BNP-guided therapy for chronic heart failure: anything more than just an attractive concept?

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This editorial refers to ‘Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis’†, by R. Troughton et al., on page 1559

The measurement of plasma natriuretic peptides (NPs) is well established in the diagnostic work-up of patients with suspected heart failure (HF), and is known to be a powerful prognostic tool, but the evidence that serial measurement can help improve the outcome of patients with HF has been elusive. As yet, no international guideline supports such use.

The theoretical appeal of such an approach is clear. Other chronic conditions are monitored, and treatment adjusted, according to biomarkers: thyroid disease and diabetes mellitus are obvious examples. The plasma concentration of NPs (including BNP and NT-proBNP) falls with better control of the HF syndrome: this is seen with the ‘de-congestion’ produced by diuretics, but also with increased chronic dosing with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and aldosterone-blockers. The attraction of having a simple, single numerical target to guide management is clear, particularly when underdosing of lifesaving medication for HF is a well-recognized problem.

Pilot and early studies were promising, suggesting benefit in terms of mortality and HF hospitalization, albeit in small numbers of patients and with short-term follow-up. Larger randomized trials have now been published, with the largest being TIME-CHF, with ~ 500 patients with systolic HF followed for 18 months. This reported a 24% reduction in all-cause mortality and a 30% reduction in HF hospitalization, but neither of these effects reached statistical significance. Pre-specified subgroup analysis suggested that the benefit of an NP-guided strategy was confined to younger patients (aged < 75 years).

Several aggregate data meta-analyses have been published, suggesting that an NP-guided treatment strategy might be associated with a 20–30% reduction in all-cause mortality, but these have not persuaded guideline committees or reimbursement authorities.

Troughton and colleagues are to be congratulated on performing an individual patient data (IPD) meta-analysis, including 9 of the 11 published randomized trials in this area, with 1081 patients randomized to BNP-guided therapy and 1070 to usual clinical care at the recruiting centres. The IPD allows a standardized approach to the clinical endpoints, and an exploration of potential effect modifiers across the studies. Two further studies have provided aggregate data.

The vast majority of patients in the trials had reduced systolic function (only 9% had an ejection fraction > 45%), 67% were male, and the average age was 72 years. Use of disease-modifying therapy was much better than in typical practice, with 90% on an ACE inhibitor or angiotensin receptor blocker (ARB) at baseline, 76% on a beta-blocker, and 29% on an aldosterone antagonist. About half of the studies followed patients for at least 12 months, and most had a single target BNP or NT-proBNP plasma concentration.

The IPD meta-analysis suggests that there is consistent evidence of a reduction in all-cause mortality in the younger subgroup (those aged < 75 years) randomized to NP-guided therapy [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.45–0.85, P = 0.004], but no effect on all-cause mortality in those aged ≥ 75 years (HR 0.98, 95% CI 0.75–1.3, P = 0.96). In addition, there appeared to be a consistent reduction in HF hospitalization across both age groups with an HR of 0.80 (95% CI 0.67–0.94, P = 0.009). The effect on cardiovascular hospitalization was similar but only just reached statistical significance (HR 0.82, 95% CI 0.67–0.99, P = 0.048), and there was no difference in total hospitalizations (HR 0.94, 95% CI 0.84–1.07, P = 0.38).

The meta-analysis raises many questions. How might using serial measurement of plasma NP concentration improve survival for younger patients with chronic HF, but not in older patients? Does providing the physician (and perhaps the patient) with a single numerical target merely improve physician and patient adherence to guideline-recommended therapy? And, ultimately, could other less costly strategies, such as education, decision support software, or pay for performance measures, have the same effect?

Troughton and colleagues explore some of these issues. Although baseline therapy was better than found in usual practice, as is often the case in randomized trials, it improved further during the trials. Overall, the dosing of ACE inhibitors (or ARBs) improved...
only in those randomized to NP monitoring, with the largest effect of NP guidance being seen in the older patients. Beta-blockade use increased across the board, but with little evidence that knowing the NP concentration made a difference. The change in proportion of patients not exposed to these drug classes is not reported in the meta-analysis.

Statistical analysis suggested that the effect on all-cause mortality was strongly associated with changes in the use of the disease-modifying drugs, but, even after controlling for this, there was benefit associated with being randomized to the NP-guided strategy. Perhaps compliance (to medication, lifestyle changes, and self-monitoring) was better in some of the studies when the patients knew that a blood test would be performed.

Why was the mortality benefit not found in those aged ≥ 75 years? Age is easily measured but may often merely be a marker of co-morbidity or frailty, rather than a strong biological construct. Co-morbidity increases with age, and recent data suggest that very few elderly patients with HF have no co-morbidity: 55% of HF patients had at least five other chronic health conditions in the most recent report from USA Medicare. Perhaps therapies only directed at one pathology have less impact in patients with multiple medical problems. There is a suggestion of this in the TIME-CHF trial, where patients with two or more co-morbidities saw less benefit. Alternatively, the potentially more ‘aggressive’ NP-guided strategy might be more toxic in patients with greater co-morbidity or frailty. However, although the IPD meta-analysis did not formally examine this, there appeared to be no detrimental effect (on average) on renal function in the NP-guided groups, nor an increase in all-cause hospitalizations.

Heart failure accounted for almost a half of all hospitalizations in the studies, and the evidence that this was reduced is robust across the studies, and in both the younger and older patients. This does suggest that the control of the HF syndrome was improved by guiding therapy with serial NP measurement. This reduction would help offset the costs of such monitoring and decision-making, but the lack of an effect on total hospitalization suggests that the overall savings might be smaller than they might first appear. In healthcare systems where readmission rates are monitored closely, usually it is the all-cause (not HF-specific) readmission rate that is monitored (and penalized). An alternative explanation might be that where the NP measurement was available, physicians were less likely to admit patients with worsening symptoms if the most recent NP levels were stable or improved.

Currently, there are few published reports on the cost-effectiveness of using NPs to guide therapy. This would be useful, as the cost of serial measurement of plasma NPs in all patients with chronic HF would be substantial, and would have to be weighed up against the likely benefit, including any increase in life expectancy and changes in quality of life. Any reduction in hospitalization would help offset the additional costs. Without such data it is unlikely that health technology assessment bodies and reimbursement authorities would consider supporting such a major change in practice. It is unlikely that all patients would benefit to the same extent, and such serial measurement may be most useful after diagnosis or after a period of decompensation, rather than lifelong.

What are the implications of the evidence base for current clinical practice? All international guidelines emphasize the importance of reaching ‘target’ doses of disease-modifying drugs, and recognize the problem of ensuring implementation in routine practice. Disease management programmes are known to improve the use of such therapies, and improve outcomes, and have been set up in many countries. Perhaps the observability and simplicity of a single numerical figure as a target would encourage physicians (and patients) to use drug therapies more appropriately?

The time has come to perform a large, adequately powered, randomized trial recruiting a range of HF patients with both reduced and normal systolic function, and across the age range, and with endpoints that include mortality, hospitalization, and quality of life. Such a study would confirm (or refute) the clinical and cost-effectiveness of serial NP measurements in routine practice (for all patients or for pre-specified subgroups) and help drive a change in guidelines, clinical practice, and reimbursement. The comparator group should be patients managed in a disease management programme where education of both patients and physicians is central, and where protocols already encourage good clinical practice. If serial measurement of NPs improves outcome over such ‘standard’ best practice, then the value of this personalized biomarker approach would be difficult to challenge.
The international clinical guidelines are appropriately cautious on recommending BNP-guided therapy in routine practice at the present time—but Troughton and colleagues’ IPD meta-analysis has confirmed the urgent need for a larger, more definitive, clinical trial. In the meantime, the use of an NP target for younger patients with chronic systolic HF is unlikely to cause harm, and may help both the patient and physician apply the current evidence base more consistently.

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References