Use of Natriuretic Peptides to Guide and Monitor Heart Failure Therapy

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BACKGROUND: Plasma B-type cardiac natriuretic peptides reflect cardiac structure and function and have proven roles in assisting in the diagnosis of acute heart failure. They are independent prognostic indicators across the full spectrum of cardiovascular disease. Serial changes in plasma B-type cardiac natriuretic peptides parallel prognosis in chronic heart failure. Beneficial responses to medications and devices used in the treatment of heart failure are associated with decreases in plasma B-type peptide concentrations. This effect has led to the hypothesis that intensified treatment directed at reducing B-peptide concentrations may improve outcomes in heart failure.

CONTENT: The efficacy of serial measurements of plasma B-type peptides in guiding titration of therapy for chronic heart failure has been the subject of several randomized controlled trials reported in the peer-reviewed literature since 2000. These reports are summarized in this review. Trial design, characteristics of the heart-failure population studied, duration of follow-up, exact end points recorded, and target peptide concentrations pursued all differ somewhat between trials. In addition, in studies in which benefits were seen, the exact mechanisms mediating the improvements in outcome were unclear. However, an overall consistency is emerging that is supported by 2 metaanalyses.

SUMMARY: In aggregate the existing trial data suggest that adjustment of treatment in chronic heart failure according to serial B-type peptide measurements, used in conjunction with established clinical methods, is likely to reduce cardiac mortality and hospital admissions with heart failure, at least in patients with systolic heart failure who are younger than 75 years and relatively free of comorbidities.

Plasma concentrations of many circulating entities reflect the degree of derangement of cardiac structure and function and are related to cardiovascular clinical outcomes. The B-type cardiac natriuretic peptides [B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP)] have received the closest scrutiny and, to date, they alone have entered mainstream clinical practice, supported by authoritative management guidelines, with application to the diagnosis and risk stratification of heart failure (HF). An extensive body of published research has established their roles in diagnosis of acute HF in patients presenting with recent onset breathlessness, in determination of prognosis in all stages (A to D) of HF, and as surrogate end points in both basic science and clinical experimental settings (1–4).

Management of diabetes and dyslipidemia is facilitated by serial surveillance of blood glucose and lipid profiles, respectively, thus providing excellent guidance for titration of therapy. In contrast, the HF physician has hitherto lacked a readily accessible biochemical signal that reflects the degree of control and/or prognosis. Several findings underpin the hypothesis that superior control of chronic HF and improved clinical outcomes may be obtained by use of titration of therapy according to serial plasma concentrations of BNP/NT-proBNP in addition to the application of conventional treatment and monitoring algorithms.

First, the associations between plasma concentrations of BNP/NT-proBNP and cardiac structure and function (both systolic and diastolic), typically as assessed by echocardiography, are consistent and strong, and these markers generally outperform other circulating candidate cardiac biomarkers (5). Furthermore,

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2 Nonstandard abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; HF, heart failure; ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; STARS-BNP, Systolic Heart Failure Treatment Supported by BNP; TIME-CHF, Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure; CHF, congestive HF; HR, hazard ratio; BATTLESCARRED, NT-proBNP–Assisted Treatment to Lessen Serial Cardiac Readmissions and Death; ARB, angiotensin II– receptor blocker; PRIMA, Can Pro-brain-natriuretic peptide guided therapy of chronic heart failure IMPROVE heart failure morbidity and mortality? trial; PROTECT, Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy; SIGNAL-HF, Swedish Intervention Study; Guidelines and NT-proBNP Analysis in Heart Failure; PROTECT, Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy; HF-PF, HF with preserved EF.

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the diagnostic performance of BNP/NT-proBNP for acute HF shows excellent sensitivity, specificity, negative predictive values, and overall accuracy (1, 2). Response to anti-HF therapy is reflected in rapidly apparent parallel changes in plasma BNP/NT-proBNP with the use of diuretics and vasodilators, reflecting the rapid cardiac “decompression” achieved by volume depletion and vasodilation (6). In a proof-of-principle study Murdoch et al. demonstrated the ability to drive plasma peptide concentrations down during escalation of vasodilator therapy (7). In the case of β blockade the initial response is an increase in plasma B peptides followed weeks or months later by a decline when beneficial remodeling is established and ventricular transmural distending pressure gradients are ameliorated (8). A beneficial response to cardiac resynchronization therapy is reflected in declines in circulating BNP/NT-proBNP (9).

Changes in plasma peptide concentrations parallel corresponding shifts in prognosis. In the neurohormonal substudy to the Val Heft trial, which tested the efficacy of adding angiotensin receptor blockade to angiotensin-converting enzyme (ACE)-inhibitor therapy in chronic HF, shifts in BNP/NT-proBNP between recruitment (baseline sample) and at 4 months were reflected in mortality at 2 years (4). Therefore, plasma BNP/NT-proBNP concentrations reflect cardiac structure and function, assist in diagnosis of acute cardiac decompensation, are prognostic in both acute and chronic HF, and parallel responses to both drug and device therapy. Therefore titration or “tailoring” of treatment aimed at lowering plasma BNP/NT-proBNP concentrations toward concentrations within reference intervals (above and beyond established indications for anti-HF therapy) may result in better outcomes than conventional management based on the application of standard (“one size fits all”) treatment algorithms and reactive management of symptoms and signs.

**Trials of Hormone-Guided Therapy for Heart Failure**

During the last 10 years the hormone-guided hypothesis has been tested in a number of small- to moderate-sized randomized therapeutic trials that have included a total of more than 2000 patients. The first of these was a pilot study from Christchurch, New Zealand, in which 69 patients with a history of decompensated HF and systolic dysfunction [left ventricular ejection fraction (LVEF) <40%] were randomized to management by a standardized clinical algorithm or to clinical management with superadded hormone-guided titration of drug therapy (10). Within the hormone-guided limb of the study treatment was titrated to drive plasma concentrations of NT-proBNP below 200 pmol/L (approximately 1700 pg/mL). During more than 9 months of follow-up, patients receiving hormone-guided treatment incurred significantly fewer deaths or admissions with newly decompensated HF. This small, but positive, hypothesis-generating study was published in 2000 and was the sole contribution to the field until 2007, when the French multicenter trial Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) was reported (11). In the STARS-BNP trial patients were randomized to standard clinical management or treatment titrated to drive BNP concentrations below 100 pg/mL (corresponding to approximately 1000 pg/mL of NT-proBNP). Conducted in 17 centers with 220 patients, STARS-BNP reported approximately 50% reductions in death due to HF in the hormone guided group and in the composite end point of death from HF or hospital admission because of HF. Notably, all-cause mortality was not reduced. Both the initial pilot study from New Zealand and the multicenter trial in France recruited relatively young patients (mean age 69 years and 65 years, respectively) with reduced EF (LVEF <40 and LVEF <45%, respectively) and relatively low annualized mortality. A small study from the US [STARBRITE (Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide vs the Clinical Congestion Score)] examined the effect on 90-day event rates of titrating therapy to drive plasma BNP down toward individualized target concentrations in patients recently admitted with acute decompensated HF (12). A nonsignificant trend toward increased days out of the hospital and more frequent prescription of full doses of evidence-based drug therapy were reported.

Within the last 2 years further trials have been reported. The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) (13), conducted in 15 centers in Switzerland and Germany, intended to recruit patients with and without preserved EF but has reported initially solely on those 499 patients with reduced (<45%) EF. In contrast to the earlier reports of studies from New Zealand and France, TIME-CHF recruited patients older than 60 years (mean 76 years), who are more representative of patients seen in clinical practice, with markedly increased baseline NT-proBNP concentrations and a high prevalence of background ischemic heart disease, hypertension, and diabetes. The study aims included assessment of any interaction between age and treatment strategy. The primary end points nominated for this trial were all-cause hospital admissions and quality of life. Over a period of 18 months, therapy was guided by NT-proBNP and aimed to drive concentrations below 400 pg/mL (approximately 50 pmol/L) for patients younger than 75 years and to be-
low 800 pg/mL (approximately 100 pmol/L) for those 75 years or older, and symptom-guided therapy resulted in similar rates of all-cause admissions [41% vs 40%, respectively; hazard ratio (HR) 0.91 (95% CI, 0.72–1.14); P = 0.39]. Quality-of-life metrics over 18 months of follow-up improved similarly in both the NT-proBNP–guided and symptom-guided groups. However, compared with the symptom-guided group, survival free of hospitalization for HF, an important secondary end point, was higher among those in the NT-proBNP–guided group [72% vs 62%, respectively; HR, 0.68 (95% CI, 0.50–0.92); P = 0.01]. Notably, HF therapy guided by NT-proBNP improved mortality and HF admissions in patients 60–75 years old but not in those 75 years or older (P = 0.02 for interaction; Fig. 1). A further important subanalysis from TIME-CHF indicated that benefit was confined to patients with no more than 1 significant comorbidity in addition to HF.

The NT-proBNP–Assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) trial from New Zealand (14) randomized 364 patients to 1 of 3 treatment strategies, including usual care or intensified care with or without superadded hormone guidance to drive NT-proBNP concentrations below 150 pmol/L (approximately 1300 pg/mL). Inclusion criteria allowed both preserved and reduced EF (mean LVEF 38%). The age range of study participants extended from 18 to 89 years (median 76 years). The treatment strategies were applied for 2 years, with follow-up extended to 3 years from recruitment.

One-year mortality was less in both the hormone-guided (9.1%) and clinically guided (9.1%) groups compared with usual care (18.9%; P < 0.03). Three-year mortality was selectively reduced in patients <75 years old receiving hormone-guided treatment (15.5%) compared with their peers receiving either clinically managed treatment (30.9%; P = 0.048) or usual care (31.3%; P < 0.021; Fig. 2). Hence there is a striking concordance between the TIME-CHF and BATTLESCARRED trials in that benefit from hormone guidance primarily accrues to patients <75 years old. Notably, in distinction to both STARS-BNP and TIME-CHF, in BATTLESCARRED there was no difference in final achieved doses of ACE inhibitors/angiotensin II– receptor blockers (ARBs) or β blockers between hormone and clinically guided care. However, in accord with TIME-CHF, the frequency with which drug doses were altered (either up or down) was significantly greater in the hormone-guided group.

The “Can Pro-brain-natriuretic peptide guided therapy of chronic heart failure improve heart failure morbidity and mortality?” (PRIMA) study (15), conducted in the Netherlands in 12 university and large general hospitals, followed a different design with respect to target peptide concentrations. In this trial 345 patients (mean age 72 years) recruited after admission with decompensated HF and increased NT-proBNP concentrations (>1700 pg/mL) were randomized to clinically guided care or management guided by an individually set NT-proBNP concentration defined by the lower of values at discharge or 2 weeks thereafter. The median target peptide concentration turned out to be 2491 pg/mL (approximately 290 pmol/L); considerably higher than targets set for the TIME-CHF and BATTLESCARRED trials. Additional inclusion criteria required a decrease of at least 10% [and at least by 850 pg/mL (approximately 100 pmol/L)] during hospitalization. Across all relevant drugs (except digoxin), doses were increased significantly more often with hormone guidance, and at 12 months a significantly higher percentage of patients in the hormone-guided group were receiving ACE inhibitors and β blockers.

However, trends toward an improved primary end point (days alive and out of the hospital 685 vs 664 over median follow-up of 702 days) and reduced mortality (26% vs 33%) with hormone guidance did not reach statistical significance. Similarly, trends for greater benefit in patients less than 75 years old were not significant. Notably, by its own reported assessment, the trial was only marginally powered for the primary end point.

A recently reported trial from Austria (16) recruited a total of 278 patients in 8 Viennese hospitals with randomization to 1 of 3 groups, including usual care, nurse-guided management, and specialist-supervised management with frequent initial visits for specialist titration of treatment. In the latter group patients were kept under intensive specialist follow-up as long as their NT-proBNP concentration remained above 2200 pg/mL (approximately 260 pmol/L), with transfer to nurse-guided guided care when concentrations subsided below this threshold. After 12 months, the hormone-guided group had the highest proportion receiving triple therapy with ACE inhibitors/ARBs, β blockers, and aldosterone antagonists. This group also accumulated fewer days of HF hospitalization (488 days) compared with nurse-guided care (1254 days) and usual care (1588 days) groups (P < 0.0001). Using Kaplan-Meier analysis, first HF readmissions (28%) were lower in the hormone-guided vs nurse-led care groups (40%; P < 0.06) and in the nurse-led care vs usual care groups (61%; P < 0.01; Fig. 3). The combined end point of death or HF readmission was lower in the hormone-guided (37%) than in the nurse-led group (50%; P < 0.05) and in the nurse-led than in the usual care group (65%; P < 0.04). Death rates were similar between hormone-guided and nurse-led (both 22%) groups and both were lower than in usual care (39%; P < 0.02 compared with both other groups).
The Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) (17) trial, a single-center, open-label trial from Boston, randomized 151 patients with HF and LVEF ≤40% to standard guideline-compliant HF care or such care with the additional goal of lowering NT-proBNP to ≤1000 pg/mL (118 pmol/L). Over 10 months of follow-up, hormone-guided management resulted in reduction in the composite primary end point (58 vs 100; P = 0.009) of “total cardiovascular events” (including worsening HF,

Fig. 1. Treatment effects on main outcomes in younger compared with older patients.
The differences between treatment groups were observed only in younger and not in older patients. NT-BNP, NT-proBNP. Reproduced and adapted with permission from JAMA and the TIME-CHF original data set (13).
admission for HF, ventricular arrhythmia, acute coronary syndrome, cerebral ischemia, and cardiac death). Important discrete end points, including worsening HF and admission for HF, were significantly reduced (P < 0.001 and 0.002 respectively). Mortality was very low with only 10 cardiovascular deaths for the study population overall (approximately 5.5% annualized mortality) in this relatively young population of HF patients (mean age 63 years).

Swedish Intervention Study: Guidelines and NT-proBNP Analysis in Heart Failure (SIGNAL-HF) was a 9-month, randomized, single-blind, parallel group trial conducted in the primary care setting in Sweden in 252 patients with New York Heart Association class II–IV HF, EF < 50%, and increased NT-proBNP concentrations [males 800 ng/L (approximately 95 pmol/L); females 1000 ng/L (approximately 120 pmol/L)] (18). Patients were randomized to treatment of CHF according to guidelines with or without NT-proBNP monitoring. The choice and dose of therapy for CHF was at the investigator’s discretion. The primary outcome variable was the composite end point of days alive, days out of the hospital, and symptom score from the Kansas City Cardiomyopathy Questionnaire. Treatment doses of β-blockers and blockers of the renin–angiotensin–aldosterone system were increased toward target doses to a similar degree in both groups. However, even at the conclusion of the trial fewer than one third of patients were receiving 100% of target doses for both ACE inhibitors and β blockers. There were no differences between the groups for either the primary end point or its individual components. Notably, this trial was the only study of B-peptide–guided therapy that was conducted in the primary care setting. The mean participant age of 78 years was the oldest among the trials. The follow-up was brief. Serious events were not numerous and, in fact, days alive and days not in the hospital for cardiovascular indications were discounted from the power calculation for this study because they were expected to be, and indeed were, infrequent. The trial report does not give much detail on the burden of comorbidity carried by participants, although more than 20% were diabetic and more than 10% had chronic obstructive pulmonary disease. No defined algorithm for escalation of pharmacotherapy in response to persistent elevation of NT-proBNP, even in the absence of signs and symptoms, was given, and decisions regarding choice and dose of drugs were left to individual investigators. These were primary care practitioners who each treated only a small number of trial participants and whose patients were demonstrably not being treated according to guidelines at the study outset, when brief education was provided by a local cardiologist to encourage compliance with treatment guidelines.

The contrast with the patient population studied and methods deployed in the similarly small but clearly positive Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) trial could hardly be more stark. The mean age of PROTECT participants was 63 years, the youngest among these trials, and PROTECT patients were 15 years younger than...
SIGNAL-HF patients. Follow-up and titration were undertaken by specialist cardiologists who were experienced in introduction and adjustment of anti-HF medications and were pursuing an aggressive regimen of follow-up clinic visits and drug adjustment.

Two metaanalyses of trial summary data have been published. A report by Felker et al. (19) includes randomized data for 1627 patients from 6 studies. Pooled analysis showed a significant mortality advantage for biomarker-guided therapy (HR 0.69, 95% CI 0.55–0.86) compared to controls (Fig. 4). Porapakkham et al. (20) included 8 randomized controlled trials in their metaanalysis, which involved data for 1726 patients followed for a mean duration of 16 months, and also demonstrated an overall significantly lower risk of all-cause mortality (relative risk 0.76; 95% CI 0.63–0.91; \( P = 0.003 \)) with hormone-guided therapy.

Possible Determinants of Efficacy of a B-Peptide–Guided Strategy for Management of Chronic HF

Inspection of the details reported for these trials suggests that patient age, burden of comorbidity, presence or absence of preserved LVEF, severity of the prognosis, aggressiveness with which adjustment of therapy is pursued, and target peptide concentrations chosen may all be pertinent to the efficacy or otherwise of peptide-guided therapy.

AGE

The association of younger mean age with better outcomes from hormone-guided treatment is striking. Interestingly, the 2 largest trials to date, TIME-CHF and BATTLESCARRED, both incorporated a priori hypotheses regarding the possible effect of age on this treatment strategy. The TIME-CHF investigators suggested that NT-proBNP guidance “might be particularly attractive in older patients who are less physically active and in whom symptoms are less reliable, but they may also be more susceptible to drug related adverse effects,” (13) whereas the BATTLESCARRED investigators suggested that “Individualized treatment may be optimal for patients with few limiting factors but impossible for others, including elderly, hypotensive, or renally impaired patients.” (14) Thus both groups prospectively proposed an interaction of treatment strategy with age, with one group of investigators suggesting an advantage in elderly patients and the other a limitation of benefit with increased age. However, the 2 trials were strikingly in accord in demonstrating that most of the benefit of NT-proBNP–guided therapy was confined to those <75 years old. In both trials it was in this...
subgroup that mortality was reduced. Table 1 illustrates how positive results were associated with lower mean age. Even studies with negative results (PRIMA and SIGNAL-HF) have revealed trends toward efficacy in patients younger than 75 years compared with the absence of such trends in older patients. What mechanisms might underlie this pattern? Renal function declines with age, as does the ability of the autonomic nervous system to meet postural challenges to blood pressure in the face of volume- and pressure-lowering multidrug therapy. Therefore it is not surprising that a strategy that entails increasing doses of such drugs in the face of recalcitrant peptide concentrations will lead to intolerance (typically in the form of progressive renal impairment and/or symptomatic hypotension) more often in elderly patients. Achieved drug doses were clearly lower for all classes of anti-HF medications in the subgroup of patients older than 75 years who participated in the BATTLESCARRED trial. Intriguingly, this pattern was not mirrored in TIME-CHF for reasons that are not apparent.

### DRUG REGIMENS

Most of the trials have not deployed specific drug escalation algorithms with drug changes triggered by specific changes in standardized assessments of clinical status. Much has been left to investigator discretion. BATTLESCARRED was an exception to this pattern. Without consistent and standardized therapeutic responses to standardized clinical and peptide triggers the chances of discerning the efficacy of hormone-guided therapy are reduced. In the community setting, such as in the SIGNAL-HF trial, in which practitioners may have little expertise and experience in management of HF and may see relatively few patients with this condition, the lack of such rigor is even more likely to dilute any benefit from this approach. Additional “noise” was present in SIGNAL-HF in that prescription of evidence-based drugs at baseline was at doses far below those recommended in authoritative guidelines, in contrast to most other trials of hormone-guided treatment in which baseline drugs and doses have been close to compliant with guidelines. When there is a major thrust toward introducing standard therapy in both limbs of the trial it will be harder to discern a superadded effect of peptide-triggered dose escalation.

Achieved drug doses were consistently below target for a large proportion of trial participants in all of these trials, regardless of patient age. In both SIGNAL-HF (mean patient age 78 years) and PROTECT (mean age 63 years), fewer than one third of patients achieved 100% of target doses concurrently for both ACE inhibitors/ARBs and β-blockers. This situation speaks to an automatic limitation for any strategy. If intolerance of target drug doses occurs the physician is left with no recourse but to trim therapy, and the aim of reducing peptide concentrations to a given target must be foregone. The need to reduce drug doses below the target clearly occurred universally among these trials, as demonstrated by the fact that no trial reported achievement of the target concentration of peptide in more than half of the participants. Prognosis was consistently better in patients who commenced with lower peptide concentrations and who achieved treated values at or near reference intervals. Thus persistent elevation of plasma NT-proBNP/BNP concentrations must be regarded as an ongoing indicator of poor prognosis, and the main virtue in monitoring these markers may be to prevent therapeutic complacency (with the endemic undertreatment reported from many surveys)

### Table 1. Summary of trials (of more than 6 months duration) of cardiac B-peptide–guided therapy for chronic heart failure.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>Mean age, years</th>
<th>Baseline NT-proBNP, pg/mL</th>
<th>Follow-up, months</th>
<th>Benefit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troughton et al (10)b</td>
<td>2000</td>
<td>69</td>
<td>69</td>
<td>1979</td>
<td>9</td>
<td>+</td>
</tr>
<tr>
<td>STARS BNP [Jourdain et al. (11)]b</td>
<td>2007</td>
<td>220</td>
<td>65</td>
<td>(BNP)c</td>
<td>15</td>
<td>+</td>
</tr>
<tr>
<td>TIME-CHF [Pfister et al. (13)]b</td>
<td>2009</td>
<td>499</td>
<td>76</td>
<td>4194</td>
<td>18</td>
<td>–/+</td>
</tr>
<tr>
<td>BATTLESCARRED [Lainchbury et al. (14)]</td>
<td>2010</td>
<td>364</td>
<td>76</td>
<td>2012</td>
<td>36</td>
<td>–/+</td>
</tr>
<tr>
<td>Berger et al (16)</td>
<td>2010</td>
<td>278</td>
<td>72</td>
<td>2400</td>
<td>18</td>
<td>+</td>
</tr>
<tr>
<td>PRIMA [Eurlings et al. (15)]</td>
<td>2011</td>
<td>345</td>
<td>72</td>
<td>2491</td>
<td>23</td>
<td>–</td>
</tr>
<tr>
<td>SIGNAL HF [Persson et al. (18)]b</td>
<td>2010</td>
<td>252</td>
<td>78</td>
<td>2500</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>PROTECT [Bhardwaj et al. (17)]b</td>
<td>2011</td>
<td>151</td>
<td>63</td>
<td>2118</td>
<td>10</td>
<td>+</td>
</tr>
</tbody>
</table>

* +, Positive result; –, neutral result.
b Reduced LVEF part of inclusion criteria.
c For this study, BNP rather than NT-proBNP was measured.
and encourage continued efforts to maximize treatment.

The mechanism underlying improved outcomes with hormone guidance is unclear. Higher achieved doses of ACE/ARB and β-blocker therapy were reported for some trials with either overall positive results or apparent benefit in patients <75 years old (STARS-BNP and TIME-CHF) but not for other trials (PROTECT and BATTLESCARRED). For almost all trials, significantly more frequent adjustment of drug doses both up and down were reported in the hormone-guided groups. Perhaps the main benefit from hormone-guided titration is tighter serial optimization ("tailoring") of therapy rather than overall heavier dosing.

COMORBIDITIES
Comorbidities are to be expected among patients with HF, more so with increasing age. Diabetes, cerebrovascular disease, and chronic obstructive lung disease were present in a significant proportion of trial participants. The presence of more than 1 significant comorbidity was associated with lack of benefit from hormone guidance in TIME-CHF, and it seems likely a similar pattern would be revealed by subanalyses of the other trials. Intuitively this result seems plausible. Comorbidities place greater duress on patients in terms of pain, renal injury, immobility, lack of fitness, and impaired competence (and therefore threatened drug compliance) and may entail use of noncardiac drugs that interact adversely with anti-HF therapy.

HF WITH PRESERVED EF
The majority of trials of hormone guidance of HF management have recruited patients with reduced EF. The exceptions include BATTLESCARRED and PRIMA. With increasing age a higher proportion of patients with HF will have a preserved LVEF (HF-PEF). In BATTLESCARRED 29% of patients 75 years old or younger had LVEF over 40% compared with 53% of those older than 75 years. In PRIMA a quarter of patients had LVEF above 45%. TIME-CHF was planned to include HF-PEF but so far has reported only on those patients (n = 499) with reduced LVEF. PRIMA reported that the trends toward benefit seen in the study population overall were absent in those with preserved LVEF. These discouraging signals are perhaps to be expected. There is no pharmacotherapy proven to improve mortality in HF-PEF, and pursuing increasing doses of drugs that are ineffective in HF-PEF is probably futile at best and harmful at worst. However, the fact that the main TIME-CHF report was confined to 499 patients with reduced LVEF indicates that the lack of efficacy of hormone guidance in the aged is not solely due to lack of effective treatments in HF-PEF.

There is little evidence that any treatment improves mean outcomes in patients older than 75 years with HF. Previous therapeutic trials in HF have recruited few (21, 22) or no (23–26) patients older than 75 years, and exclusion criteria have limited the prevalence of many significant comorbidities. We must await more effective treatments in the elderly as well as in HF-PEF before we can use hormone-guided titration to best effect.

TARGET PEPTIDE CONCENTRATIONS
Target peptide concentrations, which varied extensively between trials, may influence results. Target NT-proBNP concentrations have included 1700 pg/mL (200 pmol/L), 1300 pg/mL (150 pmol/L), and 1000 pg/mL (approximately 120 pmol/L). TIME-CHF allowed for age-related changes in B peptides and set targets of 400 and 800 pg/mL (approximately 50 and 100 pmol/L) for patients <75 and >75 years old, respectively. PRIMA individualized targets in a complex manner using the concentration at, or 2 weeks after, discharge, leading to a mean target value of more than 2000 pg/mL (approximately 240 pmol/L). PRIMA restricted response to peptide concentrations to those occasions when NT-proBNP was 10% and at least 850 pg/mL (approximately 100 pmol/L) above target. This strategy potentially leads to somewhat different rates of dose escalation than a set target that triggers ongoing escalation until therapeutic options are expended. SIGNAL-HF simply aimed to reduce concentrations to 50% or less of entry values. However, this may equate to widely varying levels of abnormal increase both before and after attainment of such a target. Benefit has been most apparent in cases in which fixed targets have been set, possibly because in most patients peptide concentrations remain above these targets, thus mandating ongoing efforts to maximize therapy. In the case of blood pressure, blood lipids, and blood glucose, knowledge of healthy levels guides our choice of therapeutic targets. Perhaps the same rationale should guide our choice of B-peptide targets.

The Future
Where to next with biomarker-guided management of HF? The current body of evidence will tend to confirm both believers and skeptics in their current positions. To provide confidence further trials are required. These must be adequately powered to confirm or refute the interaction between hormone-guided strategies and age so strongly suggested by TIME-CHF and BATTLESCARRED. This confirmation study should be conducted in patients with reduced EF (<50%) and
Trials of hormone-guided management of HF conducted over the last decade have followed different designs, pursuing different BNP or NT-proBNP targets in differing populations of patients with HF for variable periods of follow-up. Despite this heterogeneity some patterns have emerged. Overall it appears that progressive titration of HF therapy in pursuit of target BNP or NT-proBNP concentrations will result in reduced HF-related or all-cause mortality together with reduced time in the hospital with HF in younger patients (<75 years old) with reduced EF. There remains a need for definitive trials with sufficient power to confirm the efficacy of this strategy for patients with HF within defined strata of age and ventricular function. However, existing evidence suggests that serial measurement of B-type peptides as an adjunct to decision making for dose titration in HF is rational and likely to improve outcomes.

Summary

Trials of hormone-guided management of HF conducted over the last decade have followed different designs, pursuing different BNP or NT-proBNP targets in differing populations of patients with HF for variable periods of follow-up. Despite this heterogeneity some patterns have emerged. Overall it appears that progressive titration of HF therapy in pursuit of target BNP or NT-proBNP concentrations will result in reduced HF-related or all-cause mortality together with reduced time in the hospital with HF in younger patients (<75 years old) with reduced EF. There remains a need for definitive trials with sufficient power to confirm the efficacy of this strategy for patients with HF within defined strata of age and ventricular function. However, existing evidence suggests that serial measurement of B-type peptides as an adjunct to decision making for dose titration in HF is rational and likely to improve outcomes.

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