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Natriuretic Peptide Goal-Directed Therapy: Are We There Yet?

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Abstract Plasma B-type cardiac natriuretic peptides reflect cardiac structure and function, and have a proven role in the diagnosis of acute heart failure. Serial changes in plasma B-type cardiac natriuretic peptides parallel prognosis in chronic heart failure suggesting that intensified treatment directed at reducing B peptide concentrations may improve outcomes in heart failure (HF). This approach has been assessed in randomized trials conducted over the last 15 years. Meta-analyses of both summary and individual patient data indicate that adjustment of treatment in chronic HF according to serial B-type peptide measurements is likely to safely reduce all-cause mortality and admissions with HF. We await definitive data from adequately powered trials in both HF with and without preserved ejection fraction. However, existing evidence supports the use of this strategy in patients with HF aged under 75 years with systolic dysfunction.

Keywords Heart Failure · Natriuretic peptides · BNP · NT-proBNP · Marker-guided trials · Survival

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Introduction

Plasma concentrations of the B-type cardiac natriuretic peptides (BNP/NT-proBNP) reflect derangement of cardiac structure and function and are independently and strongly related to cardiovascular clinical outcomes in heart failure (HF). They have entered guideline-mandated clinical practice, as an aid to diagnosis and prognosis in HF [1]. They have also been employed as a surrogate end point in therapeutic trials [2–5].

The hypothesis, that titration of therapy in chronic HF according to serial plasma concentrations of BNP or NT-proBNP may improve clinical outcomes in heart failure, is under pinned by several lines of evidence. Plasma concentrations of BNP/NT-proBNP are directly related to left ventricular (LV) filling pressures and LV and left atrial volumes whilst inversely related to LV ejection fraction as assessed by invasive measurements and by non-invasive imaging including echocardiography and cardiac magnetic resonance [6]. In acutely dyspneic patients, BNP and NT-proBNP have excellent sensitivity, specificity, negative predictive values and accuracy for the diagnosis of acute HF [1–3]. Effective therapy in HF, whether by diuretics and/or vasodilators is paralleled by falls in plasma BNP/NT-proBNP reflecting cardiac unloading and restoration of more normal intra-cardiac pressures [7]. In 1999, Murdoch et al. demonstrated plasma BNP concentrations fell during increasing vasodilator doses [8]. With beta blockade plasma B-type peptides may exhibit a biphasic pattern with an early rise followed by a fall during chronic treatment perhaps reflecting initial negative inotropism and some increase in filling pressures followed by chronic beneficial remodelling [9]. A good clinical response to cardiac resynchronisation therapy is also accompanied by falls in plasma BNP/NT-proBNP [10]. Finally, shifts in plasma

peptide concentrations are paralleled by corresponding changes in prognosis. In the Val Heft trial in patients with chronic heart failure with reduced ejection fraction, changes in BNP/NT-proBNP over the 4 months from recruitment were reflected in mortality at 2 years [5]. Titration of treatment aimed at lowering plasma BNP/NT-proBNP towards normal may offer a path towards "precision" or personalised medicine with the potential to better optimize therapy and doses for individual patients and achieve better outcomes than standard management with crude "untailored" treatment algorithms derived from randomized trials of single drug doses.

Trials of Marker-Guided Therapy in Chronic Heart Failure

Over the last 15 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 over 2000 patients (Table 1). The first pilot study from Christchurch, New Zealand recruited 69 patients with a history of decompensated HF and left ventricular ejection fraction (LVEF) <40 %. Patients were randomized to management by a standardized clinical algorithm alone or together with super-added marker-guided titration of drug therapy [11]. The aim within the NT-proBNP-guided limb of the study was to up-titrate treatments to drive plasma NT-proBNP below 200 pmol/l (~1700 pg/ml). Over 9 months follow-up, marker-guided treatment resulted in significantly fewer deaths or admissions with decompensated HF. This hypothesis-generating study was published in 2000 and remained the only fully published article on this topic until 2007 when the multi-centre study ("STARS-BNP") was reported [12]. In STARS-BNP, patients ($n = 220$ recruited from 17 centres in France) were randomized to standard clinical management or treatment titrated to a BNP target of below 100 pg/ml. Death due to HF and the composite end point of death from HF or HF admission to hospital because of HF was reduced by 50 % in the BNP-guided group although all-cause mortality was not reduced. The New Zealand pilot study and the multi-centre trial in France recruited relatively young patients (mean age 69 and 65 years, respectively) with reduced ejection fraction (LVEF <40 and LVEF <45 %, respectively) and both trial populations had low mortality. "STAR-BRITE" from the US assessed titration of therapy to drive plasma BNP down to individualized targets in patients recently admitted with acute decompensated HF (ADHF) with respect to effect upon 90-day event rates [13]. Prescription of full doses of evidence-based drug therapy was more often achieved in the marker-guided group which also exhibited a trend towards more days out of hospital.

Table 1 Trials contributing to individual patient data meta-analysis of marker-guided management of chronic heart failure

	Number (BNP-guided/clinical)	Age (years) (mean ± SD) (% >75years)	Gender (M/F)	LVEF (%) (mean ± SD) (% ≤0.45)	Creatinine (μmol/l) (mean ± SD)	NT-proBNP (pg/ml) (median [IQR])	BNP (pg/ml) (mean ± SD)
Individual patient data							
Christ church pilot [11]	33/36	70 ± 10 (35)	53/16	27 ± 8 (100)	100 ± 30	1980 (1077–2806)	–
TIME-CHF [14]	251/248	76 ± 8 (58)	327/172	30 ± 8 (100)	117 ± 38	4194 (2270–7414)	–
Vienna [18]	92/96	71 ± 12 (47)	147/76	29 ± 9 (94)	125 ± 49	2280 (1255–5192)	–
PRIMA [17]	174/171	72 ± 12 (48)	199/146	36 ± 14 (73)	138 ± 58	2949 (1318–5445)	–
SIGNAL-HF [20]	127/125	78 ± 7 (73)	180/72	32 ± 8 (98)	102 ± 38	2362 (1372–4039)	–
BATTLESCARRED [16]	121/121	74 ± 9 (57)	157/85	39 ± 15 (63)	119 ± 45	2001 (1235–2974)	–
STARBRITE [13]	68/69	60 ± 16 (18)	95/42	20 ± 6 (100)	131 ± 57	–	134 (54–346)
UP STEP [21]	140/128	71 ± 10 (39)	196/72	[a]	108 ± 34	–	608 (356–947)
PROTECT[19][b]	75/76	63 ± 14 (25)	127/24	27 ± 9 (100)	130 ± 40	2118 (1121–3830)	–
Total	1081/1070	72 ± 11 (49)	1459/692	31 ± 12 (91)	120 ± 46	2697 (1425–5110)	446 (208–821)

LVEF left ventricular ejection fraction

[a] Individual LVEF data dichotomised as <30 % or 30–45 %

[b] The PROTECT study provided only secondary end point data

The TIME-CHF trial [14], conducted in 15 centres in Switzerland and Germany recruited patients with and without preserved ejection fraction and has reported separately on those 499 patients with reduced (<45 %) ejection fraction and 123 patients with preserved LVEF [15•]. TIME-CHF recruited patients over 60 years of age (mean 76 years) representative of usual clinical practice, with markedly increased NT-proBNP concentrations. The study aims included assessment of interaction between age and treatment strategy. The primary end points nominated for this trial were all-cause hospital admissions and quality of life. Over 18 months, therapy guided by NT-proBNP aiming to drive concentrations below 400 pg/ml (~50 pmol/l) for patients aged <75 years and to below 800 pg/ml (~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 improved over 18 months of follow-up similarly in both the NT-proBNP-guided and symptom-guided groups. However, with respect to secondary end points, survival free of HF admission was higher than the NT-proBNP-guided group (72 vs 62 %, respectively; HR, 0.68 [95 % CI 0.50–0.92]; $p = 0.01$). Therapy guided by NT-proBNP improved survival and reduced HF admissions in patients below, but not in those aged 75 years or older ($p = 0.02$ for interaction). Benefit appeared confined to participants with no more than one significant co-morbidity, in addition to HF.

The "BATTLESCARRED" trial [16] randomized 364 patients to one of three treatment strategies including usual care or intensified care with or without super-added hormone guidance to drive NT-proBNP concentrations below 150 pmol/l (~1300 pg/ml). Inclusion criteria allowed both preserved and reduced ejection fraction (mean LVEF 38 %). The age range extended from 18 to 89 years (median 76 years). Treatment strategies were applied for 2 years with follow-up to 3 years from recruitment. One-year all-cause death was less frequent in both the marker-guided (9.1 %) and clinical (9.1 %) groups compared with usual care (18.9 %; $p < 0.03$). Three-year mortality was selectively reduced in patients under 75 years in the NT-proBNP-guided group (15.5 %) compared with under 75's receiving either clinical management (30.9 %; $p = 0.048$) or usual care (31.3 %; $p < 0.021$). There is agreement between TIME-CHF and BATTLESCARRED with benefit from marker guidance confined to patients under 75 years. Notably, in distinction to both STARS-BNP and TIME-CHF, in BATTLESCARRED, there was no difference in final achieved doses of ACEI/ARB or beta blockers between hormone and clinically guided care. However, as in TIME-CHF, the frequency with which drug doses were altered (either up or down) was significantly greater in the marker-guided group.

The "prima" trial [17], conducted in the Netherlands in 12 centres, followed a different design with respect to target peptide concentrations. 345 patients (mean age 72 years) recruited after admission with ADHF with elevated NT-proBNP concentrations (>1700 pg/ml), were randomized to clinically guided or marker-guided management according to individual NT-proBNP goals set as the lower of plasma concentrations measured pre-discharge or at 2 weeks post-discharge. The median target peptide concentration was 2491 pg/ml (~290 pmol/l); higher than targets set for TIME-CHF and BATTLESCARRED. Additional inclusion criteria required a fall of at least 10 % (and at least by 850 pg/ml; ~100 pmol/l) during hospitalization. Anti-HF drug doses were increased more often with marker guidance, and at 12 months a significantly higher percentage of patients in this group were receiving ACE inhibitors and beta blockers. Non-significant trends towards reduced days alive and out of hospital (685 vs 664 over median follow-up of 702 days) and reduced mortality (26 vs 33 %) and, again, a trend towards greater benefit in patients under 75 years, were observed with marker guidance.

A trial conducted in Vienna [18] recruited 278 patients in eight centres and randomized them to (i) usual care (ii) nurse-guided management and (iii) intensified specialist-supervised management. In the latter group, patients received intensive specialist follow-up, while serial NT-proBNP levels persisted over 2200 pg/ml (~260 pmol/l) with transfer to nurse-guided management when concentrations fell below this threshold. At 12 months follow-up, more patients in the marker-guided group were receiving guideline-mandated triple therapy with ACEI/ARB, beta blockers and a mineralocorticoid antagonist. Marker-prompted specialist management resulted in fewer days in hospital because of HF (488 days) compared with nurse-guided care (1254 days) and usual care (1588 days; $p < 0.0001$). HF readmissions were lower in the marker-guided, specialist-managed versus nurse-led care groups (28 vs 40 %; $p < 0.06$) and in nurse-led care versus usual care (61 %; $p < 0.01$). Death or HF readmission occurred less often in the marker-prompted, specialist-managed group than with nurse-led care (37 vs 50 %; $p < 0.05$) and in the latter than in usual care (65 %; $p < 0.04$). "Protect" [19], a single-centre, open-label trial conducted in Boston, randomized 151 patients with HF and LVEF ≤40 % to standard guideline-compliant HF care or with the additional goal of lowering NT-proBNP to ≤1000 pg/ml (118 pmol/l). Over 10 months follow-up, marker-guided management reduced the number incurring the combined primary end point (n = 58 vs 100 events; $p = 0.009$) of total cardiovascular events (including worsening HF, admission for HF, ventricular arrhythmia, acute coronary syndrome, cerebral ischemia and cardiac death). Key

individual end points (worsening HF and HF admission) were reduced ($p = 0.001$ and 0.002, respectively).

SIGNAL-HF was conducted in primary care in Sweden in 252 patients in NYHA class II–IV HF, LVEF < 50 % and elevated plasma NT-proBNP (males 800 ng/l; ~95 pmol/l, females 1000 ng/l; ~120 pmol/l) [20]. Patients were randomized, single-blind, in a parallel group trial to treatment of CHF according to guidelines with or without NT-proBNP monitoring. Adjustment of therapy was undertaken at investigator discretion rather than according to a trial-dictated algorithm. The primary composite outcome was days alive, days out of hospital, and symptom score from the Kansas City Cardiomyopathy Questionnaire. Increases in doses of established anti-HF drugs were similar in both groups. However, at 9 months less than one-third of patients were receiving full target doses of both ACE inhibitors and beta blockers. No differences were observed for the primary endpoint or its individual components. This is the sole trial of marker-guided therapy conducted in primary care. At a mean of 78 years, this is the oldest group studied in this way; follow-up was brief. Serious events were not numerous and, in fact, days alive and days not in hospital for cardiovascular indications were not used for the power calculation for this trial because they were expected to be, and were, infrequent. The published report does not give much detail on the burden of co-morbidity carried by participants although over 20 % were diabetic and over 10 % had chronic obstructive pulmonary disease. The investigators were primary care practitioners each treating only a small number of trial participants and whose patients were on average not being treated according to guidelines at the study outset when education was provided by a specialist cardiologist to prompt compliance with guidelines.

The contrast with the patient population studied and methods in the similarly small but clearly positive PROTECT trial are very clear. The mean age of PROTECT participants was 63 years, 15 years younger than SIGNAL-HF patients. Follow-up and treatment titration were undertaken by specialist cardiologists pursuing an aggressive regime of follow-up clinic visits and drug adjustment.

The UPSTEP investigators recruited 279 patients with worsening HF (NYHA class II/IV, LVEF <40 % and elevated BNP) to a multi-centre trial conducted in 19 hospitals in Sweden and Norway [21]. Patients were randomized to usual care or marker-guided care (aimed at reducing BNP to <150 pg/ml). A weak trend towards improvement in the composite primary endpoint (death, all-cause hospitalization and worsening HF) was not significant. However, the authors noted that those patients in the BNP-guided group responding to treatment by lowering BNP by more than 30 % (88/140) had markedly better outcomes than "non-responders" for the composite end point and all its components ($p < 0.001$ for all end points)with hazard ratios between 0.09 (HF mortality) and 0.37 (Cardiovascular hospitalization). Responders were younger, had better renal function and tended to have lower initial BNP values than non-responders.

At least four meta-analyses (three using pooled data and one analysing individual patient data) on marker-guided trials in HF have been published [22, 23, 24, 25•]. Pooled analysis by Felker et al. of six studies [22] including 1627 patients reported a significant mortality advantage for marker-guided therapy (HR 0.69, 95 % CI 0.55–0.86). The meta-analysis by Porapakkham et al. [23] included eight randomized controlled trials involving 1726 patients followed for a mean duration of 16 months and found lower all-cause mortality (relative risk 0.76; 95 % CI 0.63–0.91; $p = 0.003$) with marker-guided therapy. Savarese et al. [24] reported on 12 trials enrolling 2686 patients. Marker guidance reduced all-cause mortality [OR 0.74 (0.60–0.91); p = 0.005], HF admissions [OR 0.55 (0.40–0.77); $p < 0.0001$]. Finally, Troughton et al. [25•] reported an individual patient data metanalysis. Data from 2000 patients were included. All-cause mortality was reduced [HR 0.62 (0.45–0.86); $p = 0.004$; Fig. 1] with an interaction with age noted i.e. benefit accrued to those under 75 years. HF admissions were reduced [HR 0.8 (0.67–0.94); $p = 0.009$] with no interaction observed with age or LVEF.

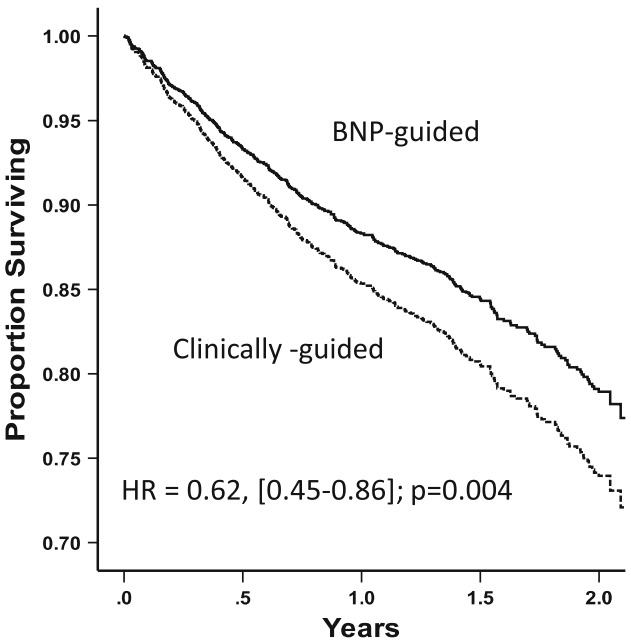

Fig. 1 Kaplan–Meier survival curves for all-cause death from individual patient data meta-analysis on 2000 participants in trials of marker-guided managmeent of chronic heart failure. [25•]

Safety

Published reports on trials of marker-guided therapy have not identified significant differences in adverse event rates between study groups. The individual patient data meta analysis from Troughton et al. [25•] did not indicate any inter-group differences in renal function despite higher doses of vasodilator and beta blocker treatment achieved in several contributing trials. Sanders van Wijk have reported in detail on adverse events incurred in the course of the TIME-CHF trial [26••, 27]. Notably, patients in this trial were older (mean 77 years) and suffered more severe HF (NYHA class ≥III in 74 % of participants and mean NT-proBNP ~4000 pg/ml) than in the other trials. The good safety profile reported in this particularly vulnerable trial population supports the probability that the approach is generally safe in the overall HF population. Severe adverse events (i.e. leading to discomfort and affecting daily life) were common (~65 %) but, importantly, did not differ according to treatment strategy or age. Symptomatic and/or severe hypotension and azotemia, the most common reasons treatment is curtailed in the treatment of HF, did not differ between treatment groups. Trauma and falls were not more common in the marker-guided group. Intriguingly, a strong trend towards reduced frequency of severe renal failure was seen with marker-guided compared with clinically guided management, both in patients under 75 years (2.8 vs 7.0 %; ns) and in older participants (2.8 vs 4.1 %). Notably, target doses of ACE inhibitors or beta blockers were achieved in little more than 50 % of cases at best in all these trials presumably reflecting restraint on prescribing due to side effects, or fear of side effects, and the safety profile outlined above must be seen in the context of this cautious prescribing environment.

Determinants of Efficacy of Marker-Guided Management of Heart Failure

Considered inspection of marker guidance trials for HF management points to age, co-morbidities, reduced versus preserved LVEF, severity of HF, the treatment algorithm for adjustment of therapy and target marker levels as all potentially relevant to their efficacy.

The strong and independent relationship of plasma BNP/NT-proBNP to outcomes has proven to be consistent throughout all trials. Gaggin et al. [28•] identified predictors of non-response (defined as failure to suppress NT-proBNP levels below 1000 pg/ml) from PROTECT data and validated them in the BATTLESCARRED data set. Echoing and expanding upon findings reported from UPSTEP, non-responders in the PROTECT and BATTLESCARRED cohorts were older, with lower eGFR, higher baseline NT-proBNP levels and more commonly in NYHA class III/IV.

Age

In their published reports on methods and design, both TIME-CHF and BATTLESCARRED incorporated a priori hypotheses on the possible effect of age on the efficacy of marker-guided treatment. The TIME-CHF investigators hypothesized 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" [14], whereas the BATTLESCARRED investigators suggested "Individualized treatment may be optimal for patients with few limiting factors but impossible for others, including the elderly, hypotensive, or renally impaired patients [16]." Both trials demonstrated that most benefit of NT-proBNP-guidance occurred in patients under 75 years. PRIMA and SIGNAL-HF also reported trends towards efficacy in those under 75 years but not in older subjects. What mechanisms might underlie this observation? 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 multi-drug therapy. Therefore, a strategy that entails increasing doses of such drugs in the face of persistently elevated marker levels may be poorly tolerated (typically manifest as worsening renal function and/or symptomatic hypotension) in the elderly. Achieved drug doses were clearly lower for all classes of anti-failure medications in the over 75 year old sub-group within BATTLESCARRED although this pattern was not mirrored in TIME-CHF.

In fact, there is little evidence that any treatment improves outcomes in HF patients over 75 years. Published trials have recruited few [29, 30] or no [31–34] patients over age 75 years, and exclusion criteria have limited the prevalence of many significant co-morbidities. Perhaps best use of marker-guided titration of anti-HF treatment must await treatments that are more effective or better tolerated in the elderly.

Co-morbidities

Co-morbidities are common in HF; the 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 one significant co-morbidity was associated with lack of benefit from hormone guidance in TIME-CHF, and it seems likely a similar pattern would be revealed by sub-

analyses of the other trials or on further inspection of the individual patient data included in the recent meta-analysis. Perhaps the interaction between the efficacy and age can be explained by the increasing burden of co-morbidities occurring with increasing age. Co-morbidities increase risks of pain, renal injury, immobility, lack of fitness, impaired competence (including drug adherence), death from non-cardiac causes, and they often entail use of non-cardiac drugs that interact adversely with anti-heart failure therapy.

Treatment Algorithms

Most of the trials have left adjustment of drug doses to individual investigator acumen rather than dictating specific drug escalation algorithms triggered by pre-defined changes in standardized assessments of clinical status or by marker levels exceeding target values. Without standardized therapeutic responses to standardized clinical and marker triggers, the ability to demonstrate efficacy of marker-guided management must be reduced. In primary care, as in the SIGNAL-HF trial, practitioners will see relatively few HF patients and the lack of specific dosing guidance is likely to obscure benefit from this approach. In SIGNAL-HF baseline, doses of evidence-based drugs were well below guideline recommendations, whereas in most other marker-guided trials mandated drugs had been introduced and titrated towards recommended doses. When standard therapy must be introduced and up-titrated in both limbs in the early stages of a brief (9 months) trial, it will be far harder to discern a super-added effect of marker-triggered dose escalation.

The mechanism(s) underlying improved outcomes with marker guidance is/are unclear. Some trials (with either overall positive results or at least with apparent benefit in patients <75 years of age) report higher achieved doses of ACE/ARB and beta blocker therapy with marker guidance (STARS-BNP and TIME-CHF) but others do not (PROTECT and BATTLESCARRED). Most trials reported significantly more frequent adjustment of drug doses both up and down in the marker-guided groups. Perhaps the main benefit from marker-guided titration is tighter serial optimisation ("tailoring") of therapy so that doses were appropriate for the individual patient for more of the time rather than benefit accruing from overall heavier dosing.

Heart Failure with Preserved Ejection Fraction

The majority of trials of marker-guided HF management have recruited solely patients with reduced LVEF. The exceptions include BATTLESCARRED and PRIMA. With increasing age, a higher proportion of patients with heart failure will have a preserved left ventricular ejection fraction (HFPEF). In BATTLESCARRED, 29 % of patients at or under 75 years of age had LVEF over 40 % compared with 53 % of those over 75 years. In PRIMA, a quarter of patients had LVEF above 45 %. Trends towards benefit seen in the PRIMA study population, overall, were absent in those with preserved LVEF. Individual patient data meta-analysis (ref) revealed no interaction between treatment effect and LVEF but this may well reflect the very small proportion (<10 %) of HFPEF cases included in that pooled analysis. TIME-CHF recruited HFPEF cases but initially only reported on HFREF cases. Recently, results from HFPEF cases included in that trial have been reported separately [15•]. Among 123 patients with LVEF >45 %, reduction in NT-proBNP and symptom relief were similar in marker-guided and clinical groups despite more aggressive treatment in the marker-guided arm. In contrast to the previously reported results in HFREF, NT-proBNP-guided treatment in HFPEF tended to worsen both 18-month survival and HF admission rate. There is no pharmacotherapy proven to improve mortality in HFPEF and these trial results taken together may indicate that increasing doses of drugs that are ineffective in this condition is futile at best and harmful at worst. Proper application of marker-guided treatment in HFPEF must await identification of effective treatments for this phenotype of HF.

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 (~120 pmol/l). TIME-CHF allowed for age-related changes in B-type peptides and set targets of 400 and 800 pg/ml (~50 and 100 pmol/l) for patients <75 and above 75 years of age, respectively. PRIMA individualized targets using the concentration at, or 2 weeks post-discharge leading to a mean target value of over 2000 pg/ml (~240 pmol/l). This variation in marker targets potentially leads to 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 elevation both before and after attainment of such a target. Benefit has been most apparent where fixed targets have been set possibly because in a high proportion of patients marker levels remained above target mandating, ongoing efforts to maximize therapy.

The Future

The evidence as it stands provides support to both protagonists and, to a lesser degree, opponents of mark-guided therapy for HF. Further definitive trials are required. These must be adequately powered to confirm or refute the interaction between efficacy and age (or possibly co-morbidities) as so strongly suggested by TIME-CHF and BATTLESCARRED. Success is most likely in patients with reduced ejection fraction (<50 %) and free of more than one significant co-morbidity. Marker targets should be age adjusted and no more than twice the upper limit of the normal reference range for that age group. The triggers for drug escalation and the dose escalation algorithm should be standardized and defined in detail, and adherence to the algorithm should be effectively policed during the conduct of the trial. Currently, the largest trial of marker-guided management of HF) is under way. "GUIDE IT" (NCT 01685840) will recruit 1100 patients and is scheduled to report in 2017. Inclusion criteria include age 18 years and older (i.e. those over 75 years are not excluded), LVEF <40 %, NT-proBNP over 2000 pg/ml and a history of decompensated HF within the 12 months prior to enrolment. Various exclusion criteria are listed but the trial will still potentially recruit participants with multiple co-morbidities. The need to standardize algorithm-driven management is paramount in trials of this kind and both achieving and documenting such adherence will be challenging. If "guide it" yields a positive result, guidelines may then recommend marker guidance using BNP or NT-proBNP in HFREF. Regrettably, even evidence of benefit from GUIDE IT will leave the role of marker guidance uncertain in many patients with HF, since most will harbour more than one co-morbidity, about half are older than 75 years and a similar proportion have preserved ejection fraction. The role of marker guidance in these settings must await development of drugs and/or devices with proven efficacy in such patients.

Future trials should take the opportunity to examine the potential utility of other markers such as ST2 or GDF15 either alone or in combination with B-type peptides. Despite uncertainties, the consistent, strong and independent relationship of B-type peptide concentrations with prognosis should encourage physicians to measure BNP or NT-proBNP early after diagnosis, and periodically thereafter, for risk stratification, to allow appropriate surveillance and to provide fully informed counselling of both the patient and their family.

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 results in reduced HF-related or all-cause mortality together with reduced time in hospital with HF in younger patients (<75 years of age) with reduced ejection fraction. 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 heart failure is rational and likely to improve outcomes.

Compliance with Ethics Guidelines

Conflict of Interest The authors of this paper both declare that they have no disclosures to declare.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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