Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH II): An individual participant data meta-analysis of randomised controlled trials

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Topic of the paper (choosing from the above-listed topics): Quality and efficiency of health care services

Presentation format (oral with or without discussant)

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research (HTA 15/80/30).

A monograph about this project is currently being submitted to NIHR HTA for peer review.

Background

With increasing numbers of people living longer with symptomatic heart failure (HF), the effectiveness and accessibility of health services for HF patients have never been more important. 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. Whilst, current national and international guidelines on the management of HF recommend exercise-based cardiac rehabilitation (ExCR), they do not differentiate according to patient subgroup.

Tailoring rehabilitation interventions to specific subgroups that might benefit more of it may improve both *quality* and *efficiency* of the healthcare system. Individual patient data (IPD) meta-analyses, i.e. gathering and analyses of multiple randomised controlled trials data of healthcare interventions, may help addressing this type of questions.

Objectives

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

The project objectives were:

1. To obtain definitive estimates of the impact of exercise-based rehabilitation interventions versus control (no exercise intervention) on mortality, hospitalisation, exercise capacity, and health-related quality of life (HRQoL) in HF patients.
2. To determine the differential (sub-group) effects of exercise-based interventions in HF patients according to their (i) age, (ii) gender, (ii) left ventricular ejection fraction, (iii) HF aetiology, (iv) New York Heart Asccoaition (NYHA) class, and (v) baseline exercise capacity.
3. To assess whether the change in patient exercise capacity mediates and is a surrogate endpoint for the impact of the exercise-based interventions on final outcomes (mortality, hospitalisation, exercise capacity, and HRQoL).

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

Methods

The study was conducted and reported in accordance with current IPD guidance and Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA IPD) statement. Randomised controlled trials for were identified from the original ExTraMATCH IPD meta-analysis and the 2014 Cochrane systematic review of ExCR for HF and were based on searches the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, EMBASE, MEDLINE, CINAHL, PsycINFO, and the NHS Centre for Reviews and Dissemination. Conference Proceedings and trial registers were also searched. Trials of exercise training for at least 3 weeks, compared with no exercise control with 6-months' follow up or longer, were included if they provided IPD data on mortality or hospitalisation (all-cause or HF-specific) time to event or exercise capacity or HRQoL. Individual patient data were combined into a single dataset. Time-to-event endpoints were analysed using Cox proportional hazards models and continuous outcomes analysed using linear models with adjustments for baseline values. Several models were used, with a fixed effect on individual study and patient-level covariates, as well as a comparison of models with a fixed effect on intervention and random effects on intervention across trials. We used both one and two-stage random and fixed effects meta-analysis models and undertook extensive sensitivity analyses. Interactions terms between ExCR and participant characteristics were used to assess potential subgroup effects. Mediation analysis and meta-analytic regressions, with estimation of R^2 at trial level and surrogate threshold effect (STE), were performed to address the question of surrogacy validity of exercise capacity in this setting.

Results

Of the 23 eligible trial, 18 contributed data to the IPD meta-analysis (3,912 patients) to the clinical events (mortality and hospitalisation) analysis, 13 trials (3,332 patients) to exercise capacity and HRQoL analysis, and 10 trials (2,656 patients) to the exercise capacity surrogate endpoint analysis.

Characteristics and quality of included trials

Patient characteristics at baseline were balanced between ExCR and control patients. The majority of patients were male (75%), with a mean age of 61 years (standard deviation (SD) 13). The mean baseline left-ventricular ejection fraction was 26.7% (SD 8.1%); no included

trials recruited patients with preserved ejection fraction heart failure (ejection fraction >45%), and most patients were in NYHA functional class II (59%) or III (37%). Trials from Europe and North America were published between 1990 and 2012. Sample size ranged from 50 to 2,130 patients. All trials evaluated an aerobic exercise intervention and this 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 to 90 weeks, with between 2 and 7 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 to 85% peak VO_2. The overall quality of included trials was judged to be moderate to good, with a median TESTEX score of 11 (range 9 to 14) out of a maximum score of 15.

Impact of ExCR on mortality and hospitalisation

Compared to control, there was no statistically significant difference in pooled time to event estimates in favour of ExCR although confidence intervals were wide: all-cause mortality: hazard ratio (HR): 0.83 (95% confidence interval (CI): 0.67 to 1.04), HF-related mortality: HR 0.84 (95% CI: 0.49 to 1.46), all-cause hospitalisation: HR 0.90 (95% CI: 0.76 to 1.06), and HF-related hospitalisation: HR 0.98 (95% CI: 0.72 to 1.35). No strong evidence was found of differential intervention effects across patient characteristics.

Impact of ExCR on exercise capacity and HRQoL

Compared to 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 six 6-minute walk test (mean: 21.0 metres, 95% CI: 1.57 to 40.4, p=0.034, $\tau^2 = 491$, $I^2 =78$ %) and Minnesota Living with HF score (mean: -5.94, 95% CI -1.0 to -10.9, p=0.018, $\tau^2 =77$, $I^2 =88\%$). No consistent evidence was found of differential intervention effects across patient characteristics.

Validation of exercise capacity as a surrogate endpoint

Using individual patient data from RCTs of ExCR for HF, we formally evaluated the evidence for exercise capacity as a mediator and surrogate endpoint for the final patient-relevant outcomes of mortality, hospitalisation, and HRQoL, Moderate to good levels of correlation ($R^2_{trial} > 50\%$ and $\rho > 0.50$) 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/min for

VO_2peak. Although, subject to considerably statistical uncertainty, our results provide indicative evidence that VO_2peak and 6MWT may suitable surrogate endpoints for the treatment effect of ExCR on mortality and HRQoL in HF. Our analyses highlight the major shortcomings of the mediation approach for surrogate validation.

Discussion

ExCR did not have a statistically significant effect on the risk of mortality and hospitalisation in reduced ejection fraction HF. However, uncertainty around effect estimates precludes drawing definitive conclusions in these event outcomes. ExCR significantly improves exercise capacity and HRQoL in reduced ejection fraction HF. We found no consistent differences in ExCR effects across patient subgroups. Although, subject to considerably statistical uncertainty, our results provide indicative evidence that VO_2peak and 6MWT may suitable surrogate endpoints for the treatment effect of ExCR on final outcomes in HF. These conclusions need confirmation by future IPD meta-analyses of trials in HF.

Recommendations for further research

Two central aspects of future data collection include a consensus on the definition, collection, and reporting of core sets of outcomes data, especially hospitalisation, plus 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 datasets available, either by depositing in publicly available repositories or shared with IPD meta-analysis collaborations when directly requested.

Study registration

This study is registered as PROSPERO number CRD42014007170.