectively measured and evaluated as an indicator of normal physiologic processes, pathogenic processes, or the response to a therapeutic intervention.”5 As recently reviewed by Braunwald, biomarkers should fulfill several key criteria in order to be clinically useful.6 Measurements need to be obtained quickly, accurately, and at a reasonable cost. Biomarkers need to add information to routine clinical assessment and assist with diagnosis, prognosis, and management by reflecting improvement during evidence-based therapy. While no biomarker satisfies all of these criteria, recognizing the performance characteristics of specific biomarkers allows for appropriate clinical use.

The concept of using biomarkers as biological targets to guide management is commonplace in many chronic diseases. Two examples from cardiovascular (CV) medicine include hyperlipidemia and diabetes. In each of these conditions, therapy is titrated to achieve a specific biomarker level (low-density lipoprotein cholesterol <100mg/dl or hemoglobin A1c <7%) that has been shown to improve outcomes. These biomarkers allow clinicians to differentiate responders from non-responders and adjust therapy appropriately (eg, medication addition, uptitration, or substitution). In contrast, in contemporary HF care, the use of biomarkers has been limited to diagnosis, prognosis, and risk stratification.7 Adjustment of chronic therapy has focused primarily on patient symptomatology and target doses from clinical trials rather than individualized dosing based on physiologic parameters. However, these trial doses may be too high for some patients and too low for others. Some patients experience unnecessary side effects while others might be undertreated. Individualization of drug regimens based on biomarker data might prove more efficacious than treatment dictated by a “one-size fits all” approach, a hypothesis that has been tested in the clinical trials reviewed below.

Physiology of Natriuretic Peptides (NP)

NP are the most extensively studied and validated biomarkers in HF. NP provide information about elevated filling pressure as...
well as chronic cardiac dysfunction and remodeling. B-type natriuretic peptide (BNP) is synthesized in myocytes as proBNP, released in response to ventricular stress and subsequently cleaved into the active peptide hormone (BNP) and the inactive N-terminal peptide fragment (NT-proBNP). BNP opposes many of the abnormalities of HF with a role in natriuresis, vasodilation, enhancement of ventricular relaxation, inhibition of fibroblast activation, and suppression of the renin-angiotensin-aldosterone system.11

Both BNP and NT-proBNP have been evaluated in HF patients and provide similar information, but the 2 biomarkers have important distinctions.11,12 BNP is the active hormone, degraded by endopeptidases, with a half-life of 5–10 min. NT-proBNP is inactive, cleared primarily by the kidneys, and has a half-life of 25–120 min.12 The 2 also have different ranges and proposed normal cut-off ranges (Table 1).

### Table 1. The Natriuretic Peptides

<table>
<thead>
<tr>
<th>Activity</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal concentration (pg/ml)</td>
<td>Bioactive</td>
<td>Inactive</td>
</tr>
<tr>
<td>5–50</td>
<td>7–160</td>
<td></td>
</tr>
<tr>
<td>Half-life (min)</td>
<td>5–10</td>
<td>25–120</td>
</tr>
<tr>
<td>Time to reflect meaningful change in hemodynamics (h)</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Approved cut-off to define abnormal range (pg/ml)</td>
<td>100</td>
<td>125 (&lt;75 years old), 450 (≥75 years old)</td>
</tr>
</tbody>
</table>

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

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### Guiding Therapy With NP: Observational Data

Observational data provide the rationale for guiding therapy based on NP concentrations.4 HF therapies proven to have beneficial long-term effects on morbidity and mortality, such as angiotensin converting enzyme (ACE)-inhibitors,13 angiotensin receptor blockers,14 β-blockers,15 aldosterone antagonists,16 and cardiac resynchronization therapy,17 all generally decrease NP levels when given chronically. In both the acute and chronic setting, higher NP levels are strong predictors of subsequent mortality.18–24 Additionally, observational studies have shown an association between decreasing NP levels over time and improved outcomes in both inpatients and outpatients.
In a representative study, Masson et al examined the prognostic value of baseline and 4 month NT-proBNP values in a prospective substudy of patients enrolled in the placebo arm of the Valsartan Heart Failure (Val-HeFT) study. This study demonstrated the powerful association of change in NT-proBNP concentrations across a threshold level over time with subsequent clinical outcomes. Patients in whom NP concentrations decreased in response to ongoing therapy had a better prognosis than patients in whom concentrations did not change or increased (Figure 1). A similar analysis focusing on BNP by Latini et al demonstrated substantially similar results.

These findings appear to be consistent across multiple studies and provide a strong observational foundation for the concept of NP-guided therapy in HF.

### Biomarker-Guided Therapy for HF: Clinical Trials

Several small, randomized trials of BGT have been published. These studies have generally had mixed results with 4 meeting their primary efficacy endpoint and 5 being neutral (Table 2).

| Table 2. Summary of Randomized Controlled Trials of Biomarker Guided Therapy in Heart Failure |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| N    | Troughton | STARS-BNP | STARBRIT | TIME-CHF | BATTLE-SCARRED | PRIMA | Berger | SIGNAL-HF | PROTECT |
| Marker | NT-proBNP | BNP | BNP | NT-proBNP | NT-proBNP | NT-proBNP | NT-proBNP | NT-proBNP | NT-proBNP |
| Target | 1,692 pg/ml | 100 pg/ml | <2×D/C level | 400 or 800 pg/ml* | 1,270 pg/ml | D/C level | 2,200 pg/ml | 50% reduction | 1,000 pg/ml |
| Follow-up (months) | 9.6 | 15 | 3 | 18 | 12 | 12 | 15 | 9 | 10 |
| Primary endpoint | CV death + CV hospitalization + WHF | HF death + HF hospitalization + WHF | Days alive and out of hospital | All-cause death or hospitalization | All-cause death | Days alive and out of hospital | Total days of HF hospitalization | Days alive and out of hospital | Total CV events |
| Result for primary endpoint | + | + | Neutral | Neutral | Neutral | Neutral | + | Neutral | + |

*400 pg/ml if age <75 and 800 pg/ml if age >75.

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### Troughton et al

Troughton et al conducted the first pilot study of BGT vs. clinical assessment alone in HF. This small, unblinded study prior to the widespread use of β-blockers tested treatment intensification targeting a relatively high NT-proBNP goal. BGT resulted in a significant reduction in the composite endpoint of CV death, CV hospitalization, and worsening HF. BGT resulted in slightly higher doses of ACE-inhibitors as well as a greater likelihood of spironolactone prescription without increased adverse events. The trial supported the hypothesis that drug treatment guided by BNP concentration could reduce total CV events and laid the groundwork for larger studies.

### STARS-BNP

The STARS-BNP trial confirmed several findings from the Troughton study in a well-treated ambulatory HF population. The unblinded, multicenter investigation studied patients who underwent drug optimization prior to the study and were randomized to BNP-guided therapy or usual care. The study showed a significant reduction in the primary composite end-
point of HF death and HF hospitalization in the BGT arm that was mainly driven by a reduction in HF hospitalization. There was no significant difference in the secondary endpoints of all-cause mortality or all-cause hospitalization. The study protocol did not provide specific guidance on how to achieve target NP values. Nonetheless, the BGT arm experienced more frequent and greater dose up-titration for ACE-inhibitors, β-blockers, and spironolactone compared with usual care (Figure 2) with the BNP value triggering adjustment of therapy 79% of the time. STARS-BNP highlighted the practical difficulties of reaching very rigorous NP target values with only a third of the patients reaching goal at 3 months.

**STARBRITE**
The STARBRITE study was designed to investigate a role for individualized BGT in reduction of all-cause mortality and hospitalization.39 It was a small, unblinded study of HF patients enrolled at the time of hospital discharge at 3 referral centers with a patient population that tended to be younger and sicker than other BGT trials, possibly limiting the generalizability.33 The individualized target BNP was based on the final BNP measurement drawn during the index admission (goal BNP ≤2×discharge value). The trial’s primary endpoint was total days alive and out of the hospital over a relatively short follow-up of 3 months. Similar to the secondary endpoints in the STARS-BNP study, in STARBRITE there was no benefit for the endpoint of all-cause mortality and hospitalization. As in the earlier trials, STARBRITE demonstrated a significant increase of ACE-inhibitor use and a trend toward greater use of β-blockers with BGT.

**TIME-CHF**
Given the variable results of these earlier BGT trials, the TIME-CHF trial was designed to be a large trial including the very elderly with an age-adjusted NP target and a suggested drug escalation protocol.34 BGT reduced NT-proBNP levels to a similar degree compared to clinical assessment alone and had no significant effect on the primary endpoint of hospitalization-free survival. For the secondary endpoint of survival free of HF hospitalization, BGT resulted in improved outcomes with a hazard ratio 0.68 (95%CI, 0.50–0.92). This was generally consistent with prior trials, showing a benefit with respect to CV-related endpoints but not for all-cause endpoints. However, the TIME-CHF results also hinted at an overall mortality benefit confined to patients younger than 75. In younger patients, BGT improved hospitalization-free survival, HF-hospitalization-free survival and overall survival by 30%, 58%, and 59% (P≤0.05), respectively. Conversely, there was a suggestion that BGT might have caused more serious adverse events in the older group.

Patients in the BGT arm had a greater up-titration of ACE-inhibitors/angiotensin receptor blockers, β-blockers, and spironolactone than the control group. However, the older patients had less intensification of β-blockers in both study arms. In the appropriate patient (paricularly those <75 years old), it seemed possible to further optimize and uptitrate medical therapy even in the absence of worsening symptoms.35 Alternatively, some questioned the utility of BGT in older patients because they might be harmed by uptitrating doses too high.36 However, those patient in the trial that were >75 years old tended to be sicker (eg, more coronary artery disease, worse renal function, lower ejection fraction, and other symptoms) than the younger patients. Potentially, the less aggressive uptitration of evidence-based medications in the elderly might have been observed as a result of confounding and could have played a role in the lack of benefit for BGT in this age group. The data supported a benefit to BGT but the mixed results depending on study endpoints and age stratification indicated that the expected benefit and optimal BNP target levels are unlikely to be uniform in the heterogenous HF population.

**PRIMA**
PRIMA was a fairly large, single-blind study of BGT vs. symptom-based management targeting an individualized NT-proBNP target level set as the lowest level at discharge or 2 weeks after.38 A high NP level entry criteria and threshold for intensification as well as the atypical patient population (<40% had a history of HF) have been cited as possible limitations to generalizability.32 The study demonstrated no difference in the primary endpoint of days alive and out of the hospital or for the secondary endpoints of total mortality, CV mortality, and days admitted to the hospital. Interestingly, BGT led to a 21% reduction in mortality but a study of 2,000 patients would have been required to attain statistical significance.36 In patients ≤75 years old, there was a trend toward improved outcome with BGT for the primary endpoint. BGT significantly increased use of evidence-based HF medications. At 1-year follow-up, 80% of patients met their target level suggesting that the target level might not have been low enough to derive a significant benefit from BGT.

**BATTLESCARRED**
BATTLESCARRED was the second largest BGT trial to date exploring long-term BGT and its effect on all-cause mortality.37 The double-blind, 3-arm study evaluated BGT compared to intensive clinical management guided by a HF score or usual care. Treatment strategies were carried out for 2 years with pre-specified age stratification. NT-proBNP concentrations fell similarly in both the BGT and intensive management groups with levels above the goal in more than half of the patients. The primary outcome of total mortality was similar between BGT and intensive management at 1 year, while 3-year mortality was selectively reduced in those ≤75 years old in the BGT arm. Notably, the overall number of events was low (<20 deaths in all groups). The authors hypothesized that perhaps BGT allowed for the establishment of more effective individualized therapy during the 2-year treatment with resultant sustained benefit. No benefit for BGT was observed for patients >75 years old. This benefit of BGT confined to the younger age group parallels the results of TIME-CHF as well as to the 2 prior positive studies that enrolled younger patients.30,31

In terms of medication adjustment, ACE-inhibitor doses were not uptitrated significantly in any of the arms and β-blocker doses increased similarly in both the BGT and intensive management study arms. Interestingly, spironolactone use was observed to significantly drop within the BGT group. With regard to age, the older patient subgroup received only 79% and 50% of the ACE-inhibitor and β-blocker doses, respectively, of younger patients and met target doses significantly less frequently. To what extent these differences were a result of patients’ tolerability and/or physician interpretation remains to be characterized. The combination of lower doses of medical therapy and a higher proportion of patients with preserved ejection fraction (where efficacy of these agents is uncertain) as well as more comorbidities are potential reasons for the lack of observed benefit in older patients.

**Berger et al**
One potential criticism of BGT is that it is simply another type of HF disease management intervention. A recently completed
The study specifically addressed whether BGT had additive effects beyond that of disease management alone. The prospective study randomized patients at the time of discharge from a HF hospitalization to 1 of 3 arms: usual care, a multidisciplinary disease management program, or disease management plus individualized HF therapy based on NT-proBNP concentrations. In the biomarker-guided arm, both the frequency of visits and the titration of HF treatment were based on serial measurement of NT-proBNP concentrations. BGT was associated with a greater proportion of patients receiving intensified medical therapy (defined as being treated with spironolactone as well as ACE-inhibitors and β-blockers at ≥50% of target doses) compared to usual care or disease management, and this greater intensification of proven therapies resulted in a significantly greater reduction of NT-proBNP concentrations in the BGT arm than in the disease management arm. Most importantly, randomization to BGT was associated with a significant improvement in the survival free of HF hospitalization (37%) compared to disease management alone (50%) or usual care (65%) at 18 months. Interestingly, the number of visits with a HF specialist was similar in the BGT and multidisciplinary care arms due to the increased number of scheduled contacts and reduced number of unscheduled visits with BGT. These data suggest that BGT has additional biologic effects and provides additive and clinically important benefits above and beyond that provided by intensified disease management alone.

**SIGNAL-HF**

Persson et al performed the first trial of BGT in the primary care setting. The BGT target was at least a 50% reduction from baseline NT-proBNP regardless of symptoms. There was no difference between groups for the primary composite endpoint using a rank score of days alive, days out of the hospital, and a symptom score. Similar symptom improvement, drug escalation, and NP reduction were observed in both study arms. A potential criticism of the trial is that it was underpowered to show a significant difference in the primary endpoint.

**PROTECT**

The recently presented results of the PROTECT study highlighted the apparent benefit of BGT for CV endpoints and demonstrated an intriguing finding with respect to age interaction. The single-center study of BGT was halted early when an interim analysis found a significant reduction in the primary composite endpoint of total CV events with a hazard ratio of 0.44 (P=0.019) that was driven mainly by improvement in worsening HF and HF hospitalization with a non-significant reduction in CV death. Interestingly, in PROTECT the outcome benefit was more pronounced in patients ≥75 years old than in younger patients. The investigators noted that the elderly were seen more frequently in follow-up and had smaller incremental changes made in their medical regimens. These data argue against assertions about the lack of benefit of BGT in the elderly and suggests that physicians must adjust the way they approach the elderly clinically. Additional findings of the trial included a significant drop in the use of loop diuretics with BGT, which was hypothesized to occur because of significant suppression of neurohormonal activity as a result of aldosterone antagonist up titration. While there was a trend toward greater β-blocker up titration with BGT, there was a significant increase in angiotensin receptor-blocker use with standard care compared to BGT.

**Data From Meta-Analyses and Trial Data Summary**

These studies investigating different populations, NP targets, clinical endpoints, and control groups demonstrate the heterogeneity of BGT. A recent meta-analysis of the first 6 trials discussed above showed that BGT was superior to control strategies with an approximately 30% reduction in all-cause
mortality (Figure 3). The heterogeneity across the studies with respect to non-fatal endpoints precluded formal meta-analysis, but in general, disease-specific hospitalizations appeared to be reduced by BGT, whereas all-cause and non-cardiac hospitalizations were less impacted. Similar findings were seen in a subsequent meta-analysis where BGT resulted in a relative risk of all-cause mortality of 0.76 (95%CI 0.63–0.91) with benefit confined to those <75 years old.

Several recurrent themes emerge from the review of the trial data. The totality of the current evidence suggests that BGT appears to be effective particularly in younger patients (those <75), although the PROTECT data actually showed a larger treatment effect in the elderly than in younger patients. Absolute NP targets, in particular low targets, seem to be more efficacious than relative or individualized targets. BGT performs better in patients with systolic dysfunction than in those with preserved ejection fraction as evidenced by the observation that all studies that included a significant number of HF patients with preserved ejection failed. Finally, BGT has tended to show a more powerful signal for disease-specific endpoints rather than all-cause endpoints (similar to most other efficacious HF interventions).

Unresolved Issues

Is BGT Proven Effective?
Although suggestive, underpowered trials and meta-analyses do not provide definitive evidence of benefit. BGT is not recommended by any of the current HF guidelines, and none of the previous studies have been adequately powered to address questions of morbidity and mortality in a contemporary, well-treated population with systolic HF. Braunwald’s recent comprehensive review on the topic of BGT for HF concludes “additional well-powered trials will be important for further establishing NP goals and the clinical benefit of a NP guided approach to HF management”.

Is It Safe?
One important uncertainty about BGT is whether more aggressive titration of HF therapy towards specific NP targets will be safe, particularly with regard to hypotension, hyperkalemia, and worsening renal function. None of the studies published to date have reported an increase in adverse events associated with BGT, but in general previous trials have been too small for important safety signals to emerge.

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. Two prior studies (TIME-CHF and BATTLESCARRED) stratified randomization and pre-specified sub-group analysis based on age. Although these subgroups were small, the beneficial effects of biomarker guidance in both studies appeared to be primarily limited to younger patients. Two prior studies of BGT have been conducted in academic settings, and the SIGNAL-HF in primary care practices found no significant benefits to BGT over usual care.

Conclusions and Future Directions
The use of biomarkers such as NP to titrate medical therapy for chronic HF is biologically attractive but as yet unproven. The data from multiple small, randomized trials are mixed, but the totality of evidence suggests that carefully implemented BGT might improve disease-specific outcomes, particularly in patients under age 75. The current body of evidence regarding BGT provides the foundation for future large-scale trials to definitively establish the role of BGT in the management of patients with HF with regard to clinical effectiveness, safety, cost-effectiveness, and generalizability.

Disclosures
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