

BMJ Open Efficacy and safety of different modes of exercise-based cardiac rehabilitation delivery for patients with heart failure: a protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction The prevalence of heart failure (HF) is increasing. Exercise-based cardiac rehabilitation (CR) reduces mortality and further improves the prognosis of patients with HF. However, the effect of different modes of CR delivery on HF remains unclear. Thus, the purpose of this study is to find out the relative efficacy and safety of different modes of CR delivery for individuals with HF using a network meta-analysis.

Methods and analysis We will perform a systematic review and network meta-analysis of randomised controlled trials which compare different modes of exercise-based CR delivery for patients with HF. Databases including Embase, Medline, the Cochrane Central Register of Controlled Trials and Web of Science will be searched up to May 2022. The primary outcomes will focus on the functional capacity and the health-related quality of life (hr-QoL). Functional capacity will be evaluated by peak oxygen consumption (mL/kg/min) and 6 min walking test (metres). The Minnesota Living with Heart Failure questionnaire, Short Form-36, Psychometric properties of the Kansas City cardiomyopathy questionnaire and EuroQol five dimensions questionnaire will serve as measures of hr-QoL. As secondary outcomes, we will assess hospital admissions (all-cause and cardiac) and all-cause mortality, which required a minimum follow-up of 6 months, as well as adverse events during exercise training. The risk of bias for individual studies will be evaluated according to the Cochrane Handbook. The quality of evidence will be assessed by the Grading of Recommendations, Assessment, Development and Evaluation approach.

Ethics and dissemination This study does not require ethics approval as it is based on published trials. Results of this systematic review and network meta-analysis will be submitted to a peer-reviewed journal for future publication.

Trial registration number CRD42021278351.

INTRODUCTION

Heart failure (HF) is a complex disease characterised by structural and/or functional abnormalities of the heart that ultimately result in the heart's inability to deliver

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This will be the first network meta-analysis comparing different modes of cardiac rehabilitation (CR) delivery for patients with heart failure (HF).
- ⇒ The current network meta-analysis will compare simultaneously the efficacy and safety of multiple CR modes within and between studies and rank treatments according to their effectiveness.
- ⇒ Grading of Recommendations Assessment, Development and Evaluation approach will be used to evaluate the quality of evidence.
- ⇒ Findings from our study may serve as a reference for doctors and patients to select appropriate CR modes, which may reduce healthcare costs and improve the outcomes of patients with HF.
- ⇒ Our results will be limited by both the quantity and quality of the available studies for review.

sufficient blood and oxygen to other organs. It is estimated that 1%–2% of the adult population in developed countries suffers from HF, and that number rises to 10% in the 70+ age group.^{1,2} Furthermore, patients with HF have a high overall mortality rate, with 18% and 7% for those hospitalised and stable, as well as 12-month readmission rates of 44% and 32%, respectively.¹

As a comprehensive medically supervised programme for patients with HF, cardiac rehabilitation (CR) improves the exercise capacity of patients, as well as health-related quality of life (hr-QoL), and reduces the risks of rehospitalisation and all-cause mortality.^{3–5} For most cardiology departments, exercise is the core component.⁶ So far, CR has been recognised as essential care to patients with HF.^{1,3}

However, several factors, including high cost, lack of capacity of CR centres/hospitals, transportation or conflicting time schedules,

prevent patients with HF from participating in centre-based cardiac rehabilitation (CBCR).^{7,8} In those cases, home-based cardiac rehabilitation (HBCR) and cardiac telerehabilitation (CTR) can be the alternatives. In addition, hybrid cardiac rehabilitation (HCR), which combines short-term CBCR with HBCR or CTR, is a viable option to either HBCR or CBCR alone.^{9–11} Previous network meta-analyses elaborated the effects of different modes of CR delivery on coronary heart disease and chronic heart disease (HF excluded).^{12,13} Unfortunately, to date, no systematic comparison or ranking has been performed to identify the most comparatively effective and safe CR delivery methods for patients with HF. Previous traditional meta-analysis showed that patients with HF benefited from all modes of CR delivery.^{9,14,15} Unlike pairwise meta-analyses, network meta-analyses combine direct and indirect evidence to evaluate the relative efficacy and safety of multiple treatments. Hence, in this paper, we will conduct a systematic review and network meta-analysis to summarise the evidence of different modes of CR delivery and identify the comparative effects for the management of HF for both patients and doctors.

METHODS

Design and registration

We registered the research on PROSPERO (registration number: CRD42021278351) and will report our systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol.¹⁶

Eligibility criteria

Type of studies

Only randomised controlled trials (RCTs) in English will be included. The following types of papers will be excluded: qualitative studies, editorials, reviews, opinion papers and case studies. Non-experimental studies such as cohort, case-control and pre-post studies will also be excluded.

Participants

Participants in the included studies were all diagnosed with HF, with reduced ejection fraction or preserved ejection fraction, and finished at least 8 weeks of exercise-based CR.

Type of interventions

RCTs comparing different modes of CR delivery (CBCR, HBCR, CTR or HCR) in patients with HF will be considered. Trials evaluating CR and usual care (the patients with usual care were asked to maintain usual activities of daily living without CR intervention¹⁷) will also be included.

Outcomes of interest

Primary outcomes

As primary outcomes, functional capacity and hr-QoL will be analysed. The assessment of functional capacity included peak oxygen consumption (mL/kg/min) and 6 min walking test (metres). The measurement of hr-QoL is provided by the Minnesota Living with Heart Failure questionnaire and

Short Form-36, Psychometric properties of the Kansas City cardiomyopathy questionnaire and EuroQol five dimensions questionnaire.^{18,19}

Secondary outcomes

The secondary outcomes will include hospital admission (all-cause and cardiac) and all-cause mortality, within a follow-up period of at least 6 months, as well as adverse events during exercise training.

Data sources and search strategy

A literature search will be performed to identify RCTs of exercise-based CR in English. RCTs will be searched systematically up to May 2022 in the following databases: Embase, Medline, the Cochrane Central Register of Controlled Trials and Web of Science. Searches will combine the free text words and MeSH terms regarding 'heart failure' and 'Cardiac Rehabilitation' to identify target trials. The detail of the search strategy for PubMed is shown in the online supplemental material S1. Corresponding search strategies will be modified for other databases as required.

Study selection

All retrieved studies will be imported into Endnote X9 and duplicates will be removed. Titles and abstracts will be screened through an initial search by two reviewers independently. After excluding irrelevant publications, another two reviewers will download the full text of all potentially relevant studies for further independent assessment. We will review the full text of the remaining publications against the same eligibility criteria. Disagreements will be resolved through team discussion or consultation with a third reviewer. The third investigator will report and confirm the excluded publications and the reasons for exclusion.

Data extraction

Two authors will independently extract data with Excel. Any disputes will be resolved by discussion until the consensus is reached or by consulting a third investigator.

The following data will be extracted:

1. General information: title, authors, country, the language of publication, year of publication, sponsors, settings.
2. Trial characteristics: study design, total study duration, sequence generation, allocation sequence concealment, blinding.
3. Participants: diagnostic criteria, type of HF, ejection fraction, total number, age, gender, country, ethnicity.
4. Interventions: timing of treatment initiation, exercise prescription (exercise time, exercise intensity, exercise frequency), duration of treatment, additional interventions.
5. Outcomes: all specified primary and secondary outcomes, other reported outcomes, follow-up time, number of participants with complete follow-up and reasons for loss to follow-up.

Data estimates (eg, mean, SD) that may be accessed visually from figures of publications will be extracted using a Plot Digitizer (an electronic ruler).²⁰ If both SD and SE are

missing but p values or CIs are available, we will calculate SD according to the Cochrane Handbook guidelines.

Risk of bias assessment

In line with the Cochrane Handbook, the methodological quality of each included study will be independently assessed by two review authors based on the relevant criteria (<https://training.cochrane.org/handbook>).²¹ A Risk of Bias table will be built for each study, which will include the description and judgement (low, high or unclear risk of bias) for each of the seven types of possible bias. Studies with three or more entries of high or unclear risk of bias will be considered as low methodological quality. We will summarise the risk of bias in the Risk of Bias graph by Review Manager V.5.3.

Statistical analysis

Pairwise meta-analyses

All statistical analyses will be done in R (R Foundation) using the meta and network meta-analysis packages.²² We will analyse the data with pairwise meta-analysis. The clinical and methodological heterogeneity will be checked via patients' baseline characteristics, methods and interventions, and the outcome of the included studies. The mean difference (MD) or standardised mean difference (SMD) with 95% CI will be calculated for continuous data. ORs with 95% CI will be computed for dichotomous data. We will evaluate the statistical heterogeneity across studies with the I^2 statistics. I^2 values over 50% will indicate considerable heterogeneity.²³

Network meta-analysis

We will perform network meta-analyses to merge direct and indirect comparisons which discuss the efficacy and safety of selected exercise-based CR modes and usual care. All network meta-analyses will be conducted using GeMTC package in R software (<https://drugis.org/software/rpackages/gemtc>). Random-effects and consistency modes will be adopted in this network meta-analysis, as they are considered to be the most conservative approach to deal with between-study heterogeneity.²⁴ MD or SMD and 95% CI will be used as summary statistics to quantitatively evaluate different modes of CR delivery. We will use Markov chain Monte Carlo simulations with 50 000 iterations in which the first 20 000 iterations will be abandoned as burn-in. The convergence of iterations will be examined with the Gelman-Rubin-Brooks diagnostic plots.²⁵ For any specific outcomes, the probability of each intervention will be ranked the best (superior to all other interventions), second best, third best, and so on.

Evaluation of the transitivity assumption

Transitivity between treatment comparisons will be assessed using boxplots, and we propose the following main hypotheses to account for between-study variability as possible impact modifiers: (1) patient characteristics (mean patient age, gender distribution, disease severity, HF comorbidities), (2) exercise prescription (exercise intensity, exercise frequency, exercise type, treatment duration), (3) methodological quality of the study (low risk of bias, high risk of bias), sample size (large vs small studies) and (4) follow-up time. Routing

care for HF will be assessed for their similarity in treatment comparisons using network meta-analysis.

Assessment of consistency

Node splitting (GeMTC package in the R environment, V.3.6.2) will be performed to check consistency between direct and indirect evidence. If the inconsistency is identified, subgroup analyses and multiple meta-regression will be performed to determine the impact of patient characteristics, the design of research.

Quality of evidence

We will grade the evidence from the network meta-analysis in four steps according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) group with GRADE Pro software: first, it presents the effect sizes and CIs for direct and indirect comparisons between the two interventions. Second, the quality of the evidence is assessed separately. Third, the results of the network meta-analysis are presented. Finally, the quality of evidence for the results of the network meta-analysis is assessed.²⁶ The grading method for direct comparison evidence will be similar to the traditional Meta-analysis GRADE evidence grading. The grading of indirect comparison evidence will be based on the principle of lowering the group with lower quality of evidence in its direct comparison. The quality of evidence for network meta-analysis results based on mixed comparisons will be determined based on the highest quality of evidence from both direct and indirect comparisons as the final grade.

Sensitivity analysis

To verify the robustness of the study conclusions, a sensitivity analysis of primary outcomes will be performed. Heterogeneity on variables such as demographics and exercise prescriptions for CR will be analysed using meta-regression by GeMTC package, whereas subgroup analysis will be performed to identify possible sources of variation. If sensitivity analysis shows a fundamental change in the heterogeneity or the findings of meta-analysis, then the stability of the meta-analysis will be determined as poor.

Assessment of publication biases

There will be a comprehensive evaluation for all trials contained according to the Consolidated Standards of Reporting Trials. Egger's test and funnel plots will be used to evaluate the publication bias of the included studies for outcomes. If the funnel plots are found to be asymmetrical, we will attempt to explain the asymmetry.²⁷

Patient and public involvement

The protocol will not involve patients or members of the public.

ETHICS AND DISSEMINATION

Ethical issues

No ethical approval is required since all the data will be collected from published research.

Publication plan

This study was registered with PROSPERO. The results will be submitted to a peer-reviewed journal for publication.

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Contributors XH, YX and KW will perform the data collection and analyses. JX tested the feasibility of the study. BL provided methodological advice. YL and LJ conceptualised the study, designed the study and wrote the manuscript. RW polished and revised the manuscript. All authors approved the final version of the manuscript.

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