Biomarker-Guided Treatment of Heart Failure

Still Waiting for a Definitive Answer*

Richard W. Troughton, MB ChB, PhD,
Chris M. Frampton, PhD, M. Gary Nicholls, MD
Christchurch, New Zealand

Whether clinicians need a biomarker to guide heart failure therapy is a question that has generated considerable debate in the last decade (1,2). The concept of tailoring heart failure treatment to achieve a target level of B-type natriuretic peptide (BNP) and thereby reduce cardiovascular event rates was first tested in the late 1990s (3,4). Since then, a series of studies using a variety of study designs have addressed this strategy in small and moderate-sized cohorts (5–8).

The rationale for attempting to improve the treatment of heart failure is undisputed: heart failure prevalence is increasing, and associated mortality and hospitalization rates remain high even with modern therapies and multidisciplinary care (9,10). There is currently no reliable objective guide to optimal pharmacotherapy of heart failure that can be easily applied to individual patients in the ambulant chronic heart failure setting. Additionally, despite clear treatment guidelines, target doses for medications that have been shown in controlled trials to improve clinical outcomes are frequently not achieved in the real world. This undertreatment is not explained simply by differences in patient populations (10–12). The reasons for suboptimal treatment are many, but of particular importance is the fact that clinical assessment is insensitive and frequently does not identify hemodynamic decompensation or allow accurate assessment of filling pressures, making it an inexact guide to diuretic dosing (13). Treatment options for systolic heart failure have become complex, and a range of medications and devices with proven efficacy now need to be considered, often in combination (10). In contrast, the optimal choice of treatment and dosing in heart failure with preserved ejection fraction remains uncertain (14). There is also inherent and understandable hesitancy when it comes to up-titration of treatment in apparently stable patients, especially when there are concerns about hypotension, azotemia, or other adverse medication effects.

The B-type natriuretic peptides (BNP and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) stand out as biomarkers with the potential to guide therapy. Commercial assays for both peptides are readily available and analytical variation is minimal, particularly for NT-proBNP (15). Plasma levels of both peptides reflect cardiac function and filling pressures and are powerful predictors of mortality and clinical outcome (16). Irrespective of innate within-patient variation, serial peptide measurements provide incremental prognostic value in both the in- and out-patient setting, with a fall in peptide levels being associated with better outcomes (17,18). Additionally, plasma levels of both peptides fall during treatment with proven therapies and mirror beneficial changes in left ventricular structure and function (19,20).

The hypothesis that BNP levels could be used to guide therapy is appealing as it offers the possibility of individualizing therapy according to an objective measure of function and risk. With this strategy, patients with high BNP/NT-proBNP levels—who are at higher risk for adverse events—are targeted to receive higher doses of medications that are proven to increase survival. Conversely, patients with low or normal peptide levels are spared higher doses that may be associated with adverse medication effects. To date, 5 published studies have tested this strategy, with slightly different study designs, but all with 1 central characteristic that an absolute peptide level was targeted in the treatment group assigned to BNP- or NT-proBNP–guided care (4–8). In the largest of these studies—TIME-CHF (Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure)—a higher NT-proBNP level was used as a target for subjects over 75 years of age (800 pg/ml) compared with those ages 60 to 74 years (400 pg/ml) (7). Findings from these 5 studies have varied, with some documenting significant clinical benefit from biomarker-guided management, at least in younger patients (4–7), but 2 larger studies reporting no overall improvement in clinical outcomes or quality of life (5,7).

Critics of the concept of biomarker-guided treatment of heart failure question the need for a biomarker to prompt up-titration of proven therapy, stating that all patients should automatically be titrated to tolerated maximal dose (2). They also note that common peptide targets were frequently not achieved in earlier biomarker-guided studies and suggest that individualized targets may be more achievable. In the face of confounders of BNP/NT-proBNP levels, such as renal dysfunction, myocardial ischemia, and atrial fibrillation, some critics of biomarker-guided treat-

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From the Christchurch Cardioendocrine Research Group and the University of Otago, Christchurch, New Zealand. Dr. Troughton has received honoraria (modest) from Roche Diagnostics. All other authors have reported that they have no relationships to disclose.
ment question whether a true feedback loop can be achieved and whether peptide levels can be consistently lowered by intensifying therapy. Others have expressed caution in using the biomarker approach in view of intrapatient variability of natriuretic peptide levels (21).

In a novel study published in this issue of the Journal, Eurlings et al. (22) address 1 criticism of earlier studies by testing an individualized NT-proBNP level as a target. The PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMProve heart FAllure morbidity and mortality?) study recruited 345 patients who had been hospitalized with decompensated symptomatic heart failure. Eligibility required an NT-proBNP level ≥1,700 pg/ml (a higher level than other biomarker-guided studies), and subjects also had to demonstrate a fall in NT-proBNP of >10% and at least 850 pg/ml during hospitalization (not a requirement of earlier studies). For the 174 subjects randomized to the NT-proBNP–guided group, an individualized target NT-proBNP level was identified based on the lowest NT-proBNP level obtained at discharge or within 2 weeks after discharge. For these subjects, up-titration of treatment was triggered if their NT-proBNP level at scheduled 3-monthly visits was >10% and at least 850 pg/ml above their individual baseline level. For the 171 subjects in the comparator clinically guided group, treatment was up-titrated on the basis of standard clinical assessment. After a median follow-up of 702 days, no difference was found in the primary end point of days alive and out of hospital, despite the fact that there was greater up-titration of treatment in the NT-proBNP–guided group—especially in the use of inhibitors of the renin-angiotensin system and in diuretic dosing—and despite the fact that 80% of subjects achieved NT-proBNP levels below their individualized target level at 1-year follow-up. The investigators did observe fewer deaths in the NT-proBNP–guided group, particularly in patients younger than age 75 years and in subjects with a left ventricular ejection fraction below 45%, although none of these comparisons achieved statistical significance. Neither was there any statistically significant difference between groups in hospitalization rates, quality of life scores, or estimated glomerular filtration rates.

The PRIMA study is the largest to study an individualized NT-proBNP target, and the investigators should be congratulated for addressing this question and undertaking such a comprehensive study of this strategy. Why did the PRIMA study not show a significant benefit from treatment guided by an individualized NT-proBNP target? The first possibility is that there is indeed no significant benefit to be gained by the approach taken in this study. Perhaps more likely is the possibility that aspects of the PRIMA study design may have served to obscure benefits of biomarker guidance.

First, the study highlights 1 potential limitation of treatment based on an individualized NT-proBNP target. If the target is derived from a BNP or NT-proBNP level that is set too high and therefore is not a reasonable estimate of the nadir, this will reduce the occasions when up-titration of therapy is prompted. In the PRIMA study, the NT-proBNP target level was based on the lowest plasma level for an individual either at baseline or 2 weeks after hospital discharge. The timing of this assessment may partly explain the relatively high median target level of 2,491 pg/ml. It is likely that levels measured at this time would not represent the true nadir for most patients. Findings from observational studies and the control arm of earlier biomarker-guided treatment trials indicate that in the absence of clinical deterioration, BNP or NT-proBNP levels continue to fall for months after discharge (5,7,23). The PRIMA investigators report that 80% of subjects achieved levels lower than their individual target NT-proBNP levels by 1 year and that NT-proBNP levels were only above target on 23% of occasions during follow-up. Therefore, on the remaining 77% visits where NT-proBNP levels were at or below target, up-titration of therapy would not have been triggered, despite the fact that NT-proBNP levels may have been at levels generally associated with increased risk of adverse events. By comparison, previous studies showing benefits from biomarker-guided therapy used comparatively stringent absolute levels of NT-proBNP or BNP, and although target NT-proBNP levels were achieved in only 40% to 70% of subjects, up-titration of therapy was triggered on more occasions than in the current study (5–7).

Second, the definition of an “off-target” NT-proBNP may have further reduced the occasions when up-titration of therapy for patients in the NT-proBNP group was triggered. The PRIMA study design mandated that to trigger an increase in treatment, NT-proBNP levels at follow-up had to be higher than target level by at least 10% and by a minimum of 850 pg/ml. For one-half of the cohort with NT-proBNP levels at or below the median of 2,491 pg/ml, a rise of 850 pg/ml, required to trigger increasing treatment, actually represents an increase of 30% or more. A patient in PRIMA with a median NT-proBNP level at baseline would have therefore required an NT-proBNP level of 3,350 pg/ml at follow-up to trigger treatment titration, a level that is nearly 3× higher than required in the biomarker-guided arm of BATTLESACRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial and between 4× and 8× higher than age-stratified targets in TIME-CHF (5,7). As a result, for many patients, this feature of the PRIMA study design may have further limited the opportunity to apply the treatment strategy, possibly diluting its effect. Whether target levels should take account of variability in peptide measurements on serial testing is debatable. In our view, this is unnecessary, especially for NT-proBNP, where analytical variability is very low. Although innate within-patient variability in peptide levels has been recognized in apparently stable patients, the causes are poorly understood. Many contributing factors such as myocardial ischemia or subclinical arrhythmia are clinically relevant and could contribute to adverse outcomes. Regardless, it is clear that even small
changes in NT-proBNP levels during serial testing are predictive of outcome (23). In this context, application of an absolute BNP or NT-proBNP level seems appropriate. How best to determine the target level? Data from earlier biomarker-guided studies and observational studies may be helpful in this regard. An approach similar to that used in the TIME-CHF study may have greatest merit—choosing levels associated with increased risk and using simple stratification based on age (1,7).

Third, like earlier biomarker-guided studies, PRIMA suffered from inadequate power to test the effect of biomarker-guided treatment on some hard clinical outcomes. The initial power calculation optimistically estimated a 50% reduction in cardiovascular events by NT-proBNP-guided treatment. The primary end point was changed prior to the initiation of recruitment to “days alive and out of hospital”—arguably a less robust end point for heart failure trials that may be skewed by the potentially large number of subjects who do not suffer a hospitalization (24). Mortality and hospitalization are more robust and unbiased outcome measures that were routinely used as primary end points in other biomarker-guided studies. It is interesting to note that in PRIMA, there was a nonsignificant 21% lowering of mortality rates in the NT-proBNP–guided arm. However, PRIMA was not powered to test mortality, and the modified target sample size further reduced the ability to detect clinically significant reductions in this end point. For the observed mortality rate and effect size described in PRIMA, a study of about 2,000 patients would have been needed to provide adequate power. The trend to lower mortality in PRIMA mirrors the trends seen in trials such as TIME-CHF and BATTLESCARRED, where there were reductions in mortality, particularly in younger patients. In an attempt to address the issue of inadequate power from individual studies, 2 recently published literature-based meta-analyses combining recent biomarker-guided studies, including PRIMA, suggest that treatment guided by BNP or NT-proBNP may in fact be associated with up to a 30% mortality reduction compared with usual clinical care (25,26). These meta-analyses, however, cannot be seen as definitive since they were based only on the available summary data extracted from reports.

The PRIMA study is an important addition to the series of biomarker-guided heart failure studies and provides valuable new insights. How should we therefore interpret PRIMA and other recent studies of biomarker-guided care? First, an overview of trials—including recent meta-analyses—suggests that BNP- or NT-proBNP–guided therapy may reduce mortality, especially in younger patients. Thus, it may have a role as an adjunct to standard of care, especially in younger patients, particularly those with systolic dysfunction. Second, the PRIMA study highlights the potential limitations of using an individualized target NT-proBNP level. Use of a single target level of BNP or NT-proBNP, perhaps adjusted for clinical covariates such as age (7,27), appears to offer the best opportunity for the biomarker-guided strategy to alter management. As is the case for their use as diagnostic markers, changes in serial BNP and NT-proBNP levels should be interpreted within the entire clinical context, including reference to other tests, such as those for renal function.

Finally, further data are needed from more robust, adequately powered trials with hard clinical outcomes and from a meta-analysis utilizing individual patient data (rather than summary grouped data) before guidelines can confidently endorse a biomarker-guided strategy. Recent studies, including biomarker-guided studies, have highlighted the lack of efficacy of medical therapy in heart failure with preserved systolic function and more particularly in elderly patients (5,7,28). Whether the biomarker-guided strategy is applicable to elderly patients and those with heart failure and preserved left ventricular ejection fraction remains unclear and needs further evaluation.

Reprint requests and correspondence: Dr. Richard W. Troughton, Department of Medicine, University of Otago, Christchurch, P.O. Box 4345, Christchurch 8140, New Zealand. E-mail: richard.troughton@cdhb.govt.nz.

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