Effectiveness and cost-effectiveness of serum B-type natriuretic peptide testing and monitoring in patients with heart failure in primary and secondary care: an evidence synthesis, cohort study and cost-effectiveness model

Maria Pufulete,[1] Rachel Maishman,[1] Lucy Dabner,[1] Syed Mohiuddin,[2] William Hollingworth,[2] Chris A Rogers,[1] Julian Higgins,[2] Mark Dayer,[3] John Macleod,[2] Sarah Purdy,[2] Theresa McDonagh,[4] Angus Nightingale,[5] Rachael Williams[6] and Barnaby C Reeves[1]*

[1]Clinical Trials and Evaluation Unit, School of Clinical Sciences, University of Bristol, Bristol, UK
[2]School of Social and Community Medicine, University of Bristol, Bristol, UK
[3]Department of Cardiology, Taunton and Somerset NHS Foundation Trust, Taunton, UK
[4]Cardiovascular Division, King's College London, King's College Hospital, London, UK
[5]Department of Cardiology, Bristol Heart Institute, Bristol Royal Infirmary, Bristol, UK
[6]Clinical Practice Research Datalink, Medicines and Healthcare products Regulatory Agency, London, UK

*Corresponding author barney.reeves@bristol.ac.uk

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Scientific summary

Serum BNP testing/monitoring in heart failure patients

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Scientific summary

Background

Heart failure (HF) affects ≈500,000 people in the UK and is associated with a poor prognosis; up to 40% of newly diagnosed patients die within 1 year. HF is one of the most costly conditions treated in the NHS, consuming about 2% of the NHS budget. The most common causes for HF are ischaemic heart disease and high blood pressure.

Treatment is complex. Many drugs are indicated for HF, and national and international guidelines recommend increasing drug doses to target, or maximally tolerated, levels. One reason for poor prognosis is because some doctors prescribe less intensive treatment to avoid potential side effects, and B-type natriuretic peptide (BNP)-guided therapy may help to optimise treatment. Surveys have shown poor confidence in diagnosing and managing HF among general practitioners (GPs), cardiologists and HF nurses.

Objective

This study aimed to evaluate the clinical effectiveness and cost-effectiveness of BNP-guided therapy (BNP monitoring) compared with symptom-guided therapy (usual care) in patients with HF.

Design

The study had three components: a systematic review and meta-analysis of individual participant data (IPD) and aggregate data; an analysis of a historic cohort of patients with HF in the UK; and a lifetime cost-effectiveness model to evaluate the cost per quality-adjusted life-year (QALY) gained by BNP-guided therapy versus symptom-guided therapy.

Setting

Systematic review

The setting for the systematic review was randomised controlled trials (RCTs) of BNP-guided therapy versus symptom-guided therapy in specialist HF clinics.

Cohort study

The setting for the cohort study was primary and secondary care, characterised by data from the sources used to create the cohort.

Participants

Systematic review

The systematic review was carried out in participants with HF aged > 18 years in eligible RCTs of BNP-guided therapy versus symptom-guided therapy in primary or secondary care. We characterised participants by age (< 75 vs. ≥ 75 years), sex, New York Heart Association (NYHA) class (class I/II vs. class III/IV), type of HF [heart failure with a reduced ejection fraction (HFrEF) vs. heart failure with a preserved ejection fraction (HFpEF)], diabetes status, BNP level [≤ vs. > median across all trial participants but separately for BNP and N-terminal pro-B-type natriuretic peptide (NT-proBNP)] and cause of HF (ischaemic/non-ischaemic).

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Cohort study

The cohort study was carried out in UK patients who have incident HF managed in general practices contributing to the Clinical Practice Research Datalink (CPRD) and patients in the National Heart Failure Audit (NHFA).

Interventions

Systematic review

Trial participants received treatment guided by serial BNP or NT-proBNP measurements (BNP-guided therapy) or treatment guided by clinical assessment (symptom-guided therapy) in primary or secondary care.

Cohort study

Patients were classified as BNP monitored ($\geq$ 6 months of observation time *and* three or more BNP tests *and* two or more tests per year), BNP tested (one or more BNP test but not meeting criteria for BNP monitored) or never tested (reference group; no BNP test recorded in the CPRD) based on the rate of BNP testing. In the NHFA data set, admissions were classified according to whether or not a BNP test was carried out during the admission.

Cost-effectiveness model

The intervention was BNP-guided therapy provided in a specialist clinic.

Main outcome measures

The outcomes of interest for the review and cohort study were all-cause mortality, HF-related death, cardiovascular death, all-cause hospital admission, HF-specific hospital admission, adverse events and quality of life. The outcome for the cost-effectiveness model was QALYs.

Data sources

Systematic review

Existing RCTs were identified by the review methods described below. IPD were sought for all included RCTs. Aggregate data were extracted from publications when IPD were not available.

Cohort study

We obtained CPRD GOLD data from the General Practice Research Database through the CPRD; these data are linked with Hospital Episode Statistics (HES) inpatient and outpatient data sets and the Office for National Statistics mortality data set. We also obtained data from the NHFA for patients with unscheduled admissions to a participating hospital. The NHFA provides clinical information, test results, medications and diagnoses during admission, which are not captured in HES. NHFA were not linked with the CPRD cohort because this link had not been performed previously and required additional approvals.

Cost-effectiveness model

Estimates of model parameters were obtained from the review and the cohort study. Estimates of utility were obtained from the literature.

Review methods

We searched MEDLINE (via Ovid) from 1950 to 9 June 2016, EMBASE (via Ovid) from 1980 to 2016, The Cochrane Library, Web of Science (Citations Index and Conference Proceedings) databases for published

RCTs, the World Health Organization International Clinical Trials Registry Platform and Current Controlled Trials for ongoing RCTs. Reference lists of full-text papers were reviewed and grey literature was searched for unpublished studies. Study selection, data extraction and risk-of-bias assessment were carried out in duplicate.

Results

Systematic review

Five RCTs contributed IPD and eight RCTs contributed aggregate data for one or more outcomes; 3074 patients who had HF were randomised (1536 to BNP-guided therapy and 1538 to symptom-guided therapy). Hazard ratios (HRs) for BNP-guided therapy were 0.87 for all-cause mortality [95% confidence interval (CI) 0.73 to 1.04], 0.97 for hospitalisation for any cause (95% CI 0.85 to 1.10) and 0.78 for HF-specific admission (95% CI 0.65 to 0.95).

For all-cause mortality, there were significant interactions between treatment and age ($p = 0.034$) and between treatment and type of HF ($p = 0.026$). BNP-guided therapy was beneficial for trial participants who were < 75 years old (HR 0.70, 95% CI 0.53 to 0.92) but not for trial participants who were ≥ 75 years old (HR 1.07, 95% CI 0.84 to 1.37) and for trial participants who had HFrEF (HR 0.83, 95% CI 0.68 to 1.01) but not for trial participants who had HFpEF (HR 1.33, 95% CI 0.83 to 2.11). There was no interaction between treatment strategy and age or left ventricular ejection fraction for other outcomes, but stratum-specific estimates were consistent with those for all-cause mortality, suggesting benefit of BNP-guided therapy for participants who are aged < 75 years or with HFrEF.

There was no statistically significant interaction between treatment strategy and age, sex, NYHA class, diabetes or baseline BNP/NT-proBNP for any outcome.

Most RCTs provided no data on adverse events, precluding any meta-analysis, but some reported that there were no apparent harms of BNP monitoring.

Cohort study

A total of 17,095 patients had incident HF between 1 April 2005 and 31 March 2013; this number accrued linearly over time. We classified 13,632, 3392 and 71 patients, respectively, as never tested, BNP tested and BNP monitored. Patients classified as BNP monitored were older, more likely to be female and less likely to be overweight or obese; similar proportions in the three groups had any comorbidity but there appeared to be differences for specific morbidities. There was no obvious pattern in the timing or frequency of BNP tests in the monitored group. The number of BNP tests increased slightly faster than the number of patients.

Overall, 49% of patients died during follow-up. The crude death rate was 141.5 (95% CI 138.5 to 144.6) per 1000 person-years. Median survival was 5 years. The death rate was higher in the BNP-monitored group than in the BNP-tested and never tested groups (186.5 vs. 130.6 and 186.5 vs. 143.9 per 1000 patient-years, respectively). The percentages of patients alive at 1, 2, 3 and 4 years after HF diagnosis were 84%, 74%, 64% and 56% in the never-tested group, 85%, 76%, 67% and 60% in the BNP-tested group and 86%, 72%, 57% and 44% in the BNP-monitored group. Rates of admission to hospital were also highest for the BNP-monitored group and lowest for the BNP-tested group.

Across the cohort, there was an average of 17 GP consultations per year (17 per year in BNP-tested and never tested groups; 22 per year in the BNP-monitored group) but only 40% of patients had GP consultations coded as HF or with HF-specific symptoms. There were no obvious differences between groups in relation to different classes of medication, although a higher proportion of patients in the BNP-monitored group appeared to be prescribed medications.

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The NHFA data described 163,244 admissions in 130,433 patients between 1 January 2007 and 31 March 2013. The characteristics of patients in the NHFA were broadly similar to those of patients in the CPRD cohort; NHFA patients were slightly older and had more comorbidities or previous events, such as myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery. Most patients (97%) in the NHFA data set met the definition for incident HF admission. Median survival time in the NHFA cohort was 2.2 years shorter than in the CPRD cohort. The admission rate in patients with an incident HF admission was 1.1 per year [interquartile range (IQR) 0.5–3.5]; 17% were readmitted during follow-up, with a median of 1 readmission (IQR 1–2). BNP tests were carried out during 10,114 admissions (6%), increasing from 0% to 10% over the period analysed.

Cost-effectiveness model

B-type natriuretic peptide-guided therapy is more costly but more effective than symptoms-guided therapy over the lifetime of patients who are < 75 years and have any type of HF. If the relative reduction in mortality is sustained for 4 years, median survival is approximately 1.5 years longer in patients who receive BNP-guided therapy (7.98 vs. 6.46 years). The difference in mean QALYs is smaller (5.68 vs. 5.02), reflecting the imperfect health of survivors and discounting of health gained in future years. Lifetime costs are substantially higher in patients who receive BNP-guided therapy (£64,777 vs. £58,139), as the potential for decreased hospitalisation observed in RCTs is more than offset by the costs of BNP testing, medications and health care during the extended survival period. The positive incremental net monetary benefit (iNMB; £6426, 95% CI £2401 to £10,075) indicates that BNP-guided therapy is cost-effective in this patient subgroup at the £20,000 per QALY threshold used by the National Institute for Health and Care Excellence (NICE). The evidence that BNP-guided therapy is cost-effective was stronger for patients with HFrEF than for those with HFpEF.

There is some evidence that BNP-guided therapy has the potential to be cost-effective in older patients with HFrEF. The estimated QALY gain (2.39 vs. 2.20) and iNMB is relatively small (£2267, 95% CI –£1524 to £6074) but there is a relatively high probability (0.88) that BNP-guided therapy is cost-effective at the NICE £20,000 per QALY threshold.

Limitations

Systematic review

The main limitation of the systematic review was the inability to obtain IPD from most trials included in a previous meta-analysis, which restricted the subgroup analyses that could be conducted; we could not combine IPD subgroup estimates with other reported subgroup effects for all subgroups.

Other limitations were a result of features of the included RCTs. There was heterogeneity in the BNP-monitoring and symptom-guided therapy interventions, predominant recruitment of patients < 75 years of age with HFrEF and who are without comorbidities constrained application of the results to a broader HF population and, in most of the RCTs, clinicians and participants were not blinded to treatment.

Cohort study

The main limitation of the cohort study was uncertainty about whether or not patients classified as BNP monitored were in fact monitored, given the diversity in the patterns of BNP tests recorded. A proportion of patients with short follow-up were classified as BNP tested but might have received BNP monitoring. Serial BNP tests in the CPRD could have arisen from monitoring, cross-sectional testing to check HF severity, or testing in relation to hospital admissions or outpatient appointments.

We could not determine medication doses accurately in the CPRD therapy data set, preventing any investigation of changes in medication in patients classified as BNP monitored.

We were unable to distinguish between patients with HFrEF and those with HFpEF because Read Codes were not used consistently. The linkage between CPRD GOLD and the NHFA data could not be performed in time; the NHFA data set would have provided more detailed clinical information on medications and types of HF.

Some HF patients in the UK are managed in community HF clinics or at home by HF specialist nurses. Community care databases are not linked with CPRD GOLD. Therefore, data for these patients were missing from the CPRD GOLD data set.

Cost-effectiveness model

The model used a highly simplified two-state Markov model to track costs and patient outcomes. A more complex model tracking dysfunction would provide a more realistic representation of disease progression. Our model may lead to poor estimates of cost-effectiveness if BNP-guided therapy has a large effect (positive or negative) on functional decline among survivors, but RCTs have reported that monitoring makes no difference to quality of life.

Our analyses focus on costs to the health service, rather than wider costs falling on social care or patients and families. BNP-guided therapy may be more cost-effective from a broader societal perspective if, for example, it results in fewer admissions to residential or nursing homes.

The available evidence limited our ability to draw conclusions about cost-effectiveness in HFpEF patients who are aged < 75 years and HFrEF patients aged ≥ 75 years. There was also no evidence on all-cause hospitalisation stratified by patient subgroup.

Conclusions

The efficacy of BNP-guided therapy implemented in specialist HF clinics is uncertain, although, if efficacious, it would be cost-effective among HF patients similar to those recruited to the RCTs and who were < 75 years of age or who had HFrEF. Implemented in specialist clinics, it may also be efficacious and cost-effective in patients < 75 years of age with HFpEF or in patients ≥ 75 years with HFrEF, but this is more uncertain.

The applicability of this evidence to HF patients in the UK is uncertain because UK patients are not usually managed in specialist clinics, because there is evidence that clinical outcomes are worse in patients managed in primary care and because differences in BNP levels or HF medications between groups in RCTs were not associated with the magnitude of the benefit from BNP-guided therapy. Moreover, BNP-guided therapy was implemented in diverse ways in RCTs and it is not clear how it should best be implemented.

Future work

The systematic review could not identify an optimal monitoring strategy, and no group of researchers has defined one. Future research should attempt to do so, for example through a formal consensus process involving relevant stakeholders.

In the RCTs, HF medications increased in both BNP-guided and symptom-guided therapy groups, suggesting that HF management outside the RCTs was suboptimal. Research is needed to identify ways to optimise management of HF in accordance with current guidelines.

Depending on the findings from the above research, there might be a need for a large pragmatic RCT of BNP monitoring in the UK, evaluating the consensus-based optimal monitoring strategy in a clinical setting that has optimised HF management.

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Most of the uncertainty about the cost-effectiveness of BNP monitoring is caused by wide CIs for the effect sizes, particularly in patient subgroups not well represented in RCTs. The uncertainty could be reduced by including results from the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial in an updated IPD meta-analysis. This trial was recently terminated early for futility (https://dcri.org/dcri-announces-halt-guide-trial/; accessed 7 March 2017), but the results would almost certainly shift pooled effect estimates closer to no effect.

The cost-effectiveness model would also benefit from more evidence about the sustainability of the treatment effect for BNP monitoring. This could be achieved by research to collect routine data on long-term mortality and hospitalisation in completed and ongoing RCTs.

Finally, there is surprisingly little research on the economic impact of HF on health systems, families and societies. Future research is required, particularly on residential care needs, informal care needs and productivity losses due to HF in order to better judge the economic case for interventions such as BNP-guided monitoring.

Trial registration

This trial is registered as ISRCTN37248047 and PROSPERO CRD42013005335.

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