Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials
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CRD summary
The review found that biomarker-guided therapy using serial B-type or N-terminal pro-B-type natriuretic peptide levels significantly reduced all-cause mortality from chronic heart failure, compared with usual care. The review was generally well conducted and findings were consistent. However, as most trials were unblinded and review methods were not fully reported, some caution may be advisable in interpreting the authors' conclusions.

Authors' objectives
To evaluate the effect of biomarker-guided therapy on mortality rates in chronic heart failure.

Searching
MEDLINE, Web of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched from 1996 to May 2009. Search terms were reported. Design papers of ongoing studies, proceedings of major cardiology meetings in the USA and Europe (2000 to 2009), and reference lists of secondary sources were checked.

Study selection
Randomised controlled parallel-group trials (RCTs) of biomarker-guided therapy for chronic heart failure were eligible for inclusion, provided they reported all-cause mortality (the primary review outcome). The intervention was defined as titration of medical therapy according to the level of a circulating biomarker.

Most participants in the included trials had left ventricular systolic dysfunction; mean participant age ranged from 61 to 77 years; the proportion of males ranged from 5 to 76%; mean ejection fraction ranged from 20 to 37%; and ischaemic cause of heart failure ranged from 44 to 74% (where reported). Most participants were receiving evidence-based therapy at baseline.

Use of medical therapies intensified in intervention and control groups during the trial, but with a greater increase in the use of specific drugs (listed in the review) in the intervention group. The biomarkers used were either B-type natriuretic peptide or N-terminal pro-BNP B-type natriuretic peptide. Biomarker targets and treatment strategies differed within and across trials. Control groups received usual care and/or strategies based on symptoms or symptom scores. As well as mortality, the review reported adverse events and non-fatal clinical events.

Two reviewers retrieved potentially relevant studies for inclusion.

Assessment of study quality
Some components of trial quality were apparently assessed (i.e. blinding, intention-to-treat analysis), but the authors did not state what criteria were used or how the validity assessment was performed.

Data extraction
Risk ratios (RRs) for mortality were extracted or calculated for each trial, with 95% confidence intervals (CIs). Descriptive data were extracted for other outcomes. One trial included two control groups; their data were combined in the main analysis.

Methods of synthesis
Trials were combined to calculate pooled risk ratios (hazard ratios (HRs)) and 95% confidence intervals using an empirical Bayes random-effect estimator (Hedges 1985). The profiles test was used to assess heterogeneity. Sensitivity analyses were conducted based on publication status, length of follow-up and design of control conditions. The impact of age on treatment effect was checked in subgroup analysis.
Results of the review
Six RCTs were included in the review, including 1,627 patients (based on text) or 1,634 patients (based on tables) (range 69 to 499). One RCT was double-blinded, two were single blinded and three were unblinded. All RCTs used intention-to-treat analysis. Duration of follow-up ranged from three to 18 months.

Mortality was significantly lower in the intervention group (HR 0.69, 95% CI 0.55 to 0.86; six RCTs), without significant heterogeneity (profiles test p=0.42). Sensitivity analyses did not change the significance of these findings. The effect of the intervention was stronger in patients younger than 75 years (two RCTs).

Other outcomes were unsuitable for meta-analysis. Generally rates of disease-specific hospitalisation appeared to be reduced by the intervention. The effect on all-case and non-cardiac hospitalisation was less clear (six RCTs). None of the trials reported an increase in adverse events associated with the intervention (four RCTs).

Authors' conclusions
Biomarker-guided therapy using serial B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide levels significantly reduced all-cause mortality from chronic heart failure, compared with usual care.

CRD commentary
The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies without restriction by publication status. It was unclear whether the search was limited by language. It was also unclear whether the risk of reviewer bias and error was minimised by having two reviewers independently involved in all stages of study selection. The processes of data extraction and validity assessment were not described. These factors made it difficult to assess the reliability of the evidence presented.

Appropriate statistical techniques appear to have been used to combine the data, assess for heterogeneity and explore differences between the trials. The review was well conducted in most respects and findings for the main outcome were consistent across trials.

However, as most trials were unblinded and review methods were not fully reported, some caution may be advisable in interpreting the authors' conclusions.

Implications of the review for practice and research
Practice: The authors stated that biomarker-guided therapy appears to lead to a 30% improvement in survival among patients with chronic heart failure, without an increase in therapy-related adverse events. The therapy may be less effective in older patients (over 75 years).

Research: The authors stated that a well-powered RCT should be considered, in order to determine conclusively the efficacy of biomarker-guided therapy on clinical outcomes.

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