Exercise-based cardiac rehabilitation for chronic heart failure: the EXTRAMATCH II individual participant data meta-analysis

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Scientific summary

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Scientific summary

Background

People with symptomatic heart failure (HF) are living for longer following the onset of their condition, increasing the importance of effective and accessible services for these patients. Exercise-based cardiac rehabilitation (ExCR) is recognised as integral to the comprehensive care of HF patients. ExCR is a process by which patients, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health. Current national [National Institute for Health and Care Excellence. *Chronic Heart Failure in Adults: Management*. Clinical Guideline [CG108]. URL: www.nice.org.uk/guidance/CG108 (accessed 25 June 2018)] and international [Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;**128**:e240–327; Working Group on Cardiac Rehabilitation; Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise training in chronic heart failure patients. *Eur Heart J* 2001;**22**:125–35; and McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al.* ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–847] guidelines on the management of HF recommend ExCR, but do not differentiate according to patient subgroups.

Objectives

The Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH/ExTraMATCH II) project aimed to determine which HF patient subgroups benefit most from ExCR using individual participant data (IPD) meta-analysis.

The project had three objectives:

1. To obtain definitive estimates of the impact of ExCR interventions compared with no exercise intervention (control) on mortality, hospitalisation, exercise capacity and health-related quality of life (HRQoL) in HF patients.
2. To determine the differential (subgroup) effects of ExCR in HF patients according to their:
    - age
    - sex
    - left ventricular ejection fraction
    - HF aetiology
    - New York Heart Association (NYHA) class
    - baseline exercise capacity.
3. To assess whether or not the change in patient exercise capacity mediates, and is an acceptable surrogate end point for, the impact of ExCR on final outcomes of mortality, hospitalisation and HRQoL.

The information gained from the ExTraMATCH II project will inform future UK and international clinical and policy decision-making on the use of ExCR in HF.

Methods

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) IPD statement. Randomised controlled trials were identified from the original ExTraMATCH IPD meta-analysis [Piepoli MF, Davos C, Francis DP, Coats AJ, ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;**328**:189] and the 2014 Cochrane systematic review of ExCR for HF (Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, *et al*. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014;**4**:CD003331). ExTraMATCH and the Cochrane systematic review were based on searches of the following electronic databases: Cochrane Central Register of Controlled Trials in The Cochrane Library, EMBASE, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and the NHS Centre for Reviews and Dissemination. Conference proceedings and trial registers were also searched. In keeping with the original ExTraMATCH IPD meta-analysis, trials of exercise training (for at least 3 weeks) compared with no exercise control with ≥ 6 months' follow-up were included if they provided IPD on all-cause or HF-specific mortality, hospitalisation, exercise capacity or HRQoL. The data sets of IPD were combined into a single data set. One-stage fixed-effect meta-analyses of time-to-event end points were performed using Cox proportional hazards models, stratified by study. One-stage meta-analyses of continuous outcomes were performed using hierarchical linear models with adjustments for baseline values and a random effect on study. Two-stage models using fixed and random effects were also performed. Interaction terms between ExCR and participant characteristics were used to assess potential differential effects of ExCR across subgroups. Mediational analyses and meta-analytic regressions, with estimation of R^2 at the trial level, and surrogate threshold effect (STE), were performed to assess the question of surrogate validity for exercise capacity outcomes of peak oxygen uptake (VO_2peak) and the 6-minute walk test (6MWT).

Results

Of the 23 eligible trials (4398 patients), 19 trials contributed data to the IPD meta-analysis [18 trials (3912 patients) to the clinical events (mortality and hospitalisation) analysis, 13 trials (3332 patients) to exercise capacity and HRQoL analysis, and 10 trials (2656 patients) to the exercise capacity mediational/surrogate end-point analysis].

Characteristics and quality of included trials

Patient characteristics at baseline were well balanced between ExCR and control group patients. The majority of patients were male (74%), had a mean age of 61 years, had experienced heart failure with reduced ejection fraction (HFrEF) (mean baseline left ventricular ejection fraction 26.7%), and most patients were in NYHA functional class II (59%) or III (37%). No included trials recruited patients with HF with a preserved ejection fraction of > 45%. Trials were conducted in Europe and North America and were published between 1990 and 2012, and the sample sizes ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention, which was most commonly delivered in either an exclusively centre-based setting or a centre-based setting in combination with some home exercise sessions. The dose of exercise training ranged widely across trials. ExCR was delivered over a period of 12–90 weeks, with between two and seven sessions per week (median session duration was between 15 and 120 minutes, including warm-up and cool-down). The intensity of exercise ranged between 50% and 85% VO_2peak. The overall quality of included trials was measured using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX), a measure of study quality and reporting. Most studies were judged as being moderate to good, with a median TESTEX score of 11 (range 9–14) out of a maximum score of 15.

Impact of ExCR on mortality and hospitalisation

Compared with control, there was no statistically significant difference in pooled time-to-event estimates in favour of ExCR, although confidence intervals (CIs) were wide: all-cause mortality had a hazard ratio (HR) of 0.83 (95% CI 0.67 to 1.04); HF-related mortality had a HR of 0.84 (95% CI 0.49 to 1.46); all-cause

hospitalisation had a HR of 0.90 (95% CI 0.76 to 1.06); and HF-related hospitalisation had a HR of 0.98 (95% CI 0.72 to 1.35). No strong evidence for differential intervention effects across patient characteristics was found.

Impact of ExCR on exercise capacity and health-related quality of life

Compared with the control, there was a statistically significant difference in favour of ExCR for exercise capacity and HRQoL. For example, at 12 months' follow-up, improvements were seen in the 6MWT (mean 21.0 m, 95% CI 1.57 to 40.4 m; $p = 0.034$, $\tau^2 = 491$, $I^2 = 78\%$) and the Minnesota Living with Heart Failure Questionnaire score (mean –5.94, 95% CI –1.0 to –10.9; $p = 0.018$, $\tau^2 = 77$, $I^2 = 88\%$); lower scores indicate improved HRQoL. No strong evidence for differential intervention effects across patient characteristics was found.

Validation of exercise capacity as a surrogate end point

Moderate to good levels of correlation ($R^2_{trial} > 50\%$ and $p > 0.50$) between exercise capacity VO_2peak or 6MWT with mortality and HRQoL were seen. Estimated STE was an increase of 1.6 to 4.6 ml/kg/minute for VO_2peak. The results indicate that an increase in VO_2peak or an improvement in the 6MWT with ExCR is a potentially weak mediator of final outcomes.

Discussion

In HFrEF patients, ExCR did not have a statistically significant effect on the risk of mortality and hospitalisation. However, uncertainty around effect estimates and lack of IPD on exercise adherence precludes drawing definitive conclusions in these event outcomes. ExCR significantly improves exercise capacity and HRQoL. No consistent differences were found in ExCR effects across patient subgroups. The results provide indicative evidence that VO_2peak and the 6MWT may be suitable surrogate end points for the treatment effect of ExCR on final outcomes in HF.

Recommendations for further research

Two central aspects of future data collection are (1) a consensus on the definition, collection and reporting of core sets of outcome data, concomitant disease/comorbidities and metrics of therapy delivery/uptake; and (2) the capture of data on patient-level adherence to the amount of exercise training during the ExCR intervention period. More generally, the research community should continue to implement policies that encourage primary study authors to make their data sets available, by either depositing in publicly available repositories or sharing with IPD meta-analysis collaborations when directly requested.

Study registration

This study is registered as PROSPERO CRD42014007170.

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