**Exercise training meta-analysis of trials in patients with chronic heart failure**

(ExTraMATCH)

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**CRD summary**

The authors pooled individual patient data from nine trials comparing exercise training with standard care. They concluded that exercise training is associated with a significant reduction in mortality. The lack of individual trial results and the statistical methods used make it difficult to assess the reliability of the conclusions.

**Authors' objectives**

To determine the effect of exercise training on survival in patients with heart failure caused by left ventricular dysfunction.

**Searching**

The authors searched MEDLINE, reference lists of review articles, and abstracts presented at scientific meetings and published in Circulation, the Journal of the American College of Cardiology and the European Heart Journal. They also consulted researchers in exercise physiology and heart failure. A subsequent search of the Cochrane Database of Systematic Reviews did not identify any further studies.

A collaborative group was established to conduct the meta-analysis. A prospective protocol was written and agreed before any data collection or analysis took place.

**Study selection**

**Study designs of evaluations included in the review**

The review included individual patient data (IPD) from randomised controlled trials (RCTs).

**Specific interventions included in the review**

Studies of exercise programmes (without other simultaneous interventions) lasting 8 weeks or more and involving training of at least both legs were eligible for inclusion; survival follow-up of at least 3 months was also required. The duration of training in the included studies ranged from 8 weeks to over a year, and the intensity ranged from 50 to 80% of peak oxygen consumption or peak heart rate.

**Participants included in the review**

The participants were required to be patients with chronic heart failure (stable for at least 3 months) associated with left ventricular dysfunction (a left ventricular ejection fraction, LVEF, of less than 50%). The participants in the included studies were mostly male (88%) with a mean age of 60 years, mean LVEF of 27% and mean New York Heart Association (NYHA) functional class of 2.5. The majority were taking angiotensin-converting enzyme inhibitors (73%) and diuretics (69%).

**Outcomes assessed in the review**

The primary outcome was time to death from any cause. A secondary outcome was a composite of death and time to first admission to hospital (for any reason).

**How were decisions on the relevance of primary studies made?**

The authors did not state how decisions on the relevance of primary studies were made.

**Assessment of study quality**

The data were checked for completeness and consistency. Queries were resolved by contacting the principal investigator. The authors did not state how judgements of validity were made.
Data extraction
Investigators provided IPD for their trials. The data requested included presence or absence of ischaemic heart disease, NYHA functional class, LVEF, exercise peak oxygen consumption, admission to hospital and dates of randomisation, follow-up and death.

Methods of synthesis
How were the studies combined?
The treatment arms from the included studies were all combined into one arm, as were the control groups. Kaplan-Meier survival curves were plotted for each end point, over 2 years’ follow-up. Hazard ratios (HRs) and their associated 95% confidence intervals (CIs) were calculated for the primary and secondary end points. The survival curves for the treatment and control groups were compared using a Mantel-Cox log rank test.

The analyses were conducted on an intention-to-treat basis.

The potential for publication bias was investigated using a funnel plot and Egger’s test. In addition, the association between variance and effect size across the included studies was analysed by rank correlation.

How were differences between studies investigated?
Pre-specified subgroup analyses were performed to assess the effects of differences in participant characteristics (gender, NYHA class, ischaemic heart disease, age, peak oxygen uptake and LVEF) and duration of the training programme (less than 28 weeks versus 28 weeks or longer).

Results of the review
IPD from 9 RCTs (n=801) were included. One RCT (n=25) was excluded because raw data could not be obtained.

Exercise training significantly reduced mortality (HR 0.65, 95% CI: 0.46, 0.92, P=0.015). The secondary end point of death or hospital admission was also reduced (HR 0.72, 95% CI: 0.56, 0.93, P=0.011). The subgroup analyses found no evidence that the effect of exercise training differed within subgroups. Tests for publication bias were not statistically significant.

Authors’ conclusions
Exercise training significantly improves survival in patients with chronic heart failure caused by left ventricular dysfunction. Time to death or admission to hospital was also significantly extended.

CRD commentary
The meta-analysis had a clear objective and inclusion criteria. It was conducted by a collaborative group using a pre-specified protocol. The search appeared adequate, although details of the search strategy were not reported. Data were obtained from investigators and checked for completeness and consistency; again, few details were reported. The results of individual studies were not presented and this makes it difficult to judge the appropriateness of the meta-analysis methods and conclusions. Reasons for excluding trials were reported. One trial was excluded because raw data could not be obtained, although the authors noted that this was a small trial and its exclusion was unlikely to have affected the overall conclusions.

In their analysis the authors pooled data from all the treatment arms and all the control arms, and do not appear to have accounted for the fact that the data came from different studies. The possible impact of this on the results of the meta-analysis is unclear. Sources of clinical heterogeneity were investigated in pre-specified subgroup analyses. The risk of publication bias was assessed using standard methods. The authors’ conclusions are in line with the evidence presented, but the reporting and statistical issues noted above make it difficult to assess the reliability of the conclusions.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that there is a need for research to optimise exercise programmes and to identify the patient groups that would benefit most from exercise.

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Other publications of related interest
This additional published commentary may also be of interest. Massie B. Review: exercise training delays death and hospital admission in chronic heart failure. Evid Based Med 2004;9:137.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.