B-type natriuretic peptide-guided therapy for heart failure: an individual participant data (IPD) meta-analysis

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1. Background

Heart failure (HF) is a complex syndrome in which the heart is unable to maintain the circulation of blood through the body. There are two definitions for HF: (a) left ventricular systolic dysfunction (LVSD), characterised by reduced contraction of the left ventricle (low ejection fraction); and (b) preserved ejection fraction (HFPEF). Just over half of patients with HF have predominantly LVSD and just under half have predominantly HFPEF, although there is no agreement on the cut-off point that defines low ejection fraction; a range between <35% and <50% has been used in clinical trials. Patients with LVSD and HFPEF have different demographic and clinical characteristics (patients with HFPEF are older and more likely to be women, and to have hypertensive heart disease, renal failure, anaemia, atrial fibrillation and obesity; patients with LVSD are more likely to have ischemic heart disease, dilated cardiomyopathy and hyperlipidaemia). Morbidity and mortality are similar in both groups.

HF mainly affects older people, with an estimated prevalence of 6 to 10% in people >65 years (1), increasing to 14% in people >85 years (2). Prevalence is expected to increase as a result of the ageing population and improved survival of

people with ischaemic heart disease. The prognosis of patients with HF is poor; up to 40% of newly diagnosed patients die within one year (3, 4). HF is one of the most costly conditions to manage an also markedly impairs quality of life.

Pharmacological treatment for HF includes angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers and beta-blockers, drugs which are currently administered at doses that have been used in clinical trials. However, many patients receive sub-optimal treatment because doctors are reluctant to increase medication doses after the initial clinical improvement, to avoid potential side effects such as renal failure and hypotension.

Serum natriuretic peptides (B-type natriuretic peptide, BNP; or its derivative N-terminal pro-B-type natriuretic peptide, NT-BNP, collectively referred to here as BNP) are biomarkers of HF. BNP is a hormone secreted in the ventricular myocardium during periods of increased ventricular stretch and wall tension. BNP levels are raised in patients with HF, with concentrations rising in line with the severity of symptoms (New York Heart Association (NYHA) class). BNP is therefore useful for ruling out HF (5, 6) and for risk stratification; for every 100ng/l increase in BNP level, there is a corresponding 35% relative increase in the risk of death (7). BNP levels reflect cardiac function. Treating HF with appropriate drugs leads to a reduction in BNP levels. Therefore, researchers have been interested in whether monitoring BNP could improve clinical outcomes by using BNP levels to guide up-titration of medication. BNP-guided therapy has been evaluated in several randomised controlled trials (RCTs).

To date there have been four aggregate data meta-analyses of RCTs: including 6 (n=1627), 8 (n=1726), 11 (n=2414) and 12 (n=2686) RCTs (8-11), with patients followed for an average of 12 to 16 months. There is also a published

protocol for a Cochrane review (12). All four published meta-analyses reported a reduction in all-cause mortality in the BNP-guided therapy group when compared with standard care (symptom-based therapy) (HR 0.69, 95% CI 0.55 to 0.86; RR 0.76 95% CI 0.63 to 0.91; RR 0.83, 95% CI 0.69 to 0.99; OR 0.74, 95% CI 0.60 to 0.91, respectively). The two latter meta-analyses, including 11 and 12 RCTs also reported a decrease in HF-related rehospitalisation (RR 0.65, 95% CI 0.50-0.84; OR 0.53, 95% CI 0.35 to 0.81, respectively). In sub-group analyses (using RCTs that provided data on patients younger or older than 75 years), the reduction in mortality was only observed in younger patients (≤ 75 years) (9-11), suggesting that BNP-guided therapy may not benefit the elderly HF population. Patients >75 years are more likely to have HFPEF, in which the drug therapies used for LVSD have generally been shown to be ineffective (13). However, the results of these sub group analyses need to be interpreted with caution because none of the meta-analyses investigated treatment effect modification, but simply compared the effect estimates and their statistical significance in each sub group. It is unclear whether there are effect modifications for other subgroups. The identification of relevant treatment subgroups is important because it is known that some patients do not benefit from, and may be harmed by, drug therapies for HF. For example, in elderly patients with multiple co-morbidities, the risks of adverse outcomes from intensified therapy might outweigh any benefits; up-titration of diuretics, angiotensin converting enzyme inhibitors, and beta-blockers may worsen clinical outcomes in elderly patients by causing hypotension and aggravating renal failure (14).

Aggregate data meta-analyses combine study-level data to estimate one overall effect. Information is averaged or estimated across all individuals in a study (e.g. mean treatment effect, mean age, proportion male, etc.). The main

disadvantage of this type of meta-analysis is the reliance on data reported by the original RCT – data may be reported inconsistently, or be incompatible for other reasons, across trials (e.g., outcomes reported at different points in time or with different periods of follow-up), or may be selectively reported. Individual participant data (IPD) meta-analysis uses 'raw' individual-level data obtained from each study to estimate an overall effect, avoiding limitations arising from reporting. IPD meta-analysis is widely regarded as the gold standard and has several advantages over aggregate data meta-analysis. It allows time-to-event and subgroup analyses, a more flexible analysis of outcomes, detailed data checking to ensure consistency, and an assessment of the quality of randomisation and follow-up. The IPD can also be updated with follow-up information. More importantly, an IPD meta-analysis allows a more powerful and detailed analysis of treatment effect modification, because it can use within-trial data to estimate how patients' characteristics modify treatment benefit (15).

We propose to conduct an IPD meta-analysis to determine whether BNP-guided therapy improves outcomes in patients with heart failure. The IPD meta-analysis will also allow us to determine which subgroups of patients are likely to benefit most from BNP-guided therapy, and possibly identify specific components of the interventions responsible for the improved outcomes observed in individual RCTs. There is an existing IPD meta-analysis of 7 RCTs (including 1732 patients) that has been published in abstract form (16). However, this IPD meta-analysis does not include data from more recent trials.

2. Aims and objectives

The main aim of the IPD meta-analysis is to determine the clinical effectiveness of BNP-guided therapy versus standard care. Specific objectives are as follows:

A. To estimate the effect of treatment guided by serial BNP monitoring on clinical outcomes (see section 3.1) compared with standard care (symptom-based therapy).
B. To estimate the extent of effect modification for clinically important subgroups (e.g. age, gender, type of HF, severity of HF, baseline BNP levels, etc.).
C. To quantify the extent to which improved outcomes are explained by up-titration of medication and/or reduction in BNP levels (if data describing titration of medication are available).
D. To pool adverse event and discontinuation data to describe the safety of BNP-guided therapy in patients with HF.

3. Methods

The IPD meta-analysis will be conducted in accordance with the methods recommended by the Individual Participant Data (IPD) Meta-analysis Methods Group of the Cochrane Collaboration (17) and other published guidelines (18).

3.1. Criteria for considering studies for the review

- *Types of studies*: RCTs of BNP-guided treatment for HF that report a clinical outcome.
- *Population*: All patients >18 years who are being treated for HF in primary or secondary care.
- *Intervention*: Treatment guided by serial BNP measurements (BNP-guided therapy).

- *Comparator*: Treatment guided by clinical assessment (standard care).
- *Primary outcome*: Time to all-cause mortality.
- *Secondary outcomes*: Death related to HF; All-cause hospital admission; Hospital admission for HF; Adverse events; Quality of life.

3.2. Search methods for identification of studies

We initially used published systematic reviews (8-11) to identify relevant trials. We will supplement these with additional searches of Medline, Embase, The Cochrane Library and ISI Web of Science (Citations Index and Conference Proceedings). A search strategy has been developed (see Appendix 1). We will search the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; http://apps.who.int/trialsearch/) and Current Controlled Trials (http://www.controlled-trials.com) to identify trials in progress. We will also review the reference of all full text papers and correspond with all trial authors to identify any trials that we may have missed.

3.3. Inclusion of studies

- *Study selection*: Two members of the review team (not authors on any of the included trials) will independently review the titles and abstracts to remove those that are clearly inappropriate. The remaining papers will have clear inclusion criteria applied to them. Disagreements about study inclusion will be resolved by discussion with a third review author. RCT authors will be contacted, if necessary, to clarify details such as allocation concealment. Adequate allocation procedures include centralised randomisation or use of consecutively numbered, opaque sealed envelopes containing the allocation

information kept by a person otherwise not involved in the study and not made available to the person recruiting a participant until a participant has been shown to be eligible and has given informed consent. All trials excluded from the review will be given reasons for exclusion as follows: not a randomised trial, allocation unclear or inadequate, no clinical outcome, inappropriate control.

- *Trial size:* There will be no restriction on the size of the RCT.
- *Language*: No language restrictions will apply. All RCTs in languages other than English will be translated into English. The English text will be made available to all collaborators.

3.4. Quality assessment

- *Risk of bias in included studies*: Contributors will be expected to provide their study protocol to assist the risk of bias assessment. Two members of the review team will independently assess the risk of bias in each included study using the domain-based evaluation tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (19). Disagreements will be resolved by discussion with a third review author. We will assess the following domains as low risk of bias, unclear or high risk of bias. Where the risk of bias for a domain remains unclear, contributors will be asked to provide additional information to resolve the uncertainty.
    - Generation of allocation sequence (selection bias)
    - Allocation concealment (selection bias)
    - Blinding of participants, personnel and outcome assessors (performance bias)

- Incomplete outcome data (attrition bias)*
- Selective reporting (reporting bias)*
- Other sources of bias

* These assessments will only be used for the aggregate data meta-analysis (see section 3.6). Detection bias is not on the list because the primary outcome is all cause mortality (which is objective).

3.5. Development of the database

IPD will be requested from authors of selected studies. We will identify contact information for study authors from the published RCT or a Google search. We will contact the main trial author (corresponding author) and provide them with a cover letter explaining what the study is about and the IPD meta-analysis protocol. IPD will be sought from all included RCTs and collated into a single database. We will request the data for all randomised patients, regardless of whether they received the allocated treatment and provided outcome data. If we receive no response from the corresponding author, another investigator from the study will be contacted.

- *Data collection*: We will accept trial data in all formats in order to minimise the amount of work for trial authors and ensure maximum participation (however, the data will ideally be provided in a two dimensional spreadsheet format with one subject per row and all variables listed in columns). However, we will seek access to additional variables where they are included in a number of datasets and where there is the possibility of pooled analyses.
- Raw data can be transferred by a variety of secure methods (courier, email, or secure electronic transfer) depending on the preference of the authors' institutions. All raw data will be stored on a secure University of Bristol server.

Raw datasets will be saved in their original formats and then converted to a common format by renaming and labelling the variables for each study in a consistent manner. We will develop a framework for mapping and classifying sufficiently similar variables; this will be discussed/agreed within the collaborative group and carefully documented.

- *Data checking*: We will carry out various checks on the data (see examples below), and discuss and clarify discrepancies with study authors.
    - For each variable, we will calculate the proportion of missing observations and check against data in the original publication.
    - We will carry out range checks for all included variables to ensure that all values are reasonable.
    - We will tabulate categorical variables and check against the values tabulated in the original publication. .

Datasets that have passed the checks or where queries have been resolved with study authors will be combined to form a new master dataset with a new variable added to indicate the original study.

3.6. Data analysis

- *Checking for publication and data availability bias*: We will follow the recommendations set out by Ahmed et al (20) to check for publication bias and data availability bias. We will assess publication bias using funnel plot asymmetry, with and without studies lacking IPD. We will describe study-level and patient-level characteristics of included studies. We will report:
    - The meta-analysis of IPD from trials that have supplied IPD.
    - A meta-analysis of aggregate data from all trials.

- A meta-analysis that combines the individual participant data with the aggregate data from the trials lacking individual participant data.

- *Aggregate data meta-analysis*: We will use standard methods of analysis to conduct meta-analysis and meta-regression analyses based on aggregate data. We will assess the effect of BNP-therapy on primary and secondary outcomes and the impact of study-level variables such as BNP-guided intervention characteristics. We will conduct both fixed-effect and random-effects meta-analysis with restricted maximum likelihood (REML) estimates of heterogeneity variance to estimate the average treatment effect and its 95% CI for each outcome. We will describe between-study inconsistency using the I^2 statistic (19). We will use random-effects estimates, along with prediction intervals to represent heterogeneity, to present results unless there is evidence that the underlying assumption of a normal distribution for true treatment effects is not reasonable. The comparison of fixed-effect meta-analyses with random-effects meta-analyses will be used as an initial check of the possible impact of funnel plot asymmetry. We will investigate the tendency for smaller studies to report more significant and positive findings than larger studies using contour enhanced funnel plots and tests for funnel plot asymmetry (21, 22).
- *IPD meta-analysis:* We will use standard meta-analysis methods incorporating all available IPD. All analyses will be performed on an intention-to-treat basis. The primary outcome will be time to all-cause mortality, defined as the time from randomisation to death from any cause, which will be analysed by survival methods. Hazard ratios (HR) will be estimated using Cox regression models within each trial. The estimated log HRs will be combined across

studies using standard fixed-effect and random-effects meta-analysis methods as above. Subgroup effects (including age, gender, baseline BNP level, NYHA class, presence of co-morbidities) will be estimated by estimating treatment-by-covariate interaction terms within studies and combining these across studies in the same way (12). Other sub-groups will investigate study-level variables such as BNP-guided intervention characteristics (comparisons to be specified when study level data have been extracted). Forest plots will be produced for overall effects and for interaction effects. Interaction effects will be interpreted by applying them to meta-analyses of the participants in a reference subgroup (for example, when looking at the effect in males vs females, the meta-analytic interaction coefficient will be added to the result of a meta-analysis of HRs among females only to obtain an estimate HR for among males). As above, we intend to present random-effects estimates, along with prediction intervals to represent heterogeneity.

- *Sensitivity analysis:* For both the aggregate meta-analysis and IPD meta-analysis we plan to conduct a sensitivity analysis on trials classified as having low risk of bias overall versus those classified as having a high risk of bias overall. We will also conduct a sensitivity analysis based on allocation concealment (good allocation concealment versus poor allocation concealment), since this has been shown to be the most important source of bias in RCTs (23, 24).

4. *How the IPD collaboration will work*

The BNP-Guided Therapy for Heart Failure IPD Meta-Analysis Group will include a representative from each of the included trials. New collaborators will be invited as

eligible trials are completed. The local project team includes members from the Bristol Clinical Trials and Evaluation Unit (CTEU, see http://cteu.bris.ac.uk/), a UKCRN-registered trials unit at the University of Bristol and a Professor of Evidence Synthesis at the University of Bristol, who has extensive experience in conducting meta-analyses and systematic reviews. The local project team developed the IPD meta-analysis protocol, will contact the study authors, will liaise between members of the collaborative group and organise all necessary interactions between study members.

Members of the Collaborative Group will be given the opportunity to participate in decision-making regarding the study design and analyses, and will be consulted at key stages of the project. Publications resulting from the meta-analysis will be prepared by the local project team and circulated to all members of the Collaborative Group for comment. All publications will be authored by the collaborative group with contribution of members being described at the end of the paper.

5. *Ethical issues*

The IPD meta-analysis is exempt from ethical approval as we will be collecting and synthesising data from previous clinical trials where informed consent has already been obtained by the trial investigators and our meta-analysis will essentially address the same question for which the data were collected (and patients gave consent). Moreover, we will request contributors only to submit fully anonymised datasets (i.e. the key linking study number to identifiable patient data will be retained by the contributor and not shared with the project team). Each main trial author will be asked to sign a consent form which will give the Collaborative Group permission

to use their data and specify any restrictions on data usage or storage that they may wish to impose.

6. *Dissemination plans*

Findings from both meta-analyses will be reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).(23) We will also adhere to additional reporting guidelines recommended for IPD meta-analysis (18) .

7. References

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Appendix 1. Search strategy

Medline (Ovid) 1950 to present

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1 (BNP adj5 (guide$ or monitor$ or target$ or predict$)).tw. (732)
2 (proBNP adj5 (guide or monitor$ or target$ or predict$)).tw. (462)
3 (NTproBNP adj5 (guide$ or monitor$ or target$ or predict$)).tw. (22)
4 ((natriuretic peptide or natriuretic propeptide) adj5 (guide$ or monitor$ or target$ or predict$)).tw. (650)
5 ((NTproBNP or Natriuretic Peptide or natriuretic propeptide or BNP or proBNP) adj5 (retest$ or serial or series)).tw. (153)
6 ((NTproBNP or Natriuretic Peptide or natriuretic propeptide or BNP or proBNP) adj5 (manag$ or tailor$ or treat$ or therap$ or strateg$)).tw. (863)
7 or/1-6 (2266)
8 exp Heart Failure/ (77650)
9 heart failure.tw. (88345)
10 cardiac failure.tw. (9104)
11 HF.tw. (15642)
12 CHF.tw. (9142)
13 or/8-12 (132395)
14 Natriuretic Peptide, Brain/ (8154)
15 Monitoring, Physiologic/ (42028)
16 "Predictive Value of Tests"/ (121365)
17 "Health Status Indicators"/ (17985)
18 or/15-17 (179642)
19 14 and 18 (1234)
20 (BNP adj5 (guide$ or monitor$ or target$ or predict$)).tw. (732)
21 (proBNP adj5 (guide or monitor$ or target$ or predict$)).tw. (462)
22 (NTproBNP adj5 (guide$ or monitor$ or target$ or predict$)).tw. (22)
23 ((natriuretic peptide or natriuretic propeptide) adj5 (guide$ or monitor$ or target$ or predict$)).tw. (650)
24 ((NTproBNP or Natriuretic Peptide or natriuretic propeptide or BNP or proBNP) adj5 (retest$ or serial or series)).tw. (153)
25 ((NTproBNP or Natriuretic Peptide or natriuretic propeptide or BNP or proBNP) adj5 (manag$ or tailor$ or therap$ or strateg$)).tw. (461)
26 or/20-25 (1923)
27 19 or 26 (2616)
28 13 and 27 (1471)
29 randomized controlled trial.pt. (330201)
30 controlled clinical trial.pt. (84375)
31 randomized.ab. (233876)
32 placebo.ab. (132230)
33 drug therapy.fs. (1543331)
34 randomly.ab. (168558)
35 trial.ab. (242070)
36 groups.ab. (1106725)
37 or/29-36 (2867649)
38 exp animals/ not humans/ (3736636)
39 37 not 38 (2435187)
40 28 and 39 (506)

Embase (Ovid) <1980 to 2012 Week 26>

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1 exp heart failure/ (240304)
2 heart failure.tw. (125430)
3 cardiac failure.tw. (11574)
4 CHF.tw. (13935)
5 HF.tw. (26271)
6 or/1-5 (284966)
7 brain natriuretic peptide/ (13290)
8 monitoring/ (68421)
9 predictive value/ (18283)
10 "disease course"/ (253029)
11 "symptom"/ (82438)
12 disease course/ (253029)
13 "pathophysiology"/ (552261)
14 patient monitoring/ (57907)
15 biological monitoring/ (11401)
16 hemodynamic monitoring/ (11474)
17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (1015916)
18 7 and 17 (2351)
19 (BNP adj5 (guide$ or monitor$ or target$ or predict$)).tw. (1252)
20 (proBNP adj5 (guide or monitor$ or target$ or predict$)).tw. (813)
21 (NTproBNP adj5 (guide$ or monitor$ or target$ or predict$)).tw. (111)
22 ((natriuretic peptide or natriuretic propeptide) adj5 (guide$ or monitor$ or target$ or predict$)).tw. (894)
23 ((NTproBNP or Natriuretic Peptide or natriuretic propeptide or BNP or proBNP) adj5 (retest$ or serial or series)).tw. (236)
24 ((NTproBNP or Natriuretic Peptide or natriuretic propeptide or BNP or proBNP) adj5 (manag$ or tailor$ or treat$ or therap$ or strateg$)).tw. (1373)
25 or/19-24 (3676)
26 18 or 25 (5641)
27 6 and 26 (3599)
28 random$.tw. (734627)
29 factorial$.tw. (18994)
30 (crossover$ or cross-over$).tw. (61441)
31 placebo$.tw. (175748)
32 (doubl$ adj blind$).tw. (128507)
33 (singl$ adj blind$).tw. (12267)
34 assign$.tw. (204642)
35 allocat$.tw. (68787)
36 volunteer$.tw. (157058)
37 Crossover Procedure/ (34246)
38 Double-blind Procedure/ (109462)
39 Randomized Controlled Trial/ (324293)
40 Single-blind Procedure/ (16047)
41 or/28-40 (1210587)
42 (animal/ or nonhuman/) not human/ (4452630)
43 41 not 42 (1063367)

44 27 and 43 (461)
45 limit 44 to embase (395)

The Cochrane Library

#1 MeSH descriptor Heart Failure explode all trees
#2 "heart failure"
#3 "cardiac failure"
#4 CHF
#5 HF
#6 (#1 OR #2 OR #2 OR #4 OR #5)
#7 MeSH descriptor Natriuretic Peptide, Brain, this term only
#8 (BNP near/5 (guide* or monitor* or target* or predict*))
#9 (NTproBNP near/5 (guide* or monitor* or target* or predict*))
#10 (("natriuretic peptide") near/5 (guide* or monitor* or target* or predict*))
#11 ((NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) near/5 (retest* or serial or series))
#12 ("natriuretic propeptide" near/5 (guide* or monitor* or target* or predict*))
#13 (NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP):ti
#14 (NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) near/5 (manag* or tailor* or therap* or strateg*)
#15 (proBNP near/5 (guide* or monitor* or target* or predict*))
#16 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#6 AND #16)

ISI Web of Science (Citations Index and Conference Proceedings)

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18 #17 AND #16
17 TS=(random* or trial or placebo* or groups (double same blind*) or (single same blind*))
16 #15 AND #1
15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
14 TS=((NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) NEAR (strateg*))
13 TS=((NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) NEAR (therap*))
12 TS=((NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) NEAR (tailor*))
11 TS=((NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) NEAR (manag*))
10 TS=((NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) NEAR series)
9 TS=((NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) NEAR serial*)
8 TS=((NTproBNP or "Natriuretic Peptide" or "natriuretic propeptide" or BNP or proBNP) NEAR retest*)

7 TS=("natriuretic propeptide" NEAR (guide* or monitor* or target* or predict*))
6 TS=("natriuretic peptide" NEAR (guide* or monitor* or target* or predict*))
5 TS=(NTproBNP NEAR (guide* or monitor* or target* or predict*))
4 TS=(proBNP NEAR (guide or monitor* or target* or predict*))
3 TS=(BNP NEAR (guide* or monitor* or target* or predict*))
2 TS=("natriuretic peptide" NEAR target*) or TS=("natriuretic propeptide" NEAR target*)
1 TS=("heart failure" or "cardiac failure" or CHF or HF)