REVIEW

The role of natriuretic peptide testing in guiding chronic heart failure management: Review of available data and recommendations for use

Rôle des peptides natriurétiques pour guider le traitement de l’insuffisance cardiaque chronique : revue des données disponibles et recommandations

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KEYWORDS
Natriuretic peptides; Heart failure; Outcomes

Summary The care of patients with heart failure can be challenging, with few objective tools available to assist in therapy decision-making. Natriuretic peptides are powerfully prognostic biomarkers in patients with heart failure and may represent an objective target for therapy. Accordingly, the use of biomarker-guided care with either B-type natriuretic peptide (BNP) or amino-terminal pro-B-type natriuretic peptide (NT-proBNP) has been recently explored. Over the past few years, a number of studies with heterogeneous inclusion criteria, methods and results have been performed. We have reviewed the available literature, summarizing the results of biomarker-guided heart failure trials and deriving recommendations for optimal application of biomarker-guided heart failure care based on the experience gained. In general, positive studies had low BNP or NT-proBNP target concentrations (~100 pg/mL and ~1000 pg/mL, respectively) and achieved lower natriuretic peptide concentrations compared with standard care. Patients in the biomarker-guided arms of the studies typically received more aggressive heart failure care and had no excess adverse outcomes. In the recent ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study, patients treated with biomarker-guided care also had improved quality of life and significantly better reverse remodeling on echocardiography compared with patients who received standard care. In conclusion,

Abbreviations: ACE, Angiotensin-converting enzyme; ARBs, Angiotensin receptor blockers; BNP, B-type natriuretic peptide; HF, Heart failure; HFpEF, Heart failure with preserved ejection fraction; LVSD, Left ventricular systolic dysfunction; NT-proBNP, Amino-terminal pro-B-type natriuretic peptide.

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Background

In modern practice, there are numerous challenges to be faced when trying to deliver optimal care to patients with chronic HF. Among these are the fact that it is a major challenge to achieve an optimal medical programme that minimizes HF symptoms and potential side effects while achieving the pre-specified goal doses of these therapies. Further, it is a challenge to easily identify when those goal doses are achieved. Frequent office visits with constant evaluation and management are often needed to optimize care; this, more often than not, requires great skill in recognizing opportunities to titrate therapies and the acumen to implement such changes.

Despite clearly defined targets for HF care worldwide, there is well-documented inconsistency in adherence to HF practice guidelines [1], with eligible patients being undertreated and opportunities to optimize care frequently being missed. This has led to a considerable focus on methods to identify those patients in need of therapy titration and to stratify risk in an objective manner, in order to better deliver care to those patients at highest risk of an adverse outcome. Very few tools for this exist, beyond clinical judgment, and the everyday clinician has very few easily-obtainable, inexpensive and widely-available resources to draw on to support their judgment regarding the management of a patient with chronic HF. Several emerging options are listed in Table 1.

Haemodynamic monitoring devices offer promise but almost universally require invasive placement, while non-invasive haemodynamic and impedance monitors require validation and lack substantial data regarding their usefulness in guiding therapy [2–4]. One intriguing option is

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Examples of available or proposed options for advanced monitoring of patients with chronic heart failure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive</td>
<td>Invasive</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Transthoracic impedance monitoring</td>
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<tr>
<td>Bio-impedance vector monitoring</td>
<td>Left atrial pressure monitoring</td>
</tr>
<tr>
<td>Auditory S3 monitoring</td>
<td>Pulmonary artery pressure monitoring</td>
</tr>
<tr>
<td>Non-invasive cardiac output monitoring</td>
<td>Biomarker-guided monitoring</td>
</tr>
</tbody>
</table>
the use of biomarkers to assist in therapeutic decision-making, which is attractive, given their wide availability and easy measurement, and the non-invasive nature of the approach. Indeed, the natriuretic peptides — BNP and its amino-terminal propeptide equivalent (NT-proBNP) — have been shown to provide easily-obtainable and meaningful prognostic information in chronic HF, which is linked directly to the biology of the diagnosis and is additive to other objective means of assessing risk. Importantly, as will be discussed, both BNP and NT-proBNP appear not only to be able to identify those at higher risk of adverse outcome but also to show interaction with HF therapies, such that their serial measurement may also provide information about the success or failure of therapy changes, thus allowing BNP or NT-proBNP to act as targets for HF care, in a similar manner to blood pressure or heart rate.

In order to better understand the potential role of BNP or NT-proBNP in guiding HF management, a brief summary of the important topics relating to their release, their prognostic value and methods for interpreting their values is worthwhile. This will be followed by a review of studies examining “biomarker-guided” therapy, an interpretation of their results and recommendations for application of BNP or NT-proBNP for HF care.

Interpretation of natriuretic peptide concentrations in ambulatory heart failure (HF)

Triggers for B-type natriuretic peptide (BNP) or amino-terminal pro-B-type natriuretic peptide (NT-proBNP) release

While the topic of natriuretic peptide release in patients with chronic HF is extensive and exceeds the scope of this document, certain concepts are worthwhile discussing in detail.

Physiologically, it is reasonable to consider the concentration of either BNP or NT-proBNP as being the sum of two separate components: fluid and function.

It is well established that myocardial stretch consequent to volume status is an important trigger for the release of natriuretic peptides [5]. When interpreting results for either BNP or NT-proBNP, clinicians should remember that a significant percentage of their release is triggered by filling pressures, particularly when there are very high concentrations of either peptide (e.g. BNP > 500 pg/mL or NT-proBNP > 5000 pg/mL).

Importantly, however, it is well established that filling pressures are only one trigger for BNP or NT-proBNP secretion [6–8]. Of the wide variety of structural and functional cardiac abnormalities leading to the release of both natriuretic peptides (detailed in Table 1), it is fair to assert that the prognostic importance of each is known and that potential therapeutic interventions exist for their treatment. Such abnormalities of cardiac structure and function include left ventricular systolic and diastolic dysfunction, pulmonary artery hypertension, abnormal right ventricular size and function, valvular heart disease and heart rhythm abnormalities that are prevalent in patients with compensated HF. Therapeutic interventions to address each are considered below.

Natriuretic peptides and prognosis in ambulatory heart failure (HF)

This topic has been recently reviewed in detail [9]. Both BNP and NT-proBNP represent the biomarker “gold standard” for prognostication in chronic HF, providing independent information regarding risk of progression of HF, ventricular remodeling, hospitalization for HF, need for transplantation or death. Concentrations of both peptides also predict the risk of arrhythmias [10], underscoring their value to prognosticate across a wide range of adverse outcomes in HF, from pump complications to heart rhythm abnormalities.

While a single measurement of BNP or NT-proBNP provides useful prognostic data for such adverse outcomes, it is well established that serial measurement provides incrementally unique information [11–13]. Indeed, compared with a single point measurement, the addition of subsequent analysis of BNP or NT-proBNP allows for the identification of changes in risk over time: some patients have a falling natriuretic peptide, which predicts a lower risk than a baseline value might suggest, while others develop a rising pattern, which predicts a higher likelihood of impending complications (Fig. 1).

Table 1 Cardiac abnormalities associated with elevation of B-type natriuretic peptide (BNP) or amino-terminal pro-B-type natriuretic peptide (NT-proBNP).

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>Myocardial processes</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
</tr>
<tr>
<td>Fibrosis/scar</td>
</tr>
<tr>
<td>Hypertrophy</td>
</tr>
<tr>
<td>Infiltrative diseases</td>
</tr>
<tr>
<td>Valvular abnormalities</td>
</tr>
<tr>
<td>Mitral stenosis, regurgitation</td>
</tr>
<tr>
<td>Aortic stenosis, regurgitation</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
</tr>
<tr>
<td>Pulmonic stenosis</td>
</tr>
<tr>
<td>Cardiac chamber size</td>
</tr>
<tr>
<td>Ventricular enlargement</td>
</tr>
<tr>
<td>Atrial enlargement</td>
</tr>
<tr>
<td>Filling pressures</td>
</tr>
<tr>
<td>Atrial, ventricular</td>
</tr>
<tr>
<td>Pulmonary</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>Coronary artery ischaemia</td>
</tr>
<tr>
<td>Heart rhythm abnormalities</td>
</tr>
<tr>
<td>Atrial fibrillation, flutter</td>
</tr>
<tr>
<td>Pericardial diseases</td>
</tr>
<tr>
<td>Constriction, tamponade</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td>Shunts, stenotic lesions</td>
</tr>
</tbody>
</table>
The link between these secular trends in natriuretic peptide concentrations and outcome is quite important, as it implies a potential value of BNP or NT-proBNP for "monitoring" patients at each office visit. Indeed, recent guidelines stress the importance of serial measurement of BNP or NT-proBNP for this indication [14]. Logically, one recognizes the importance of a stable natriuretic peptide concentration for identifying those patients who are less likely to have progressive HF, while in those with a high or changing concentration, such complications are more likely and more careful monitoring would be recommended.

The prognostic thresholds of BNP or NT-proBNP for adverse outcomes of all types have been identified [13,15] and tend to be at the lower end of the scale of what is expected relative to concentrations seen in patients with acutely decompensated HF. For BNP, as indicated by Mason et al. [13], it would appear that a concentration of ~125 pg/mL represents the inflection point for risk, while repeated studies have more solidly established a concentration of 1000 pg/mL for NT-proBNP. Above these risk thresholds, one may see a higher risk of adverse outcome, while below these concentrations, the risk tends to be considerably lower.

When a patient is truly optimally managed, their BNP or NT-proBNP concentration may be considered as the "dry" value. This "dry" natriuretic peptide value — ostensibly the best result a patient can reach — may then be used to assess risk of mortality and morbidity, if still elevated above prognostic thresholds, as will be discussed next.

**Interpreting B-type natriuretic peptide (BNP) or amino-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in the office: understanding changes and timing of measurement**

When measuring biomarkers, it is common to see a rise and/or fall in multiple measures of physiological function; when in the absence of an obvious pathological process, this change in the biomarker is known as biological variability. In the case of natriuretic peptides, biological variability is likely to be related to subtle changes in BNP synthesis, as well as to dynamic changes in cardiac filling pressures, pulmonary pressure, haemodynamics and changes in the clearance of BNP or NT-proBNP.

While biological variability is considerably higher at low concentrations of BNP and NT-proBNP, at the ranges seen in HF, a biological variability of 25% for NT-proBNP and 40% for BNP is more to be expected [16–18]. NT-proBNP has a longer half-life, which may be responsible for lower biological variability than BNP. Thus, a rise or fall of 25% (NT-proBNP) to 40% (BNP) implies a significant change in physiology. This point is particularly important to know when making decisions about changing drug therapy based on BNP or NT-proBNP concentrations. Given that BNP (with its shorter half-life) is more likely to be labile compared with NT-proBNP (with its longer half-life), differences in monitoring (and treatment approaches) using the two peptides are likely to exist, with greater day-to-day excursions with the former peptide and a smoother integration of daily physiology with the latter. How this relates to decisions about timing and method of intervention with BNP versus NT-proBNP remains somewhat less clear.

Another important topic relevant to serial testing is the amount of time it takes after a physiological change for BNP or NT-proBNP to achieve a new "steady state". While biological data are largely lacking in this regard, on a clinical level it has been suggested that the largest prognostic value relative to changes in NT-proBNP concentration is observed 2 weeks after a therapy change [19].

**Effect of heart failure (HF) therapies on natriuretic peptide concentrations**

Therapies for HF directly affect the processes that contribute the rise of BNP or NT-proBNP and are likely to affect...
the biological variability of natriuretic peptides. Thus, it is well established that many HF therapies lower the concentrations of BNP and NT-proBNP (Table 3). These include, of course, loop diuretics, but also ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists, exercise therapy and cardiac resynchronization therapy [5,20-37].

It is easy to understand how loop diuretics decrease the concentrations of BNP and NT-proBNP through their effect on cardiac filling pressures; when diuretics are withheld, unequivocal increases in BNP and NT-proBNP concentrations may be seen [5]. On the other hand, non-loop diuretics such as spironolactone or eplerenone (which have relatively modest diuretic effects) also have a substantial effect on natriuretic peptide concentrations.

On the other hand, neurohormonal agents, such as ACE inhibitors and ARBs, cause peptide concentrations to fall due to their favourable effects on filling pressures and cardiac haemodynamics as well as their effects on ventricular remodeling, while non-vasodilating beta-blockers may initially increase natriuretic peptide concentrations, which typically does not reflect clinical decompensation. However, in chronic optimal beta-blocker therapy, the concentrations of natriuretic peptides fall, reflecting the remodeling of the left ventricle. Importantly, an unequivocal interaction between natriuretic peptides and response to beta-blocker therapy has been found in the ANZ Heart Failure and COPERNICUS trials of carvedilol in advanced HF; subjects with the highest NT-proBNP concentrations appeared to gain the greatest benefit from treatment with carvedilol.

In addition to drug therapy, BNP or NT-proBNP can also be lowered by exercise therapy [25,33] and cardiac resynchronization therapy [29], both important adjuncts to the care of the HF patient.

### Natriuretic peptides for guiding heart failure (HF) management

The concept of utilizing a natriuretic peptide as a target for therapy was first examined more than 10 years ago by Troughton et al. [38] in the Christchurch Cardiorenal Group. In their seminal study, the investigators

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Therapies for heart failure that may lower B-type natriuretic peptide (BNP) or amino-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>Effect on BNP/NT-proBNP</td>
</tr>
<tr>
<td>Diuresis (loop or thiazide)</td>
<td>↓</td>
</tr>
<tr>
<td>ACE-I</td>
<td>↓</td>
</tr>
<tr>
<td>ARB</td>
<td>↓</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Some transiently ↑, most ↓</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>↓</td>
</tr>
<tr>
<td>CRT</td>
<td>↓</td>
</tr>
<tr>
<td>Exercise</td>
<td>↓</td>
</tr>
<tr>
<td>Rate control of AF</td>
<td>↓</td>
</tr>
<tr>
<td>BNP infusions</td>
<td>N-BNP ↓, BNP ↑ then ↓</td>
</tr>
</tbody>
</table>

ACE-I: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; BNP: B-type natriuretic peptide; CRT: cardiac resynchronization therapy; NT-proBNP: amino-terminal pro-B-type natriuretic peptide.

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<table>
<thead>
<tr>
<th>Table 4</th>
<th>Summary of biomarker-guided therapy studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>HFP EF</td>
</tr>
<tr>
<td><strong>Negative studies</strong></td>
<td></td>
</tr>
<tr>
<td>STARBRITE [46]</td>
<td>60</td>
</tr>
<tr>
<td>TIME-CHF [45]</td>
<td>77</td>
</tr>
<tr>
<td>BATTLESCARRED [43] PRIMA [42]</td>
<td>76</td>
</tr>
<tr>
<td>SIGNAL-HF [44]</td>
<td>78</td>
</tr>
<tr>
<td><strong>Positive studies</strong></td>
<td></td>
</tr>
<tr>
<td>Troughton et al. [38]</td>
<td>70</td>
</tr>
<tr>
<td>STARS-BNP [41]</td>
<td>65</td>
</tr>
<tr>
<td>Berger et al. [39]</td>
<td>71</td>
</tr>
<tr>
<td>PROTECT [40,49]</td>
<td>63</td>
</tr>
</tbody>
</table>

BNP: B-type natriuretic peptide; HFP EF: heart failure with preserved ejection fraction; NP: natriuretic peptide; NT-proBNP: amino-terminal pro-B-type natriuretic peptide.
demonstrated that, compared with HF care "guided" by a congestion score, therapy with the goal of suppressing NT-proBNP concentration was associated with superior event-free survival. Since then, several other trials have explored the concept, some with benefit from guided therapy [39–41] and others without [42–46] (Table 4). Before reviewing the experience gained from these studies, it is worthwhile emphasizing that whether positive or negative, pooled analyses of all the studies in this area (positive and negative) indicate a 20 to 25% adjusted reduction in mortality associated with biomarker-guided care on top of standard management (Fig. 2) [47,48].

In addition to the fact that most BNP- or NT-proBNP-guided HF studies were small and heterogeneous in size compared with each other, guided therapy studies have had variable inclusion criteria, different types of clinicians delivering the care and a wide range of goal natriuretic peptide concentrations, and the interventions to achieve the goal concentrations have been variably applied and variably successful. From this experience, however, more and more clarity is being gained about how biomarker-guided care may be of greatest value. Indeed, in retrospect, it is possible to understand why some trials failed and others did not. With such an understanding, it may be possible to identify where the approach may be best applied [49], based on the experience gained, in order to be successful with BNP- or NT-proBNP-guided care.

A low target natriuretic peptide concentration is necessary

Most of the negative trials typically chose BNP or NT-proBNP target concentrations that were too high to improve outcomes in patients managed with guided therapy. For example, in STARBRITE [46], the goal BNP concentration was close to 450 pg/mL, with a nominal change by the end of the study (to 413 pg/mL), which was no different from biological variability for the peptide. In contrast, in the positive STARS-BNP trial, the goal BNP concentration was 100 pg/mL [41].

In addition to having inappropriately high target natriuretic peptide concentrations, many negative trials, including STARBRITE, achieved no natriuretic peptide separation between the guided therapy and standard care arms, leaving the strategy untested. To be successful, achievement of a proper target concentration is necessary (as stated, for BNP, the optimal target is ~125 pg/mL, while for NT-proBNP it is ~1000 pg/mL). Notably, studies that achieved improved outcome associated with guided therapy, such as the STARS-BNP or ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) trials [40,50], had a low target natriuretic peptide concentration (BNP, 100 pg/mL; NT-proBNP, 1000 pg/mL).

Interestingly, one reason for negative trials in this area was that the control arm received high-quality care with parallel suppression of the BNP or NT-proBNP, frequently comparable to the unblinded arm [43]. Thus, a low post-treatment natriuretic peptide concentration is desirable, whether as a consequence of guided therapy or simply excellent care.

Respect the prognostic value of B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP)

A common scenario is that a patient may have an elevated BNP or NT-proBNP concentration, but his/her clinician feels...
the patient is stable and does not adjust his/her therapy.
Experience has taught, again and again, that no matter how
stable a patient with HF appears, when BNP or NT-proBNP
centrations are elevated above their prognostic thresh-
old, a measurable and imminent risk is present. Ignoring such
a powerful objective signal of risk increases the likelihood
for a missed opportunity to improve outcome. Tellingly, in
most of the negative trials, there was no difference in office
visits between guided versus control arms [42,44], whereas
a trade-off of increased outpatient visits was seen in the
successful studies.

It may take time and effort to lower B-type
natriuretic peptide (BNP) and amino-terminal
pro-B-type natriuretic peptide (NT-proBNP)
centrations

While the low target BNP or NT-proBNP concentrations may
seem unreachable in many patients, the successful trials of
guided therapy would argue otherwise — the lesson learned
is that it takes gradual drug titration and more office visits
to achieve these goals. In the PROTECT study, one of the
most thoroughly executed studies of NT-proBNP-guided care
to date, significant lowering of NT-proBNP was achieved in
the biomarker-guided arm but it required extra office visits
compared with standard HF management.

In practice, it is common to find patients in whom con-
centrations of BNP or NT-proBNP are lowered, but do not
achieve the goal value, no matter how hard a clinician
adjusts the therapy. Aggregate experience would suggest
that any lowering is better than no lowering at all; in one
negative trial, those patients in the trial who actually had
a robust reduction in NT-proBNP concentration had improve-
ment in outcome, despite the negative overall trial results
[42]. Lending further support to this, in the PROTECT study,
a clear gradient of risk was present relative to achieved
NT-proBNP concentrations: those patients achieving the
target of 1000 pg/mL had considerably lower risk than those at
intermediate or higher values (Fig. 3). While some patients
achieved the target concentration set in PROTECT and were
maintained below it, others only achieved it intermittently
and some did not achieve it at all; those constantly below
an NT-proBNP concentration of 1000 pg/mL had the best
outcomes, while those who achieved this intermittently
had intermediate outcomes and those with concentrations
constantly above it had the worst outcomes (Fig. 4). This
concept of "therapeutic time in response" is very similar
to that seen with respect to benefits predicted by interna-
tional normalized ratio testing during vitamin K antagonist
therapy [51], where more time "in range" is associated with
greater benefit.

In summary, ensuring that patients get as close to the
target natriuretic peptide concentration as possible and
maintaining them at this concentration is crucially im-
portant; the goal is attainable but it takes time and effort.

When using biomarker-guided therapy,
addition or up-titration of therapies should be
based on a treatment approach that reduces
morbidity and mortality and be done with
good clinical judgment

When titrating therapies to lower BNP or NT-proBNP con-
centrations in patients with LVSD, it is important to recognize
that while diuretics are particularly potent in lowering
both natriuretic peptides in the context of marked
elevations of these biomarkers (i.e. BNP ≥ 500 pg/mL;
NT-proBNP ≥ 5000 pg/mL), titration of other agents such as
vasodilators, beta-blockers or aldosterone antagonists
would be indicated first, as would continuous reassess-
ment of salt and water restriction, medication adherence,
 improvement of heart rhythm control for those with atrial
fibrillation, consideration for exercise prescription and optimization of cardiac resynchronization therapy. Indeed, while loop diuretics may be useful for controlling very high concentrations of BNP or NT-proBNP, high doses of these agents are potentially deleterious and biomarker-guided care should not be used as a "diuretic only" approach for care. Indeed, studies have not only suggested that it is possible to improve care of patients using BNP or NT-proBNP through up-titration of agents other than loop diuretics (Fig. 5), but in one study, NT-proBNP-guided care allowed for the downward titration of loop diuretics [40] — a desirable outcome. Thus, biomarker-guided management appears to result in an improvement in both the assiduousness of care and the choice of agents used. Given that an elevated BNP or NT-proBNP concentration identifies those at highest risk for adverse outcome, it allows for closure of the well-recognized gap that exists in such highest-risk patients.

Importantly, across all studies, BNP- or NT-proBNP-guided therapy did not lead to excessive risk of treatment-related complications consequent to mindless up-titration of therapies with subsequent therapy-related adverse outcomes; this reassures that clinicians did not just use the biomarker measurement while ignoring the rest of the information gained at the bedside, such as symptoms and vital signs.

Table 5 Recommendations for optimal application of biomarker-guided heart failure care.

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Clinicians should be familiar with the complex physiology that influences BNP or NT-proBNP concentrations in chronic HF</td>
</tr>
<tr>
<td>BNP and NT-proBNP concentrations should be regarded as the biochemical &quot;gold standard&quot; for prognostication</td>
</tr>
<tr>
<td>Caregivers should serially measure BNP or NT-proBNP concentrations in chronic HF patients, as routine repeated measurements provide superior prognostic information to single measurements</td>
</tr>
<tr>
<td>When using BNP or NT-proBNP, good knowledge of the target concentration for each is recommended (BNP ∼125 pg/mL; NT-proBNP 1000 pg/mL); the closer to the target, the lower the risk</td>
</tr>
<tr>
<td>Clinicians should be aware that a rise or fall of 25% (NT-proBNP) to 40% (BNP) is a biologically meaningful change, reflecting significant change in one or more of the factors determining release of these peptides</td>
</tr>
<tr>
<td>Clinicians should be knowledgeable about the wide range of therapeutic interventions with favourable effects on BNP or NT-proBNP concentrations</td>
</tr>
<tr>
<td>In order to be successful in biomarker-guided care, a low target concentration for BNP (∼125 pg/mL) or NT-proBNP (1000 pg/mL) is necessary</td>
</tr>
<tr>
<td>Clinicians should respect the importance of natriuretic peptide concentrations in patients with chronic HF; there is no such thing as a &quot;reassuring&quot; BNP or NT-proBNP concentration that is above the target value, no matter how stable the patient may appear</td>
</tr>
<tr>
<td>It may take time and effort to suppress natriuretic peptide concentrations; more frequent office visits and drug therapy titrations may be needed to achieve the goal</td>
</tr>
<tr>
<td>Unless in cases of significant congestion or marked elevation of BNP or NT-proBNP, strategies for lowering natriuretic peptide concentrations should focus on therapies with mortality benefit in chronic HF care, such as ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists, exercise therapy or optimization (or placement) of cardiac resynchronization therapy</td>
</tr>
<tr>
<td>Not all patients show &quot;response&quot; to BNP- or NT-proBNP-guided care; in this setting, continued optimization of medication is advised, with review of salt/water restriction, diet, lifestyle and medication adherence</td>
</tr>
<tr>
<td>When a patient is truly optimized but is a BNP or NT-proBNP &quot;non-responder&quot; with an elevated &quot;dry&quot; natriuretic peptide value, their prognosis is poor and alternative modes of therapy should be considered</td>
</tr>
</tbody>
</table>

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BNP: B-type natriuretic peptide; HF: heart failure; NT-proBNP: amino-terminal pro-B-type natriuretic peptide.
Thus, with confidence, it is fair to say biomarker-guided therapy does not replace clinical judgment — it supplements it.

Not all patients respond equally to biomarker-guided care

This says less about biomarker-guided HF care and more about the varied responses that patients show to therapeutic intervention in HF. For example, based on experience gained from two of the larger studies of this approach [43,45], a commonly held belief is that older patients benefit less than younger patients. In point of fact, this observation is likely to have less to do with the inadequacies of guided therapy and more to do with the effects of age on HF care. Compared with the younger HF patient, the elderly patient typically requires a different management approach, with more gradual and careful drug titration. Intolerances to therapies are greater in older patients and goal drug doses are less likely to be achieved as a consequence.

The results of successful versus unsuccessful trials follow. Although not universal, the unsuccessful guided HF therapy trials more often enrolled patients that were generally older. This is not to say that elderly patients cannot respond to biomarker-guided care; indeed, recent data from the PROTECT study imply that older patients not only responded to NT-proBNP-guided care but had the greatest event rate reduction related to guided therapy and drove the primary endpoint of the study. Presumably, the answer lies in how care is optimized in older subjects treated with guided therapy: more gradual care and careful up-titration may be needed in such patients. For example, in PROTECT, older patients were seen considerably more frequently than younger patients to achieve the intended biomarker reduction.

Another important consideration is the effect of guided therapy on outcomes from HF due to LVSD versus from HFrEF. Given the lack of a clearly effective treatment strategy of care for those with HFrEF, it is reasonable to expect that guided therapy may be more effective in patients with LVSD. This is not to say that certain patients with HFrEF may not benefit from monitoring using BNP or NT-proBNP — the value of biomarker-guided care in HFrEF remains debated — but the fact remains that the therapeutic approach for HFrEF is unproven and clearly differs from that for HF due to LVSD.

Resistance to natriuretic peptide lowering in certain situations is not without significance: whether in an older patient, one with HFrEF or in any other scenario. "Non-response" in the course of HF therapy (whether guided by the natriuretic peptide concentration or by standard HF care) is associated with a terrible prognosis. As above, in this setting, review of the choice of and adherence to HF medications, as well as careful examination of lifestyle would be indicated.

If truly optimized, the "dry" BNP or NT-proBNP value is an important piece of data to consider in patients apparently managed as optimally as possible; if elevated, despite a truly optimized management programme, strong consideration of alternative therapeutic strategies — including invasive haemodynamic monitors, mechanical support, cardiac transplantation or palliative care initiation — would be reasonable, given the high likelihood for impending adverse outcome.

Conclusion

In conclusion, biomarker-guided care using either BNP or NT-proBNP now has a sufficient evidence base to recommend its increased use in the office. The available data imply that when utilized in a manner consistent with successful clinical trials, BNP- or NT-proBNP-guided care allows for safe optimization of HF therapies and is associated with significant reductions in adverse outcomes. Recommendations for optimal application of biomarker-guided heart failure care are summarized in Table 5.

Disclosure of interest

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